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UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE

**The epidemiology and interaction of knee alignment and
body mass on knee osteoarthritis**

by

Lyndsey Goulston

Thesis submitted for the degree of Doctor of Philosophy

September 2015

ABSTRACT

UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE

Human Development and Health

Doctor of Philosophy

THE EPIDEMIOLOGY AND INTERACTION OF KNEE ALIGNMENT AND BODY MASS ON KNEE OSTEOARTHRITIS

By Lyndsey Goulston

The growing prevalence of knee osteoarthritis (KOA) is fuelled by the rising obesity epidemic and an ageing population. The lack of a KOA cure drives the need to identify prevention strategies with alternative treatments to surgery a priority. This requires careful investigation of risk factors and their interaction. Knee mal-alignment and excess body mass are KOA risk factors but their combined effect is less understood.

These five studies examine knee alignment and body mass as separate risk factors, describing their natural history and their association with prevalence and incidence of symptomatic radiographic knee osteoarthritis (SRKOA), radiographic knee osteoarthritis (RKOA) and knee pain outcomes in a long-standing female cohort. The cross-sectional interaction of these risk factors and outcomes is examined. One-point (1P) versus two-point (2P) anatomic axis (AA) knee alignment measurements, and body mass index (BMI) versus waist circumference (WC) measurements are also compared.

Differences between 1P and 2P measurements indicate method specific alignment categories are required. Improvements are identified in AA angle measurement that require further validation to establish a gold standard AA alignment method. Changes in AA alignment over 10 years were small, but limited by identification of rotated knees.

Over 19 years the tripling amount of obese women, was associated with increased prevalence and incidence of SRKOA, RKOA and knee pain. WC measurement offers no advantage over BMI in predicting SRKOA, but it could be substituted where height or weight measurement is difficult.

Results suggest a cross-sectional interaction between BMI and alignment with SRKOA and RKOA but not with knee pain, indicating that it may be driven by structure. This is important for targeting timely treatment of these risk factors.

This new knowledge should assist in identification of individuals who would benefit from early intervention and treatment, to reduce pain, suffering and high future costs of KOA.

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List of publications & presentations

The following publications and presentations have resulted from the work completed as part of this candidature for Doctor of Philosophy:

Articles published:

- **Goulston LM**, Kiran A, Javaid MK, Soni A, White KM, Hart DJ, Spector TD, Arden NK. Does obesity predict knee pain over fourteen years in women, independently of radiographic changes? *Arthritis Care & Research*. 2011, 63 (10): 1398 – 1406.

Articles under review:

- **Goulston L**, Sanchez-Santos M, D'Angelo S, Leyland K, Hart D, Spector T, Cooper C, Dennison E, Hunter D, Arden N. A comparison of radiographic anatomic axis knee alignment measurements and cross-sectional associations with knee osteoarthritis. *Osteoarthritis & Cartilage*. 2015

Conference presentations:

- **Goulston L**, Soni A, White K, Kiran A, Javaid M, Hart D, Spector T, Arden N. Baseline but not change in body mass index is a risk factor for bilateral knee pain at fifteen years. Oral presentation. *British Society of Rheumatology annual conference 2010*. *Rheumatology*. 2010, 49 (supp 1): i8.

Conference poster presentations:

- **Goulston L**, Culliford D, Hart D, Spector T, Arden N. Knee pain – is the association with obesity mechanical or metabolic? Poster presentation. *OARSI annual conference 2012*. *Osteoarthritis & Cartilage*. 2012, 20 (supp 1): S256.

- **Goulston L**, Hooper L, Gates L, Metcalf C, Bowen C, Warner M, Culliford D, Maskell J, Leyland K, Burridge J, Stokes M, Arden N. Static and dynamic knee alignment in osteoarthritis. Poster presentation. *EULAR annual conference 2011. Annals of the Rheumatic Diseases. 2011, 70 (supp 3): 702.*
- **Goulston L**, Javaid M, Hart D, Spector T, Arden N. Predictors of knee pain at fifteen years in the Chingford Study – is there an interaction between baseline body weight and radiographic osteoarthritis? Poster presentation. *British Society of Rheumatology annual conference 2009. Rheumatology. 2009, 48 (supp 1): i99.*

Other associated publications:

- Leyland KM, Hart DJ, Javaid MK, Judge A, Kiran A, Soni A, **Goulston LM**, Cooper C, Spector TD, Arden NK. The natural history of radiographic knee osteoarthritis: a fourteen year population-based cohort study. *Arthritis & Rheumatism. 2012, 64 (7): 2243 – 2251.*
- Soni A, Kiran A, Hart DJ, Leyland KM, **Goulston LM**, Cooper C, Javaid MK, Spector TD, Arden NK. Prevalence of reported knee pain over twelve years in a community-based cohort. *Arthritis & Rheumatism. 2012, 64 (4): 1145 – 1152.*

Declaration of authorship

I, Lyndsey Goulston

declare that the thesis entitled:

‘The epidemiology and interaction of knee alignment and body mass on knee osteoarthritis’

and the work presented in this thesis, is both my own and has been generated by me as a result of my own original research. I confirm that:

- ❖ This work was done wholly or mainly while in candidature for a research degree at this University;
- ❖ Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- ❖ Where I have consulted the published work of others, this is always clearly attributed;
- ❖ Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- ❖ I have acknowledged all main sources of help;
- ❖ Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself; *
- ❖ Parts of this work have been published as listed previously.

Signed:

Date:

* The baseline and 14 year follow-up data used within this thesis to allow longitudinal data analysis was completed by previous researchers and should not be considered as part of the author’s own or original work.

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List of abbreviations

AA	Anatomic axis
AP	Antero-posterior
ACL	Anterior cruciate ligament
ACR	American College of Rheumatology
ADLs	Activities of daily living
AJC	Ankle joint centre
ANOVA	Analysis of variance
BF	Body fat
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BML	Bone marrow lesion
BOKS	Boston Osteoarthritis Study
CAA	Computer assisted analysis
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardio-vascular disease
DALY	Disability-adjusted life year
DC	David Culliford (study team member)
DCF	Data collection form
DEXA	Dual energy x-ray absorptiometry
DH	Deborah Hart (study team member)
DHU	David Hunter (study team member)
DICOM	Digital Imaging and Communications in Medicine
DIP	Distal inter-phalangeal
DM	Diabetes mellitus

DPI	dots per inch
F	Female
FAA	Femoral anatomic axis
FE	Full extension
FF	Full flexion
FMA	Femoral mechanical axis
FN	Femoral notch
FTA	Femoral tibial angle
FLR	Full limb radiograph
GCP	Good clinical practice
GEE	General estimating equation
GNP	Gross national product
GOAL	Genetics of Osteoarthritis and Lifestyle
GP	General Practitioner
GPRD	General Practice Research Database
HC	Hip circumference
HJC	Hip joint centre
HKA	Hip knee ankle
HN	Heberden's node
ICC	Intra-class correlation coefficient
ICH	International Conference of Harmonisation
IQR	Inter-quartile range
JSL	Joint space loss
JSN	Joint space narrowing
JSW	Joint space width
KAM	Knee adduction moment
KJ	Kassim Javaid (study team member)

KJC	Knee joint centre
KL	Kirsten Leyland (study team member)
KOACAD	Knee OA Computer-Aided Diagnosis
K&L	Kellgren and Lawrence
KIDA	Knee Images Digital Analysis
KOA	Knee osteoarthritis
L	Left
LG	Lyndsey Goulston (author)
LBA	Load bearing axis
LCL	Lateral collateral ligament
LoA	Limits of agreement
M	Male
MA	Mechanical axis
MCL	Medial collateral ligament
MD	Maxine Daniels (study team member)
METs	Metabolic syndrome
MRI	Magnetic resonance imaging
MS	Maria Sanchez (study team member)
MOST	Multicentre Osteoarthritis Study
NA	Nigel Arden (study team member)
NB	Nicholas Bottomley (study team member)
NCD	Non-communicable disease
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
N/S	Not stated

OA	Osteoarthritis
OAI	Osteoarthritis Initiative
OARSI	Osteoarthritis Research Society International
OP	Osteoporosis
ONS	Office of National Statistics
OR	Odds ratio
PA	Posterior-anterior
PCL	Posterior cruciate ligament
QIC	Quasi-likelihood under the Independence Criterion
R	Right
RG	Richard Gill (study team member)
RCT	Randomised controlled trial
RKOA	Radiographic knee osteoarthritis
ROAD	Research on OA against Disability
SA	Sensitivity analysis
SD	Standard deviation
SDA	Stefania D'Angelo (study team member)
SE	Standard error
SF	Semi-flexed
SJ	Sam James (study team member)
SLR	Short limb radiograph
SOP	Standard operating procedure
SQL	Structured Query Language
SRKOA	Symptomatic radiographic knee osteoarthritis
TAA	Tibial anatomic axis
THR	Total hip replacement
TKR	Total knee replacement

TMA	Tibial mechanical axis
TS	Tibial spine
TDS	Tim Spector (study team member)
UK	United Kingdom
USA	United States of America
UKR	Uni-condylar knee replacement
WC	Waist circumference
WHO	World Health Organization
WHR	Waist hip ratio
Y1	Year 1
Y15	Year 15
Y20	Year 20
1P	One-point
2P	Two-point

1. Chapter 1: Introduction

1.1 Introduction

Osteoarthritis (OA) is the most common joint disorder world-wide, however its complexity ensures that treatment of this condition currently remains an enigma. Consensus on its precise definition is a continuing debate. Previously considered a disease of the articular cartilage, it is generally now thought to be primarily a bone disease with secondary cartilage damage and all tissues of the joint being involved in the process, leading to a possible end result of OA representing failure of the joint as an organ (Arden and Cooper, 2006). OA is often incorrectly described as 'wear and tear', however it is now known to be a metabolically active process involving all joint tissues and the term 'tear, flare and repair' has been proposed as a better representation of the pathology involved (Birrell et al., 2011). OA predominantly affects the weight-bearing synovial joints of the body, the knee and hip being the most common sites with joint pain being the most dominant OA symptom. This condition is a major cause of morbidity with a huge expenditure in terms of health care and its growing prevalence will continue to be fuelled by the rising obesity epidemic and an ageing population.

The pain and suffering experienced by people as a result of having OA is a subject close to my heart, with my mother receiving bilateral hip joint resurfacing as a result of severe hip OA, and various other close family members receiving total hip and total knee replacement surgery also due to severe OA over recent years. Whilst treating patients from a physiotherapy perspective with this condition and assisting family members with their pre- and post-op rehabilitation, it is frustrating to know that in this day and age the treatment options for OA still remain fairly limited with the final resolution being joint surgery, which although hugely effective is costly, and is soon to become unsustainable with the growing OA prevalence. It is a challenge to develop effective treatments for a condition where the aetiology and pathology remain unclear. This encouraged me to start looking at how this situation could be improved and inspired me to study this condition from an epidemiological perspective.

The lack of cure for this condition drives the need to identify prevention strategies, and alternative treatment options to joint replacement surgery are a priority. This requires careful consideration of risk factors and their interaction in the part they play within the disease process. There are many factors that are known to contribute to the cause of knee osteoarthritis (KOA). These risk factors have been extensively studied in terms of disease incidence but less so on disease progression and interaction data between important risk factors are limited. Risk factor interaction is an area that is under-researched and could be a focus for improving the phenotyping of people with KOA, allowing stratification of incident cases and quick progressing cases so that their treatment can be targeted more effectively. The overall outcome of this thesis is to study the natural history of two well known KOA risk factors, knee alignment and body mass, and to assess if interactions between these two risk factors over time influence the likelihood of KOA development over a 19 year period in a well established female cohort population based in Chingford, Essex, United Kingdom (UK) known as the Chingford 1,000 Women Study. It is hoped that the findings from this work will enable the identification of individuals who would benefit from early intervention and treatment, thereby reducing the pain, suffering and high future costs of KOA.

2. Chapter 2: Background & literature review

2.1 Introduction

This chapter provides a critical review of the academic literature on the epidemiology of KOA including its definition, diagnosis and classification in section 2.2.1; the prevalence, incidence, progression and impact in section 2.2.4; aetiological and pathological processes involved in section 2.3, and an account of the systemic and mechanical risk factors associated with KOA in section 2.4. Obesity and knee alignment risk factors are discussed in sections 2.5 and 2.6 respectively, with discussion on the importance of examining interaction between these risk factors in section 2.7.

An in-depth literature search was performed using the following keywords in various combinations: obesity, weight, body weight, body mass, body mass index, anthropometric, anthropometry, adiposity, mal-alignment, varus alignment, valgus alignment with arthritis or osteoarthritis. MEDLINE, EMBASE and Cochrane computerised databases were searched to identify eligible studies about humans in English-language journals before April 2015 for inclusion in this literature review.

2.2 Osteoarthritis

OA is the most common joint disorder globally, although its precise definition is an ongoing debate. Osteoarthritis derives from the Latin: ‘osteo’ bone, ‘arthro’ joints and ‘itis’ inflammation. In theory, the term OA should relate to inflammation of the bones in the joint, but it is known that the bones themselves are not inflamed, rather the whole joint may be inflamed by the disease process. OA is now widely considered to be:

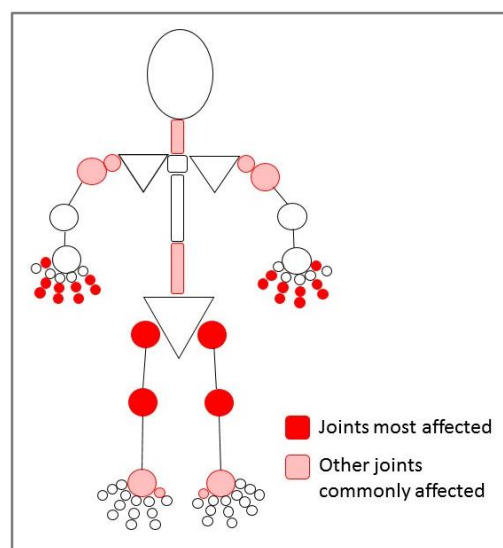
‘an age-related dynamic reaction pattern of a joint in response to insult or injury.’ (Arden and Cooper, 2006)

Focal loss of articular cartilage and changes in articulating bony surfaces are the main disease features affecting synovial joints. It now appears that all tissues of the synovial joint encompassing the surrounding musculature,

ligaments and joint capsule, in addition to the bone and cartilage, are involved in this common complex disorder, leading to OA representing failure of the joint as an organ (Arden and Cooper, 2006).

Although OA can affect any synovial joint in the body the most commonly affected joints are the distal inter-phalangeal (DIP) and the proximal inter-phalangeal (PIP) joints of the hands, the base of the thumb and the weight-bearing hips and knees. Less commonly affected are the spinal inter-vertebral facet joints, shoulders, ankles and feet (Figure 1). OA may also occur in other joints of the body following trauma. OA may be localised to a single joint, a few joints, or generalised. Rather than being a single disease of the joint, OA is believed to be a collection of diseases and 'OA phenotyping' may address the variability of OA with respect to pattern, site of joint involvement and clinical presentation (Kerkhof et al., 2011, Valdes et al., 2010). An improved understanding of the phenotypes of OA is required and this may enhance the specificity of treatment selection.

Figure 1: Body joints affected by OA



2.2.1 Defining knee osteoarthritis terms

KOA is the most frequent form of lower limb OA (Oliveria et al., 1995) and is the focus of this thesis. The case definition of KOA varies widely in reported studies (Felson and Zhang, 1998), it can be defined by structural pathology, on a radiograph for example, or by joint symptoms, using knee pain for example,

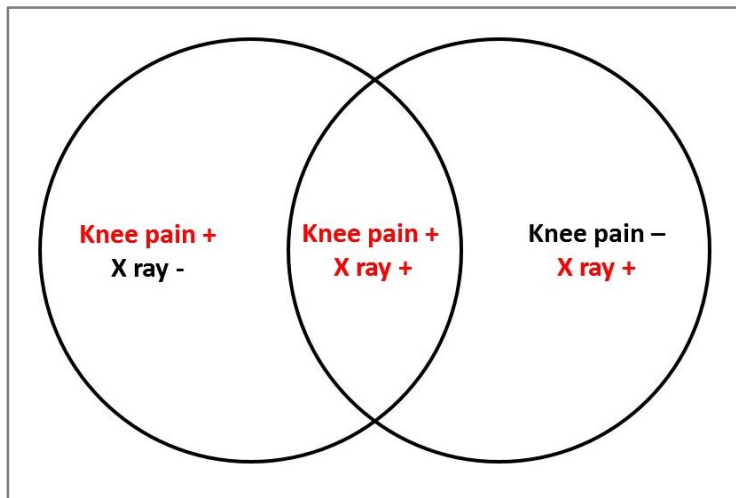
or a combination of the two. A systematic review by Schiphof and colleagues in 2008 identified 25 different criteria for identifying KOA which presents difficulties in analyses, reducing the statistical power to find consistent associations (Schiphof et al., 2008).

In epidemiology studies, KOA is most often defined by radiographic assessment and therefore the term often used is 'radiographic knee osteoarthritis' (RKOA) (Neogi, 2013). The term 'symptomatic radiographic knee osteoarthritis' (SRKOA) indicates RKOA and symptoms (e.g. knee pain) are both present. This is also reported as 'clinical KOA' (Altman et al., 1986).

The discordance between reported symptoms and RKOA is well documented (Hart et al., 1991, Felson, 1990, Claessens et al., 1990, Dieppe et al., 1997, Hannan et al., 2000). Knee pain has been reported as an imprecise marker of RKOA, and likewise RKOA an imprecise marker of knee pain (Bedson and Croft, 2008). The two in combination as the presence of pain plus radiographic change are thought to be the most useful for both clinical diagnosis and consideration of the true public health burden (Murphy et al., 2008, Arden and Nevitt, 2006) (Figure 2). For this reason SRKOA was chosen as the main outcome of interest in this thesis, thereby allowing associations to be explored for the worst case scenario outcome of knee pain combined with structural OA involving knee joint pathology. Knee pain itself was not chosen as the main outcome due to its varied nature, it may not be directly related to local pathology at the knee joint. For example, knee pain could incorporate injuries to soft tissue structures around the joint such as tendonitis; or inclusion of systemic diseases with referred pain; or more widespread chronic pain disorders that could be linked to cognitive issues and emotional states such as depression. However to allow comparison with SRKOA, both RKOA and knee pain were reported as secondary outcomes in this thesis. Few epidemiology studies report associations across all three of these outcomes and the capacity to do so at more than one time point is a strength of this cohort study.

The term KOA is used in this thesis as an umbrella term incorporating the inclusion of all three SRKOA, RKOA and knee pain outcomes.

Figure 2: The discordant relationship



2.2.2 Diagnostic criteria

The development of diagnostic criteria for OA has been a difficult task due to its non-specific nature, the large asymptomatic proportion of the population, and the distinct lack of an appropriate diagnostic test. The American College of Rheumatology (ACR) has developed the most widely used diagnostic criteria to date and those specific to the knee joint are shown in Table 1 (Altman et al., 1986).

Table 1: Diagnostic criteria for KOA

Where ESR=erythrocyte sedimentation rate; RF=rheumatoid factor; SF OA=synovial fluid signs of OA.

Clinical Knee pain & at least 3 of 6	Clinical & radiographic Knee pain & osteophytes & at least 1 of 3	Clinical & laboratory Knee pain & at least 5 of 9
1) age >50 years 2) stiffness <30 mins 3) crepitus 4) bony tenderness 5) bony enlargement 6) no palpable warmth	1) age >50 years 2) stiffness <30 mins 3) crepitus	1) age >50 years 2) stiffness <30 mins 3) crepitus 4) bony tenderness 5) bony enlargement 6) no palpable warmth 7) ESR <40 mm/hour 8) RF <1:40 9) SF OA
95% sensitive 69% specific	91% sensitive 86% specific	92% sensitive 75% specific

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Contrasting with previous diagnoses that rely solely on RKOA, the ACR criteria specifically focus on identifying symptomatic KOA by using knee joint pain for most days of the previous month as the main inclusion factor. A comparison of a range of clinical and radiographic measures on individuals with OA (n=130) and controls with knee pain due to other arthritic or musculoskeletal conditions (n=107, 55 of whom had rheumatoid arthritis), identified acceptable levels of sensitivity, specificity and accuracy of discrimination between these two population groups with these diagnostic criteria (Altman et al., 1986).

Whilst these diagnostic criteria are useful, particularly for clinical studies and randomised clinical trials (RCTs) where it is vital to identify individual correct diagnosis, in population-based studies the diagnostic criteria tend to be biased towards more severe, established disease, which will not help in the identification of early or mild forms of KOA (Peat et al., 2006).

Knee pain was defined in this study using the question:

‘Have you ever had pain in or around your knee on most days in the last month?’

This question was derived from the National Health and Nutrition Examination Survey (NHANES) which is a long running program of studies (started in the early 1960s) designed to assess the health and nutritional status of adults and children in America. NHANES was one of the first cohort studies to define knee pain on interview (Anderson and Felson, 1988) and it has since become a standard epidemiology knee pain question, and is used to define knee pain throughout the Chingford study. Further detail is provided in section 3.5.2.

2.2.3 Classification

OA can be classified into two main systems: aetiologic and articular (Altman et al., 1986). The aetiologic system is categorized into primary (idiopathic) and secondary OA. Several disorders can contribute to secondary OA and can be divided into four main sub-categories: metabolic, anatomic, traumatic and inflammatory (Table 2). The distinction between primary and secondary OA is not always clear cut. It can sometimes be difficult to judge whether an abnormality reported in an individual’s medical history occurring years previously is of any significance to the current OA problem.

Table 2: Classification of OA

Classification systems	
Aetiologic classification	
Primary = idiopathic	
Secondary indicated a likely cause can be identified from the following:	
Metabolic	e.g. ochronosis, acromegaly, hemochromatosis, calcium crystal deposition
Anatomic	e.g. slipped femoral epiphysis, epiphyseal dysplasias, Blount's disease, Legge-Perthe disease, hip congenital dislocation, leg length inequality, hypermobility syndromes
Traumatic	e.g. major joint trauma, fracture through a joint, osteonecrosis, joint surgery (meniscectomy), chronic injury (occupational arthropathies)
Inflammatory	e.g. any inflammatory arthropathy, septic arthritis
Articular classification	
Monoarticular, oligoarticular or polyarticular (generalised)	
Chief joint side (index joint site) and localisation within the joint:	
Hip (superior pole, medial pole or concentric)	
Knee (medial, lateral, patella-femoral compartments)	
Hand (interphalangeal joints and/or thumb base)	
Spine (apophyseal joints or intervertebral disc disease)	
Others	

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The articular system relates to the number and distribution of affected joints sites. The pattern of joint distribution varies widely in different individuals. The sites most commonly affected by OA (Figure 1) are the distal interphalangeal (DIP) joints of the hand, the base of the thumb, the knee, hip and intra-vertebral facet joints in the spine. Involvement of more than one joint is common, and there are differences between the degree of association of OA at different joint sites. For example, in the Caucasian population there is a stronger association between hand and knee OA, than between hand and hip OA. (Cushnaghan and Dieppe, 1991), which justifies the approach that OA present at different sites should be treated as individual conditions.

2.2.3.1 Radiographic classification

OA is most often evaluated diagnostically using radiographs. Other imaging modalities such as magnetic resonance imaging (MRI) are now being used, but a valid and reproducible MRI classification for OA is still a focus for research, and so plain film radiography remains the most widely used.

The system for grading radiographs for OA which divides the disease into severity grades (Table 3) by radiological features (Table 4) was first defined by Kellgren & Lawrence in 1957.

Table 3: Kellgren & Lawrence radiograph assessment OA grading system

OA grade	OA radiographic criteria
0 None	No features of OA
1 Doubtful	Minute osteophyte, doubtful significance
2 Minimal	Definite osteophyte, unimpaired joint space
3 Moderate	Moderate diminution of joint space
4 Severe	Joint space greatly impaired with sclerosis of sub-chondral bone

Table 4: Kellgren & Lawrence global score radiographic features

OA grade	Osteophytes	Joint space narrowing	Sclerosis	Joint contour deformation
0 None	None	None	None	None
1 Doubtful	Possible	None	None	None
2 Minimal	Definite	Possible	None	None
3 Moderate	Multiple	Definite	Some	Possible
4 Severe	Large	Marked	Severe	Definite

Reproduced from Kellgren & Lawrence (Kellgren and Lawrence, 1957), *Annals of the Rheumatic Diseases*
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By comparison with a radiographic atlas, this Kellgren & Lawrence (K&L) system assigns one of five grades (0 – 4) to OA at various joint sites. The K&L criteria assume sequential appearance of osteophytes, joint space narrowing (JSN), sclerosis and joint contour deformation. Grade 0 indicates a definite absence of radiographic OA, while grade 2 or above is defined as radiographic OA being present at minimal severity (Kellgren and Lawrence, 1957). This composite grading system helped in the diagnosis and classification of OA, and remains a gold standard today, but it does have its limitations:

- Inconsistent descriptions of radiographic OA features mean studies have been performed using discordant K&L criteria (Spector and Cooper, 1993).
- Assumptions are made that progression of distinct OA features like JSN and osteophyte formation are linear and constant which is not necessarily the case (Oka et al., 2008).
- The system biases the development of osteophytes, making correct grading of joints with severe JSN but no osteophyte formation difficult.
- Only the tibio-femoral joint is assessed, the patella-femoral joint is not considered.

To overcome the limitations of the K&L grading system, Osteoarthritis Research Society International (OARSI) published a radiographic atlas of individual OA features in 1995 (Altman et al., 1995) with a revised version published in 2007 (Altman and Gold, 2007). The OARSI grading system (Table 5) assesses osteophyte formation and JSN separately into four severity grade (0 – 3) categories at the medial and lateral tibio-femoral compartments on radiographs, and also assesses other features of attrition and sclerosis.

Table 5: OARSI grading system

Where N/A=not applicable.

OA grade	0 Normal	1 Mild	2 Moderate	3 Severe	Absent	Present
Marginal osteophytes						
medial femoral condyle	0	1	2	3	N/A	N/A
medial tibial plateau	0	1	2	3	N/A	N/A
lateral femoral condyle	0	1	2	3	N/A	N/A
lateral tibial plateau	0	1	2	3	N/A	N/A
Joint space narrowing						
medial compartment	0	1	2	3	N/A	N/A
lateral compartment	0	1	2	3	N/A	N/A
Other features						
medial tibial attrition	N/A	N/A	N/A	N/A	Absent	Present
medial tibial sclerosis	N/A	N/A	N/A	N/A	Absent	Present
lateral femoral sclerosis	N/A	N/A	N/A	N/A	Absent	Present

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This grading system is an improvement on the K&L system as individual features are considered separately, and via sky line views, it permits scoring of the patella-femoral joint in addition to the tibio-femoral joint. However, the ordinal grades for JSN and osteophyte size do not strictly increase geometrically and it is still somewhat limited in reproducibility and sensitivity due to the subjective judgment of individual observers, although specific training can help.

Further work in this area has been completed by Doherty and colleagues from the Nottingham group who have developed an atlas containing a series of line drawings for grading of tri-compartmental knee OA (Nagaosa et al., 2000). This atlas focuses solely on the two cardinal radiographic structural OA features of JSN and osteophytes as they can be easily reproduced by line

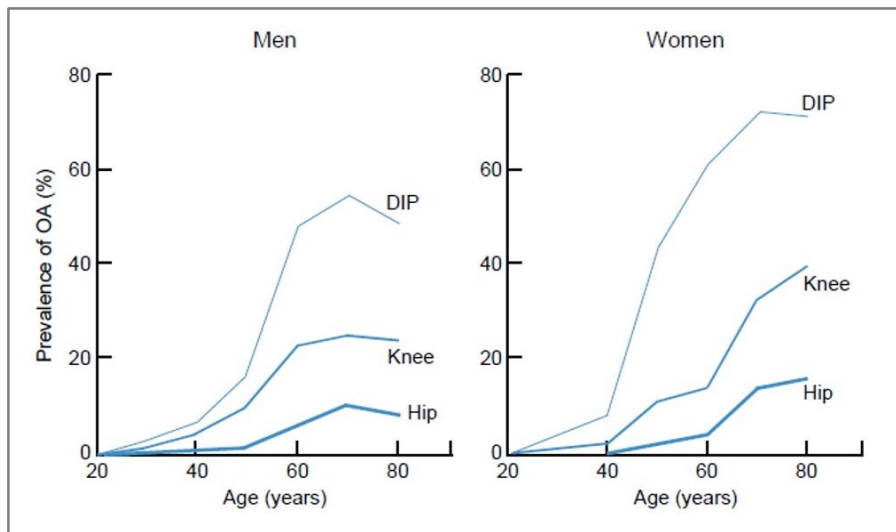
drawings. Unlike the OARSI atlas, it provides different options for JSN for men and women, however similarly to the OARSI atlas, each feature is scored from 0 to 3. The grades are mathematically calculated from normal JSW and maximum size of osteophyte giving excellent face validity and it has been shown to be comparable with the OARSI atlas for intra- and inter-observer reproducibility (Nagaosa et al., 2000), and it therefore offers some advantages. However, as regulatory authorities continue to use K&L grading as their gold standard and as previous Chingford Cohort tibio-femoral radiographs taken at Y1 and Y10 visits have been scored using the K&L grading system, then for consistency and comparative purposes this was the grading system of choice. However, all tibio-femoral radiographs taken at the Y20 visit were scored for K&L, OARSI and Nottingham line drawing grades by Dr Kirsten Leyland (KL). Further detail is provided in section 3.5.3.

2.2.4 Prevalence

OA is the most frequently reported joint disorder in older people, affecting approximately 30% of adults over the age of 60 (Felson et al., 1987). It is a major cause of morbidity with a huge expenditure in terms of health care (Felson et al., 2003). With increased life expectancy and an ageing population, OA is expected to become the fourth leading cause of disability by the year 2020 (Woolf and Pfleger, 2003).

Most of the information on OA prevalence comes from population-based radiographic surveys. In a Dutch study on 6585 randomly selected village inhabitants, van Sasse and colleagues reported that radiological OA was uncommon under the age of 45, but its prevalence rose steeply with age at all joint sites for both men and women (Figure 3) (van Saase et al., 1989). Significant increases in prevalence of radiographic OA for women compared to men were seen for the knee, hip (after the age of 65) and hand DIP joints.

Figure 3: Prevalence of OA affecting the DIP joint, knee and hip in a large Dutch population



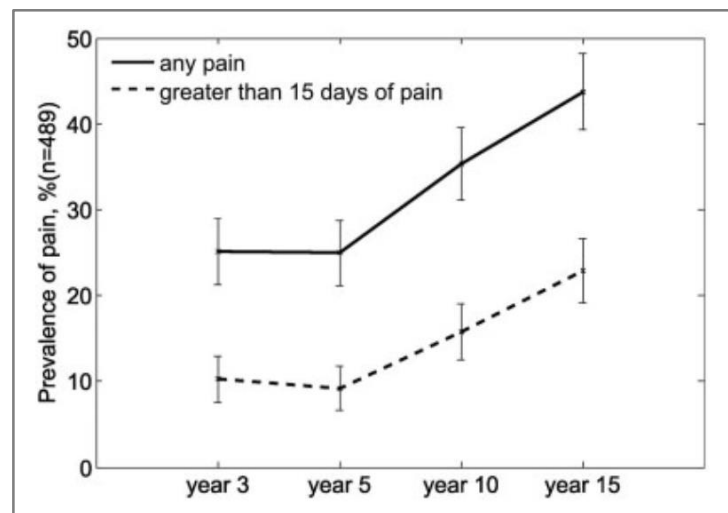
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Although most OA prevalence studies are based on radiographic changes, there is now increasing research into the prevalence of pain, which is the dominant symptom of OA.

In the UK there are suggested estimates of up to 8.5 million people being affected by joint pain that may be attributed to OA (Arthritis Care, 2004). The most common site of peripheral joint pain lasting for more than one week in the past month for adults aged 45 and over is in the knee (19%), and the highest prevalence of knee pain (35%) is reported in women aged 75 and over (Urwin et al., 1998).

A more recent prevalence study by Jinks in 2004 reports up to half of people aged 50 and over have knee pain during the course of a year, with a quarter of them having severe and disabling knee pain (Jinks et al., 2004). A similar level of knee pain (defined as having greater than 15 days of pain in the last month) at 23% was reported at Y15 in the Chingford study by 489 middle aged women (Soni et al., 2012). Figure 4 demonstrates the increasing prevalence of knee pain in this female cohort over a 12 year period.

Figure 4: The prevalence of knee pain in the Chingford cohort

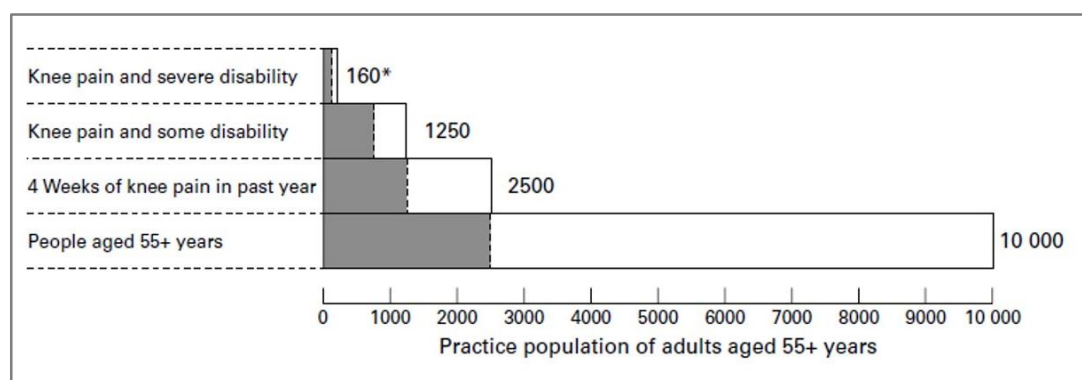


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Data on symptomatic and radiographic KOA from a variety of population studies, Peat and colleagues in 2001 showed that approximately one quarter of UK adults over the age of 55, complained of significant knee pain in the previous year, with approximately 50% of these reporting disability as a result (Figure 5) (Peat et al., 2001). Approximately half of patients with knee pain will have RKOA and can therefore be classified as SRKOA. Prevalence of RKOA in the study was 25% and of SRKOA was 13% which highlights the important discordance between reported symptoms and radiographic evidence of KOA.

Figure 5: The knee pain prevalence staircase

Where: shading represents the proportion in each category with RKOA; * the proportion with RKOA in this category is not known, though seems likely to be high.



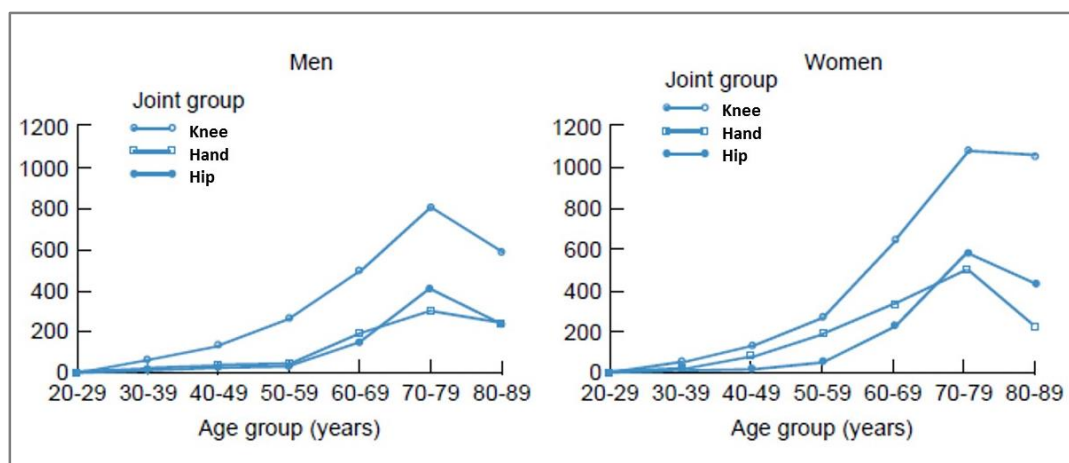
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Geographic variation in KOA prevalence has been reported, though differences in sampling methods and radiographic techniques can hinder interpretation. Data from European and American knee studies are generally similar, though African-American women tend to have a higher age-adjusted prevalence of KOA than their Caucasian counterparts (Anderson and Felson, 1988). Despite the lower hip OA rate, KOA is more common amongst Chinese women than Caucasian women, whilst the KOA prevalence for men remains comparable (Zhang et al., 2001).

2.2.5 Incidence

The incidence of symptomatic hand, hip and KOA has been reported by an American health maintenance organisation called the Fallon Community Health Plan (Figure 6) (Oliveria et al., 1995). Incidence rates for all three joint sites increased with age, and above the age of 50 women displayed higher rates than men. Rates peaked and then levelled off for both genders at all joint sites around age 80. The age and sex standardised incidence rate for KOA was greatest at 240 per 100,000 person-years.

Figure 6: Incidence of symptomatic OA of hand, knee and hip



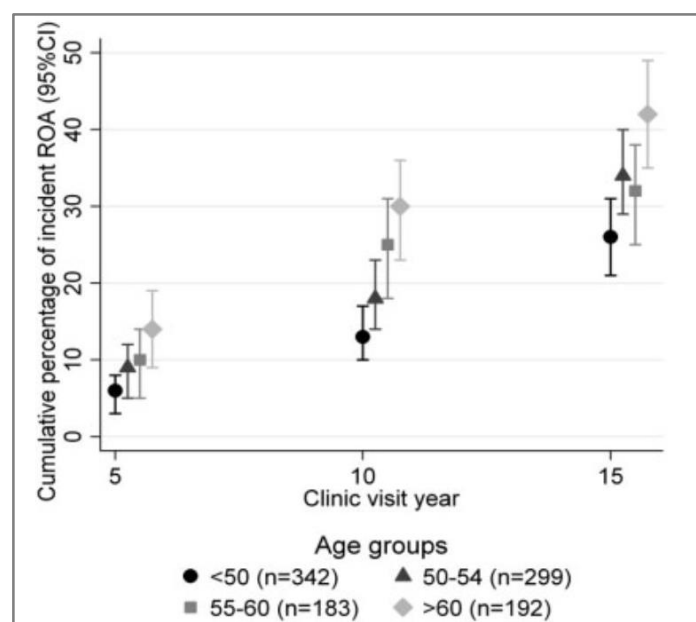
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The annual incidence of RKOA determined from longitudinal radiographic community-based cohort studies ranges between 2% and 4% (Cooper et al., 2000, Felson et al., 1995, Hart et al., 1999, Schouten et al., 1992). Rates of

RKOA are significantly higher in women than men, and rates of incident RKOA are twice as high as incident symptomatic KOA (Felson et al., 1995).

The longest natural history study of RKOA from the Chingford cohort recently reported an annual cumulative RKOA incidence rate of 2.3% over 14 years in 561 women (Leyland et al., 2012). When at 5 year intervals RKOA cumulative incidence was stratified by baseline age quartiles at each time point, a linear trend ($p < 0.002$) was seen (Figure 7), with the oldest age group of women having the highest incidence RKOA.

Figure 7: Cumulative incident RKOA in the Chingford Cohort



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The lifetime risk of developing SRKOA in at least one knee was most recently reported as 45% (95% CI 40.0 – 49.3%) following a longitudinal study of over 3,000 black and white Americans participating in the Johnston County Osteoarthritis Project (Murphy et al., 2008). This risk was increased to 57% for those reporting a history of knee injury, and it also rose with increasing BMI to a 2 in 3 risk among obese participants.

2.2.6 Progression

Annual rates of RKOA progression observed in community-based cohorts range from 3.5 - 8% for progression (Cooper et al., 2000, Felson et al., 1995,

Thorstensson et al., 2009) and 4.4% for worsening (Cooper et al., 2000). Slightly lower rates, 2.8% for RKO progression and 3.0% for RKO worsening, are reported in the 14 year follow-up study of the Chingford cohort by Leyland and colleagues (Leyland et al., 2012). These lower rates are possibly a result of the relatively young age (45-65) of the cohort at baseline and the length of the study in total. Of the women who developed incident RKO, approximately one-third developed bilateral RKO while the remaining two-thirds developed unilateral RKO. Over one-third of the unilateral knees progressed to bilateral disease between each clinic visit, while the rest remained stable. From this data it is possible to identify distinct RKO subsets that may exist, where some women have slow progression from no disease through unilateral then bilateral RKO, while others experience a more rapid progression to bilateral disease within a five year period. Further work is required to establish if these patterns could be due to environmental (i.e. the functional effect of having contra-lateral KO) and/or genetic factors.

The evolution of KO is a slow process, usually taking several years. In one of the first natural history studies of KO by Hernborg & Nilsson in 1977, the majority of participants with radiographic structural change, for example with femoral or tibial sclerosis, experienced radiographic and symptomatic deterioration over 15 years (Hernborg and Nilsson, 1977). Far fewer of the participants suffered deterioration if they only had osteophytes on baseline radiographs. These findings were superseded by an ACR study in 1987 (Altman et al., 1987), where JSN was reported to be a more important determinant of KO progression, than the presence of osteophytes. This study concluded that a combination score based on JSN, osteophytes and sclerosis was not only reproducible but a better predictor of KO progression than any other combination, hence the inclusion of these parameters in the OARSI radiographic grading system (section 2.2.3.1).

In a UK study on KO progression of 63 participants with baseline and 11 year follow-up knee radiographs, only one third demonstrated deterioration in K&L score over the period and the majority of knees did not show any worsening over 11 years (Spector et al., 1992). When a more sensitive global radiographic scoring system was used on paired films, the proportion showing deterioration increased to 50%. The visual analogue pain scores remained stable over the period, but a greater chance of progression was found in those subjects

reporting knee pain at baseline and in those with existing OA in the contra-lateral knee. A follow-on study was carried out using the Chingford cohort (Spector et al., 1994) with 58 women with unilateral KOA (K&L ≥ 2 at baseline) aged 45 – 64 from the general population. Repeat radiographs at the 2 year follow-up visit showed that 22% of women had progressed radiographically in the index knee and 34% developed OA in the contra-lateral knee. Another UK study looking at the change in radiographic score of KOA in 354 men and women aged 55 or over during a 5 year follow-up showed that KOA in approximately 75% of subjects did not progress over time period (Cooper et al., 2000).

These studies demonstrate the many unanswered questions about KOA progression. Progression of KOA beyond the mild stage is responsible for most of its extensive burden, and limiting KOA progression is thought to be a more effective public health strategy than trying to prevent its initial development. Understanding risk factors for progression is imperative (Cooper et al., 2000). There is a lack of longitudinal information on exactly which risk factors acting at the knee joint result in a high risk of OA progression and their identification may allow better understanding of the KOA disease process (Felson et al., 2003).

2.2.7 Impact on the individual

OA affects individuals in many ways as a result of:

- symptoms
- loss of function
- restricted participation in activities
- reduced quality of life
- co-morbidities
- mortality

Symptoms

Joint pain is the most common reason for individuals to present to their general practitioner (GP). Over half of all people with OA report pain as being their worst problem (Arthritis Care, 2004, Arthritis Research Campaign, 2002). The descriptions of pain vary, it may be a dull ache, burning, or sharp, and the

relationship between pain and activity may also vary, being worse on knee flexion, in bed at night and/or after prolonged immobility.

Stiffness is another major complaint, particularly with KOA. It is usually worse in the morning on first arising from bed, generally lasting less than 30 minutes (Altman et al., 1986). This is different from longer early morning joint stiffness that is more indicative of an inflammatory arthritis such as rheumatoid arthritis. Joint stiffness can occur after resting during the day, usually this lasts for 2-3 minutes and is described as 'gelling'. Joint movement and exercises can help with this osteoarthritic stiffness (Arden et al., 2008).

Loss of function

The UK OA Nation Report by Arthritis Care in 2004 (Arthritis Care, 2004) surveyed 1,762 individuals with OA, with an average of 12 years of symptoms, 81% of respondents had constant pain or were limited in their scope to perform everyday tasks. When their OA pain was 'bad', over 50% struggled even to get out of bed. For people with multiple joint pains these problems were even worse. A postal questionnaire study on multiple joint pain (Keenan et al., 2006) concluded that people with knee pain alone have three times more difficulty walking than people without knee pain, but the combination of knee, back and foot pain increases the difficulty by a factor of 30.

Restricted participation in activities

Depending on the site and severity of the OA, individuals can report difficulties with occupational as well as certain leisure activities and activities of daily living (ADLs) (Arthritis Care, 2004, Arthritis Research Campaign, 2002).

Reduced quality of life

Some people with OA may report poor self-esteem, loss of independence and varying levels of depression that can all have a considerable effect on close relationships and overall quality of life (Hawker et al., 2011).

Co-morbidities

After adjusting for age, sex and social class, people with OA are at least twice as likely to have co-morbid conditions than the rest of the general population

(Kadam and Croft, 2007). Generally, over half of the OA population demonstrate at least one co-morbid condition, including obesity, hypertension, cardiovascular disease (CVD) or stomach / ulcer problems (Kadam and Croft, 2007, Arthritis Care, 2004, van Dijk et al., 2008). The non-fatal nature of OA means individuals can live for many years in various states of disability, contributing to morbidity estimates. The disability morbidity associated with OA is mostly attributable to the hip and knee weight-bearing joints (Busija et al., 2010). OA of the large joints often reduces mobility and it accounts for more problems with walking and climbing stairs than any other condition (Felson et al., 2000). As a result of immobility, obesity is one of the main co-morbidities, (Anderson and Felson, 1988). It is plausible therefore to think that people with OA may have an increased mortality as well as morbidity.

Mortality

OA is not regarded as a fatal disease. Only a small number of studies have examined its mortality among individuals. In a recent large population-based study in the UK by Nuesch and colleagues, excess mortality was seen in people with symptomatic and radiographic OA knee or hip compared with the general population, irrespective of the cause of death (Nuesch et al., 2011). Apart from older age and male gender, the most important risk factors for all-cause mortality in OA were a history of diabetes, CVD, or cancer and increased walking disability. People with a walking disability had an increased risk of death from cardiovascular causes, and the more severe the walking disability, the more likely a person was to die early. More recently Hawker and colleagues reported that severity of OA disability was associated with a significant increase in all-cause mortality and serious CVD events after controlling for multiple confounders in individuals with symptomatic hip OA and/or KOA (Hawker et al., 2014). These studies indicate that effective treatment of cardiovascular risk factors and co-morbidities is important in those with OA and walking disability. It is vital to encourage these people to become more active despite their painful OA.

2.2.8 Economic impact

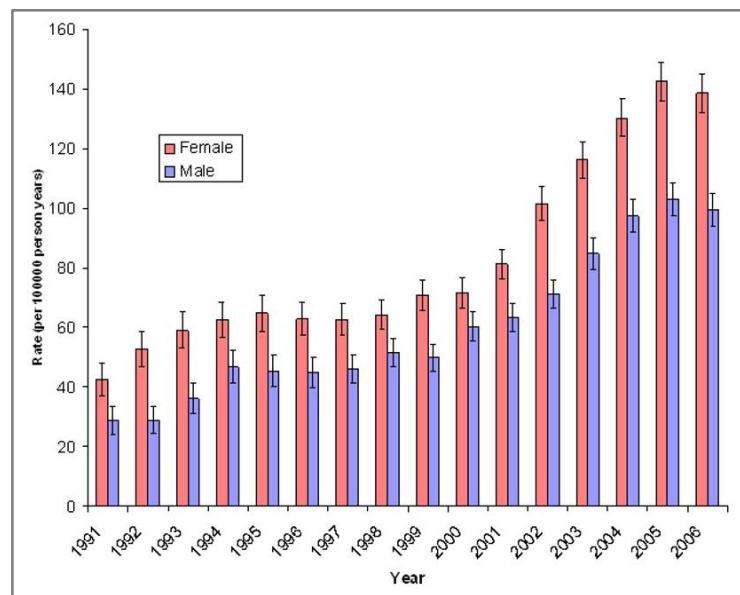
OA is one of the leading health burdens and its economic impact is increasing. It has significant negative impact on the UK economy. Its approximate total

cost is 1% of gross national product (GNP) (Arthritis and Musculoskeletal Alliance, 2004). In the UK, an estimated 7.1 million people, 12% of the overall population, experience long-term health problems due to arthritis and related conditions, at a cost of £5.5 billion annually to the economy (Arthritis Research Campaign, 2002). Significant difficulties are placed on individuals with OA suffering pain, and on society as a result of a combination of lost working days and economic strains on the health service. 36 million working days were lost to OA in 1999-2000 with an estimated £3.2 billion in lost production. In addition £43 million was spent on community services and £215 million on social services for OA related cases (National Institute for Health and Care Excellence, 2014b).

The World Health Organisation (WHO) report on the global burden of disease indicates that OA is likely to become the fourth most important cause of disability in women and the eighth most important cause in men (Murray and Lopez, 1996). Consequently there is a substantial burden on health in terms of morbidity and cost that is likely to increase significantly due to increasing rates of obesity and the rapid ageing of Western societies.

The current treatment of KOA is symptomatic or surgical. The rate of TKRs in the UK has tripled between 1991 and 2006 as shown in the General Practice Research Database (GPRD) by Culliford and colleagues (Culliford et al., 2010) (Figure 8). This trend is also seen in the United States (US) with 54% more TKRs performed in 2004 than in 2000. This number is expected to increase to 1.4 million by the year 2015 (Kim, 2008). In 2004, the cost of TKRs for KOA in the US was \$14.6 billion. This excludes additional expenses incurred from work hours lost, pain management, physiotherapy and revision surgery (Kim, 2008).

Figure 8: Trends in primary TKR rates



Reproduced from Culliford et al (Culliford et al., 2010), The British Journal of Bone & Joint Surgery © 2010 with permission from The British Editorial Society of Bone & Joint Surgery.

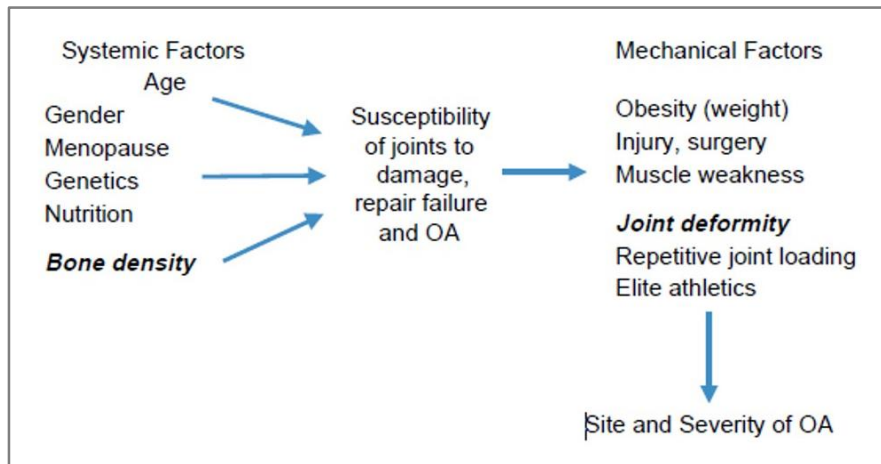
With an ageing population and a projected 45% lifetime risk of developing SRKOA (Murphy et al., 2008) increasing the current KOA health burden, there is an urgent need to improve understanding of the natural course of KOA in order to reduce known incidence and progression risk factors to allow preventative therapies to be targeted appropriately.

2.3 Aetiology & pathology

Despite the high prevalence of KOA, the aetiology and pathogenesis of this condition is not yet fully understood. With increasing disease severity, pain, swelling, cartilage loss, bone spur formation and decreased range of movement can occur. Despite these changes in the knee joint morphology, KOA aetiology remains unclear and is subject to ongoing investigation.

Epidemiological patterns in OA, for example the characteristics of individuals who develop the condition, the joints affected and the age of occurrence all provide clues to the pathogenesis of this condition. A conceptual model for the pathogenesis of OA by Dieppe (Dieppe, 1995) has gained acceptance over the years, an adapted version by Arden & Nevitt (Arden and Nevitt, 2006) is shown (Figure 9).

Figure 9: A conceptual model for the pathogenesis of OA



Adapted with permission from Dieppe 1995 (Dieppe, 1995). Figure reproduced from Arden & Nevitt (Arden and Nevitt, 2006), Best Practice & Research Clinical Rheumatology © 2006 with permission from Elsevier.

Within this conceptual model cartilage, bone, muscles, ligaments and other joint tissues and structures function as a healthy whole joint organ system that maintains a normal range of motion and prevents excessive loading within the local joint environment. Systemic factors that increase overall susceptibility to joint degeneration and local mechanical factors that impair the optimal joint functioning both play a significant role in determining the risk of developing OA. Within the local joint environment, the systemic and mechanical factors interact to determine which joints develop OA and how rapidly the condition may progress in an affected joint. The interactions between risk factors for OA are not yet fully understood and require further investigation (Lohmander and Felson, 2004).

2.3.1 Pathological features

OA has long been considered a condition of 'wear and tear' affecting the cartilage of a joint but this is now thought not to be an accurate reflection of OA pathogenesis (Berenbaum, 2013). With recent advances in molecular biology, it is now known to be a metabolically active process involving all joint tissues with inflammatory mediators released by cartilage, bone and synovium (Kapoor et al., 2011, Loeser et al., 2012, Goldring and Otero, 2011). There is also now growing evidence to suggest a systemic inflammatory component

relating to the role of obesity may play an active part in the pathological process – this will be discussed further in section 2.5.

The term ‘tear, flare and repair’ is now proposed as a better representation of the pathology involved (Birrell et al., 2011). This term envelops the key roles involved in the OA process:

- the aetiological role of risk factors such as obesity or mal-alignment represent the ‘tear’ aspect;
- the role inflammation plays in pain and progression of OA represents the ‘flare’;
- and the role of repair processes in and around the joint represents the ‘repair’.

A common public misconception is that OA is a slowly progressive condition that inevitably worsens with age. However, not all older people develop OA and the attempted repair processes within a joint may limit the damage and symptoms in many people (National Institute for Health and Care Excellence, 2014b).

All in all the pathology of OA is diverse with the whole joint involved in the disease process that includes focal and progressive hyaline articular cartilage loss with subsequent changes in the underlying bone, development of osteophytes, thickening or sclerosis of the bone, and attrition of sub-articular bone. Soft tissue structures within and surrounding the joint are also affected, including the synovium (due to synovial inflammation), ligamentous laxity and peri-articular muscle weakness (Felson et al., 2000, Elahi et al., 2000). These pathological features shown in Figure 10 are now discussed briefly.

Figure 10: OA joint pathology features

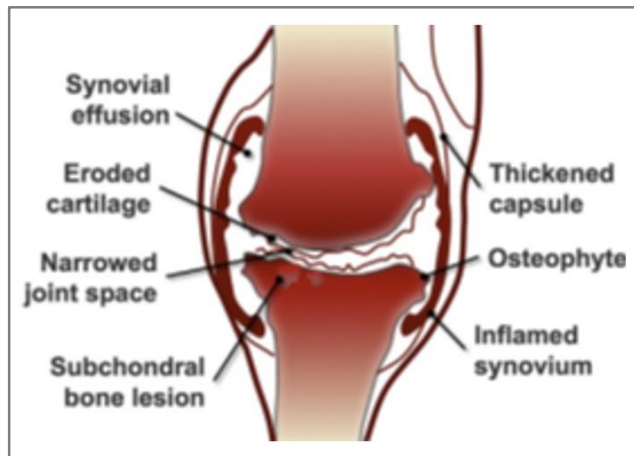


Figure reproduced from Wang et al (Wang et al., 2015), *Osteoarthritis & Cartilage* © 2015 with permission from Elsevier.

2.3.1.1 Articular cartilage

Articular cartilage is the tissue that has received most attention in relation to the pathogenesis of OA, largely due to significant changes in this tissue as OA progresses.

The surfaces of synovial joints are covered by a thin layer of articular cartilage under which lies sub-chondral bone. Articular cartilage is aneural and lacks a blood supply, therefore it is unable to regenerate itself. In a healthy joint, the main function of cartilage is to distribute joint loading by acting as a shock absorber and to reduce friction on movement.

Cartilage cells live in a matrix structure rich in collagen and proteoglycans. The quality of this matrix structure is critical for maintaining the functional properties of cartilage. With the pathological process of OA, this matrix structure starts to breakdown, chondrocytes try to repair components of the matrix as best they can, however these repaired components are structurally altered and therefore do not function at the same capacity leaving weaknesses in the matrix structure. These molecular level developments result in early morphological changes such as cartilage surface fibrillation and cleft formation (Dieppe and Lohmander, 2005). With a weakened matrix structure, cartilage is less able to withstand its usual loading, resulting in further traumatic damage to its surface and this can propagate downwards towards the sub-chondral bone, the result being a loss of articular cartilage at focal points.

As the OA process progresses, the changes are usually present over both opposing articular surfaces in the synovial joint. Radiographically this loss in articular cartilage presents as loss of joint space width (JSW) or JSN and in severe cases complete loss of articular cartilage leads to eburnation where the exposed bone is worn down to form a smooth hard surface (Arden and Cooper, 2006).

2.3.1.2 Sub-chondral bone

The pathological features of KOA found within the sub-chondral bone (also known as the cartilage/bone interface) include bone attrition, bone marrow lesions (BMLs) and sub-chondral cysts. Sub-chondral bone attrition is defined as a flattening or a depression of the osseous articular surface (Roemer et al., 2010). The causes of attrition are at the moment unknown, however remodelling processes due to chronic overloading that are reflected as BMLs on MRI might predispose the sub-chondral bone to subsequent attrition. Recent MRI studies have shown that bone attrition may be a marker of increased compartment-specific mechanical load (Neogi et al., 2010).

BMLs are reported on MRIs as ill-defined hyper-intensity regions (Zanetti et al., 2000). MRI studies have also shown that BMLs strongly predict incident sub-chondral cyst-like lesions in the same knee sub-region (Crema et al., 2010) and that BMLs are highly associated with and predict bone attrition longitudinally (Roemer et al., 2010). BMLs have also been shown to be related to dynamic knee loading, which supports the hypothesis that greater mechanical loading of the medial compartment plays a role in the pathogenesis of BML in medial tibio-femoral OA (Bennell et al., 2010). There is continuing debate as to whether the earliest changes depicting OA take place within the sub-chondral bone, which leads onto the issue of whether OA should generally be classified a disease of the bone as opposed to historically being classified as a disease of the cartilage.

2.3.1.3 Osteophytes

Osteophytes are a common radiographic feature of OA and have been used to define the presence of disease (Altman et al., 1986). They initially appear as outgrowths of cartilage at joint margins, and subsequently undergo ossification. Development of osteophytes is thought to occur to stabilize an

osteoarthritic joint and thereby prevent structural progression, for example after an anterior cruciate ligament (ACL) tear in the knee, osteophytes develop anteriorly and posteriorly to limit movement of the femur on the tibia thereby stabilizing the knee in the sagittal plane (Felson et al., 2005). With this in mind, it is plausible that OA knees with large osteophytes experience less progression over time than OA knees with smaller osteophytes. However, two longitudinal RKO studies using conventional radiography (Dieppe et al., 1997, Wolfe and Lane, 2002) reported that knees with large osteophytes have an increased risk of joint space loss (JSL), suggesting cartilage loss resulting in greater, rather than less progression.

Another longitudinal osteophyte study by Felson and colleagues confirmed that large osteophytes do not affect the risk of structural progression in RKO, they are in fact strongly associated with mal-alignment to the side of the osteophyte, and therefore any relationship they may have with progression is likely to be mediated by the association of mal-alignment with progression (Felson et al., 2005).

2.3.1.4 Synovium

The capsule in a synovial joint is lined by synovium which produces synovial fluid. Synovial fluid is usually viscous and acts as a joint lubricant. In OA, the synovium changes its appearance by becoming thicker due to an increase in the number and size of synoviocytes in the synovial membrane (Arden and Cooper, 2006). The synovium can also appear inflamed, particularly early in the course of the OA process, due to increased blood flow and the presence of mast cells in the synovium and synovial fluid (Dean et al., 1993). The thickened, inflamed synovium produces more synovial fluid than normal, which accumulates in the joint resulting in joint swelling, leading to stretching of peri-articular structures such as the joint capsule and collateral ligaments.

2.3.1.5 Meniscal damage

The menisci are semi-circular wedges of fibro-cartilage located inside the knee joint between the articular surfaces of the femur and tibia in the medial and lateral joint compartments; their main function being load transmission and shock absorption (Englund, 2010). In terms of pathogenesis, damage to either the medial or lateral meniscus and any meniscal extrusion, will cause abnormal

loading through the adjacent articular cartilage and can lead to KOA (Englund et al., 2009a).

2.3.1.6 Ligamentous laxity

The ligaments in the knee joint are passive stabilizers. The medial and lateral collateral ligaments (MCL & LCL respectively) are important in side-to-side or varus (bow-legged)/valgus (knock-knee) stability, whereas the anterior and posterior cruciate ligaments (ACL & PCL respectively) provide forward/backward or sagittal stability (Englund, 2010). Laxity is defined as the rotation or the displacement of the tibia in a varus-valgus direction with respect to the femur (Sharma et al., 1999a, Sharma et al., 1999b). Knee joint laxity is induced as the loss of articular cartilage reduces the distance between the tibial and femoral knee joint surfaces, and therefore decreases the restraining capabilities of the surrounding capsule and ligaments. JSN, osteophyte formation and knee joint laxity are thought to be inter-related (Sharma et al., 1999b, Sharma et al., 2003)

2.3.1.7 Muscle weakness

Muscles act as dynamic stabilizers of the knee joint and the quadriceps femoris is the main muscle group involved in knee joint stability (Englund, 2010). These four muscles (rectus femoris, vastus medialis, vastus lateralis and vastus intermedius) extend the knee and work eccentrically to control the rate and degree of flexion shortly after heel strike during gait. Quadriceps muscle weakness is common in people with KOA (Felson et al., 2000, Slemenda et al., 1997, Slemenda et al., 1998). This weakness can be attributed to disuse atrophy as symptomatic individuals can minimize use of the painful limb, however a cohort study by Slemenda and colleagues suggests that quadriceps weakness may precede KOA onset as reduced quadriceps strength was shown in women who developed KOA compared to those who did not (Slemenda et al., 1998). Another study by Mikesky and colleagues on women with healthy knees, found significantly higher knee joint loading in women with weak concentric and eccentric quadriceps and hamstrings compared to women with greater strength, implying that weak knee muscle support increases loading on articular cartilage, possibly resulting in knee joint pathology (Mikesky et al., 2000).

Quadriceps strengthening may improve KOA symptoms, but surprisingly greater baseline quadriceps strength has been shown to increase OA progression in mal-aligned and lax knees (Sharma et al., 2003) meaning careful and appropriate timing of exercise advice is required. Further research is needed to establish the contribution of muscular support to pathogenesis, and the role and timing during the OA process of muscle strengthening as a treatment of KOA.

2.3.2 Causes of joint pain

The cause of joint pain in OA is not yet understood. Approximately 8.5 million people in the UK are affected by joint pain that may be attributed to OA (Arthritis Care, 2004). Previously, it was thought that OA-related pain occurred as a result of joint tissue destruction and was nociceptive in origin (Dieppe and Lohmander, 2005). However, there is now increasing evidence from animal and human studies that due to peripheral and/or central pain sensitization, a neuropathic type of pain exists in some individuals with OA (Dieppe and Lohmander, 2005, Hochman et al., 2010). It is possible that individuals with painful OA may either have a predominantly nociceptive type pain, predominantly neuropathic type pain, or a possible mix of the two pain origins. Further research is needed in this area to pinpoint OA pain mechanisms, with better characterization of the nature of OA pain which could then allow for targeted treatment to specific pain types.

Although articular cartilage is generally viewed as the major tissue targeted in KOA, it is aneural and therefore cannot be the primary source of knee joint pain (Dieppe and Lohmander, 2005). However, knee pain could come from a number of different knee joint structures; sub chondral bone, periosteum, synovium, bursae, ligaments and the joint capsule are all richly innervated and contain nerve endings that may be the source of the nociceptive type pain in KOA. Recent knee joint imaging studies have shown a correlation between:

- knee pain and synovitis/effusions (Hill et al., 2001, Lo et al., 2009b).
- knee pain and sub-chondral bone changes including BMLs (Felson et al., 2001, Hunter et al., 2009a, Lo et al., 2009a, Torres et al., 2006, Davies-Tuck et al., 2009).

- knee pain and peri-articular lesions including anserine bursitis (Hill et al., 2003, Wood et al., 2008).

Identifying which structures are directly at fault is a difficult task, and is certainly not helped by the discordant relationship between OA symptoms and radiographic structure as discussed earlier in section 2.2.1. Careful clinical examination is needed, for example in identifying pain from peri-articular structures like anserine bursitis. MRI studies are helping but unfortunately many questions still remain unanswered.

2.4 Risk factors

The aetiology of OA is multi-factorial and risk factors can be divided into generalised systemic factors, for example age, gender, ethnicity, genetics, presence of Heberden's nodes (HN), and local adverse mechanical factors, for example obesity, trauma, deformity or loading (Figure 9) (Cooper et al., 2000, Felson et al., 2000).

KOA risk factors have been extensively studied in terms of disease prevalence and incidence but there are less data on their influence on disease progression, particularly for SKOA and knee pain. Furthermore there is limited data on the interaction between these important risk factors. While there is currently no cure for KOA, identification of risk factors to inform prevention strategies is paramount. A better understanding of potentially modifiable risk factors for KOA could inform future management and/or prevention strategies beyond the current focus of treating the symptoms. Identifying the role of risk factors that are not modifiable is equally important as they can still be used to identify high-risk groups, which may have implications for medical treatment (Lohmander and Felson, 2004). A description of the main risk factors for KOA follows.

2.4.1 Systemic risk factors

These risk factors are thought to influence general susceptibility to KOA:

2.4.1.1 Age

The prevalence (Figure 3) and incidence (Figure 6) of KOA increase substantially with age (Felson et al., 1987, Felson et al., 1995, Lawrence et al.,

1966, Lawrence et al., 1998, Oliveria et al., 1995, van Saase et al., 1989). The reasons for the association between OA and age are not fully understood, it may be a result of cumulative joint damage over the life course, combined with the reduced capacity for tissue repair (Arden and Nevitt, 2006, Busija et al., 2010).

Mixed results are reported regarding the association between age and KOA progression. Studies by Schouten and colleagues (Schouten et al., 1992) and Miyazaki and colleagues (Miyazaki et al., 2002) report significant associations between age and KOA, however Dieppe (Dieppe et al., 1993), Felson (Felson et al., 1995) and Wolfe (Wolfe and Lane, 2002) report no significant association.

2.4.1.2 Gender

Female sex is another strong risk factor for OA. After the age of 50, female gender appears to significantly increase the prevalence (Figure 3) and incidence (Figure 6) of OA in the hand and knee when compared to men (Oliveria et al., 1995, van Saase et al., 1989).

Hip OA is reported to progress more rapidly in women, however a gender effect on KOA progression has not yet been reported (Felson et al., 1995, Schouten et al., 1992). Oestrogen deficiency following the menopause is one of the possible explanations for the gender difference in the development of OA (Felson and Zhang, 1998), however no consistent association between oestrogen levels and the risk of OA has been confirmed (Arden and Nevitt, 2006, Felson and Zhang, 1998).

2.4.1.3 Menopause

The rise in OA incidence in women of menopausal age suggests a possible role for sex hormones, particularly oestrogen deficiency. Many studies have explored the possibility of lowering OA risk through use of oestrogen (Hannan et al., 1990, Hart et al., 1999, Samanta et al., 1993, Spector et al., 1997, Zhang et al., 1998), but reported associations could be misleading as oestrogen users are associated with a healthy lifestyle and osteoporosis, which is known to lower the risk of OA (Felson et al., 1998).

2.4.1.4 Ethnicity

A slightly higher prevalence of KOA is reported in African-Americans than in Caucasians. In the NHANES-III USA survey, the prevalence of RKOA for African Americans was 53% (95% confidence interval (CI) 47,58) versus 36% (95% CI 33,39) for Caucasians, and a similar pattern is reported respectively for SRKOA 18% (95% CI 14,22) versus 12% (95% CI 10 ,14) (Dillon et al., 2006). A 6% higher prevalence of RKOA among African-Americans than Caucasians was also reported in the American Johnson County OA study, with a similar pattern following for SRKOA (Jordan et al., 2007).

A comparison study between the Framingham Caucasian cohort based in Massachusetts, USA and an equivalent cohort of elderly subjects in Beijing, China, reported a higher prevalence, particularly in women, of both RKOA and SKOA in the Chinese cohort (Zhang et al., 2001). This difference was not explained by obesity as Chinese women were substantially thinner than Caucasian women, it may be due to excessive knee loading from squatting positions and/or other daily and occupational physical activities (Zhang et al., 2004).

2.4.1.5 Genetic factors

There appears to be a strong genetic link for OA, with a heritability component of 39 – 65% (Cicutini and Spector, 1997, Spector et al., 1996a). Studies have reported a genetic contribution to about half the population variability in susceptibility to KOA in women (Felson et al., 1998, Spector et al., 1996a, Valdes et al., 2012). It is suggested from these studies that multiple genes are likely to be involved in OA susceptibility, and environmental factors also have a substantial influence on disease progression. The search for candidate OA susceptibility genes has concentrated on genes encoding type II collagen (found in articular cartilage), other structural proteins of the extracellular cartilage matrix, the vitamin D and oestrogen receptor genes, and for bone and cartilage growth factors, and the results so far have been mixed.

2.4.1.6 Heberden's nodes

In a recent meta-analysis by Blagojevic (Blagojevic et al., 2010), five of eight studies (Coggon et al., 2000, Cooper et al., 1994b, Cooper et al., 2000, D'Souza et al., 2008, Hart et al., 1999) evaluating HN and/or hand OA

suggested this was a risk factor for future knee problems. Schouten and colleagues reported that a diagnosis of generalised OA (determined by the presence of HN) increased the likelihood of progressive knee cartilage loss by 3-fold even after adjustments were made for age, gender and BMI (Schouten et al., 1992). The co-existence of HN with KOA increased the risk of KOA progression by almost 6-fold. However, Cooper and colleagues reported that HN were only weakly associated with KOA progression (Cooper et al., 2000).

2.4.1.7 Index to ring finger length ratio

Finger length pattern, or digit ratio, is the ratio between the index second digit (2D) and the ring fourth digit (4D), expressed overall as 2D:4D ratio. This ratio is thought to be affected by the balance of androgen and oestrogen sex hormones in the womb during embryogenesis in the second trimester and it may serve as a marker for prenatal testosterone levels (de Kruijf et al., 2014). Typically males have shorter index fingers compared with ring fingers, whereas women tend to have more equal length fingers.

As hormonal factors are thought to play a role in OA pathology, the 2D:4D ratio and the risk of knee OA has been explored with varying results. Using hand radiographs, two case-control studies have shown a linear relationship between 2D:4D and increased risk of RKOA (Zhang et al., 2008, Ferraro et al., 2010), however a cross-sectional Framingham study found no association between 2D:4D and the risk of RKOA (Haugen et al., 2011). This may be due to a high proportion of post-traumatic OA or possible residual confounding by hand OA in the previous studies.

More recently, a first cohort study by Monira Hussain and colleagues using hand photocopies from the Melbourne Collaborative Cohort, examined the relationship between 2D:4D and the incidence of severe OA requiring TKR or THR, and concluded that a lower 2D:4D ratio is associated with an increased incidence of TKR (based on 580 incident TKRs over 10 years) but not THR risk (based on 499 incident THRs over 10 years) (Hussain et al., 2014). These associations persisted when participants with finger deformities due to arthritis or injury were excluded from analysis, therefore this finding requires further validation in other cohort studies.

2.4.2 Mechanical risk factors

Local biomechanical factors are also thought to be involved in the KOA process:

2.4.2.1 Obesity

It is known that being overweight is one of the strongest and most established risk factors for knee OA (Felson et al., 2000). Obesity clearly precedes the development of KOA by many years (Felson et al., 1997, Gelber et al., 1999, Spector et al., 1994) and hastens structural worsening of existing knee OA (Cooper et al., 2000, Schouten et al., 1992). Overweight adults have a high prevalence of KOA and the risk of OA increases 35% for every 5 kg weight gain (Felson et al., 2000, Hart and Spector, 1993b). Body mass is a modifiable risk factor and there is evidence that weight loss can reduce the risk of subsequent KOA development (Felson et al., 1992).

The relationship between obesity and KOA progression is not so clear. Cooper et al (Cooper et al., 2000) reported a significant relationship with BMI but only when comparing the highest BMI tertile with the lowest tertile in the group with baseline K&L grade 2 or higher. Schouten also only found a significant association in the two highest quartiles versus the lowest quartile (Schouten et al., 1992). Ledingham and colleagues only found a significant association for BMI with JSN, not change in K&L grade (Ledingham et al., 1995). Wolfe & Lane reported a borderline significant relationship between BMI and KOA progression (Wolfe and Lane, 2002). However, studies by Dieppe (Dieppe et al., 1993), Miyazaki (Miyazaki et al., 2002) and Spector (Spector et al., 1994) did not report a significant relationship between BMI and KOA progression. These differences in results highlight that the association between obesity and KOA progression requires further examination in longitudinal cohorts. This risk factor will be discussed further in section 2.5.

2.4.2.2 Knee injury

There is a very high risk of subsequent OA development in an injured knee joint following acute injury such as meniscal or cruciate ligament tear, dislocation or fracture (Cooper et al., 2000, Englund and Lohmander, 2004, Gelber et al., 2000, Roos et al., 1998). There are of course direct effects to the joint tissues with injury, and in addition there may be disruption of normal

joint biomechanics post injury leading to altered load distributions within a damaged knee joint which may also contribute to subsequent OA in later years. Studies have also shown that compared to controls, subjects with meniscal injuries that had received menisectomies up to 22 years previously were at increased risk of KOA (Englund et al., 2003, Englund and Lohmander, 2004, Roos et al., 1998).

No statistically significant relationship has been reported between previous knee injury and KOA progression (Cooper et al., 2000, Schouten et al., 1992). Schouten also reported no significant relationship between menisectomy and KOA progression (Claessens et al., 1990, Schouten et al., 1992), and Hart and colleagues showed no statistically significant relationship between history of fracture and KOA progression in the Chingford cohort women (Hart et al., 2002).

2.4.2.3 Knee joint loading

Occupation

Repetitive and excessive joint loading through specific physical activity can also increase the risk of developing OA. Occupations or activities that require kneeling, squatting, repetitive knee bending and carrying heavy loads substantially increase the risk of future KOA development (Coggon et al., 2000, Cooper et al., 1994a, Felson et al., 1991). By providing an even greater load, excess body weight is also likely to enhance the effect of knee-bending activities on KOA risk (Coggon et al., 2000).

Physical activity

Loading of knee joints through recreational running and sports participation does not specifically increase the risk of KOA independent of joint injury, but at an elite level, athletes engaged in high impact and torsional joint loading sports, such as weight lifting and football, are at increased risk of injury and subsequent OA development in affect joints, even without a major injury (Kujala et al., 1994, Kujala et al., 1995, Spector et al., 1996b). Schouten investigated the relationship between sport injury and KOA progression, but no association was found (Schouten et al., 1992). No association between regular sport activities and KOA progression was also reported by Cooper and colleagues (Cooper et al., 2000).

2.4.2.4 Knee alignment

Knee alignment is a commonly investigated KOA risk factor and is categorised as neutral, valgus or varus. Lower limb mal-alignment in either valgus or varus direction, influences the load distribution across the knee joint articular surfaces (Tetsworth and Paley, 1994). It is these changes in loading that are thought to increase stress on articular cartilage and other knee joint structures, which subsequently lead to degenerative KOA changes. In a neutrally aligned knee, 60-70% of the weight bearing load is transmitted through the medial compartment (Morrison, 1970) which accounts for the common occurrence of medial compartment involvement in knees with OA (Andriacchi, 1994). Mal-alignment has been shown to be an independent risk factor for KOA progression (Cerejo et al., 2002, Miyazaki et al., 2002, Sharma et al., 2001), however there are discrepancies in the relationship between knee mal-alignment and risk of incident KOA (Brouwer et al., 2007, Hunter et al., 2007) and therefore this area warrants further study. Knee alignment as a risk factor is discussed in further detail in section 2.6.

2.4.2.5 Muscle strength

The relationship between muscle activity and joint load is complex. In the knee joint, greater quadriceps strength may protect against osteoarthritis, as shown by a longitudinal study reporting quadriceps weakness increased the risk for subsequent RKOA development in women (Slemenda et al., 1998). However, other studies supporting this protective effect are lacking. Established OA knees tend to have weaker quadriceps than knees without OA, particularly when symptoms are present (probably due to disuse atrophy with secondary pain inhibition) but weakness can also exist in knees without pain or evidence of muscular atrophy, and this may be due to muscle dysfunction (Slemenda et al., 1997). It is uncertain if a greater quadriceps strength can protect against further KOA progression. Brandt and colleagues reported a stronger quadriceps was not associated with reduced KOA progression in women (Brandt et al., 1999), however Sharma's group (Sharma et al., 2003) reported a stronger quadriceps was associated with greater KOA progression in knees with a varus or valgus mal-alignment and in knees with medial or lateral laxity. Therefore, protection of KOA progression via increased muscle strength

may depend on interaction with other local factors that influence load distribution.

2.4.3 Summary

A summary of the main KOA risk factors discussed is provided in Table 6.

Table 6: Summary of main KOA risk factors

Where: KOA=knee osteoarthritis; HN=Heberden's nodes.

Risk factor	KOA incidence	KOA progression
Systemic		
Age	++	+
Female gender	++	~
Post menopause	--	-
Ethnicity	+	?
Genetics	++	?
HN	+	+
Mechanical		
Obesity	++	?
Injury	++	~
Loading	++	?
Alignment	?	++
Muscle strength	-	?

++ strong evidence of increased risk

+ moderate evidence of increased risk

~ evidence suggests no effect

-- strong evidence of protective effect

- moderate evidence of protective effect

? insufficient or conflicting evidence

- Conflicting associations for knee mal-alignment as a risk factor for KOA incidence warrants further investigation.

2.5 Obesity as a KOA risk factor

Obesity is defined by the WHO as:

‘abnormal or excessive fat accumulation that may impair health’ (World Health Organization, 2015)

The main cause of obesity is an energy imbalance between calories consumed and calories expended. Obesity is becoming a global issue due to increased energy-dense food intake that is high in fat, salt and sugars but low in vitamins, minerals and other micronutrients; combined with a decrease in

physical activity due to sedentary forms of work, changing modes of transportation, and increasing urbanisation. It is no wonder that obesity is a growing problem worldwide and the consequences from this are now starting to be felt through the range of associated co-morbidities. OA develops through different pathways within which being overweight plays a major part (Belo et al., 2007, Blagojevic et al., 2010). The role of obesity as a risk factor for KOA will now be discussed in further detail.

2.5.1 The burden of obesity

The current obesity epidemic is recognised as being one of the most important public health problems in the world today. The WHO reports that worldwide obesity has more than doubled since 1980 and most of the world's population live in countries where overweight and obesity kills more people than underweight (World Health Organization, 2015). This rise in obesity has subsequently contributed to epidemics in a range of non-communicable diseases (NCDs) such as type 2 diabetes mellitus (DM), hypertension, CVD, cancer and musculoskeletal conditions such as OA (International Association for the Study of Obesity, 2011). Consequently, this is leading to obesity becoming an important cause of morbidity, disability and premature death. In 2004, the disability attributable to obesity and its consequences was calculated at over 36 million disability-adjusted life years (DALYs) primarily due to CVD and type 2 DM (World Health Organization, 2004).

The economic burden of obesity is equally huge. There are substantial direct and indirect costs to healthcare and social resources. Direct costs equate to between 2 – 8% of European health care budgets due to the preventative, diagnostic and treatment service costs relating to being overweight and its associated co-morbidities (International Association for the Study of Obesity, 2011). In the UK, obesity already costs the economy over three billion pounds per year, and this cost is expected to increase year on year up to a possible £45.5 billion by the year 2050 (Arthritis Research Campaign, 2009). Indirect costs to society may be substantially higher as a result of income lost from reduced productivity, restricted activity, illness, absenteeism and premature death. There are also high costs associated with changes to infrastructure required to manage obese people in healthcare settings with the need for

specialised bariatric equipment including reinforced beds and operating tables, extra large chairs and wheelchairs.

From an OA perspective, the burden from obesity is escalating. Obese people are up to four times more likely to develop KOA than they are to develop hypertension or type 2 DM (Arthritis Research Campaign, 2009). Whereas hypertension and type 2 DM can be substantially improved with weight loss and are relatively easy to control with correct medication, OA is irreversible with long lasting effects. Of preventable factors, obesity is by far the single biggest cause of OA in weight bearing joints, and the earlier an individual is overweight or obese, the greater the risk of developing OA. In fact, the risk of developing KOA increases progressively throughout the BMI categories as shown by Coggon and colleagues in a population of 525 men and women aged 45 and above (Coggon et al., 2001). This study highlighted that at the most extreme, very obese individuals with a BMI ≥ 36 have a 14-fold higher risk of KOA compared to individuals with a healthy BMI. The increase in KOA due to obesity has a subsequent effect on the need for joint replacement surgery. More than two out of three TKRs and one in four total hip replacements (THRs) in middle aged UK women are attributable to obesity (Arthritis Research Campaign, 2009). A study by Liu and colleagues in a British cohort of nearly half a million women aged 50 to 69, identified that obese women were ten times more likely to need TKRs and two to three times more likely to need THRs compared to healthy weight women, highlighting that the body weight of a woman with OA is a major factor in whether or not joint replacement surgery will be required (Liu et al., 2007). With the burden of obesity becoming ever greater, subsequent increases in KOA are inevitable and with no current cure for OA, it is likely that the requirement for joint replacement surgery will become unsustainable, therefore alternative treatment options and appropriate prevention strategies must be found.

2.5.2 Prevalence

In 2014, approximately 13% of the world's adult population (11% of men and 15% of women) were obese and greater percentages were reported as overweight at 39% of adults (38% of men and 40% of women) (World Health Organization, 2015).

As Figure 11 and Figure reproduced from Global Health Observatory Map Gallery © 2014 with permission from WHO.

Figure 12 show it is not only the developed world that has growing obesity problems, many low and middle-income countries are facing this issue too. In the UK, obesity rates have nearly doubled from 13% of men and 16% of women in 1993, to 24% of men and 26% of women in 2011 (National Institute for Health and Care Excellence, 2014a).

2.5.3 Childhood obesity

With lifestyles becoming increasingly sedentary and the predominance of convenience food, it is unsurprising that childhood obesity is also a growing problem, and is already prevalent with approximately 42 million children under five being overweight or obese in 2013 (World Health Organization, 2015). Becoming obese earlier in life is likely to amplify certain health risks, especially for the NCDs and type 2 DM in particular. Childhood obesity is also associated with a higher chance of obesity, premature death and disability in adulthood (World Health Organization, 2015).

The effect of childhood obesity on knee joint pain at a later age has recently been shown by Macfarlane and colleagues who demonstrated a significant association with high BMI from as early as age 11 and knee pain at the age of 45 in the 1958 birth cohort study (Macfarlane et al., 2011). It is clear that early intervention programmes to reduce and maintain weight loss need to be targeted at children as well as adults.

Figure 11: Male world prevalence of obesity

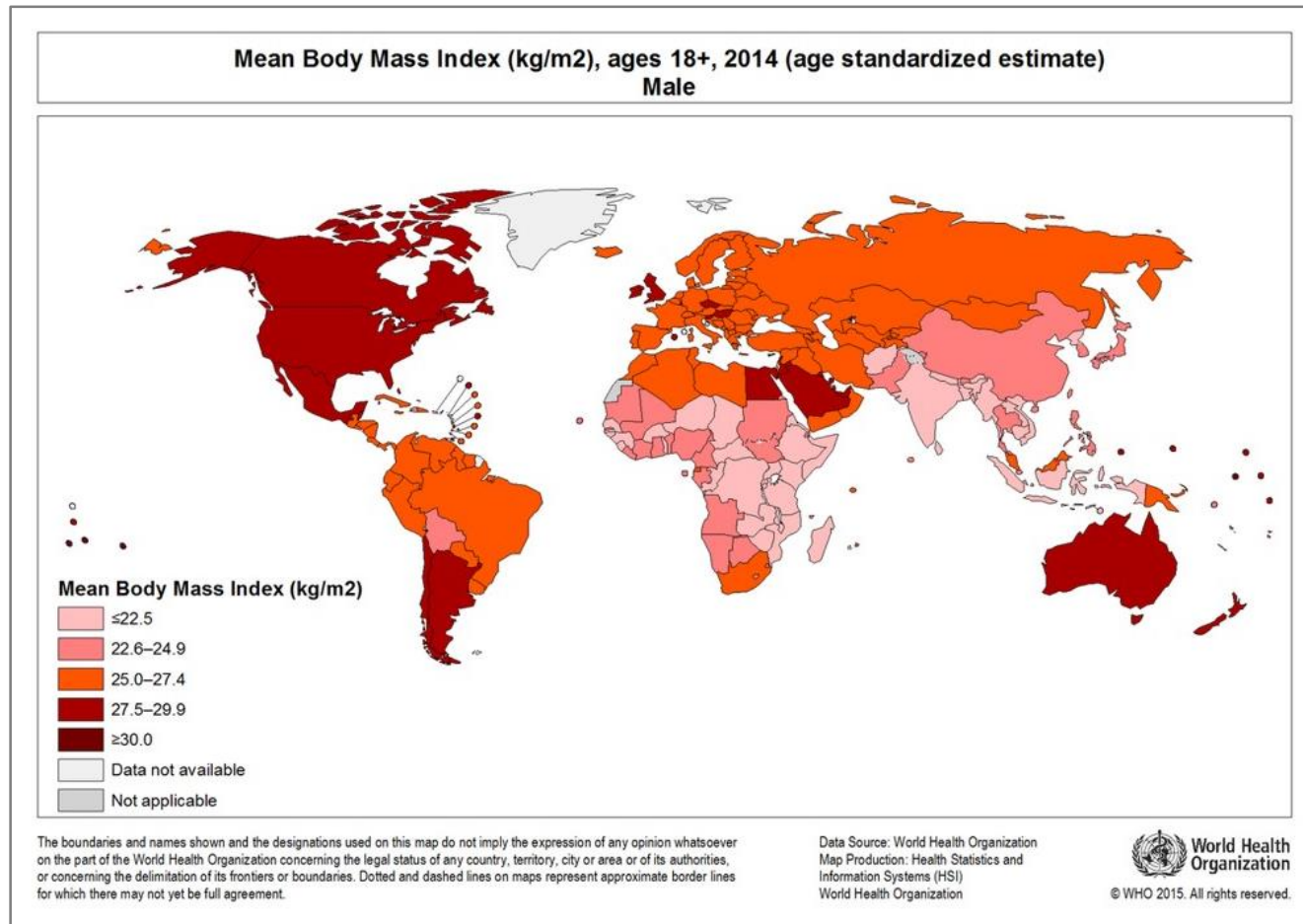


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Figure 12: Female world prevalence of obesity

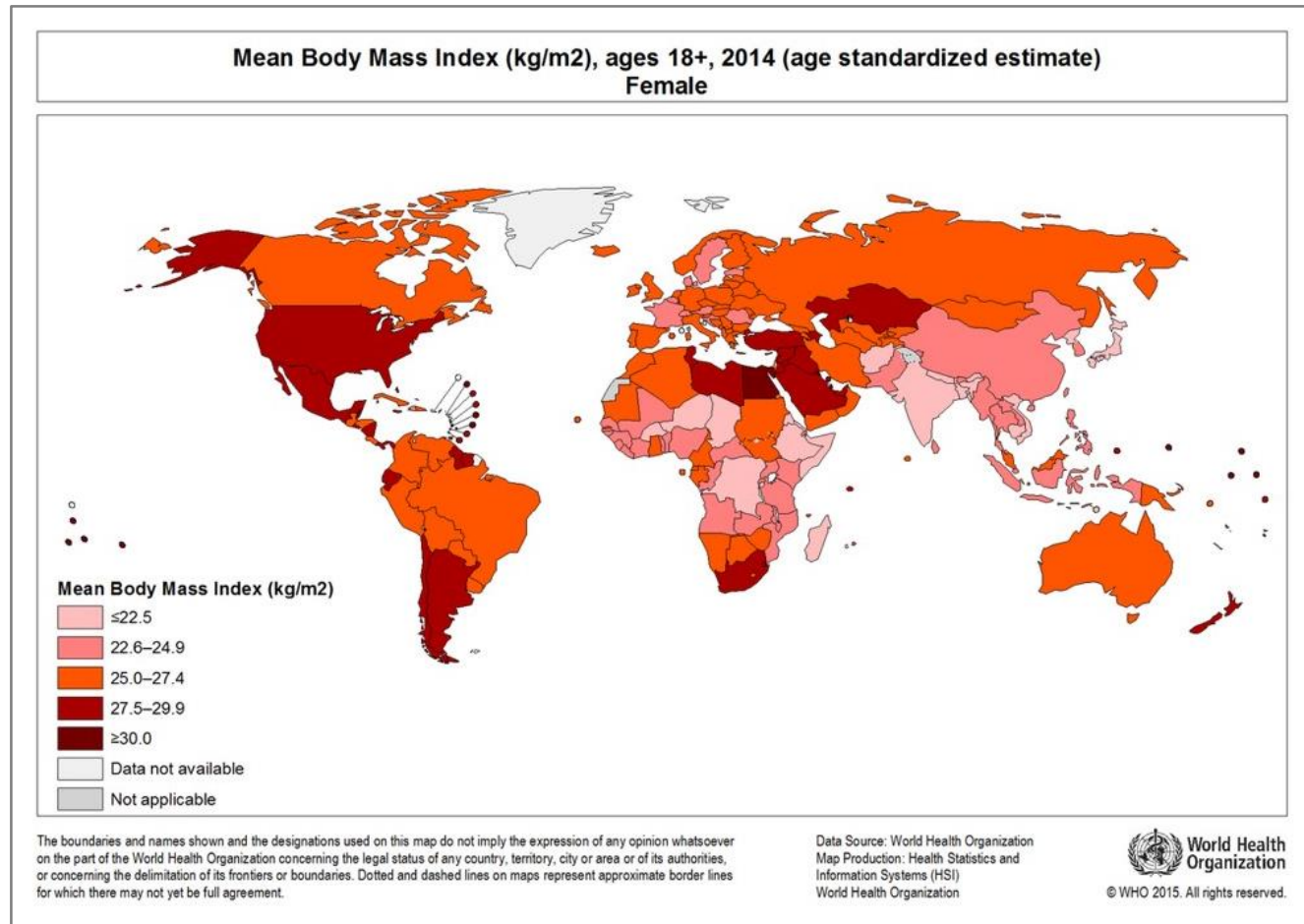


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2.5.4 Reducing obesity

What is to be done about this growing problem? In 2004, the World Health Assembly adopted the WHO Global Strategy on Diet, Physical Activity and Health (World Health Organization, 2004) which describes the actions required to support healthy diets and regular physical activity. This strategy suggests that all stakeholders at global, regional and local levels take action to improve diets and physical activity at the population level. At an individual level, that strategy suggests people can:

- limit energy intake from total fats
- limit sugar intake
- increase consumption of fruit and vegetables, whole grains and nuts
- engage in regular physical activity
- achieve energy balance and a healthy weight

However, individual responsibility can only achieve a full effect when people have access to a healthier lifestyle, therefore at the societal level it is important to:

- support individuals in following the above recommendations, through sustained political commitment and collaboration of public and private stakeholders
- ensure healthier dietary patterns and regular physical activity are affordable and easily accessible to all, particularly the poorest individuals

The food industry can also play its part in promoting healthy diets by:

- reducing fat, sugar and salt content of processed foods
- ensuring healthy and nutritious choices are available and affordable to all consumers
- practice responsible marketing, including appropriate food labelling
- ensuring availability of healthy food choices and supporting regular physical activity in the workplace

In the UK, the most recent guidance from National Institute for Health and Care Excellence (NICE) in 2006 and updated in 2014, details the current

recommendations for the National Health Service (NHS) on the prevention, identification, assessment and management of overweight and obesity in adults and children (National Institute for Health and Care Excellence, 2014a).

The key priorities for implementation are summarised as follows:

- weight management programmes should include behaviour change strategies and follow the best standards of practice set out in the NICE guidance
- child interventions should address lifestyle within the family and in social settings
- consideration of referral to an appropriate specialist for overweight or obese children with significant co-morbidity or complex needs
- drug treatment for adults is only prescribed with appropriate follow up from health professionals and patient support programmes
- bariatric surgery is only recommended as a treatment option if an adult:
 - a) is $>40 \text{ kg/m}^2$
 - b) is between $35 - 40 \text{ kg/m}^2$ with a significant co-morbidity that will improve with weight loss
 - c) has failed all non-surgical measures to achieve beneficial weight loss for at least 6 months
 - d) is fit for surgery
 - e) is committed to the need for long-term follow-up

There are few high quality RCTs examining changes in pain and function when overweight individuals with KOA achieve weight loss. The most relevant RCT studies (Christensen et al., 2005, Messier et al., 2004, Toda et al., 1998) were recently assessed by Christensen and colleagues by meta-analysis and the results showed that disability could be significantly reduced with weight loss of $>5\%$ in a 20 week period at a reduction of 0.25% per week (Christensen et al., 2007). One of the largest weight loss studies to date, the US-based Arthritis, Diet and Activity Promotion Trial (ADAPT) (Messier et al., 2004) monitored the impact of diet and activity on 316 overweight and obese adults with KOA. Participants were divided into four groups: diet only, exercise only, diet with exercise, or a healthy lifestyle group receiving no specific intervention except written information on lifestyle change. After 18 months the best outcome was seen in the diet with exercise group where participants experienced the

greatest reduction in pain levels and improvement in physical function including walking and stair climbing. The healthy lifestyle group had the least successful outcome, indicating that simply providing appropriate information on the subject of weight loss is not sufficient, behaviour change interventions are required as indicated by the NICE 2006 guidance. The limitations to all studies so far on weight loss and KOA is the short term follow-up lasting only 18 months to 2 years maximum.

2.5.5 Measuring obesity

2.5.5.1 Body mass index

BMI is a simple weight-for-height index that is commonly used to classify bodyweight in the adult population (Table 7).

Table 7: International adult BMI classification

Classification	BMI (kg/m ²) Principal cut-off points
Underweight	<18.5
Normal	18.5 – 24.9
Overweight	≥25.0
Pre-obese	25.0 – 29.9
Obese	≥30.0
Obesity class I	30.0 - 34.9
Obesity class II	35.0 - 39.9
Obesity class III	≥40

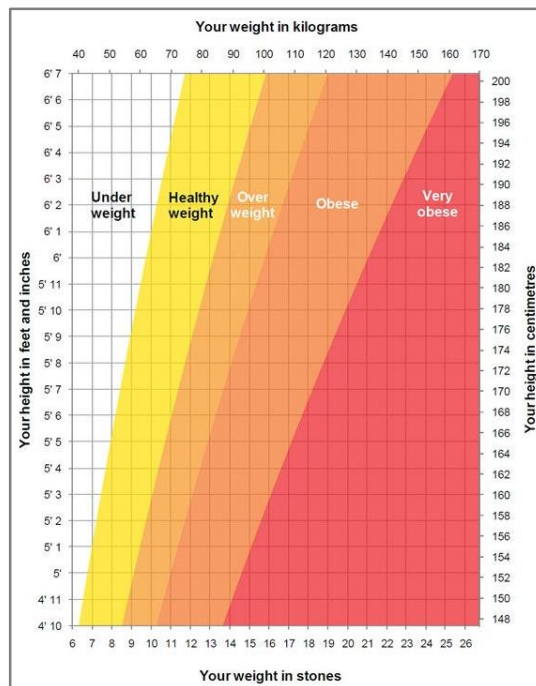
Reproduced © 1995 with permission from WHO (World Health Organization, 1995).

BMI is the most useful population-level measure of overweight and obesity as the values are the same for all adult ages and both genders. The BMI calculation used with children and teenagers is an age and sex specific percentile system (not shown).

Adult BMI is easily calculated using the formula below (World Health Organization, 1995) and it is relatively easy for the general population to monitor their own BMI using a similar charts to Figure 13.

$$\text{BMI (kg/m}^2\text{)} = \frac{\text{mass (kg)}}{(\text{height (m)})^2}$$

Figure 13: Monitoring height and weight chart



Reproduced with permission from NHS Choices: <http://www.nhs.uk>.

Most research studies examining body weight and KOA report on BMI values as their chosen measure of overweight and obesity. However, caution must be taken when interpreting BMI, as it does not provide a measure of percentage body fat. Therefore BMI values may not correspond to the same degree of fatness in different types of populations due, in part, to different body proportions. The interpretation of BMI grading in relation to risk may therefore differ for various population types (World Health Organization, 2015).

There has been growing debate in recent years on whether alternative BMI cut-off points are needed for different ethnic groups due to increasing evidence

showing associations between BMI, percentage of body fat and body fat distribution differ across populations, indicating that health risks may increase before the current 25 kg/m² overweight cut-off point. In 2004, a WHO expert consultation group (World Health Organization, 2004) concluded that there is a substantial proportion of the Asian population with high risk of type 2 DM and CVD with BMI values lower than the current WHO cut-off point for overweight at ≥ 25 kg/m². However, the cut-off point for observed risk varied between 22 – 25 kg/m² and between 26 – 31 kg/m² for high risk in different Asian populations, therefore the consultation group recommended that the current WHO international classification BMI cut-off points should be retained.

The BMI formula depends only upon weight and height values for its calculation, therefore the assumptions BMI makes about lean mass and adipose tissue or body fat distribution are not always exact. As a result BMI can overestimate body fat in athletes and others with a lean body mass or muscular build, and it may equally underestimate body fat in those with less lean body mass such as older people and others who have lost muscle bulk. These issues with BMI were highlighted by Romero-Corral and colleagues in 2008, when they examined 13, 601 individuals as part of the Third NHANES III in the United States (Romero-Corral et al., 2008). By calculating BMI and estimating percentage body fat (BF %) with bioelectrical impedance analysis, they reported that BMI-defined obesity (≥ 30 kg/m²) was present in 19% of males and 25% of females in their study population, however BF %-defined obesity ($>25\%$ in men and $>35\%$ in women) was found in 44% of males and 52% of females. A BMI of ≥ 30 kg/m² showed high specificity (men 95%, CI 94 - 96% and women 99%, CI 98 - 100%) but a poor sensitivity (men 36%, CI 35 - 37% and women 49%, CI 48 - 50%) to detect BF % defined obesity in this study, highlighting the limitation of using BMI in diagnosing obesity.

A further limitation of BMI is the loss of height through aging, and as a result BMI will increase without any corresponding increase in weight. In addition, BMI does not account for body frame size. An individual may have a small body frame and be carrying excess fat but the BMI calculation reflects that they fall in to the normal range. Conversely, an individual with a large body frame and a fairly low BF % may be classified as overweight by BMI calculation. As a result of these limitations with the BMI calculation, alternative body composition measurements can be used.

2.5.5.2 Body composition

The percentages of fat, muscle and bone contribute to human body composition. Muscle tissue takes up less space than fat tissue in the body, therefore body composition and body weight, determine an individual's leanness. Two people with the same height and body weight can be completely different from each other due to differing body compositions. The WHO proposed a standard definition on BF % obesity as >25% in men and >35% in women (World Health Organization, 1995).

Body composition, particularly BF %, can be measured in several ways. Skin fold tests using a set of measurement callipers to measure subcutaneous fat thickness at several standardised points on the body are the most common method. Bioelectrical impedance analysis (BIA) uses the resistance of electrical flow through the body to estimate BF %. However there can be issues with sources of error as these measurements are very much dependent on the observer taking them. Body composition can be measured very accurately with dual energy x-ray absorptiometry (DEXA) machine scans (Glickman et al., 2004). However, the main problem with all these body composition measurements are that they require availability of specific machinery.

The most useful indicator of central fat distribution is measurement of waist circumference (WC) which can easily be achieved using a simple tape measure. The recommended WC measurements to determine central obesity for the European population are provided by the International Diabetes Federation (International Diabetes Federation, 2006) and World Health Organisation (World Health Organization, 2011) in Table 8.

Table 8: WC measurement classification

Classification	Male WC (cm)	Female WC (cm)
Normal	<94	<80
Central obesity	94 - 102	80 - 88
Severe obesity	≥102	≥88

Central obesity describes the fat tissue distribution around the trunk and abdomen. It is also known as 'android fat distribution' and can be referred to as 'apple shape'. It is more common in males than females and is directly related to an increase in CVD (Donahue et al., 1987) as well as indirectly

through lipid profiles associated with CVD risk (Despres et al., 1985), whereas gynoid (pear shape) fat distribution around the hips is not.

Android and gynoid fat distributions can also be measured by waist and hip circumference respectively. Waist-hip ratio (WHR) can then be calculated by dividing WC by hip circumference (HC) (World Health Organization, 1995):

$$\text{WHR} = \frac{\text{WC (cm)}}{\text{HC (cm)}}$$

A WHR >0.9 in men and >0.85 in women indicates central obesity as defined by WHO (World Health Organization, 1995). Body fat distribution and central obesity as measured by WC and WHR, are associated with increased risk of type 2 DM (Carey et al., 1997, Wang et al., 2005), coronary heart disease (CHD) (Canoy, 2008) and with all-cause mortality (Pischon et al., 2008). These effects are independent of overall adiposity as measured by BMI.

WC and BMI measurements will be used in this thesis to provide a more accurate indicator of the possible metabolic component of obesity and KOA.

2.5.6 Obesity and KOA associations

Cohort studies to date looking at the body weight and KOA relationship have demonstrated strong associations between obesity and RKOA (Cooper et al., 2000, Cooper et al., 1994b, Felson et al., 1992, Felson et al., 1997, Gelber et al., 1999, Grotle et al., 2008, Hochberg et al., 1995, Lohmander et al., 2009, Reijman et al., 2007, Rogers and Wilder, 2008, Spector et al., 1994). However most of the published cohort study research is either cross-sectional in design (Cooper et al., 1994b, Hochberg et al., 1995, Rogers and Wilder, 2008) uses body weight measurements taken at baseline but not at follow-up visits (Lohmander et al., 2009, Reijman et al., 2007), or uses self-reported body weight and height measurements (Gelber et al., 1999, Grotle et al., 2008) which are likely to have a potential for bias. There are few longitudinal cohorts with physical measurements of height and weight at various time points that can be used to examine the obesity and RKOA relationship over time. Holliday and colleagues recently looked at lifetime BMI and other anthropometric measures of obesity and risk of knee/hip OA in the Genetics of Osteoarthritis and Lifestyle (GOAL) case-control study (Holliday et al., 2011). The authors

concluded that being overweight earlier in adult life increased KOA and hip OA risk, however this conclusion relies heavily on retrospective self-reported estimates of lifetime weight and body shape. The Framingham study is one cohort study to look at body weight longitudinally (Felson et al., 1992). Felson and colleagues examined the change in BMI in women up to 12 years prior to KOA symptom onset, however all BMI calculations were based on baseline height measurements, which are known to change with age. Findings from the Chingford study (Hart and Spector, 1993b, Spector et al., 1994) support data from the Framingham cohort study (Felson et al., 1988) that asymptomatic obese women are at increased risk of developing symptomatic RKOA, which leans toward a causal effect of obesity. However, there have been even fewer studies conducted to determine the association between obesity and knee pain, which is the major presenting complaint of KOA (Adamson et al., 2006, Jinks et al., 2006, Macfarlane et al., 2011).

Although the study by Adamson demonstrated a strong relationship between obesity and knee pain, it was a cross-sectional study design (Adamson et al., 2006). Jinks and colleagues investigated the effect of overweight and obesity on the onset and progression of knee pain in older adults living in a North Staffordshire, UK community (Jinks et al., 2006), and in a later study described the predictors of onset and progression of knee pain in adults (Jinks et al., 2008). Both studies relied on self-reported height and weight measurements with follow-up limited to three years, and no radiographs were taken to be able to confirm KOA diagnosis. The only long-term study looking at the effects of weight on knee pain has very recently been published using data from the 1958 birth cohort study by Macfarlane and colleagues (Macfarlane et al., 2011). This cohort population have been followed up throughout childhood and adulthood, most recently at 45 years, when knee pain information was collected on 8,579 participants out of an original 18,558 therefore 54% were lost to follow-up. BMI data was collected at age 7, 11, 16, 23, 33 and 45 years. BMI was associated with knee pain, obese participants at 23, 33 or 45 years experienced an approximate doubling in the risk of knee pain at 45 years, and while the association with adult obesity is the strongest, this association can begin as early as age 11 years. Unfortunately as knee pain data was only gathered at the age of 45 years there is no ability to examine the timing of knee pain onset, and this population are still relatively young in terms of

relating these findings to KOA, and this will not be possible as radiographs to confirm KOA diagnosis have not been taken in this cohort.

The need to look at the potential longitudinal relationship between body weight and knee pain and KOA is of great importance, since obesity is fast becoming an increasingly serious public health problem worldwide (World Health Organization, 2015). There is currently no cure for KOA; therefore identification of risk factors that influence symptomatic RKOA is important. Body weight, WC, SRKOA, RKOA and knee pain will be looked at longitudinally in the Chingford cohort. With 19 years of follow-up there is scope to explore the obesity and KOA relationship thoroughly.

2.5.7 Mechanism of association

Not all obese individuals develop KOA, neither are all individuals with KOA obese. This must therefore be accounted for by mechanisms of association. Hypotheses explaining the obesity – OA relationship fall into two categories: mechanical and metabolic. In addition to the higher mechanical load experienced with being overweight or obese, there are also possible systemic effects of fat that can lead to further cartilage damage, which is known to be the main pathological feature of OA (Pottie et al., 2006).

2.5.7.1 Mechanical loading theory

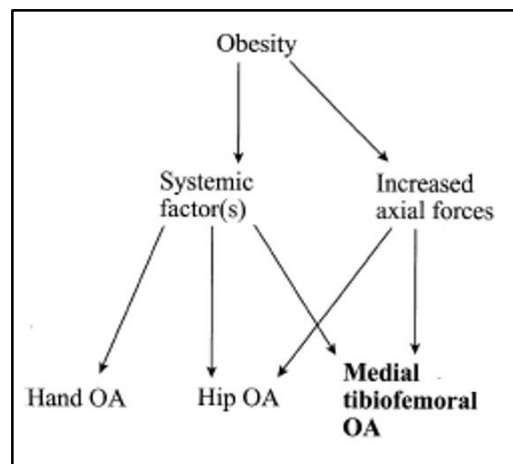
The mechanical loading hypothesis is thought to be the resultant effect of excess weight overloading the joint during weight bearing activities, causing the start of the OA process by breakdown of cartilage, and damage to ligaments and other joint support structures (Arden and Nevitt, 2006). A dose-response relationship between BMI and the risk of KOA was first identified in 1988 in the large American population-based NHANES study (Anderson and Felson, 1988). The role of high BMI in the development of KOA was further supported in a prospective follow-up study using the Framingham cohort, where those who were obese or overweight at baseline almost doubled the risk of developing KOA (Felson et al., 1988). Individuals who lost weight during the follow-up period had a lower risk of developing KOA than those whose weight remained stable (Felson et al., 1992).

The mechanical loading hypothesis is thought to be the primary mechanism of association for obesity and KOA. Clinical and animal studies of joint loading

provide evidence that abnormal loads can lead to changes in composition, structure and mechanical properties of articular cartilage (Guilak et al., 2004, Ramage et al., 2009), and recent findings of mechanoreceptors sensitive to pressure at the surface of chondrocytes also favour the mechanical loading theory of OA (Ramage et al., 2009).

However, this association cannot be fully attributed to the increase in mechanical load, as there is no consistent association between body weight and the risk of hip OA, the hip being another major weight-bearing joint in the same biomechanical chain as the knee joint (Grotle et al., 2008, Oliveria et al., 1999, Reijman et al., 2007). In addition, several studies have identified an increased risk of hand OA with increasing body weight (Carman et al., 1994, Grotle et al., 2008, Oliveria et al., 1999) demonstrating alternative association mechanisms exist (Figure 14).

Figure 14: Mechanism of association between obesity & OA at different sites



Reproduced from Sharma et al (Sharma et al., 2000) *Arthritis & Rheumatism* © 2000 with permission from John Wiley & Sons. Inc.

2.5.7.2 Metabolic theory

An alternative mechanism, or possibly an adjunctive mechanism, of the obesity and KOA association is due to metabolic factors. The framework for considering KOA is now shifting from a 'wear and tear' condition with a minimal inflammatory response, to recognition of the inflammatory environment associated with obesity. Adipose tissue, previously considered to be a passive energy store, is now recognised as being a highly active metabolic endocrine organ secreting chemical messengers known as adipocytokines,

such as leptin, resistin and adiponectin. Adipocytokines are a current focus for OA research as they may play an important role in cartilage homeostasis and could have potential as therapeutic targets. Leptin, adiponectin and resistin levels have been found in the synovial fluid and plasma of individuals with KOA (Chen et al., 2006, Dumond et al., 2003). These adipocytokines are thought to influence OA either through direct joint degeneration or via controlling local inflammatory processes (Sowers and Karvonen-Gutierrez, 2010).

Obesity may generate other systemic effects related to OA via metabolic factors for glucose and lipid metabolism. Changes in metabolism due to insulin resistance and increased glucose load are closely related to the production of pro-inflammatory cytokines, which are a characteristic of a chronic inflammatory state. Significant associations between KOA, hand OA and cardiovascular risk factors such as uric acid, cholesterol levels, hypertension and fasting plasma glucose were shown in early reports (Acheson and Collart, 1975, Hart et al., 1995). However, support in the metabolic link with OA lessened due to inconsistent results from studies, the NHANES-I study in particular (Davis et al., 1988, Davis et al., 1990a, Davis et al., 1990b), looking at the association between OA and metabolic factors such as glucose, lipids and blood pressure.

More recently, Sowers and colleagues reported on the role of obesity and metabolic dysfunction with KOA in 482 women (Sowers et al., 2009). Middle-aged obese women (≥ 30 kg/m²) with two or more cardio-vascular risk factors, from cholesterol levels, triglycerides, blood pressure, C reactive protein (CRP), glucose and WHR, had more than six times increased odds of having prevalent KOA compared with non-obese women without cardio-vascular risk factors. Interest in the OA – metabolic link has re-emerged since the identification of adipocytokines, however why some obesity is associated with intense metabolic activity whereas other obesity is less so remains to be determined. This newly acquired inflammatory component of OA could explain the association between obesity and hand OA.

2.5.8 Obesity summary

- The global obesity epidemic will lead to inevitable increases in KOA, therefore alternative treatment and prevention strategies are required as joint replacement surgery will become unsustainable.
- Substantial evidence supporting the obesity – KOA – pain association exists, but determination of the processes in which adipose tissue impacts on pain and KOA joint damage is needed.
- The use of BMI measurement on its own is insufficient to fully understand the obesity – KOA – pain relationship.
- Further measures of body composition are required to reflect the multidimensional aspects of obesity and KOA.
- Data from the Chingford cohort will be used to study body mass measured by BMI and WC, and their cross-sectional and longitudinal associations with SRKOA, RKOA and knee pain.

2.6 Knee alignment as a KOA risk factor

Biomechanical factors are known to play a part in the KOA process; they have been implicated in both the onset and progression of KOA. Knee mal-alignment in the frontal (coronal) plane is a common clinical sign of KOA, however it is uncertain if this precedes disease onset or results as a consequence (Hinman et al., 2006). To improve understanding of KOA aetiology and to develop effective preventative interventions, it is essential to clarify the role of knee mal-alignment in both the development of KOA and its progression. This role of knee alignment as a risk factor for KOA will now be discussed in further detail.

2.6.1 Alignment methods

Evaluation of lower limb alignment in the frontal (coronal) plane, requires consideration of two factors:

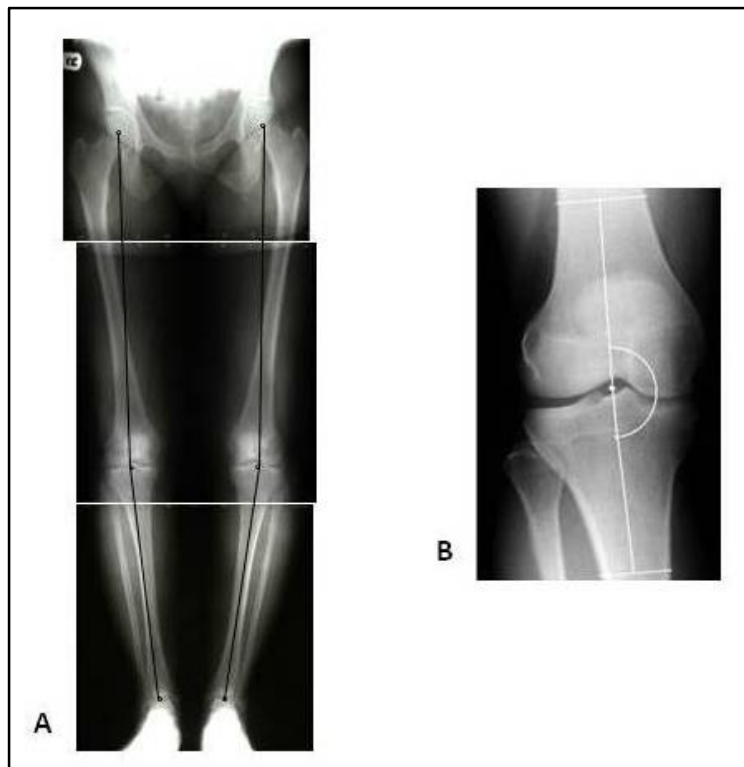
- 1) alignment of lower limb joints; referring to the co-linearity of the hip, knee and ankle joints
- 2) orientation of articular surfaces; referring to each articular surface position relative to the individual limb segment axes (tibia and femur)

As shown in Figure 15, there are two possible radiographic methods to examine frontal plane knee alignment:

- a) mechanical axis (MA) alignment, also known as the hip-knee-ankle (HKA) angle, is the angle between the mechanical axes of the femur and tibia measured on a full limb radiograph (FLR);
- b) anatomical axis (AA) alignment, also known as the femoral-tibial angle (FTA), is the angle between the anatomical axes of the femur and tibia measured on a standard (14 x 17 inch) limb radiograph (SLR).

Figure 15: Radiographic methods of frontal plane knee alignment

Where A=full limb radiograph; B=short limb radiograph



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The advantages and disadvantages of using these radiographic methods are discussed in Table 9.

Table 9: Advantages & disadvantages of using FLRs & SLRs

Method	SLR	FLR
Advantages	<ul style="list-style-type: none"> *cost effective *routine test *less radiation *apply retrospectively 	<ul style="list-style-type: none"> *gold standard method *allows measurement of alignment features
Disadvantages	<ul style="list-style-type: none"> *no gold standard method *off-set required to make comparable to MA 	<ul style="list-style-type: none"> *increased radiation exposure *specialised equipment *costly *more time consuming to measure *not a routine test

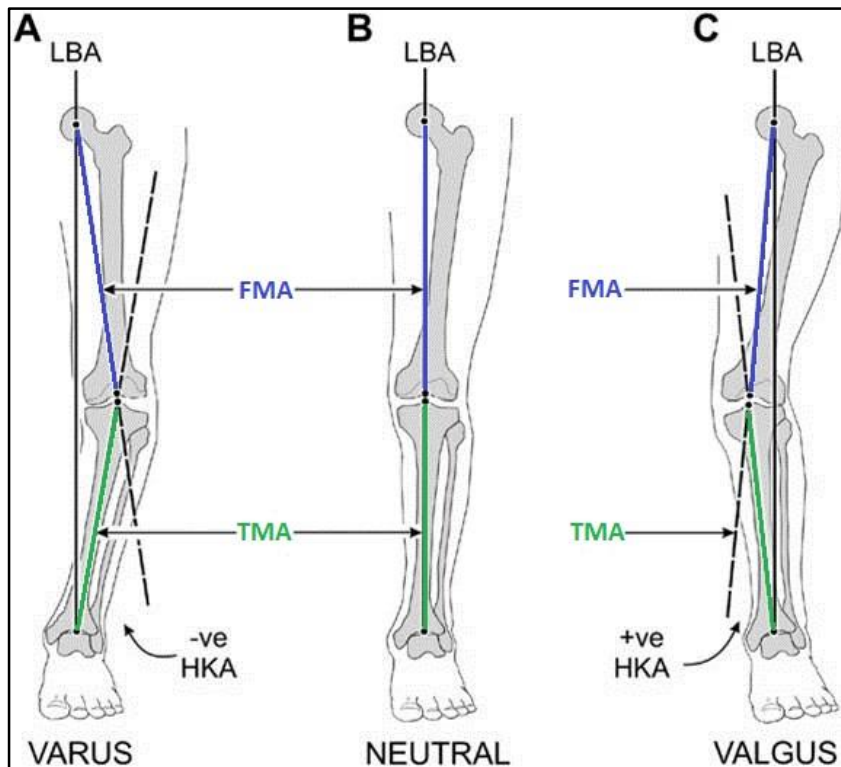
MA alignment using the HKA angle on a FLR is considered to be the gold standard method for biomechanical assessment of knee alignment measurement (Hsu et al., 1990, Tetsworth and Paley, 1994). However, Table 9 highlights the drawbacks to this method with regard to increased cost, greater radiation exposure and other considerations. It is therefore not surprising that the AA alignment using the FTA on SLRs, is considered a more convenient method, however as the hip and ankle joints cannot be included in these radiographs, the MA of the femur and tibia can only be estimated using this method. Several factors may influence the measurement of angles and distances on lower limb radiographs. These include the positioning of the limb, morphological differences in the femur and tibia, the projected view and quality of radiographs and the use of FLR or SLRs, all of which will be discussed further here.

2.6.2 Knee mal-alignment

Mal-alignment arises when there is a disturbance in the co-linear relationship of the hip, knee & ankle joints in the lower limb (Hsu et al., 1990, Tetsworth and Paley, 1994). This affects the transmission of load across the joint surfaces, the knee joint being the key determinant of load distribution through the lower limb (Tetsworth and Paley, 1994).

Figure 16: Categories of knee alignment on FLRs

Where: LBA=load bearing axis; FMA=femoral mechanical axis; TMA=tibial mechanical axis; HKA=hip-knee-ankle alignment (mechanical axis)



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The load-bearing axis (LBA) is the force transmission path relative to the lower limb and is represented by a line extending from the centre of the femoral head to the centre of the ankle joint (Figure 16b) (Tetsworth and Paley, 1994).

This LBA can be disturbed by any deformity in the frontal plane that alters alignment of the lower limb joints. If the LBA passes medial or lateral to the centre of the knee, a moment arm is created which acts to increase force transmitted across either the medial or lateral tibio-femoral compartment respectively. Thereby in a varus aligned knee, the LBA passes medial to the knee joint centre (KJC), creating a moment arm which increases force across the medial compartment Figure 16a.

In a valgus knee, the LBA passes laterally to the KJC, creating a moment arm which increases force across the lateral compartment Figure 16c (Tetsworth and Paley, 1994). Varus – valgus alignment is a key determinant of this moment, and with the resultant effects on the altered force distribution

through the knee suggests it is biologically plausible that both varus and valgus alignment contribute to KOA progression (Sharma et al., 2001).

Usually, the load transmitted through the knee is distributed unequally between the medial and lateral compartments (Harrington, 1983, Hsu et al., 1990, Johnson et al., 1980) with neutral alignment, up to 70% of the load transmitted across the knee is through the medial compartment (Schipplein and Andriacchi, 1991). As long ago as 1970, Morrison reported that load is disproportionately transmitted to the medial compartment in the normally aligned ambulating knee (Morrison 1970). Knee alignment influences the medial to lateral compartment load distribution, (Sharma et al., 2001) with any shift from neutral alignment of the hip, knee and ankle affecting the load distribution at the knee joint (Tetsworth and Paley, 1994). With just 4 - 6° of varus alignment, the load through the medial compartment can be increased by up to 90% (Hsu et al., 1990). Valgus alignment is associated with an increase in lateral compartment loading (Bruns et al., 1993) however, greater load is taken through the medial compartment until a more severe valgus deformity is present (Harrington, 1983, Johnson et al., 1980).

With this in mind Sharma and colleagues were surprised to find the effects of varus and valgus alignment to be similar in magnitude as they had expected to find a greater progression risk on medial compartment with varus alignment than lateral compartment progression with valgus alignment (Sharma et al., 2001). It is these increases in compartment loading that are thought to increase the stress on articular cartilage and surrounding knee joint structures, which subsequently lead to degenerative KOA changes.

Varus mal-alignment is the most common deformity in people with KOA, with a reported prevalence of 53 - 76% (Cahue et al., 2004, Felson et al., 2004). This is likely to be related to the high prevalence of medial tibio-femoral KOA compared to lateral tibio-femoral KOA (McAlindon et al., 1992) and progressive medial compartment cartilage loss is likely to result in greater varus knee joint deformity.

2.6.3 Lower limb alignment

2.6.3.1 Mechanical axis & anatomic axis alignment

Lower limb joint alignment in stance is defined as the line extending from the hip joint centre (HJC) to the ankle joint centre (AJC), this line termed the MA runs through the femur, known as the femoral mechanical axis (FMA), and through the tibia forming the tibial mechanical axis (TMA) in the lower limb (Tetsworth and Paley, 1994).

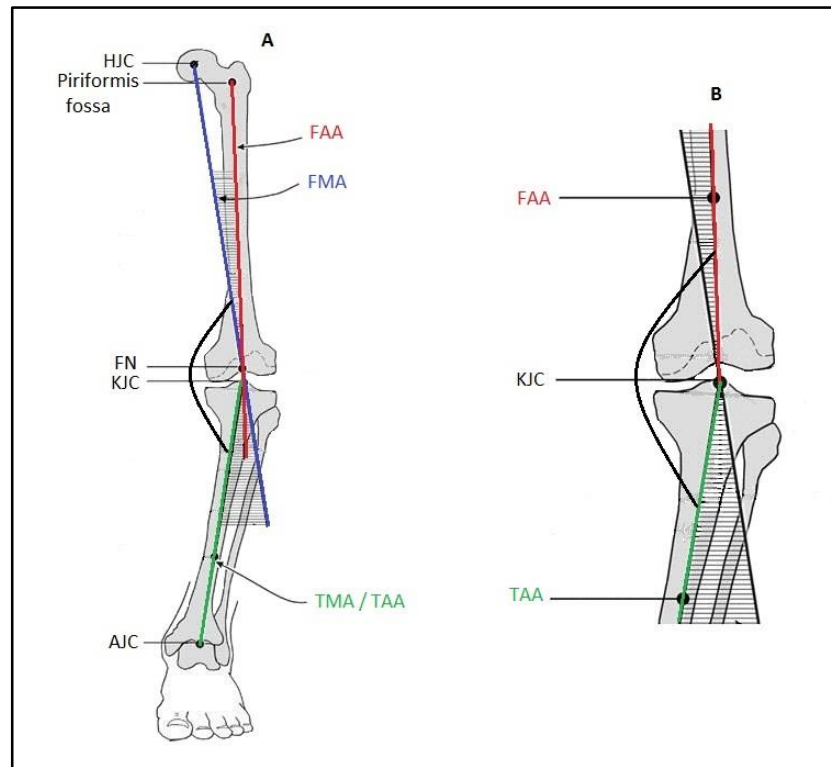
The MA of the individual femur and tibia limb segments are important in weight bearing. In the tibia, the MA and AA are the same (Moreland et al., 1987) but in the femur they are different (Figure 17).

The TMA is defined as the line from the knee joint at the centre of the tibial plateau (tibial spine mid-point in Figure 17) extending distally to the ankle joint at the centre of the tibial plafond (Yoshioka et al., 1989).

The FMA is defined as the line from the femoral head centre running distally to the mid-condylar point between the cruciate ligaments in the knee joint centre (Yoshioka et al., 1987). Due to the angulation of the femoral head, the FMA typically subtends a 6° angle to the femoral AA (FAA) (Hsu et al., 1990, Moreland et al., 1987, Yoshioka et al., 1987) which runs straight down the femoral shaft from the piriformis fossa to the KJC.

Figure 17: MA & AA alignment in the lower limb

Where: A=MA alignment or HKA angle; B=AA alignment or FTA angle; HJC=hip joint centre (centre of femoral head); FMA=femoral mechanical axis; FAA=femoral anatomic axis; FN=femoral notch; KJC=knee joint centre (tibial spine mid-point); TMA=tibial mechanical axis; TAA=tibial anatomic axis; AJC=ankle joint centre (tibial plafond mid-point).



Reproduced from Sheehy et al (Sheehy et al., 2011), Osteoarthritis & Cartilage © 2011 with permission from Elsevier

Although it is useful to identify individuals that may be at risk for SRKOA based on their alignment parameters from normal values, it raises the difficult question of defining what is normal. Epidemiological studies are really the only way to define normal lower limb alignment, however there is great variation in the techniques chosen to measure lower limb alignment in terms of:

- alignment method chosen - MA using FLR or AA using SLR
- radiograph views may be either anterior-posterior (AP) or posterior-anterior (PA)
- knee joint positioning can vary from full extension (FE), semi-flexed (SF) or full-flexion (FF) and these positions may be with or without a positioning frame
- use of different cut off points for defining neutral / varus / valgus

- definitions of KJC vary (e.g. tibial spines tips, tibial spine bases) or may not be described

It is therefore not surprising that alignment angles obtained thus far have large standard deviations, making it difficult to distinguish between what is normal alignment and what is abnormal. It is also difficult to assess the degree of tolerable alignment deviation before a knee joint may be considered to have abnormal biomechanics. A summary of published alignment studies from healthy and KOA participants are shown in Table 10, Table 11 and Table 12 indicating the variation available in KJC location, radiograph view and knee positioning whilst measuring alignment.

2.6.3.2 Mechanical axis alignment

The HKA angle measuring MA alignment of the lower limb on a FLR is the angle formed at the knee between the FMA and TMA (Figure 17). This angle is measured as a deviation from 180° , where 180° or 0° is the ideal angle denoting neutral alignment, $< 180^\circ$ or a negative angle denotes varus alignment and $> 180^\circ$ or a positive angle denotes valgus alignment (Cooke et al., 1991). A neutrally aligned limb is often depicted with the FMA and TMA passing straight through the centre of the knee, as they are co-linear, resulting in the HKA angle being near to or at 180° or 0° . However when a line is physically drawn from the centre of the femoral head to the ankle joint centre on a FLR it may pass medially to the KJC, resulting in a slight varus lower limb position which may still be deemed within the neutral alignment category.

The MA alignment observations from studies on healthy participants (self-reported as absence of KOA) using FLRs shown in Table 10 give an indication of the range of mean values, between 178.7° – 179.0° (i.e. slightly varus) of neutral lower limb alignment available in healthy populations. This range on the whole becomes more varus in KOA populations up to a mean of 168.5° is reported and expected with medial compartment disease, however a mean maximum of 183.2° is reported for lateral compartment disease in Sharma's study (Sharma et al., 2001).

Table 10: MA knee alignment in FLRs studies

Where: AP=anterior-posterior; F=female; FE=full extension; FLR=full limb radiograph; FN=femoral notch; KJC=knee joint centre; KOA=knee osteoarthritis; L=left; M=male; MA=mechanical axis; N/S=not-stated; R=right; TS=tibial spine; ^= use of positioning frame; HKA measured as deviation from 180° with cut off points based on: ^a varus <180°, valgus >180°, or ^b neutral 178.5-180°, varus <175.5°, valgus >180° (Moreland 1987).

Author & Study population	Subjects (n)	FLR view (position)	Mean MA° (±SD°)	KJC
Healthy				
Chao 1994	127	AP (FE)	178.8 (2.2)	TS mid point
Colebatch 2009	F 40	AP (FE)	178.9 (2.1) ^a	TS mid-point
Cooke 1997	119	AP (FE) [^]	179.0 (2.8) ^a	N/S
Hsu 1990	120	AP (FE)	178.8 (2.2)	TS mid point
Moreland 1987	25	AP (FE)	R 178.7 (2.0) ^a	N/S
	25	AP (FE)	L 178.9 (2.1) ^a	N/S
Cohort				
Felson 2009 OAI	143	N/S (FE)	178.7 (4.0) ^a	FN & TS mid point
BOKS	183	N/S (FE)	177.7 (4.3) ^a	FN & TS mid point
KOA				
Cooke 1957	167	AP (FE) [^]	176.1 (7.7) ^a	N/S
Cooke 2002	182	AP (FE) [^]	168.5 (N/S) ^a	N/S
Felson 2005	270	N/S (FE)	177.4 (4.7)	Middle of knee
Hinman 2006	40	AP (FE)	174.2 (4.9) ^a	FN & TS centre
Kraus 2005	F 40	AP (N/S)	F 178.3 (4.8) ^b	TS centre
	M 17	AP (N/S)	M 177.4 (4.9) ^b	TS centre
Miyazaki 2002	106	AP (SF)	173.5 (4.7)	Tib plateau centre
Sharma 2001	230	AP (N/S)	176.7 (N/S) ^a	FN & TS tips
		AP (N/S)	183.2 (N/S) ^a	FN & TS tips
Sharma 2003	236	AP (N/S)	174.9 (3.4)	FN & TS tips
Sheehy 2011	F 73	AP (FE)	F 181.4 (N/S) ^a	FN & TS base
	M 47	AP (FE)	M 178.0 (N/S) ^a	FN & TS base
Van Raaij 2009	68	AP (FE)	173.1 (3.7)	FN & TS centre

2.6.3.3 Anatomical axis alignment

It is often not possible to have access to FLRs, therefore measurement of MA lower limb alignment is not always available. SLRs are often more accessible clinically and allow the AA alignment, as opposed to the full length MA alignment, of the lower limb to be measured using the FTA. This is the angle formed at the knee between the FAA and the TAA Figure 17. Similar to the HKA angle it is measured as a deviation from 180°, where 180° or 0° is the ideal

angle denoting neutral alignment, $<180^\circ$ or a negative angle denotes varus alignment and $>180^\circ$ or a positive angle denotes valgus alignment.

However consensus regarding the optimal AA alignment method has not yet been reached (McDaniel et al., 2010). In the current literature, there is great variation in the AA alignment methods used and the same variation points listed for MA measures such as radiograph view and positioning, alignment cut-off points, and varying KJC definitions apply to the current AA methods and additional consideration is required of the following factors:

- use of a single point (1P) (e.g. tibial spine tip midpoint) or a two point (2P) (e.g. femoral notch & tibial spine tip midpoint) AA measurement technique to define the KJC location
- varying use of a valgus offset angle to account for the difference between AA alignment to MA alignment

The AA alignment observations from studies on healthy participants using SLRs shown in Table 11 give an indication of the range, between $179 - 184.5^\circ$ (with no offset angle & disregarding the Asian population angles) of neutral AA lower limb alignment available in healthy (self-reported absence of KOA) populations. Despite not using a valgus offset angle, this range is more of a valgus range of normal compared to the slight varus range of normal ($178.7^\circ - 179.0^\circ$) shown from the MA alignment studies. In the KOA populations the AA alignment range becomes increasingly varus in individuals with medial compartment disease up to 175.2° , and increasingly valgus up to 186.0° with lateral compartment disease as expected.

Table 11: AA knee alignment in SLR studies

Where: AP=anterior-posterior; F=female; FE=full extension; FLR=full limb radiograph; FN=femoral notch; KJC=knee joint centre; KOA=knee osteoarthritis; L=left; M=male; MA=mechanical axis; N/S=not-stated; R=right; SF=semi-flexed; TS=tibial spine; ^= use of positioning frame; * Asian population; ~ FTA measured on FLR; FTA measured as deviation from 180° with cut off points based on: ^a varus <180°, valgus >180°; ^b neutral 178.5-180°, varus <175.5°, valgus >180° (Moreland 1987); ^c neutral 2-6°, varus <2°, valgus >6°; ^d neutral 182-184°, varus <182°, valgus >184°.

Author & study population	Subjects (n)	SLR view (position)	Mean MA° (±SD°)	Offset used	KJC
Healthy					
Colebatch 2009	F 40	AP (FE)	179.0 (2.1) ^a	No	TS tips mid-point
Felson 2002	F 25	AP (FE)	4.5 (N/S)	No	TS centre
	F 25	AP (FE)	4.7 (N/S)	No	TS centre
	M 25	AP (FE)	2.7 (N/S)	No	TS centre
	*M 25	AP (FE)	4.5 (N/S)	No	TS centre
Hunter 2007	178	AP (FE)	182.2 (3.2) ^a	No	TS tips
Jan'manan 2008	128	AP (N/S)	180.7 (3.7)	No	TS centre
Wong 2009	16	PA (FF)	179.2 (1.8) ^b	Yes	TS tips
Cohort					
Brouwer 2007	1501	AP (FE)	L 183.9 (3.6) ^d	+4	TS centre
	1501	AP (FE)	R 183.3 (3.3)	+4	TS centre
Felson 2009 OAI BOKS	143	PA (FF)^	2.4 (3.9) ^c	+4	FN & TS centre
	183	PA (SF)	3.0 (4.2)		FN & TS centre
KOA					
..Cicuttini 2004	117	AP (FE)	180.8 (5.8) ^a	No	TS centre
Hinman 2006	40	AP (FE)	175.2 (4.7) ^a	No	TS centre
Hunter 2007	76	AP (FE)	182.0 (3.0) ^a	No	TS tips
Jan'manan 2008	74	AP (N/S)	181.2 (6.6)	No	TS centre
Kraus 2005	F 40	PA (FF)^	F 181.0 (4.9) ^b	No	TS tips
	M 17	PA (FF)^	M 181.3 (5.3) ^b	No	TS tips
	F 40	AP (N/S)~	F 180.9 (4.5) ^b	No	TS tips
	M 17	AP (N/S)~	M 182.5 (3.8) ^b	No	TS tips
Sheehy 2011	F 73	AP (FE)~	F 186.0 (N/S) ^a	No	FN & TS base
	M 47	AP (FE)~	M 184.0 (N/S) ^b	No	FN & TS base
Teichtahl 2006	121	AP (FE)	180.6 (5.8)	No	TS centre
Van Raaij 2009	68	AP (FE)~	178.8 (3.1) ^b	No	FN
Wong 2009	30	PA (FF)	175.3 (5.1) ^b	Yes	TS tips

2.6.3.4 Comparative alignment studies

Several studies have examined whether the measurement of AA alignment, obtained using SLR is comparable to MA alignment, measured on FLR. These studies are shown in Table 12.

Table 12: MA v AA knee alignment studies

Where: AP=anterior-posterior; CI=confidence interval 95%; F=female; FE=full extension; FLR=full limb radiograph; FN=femoral notch; KJC=knee joint centre; KOA=knee osteoarthritis; L=left; M=male; MA=mechanical axis; N/S=not-stated; R=right; SF=semi-flexed; SLR=short limb radiograph; TS=tibial spine; ^= use of positioning frame; ~FTA measured on FLR

Author & Study population	Subjects(n) (M:F)	SLR view (position) KJC	FLR view (position) KJC	Offset	Agreement (p value/ 95% CI)
Healthy					
Colebatch 2009	40 (0:40)	AP (FE) TS tips mid-point	AP (FE) TS mid-point	No	r = 0.81 (N/S)
Chang 2010	99 (54:45)	AP (FE) FN & TS tip centre	AP (FE) FN & TS tip centre	No	r = 0.54 (p<0.005)
Cohort					
Felson 2009	143 (70:73)	PA (FF)^ FN & TS middle	N/S (FE) FN & TS middle	+4	r = 0.66 (p<0.001)
KOA					
Kraus 2005	57 (34:80)	PA (FF)^ AP (N/S)~ TS tips	AP (N/S) TS centre	+4.2	r = 0.75 (p<0.001)
Hinman 2006	40 (16:24)	AP (FE)~ TS centre	AP (FE) FN & TS centre	No	r = 0.88 (p<0.001)
Issa 2007	146 (37:109)	AP (SF)~ TS mid-point	AP (SF) FN & TS tips	+3.4	r = 0.86 (0.81-0.9)
Sheehy 2011	120 (47:73)	AP (FE)~ FN & TS base	AP (FE) FN & TS base	+5.0	r = 0.88 (p<0.05)
Van Raaij 2009	68 (32:36)	AP (FE)~ FN & TS centre	AP (FE) FN	No	r = 0.34 (p<0.005)

In practice, AA alignment is regularly assessed from SLRs from which the AA of the femoral shaft and tibial shaft are located. The FMA is not available on SLRs, but it can be estimated as the FAA and the FMA have a conservative angular offset from each other of around 4 - 5° (with low variance) (Hsu et al., 1990, Issa et al., 2007, Kraus et al., 2005, Moreland et al., 1987).

Correlations (r) between AA alignment from SLRs and MA alignment from FLRs range from 0.75 to 0.88 (Hinman et al., 2006, Issa et al., 2007, Kraus et al., 2005). Estimation of FMA from SLRs can be a useful surrogate, but measuring the true FMA on a FLR remains the definitive MA alignment measurement. In most cases the AA is sensitive and specific enough to differentiate varus and valgus alignment (Issa et al., 2007) but AA alignment may not be reliable in limbs with proximal femoral or distal tibial bone deformities as SLR views may miss these types of deformities (Cooke et al., 2007).

In a self-reported healthy population, Colebatch and colleagues have been the only group to show that measuring AA knee alignment from an AP SLR is reproducible, inter-observer agreement $r = 0.99$ ($p < 0.001$) and intra-observer agreement $r = 0.99$ (< 0.001), and correlates with MA knee alignment from a FLR (Colebatch et al., 2009). These data suggest that the AA method measured on AP SLRs is useful for assessing alignment in population cohort studies with AP radiographs.

In symptomatic KOA populations, studies by Kraus (Kraus et al., 2005), Issa (Issa et al., 2007) and Hinman (Hinman et al., 2006) all showed that AA alignment on SLRs correlated well ($r = 0.75$ to 0.88) with MA alignment on FLRs. Felson and colleagues found only moderate agreement between the two alignment measurements in their Osteoarthritis Initiative (OAI) cohort population (Felson et al., 2009). Whether using their two-point FTA alignment method, when all other comparison studies have used single point methods, or comparing fixed-flexion SLRs to full extension FLRs has any bearing on this result is not clearly ascertained.

The study by Felson's group showed that some knees classified as valgus on SLR were classified varus on FLR and vice versa, suggesting that the AA alignment assessed from a SLR is not exactly the same as a MA alignment measurement from the FLR (Felson et al., 2009). However, AA alignment on SLR effectively predicted the risk of JSN. In the second part of their study using the Boston OA Knee Study (BOKS) cohort, varus MA and AA mal-alignment yielded almost exactly the same risk of progression. Given the frequent misclassification of mal-alignment when AA alignment on SLR was compared with the gold standard MA on FLR, there were surprisingly high levels of predictive validity of AA alignment measured from a SF SLR. This suggests that flexed knee radiographs may provide useful and valid information regarding relevant mal-alignment. It is possible that flexed knee radiographs are more likely to show disease and may better represent the position that poses a risk to the knee during activity than radiographs obtained in full extension standing. However, this flexed SLR view does not necessarily provide a particularly accurate surrogate for MA, therefore the predictive validity of AA alignment obtained with fixed-flexion and fully extended views needs to be tested.

Sheehy and colleagues are the first group to suggest that the relationship between MA and AA differs according to the direction and degree of deformity of the lower limb, specifically for varus limbs the offset increased and for valgus limbs the offset decreased (Sheehy et al., 2011). They also found that using shorter femoral and tibial shaft lengths to estimate MA weakened the AA and MA alignment relationship in their sample of 120 KOA subjects from the Multicentre Osteoarthritis Study (MOST) population. This is also supported by Chang's study (Chang et al., 2010) who showed greater correlations of AA measurement to MA using 15cm shaft length ($r = 0.81$ males, $r = 0.88$ females) than those taken using a 10cm shaft length ($r = 0.69$ males, $r = 0.80$ females). Sheehy and colleagues report that the relationship of AA and MA alignment was most attenuated when both shorter shaft lengths were used and sub-categories of varus/valgus knee alignment were studied, suggesting it is better to use the longest shaft lengths possible on SLRs and to avoid categorization of alignment (Sheehy et al., 2011). Sheehy's study identifies significant limitations to using AA to predict MA alignment, and therefore recommends that FLRs are used whenever an accurate measurement of lower limb MA alignment is required. This is due to the offset between MA and AA measurement being variable, and it being influenced by the direction and degree of mal-alignment present in the lower limb. It is difficult to accurately predict the MA due to imprecision around the correction factor, however, broad categories of alignment can be estimated using AA from SLRs, particularly if there is a variety of varus, neutral and valgus limbs.

Offset angle

Previous knee alignment studies (Chang et al., 2010, Felson et al., 2009, Issa et al., 2007, Kraus et al., 2005, Sheehy et al., 2011) describe a valgus offset angle between the AA and MA angles to account for the difference between AA alignment to MA alignment. The part of the femoral shaft used to determine AA alignment does not include the femoral neck that protrudes medially from the upper femoral shaft which is used in determining the MA alignment. The offset angle can vary between the sexes (Chang et al., 2010, Issa et al., 2007, Kraus et al., 2005). The mean offset for KOA females is reported between 3.0° - 3.5° and for KOA males is between 4.7° - 6.4° (Issa et al., 2007, Kraus et al.,

2005) however the studies that these offsets are based on use differing radiograph views and knee joint positioning.

The study by Kraus used fixed flexion PA SLRs and FLRs (Kraus et al., 2005), whereas the study by Issa used semi-flexed AP SLRs and FLRs (Issa et al., 2007). Chang and colleagues reported the opposite trend, with KOA females having a larger offset than KOA males (7.3° vs 6.0° respectively measured with 15 cm shaft lengths) (Chang et al., 2010), and the study by Sheehy and colleagues found no significant differences (with only two exceptions) between the sexes with respect to various angles and offsets (Sheehy et al., 2011). It appears that further comparisons of females and males with KOA are needed to confirm if real differences exist and in which direction.

The Felson group suggest that the appropriate offset depends on whether the knee is flexed or extended when it is imaged. In full extension, they suggest the appropriate offset is close to 5° , whereas it is around 4° in a flexed position as the knee is already in more varus when flexed (Felson et al., 2009).

However, when comparing fully extended AP SLR and FLR, the Colebatch study found no evidence of needing to use an offset angle either in terms of the mean alignment or those classified as valgus (Colebatch et al., 2009). This may be as a result of studying a healthy population in comparison to Kraus and Issa who studied RKOA populations, as opposed to the use of a fully extended knee position compared to fixed flexion or semi-flexed radiographic views. After offset correction, AA identification of both a varus and valgus MA angle are high for sensitivity, specificity, and for the area under the receiver operating curve (Issa et al., 2007).

Sharma suggests that this result and the findings from Kraus and Hinman indicate that when using a sex-specific offset correction, AA from a SLR is an acceptable alternative to MA angle from a FLR and should be considered in research and clinical settings (Sharma, 2007). A point to note is that the studies by Hinman, Kraus and Issa all measured their AA alignment from their FLRs images as opposed to measuring AA alignment from a SLR. Whether this has any relevance to the accuracy of these measurements can only be explained by further studies on this matter.

As the Chingford study is a cohort population containing a mix of healthy and KOA women, and only has access to AP SLRs taken in the fully extended

position, it is appropriate to use the AA method to measure knee alignment. AA alignment will be correlated with SRKOA, RKO A and knee pain outcomes, therefore an offset correction will not be needed for these correlations. Unfortunately no FLR images have been taken in the Chingford cohort so AA and MA alignment cannot be compared.

Knee joint centre

A limitation to consider is the variation across knee alignment studies to identify the KJC in order to measure knee alignment in both the AA and MA alignment methods. Some studies, including Moreland's seminal MA knee alignment study in healthy young men (Moreland et al., 1987), are rather vague in defining the actual KJC point used:

“5 possible KJC were determined:

- 1) the centre of the soft tissue at the level of the cartilaginous space,
- 2) the centre of the tibia,
- 3) the centre of the femoral condyles at the level of the top of the intercondylar notch,
- 4) the centre of the tips of the tibial spines,
- 5) the centre of the femoral intercondylar notch.

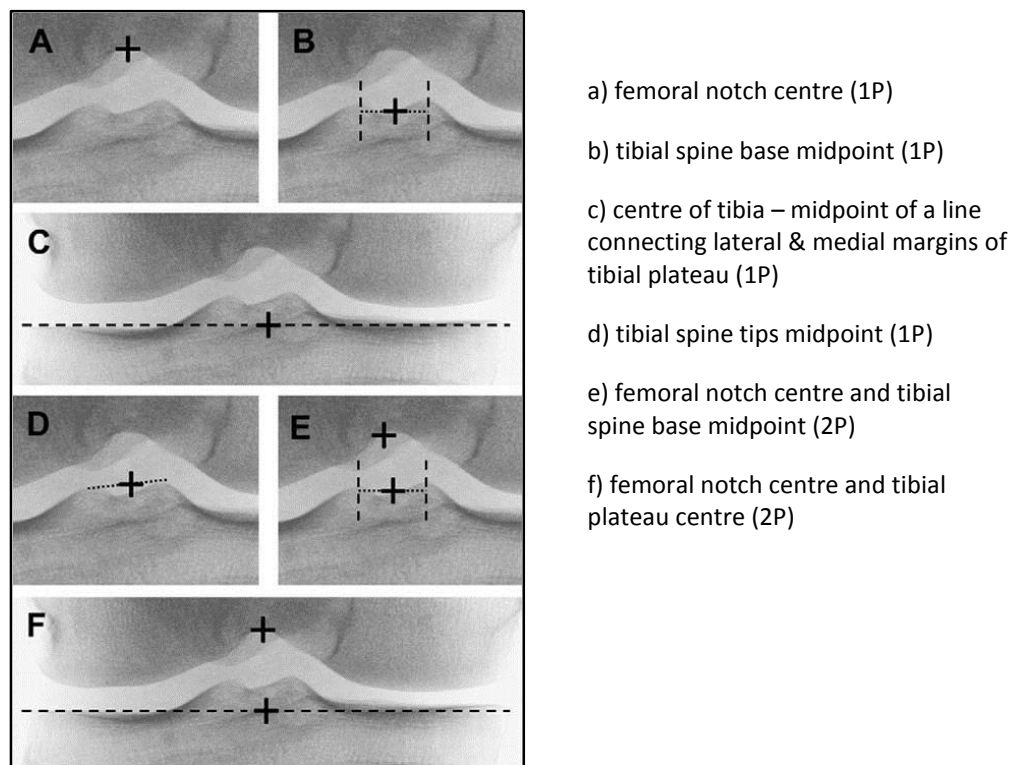
All five points were found to be close to each other, usually within five millimetres horizontally. The most medial point was usually the centre of the femoral notch and the most lateral point was usually the centre of the tibial plateau. For the centre of the knee, a visually selected mid-point of these five points was used.”

This vague KJC description (underlined) means it is difficult to replicate results and this contributes to the variation found in descriptions of MA and AA knee alignment methods. Various knee alignment studies state using ‘the centre of the tibial spines’ or the ‘midpoint of the tibial spines’ as their KJC in their method section, however they offer no further explanation as to whether this is referring to the midpoint at the base, or at the tips of the tibial spines. There are also often difficulties in using the tibial spines as a KJC in subjects with

KOA due to knee deformity and possible overlying chondrocalcinosis and/or osteophytes.

McDaniel and colleagues (McDaniel et al., 2010) recently published a brief report to investigate the performance metrics of methods of AA measurement currently used to determine whether a specific protocol could be recommended. A total of five AA methods with differing femoral and tibial KJCs were tested Figure 18.

Figure 18: KJCs in AA alignment



Reproduced from McDaniel et al (McDaniel et al., 2010), Osteoarthritis & Cartilage © 2010 with permission from Elsevier.

Three of these methods were based on Moreland's KJC landmarks (Moreland et al., 1987), McDaniel states these three were methods a, b and c, however on closer comparison it is actually methods a, c and d. McDaniel's study (McDaniel et al., 2010) found all methods of AA measurement were highly reproducible, but varied in their accuracy and sensitivity to detect meaningful differences. Based on these parameters, they recommend using the tibial spine base midpoint (method b) or centre of tibia (method c) and suggest comparing single-point (1P) and two-point (2P) methods in larger studies.

There are several limitations to this study:

- the sample size is small at 50 (43 females and 7 males)
- the intra-rater reliability could have been affected by reader bias as all measurements were taken by the reader before moving to the next film
- the SLRs were PA fixed-flexion views obtained using a lower limb positioning frame, whereas the FLRs were AP views. The FLR position is not stated in the methods section, no use of a frame is mentioned and it is likely the FLR images have been taken in full knee extension which would not necessarily correspond directly to the SLR views, thereby introducing further bias.

However, this is a useful study to consider as little has been published in this area and it is a good starting point for consideration of appropriate AA knee alignment methods to use in the Chingford cohort. It is possible to compare various 1P and 2P AA methods on the SLR images in the Chingford cohort, unfortunately it is not possible to compare them to MA angles as FLRs are not available. However it will be beneficial to identify which AA method correlates best with SRKOA, RKOAs and knee pain outcomes for clinical relevance.

Limb positioning.

A lack of standardization in limb positioning for imaging means that errors can often arise, most commonly from poor control of limb rotation. Variations in lower limb position, particularly rotation, can significantly influence knee alignment measurements (Siu et al., 1991, Sanfridsson et al., 2001). Previous MA alignment studies on FLRs by Cooke and colleagues suggest using a positioning frame to standardize placement of the entire limb, thereby increasing reproducibility by reducing positional error (Cooke et al., 1991, Siu et al., 1991). The images taken using the frame are with the knee extended, though Sanfridsson and colleagues found differences of less than 1° between semi-flexed and extended lower limb positions in an analysis of MA and AA measurement in healthy volunteers using a similar positioning frame (Sanfridsson et al., 1996). In the absence of using a positioning frame, Cooke has outlined the optimum limb position for measuring AA alignment from SLRs, suggesting that the knee's plane of flexion aligned within the sagittal plane should be used as the common reference for positioning (Cooke and

Sled, 2009). This method is suggested as it is more reproducible than aligning the knee via fixed foot rotation, tibial tubercles, patellar orientation or co-linearity of the posterior profiles of the femoral condyles, as all these positions can be affected by the OA process itself in those with KOA. This is useful information for prospective studies, however most cohort studies, including Chingford, used a radiograph protocol based on imaging advice at the time recommending AP radiograph views in a fully extended knee position with tibial tubercles facing forward. It may be possible in this information technology age to devise a method of identifying a rotated or flexed knee radiograph image to which an adjustment factor could be added to correct for any positional deformity found.

2.6.4 Alignment & KOA associations

2.6.4.1 Knee alignment and KOA incidence and progression

Documentation describing the true history of knee alignment over time is somewhat lacking, this is likely to be due to the slow progression of the condition, its poor tolerance by patients and the available treatment alternatives. One of the first longitudinal studies on knee alignment natural history was by Hernborg & Nilsson in 1977. After 10 – 18 years follow-up, 94 knees in 71 patients were reviewed after baseline radiographs diagnosed OA (un-treated surgically). Unsurprisingly, they demonstrated that the disease course was unfavourable; improvement was rare and 50% had clinical deterioration. Varus deformity, particularly in women, was associated with a poor prognosis (Hernborg and Nilsson, 1977).

A systematic review by Tanamas and colleagues (Tanamas et al., 2009), shows that there are now a number of epidemiological studies identifying severity of mal-alignment as a predictor of KOA progression (Cerejo et al., 2002, Cicuttini et al., 2004, Felson et al., 2004, Janakiramanan et al., 2008, Sharma et al., 2001, Teichtahl et al., 2009a) however there is still some debate as to the role knee alignment plays with regard to the incidence of KOA (Brouwer et al., 2007, Hunter et al., 2007, Sharma, 2007).

Studies by Brouwer (Brouwer et al., 2007) and Sharma (Sharma, 2007) found varus knee mal-alignment to be a risk factor for incident OA, however Hunter et al (Hunter et al., 2007) reported knee alignment was not associated with OA

incidence in the Framingham OA cohort, and a study by Zhai and colleagues found no evidence of baseline mal-alignment predicting subsequent loss of knee cartilage volume or progression of chondral defects on MRI in their mainly healthy knee population (Zhai et al., 2007). It is suggested by Sharma that major contributors to these conflicting results were differences between studies in methodology and participant characteristics, including different techniques to measure joint alignment, whether general or compartment-specific KOA was examined, and variation in mean BMI and severity of KOA at baseline (Sharma, 2007). Sharma's study assessed MA alignment on FLRs in the MOST cohort, whereas the studies by Brouwer and Hunter assessed AA alignment measured on AP FE SLRs. There are a few inherent differences between their study methods that may explain their differing results. Hunter used a subset of people from the Framingham OA cohort with mean follow up of 8.75 years, they measured AA alignment using the centre of the TS tips (a KJC originally described by Kraus as their KJC but they did not use an offset in their calculations. Brouwer's study used a population based cohort in Rotterdam who were slightly older with a lower BMI. Their mean follow-up was 6.6 years and they measured AA alignment using the centre of the TS as their KJC (the diagram included in their paper, identifies the KJC as the base of TS, however the text states neither TS base nor TS tips, so exact KJC location is questionable), they also used a +4° valgus offset in their calculations and unlike the Framingham study they categorised their exposure by direction of alignment into varus, valgus or neutral, presumably to allow for greater power, although this undermines evaluation for a dose-response relationship. To perform this evaluation, the mal-alignment must be quantified and the subjects stratified on the basis of the degree of deformity, this was completed in the Framingham study and no dose-response relationship was found.

Brouwer further stratified his study by BMI categories showing that an increased risk of mal-alignment was seen in the overweight and obese but not healthy weight subjects. This stratification of BMI risk raises the question of whether or not there is effect-measure modification (or interaction) by BMI on the relationship between alignment and incident OA, but the authors did not indicate that this was done. It could also be argued that both these follow-up periods are possibly too short for KOA to develop, and using a continuous

measurement of AA alignment as done so by Kraus (Kraus et al., 2005) may have been more appropriate than categorising into varus, valgus or neutral.

The studies by Sharma (Sharma, 2007) and Brouwer (Brouwer et al., 2007) used similar varus and valgus definitions with neutral knees as reference, and both observed that varus but not valgus alignment increased the risk of KOA, whereas instead of using neutral knees as reference, the Framingham cohort case-control study by Hunter (Hunter et al., 2007) compared the most varus (1 - 7° varus) knees to the most valgus quartile (5 - 10° valgus) which answers a slightly different question. The stronger finding for varus over valgus alignment is expected as explained previously: neutrally aligned healthy knees have a greater load pass medially than laterally (Andriacchi, 1994, Morrison, 1970) resulting in a larger medial stance phase knee adduction moment (KAM). This KAM magnitude increases with greater varus alignment (Hurwitz et al., 2002) and it predicts KOA progression (Miyazaki et al., 2002) therefore KAM is likely to be on the causal pathway between varus alignment and KOA progression. Although valgus alignment is associated with greater peak pressures in the lateral tibio-femoral compartment (Bruns et al., 1993) the medial compartment continues to bear more load until a severe valgus deformity develops (Harrington, 1983, Johnson et al., 1980).

Further longitudinal studies of knee alignment are required to reach a consensus in this area and to help determine the cause and effect relationship that knee alignment has with KOA. It is still not clear whether mal-alignment precedes the development of KOA, whether mal-alignment is a result of OA, or whether the relationship between mal-alignment and KOA is bi-directional, which may be more likely. Mal-alignment occurring prior to KOA starting may be a result of genetic, developmental or post-trauma factors. A link between pre-existing mal-alignment and development of OA is supported by animal model data (Tetsworth and Paley, 1994) and now in human knees in studies by Brouwer (Brouwer et al., 2007) and Sharma (Sharma, 2007).

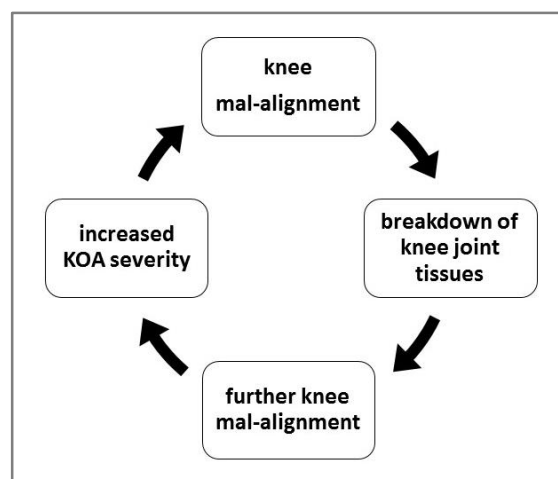
Knee mal-alignment that occurs as a consequence of KOA could be due to loss of bone height and cartilage leading to JSN and subsequent changes in joint alignment. Zhai and colleagues report this is not the case: in their mainly healthy knee population there was no evidence that baseline mal-alignment predicted subsequent knee cartilage loss on MRI, suggesting that mal-

alignment is a marker of OA rather than a cause of KOA disease (Zhai et al., 2007). It is possible that an increase in varus alignment occurs with normal ageing and that this then predisposes people to develop KOA (Cooke et al., 2003). As ageing may only cause cartilage loss in later life, there is further need to study older populations with longer follow-up periods for confirmation of these ideas.

2.6.4.2 Knee alignment & structural features

Frontal plane mal-alignment is clearly associated with an increase in structural damage to the knee joint, although it still remains unclear whether mal-alignment is the cause or the consequence of this worsening disease (Hunter et al., 2005). Until recently, little was known of the factors that actually contributed to knee alignment and their relative contribution was unclear. Previously, Cooke and colleagues suggested that loss of joint space may account for some mal-alignment, but this was not quantified (Cooke et al., 2003). It is now known that mal-alignment does not just have a direct effect on articular cartilage, it has also been associated with the structural breakdown of other knee joint tissues such as menisci, ligaments, sub-chondral bone and bone marrow (Felson et al., 2003). The breakdown of all these types of tissues in the knee joint could result in further mal-alignment leading to the start of a vicious KOA progression cycle (Figure 19).

Figure 19: The mal-alignment KOA progression cycle



Although many studies examining knee alignment use radiographic outcomes, only a few have actually looked at the relationship between knee alignment and

radiographic features of KOA. Felson and colleagues showed that greater varus or valgus alignment increased the risk of more severe medial or lateral compartment osteophytes respectively (Felson et al., 2005), and Sharma demonstrated that compartment-specific JSN is associated with knee alignment (Sharma et al., 2001).

A cross-sectional study by Teichtahl (Teichtahl et al., 2006) found that the two co-existed where static knee alignment, measured as a continuous variable, identified increasing varus or valgus knee alignment and was associated with greater risk of medial or lateral compartment JSN and osteophytes respectively. More recently a cross-sectional MRI study (Janakiramanan et al., 2008) demonstrated that static knee alignment is associated with the risk of compartment specific knee cartilage defects in both healthy and KOA groups. Another cross-sectional MRI study in the BOKS by Hunter (Hunter et al., 2005) suggested that multiple factors, including cartilage loss, meniscal positioning and degeneration, ligament damage, bone attrition and osteophytes can contribute to knee mal-alignment. Many of these contributing factors to mal-alignment are also more likely to progress rapidly themselves as a result of increasing mal-alignment, thereby adding to the vicious cycle of joint destruction.

Unfortunately all of these studies on structural features have so far been cross-sectional in design. However Felson's group have studied bone marrow oedema lesions on MRI, MA alignment on FLR and longitudinal radiographic knee JSN progression over 30 months in a KOA population (Felson et al., 2003). The bone marrow oedema lesions markedly increased KOA structural progression risk, particularly in the compartment affected by the bone marrow lesion, and were also strongly related to mal-alignment toward the side of the lesion. As MA alignment was only measured at one time point part way through the study (unfortunately not at baseline), the KOA progression in those with bone marrow lesions could either be the consequence of the lesions themselves, or mal-alignment could produce the bone marrow lesions and the JSN. A second longitudinal study by Felson using the same KOA population, confirmed that large osteophytes do not affect the risk of structural progression in KOA, they are in fact strongly associated with mal-alignment to the side of the osteophyte, and therefore any relationship osteophytes may have with progression is mediated by the association of mal-alignment with

progression (Felson et al., 2005). Unfortunately, similarly to the previous study by Felson, MA alignment was only measured at one time point in the middle of the 30 month follow-up period (not at baseline), therefore if osteophytes affect limb alignment it is possible that osteophytes at baseline could have affected subsequent knee alignment (Felson et al., 2003).

In theory, natural history studies of KOA should try to consider all aspects of KOA structural joint damage, such as meniscal damage, mal-alignment and joint laxity together, to determine the effect on tibio-femoral cartilage loss and address the strong possibility of confounding by adjusting for the other local factors. The only longitudinal MRI study to date to look at all these structural features together is by Sharma and colleagues using the MAK-2 (Mechanical factors in Arthritis of the Knee, second cycle) cohort of 153 people with KOA (Sharma et al., 2008). After full adjustment of all assessed structural features and using a quantitative approach to assess cartilage loss, only medial meniscal damage and varus mal-alignment for the medial compartment, and lateral meniscal damage for the lateral compartment independently predicted tibial and femoral cartilage loss over a two year follow up period in this study. These findings are not surprising as the important function of menisci is now known: by enlarging the contact surface they reduce stress, distribute load and increase stability in the knee joint. Removal of menisci causes subsequent problems - a partial meniscectomy increases the risk of OA and a total meniscectomy causes KOA changes (Englund et al., 2003).

Although the relationship between laxity and cartilage loss was not found to be significant in this Sharma study, laxity has been reported in another study by Sharma to be significantly associated with KOA JSN (Sharma et al., 1999b). More recently knee laxity has also been found to be associated with mal-alignment in a cross-sectional study by Van der Esch although alignment was crudely measured using a goniometer as opposed to radiographic alignment measurement (van der et al., 2005). Nevertheless, it is possible that with greater mal-alignment there are increased stresses on the passive knee joint restraint system involving the ligaments, joint capsule and other soft tissue. As a result, the passive restraint system may stretch in length causing a reduction in its restraining capabilities and thereby enhance laxity. Only further longitudinal analysis in those with and without knee pain and KOA will

determine the cause and effect relationships between all of these structural factors and knee mal-alignment.

2.6.4.3 Knee alignment & disease severity

The increase in structural knee joint damage may help the vicious cycle of events to bring about further mal-alignment, this consequently places further strain on already damaged tissue, leading to a perpetual cycle of mal-alignment resulting in worsening of KOA thereby increasing KOA severity, which in turn leads to worse mal-alignment (Figure 19). Both varus and valgus lower limb alignments increase the chance of JSN occurring, and JSN progression is correlated with the severity of the deformity (Sharma et al., 2001). However, Hunter and colleagues have shown the initial presence of mal-alignment does not significantly increase the risk posed to healthy knees (Hunter et al., 2007). This is consistent with previous studies suggesting that OA knees with greater disease severity are increasingly mal-aligned (Wada et al., 2001) and that the alignment association with KOA progression differs according to the severity of the disease (Cerejo et al., 2002). An 18 month follow-up study by Cerejo found that in knees with mild OA (K&L grade 2) and varus MA alignment at baseline, there was a 4-fold increase in medial compartment progression (Cerejo et al., 2002). In the equivalent knees with valgus MA alignment at baseline, there was a near significant 2-fold increase in lateral compartment progression. The effect on progression was more substantial (>10-fold increase) in moderate OA (K&L grade 3) knees with varus or valgus alignment at baseline. The weaker effect of valgus alignment on lateral progression compared to the varus alignment effect on medial progression is likely to be a result of the disproportionate load transmitted to the medial compartment in the normally aligned, ambulating knee (Morrison, 1970). Despite valgus alignment increasing lateral compartment loading, the medial compartment often continues to bear more load than the lateral compartment until severe valgus deformity is present (Harrington, 1983, Johnson et al., 1980). Cerejo's study supports the concept that the alignment effect is more pronounced as disease severity advances, but the alignment effect on a healthy knee cannot be assumed to be the same as the alignment effect on OA knee, therefore further longitudinal studies examining this are required.

2.6.4.4 Knee alignment & symptoms

To fully understand the risk factors for pain and other KOA symptoms requires consideration of a host of biopsychosocial factors (Dieppe and Lohmander, 2005). KOA symptoms are typically described as ‘mechanical’ in that they occur on movement and/or on physical activity. A common phenomenon that is poorly understood and remains a focus for current research is that KOA individuals with the same degree of structural knee joint damage can experience widely different levels of pain (Hannan et al., 2000), for example a grade 4 K&L knee subject reporting no pain whatsoever and a grade 1 K&L subject reporting severe pain. This dissociation between radiographic structural findings and pain may be partly explained by the differences in joint forces and joint stress during functional activities. Previously, mal-alignment has been shown to be a predictor for functional decline in KOA and may play a role in the ‘mechanical’ nature of KOA pain (Sharma et al., 2001). Further longitudinal studies are needed to fully understand the alignment – pain – KOA association.

2.6.5 KneeMorf alignment software

Traditionally, knee alignment measurements have been taken by hand, requiring the clinician to draw lines representing the femoral and tibial MA or AA on the radiograph and to manually measure the resulting angle with a goniometer. This manual method introduces significant variability due to the subjectivity of the observer in the placement of the axis lines (Ilahi et al., 2001). With the introduction of digital imaging, traditional radiographs are rapidly being replaced with digital images such as DICOM (Digital Imaging and Communication in Medicine) format files. It is not possible to measure digital images manually therefore computer assisted analysis (CAA) software programs with electronic tools have been developed to provide digital radiograph knee alignment measurement (Cooke et al., 1991, Hankemeier et al., 2006, Prakash et al., 2001, Cooke and Sled, 2009, Specogna et al., 2004, Takahashi et al., 2004).

2.6.5.1 Computer assisted analysis for measuring knee alignment

In the current literature a variety of CAA software programs have been developed and comparison studies have shown good reliability between

manual and CAA knee alignment measurement, with a tendency to demonstrate greater reliability using CAA measurement (Cooke et al., 1991, Goker and Block, 2007, Hankemeier et al., 2006, Prakash et al., 2001, Sailer et al., 2005, Sanfridsson et al., 1996, Sled et al., 2011, Specogna et al., 2004, Takahashi et al., 2004, Oka et al., 2008, Wong et al., 2009). The majority of these studies focus on measuring MA alignment on FLRs, only four studies to date have developed and tested the reliability CAA software programs to measure AA alignment on SLRs (Prakash et al., 2001, Takahashi et al., 2004, Oka et al., 2008, Wong et al., 2009) see Table 13.

Table 13: Comparing CAA software programs to measure AA alignment on SLRs

Where: AA=anatomic axis; AP=anterior-posterior; FE=full extension; FF=flexion; ICC=intra-class correlation coefficient; OA=osteoarthritis; PA=posterior-anterior.

Study	Study population	XR image, view & position	Level of automation	Parameters measured	AA method	Results
Prakash 2001	58 OA knees read twice 2 weeks apart; UK cohort.	Scanned AP FE	Full (via edge detect)	AA angle only, measured manually by 2 doctors & on computer by 2 clerical staff.	Subtended angle by mid-diaphyseal lines of femur & tibia shafts.	No sig. diff. between any paired comparisons; mean correlation 0.75; largest mean diff. 1.19° but gross discrepancies with metal artefacts.
Takahashi 2004	73 OA knees read twice 2 weeks apart; Japanese cohort.	Scanned AP FE	Semi (8 points via mouse)	AA angle only, measured manually by 1 doctor & on computer by 3 doctors.	Subtended angle by mid-diaphyseal lines of femur & tibia shafts.	Intra- & inter-observer ICC 0.97, inter-system ICC 0.92.
Oka 2008	50 OA knees from 1979; Japanese cohort (ROAD).	DICOM AP FE	Full (via edge detect)	6 measured by computer: joint space area, med & lat jsa, osteophyte area, AA angle.	Lateral angle between mid-diaphyseal regression lines of femur & tibia shafts.	Measures all 6 parameters in <1 second without intra- or inter-observer variability as fully automated, 0.75 & 0.72 ICCs when compared to semi-automatic method.
Wong 2009	38 OA knees & 16 healthy knees read twice 1 week apart; Canadian cohort.	Scanned PA FF	Semi (all points via mouse)	AA angle only, measured manually & on computer by 2 experienced & 1 inexperienced reader.	Medial angle formed at intersection of 10cm femoral & tibial shaft lengths from tibial spine tips.	High degree of inter- & intra-observer, test-retest & experience-inexperience reproducibility with variances below 1%.

Unfortunately, none of the AA alignment CAA programs described in Table 13 are capable of measuring femoral and tibial joint orientation geometry angles. It is not possible to measure these geometry angles when a mid-diaphyseal line AA method is used, a KJC point method is required for femoral and tibial joint orientation geometry angles to be measured.

On the whole, CAA appears to be more reliable than manual measurement, and it is also reported to be significantly quicker in terms of time effectiveness with a 44 - 78% reduction in measuring time (Hankemeier et al., 2006, Sailer et al., 2005, Sled et al., 2011).

As a result of the limitations highlighted above of the CAA software programs currently available, it was apparent that a new CAA software tool would be required to accommodate and make full use of the range of short limb knee radiograph images available in the Chingford Study.

Due to the length of follow-up in the Chingford Study, some of the plain-film radiographs are over 20 years old and were only later digitised (by a scanner) after being stored for 10-15 years resulting in digitised images that are not as high in quality, compared to newer DICOM images, for edge-detection algorithms to be used. The most recent year 20 visit knee radiographs were taken as digital DICOM images, therefore any newly designed CAA software program for the Chingford cohort radiographs is required to manage both plain film radiograph images that have been digitised and the more recent DICOM digital images, which is not something that can be managed by the current AA alignment CAA programs available. This has led to the development of a new CAA software tool called 'OxMorf' designed by a team of researchers at the University of Oxford that allows morphometric measurements to be taken at any joint site from digital SLRs and from plain film radiograph images digitised by a scanner, making this a unique software tool. Further details on the KneeMorf software which is the knee joint measuring aspect of the tool are provided in the methodology chapter section 3.5.4.2 and in appendix A19.

2.6.6 Alignment summary

- The natural history of knee alignment in healthy and KOA populations is lacking.
- Further work is required to establish if knee mal-alignment is a risk factor for KOA incidence.
- Consensus regarding the optimal FTA method has not yet been reached.
- 1P and 2P AA alignment methods will be examined using difference KJCs with the new KneeMorf software
- Cross-sectional and longitudinal associations between knee alignment and SRKOA, RKOA and knee pain will be examined.
- Further knowledge of factors that influence knee alignment may contribute to the patho-physiology of KOA and provide insight into therapeutic options.

2.7 Risk factor interaction

Existing epidemiological risk factor studies for knee, hip and hand OA are consistent with the possibility that OA pathogenesis is likely to be an interaction between specific systemic risk factors and local mechanical risk factors, that combine with the underlying susceptibility of a joint to tissue damage and repair failure, which then determines the site of joint degeneration and the severity of disease (Arden and Nevitt, 2006).

Evidence of constitutional risk factors interacting with local risk factors already exists, for example, the increased risk and severity of post-meniscectomy KOA in people with HN (Englund et al., 2009b).

There are also other risk factor interaction examples in KOA. Sharma and colleagues have shown that the association of muscle strength with the radiographic progression of KOA varies according to the alignment of the knee with increased progression in mal-aligned knees (Sharma et al., 2003).

Contrary to popular thought, this study concluded that greater quadriceps strength at baseline did not protect against subsequent progression of KOA and, in mal-aligned knees and in lax knees, greater quadriceps strength was associated with increased likelihood of tibio-femoral OA progression.

The Framingham study has also demonstrated that the risk of developing KOA as a result of regular, heavy physical activity was greater in those patients with the highest BMI (McAlindon et al., 1999).

It is therefore important in epidemiological studies to formally search for such interactions, and there is still a need for further long-term prospective cohort studies that can untangle which risk factors affect incidence, which affect progression, and which risk factors may interact.

2.7.1 Defining an interaction

There is very good reason to be interested in interaction as some form of causal interaction occurs in every case of every disease (Rothman, 2002). A well-known example of a causal interaction is the public-health campaign against drunk driving. Alcohol consumption and driving are both risk factors for injury, but their combined effect is a much more potent cause of injury than either of these risk factors acting alone. There is however much confusion surrounding the evaluation of interaction, which is mostly due to the fact that the term ‘interaction’ is used differently in statistics and epidemiology.

In statistical terms, ‘interaction’ is used in reference to departure from the normal underlying form of a statistical model, and unfortunately as there are numerous statistical models available, interaction does not have a consistent universal meaning. In epidemiological terms this situation is known as ‘effect-measure modification’ in which a measure of effect changes over values of some other variable. A statistical interaction therefore should not be confused with a biological interaction. A biological interaction between two causes occurs whenever the effect of one is dependent on the presence of the other, for example the development of melanoma among individuals with high level exposure to ultraviolet light who also have fair skin. Dark skin is protective against the adverse effects of ultraviolet light exposure, whereas those with fair skin experience a much greater risk, or are ‘susceptible’ or ‘predisposed’ to ultraviolet light exposure (Rothman, 2002).

2.7.2 Understanding interactions between risk factors

Conditions such as OA are often the result of interplay between causes (Felson, 2013). One cause, a major knee injury for example, when combined with older age at the time of injury is more likely to result in KOA than a major injury itself (Roos et al., 1994). Overweight young people have a modest risk of KOA, this KOA risk is substantially increased in those who are older and overweight, and the risk is further increased if the person is female (Felson, 2013).

Interactions between risk factors for OA are not yet fully understood (Lohmander and Felson, 2004). In the context of KOA risk factors many outstanding questions remain. For example, if a 'background' rate of progression (or incidence) of KOA is assumed in the general population, what effect is caused by adding a specific risk factor such as risk of obesity or knee mal-alignment? Would the proportion of the population starting the OA process increase, and the rate of progression remain unchanged in the presence of these risk factors? Or could the addition of specific risk factors change the background rate of disease progression? Could certain risk factors for KOA only become active in specific environments, for example in the presence of other risk factors? The answers to the questions are not yet known and demonstrate a critical gap in the knowledge of understanding risk factors and the relationships between them which is vital for developing effective ways of treating and managing KOA.

2.7.3 Alignment & body mass interaction in KOA

How knee alignment and body weight interact on progression of KOA is a topic of interest. Although the association between BMI and KOA progression is currently inconsistent (Belo et al., 2007, Niu et al., 2009, Reijman et al., 2007), maligned knees are at a higher risk of KOA progression (Brouwer et al., 2007, Sharma et al., 2001, Sharma et al., 2010, Tanamas et al., 2009). It is thought that when the two exertion forces, overweight and mal-alignment, are present in one knee then there could be an increase in KOA progression (Yusuf et al., 2011). Greater varus alignment is consistently reported to be strongly associated with KOA progression (Brouwer et al., 2007, Sharma et al., 2001) but the effect of body mass is less clear and may depend on the extent of mal-alignment (Felson et al., 2004, Niu et al., 2009, Reijman et al., 2007).

A possible biomechanical hypothesis is that alignment and body mass combined produce interaction effects on knee joint loading, in particular a greater body mass may modify the well-established association between alignment and medial compartment loading of the knee joint. Should a significant interaction exist, those with mal-alignment and increased body mass would be at greatest risk for KOA progression. However, the current literature on the effect of obesity on KOA progression in those with mal-alignment is inconsistent (Felson et al., 2004, Niu et al., 2009, Sharma et al., 2000). Sharma et al (Sharma et al., 2000) reported BMI was related to OA severity in knees with varus mal-alignment. Felson et al (Felson et al., 2004) report that KOA progression was affected by BMI in knees with moderate (3° - 6°) but not severe ($\geq 7^{\circ}$) varus or valgus mal-alignment. Whereas, a study by Niu and colleagues reported that obesity had no effect on radiographic progression in varus aligned knees but it did effect progression in neutral or valgus aligned knees (Niu et al., 2009).

One of the few studies to test for interaction between HKA angle alignment and body mass on knee joint load (measured by KAM) in KOA is by Moyer and colleagues (Moyer et al., 2010). This group found the association between frontal plane alignment and medial compartment load during walking depends on mass, with a higher association seen in those with a greater mass. For example, in the highest mass tertile, there was a 3.2 N m (approximately 6% of the mean value) increase in KAM for every 1° increase in varus alignment. If the effects of mal-alignment are made worse by obesity, then mal-alignment may only really be of importance in those who are overweight. Unfortunately these cross-sectional study results cannot determine the direction of relationships: is it that obesity contributes to knee mal-alignment which contributes to KOA? Or, is it that obesity leads to KOA and knee mal-alignment develops as a consequence? These questions can only be answered with longitudinal studies containing knee alignment, body weight and KOA outcomes at a range of time points which the Chingford cohort is able to provide.

The study by Niu and colleagues identified the association between BMI and KOA progression could be modified by knee alignment status (Niu et al., 2009). When examining knees of very obese subjects, a higher risk of KOA progression was seen in those with neutral but not varus or valgus knee

alignment, although overall no association between BMI and KOA progression was reported in this study.

In comparison, Yusuf and colleagues have recently published their study showing both obesity and mal-alignment were associated with KOA progression, and that mal-alignment modified the obesity and KOA progression association in some amount (Yusuf et al., 2011). The main differences between these two studies that may explain their differing results may be due to: a greater percentage of overweight patients (84%) in the Niu study compared to 66% in the Yusuf study; differing starting points at baseline - Yusuf study investigated KOA progression in baseline knees with K&L score ≥ 1 and moving from K&L grade 1 to 2 was characterised as progression, whereas in the Niu study this move in K&L grade was characterised as incidence of KOA. In a sensitivity analysis with K&L ≥ 2 knees in the Yusuf study, obesity was still associated with KOA progression with smaller risk ratios and overweight remained positively associated although the association was no longer significant. A higher BMI was associated with KOA progression among varus knees but not in normal or valgus knees within this sensitivity analysis subgroup. The lack of association in the normal or valgus obese knees may be due to small numbers in the obese category, but these results contrast with Niu's study who did not report an association between obesity and KOA progression in varus knees. Niu's group measured knee alignment using the HKA angle on FLRs, whereas Yusuf's group measured the FTA on SLRs and whilst they used a 4° valgus offset these two alignment measurement techniques are not strictly comparable.

Niu's study did report an association between obesity and KOA incidence (K&L grade ≥ 2 at 30 months follow-up) in varus knees with K&L grade ≤ 1 at baseline. From this they suggested that the effect of varus alignment alters across the different stages of OA, with varus alignment having a smaller role in OA incidence than obesity, but it may drive OA progression more than obesity. However, this may not be the case as the study by Yusuf still found an association between obesity and KOA progression in varus knees with K&L grade ≥ 2 at baseline. All in all this is a grey area and further studies in risk factor interaction are warranted to determine whether the influence of obesity on KOA progression acts largely through mal-alignment thereby clarifying the relationship between obesity, knee alignment and KOA.

Due to their contributions to increase joint loading (Brouwer et al., 2007, Felson et al., 2004, Reijman et al., 2007, Niu et al., 2009, Sharma et al., 2000, Sharma et al., 2001) it appears that mal-alignment and obesity are two potent KOA progression risk factors that may have a synergistic relationship, and it is likely that there may be more risk factors that follow suit (Hunter et al., 2009b).

Other knee alignment studies also suggest interaction effects. The effect of muscle strength on KOA progression (Sharma et al., 2003) and the effect of strengthening interventions on pain relief (Lim et al., 2008b) are dependent on knee alignment. Sharma's group suggest that there is a greater KOA progression risk in those with mal-aligned knees and higher strength, compared to those with lower strength (Sharma et al., 2003). In Lim's more recent RCT the benefits of quadriceps strengthening on knee pain were greater in those with neutral alignment (Lim et al., 2008b). These results highlight the importance of studying risk factors in combination in order to stratify appropriate treatment options, as it appears that not all interventions will have a beneficial effect on all patients.

A better understanding of how risk factors interact could lead to identifying which type of person with KOA will benefit most from which type of treatment. There is very little research in the area of risk factor interaction and as to how these risk factors may combine to affect the risk of KOA.

2.7.4 Interaction summary

- Better understanding of interactions between risk factors for OA should help with targeting appropriate treatments.
- Interaction between knee alignment and BMI on the associations with SRKOA, RKOAs and knee pain will be examined.

2.8 Main thesis aim

Overall this thesis aims to closely examine knee alignment and body mass as separate risk factors in the development of KOA, and then examine their interaction. The research hypothesis central to this thesis and underpinning the basis of this work is therefore:

H₁: 'Knee alignment, body mass and their interaction is clinically relevant in KOA'

H₀: 'Knee alignment, body mass and their interaction is not clinically relevant in KOA'

2.9 Thesis objectives

The main aim of this work is to determine the epidemiology and interaction of knee alignment and body mass in females with KOA. In order to achieve this aim, the main objectives are:

- 1) To complete pilot studies examining anatomic axis (AA) knee alignment methods using new KneeMorf alignment computer software (chapter 4).
- 2) To examine knee alignment cross-sectional associations with KOA (chapter 5).
- 3) To determine the natural history of knee alignment and longitudinal associations with KOA (chapter 6).
- 4) To determine the natural history, cross-sectional and longitudinal associations of body mass with KOA (chapter 7).
- 5) To determine the cross-sectional interaction between knee alignment and body mass on KOA (chapter 8).

2.10 Structure of thesis

The thesis takes the following structure:

Chapter 1 – Introduction

Chapter 2 – Background and literature review

Chapter 3 – Methodology

Chapter 4 – Alignment pilot studies

Chapter 5 – Knee alignment cross-sectional associations with KOA

Chapter 6 – Natural history and longitudinal associations of knee alignment with KOA

Chapter 7 – Natural history, cross-sectional and longitudinal associations of body mass with KOA

Chapter 8 – Cross-sectional interaction between knee alignment and body mass on KOA

Chapter 9 – Discussion, conclusions and future research

2.11 Scope of thesis

All the remaining Chingford cohort women were invited to attend the Silverthorn Osteoporosis Centre in Chingford, Essex for a one-off year 20 (Y20) study visit. This clinic visit data were collected over an 18 month period from April 2009 to December 2010 by the author and together with conclusions, is submitted for candidature of Doctor of Philosophy. The baseline (year 1) (Y1) to year 15 (Y15) follow-up data used for the longitudinal evaluation of knee alignment and body mass has previously been collected and published extensively and is not presented as the author's own work.

3. Chapter 3: Methodology

3.1 Introduction

This chapter details the research methodology for the objectives and data collection in the five studies that form this thesis.

3.2 Main thesis aim & objectives

The overall aim of this thesis was to determine the epidemiology and interaction of knee alignment and body mass in females with KOA. This was achieved through the completion of five separate studies, the main objectives of which were as follows:

- 1) To complete pilot studies examining AA knee alignment methods using new KneeMorf alignment computer software (chapter 4).
- 2) To examine knee alignment cross-sectional associations with KOA (chapter 5).
- 3) To determine the natural history of knee alignment and longitudinal associations with KOA (chapter 6).
- 4) To determine the natural history, cross-sectional and longitudinal associations of body mass with KOA (chapter 7).
- 5) To determine the cross-sectional interaction between knee alignment and body mass on KOA (chapter 8).

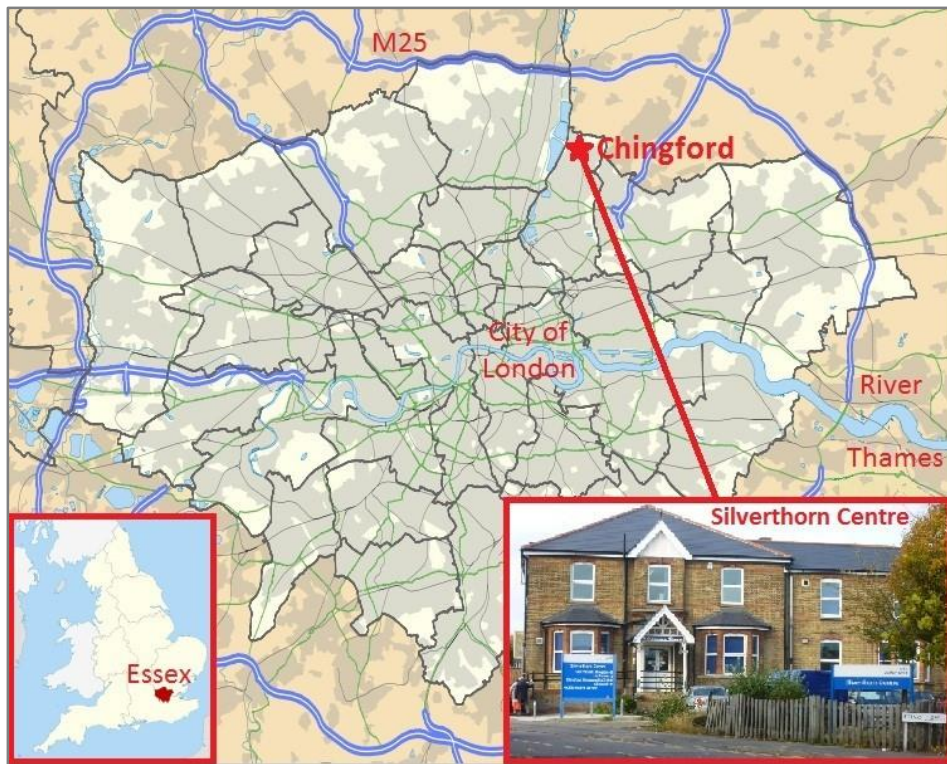
3.3 Study design

A well-characterised female cohort with 19 year follow-up was used.

3.3.1 The Chingford 1,000 Women Study

This research utilises the well-known prospective population-based cohort of the Chingford 1,000 Women Study from in Chingford, Essex, north-east London UK (Figure 20).

Figure 20: Chingford study location map

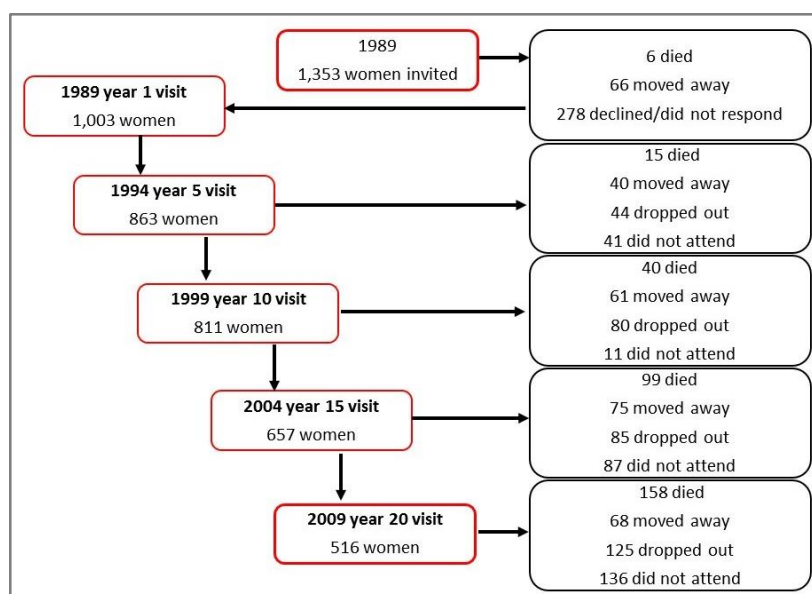


Established in 1989, the Chingford study was first set-up as a retrospective case-control study of middle-aged women from the general population to determine prevalence rates, and to assess known risk factors and their associations firstly for osteoporosis (OP) and subsequently for OA.

It has since become a longitudinal cohort of women seen annually for the first 10 years (no visit at year 7), then five yearly at 15 and 20 years. These Chingford women have been extensively phenotyped, and described in detail previously in over 70 publications. This cohort is listed by the American National Institute of Health (NIH) as an important epidemiological resource and one of few such cohorts with wide-ranging musculoskeletal data.

In 1989, all 1,353 women aged 45 – 64 years old from a large general practice register of more than 11,000 patients in Chingford, were invited to participate. Of the 1,353 women invited, 1,003 agreed to participate giving a response rate at initial recruitment of 78% ($1003/1281 \times 100$) as shown in Figure 21.

Figure 21: Chingford Women's Study attendance at 5 year intervals



These women have been seen regularly with follow-up visits at year 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 13 and 15. To summarise, existing data includes: anthropometry measurements; blood pressure; grip strength; get up and go test; DEXA scans of hips, spine, and whole body; radiographs of knees, hips, hands, spine and feet; serum biochemistry and genetic markers; extensive medical, reproductive, family, general health and lifestyle histories taken at various time points over the last 15 years (appendix A1).

The year 2009 saw the start of the Y20 follow up visit for this cohort of women. The author was involved in the organisation, running and data collection for this visit. For the remaining cohort women, the Y20 follow up visit entailed attendance at a one-off weekly run clinic at the Silverthorn Osteoporosis Centre in Chingford, Essex (Figure 20), for a physical joint examination assessment of knees, hips and hands (collected by author); anthropometry measurements including height, weight, waist / hip / thigh / quadriceps circumferences; radiographs of knees, hips and hands (knee alignment measured by author); and completion of a self-administered musculoskeletal questionnaire (checked for completion by author).

By this time 158 women had died, 68 had moved away, 125 women had dropped out and 136 did not attend the Y20 study visit, leaving a total of 516 women. This was an adjusted response rate (total baseline study population

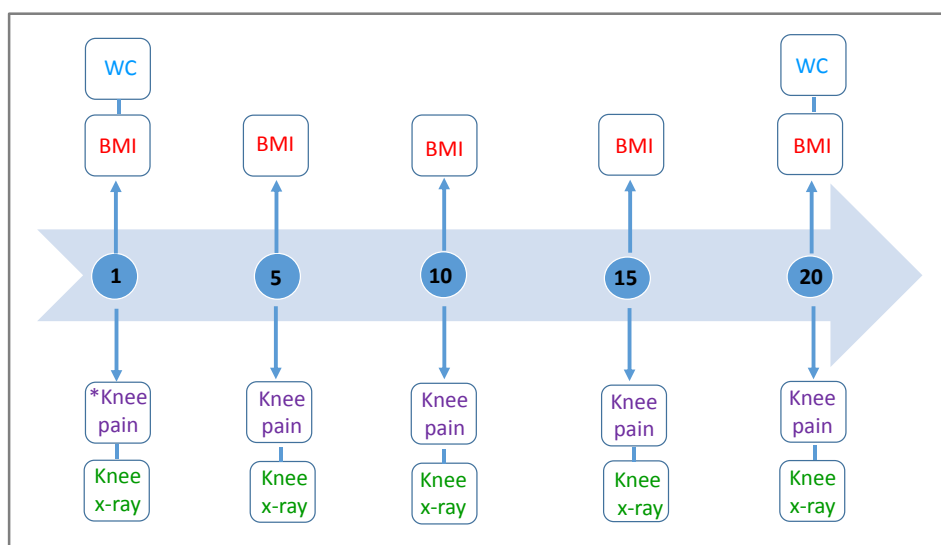
minus women who could no longer participate i.e. 1003 women minus 158 deaths = 845, $516/845 \times 100$) of 61%.

Considering this was now a 20 year cohort, having over half of the original cohort of women attend the Y20 clinic visit was an excellent response. Reasons for attaining such a good response include the close location of the clinic, continuity of well-prepared staff, care and preparation for each visit, and close GP liaison. The women participating in this cohort study are representative of the general UK female population in terms of height, weight and rates of hysterectomy, but with a lower percentage of current smokers (Hart et al., 1994, Hart and Spector, 1993a). They are also flagged so that their deaths, and any cancers that may develop, are tracked and reported by the Office of National Statistics (ONS).

The Y20 follow up visit data combined with the previous 19 year data are invaluable to study the longitudinal associations and interactions of knee alignment and body mass on KOA. The author was involved in the organisation, running and data collection of the Y20 clinic follow-up visit. The baseline and 14 year follow-up data used within this thesis to allow longitudinal data analysis (see Figure 22 for an overview) was completed by previous researchers and should not be considered as part of the author's own work.

Figure 22: Chingford visit year timeline

Where BMI=body mass index; WC=waist circumference; *Person level knee pain only.



3.3.2 Study approvals

Full ethical approval was originally obtained for the start of this cohort study in 1989 from the local research ethics committee at Redbridge and Waltham Forest (reference number: LREC R&WF 96). The baseline clinic visits began in July 1989. In addition to the measures approved in the initial application, an extension of the methodology to include physical examination measurements at the Y20 clinic visit was sought via a first substantial amendment application dated 2/12/08 (appendix A2) and a second substantial amendment application, to include some additional physical performance measures, dated 23/3/09 (appendix A3). Ethical approval was received by the Outer North East London Research Ethics Committee for substantial amendment 1 on 22/1/09 (appendix A4) and for substantial amendment 2 on 14/5/09 (appendix A5). Full approval from the local research and development department at Whipps Cross Hospital was also obtained on 5/2/09 for substantial amendment 1 (appendix A6) and on 11/5/09 for substantial amendment 2 (appendix A7). Honorary contracts were provided to cover the author for data collection as a research assistant at Whipps Cross University Hospital NHS Trust (appendix A8) & at Kings College Hospital London (appendix A9).

3.3.3 Recruitment strategy

Once the study approvals were in place, all remaining Chingford cohort study women (n=845) were posted a study information sheet (appendix A10) to read, containing an outline of the proposed Y20 clinic visit. The Chingford study coordinator (MD) then contacted each of the remaining women by telephone to see if they would like to participate in the Y20 clinic visit, and if so a mutually convenient attendance date was arranged to attend the Silverthorn Osteoporosis Centre, Chingford Essex (Figure 20). If participation in the Y20 visit was declined (n=136), the women were asked if they would like to complete and return the musculoskeletal questionnaire by post (n=49).

3.3.4 Consent

For the 516 women who attended the Y20 clinic, written consent (appendix A11) was obtained on the day of attendance at the Silverthorn Osteoporosis Centre in Chingford. At the time of obtaining written consent, the study visit protocol was reviewed face-to-face with the participant to ensure full

understanding of its requirements and to allow the opportunity to discuss any concerns or questions. Participants were reminded that withdrawal from the study was possible at any time and that this would not affect their routine clinical care. Following completion of the consent form, two photocopies of the form were taken, one provided to the participant, the second inserted in their medical notes, and the original copy of consent was filed in the site file in accordance with ICH GCP (International Conference of Harmonisation Good Clinical Practice). Verbal and written consent was also obtained from participants who agreed to have photographs taken during the Y20 clinic visit (appendix A12).

3.3.5 Withdrawal of participants

Participants had the option to withdraw from the study at any time, without having to provide a reason for doing so. All participants were reminded of this withdrawal option at the time of consent and that withdrawal from the study would not affect their routine clinical care. There were no withdrawals.

3.3.6 Publicity

Prior to starting the Y20 data collection, all Chingford cohort women were sent a Y20 newsletter (appendix A13). This newsletter was created by the Y20 Chingford study team to give an overview of what the Y20 clinic visit would entail, a resume of each Y20 study team member and details of recent publications using Chingford study data. It also contained advice on exercises and lifestyle changes that would help to keep the women healthy and reduce the risk or effects of OP and OA.

The newsletter also provided details of the 20th year anniversary tea party that was to be held at the Sir James Hawkey Hall in Woodford Green, Essex on Thursday 24th June 2010. This was certainly an afternoon to remember for the attending 350 Chingford study women (Figure 23). An extra special afternoon tea was provided with an outstanding selection of over 50 different types of dessert; a raffle with gifts and tokens donated from local stores, boutiques and restaurants; music provided by one of the local school jazz bands; and entertaining speeches provided by Professors Tim Spector and Nigel Arden. The study team put together a series of poster presentations shown at the tea party detailing the Y20 clinic visit (appendix A14a - f). This was an excellent

opportunity for the Chingford women to meet the Y20 study team and for the study team to thank the Chingford women for their invaluable participation over the last 20 years.

Figure 23: Y20 tea party photographs



3.3.7 Study funding

Throughout its lifetime the Chingford study has been generously financially supported by Arthritis Research UK (<http://www.arthritisresearchuk.org/>).

3.3.8 Data management

Data collection was conducted in adherence to the Data Protection Act 1998 and the NHS code of confidentiality. Participant paperwork was anonymised at the time of recruitment, using an alpha-numerical code which was then used on all subsequent study documentation. All hard copy data and anonymisation details were kept in a locked cabinet or on encrypted, password protected hardware/software. Access to confidential information was only granted to recognized persons for monitoring/audit/quality assurance purposes.

3.4 Study population

The overall population of interest within this thesis comprises Chingford study women with and without KOA. The inclusion and exclusion criteria for the studies contained in this thesis were defined as follows:

3.4.1 Inclusion criteria

- Any female who had previously participated in the Chingford 1,000 Women Study.

3.4.2 Exclusion criteria

- Unable or unwilling to provide informed consent.
- Unable to comply with study protocol due to a serious medical or psychological disorder.
- Any history of the following medical conditions (total n=64 excluded women from the Y20 visit):
- Any history of an inflammatory condition e.g. rheumatoid arthritis (n=19), systemic lupus erythematosus (n=2), psoriatic arthritis (n=1), ankylosing spondylitis.
- Any history of a crystal arthropathy e.g. gout or pseudo-gout (n=6).
- Any history of a neurological condition e.g. cerebro-vascular accident (n=13), Parkinson's disease (n=3), multiple sclerosis (n=1), cerebral palsy (n=1), chronic inflammatory demyelinating polyneuropathy (n=1), poliomyelitis (n=3).
- Any history of metabolic bone disease e.g. osteomalacia, Paget's disease (n=1).
- Any history of polymyalgia rheumatica (n=11) or fibromyalgia (n=2).

3.4.3 Bias

It is possible that a number of biases inherent to this study design could occur. Bias may refer to an attitude on the part of the investigator, but it is also used to describe any systematic error that occurs within a study (Rothman, 2002). Analyses were performed throughout this thesis to assess the prevalence of bias, for example comparisons between included and excluded populations, and use of sensitivity analyses where appropriate.

3.5 Data collection

Data collection for the Y20 clinic visit began in April 2009 and was completed by November 2010. Over these 19 months, all 516 participants attended a weekly held Y20 study visit clinic at the Silverthorn Osteoporosis Centre, Chingford Essex (Figure 20). The anthropometry measurements were collected following the standard operating procedures (SOPs) (appendix A15), that had been used for previous study clinic visits. The musculoskeletal questionnaire that was posted out to each participant with their study clinic appointment was collected and checked for completeness by the author. All Y20 hip, knee and hand radiographs were taken using an on-site mobile imaging unit by a private company called In Health. Further detail of the Y20 data collected now follows.

3.5.1 Anthropometry measurements

3.5.1.1 Weight

Weight was measured with shoes and outer heavy clothing removed in a seated position (Figure 24) by electronic scales (Marsden weighing company) used at previous visits (SOP appendix A15). Weight was measured once in kilograms to the nearest 0.1 kg and recorded on the data collection form (DCF) (appendix A16).

Figure 24: Photograph of weight measurement



3.5.1.2 Height

Height was measured in a standing position, shoes removed, using a wall-mounted stadiometer (Leicester Height Measure, SECA) which had been used at all previous clinic visits (Figure 25). During the measurement, the head was kept in the Frankfurt plane - a horizontal imaginary line joining the upper margin of the external auditory meatus and the lower border of the eye (SOP appendix A15). Height was measured once in centimetres to the nearest 0.1 cm and recorded on the DCF (appendix A16).

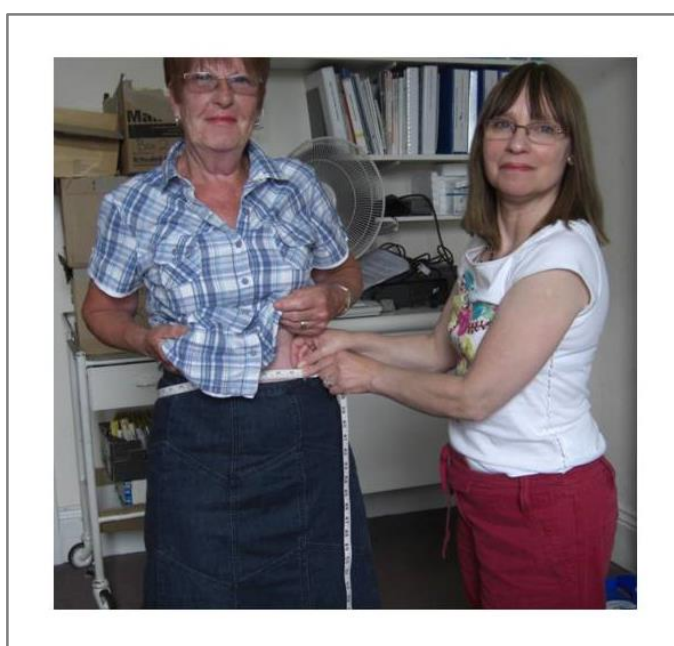
Figure 25: Photograph of height measurement



3.5.1.3 Waist circumference

Waist circumference was measured following the same protocol (Lohman et al., 1988) as previous visits at years 1 to 4 (SOP appendix A17). It was measured in a standing position at the narrowest point between the iliac crest and lower edge of the ribs (Figure 26). A standard tape measure was used and held horizontally around the participant ensuring there was no skin indentation, and all measurements to the nearest 0.1 cm were recorded on the DCF (appendix A16).

Figure 26: Photograph of waist circumference



3.5.2 Musculoskeletal questionnaire

The Y20 musculoskeletal questionnaire (appendix A18) was devised to include well known and validated questionnaire tools, combined with a selection of questions that had been completed at previous study visits thereby allowing longitudinal comparisons to be made. The knee pain questions were the sections relevant to this thesis. As knee pain is an individual experience and can present in many different forms, it was important to standardize the approach to this experience to ensure that it was measured accurately between studies and time points.

The NHANES is a program of studies designed to assess the health and nutritional status of adults and children in America. The survey is unique in that it combines interviews and physical examinations. It began in the early 1960s and continues today, examining a nationally representative sample of about 5,000 people each year. Findings from this valuable survey are used to determine the prevalence and risk factors for major diseases. One of the first publications involving KOA from this survey was in 1988 by Andersen & Felson who reported on obesity, ethnicity and occupational risk factors associated with KOA (Anderson and Felson, 1988). This publication was one of the first to define knee pain on interview, and over the course of the NHANES study this has become a standard knee pain question which is also now used in the majority of epidemiological KOA studies:

‘Have you ever had pain in or around your knee on most days in the last month?’

This question was therefore included for each knee in the Y20 questionnaire (Q35 & Q36 appendix A18). At previous Chingford clinic visits similar knee pain questions were asked for each knee at Y5, Y10 and Y15, albeit in a slightly different format:

Q1) ‘Have you had knee pain in either knee in the last month?’

A1) Yes or no.

Q2) ‘How many days of knee pain have you experienced in the last month?’

A2) 1-5 days, 6-14 days or 15+ days.

For continuity and for consistency checks with the NHANES knee pain question above, these two knee pain questions were also included in the Y20 questionnaire (Q34b & Q34c appendix A18). Those responding “yes” who also reported “15+ days” of knee pain were classified as positive for knee pain in that knee.

At the baseline Y1 clinic visit the knee pain question asked was:

‘Ever had knee pain for more than one month?’

Therefore, Y1 knee pain was classified as positive for both right and left knees if ‘yes’ was reported as it was not possible to identify knee specific pain from this question. This person level knee pain variable refers to pain lasting more

than one month, as opposed to equal to or more than 15 days for the knee pain variables at Y5, Y10, Y15 and Y20. Therefore although these may not be strictly comparable, the possible over-reporting of knee pain at Y1 is a limitation to the Y1 baseline data.

3.5.3 Knee radiographs

AP fully- extended weight bearing bilateral knee radiographs were taken at previous clinic visits at years 1, 5, 10, and 15, therefore comparable radiographs were taken at the Y20 clinic visit. Radiographs of both knees for each participant present at each visit were taken by experienced radiographers using the same equipment at years 1, 5, 10 and 15. The Y20 radiographs were taken digitally by an on-site mobile imaging unit. A standardized protocol was established at the Y1 visit which was then repeated for all subsequent radiograph visits. The back of the knee was kept in contact with the cassette, the patella was centred over the lower portion of the femur and the tibial tubercles faced forward. A 100cm tube-to-film distance was used, with the beam centred 2.5cm below the apex of the patella (Hart et al., 1999).

Previous radiographs were scored using the K&L global scoring system (Kellgren and Lawrence, 1957) (section 2.2.3.1) where:

- Grade 0 = normal;
- Grade 1 = possible osteophyte, no JSN;
- Grade 2 = definite osteophyte, possible JSN;
- Grade 3 = multiple osteophytes, definite JSN, sclerosis and possible deformity of bone ends;
- Grade 4 = large osteophytes, marked JSN, severe sclerosis and definite deformity of bone ends.

RKOA was defined present in knees with K&L grade 2 or above. Each knee radiograph was also graded with scores ranging from 0 = none, 1 = mild, 2 = moderate or 3 = severe for osteophytes and JSN in the medial and lateral compartments using the Chingford Atlas (Burnett et al., 1994). Osteophytes and JSN were considered present in knees with grade 1 or above (Spector et al., 1993).

TKRs and uni-condylar knee replacements (UKRs) were identified by a combination of self-report and GP records, and further confirmation obtained

on review of the radiograph. Radiographs were read individually by visit year and were blinded to order, patient identity and symptoms. Y1 and Y5 radiographs were read by the same two observers (TDS and DH), Y10 and Y15 radiographs were read by a single observer (DH). Inter and intra-observer reproducibility have been reported previously and were calculated by reading a subset of 100 knees for K&L grading with a three week interval. Kappas for intra-observer reproducibility were 0.88, (95% CI 0.87 - 0.89) and 0.79 (95% CI 0.78 - 0.80). Inter-observer reproducibility was also high with a kappa of 0.80 (95% CI 0.79 - 0.81) (Spector et al., 1993).

The Y20 radiographs were read for K&L grading by one observer (KL). The short term (after 1 day) and the long term (after 10 days) intra-observer reproducibility for the Y20 K&L grading by KL were both high with linear weighted kappas of 0.80 (standard error (SE) 0.09) (Leyland, 2012). KL also compared inter-observer reproducibility with original K&L grades from DH using 25 radiographs from Y15. The percent agreement of 85% and a linear weighted kappa of 0.54 (SE 0.13) showed acceptable agreement given the different reading conditions as DH was grading plain-film radiographs and KL was grading the same radiographs but digitised with access to contrast enhancements and zoom (Leyland, 2012).

Due to previous underestimation of JSN in fully extended views for KOA assessment, current opinion now promotes semi-flexed knee radiograph views (Buckland-Wright et al., 1999) and fluoroscopy-assisted positioning (Mazzuca et al., 1997, Buckland-Wright et al., 1999). However, all knee radiographs in the Chingford Study were taken in a fully extended weight-bearing AP position. Although this may now not be the current preferred radiographic view option, it is common for long-term cohort studies to continue using the same radiographic protocol as used at the baseline visit to allow change to be measured over time.

3.5.4 Measuring knee alignment

3.5.4.1 Manual measurement

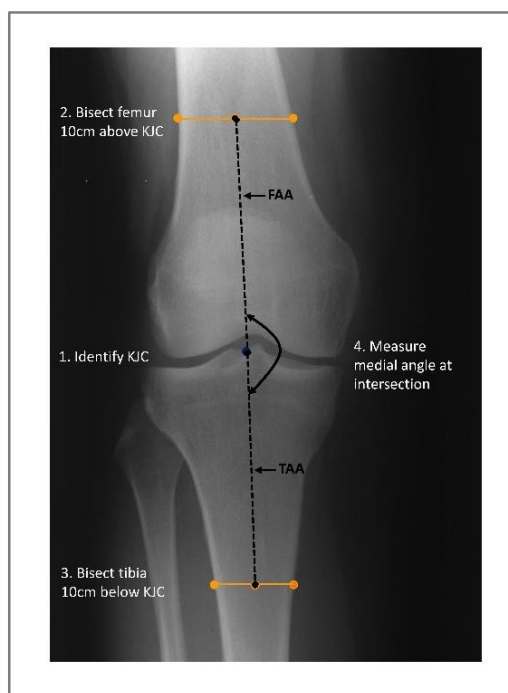
Traditionally, knee alignment measurements have been taken by hand. This requires the observer to draw axis lines representing the femoral and tibial MA or AA on the radiograph and to manually measure the resulting angle with a

hand-held goniometer as shown in Figure 27 for AA alignment measurement on a SLR.

Manual alignment measurement is usually performed on top of an x-ray light box. To avoid marking the plain film radiograph, a transparent sheet is placed on top of the radiograph, which can slip if not secured on the radiograph properly, and/or the radiograph can slip on the light box, invalidating the measurement and requiring the timely process to be repeated. With a goniometer angle measurement is limited to the nearest 1° or 0.5° at best, and the whole alignment measurement takes a minimum of 15 minutes for one knee making manual data collection very time consuming.

Figure 27: Anatomic axis alignment measurement using a goniometer

Where FAA=femoral anatomic axis; KJC=knee joint centre; TAA=tibial anatomic axis.



3.5.4.2 KneeMorf software

To overcome the inaccuracies and time consumption of the manual knee alignment measurement, the 'KneeMorf' software tool was developed. This provides an efficient and accurate way for an observer to plot points with a computer mouse on a digital SLR image to collect a variety of quantitative measurements commonly used in KOA research. Other CAA programs do not provide comprehensive data on both AA alignment and corresponding knee

joint surface orientation measurements, but KneeMorf has the unique capacity to provide both on digitised plain film images and on digital images. It also features a novel method of recording joint space width (JSW) using Bezier curves, with additional functionality to record semi-quantitative radiograph scoring methods such as K&L and OARSI grades.

The KneeMorf software was developed by a team of researchers at the University of Oxford: Professor Nigel Arden (NA) and Dr Kassim Javaid (KJ) were principal investigators, Dr Richie Gill (RG) was technological lead, Dr David Hunter (DHU) was image specialist engineer and Dr Kirsten Leyland (KL) was project manager (Leyland et al., 2011a, Leyland et al., 2011b, Leyland et al., 2013). The author (LG) and orthopaedic research fellow Dr Nicholas Bottomley (NB) were involved in designing the knee alignment measuring aspect of the program, and through a series of pilot studies (in chapter 4) the author has evaluated and tested the alignment functionality of the KneeMorf program.

The KneeMorf program has been designed for flexibility. It uses Python programming language software (version 2.7) and Structured Query Language (SQL) database management system (version 5.1) which are both open-source, allowing it to be widely accessible to researchers. Using Matlab R2011a program (version 7.12), the raw data points exported from KneeMorf are calculated into final measurements and angles, which can then be exported into a Microsoft Office Excel spreadsheet for analysis.

As there is currently no gold standard method for measuring AA alignment on a SLR, a total of six, three 1P (Figure 28a-c) and three 2P (Figure 28d-f) methods of measuring AA were tested using three different tibial KJCs:

- a) tibial spine base mid-point (KJC1)
- b) tibial spine tips mid-point (KJC2)
- c) tibial plateau centre (KJC3)

Figure 28: 1P and 2P method KJC locations

Where 1P=one point; 2P=two point; KJC=knee joint centre.

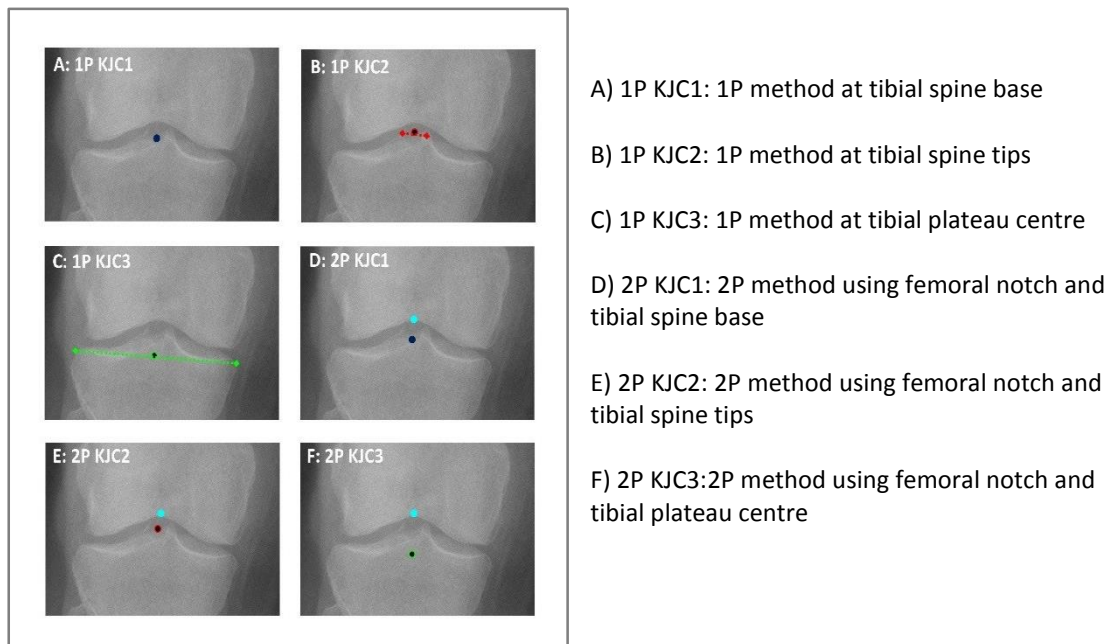


Figure 29 indicates the series of alignment points plotted on each knee radiograph by the observer (the author) using a computer mouse, further point placement details can be found in the KneeMorf alignment manual in appendix A19. A total of 40 points were plotted (this was increased to 100 points when different femoral and tibial shaft lengths were compared as in chapter 4 pilot studies) on each radiograph by the author. The subsequent rule lines generated by the KneeMorf program from these points are shown in Figure 30.

Figure 29: KneeMorf alignment plotted points

Where KJC=knee joint centre; 2P= two-point method.

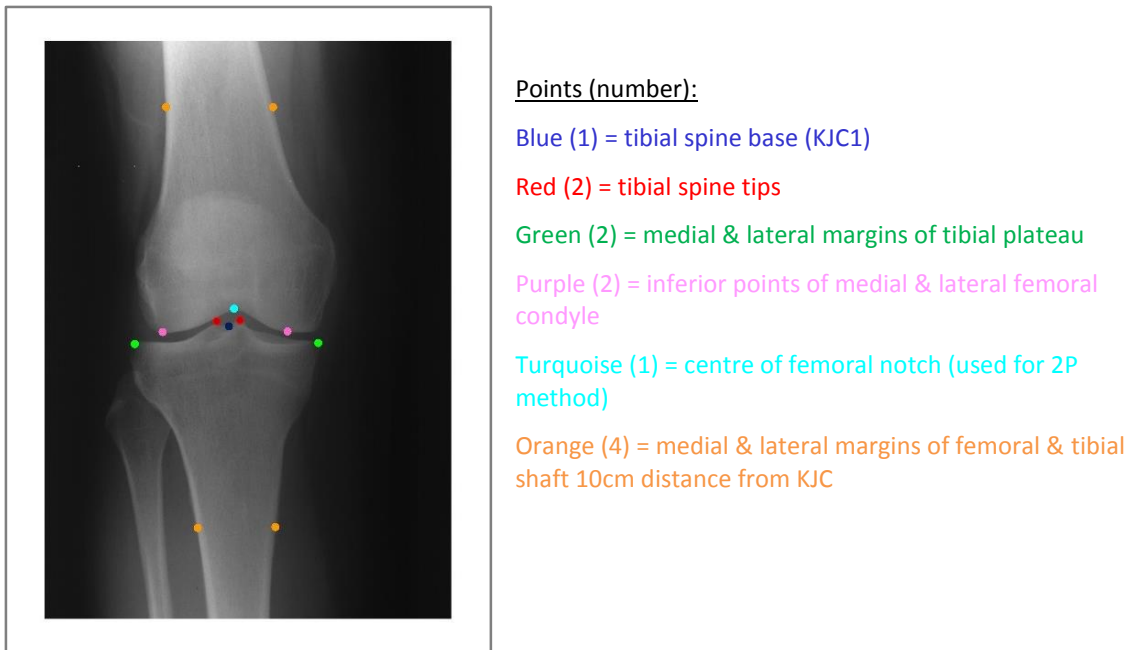
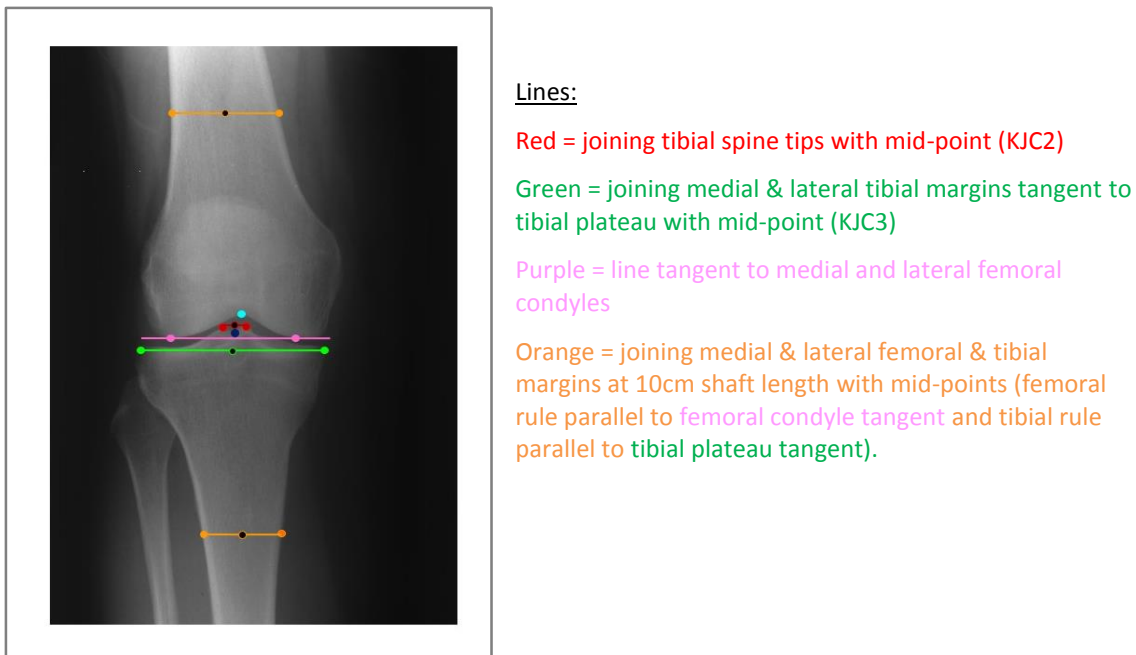


Figure 30: KneeMorf alignment generated rule lines from plotted points



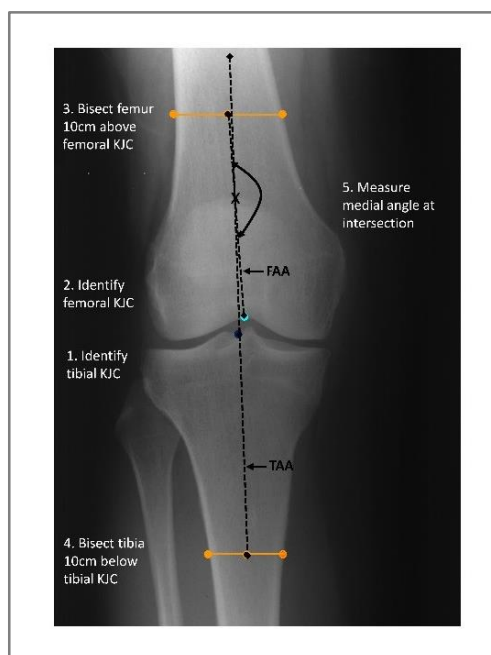
For the three 1P methods described in Figure 28a-c, the AA angle was formed between the FAA and TAA based on each of the KJC locations as shown in Figure 27.

For the three 2P methods described in Figure 28d-f, the AA angle was formed by two axes, the FAA originating from the femoral inter-condylar notch point

and the TAA originating from each of the KJC locations described previously. As the 2P method creates independent axes for the femur and the tibia, the intersection of these two axes lines may in some cases converge outside the knee joint as shown in Figure 31. In these instances a digital software Cobb angle tool was used to measure the angle of axial lines that do not intersect within the field of view of the SLR (McDaniel et al., 2010).

Figure 31: 2P anatomic axis alignment measurement

Where FAA=femoral anatomic axis; KJC=knee joint centre; TAA=tibial anatomic axis.



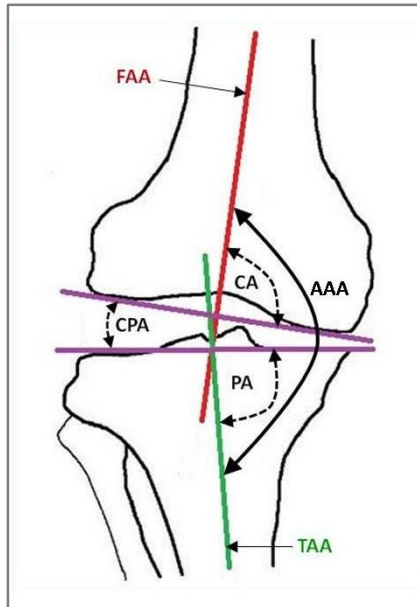
For both 1P and 2P methods the femoral shaft length guiding rule line was placed 10cm above the KJC location and parallel to the femoral condyle tangent line. The tibial shaft length guiding rule was placed 10cm below the KJC location and parallel to the tibial plateau tangent line. The end points for the femoral and tibial 10cm shaft length guiding rule lines were always placed on the outer femoral and tibial bone shaft cortex, all previously recommended by Wong and colleagues (Wong et al., 2009). Shaft length was also measured at 7cm above and below the KJC location for comparison of AA angles with 10cm shaft length in section 5.5.1.

The AA angle created by the intersection of the FAA and the TAA was measured medially and joint surface orientation angles were also calculated (Figure 32) using Matlab R2011a program (version 7.12). The final alignment

angle data were then available for analysis in the form of a Microsoft Office Excel spreadsheet.

Figure 32: KneeMorf derived alignment angles

Where FAA=femoral anatomic axis; TAA=tibial anatomic axis.



Anatomic axis angle (AAA) = medial angle of axes intersection ($<180^\circ$ = varus, $>180^\circ$ = valgus)

Condylar Angle (CA) = medial angle between FAA & femoral condyle tangent ($<90^\circ$ = varus, $>90^\circ$ = valgus)

Plateau Angle (PA) = medial angle between TAA & tibial plateau tangent ($<90^\circ$ = varus, $>90^\circ$ = valgus)

Condylar Plateau Angle (CPA) = angle between femoral condyles tangent & tibial plateau tangent (narrow medially = varus (-), narrow laterally = valgus (+))

All Y1, Y10 and Y20 SLRs (4492 radiograph images in total) were measured for AA alignment in batches of 50 images by the author. Y1 and Y10 images were plain film SLRs that were scanned on a digital scanner at 600 dots per inch (dpi) with a grey scale pixel depth of 16 bits. At Y20 digital images were taken, with inclusion of a Knee Images Digital Analysis (KIDA) wedge calibration object (Marijnissen et al., 2008). Pixel size for the digital images was determined using embedded DICOM information.

All images were read individually, in a random order and blinded to all clinical information over a six month period. All measurements were performed on one SLR before beginning measurements on another. Intra-reader agreement was examined and reported in section 4.3.2. Inter-reader agreement, although not required for this thesis as all images were read by the author, was also examined out of interest and reported in section 4.3.3.

To ensure the KneeMorf software was comparable to the traditional manual alignment method with a goniometer a further pilot study was completed and reported in section 4.3.1.

As the KneeMorf software has zoom in/out capabilities it allows accurate placement of bony landmarks on the digital radiograph images for alignment measurement. It is also much quicker in terms of time taking approximately 1.5 minutes per radiograph and all angles are measured to within 0.01°. It therefore made the task of measuring alignment on 4492 images much easier and more accurate than the manual method.

3.6 Outcome variables

The primary outcome variable in this thesis was SRKOA, RKOA and knee pain were secondary outcomes. As a large number of Y1 radiographs had tibial and/or femoral shaft lengths that were shorter than 10cm (discussed further in section 4.2.6), the Y10 clinic visit was used as the baseline time point for the alignment studies in chapter 5 (cross-sectional alignment), chapter 6 (longitudinal alignment) and chapter 8 (interaction). For chapter 7 (body mass) Y1 was used as the baseline time point to include waist circumference measurements.

3.6.1 SRKOA

SRKOA was classified positive in K&L grade 2 or above knees reporting ≥ 15 days knee pain in the last month. All remaining knees were classified SRKOA negative.

3.6.2 RKOA

RKOA was classified positive in knees with K&L grade 2 or above. All remaining knees with K&L grades 0 and 1 were classified RKOA negative.

3.6.3 Knee pain

Knee pain was classified positive if it was reported in the last month for ≥ 15 days. All remaining knees were classified knee pain negative.

3.7 Confounding variables

Confounding is the confusion, or mixing, of effects that provides an alternative explanation for an association between an exposure and an outcome

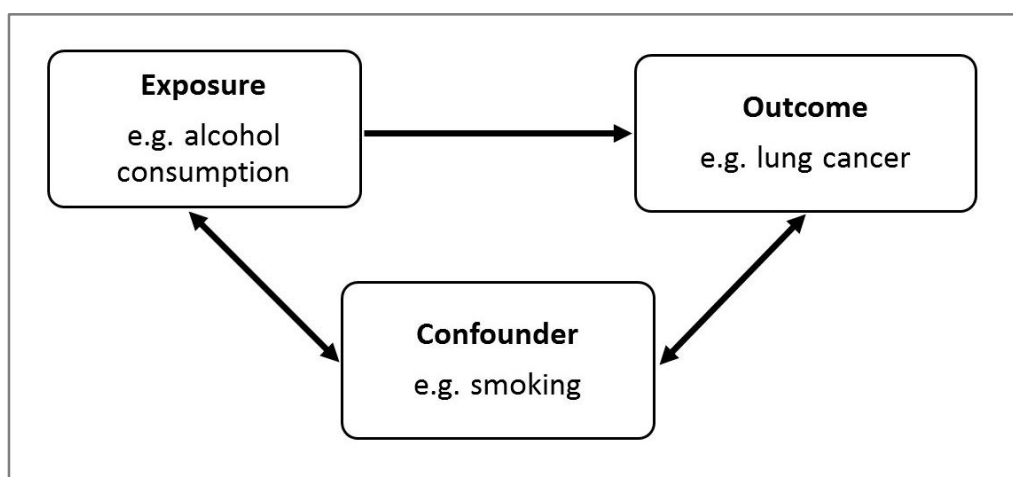
(Rothman, 2002). As Figure 33 demonstrates in order for a variable to be considered as a confounder, the variable:

- a) must be independently associated with the outcome e.g. be a risk factor
- b) must be additionally associated with the exposure under study
- c) must not lie on the causal pathway between exposure and disease.

In this thesis identification of possible confounding ‘third variables’ from the current literature included associated risk factors such as age, BMI and previous knee injury, and was completed as part of the statistical analysis. Adjustments were made for these confounders as part of the statistical analysis at Y10 for the cross-sectional alignment chapter 5 and longitudinal alignment chapter 6. Y10 age and knee injury were used for adjustments in the interaction chapter 8. Y1 age and knee injury were used for adjustments in BMI chapter 7.

Occupation was considered as a possible confounder, however this variable was only collected at Y1 and therefore unlike age, BMI and previous knee injury, was not available at the Y10 visit. At Y1, 32% of women reported having a secretarial occupation, 17% were retired and 15% were housewives, therefore given the nature of this middle-aged female cohort, occupation is unlikely to have influenced associations with knee OA.

Figure 33: The confounding effect



3.7.1 Age

Age was collected at each clinic visit as part of the self-administered questionnaire and was used as a continuous variable.

3.7.2 Body mass index

Body weight and height measurements were collected at each clinic visit as described earlier in section 3.5.1.1 and section 3.5.1.2 respectively. BMI in kg/m² was subsequently calculated (weight in kilograms divided by the square of height in metres) and used as a continuous variable.

3.7.3 Knee injury

As part of the self-administered questionnaire at the Y10 clinic visit the following question was asked ‘In the last year, have you injured your knees enough to rest them for at least one week?’ This information was combined with knee injury data collected previously at Y1 and Y2 clinic visits which asked the question ‘Have you ever injured your knees enough to rest them for a week?’ All knee injury questions were person-level therefore a cumulative person-level knee injury by Y10 yes/no variable was calculated.

3.8 Overview of statistical analysis

This section provides a simple overview of data preparation and subsequent statistical analysis techniques employed by the author in this thesis under guidance of an experienced team of statisticians (Maria Sanchez (MS), Stefania D’Angelo (SDA) and David Culliford (DC)).

3.8.1 Data preparation & analysis software

All data collected at the Y20 visit was entered into an Access 2007 database. A proportion (approximately 20%) of the collected data was entered twice by the author to check for inconsistencies, outliers and missing information.

The weight, height, waist circumference, knee pain questions and knee alignment variables were cleaned by the author. This involved consistency checks, with review of hard copy paper records or radiographs when discrepancies arose. Information confirmed as missing was annotated in the

database. The final Y20 dataset was joined to the previous 15 year dataset to allow longitudinal analysis.

All data were coded and analysed using Stata version 13.0 (Stata Corp, College Stations, Texas, USA). Normality of variables was assessed using visual inspection of histograms or scatter plots. The normality findings informed decisions regarding selection of parametric or non-parametric statistical analysis. All statistical tests conducted were two-tailed and at a significance level of 5%.

3.8.2 Descriptive statistics

The demographic and clinical characteristics of the study participants were presented as the mean or median, and standard deviation (SD) or inter-quartile range (IQR), dependent upon data distribution. Categorical variables were presented as a number and a percentage. Comparisons between included and excluded cohorts were examined using independent sample t-tests (or clustered t-tests when accounting for correlated knees was required) for normally distributed continuous variables, Kruskal Wallis tests for non-normal continuous variables, and chi-square tests for categorical variables.

Cross-tabulation, histograms, stacked bar graphs and box plots were used to describe the natural history of alignment and BMI variables over time.

3.8.3 Agreement statistics

Bland-Altman plots and associated parameters were used to assess agreement between two methods of clinical measurement (Bland and Altman, 1986). The mean difference between the two readings was calculated. Limits of agreement (LoA) were then created by adding and subtracting twice the SD of the mean difference. The SE of the mean was calculated to provide 95% CI for the likely mean disagreement between the two readings.

Intra-class correlation co-efficients (ICCs) were also used to establish intra- and inter-reader agreement (Shrout and Fleiss, 1979). An ICC ratio of 1 indicates perfect reliability with no measurement error, whilst an ICC of 0 indicates no reliability (Streiner and Norman, 2008).

3.8.4 Determination of associations

For Y10 cross-sectional and Y20 longitudinal alignment chapters 5 and 6 general estimating equations (GEE) were used to take into account the correlation between left and right knees in one individual (Zhang et al., 1996) with SRKOA, RKOAs and knee pain outcomes. These analyses were executed for varus and valgus alignment, with neutral alignment as the reference group. Odds ratios (ORs) (Figure 34) and their 95% CIs were calculated and analyses were adjusted for age, BMI and presence of knee injury. If right and left knees had been examined separately then statistical power would have been lost, therefore GEE was considered the optimal method to control for intra-pair correlation and was also consistent with previous and current alignment literature.

Figure 34: OR calculation

$$\text{Odds ratio} = \frac{(\text{number exposed in population A} / \text{number not exposed in population A})}{(\text{number exposed in population B} / \text{number not exposed in population B})}$$

An OR of 1 implies that the odds of exposure are the same amongst population A and population B, therefore there was no relationship between exposure and outcome being studied.

An OR greater than 1 implies that the odds of the outcome being studied in the exposed population is greater than the population not exposed, therefore the exposure is a potential risk factor.

An OR less than 1 implies that the odds of the outcome being studied in the exposed population is less than the population not exposed, therefore the exposure is a potential protective factor.

For body mass chapter 7 logistic regression analyses was used to study the association between Y1 BMI and WC with SRKOA, RKOAs and knee pain, adjusting for Y1 age and knee injury. Y1 cross-sectional and Y10 incidence longitudinal analyses were performed.

For the interaction chapter 8, GEE was performed to study the interaction between alignment and BMI on Y10 SRKOA, RKOAs and knee pain outcomes. These analyses were adjusted for Y10 age and knee injury.

Detailed statistical analysis is described further within each study chapter.

4. Chapter 4: Alignment pilot studies

4.1 Pilot study 1

4.1.1 Background

The AA alignment method using a 10cm shaft length was first described by Moreland and colleagues in 1987 (Moreland et al., 1987). Although regarded as a seminal alignment paper, there is little indication as to where the 10cm shaft length recommendation was derived from. Subsequently, studies examining AA alignment have used this 10cm shaft length as a standard measurement and usually opt to use the maximum shaft length possible if a 10cm shaft length is not available on the radiograph (Kraus et al., 2005, Zhai et al., 2007), which does not appear to have been previously validated. Therefore it is not known if this is comparable to using AA alignment measured at a 10cm shaft length.

In the current literature there are few studies that have used different shaft lengths to calculate knee alignment from digitised radiographs. Two studies use a longer than 10cm shaft length for comparison:

Chang and colleagues compared MA alignment on FLRs to AA alignment on SLRs using 10cm and 15cm shaft lengths, and reported that the 15cm shaft length had better correlation with the MA alignment suggesting a longer shaft length provides a more accurate estimation of MA alignment in their study population on healthy (45 female and 54 male) and KOA (52 female and 50 male) Asians from Korea (Chang et al., 2010).

Sheehy and colleagues compared MA alignment on FLRs to AA alignment on the same FLRs (as opposed to SLRs) using 10cm shaft length and a longer one-third femoral and tibial shaft length identified from splitting the femoral and tibial shaft lengths into thirds on the FLR (Sheehy et al., 2011). They reported that using shorter shaft lengths of 10cm and one-third to estimate MA alignment modestly weakened the relationship of AA with MA alignment compared to longer shaft lengths of half and two-thirds using 120 right knees from the MOST KOA cohort study population.

A third study by Wong and colleagues examined whether shorter shaft lengths of 5 – 7 cm versus a 10 ± 0.5 cm shaft length affect the precision of AA

alignment in a healthy (14 female, 2 male) and severe KOA (17 female, 13 male) Canadian population. They found using the shorter shaft length reduced AA angle precision on PA fixed-flexion SLRs (Wong et al., 2009).

As the Chingford study solely contains knee SLRs it is therefore only possible to measure AA alignment, meaning comparisons with MA alignment are not feasible. All Chingford SLRs are AP view, fully-extended knee radiographs, images taken in a different position and view to those used in Wong's study meaning direct comparisons to this study cannot be made. For this reason a first pilot study to examine the use of a 10 ± 1.0 cm shaft length in the calculation of AA alignment was completed using a range of KJCs for 1P and 2P AA alignment methods. A second pilot study is planned to examine use of shorter shaft lengths (less than 10cm).

4.1.2 Aim

- To determine if there were significant differences in AA angle and to identify which method was least susceptible to any differences, when using shaft lengths slightly greater or slightly less than 10cm from each KJC for 1P and 2P AA alignment methods on AP view, fully-extended knee SLRs.

4.1.3 Method

Twelve pairs of DICOM knee radiograph images from 12 women (n=24 knees) attending the Y20 clinic visit were randomly selected and read for AA alignment by the author at 9, 9.5, 10, 10.5 and 11cm shaft lengths from each of the three KJCs (Figure 28, section 3.5.4.2: KJC1 = tibial spine base, KJC2 = tibial spine tips, KJC3 = tibial plateau centre) using KneeMorf computer software (see appendix 19 for KneeMorf alignment manual). The knee joint AA angles (in degrees) were subsequently calculated using Matlab R2011a program (version 7.12) and exported into an Excel spreadsheet file.

4.1.4 Analysis

All analysis was completed using Stata version 13.0 (Stata Corp, College Station, Texas, USA). Agreement between angles measured at the longest shaft length 11cm and the shortest shaft length 9cm for 1P and 2P KJCs was demonstrated via Bland Altman plots which assess agreement between two

methods of clinical measurement (Bland and Altman, 1986). The mean difference between the two shaft length readings was calculated. LoA were then created by adding and subtracting twice the SD of the mean difference. The SE of the mean was calculated thereby providing 95% CI for the likely mean disagreement between the two readings.

To examine specific differences between the knee joint alignment angles from 9, 9.5, 10.5 and 11 cm shaft lengths, the mean angle difference (\pm SD) from the 10cm shaft length was calculated for each KJC for 1P and 2P method for each shaft length. As there are 12 pairs of knees from 12 women in this pilot study, paired t-tests adjusted for correlated data were performed to identify significant differences from 10cm shaft length for all 24 knees. Current literature suggests a 1° increase in varus angulation is associated with an average annual reduction of 17.7 μ L of femoral cartilage (Cicuttini et al., 2004) therefore a $\pm 1^\circ$ alteration in AA angle was considered clinically significant.

To determine if differences between knee joint alignment angles from the different shaft lengths were attributable to specific categories of knee alignment the measured AA angles at the 10cm shaft length were categorised into neutral ($178-182^\circ$), varus $<178^\circ$ and valgus $>182^\circ$ alignment categories. These alignment category cut-offs were based on findings reported by Colebatch and colleagues (Colebatch et al., 2009) who showed standard AP view SLRs could be used to measure knee alignment with good reproducibility (inter- and intra-observer agreement of $r=0.99$ ($p<0.001$)) and provide comparable results ($r=0.81$) to those obtained from AP view FLRs. Colebatch's study which used fully extended knee radiographs in a population of 40 women, found no evidence of needing to apply an offset angle which had been previously reported in other studies comparing AA and MA alignment using fixed flexion (Kraus et al., 2005) and semi-flexed (Issa et al., 2007) knee radiographs. As this thesis uses data from a female only cohort study population containing fully extended AP SLRs it was relevant to follow the recommendations from Colebatch's study. Therefore using the 10cm shaft length, knee AA angles were categorised into neutral ($178-182^\circ$), varus $<178^\circ$ and valgus $>182^\circ$ for each KJC for 1P and 2P methods. At each shaft length mean differences in alignment measured from the 10cm shaft length were calculated for each alignment category and paired t-tests adjusted for correlated data performed to identify significant differences. In addition mean

differences by alignment categories for 1P and 2P methods were plotted as line graphs.

4.1.5 Results

A demographic summary of the participating 12 women from the Y20 clinic visit is shown in Table 14. Median age was 73.5 years and median BMI was 29.5kg/m² indicating these women were overweight. There were 5 knees from 3 women showing no RKO with K&L grade 0 or 1, the remaining 19 knees from 9 women had RKO with K&L grades 2, 3 or 4.

Table 14: Pilot study 1 demographics

Where BMI=body mass index; IQR=inter-quartile range; K&L=Kellgren & Lawrence.

Y20 demographic	n=24 knees
Age (years) median (IQR)	73.5 (70-75)
BMI (kg/m ²) median (IQR)	29.5 (27.8-31.2)
K&L grade 0 (%)	12.5
K&L grade 1 (%)	8.3
K&L grade 2 (%)	8.3
K&L grade 3 (%)	41.7
K&L grade 4 (%)	29.2

The agreement parameters (Table 15) between AA angles measured at the longest shaft length 11cm and the shortest shaft length 9cm for 1P and 2P KJCs were calculated from Bland Altman plots (Bland and Altman, 1986) Figure 35 a-c for 1P method and Figure 35 d – f for 2P method.

Table 15: Bland Altman plot agreement parameters for 11 v 9cm shaft lengths

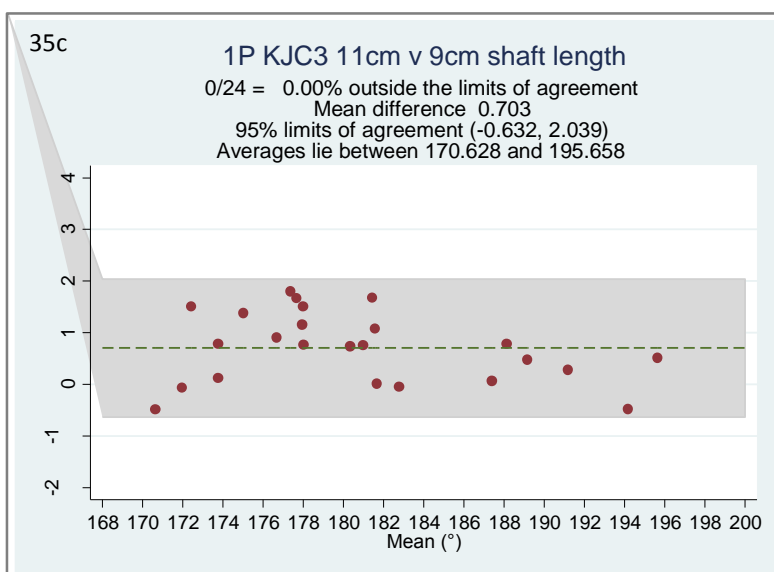
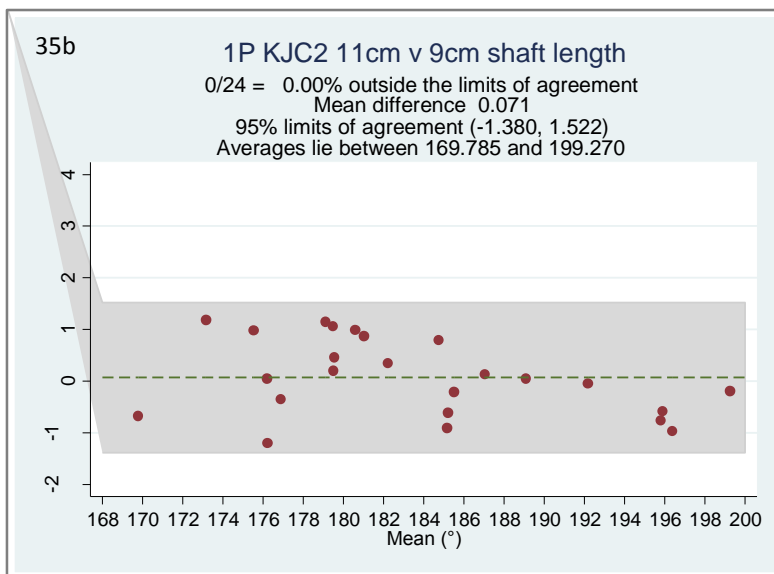
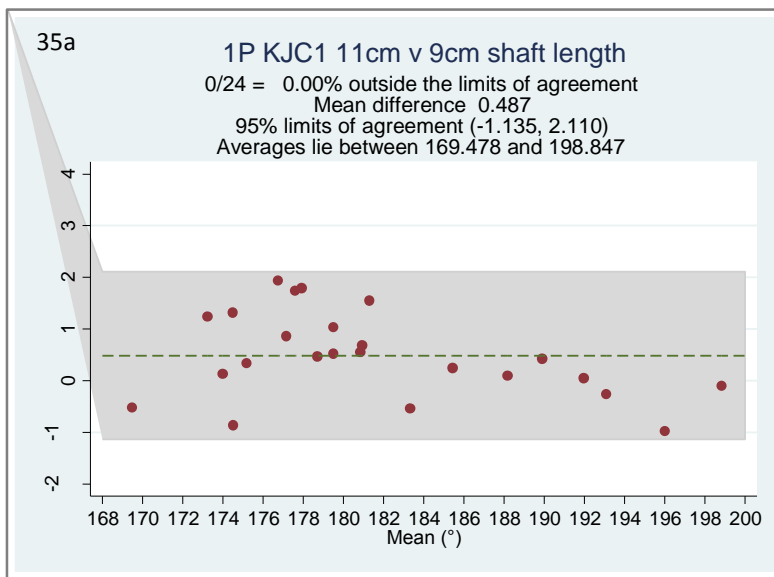
Where 1P=one-point; 2P=two-point; CI=confidence interval; diff=difference; KJC=knee joint centre; KJC1=tibial spine base; KJC2=tibial spine tips; KJC3=tibial plateau centre; LoA=limits of agreement; SD=standard deviation; SE=standard error (all units in degrees).

n=24 KJC	Mean diff.	SD	SE	95% CI	95% LoA
1P KJC1	0.49	0.83	0.17	0.14, 0.84	-1.14, 2.11
1P KJC2	0.07	0.74	0.15	-0.24, 0.38	-1.38, 1.52
1P KJC3	0.70	0.68	0.14	0.42, 0.99	-0.63, 2.04
2P KJC1	0.19	0.59	0.12	-0.06, 0.44	-0.97, 1.35
2P KJC2	0.03	0.57	0.12	-0.21, 0.27	-1.09, 1.14
2P KJC3	0.24	0.50	0.10	0.03, 0.45	-0.73, 1.22

The Bland Altman plots (Figure 35) and Table 15 results show that the mean angle difference between 11cm and 9cm shaft lengths is less than 0.70° for the 1P method and smaller for the 2P method at less than 0.24° . The standard deviation of the differences are also small at less than 0.83° for the 1P method and less than 0.59° for the 2P method, and the standard error of mean differences are similar across all KJCs at less than 0.17° . All these differences are below the clinically significant 1° (Cicuttini et al., 2004) indicating good agreement between the most extreme 11cm v 9cm shaft lengths for both 1P and 2P methods. Overall KJC2 shows the smallest mean difference of 0.07° for 1P method (Figure 35 b) and 0.03° for 2P method (Figure 35 e). The largest mean difference of 0.70° is for 1P KJC3 (Figure 35 c). On the whole 2P methods show smaller mean differences and tighter 95% LoA than 1P methods indicating there is less variation using a 2P method. No obvious bias is identified on any of the Bland Altman plots suggesting the potential variation is due to random error and all measurements fall within the upper and lower limits of two standard deviations from the mean, indicating there is good overall agreement between 11cm v 9cm shaft length knee alignment angles.

To examine specific differences between the knee joint alignment angles from 9, 9.5, 10.5 and 11cm shaft lengths, the mean angle difference (\pm SD) from the 10cm shaft length was calculated for each KJC for 1P and 2P method for each shaft length. Paired t-tests adjusted for correlated data were performed to identify significant differences from 10cm shaft length for all 24 knees, see Table 16 a-c.

Figure 35: Bland Altman plots for 11 cm v 9cm shaft length readings



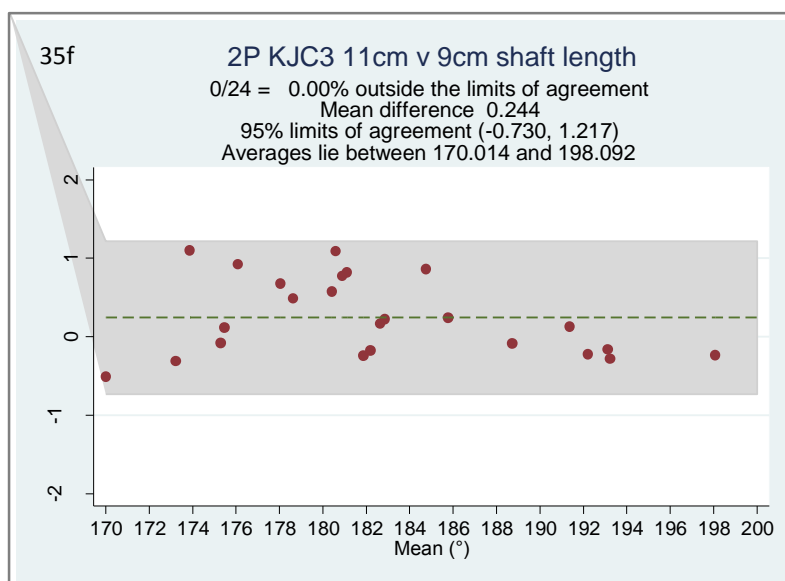
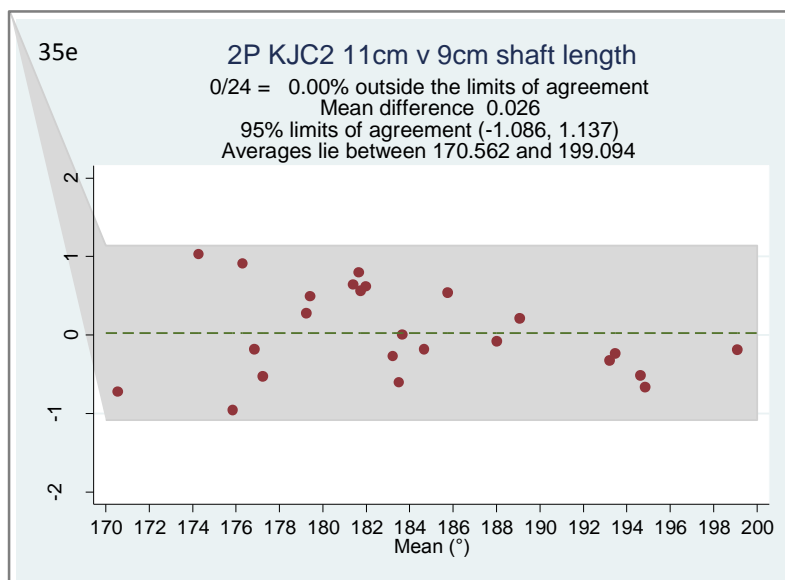
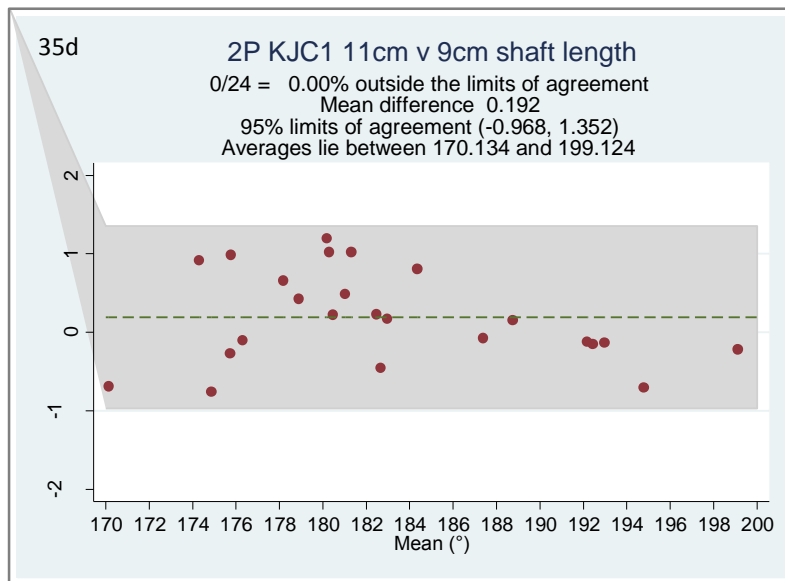


Table 16: Mean angle differences from 10cm shaft length

Where 1P=one-point; 2P=two-point; CI=confidence interval; diff=difference; KJC=knee joint centre; KJC1=tibial spine base; KJC2=tibial spine tips; KJC3=tibial plateau centre; SD=standard deviation; SE=standard error (all units in degrees).

16a: KJC1 n=24 Shaft length (cm)	Mean diff.	SD	SE	P value	95% CI
1P KJC1 9	0.28	0.48	0.12	0.045	0.01, 0.55
1P KJC1 9.5	0.13	0.25	0.06	0.071	-0.01, 0.27
1P KJC1 10.5	-0.13	0.20	0.04	0.013	-0.23, -0.03
1P KJC1 11	-0.21	0.36	0.09	0.036	-0.40, -0.02
2P KJC1 9	0.14	0.35	0.09	0.165	-0.07, 0.35
2P KJC1 9.5	0.07	0.20	0.05	0.182	-0.04, 0.18
2P KJC1 10.5	-0.04	0.17	0.04	0.335	-0.12, 0.04
2P KJC1 11	-0.05	0.27	0.07	0.455	-0.20, 0.10

16b: KJC2 n=24 Shaft length (cm)	Mean diff.	SD	SE	P value	95% CI
1P KJC2 9	0.07	0.39	0.10	0.483	-0.15, 0.30
1P KJC2 9.5	0.05	0.26	0.07	0.456	-0.09, 0.20
1P KJC2 10.5	-0.02	0.21	0.05	0.747	-0.13, 0.10
1P KJC2 11	0.01	0.37	0.10	0.976	-0.21, 0.22
2P KJC2 9	0.06	0.28	0.08	0.470	-0.11, 0.23
2P KJC2 9.5	0.05	0.20	0.05	0.330	-0.06, 0.17
2P KJC2 10.5	0.01	0.18	0.05	0.933	-0.10, 0.11
2P KJC2 11	0.32	0.30	0.08	0.702	-0.15, 0.21

16c: KJC3 n=24 Shaft length (cm)	Mean diff.	SD	SE	P value	95% CI
1P KJC3 9	0.44	0.38	0.09	0.001	0.24, 0.63
1P KJC3 9.5	0.20	0.18	0.04	<0.001	0.12, 0.29
1P KJC3 10.5	-0.15	0.21	0.04	0.008	-0.25, -0.05
1P KJC3 11	-0.27	0.32	0.08	0.005	-0.43, -0.10
2P KJC3 9	0.18	0.30	0.08	0.040	0.01, 0.36
2P KJC3 9.5	0.10	0.17	0.04	0.035	0.01, 0.19
2P KJC3 10.5	-0.05	0.17	0.03	0.195	-0.12, 0.03
2P KJC3 11	-0.06	0.22	0.06	0.309	-0.18, 0.06

Table 16a shows almost linear significant differences in knee joint alignment angle were present for 1P KJC1 (tibial spine base) at 9, 10.5 and 11cm shaft lengths compared to 10cm shaft length but not for the 2P method. However, these statistically significant mean differences were all less than 0.3° which is not considered to be clinically significant (Cicuttini et al., 2004). Table 16b shows there were no significant differences for KJC2 (tibial spine tips) for any

shaft lengths at either 1P or 2P methods. Table 16c shows again almost linear significant differences were present for 1P KJC3 (tibial plateau centre) at all shaft lengths for the 1P method and also at 9cm and 9.5cm shaft lengths for the 2P method. Again these statistically significant mean differences for KJC3 were all small differences of less than 0.5° which are not clinically significant.

To determine if these differences were attributable to specific categories of knee alignment the measured AA angles at the 10cm shaft length were categorised into neutral (178-182°), varus <178° and valgus >182° alignment categories for each KJC for 1P and 2P methods. At each shaft length mean differences in alignment measured from the 10cm shaft length were calculated and paired t-tests adjusted for correlated data were performed to identify significant differences, see Table 17 for 1P method and Table 18 for 2P method. All mean differences were also plotted in line graphs see Figure 36a-c for 1P method and Figure 37a-c for 2P method.

Table 17: 1P method mean angle differences from 10cm shaft length by alignment categories

Where 1P=one-point; CI=confidence interval; diff=difference; KJC=knee joint centre; KJC1=tibial spine base; KJC2=tibial spine tips; KJC3=tibial plateau centre; SD=standard deviation (all units in degrees).

17a: KJC1 n=24 Shaft length (cm)	Varus <178° (n=9)				Neutral 178 -182° (n=7)				Valgus >182° (n=8)			
	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI
1P KJC1 9	0.40	0.56	0.183	-0.29, 1.08	0.56	0.30	0.010	0.23, 0.90	-0.10	0.27	0.344	-0.37, 0.17
1P KJC1 9.5	0.15	0.28	0.284	-0.19, 0.50	0.30	0.19	0.019	0.08, 0.52	-0.05	0.13	0.431	-0.23, 0.12
1P KJC1 10.5	-0.21	0.25	0.061	-0.44, 0.02	-0.18	0.16	0.027	-0.33, -0.03	-0.01	0.10	0.947	-0.10, 0.10
1P KJC1 11	-0.29	0.44	0.176	-0.78, 0.20	-0.38	0.25	0.018	-0.65, -0.11	0.03	0.20	0.721	-0.19, 0.25

17b: KJC2 n=24 Shaft length (cm)	Varus <178° (n=6)				Neutral 178 -182° (n=6)				Valgus >182° (n=12)			
	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI
1P KJC2 9	0.01	0.53	0.990	-1.34, 1.35	0.42	0.19	0.050	0.00, 0.84	-0.06	0.28	0.496	-0.29, 0.16
1P KJC2 9.5	0.03	0.34	0.904	-0.87, 0.93	0.29	0.17	0.099	-0.13, 0.71	-0.05	0.17	0.114	-0.13, 0.02
1P KJC2 10.5	0.02	0.19	0.869	-0.46, 0.51	-0.23	0.12	0.012	-0.34, -0.12	0.07	0.18	0.290	-0.08, 0.22
1P KJC2 11	0.01	0.42	0.974	-1.05, 1.06	-0.36	0.22	0.042	-0.70, -0.03	0.18	0.27	0.110	-0.06, 0.43

17c: KJC3 n=24 Shaft length (cm)	Varus <178° (n=9)				Neutral 178 -182° (n=8)				Valgus >182° (n=7)			
	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI
1P KJC3 9	0.50	0.50	0.087	-0.12, 1.12	0.57	0.26	0.001	0.34, 0.80	0.20	0.25	0.078	-0.04, 0.43
1P KJC3 9.5	0.24	0.22	0.050	0.00, 0.48	0.28	0.14	0.002	0.15, 0.41	0.07	0.11	0.153	-0.04, 0.18
1P KJC3 10.5	-0.17	0.23	0.187	-0.48, 0.13	-0.22	0.20	0.026	-0.39, -0.04	-0.04	0.16	0.562	-0.22, 0.14
1P KJC3 11	-0.34	0.35	0.099	-0.79, 0.10	-0.39	0.28	0.014	-0.66, -0.12	-0.03	0.20	0.751	-0.27, 0.21

Table 18: 2P method mean angle differences from 10cm shaft length by alignment categories

Where 2P=two-point; CI=confidence interval; diff=difference; KJC=knee joint centre; KJC1=tibial spine base; KJC2=tibial spine tips; KJC3=tibial plateau centre; SD=standard deviation (all units in degrees).

18a: KJC1 n=24 Shaft length (cm)	Varus <178° (n=6)				Neutral 178 -182° (n=7)				Valgus >182° (n=11)			
	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI
2P KJC1 9	0.03	0.42	0.919	-1.10, 1.15	0.49	0.19	0.017	0.17, 0.81	-0.02	0.23	0.774	-0.19, 0.15
2P KJC1 9.5	-0.01	0.23	0.947	-0.60, 0.58	0.26	0.12	0.016	0.09, 0.43	-0.01	0.15	0.911	-0.10, 0.09
2P KJC1 10.5	-0.02	0.26	0.874	-0.60, 0.56	-0.10	0.16	0.100	-0.24, 0.04	-0.01	0.13	0.913	-0.10, 0.09
2P KJC1 11	0.02	0.37	0.945	-0.91, 0.95	-0.23	0.22	0.047	-0.46, -0.01	0.02	0.18	0.682	-0.13, 0.18

18b: KJC2 n=24 Shaft length (cm)	Varus <178° (n=6)				Neutral 178 -182° (n=6)				Valgus >182° (n=12)			
	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI
2P KJC2 9	-0.03	0.42	0.916	-1.15, 1.09	0.31	0.08	0.002	0.25, 0.38	-0.03	0.19	0.714	-0.19, 0.14
2P KJC2 9.5	-0.01	0.27	0.994	-0.72, 0.71	0.24	0.13	0.056	-0.02, 0.49	-0.01	0.13	0.770	-0.10, 0.08
2P KJC2 10.5	0.07	0.25	0.712	-0.60, 0.73	-0.16	0.09	0.051	-0.33, 0.00	0.06	0.12	0.073	-0.01, 0.12
2P KJC2 11	0.04	0.43	0.883	-1.11, 1.20	-0.25	0.20	0.052	-0.51, 0.01	0.17	0.17	0.028	0.03, 0.31

18c: KJC3 n=24 Shaft length (cm)	Varus <178° (n=6)				Neutral 178 -182° (n=7)				Valgus >182° (n=11)			
	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI
2P KJC3 9	0.13	0.37	0.613	-0.82, 1.09	0.43	0.25	0.031	0.08, 0.78	0.06	0.19	0.243	-0.05, 0.17
2P KJC3 9.5	0.07	0.17	0.502	-0.32, 0.46	0.22	0.13	0.031	0.04, 0.41	0.03	0.15	0.452	-0.07, 0.14
2P KJC3 10.5	-0.01	0.24	0.923	-0.60, 0.57	-0.10	0.16	0.062	-0.21, 0.01	-0.03	0.14	0.293	-0.10, 0.04
2P KJC3 11	-0.08	0.30	0.728	-0.89, 0.74	-0.17	0.20	0.109	-0.40, 0.07	0.02	0.18	0.703	-0.09, 0.12

Figure 36: 1P method mean angle differences from 10cm shaft length by alignment categories

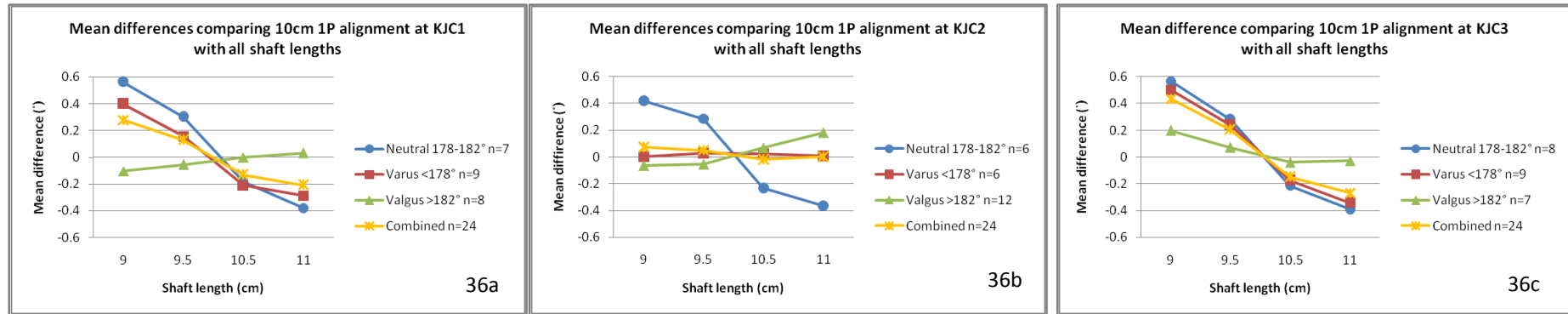


Figure 37: 2P method mean angle differences from 10cm shaft length by alignment categories

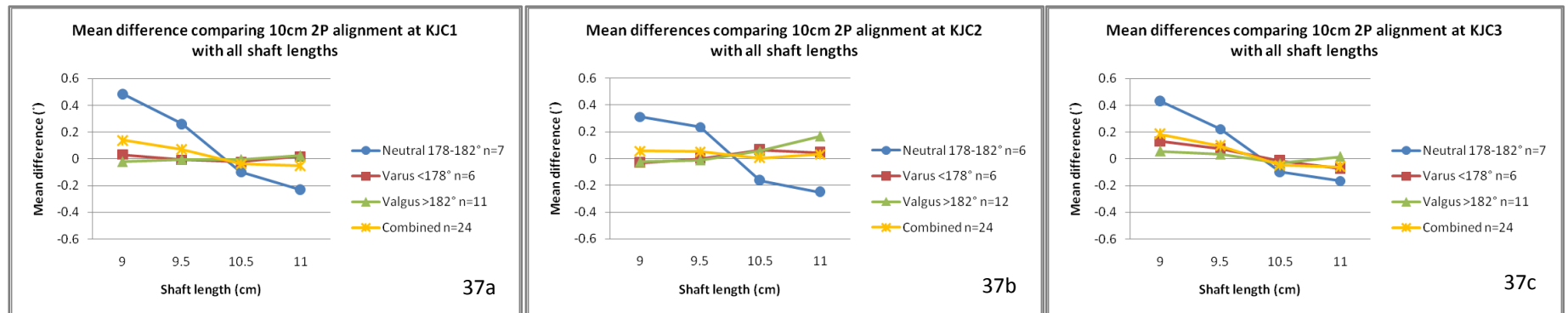


Table 17 and Table 18 show the numbers of knees classified in each alignment category as either varus, neutral or valgus were dependent on the KJC and method (1P or 2P) used. The largest difference in classification was a greater number of knees (≥ 11) classified as valgus using the 2P method (Table 18) compared with the 1P method for KJC1 and KJC3 (Table 17). Within the 1P method there were a greater number of knees ($n=12$) categorised as valgus using 1P KJC2 compared with 8 knees with 1P KJC1 and 7 knees with 1P KJC 3 (Table 17), whereas for the 2P method a similar number of knees were classified in each alignment category at each of the KJCs (Table 18).

When using the 1P method, Table 17a, b and c and Figure 36a, b and c show neutrally classified knees appear to overestimate AA alignment with the shorter 9 and 9.5cm shaft lengths, and underestimate AA alignment with the longer 10.5 and 11cm shaft lengths at all KJCs which could in theory lead to a systematic bias. Although these differences are statistically significant, in clinical terms the actual difference was no more than 0.57° overestimated at KJC3 9cm shaft length and no less than -0.39° underestimated at KJC3 11cm shaft length, both below the $\pm 1^\circ$ clinically significant threshold (Cicuttini et al., 2004). A similar pattern was noted for varus classified knees but only using KJC1 and KJC3 and mean differences were not statistically significant except 1P KJC3 at 9.5cm shaft length which was borderline statistically significant but not clinically significant at 0.24° . Valgus classified knees show the smallest mean differences from the 10cm shaft length ranging from -0.10 to 0.20° .

When using the 2P method, (Table 18a, b and c and Figure 37a, b and c) a similar pattern to the 1P method was seen only in neutrally classified knees with statistically significant overestimation at KJC1, KJC2 and KJC3 for 9cm shaft lengths, and KJC1 and KJC3 for 9.5cm shaft lengths. Statistically significant underestimation was seen at KJC1 11cm shaft length only. Again, in clinical terms the actual mean difference was small at no more than 0.49° overestimation at KJC1 9cm shaft length and no less than -0.23° underestimation at KJC1 11cm shaft length. Varus and valgus 2P classified knees show very small mean differences from the 10cm shaft length ranging from -0.08 to 0.13° for varus and -0.03 to 0.17° for valgus.

4.1.6 Conclusion

To summarise, the results from this pilot study have shown good agreement at all three KJCs when the extreme shaft lengths 11cm v 9cm were compared, with KJC2 (tibial spine tips) showing the least difference and all 2P methods showing smaller mean differences than 1P methods.

When alignment was categorised, shaft lengths less than 10cm slightly overestimate AA alignment by $\leq +0.5^\circ$, and shaft lengths greater than 10cm slightly underestimate AA alignment by $\leq -0.5^\circ$ in neutral aligned knees using 1P method. This was also shown to a lesser extent in neutral knees using the 2P method. The number of knees classified in each alignment category as either varus, neutral or valgus was dependent on the KJC and method (1P or 2P) used.

Overall mean differences between the standard 10cm shaft length and 9, 9.5, 10.5 and 11cm shaft lengths were small ($\leq \pm 0.5^\circ$) and therefore not clinically significant. Based on these pilot study results it could be acceptable to use shaft lengths of 9, 9.5, 10.5 and 11cm if needed, but for comparative purposes with previous alignment literature a 10cm shaft length will be used for future AA analysis in this thesis.

It is clear there were differences in AA alignment measurement between 1P and 2P methods, with these results suggesting that the 2P method gives less variation. However the study sample here is too small ($n=24$ knees) to make definitive choices over the 1P v 2P method or to choose a specific KJC. More pilot work is required to examine this further and also to consider shorter shaft lengths for radiographs, to see if current convention of using the maximum shaft length available on radiographs is acceptable or not.

4.2 Pilot study 2

4.2.1 Background

Results from alignment pilot study one indicate it is acceptable to use the 10cm shaft length as a standard in AA angle calculation. However if a 10cm femoral and/or tibial shaft length is not available on a radiograph current convention opts to use the maximum shaft length possible. Results from the first pilot study indicate using the maximum shaft length available may be acceptable if the shaft length is >9 and <11 cm as mean differences in AA alignment were small (approximately $\leq \pm 0.5^\circ$) and not clinically significant, but it is not known if this is the case when using a shaft length shorter than 9cm.

There has been only one study to date examining the use of shorter shaft lengths of between 5 – 7cm versus 10 ± 0.5 cm in a healthy (14 female, 2 male) and severe KOA (17 female, 13 male) Canadian population (Wong et al., 2009). They found using a shorter shaft length reduced AA angle precision on PA fixed-flexion SLRs, whether this is also the case for SLRs taken from an AP view in a fully extended knee position remains unknown. For this reason a second pilot study was completed to examine the effect on AA alignment when using lengths of 7, 8, 9, 10cm and maximum shaft length available. A 7cm shaft length was chosen as the shortest shaft length to be used in this pilot study as it is known that femoral and tibial bowing angles (which indicate femoral and tibial varus) are measured at points bisecting the femur at 5cm and 10cm above the lowest portion of the lateral femoral condyle, and at 5cm and 10cm points bisecting the tibia from the highest portion of the lateral tibial plateau (Nagamine et al., 2000, Chang et al., 2010). It was therefore relevant to avoid this area and equally important to avoid the metaphysis, known as the wide portion of the long bone between the epiphysis (condyles) and diaphysis (shaft) as it is speculated that alignment measured here could be affected by the metaphyseal-diaphyseal angle (Levine and Drennan, 1982). Therefore, a 7cm shaft length was chosen as a +2cm leeway from 5cm was considered appropriate to avoid interference from femoral and tibial bowing angles and metaphyseal-diaphyseal angles.

4.2.2 Aim

- To determine if there were significant differences in AA angle and to identify which method was least susceptible to any differences, when using shaft lengths of 7, 8, 9, 10cm and maximum shaft length available from each KJC for 1P and 2P methods on AP view, fully-extended knee SLRs.

4.2.3 Method

Twelve pairs of Y1 visit digitised knee radiograph images were randomly selected and read for AA alignment by the author at 7, 8, 9, 10cm and maximum shaft lengths available from each KJC (Figure 28, section 3.5.4.2: KJC1 = tibial spine base, KJC2 = tibial spine tips, KJC3 = tibial plateau centre) using KneeMorf computer software (see appendix 19 for KneeMorf alignment manual). The knee AA angles (in degrees) were subsequently calculated using Matlab R2011a program (version 7.12) and exported into an Excel spreadsheet file.

4.2.4 Analysis

All analysis was completed using Stata version 13.0 (Stata Corp, College Station, Texas, USA). The AA angle results for the different KJCs at 10cm and the shortest 7cm shaft lengths were compared using Bland Altman plots, to assess agreement between two methods of clinical measurement, (Bland and Altman, 1986). The mean difference, LoA and SE of the mean were calculated for 7 and 10cm shaft lengths as described previously in pilot study one (section 4.1.4).

To examine specific differences between the knee AA angles from 7, 8, 9cm and maximum shaft lengths, the mean angle difference (\pm SD) from the 10cm shaft length was calculated for each KJC for 1P and 2P method for each shaft length. Paired t-tests adjusted for correlated data were performed to identify significant differences from 10cm shaft length for all 24 knees.

To determine if differences between knee AA angles from the different shaft lengths were attributable to specific categories of knee alignment the measured AA angles at the 10cm shaft length were categorised into neutral ($178-182^\circ$), varus $<178^\circ$ and valgus $>182^\circ$ alignment categories for each KJC for

1P and 2P methods. At each shaft length mean differences in alignment measured from the 10cm shaft length were calculated and paired t-tests adjusted for correlated data were performed to identify significant differences. Mean differences by alignment categories for the 1P and 2P methods were also plotted as line graphs and absolute angle differences at all shaft lengths by alignment category were calculated.

4.2.5 Results

A demographic summary of the participating 12 women with 24 knees from the Y1 visit is shown in Table 19. The majority, 21 knees, had no RKO with K&L grade 0 or 1, the remaining 3 knees from 2 women had RKO with K&L grade 2.

Table 19: Pilot study 2 demographics

Where IQR=inter-quartile range; BMI=body mass index; K&L=Kellgren & Lawrence.

Y1 demographic	n=24 knees
Age (years) median (IQR)	54 (47.5-55)
BMI (kg/m ²) median (IQR)	25.1 (21.9-27.3)
K&L grade 0 (%)	83.3
K&L grade 1 (%)	4.2
K&L grade 2 (%)	12.5
K&L grade 3 (%)	0
K&L grade 4 (%)	0

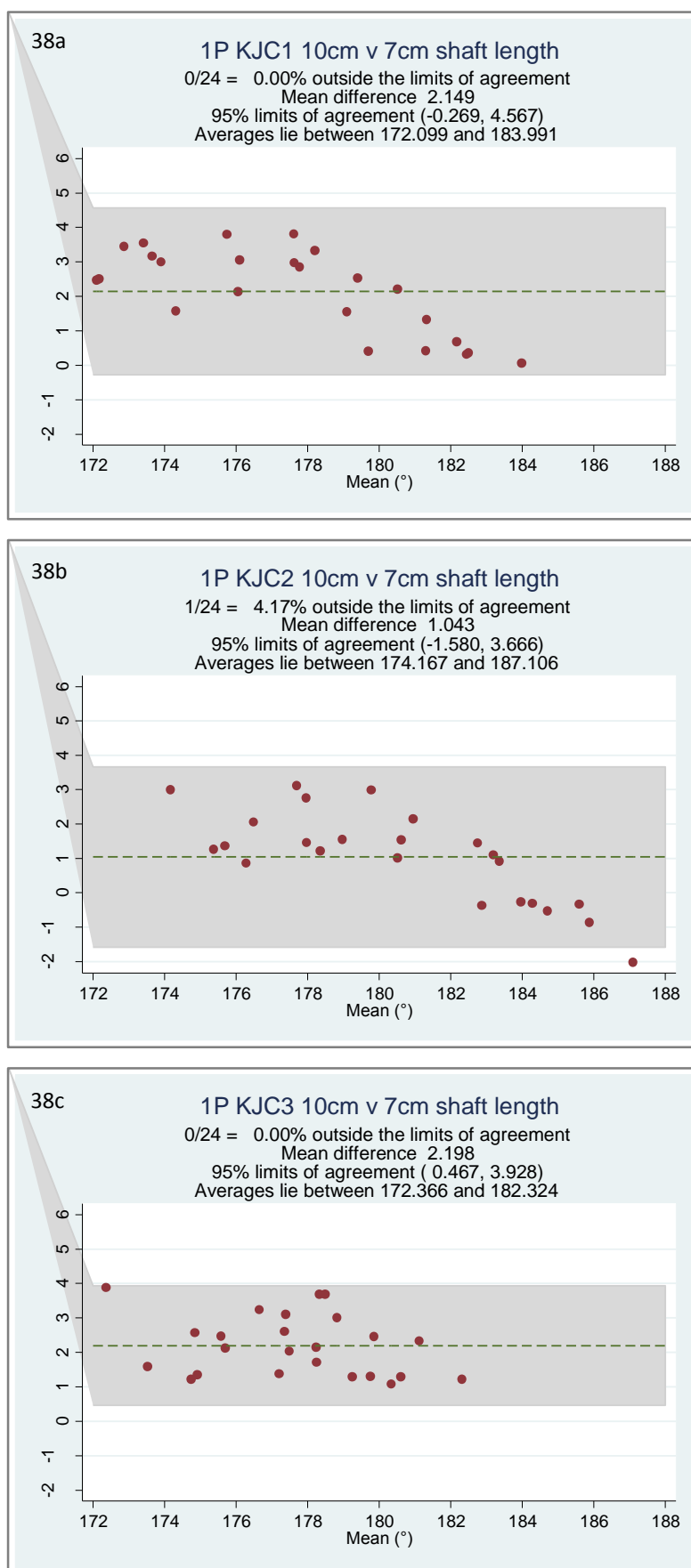
The agreement parameters (Table 20) between AA angles measured at 10cm and the shortest shaft length 7cm for 1P and 2P KJCs were calculated from Bland Altman plots (Bland and Altman, 1986) Figure 38a-c for 1P method and Figure 38d-f for 2P method.

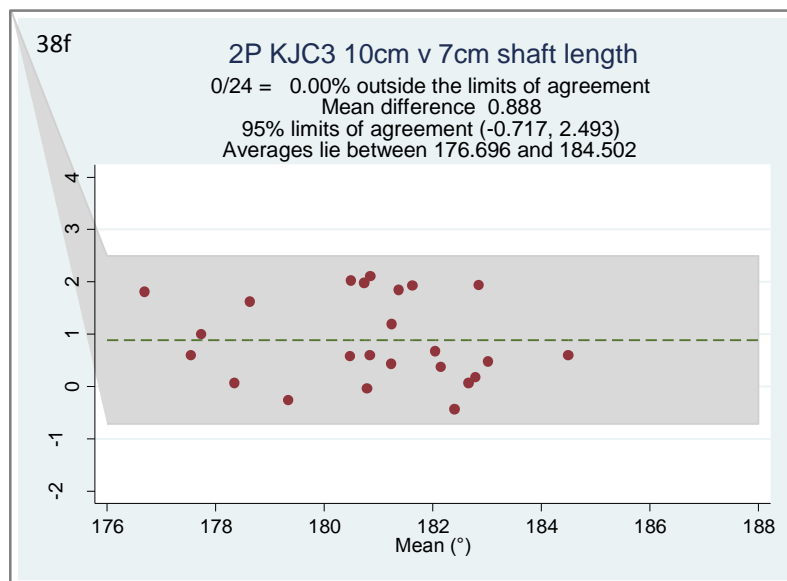
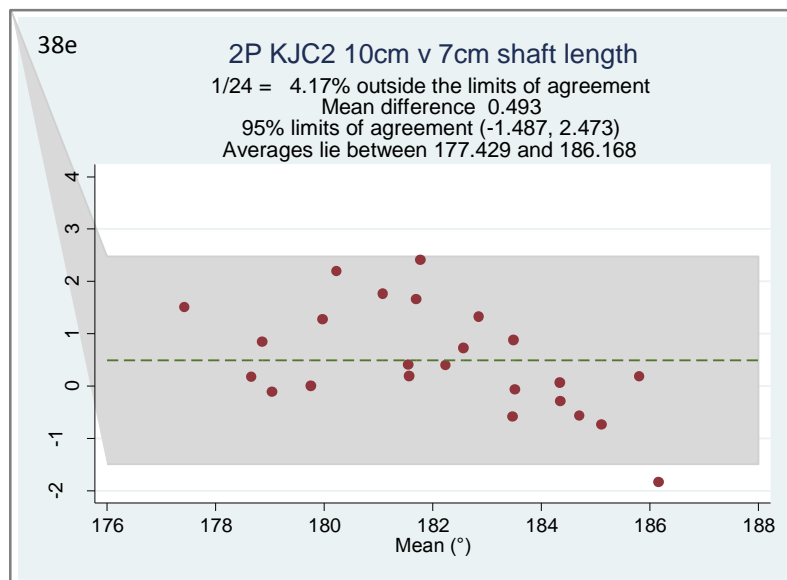
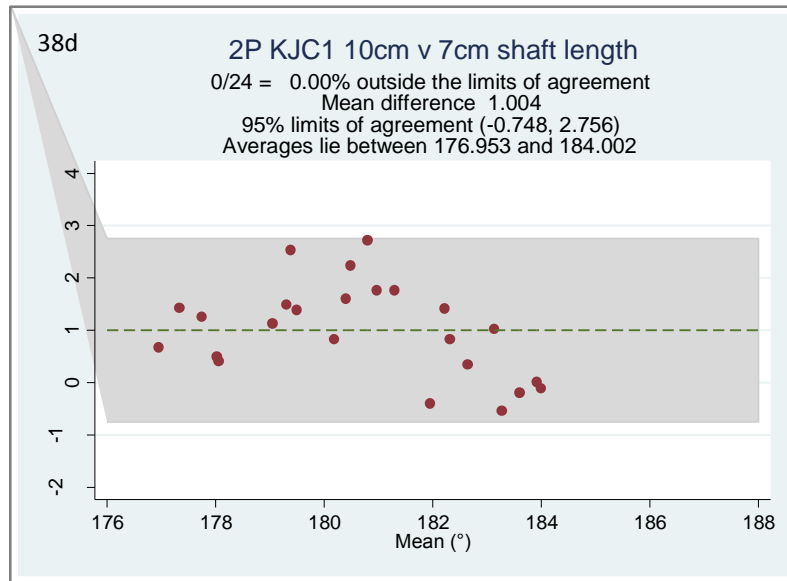
Table 20: Bland Altman plot agreement parameters for 10 v 7cm shaft lengths

Where 1P=one-point; 2P=two-point; CI=confidence interval; diff=difference; KJC=knee joint centre; KJC1=tibial spine base; KJC2=tibial spine tips; KJC3=tibial plateau centre; LoA=limits of agreement; SD=standard deviation; SE=standard error (all units in degrees).

n=24 KJC	Mean diff.	SD	SE	95% CI	95% LoA
1P KJC1	2.15	1.23	0.25	1.63, 2.67	-0.27, 4.57
1P KJC2	1.04	1.34	0.27	0.48, 1.61	-1.58, 3.67
1P KJC3	2.20	0.88	0.18	1.82, 2.57	0.47, 3.93
2P KJC1	1.00	0.89	0.18	0.63, 1.38	-0.75, 2.76
2P KJC2	0.49	1.01	0.21	0.07, 0.92	-1.49, 2.47
2P KJC3	0.89	0.82	0.17	0.54, 1.23	-0.72, 2.49

Figure 38: Bland Altman plots for 10cm v 7cm shaft length readings





The Bland Altman plots (Figure 38a-f) and Table 20 results show that the mean differences between 10cm and 7cm shaft lengths range from 1.04 to 2.15° with wide 95% LoA for KJCs using the 1P method, and smaller mean differences 0.49 to 1.00°, as too were the 95% LoA for KJCs using the 2P method. As these differences are approaching or greater than 1°, they indicate poor agreement between 10cm and 7cm shaft lengths using the 1P method, with agreement improving slightly when using the 2P method. Although KJC2 shows the smallest mean difference of 0.49° for 2P method (Figure 38e) and 1.04° for 1P method (Figure 38b), it shows the widest LoA (-1.58°, 3.67° for 1P and -1.49°, 2.47° for 2P). KJC3 displays the narrowest LOA (0.47°, 3.93° for 1P (Figure 38c) and -0.72°, 2.49° for 2P (Figure 38f). On the whole 2P methods show smaller mean differences and tighter 95% LoA than 1P methods indicating there was less variation using a 2P method which were similar to findings reported in the previous pilot study. Some bias (overestimation of varus and neutral angles, with underestimation of more valgus angles) was shown on the Bland Altman plots for KJC1 and KJC2 (Figure 38a, b, c and d) indicating that KJC3 (tibial plateau centre) was less prone to systematic bias.

To examine specific differences between the knee joint alignment angles from 7, 8, 9cm and maximum shaft lengths, the mean angle difference (\pm SD) from the 10cm shaft length was calculated for each KJC for 1P and 2P method for each shaft length. Paired t-tests adjusted for correlated data were performed to identify significant differences from 10cm shaft length for all 24 knees see Table 21a-c.

Table 21: Mean angle differences from 10cm shaft length

Where 1P=one-point; 2P=two-point; CI=confidence interval; diff=difference; KJC=knee joint centre; KJC1=tibial spine base; KJC2=tibial spine tips; KJC3=tibial plateau centre; SD=standard deviation; SE=standard error (all units in degrees).

21a: KJC1 n=24 Shaft length (cm)	Mean diff.	SD	SE	P value	95% CI
1P KJC1 7	2.15	1.23	0.34	<0.001	1.39, 2.90
1P KJC1 8	1.15	0.80	0.22	<0.001	0.67, 1.64
1P KJC1 9	0.50	0.40	0.11	0.001	0.26, 0.75
1P KJC1 max	-0.53	0.71	0.18	0.014	-0.94, -0.13
2P KJC1 7	1.00	0.89	0.25	0.002	0.46, 1.55
2P KJC1 8	0.48	0.55	0.15	0.010	0.14, 0.81
2P KJC1 9	0.20	0.28	0.08	0.027	0.03, 0.37
2P KJC1 max	-0.17	0.51	0.14	0.270	-0.48, 0.15

21b: KJC2 n=24 Shaft length (cm)	Mean diff.	SD	SE	P value	95% CI
1P KJC2 7	1.04	1.34	0.37	0.017	0.23, 1.86
1P KJC2 8	0.52	0.79	0.22	0.034	0.05, 0.99
1P KJC2 9	0.22	0.40	0.11	0.072	-0.02, 0.46
1P KJC2 max	-0.07	0.79	0.21	0.740	-0.55, 0.40
2P KJC2 7	0.49	1.01	0.28	0.111	-0.13, 1.12
2P KJC2 8	0.19	0.60	0.16	0.270	-0.17, 0.55
2P KJC2 9	0.07	0.31	0.08	0.420	-0.12, 0.26
2P KJC2 max	0.07	0.64	0.38	0.711	-0.33, 0.46

21c: KJC3 n=24 Shaft length (cm)	Mean diff.	SD	SE	P value	95% CI
1P KJC3 7	2.20	0.88	0.22	<0.001	1.71, 2.69
1P KJC3 8	1.21	0.59	0.15	<0.001	0.89, 1.53
1P KJC3 9	0.50	0.32	0.08	<0.001	0.33, 0.67
1P KJC3 max	-0.78	0.60	0.15	<0.001	-1.12, -0.45
2P KJC3 7	0.89	0.82	0.23	0.002	0.39, 1.39
2P KJC3 8	0.46	0.54	0.15	0.009	0.14, 0.78
2P KJC3 9	0.18	0.28	0.07	0.033	0.02, 0.34
2P KJC3 max	-0.16	0.46	0.12	0.202	-0.43, 0.10

Table 21a shows statistically significant linear differences in knee joint AA angle were present for 1P and 2P KJC1 (tibial spine base) at all the shorter shaft lengths compared to 10cm shaft length. Mean differences of more than 1° (considered to be clinically relevant) (Cicuttini et al., 2004) were present at 2.15° and 1.15° for the shorter shaft lengths of 7 and 8cm respectively for the 1P method. All other statistically significant differences were $\leq 1.0^\circ$ and therefore not clinically significant.

Table 21b shows statistically significant linear differences for KJC2 (tibial spine tips) at 7 and 8cm shaft lengths for the 1P method only with the mean difference at the 7cm shaft length being more than 1° therefore clinically significant.

Table 21c shows a similar pattern to Table 21a with statistically significant linear differences shown for all the shorter shaft lengths using the 1P and 2P method at KJC3 (tibial plateau centre) compared to 10cm shaft length. However, only 1P 7cm and 8cm shaft lengths had mean differences of $\geq 1^\circ$ (2.20° and 1.21° respectively), the remainder were all $\leq 0.89^\circ$ and therefore not clinically significant.

Overall, Table 21a, b and c show the shorter the shaft length the greater the mean difference from 10cm, this appears to be only clinically relevant for shaft lengths 7 and 8cm using 1P method as the mean differences for the 2P method are all $\leq 1.0^\circ$.

To see if these significant differences were attributable to specific categories of knee alignment AA angles were categorised into neutral (178° - 182°), varus $<178^\circ$ and valgus $>182^\circ$ alignment categories. Mean differences in alignment from the 10cm shaft length for each KJC at each shaft length were calculated and paired t-tests performed to identify significant differences, see Table 22 for 1P method and Table 23 for 2P method. All mean differences were also plotted in line graphs see Figure 39a-c for 1P method and Figure 40a-c for 2P method.

Table 22: 1P method mean angle differences from 10cm shaft length by alignment categories

Where 1P=one-point; CI=confidence interval; diff=difference; KJC=knee joint centre; KJC1=tibial spine base; KJC2=tibial spine tips; KJC3=tibial plateau centre; SD=standard deviation (all units in degrees).

22a: KJC1 n=24 Shaft length (cm)	Varus <178° (n=10)				Neutral 178 -182° (n=10)				Valgus >182° (n=4)			
	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI
1P KJC1 7	2.87	0.69	<0.001	2.18, 3.56	2.14	1.18	0.002	1.07, 3.22	0.36	0.25	0.119	-0.23, 0.94
1P KJC1 8	1.64	0.46	<0.001	1.18, 2.11	1.09	0.75	0.007	0.41, 1.77	0.08	0.44	0.779	-0.99, 1.15
1P KJC1 9	0.79	0.23	<0.001	0.55, 1.03	0.43	0.33	0.010	0.14, 0.72	-0.04	0.14	0.683	-0.42, 0.34
1P KJC1 max	-0.85	0.78	0.014	-1.45, -0.24	-0.43	0.66	0.115	-1.00, 0.14	-0.01	0.11	0.882	-0.28, 0.26

22b: KJC2 n=24 Shaft length (cm)	Varus <178° (n=5)				Neutral 178 -182° (n=8)				Valgus >182° (n=11)			
	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI
1P KJC2 7	1.71	0.84	0.028	0.35, 3.06	1.95	0.85	0.003	1.03, 2.87	0.08	1.19	0.841	-0.85, 1.01
1P KJC2 8	0.88	0.50	0.043	0.05, 1.71	1.08	0.46	0.002	0.62, 1.53	-0.04	0.74	0.854	-0.60, 0.51
1P KJC2 9	0.42	0.29	0.062	-0.04, 0.88	0.51	0.20	0.001	0.30, 0.72	-0.09	0.34	0.448	-0.35, 0.18
1P KJC2 max	0.02	0.65	0.948	-1.10, 1.15	-0.76	0.77	0.051	-1.53, 0.01	0.38	0.50	0.077	-0.06, 0.82

22c: KJC3 n=24 Shaft length (cm)	Varus <178° (n=8)				Neutral 178 -182° (n=14)				Valgus >182° (n=2)			
	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI
1P KJC3 7	2.07	0.90	0.005	1.03, 3.12	2.33	0.92	<0.001	1.82, 2.84	1.77	0.78	0.192	-5.26, 8.80
1P KJC3 8	1.23	0.63	0.009	0.51, 1.96	1.25	0.60	<0.001	0.92, 1.58	0.85	0.52	0.260	-3.81, 5.50
1P KJC3 9	0.51	0.31	0.014	0.17, 0.84	0.52	0.34	<0.001	0.34, 0.70	0.32	0.42	0.478	-3.47, 4.11
1P KJC3 max	-0.83	0.77	0.044	-1.63, -0.03	-0.77	0.52	0.003	-1.19, -0.34	-0.71	0.80	0.428	-7.87, 6.45

Table 23: 2P method mean angle differences from 10cm shaft length by alignment categories

Where 2P=two-point; CI=confidence interval; KJC=knee joint centre; KJC1=tibial spine base; KJC2=tibial spine tips; KJC3=tibial plateau centre; mean diff=difference, n/a=not available; SD=standard deviation (all units in degrees).

23a: KJC1 n=24 Shaft length (cm)	Varus <178° (n=1)				Neutral 178 -182° (n=13)				Valgus >182° (n=10)			
	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI
2P KJC1 7	0.67	n/a	n/a	n/a	1.24	0.78	0.001	0.71, 1.78	0.73	1.02	0.077	-0.11, 1.56
2P KJC1 8	0.23	n/a	n/a	n/a	0.65	0.44	0.002	0.33, 0.97	0.28	0.66	0.226	-0.23, 0.78
2P KJC1 9	0.15	n/a	n/a	n/a	0.33	0.23	0.002	0.16, 0.49	0.03	0.28	0.733	-0.19, 0.26
2P KJC1 max	0.34	n/a	n/a	n/a	-0.39	0.51	0.033	-0.74, -0.04	0.08	0.40	0.589	-0.26, 0.41

23b: KJC2 n=24 Shaft length (cm)	Varus <178° (n=0)				Neutral 178 -182° (n=10)				Valgus >182° (n=14)			
	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI
2P KJC2 7	n/a	n/a	n/a	n/a	0.83	0.82	0.036	0.08, 1.58	0.25	1.09	0.479	-0.54, 1.05
2P KJC2 8	n/a	n/a	n/a	n/a	0.38	0.49	0.089	-0.07, 0.83	0.06	0.66	0.774	-0.40, 0.52
2P KJC2 9	n/a	n/a	n/a	n/a	0.16	0.25	0.147	-0.07, 0.39	0.01	0.34	0.938	-0.23, 0.25
2P KJC2 max	n/a	n/a	n/a	n/a	-0.16	0.66	0.537	-0.76, 0.44	0.23	0.59	0.256	-0.20, 0.67

23c: KJC3 n=24 Shaft length (cm)	Varus <178° (n=2)				Neutral 178 -182° (n=12)				Valgus >182° (n=10)			
	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI	Mean diff.	SD	P value	95% CI
2P KJC3 7	1.20	0.86	0.299	-6.55, 8.96	0.94	0.84	0.012	0.27, 1.61	0.76	0.85	0.038	0.06, 1.47
2P KJC3 8	0.85	0.56	0.279	-4.22, 5.92	0.49	0.54	0.033	0.05, 0.93	0.35	0.54	0.114	-0.11, 0.81
2P KJC3 9	0.33	0.23	0.298	-1.78, 2.44	0.20	0.31	0.084	-0.03, 0.44	0.12	0.26	0.223	-0.10, 0.35
2P KJC3 max	-0.53	0.43	0.333	-4.40, 3.35	-0.27	0.53	0.189	-0.69, 0.16	0.03	0.29	0.768	-0.21, 0.27

Figure 39: 1P method mean angle differences from 10cm shaft length by alignment categories

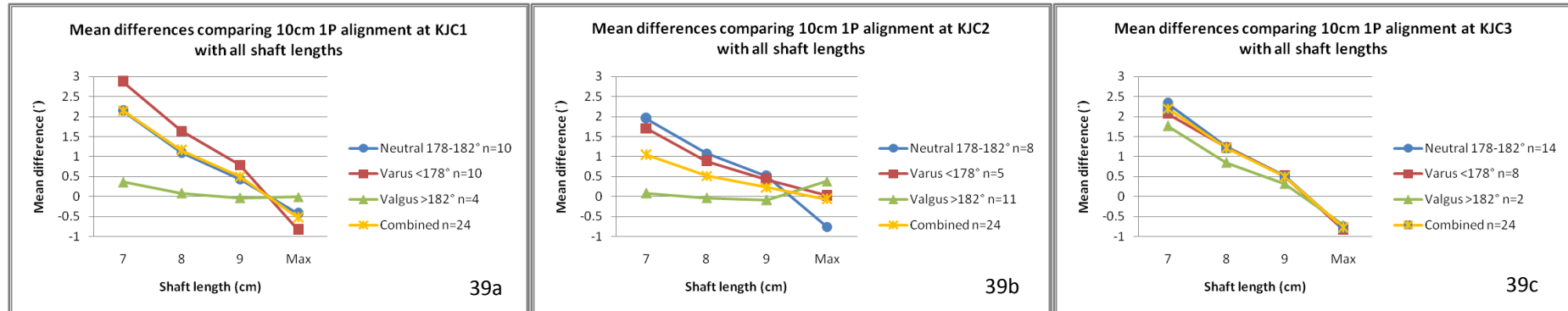


Figure 40: 2P method mean angle differences from 10cm shaft length by alignment categories

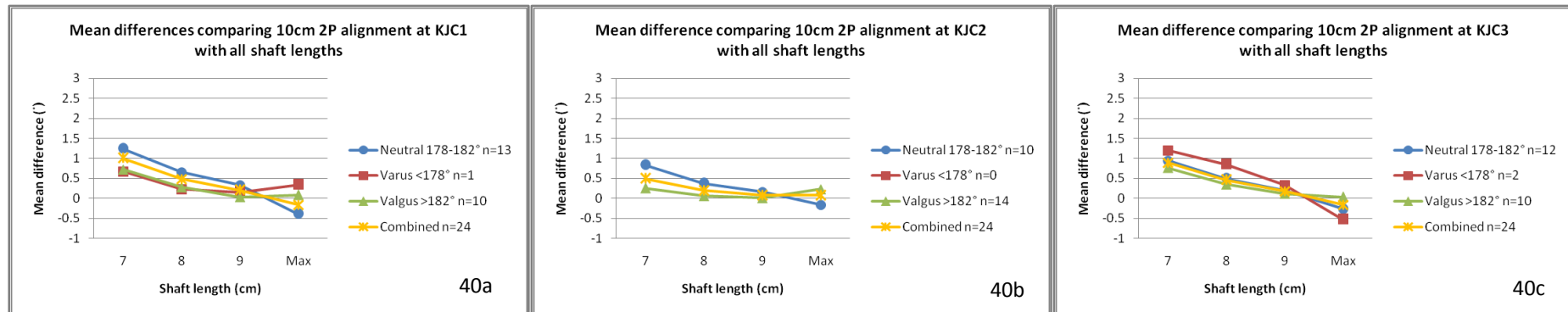


Table 22 and Table 23 show the numbers of knees classified in each alignment category as either varus, neutral or valgus was again dependent on the KJC and the method (1P or 2P) used. The largest difference was 11 knees classified as valgus using 1P KJC2 in comparison to 4 knees with 1P KJC1 and 2 knees with 1P KJC3, a similar finding was reported in pilot study one with Y20 DICOM images. For the 2P method a similar number of knees were classified in each alignment category at each of the KJCs, however overall there were fewer knees classified as varus at each KJC compared to the 1P method and a greater number of knees (≥ 10) were classified as valgus using the 2P method compared to the 1P method for KJC1 and KJC3.

When using the 1P method, Table 22a, b and c and Figure 39a, b and c show varus and neutral classified knees appear to significantly overestimate AA alignment with the shortest shaft length 7cm having the greatest mean difference at over 2° (2.87° varus, 2.14° neutral) for KJC1 and (2.07° varus, 2.33° neutral) for KJC3, and approaching 2° (1.71° varus, 1.95° neutral) for KJC2. These statistically and clinically significant differences for the 1P method would result in a systematic bias for varus and neutral knees if a shorter shaft length such as 7cm was used.

When using the 2P method (Table 23a, b and c and Figure 40a, b and c) although all mean differences are much smaller than the 1P method, neutrally classified knees also appear to significantly overestimate AA alignment with the shortest shaft length 7cm having the greatest mean difference at 1.24° for KJC1 and approaching a clinically significant 1° difference of 0.83° for KJC2 and of 0.94° for KJC3. Unfortunately there were not enough knees classified as varus with the 2P method to be able to comment and the valgus classified knees generally show small mean differences ($\leq 0.76^\circ$) from the 10cm shaft length.

Table 24 shows the absolute angle differences at all shaft lengths for all KJCs by alignment category. This reinforces the points made above for the overestimation of varus and neutral knees with shorter shaft lengths (particularly 7 and 8cm lengths) using the 1P method and to a lesser extent in neutral knees with the 2P method.

Table 24: Absolute angle differences at all shaft lengths by alignment category

Where 1P=one-point; 2P=two-point; KJC=knee joint centre; KJC1=tibial spine base; KJC2=tibial spine tips; KJC3=tibial plateau centre; n/a=not available (all mean angles in degrees (\pm SD)).

24a: 1P KJC1 (n=24) Alignment category	Shaft length (cm)				
	Max	10	9	8	7
Varus <178° (n=10)	176.31 (2.02)	175.47 (1.56)	174.68 (1.50)	173.82 (1.47)	172.60 (1.53)
Neutral 178 -182° (n=10)	180.76 (0.87)	180.33 (1.05)	179.90 (1.29)	179.24 (1.60)	178.19 (1.95)
Valgus >182° (n=4)	182.97 (0.62)	182.96 (0.71)	182.99 (0.83)	182.88 (1.11)	182.60 (0.93)

24b: 1P KJC2 (n=24) Alignment category	Shaft length (cm)				
	Max	10	9	8	7
Varus <178° (n=5)	176.43 (0.61)	176.46 (0.71)	176.04 (0.81)	175.58 (0.95)	174.75 (1.24)
Neutral 178 -182° (n=8)	180.72 (1.17)	179.96 (1.10)	179.45 (1.10)	178.88 (1.21)	178.01 (1.40)
Valgus >182° (n=11)	183.72 (0.96)	184.10 (1.21)	184.19 (1.49)	184.15 (1.83)	184.02 (2.27)

24c: 1P KJC3 (n=24) Alignment category	Shaft length (cm)				
	Max	10	9	8	7
Varus <178° (n=8)	176.73 (1.57)	175.90 (1.25)	175.39 (1.46)	174.66 (1.64)	173.82 (1.74)
Neutral 178 -182° (n=14)	180.56 (0.85)	179.80 (0.99)	179.28 (1.16)	178.54 (1.35)	177.47 (1.53)
Valgus >182° (n=2)	183.32 (0.34)	182.61 (0.45)	182.29 (0.88)	181.76 (0.97)	180.84 (1.24)

24d: 2P KJC1 (n=24) Alignment category	Shaft length (cm)				
	Max	10	9	8	7
Varus <178° (n=1)	176.95 (n/a)	177.29 (n/a)	177.14 (n/a)	177.06 (n/a)	176.62 (n/a)
Neutral 178 -182° (n=13)	180.43 (1.54)	180.04 (1.41)	179.71 (1.34)	179.39 (1.36)	178.79 (1.44)
Valgus >182° (n=10)	183.01 (0.53)	183.09 (0.65)	183.05 (0.83)	182.81 (1.15)	182.36 (1.56)

24e: 2P KJC2 (n=24) Alignment category	Shaft length (cm)				
	Max	10	9	8	7
Varus <178° (n=0)	n/a n/a	n/a (n/a)	n/a (n/a)	n/a (n/a)	n/a (n/a)
Neutral 178 -182° (n=10)	180.39 (1.72)	180.23 (1.41)	180.07 (1.33)	179.85 (1.35)	179.40 (1.42)
Valgus >182° (n=14)	183.62 (0.78)	183.85 (1.03)	183.84 (1.28)	183.79 (1.48)	183.59 (1.90)

24f: 2P KJC3 (n=24) Alignment category	Shaft length (cm)				
	Max	10	9	8	7
Varus <178° (n=2)	178.25 (0.26)	177.72 (0.17)	177.40 (0.41)	176.87 (0.74)	176.52 (1.04)
Neutral 178 -182° (n=12)	180.80 (1.70)	180.53 (1.35)	180.33 (1.19)	180.05 (1.18)	179.59 (1.22)
Valgus >182° (n=10)	182.90 (0.92)	182.93 (0.83)	182.80 (0.81)	182.58 (0.93)	182.16 (1.09)

4.2.6 Conclusion

The results from this pilot study have shown that agreement between 10cm and the shortest 7cm shaft length AA angles on Bland Altman plots (Figure 38a-f) was unsatisfactory for all KJCs using the 1P method and improved slightly, as smaller mean differences were shown, for all KJCs using the 2P method. On the whole 2P methods show smaller mean differences and tighter 95% LoA than 1P methods, indicating less variation using a 2P method, similar to findings reported in the previous pilot study. KJC3 (tibial plateau centre) displayed the narrowest LoA overall and was less prone to systematic bias than the other KJCs.

When alignment is categorised, there was consistent overestimation (up to a maximum of nearly $+3^\circ$) of AA alignment for varus and neutral knees with shaft lengths $<10\text{cm}$ using the 1P method, this was also seen to a lesser extent ($\leq 1.25^\circ$) in neutral knees using the 2P method (varus data not fully available).

Mean difference calculation from 10cm shows that greatest variation in AA angle occurs with the shortest shaft length distance of 7cm (by $\leq 2.20^\circ$) using the 1P method and this was reduced to $\leq 1^\circ$ using the 2P method. It is therefore clear from these pilot study results that using shorter shaft lengths of 7 and 8cm reduces the AA angle precision on AP view SLRs in full knee extension compared with using a 10cm shaft length. This was a similar finding to Wong and colleagues who have shown this in PA fixed flexion SLRs (Wong et al., 2009).

As current convention opts to use the maximum shaft length possible when 10cm is not available, it was also included in this pilot study. However, as the maximum shaft length can vary in each SLR then this can cause subsequent variation in the AA angle measurements, so this will not be adopted. It may be possible to use a 9cm shaft length as a substitute. However the preferred option to achieve maximum accuracy in this thesis is to include radiographs with a 10cm shaft length and exclude those that do not have a 10cm shaft length from future alignment analyses. To assess whether this potentially introduces a bias, alignment measurements were collected at 7cm and 10cm shaft lengths for further comparison in a larger sample.

4.3 Pilot study 3

Care has been taken throughout this thesis to identify, consider, adjust for and interpret potential errors or biases that may be present within each study. The term agreement is used to quantify the extent to which readings taken using two similar tools, or readings taken on two occasions by the same person or by two different people are the same or differ. The following section describes the methods utilised to calculate levels of agreement in the KneeMorf alignment data collection process.

4.3.1 Digital versus manual alignment

4.3.1.1 Background

To ensure the newly designed KneeMorf software (OxMorf 1.6.21.D4) is comparable to the traditional manual method of measuring knee joint AA angles using a goniometer, a pilot study comparing agreement between the two was completed. As the 2P method of AA alignment creates independent axes for the femur and tibia, the intersection of these axes often occurs outside of the knee (McDaniel et al., 2010) it is therefore difficult to measure these angles manually with a goniometer. Digitally this issue is overcome using a software Cobb angle tool which allows measurement of an angle subtended by lines that may not intersect within the radiograph field of view. For this reason it was only possible to assess agreement between digital and manual measurements using the 1P method.

4.3.1.2 Aim

- To assess agreement between 1P method knee joint AA angles measured using digital radiograph images with KneeMorf software compared to the traditional manual method of measuring joint alignment using a goniometer on plain film radiographs.

4.3.1.3 Method

Left and right knee AA angles using the 1P method for the different KJCs at 10cm shaft lengths from 10 Y1 visit plain film radiographs were measured with a goniometer to the nearest 0.5° by the author giving a total of 20 knees (see Figure 27, section 3.5.4.2 for details of methodology).

The equivalent 10 bilateral knee Y1 visit digitised images were read for alignment by the author using KneeMorf computer software (see appendix 19 for KneeMorf alignment manual), and the knee alignment angles (in degrees) were calculated using Matlab R2011a program (version 7.12) and exported to an Excel spreadsheet file.

4.3.1.4 Analysis

All analysis was completed using Stata version 13.0 (Stata Corp, College Station, Texas, USA). Digital and manual knee AA angle results for the different KJCs at 10 cm shaft lengths were compared using Bland Altman plots to assess the agreement between the two methods of measurement (Bland and Altman, 1986). Agreement between the digital and manual angle readings was demonstrated by calculating the mean difference between the two readings. LoA were then calculated by adding and subtracting twice the SD to the mean difference. The SE of the mean was calculated thereby providing 95% CIs for the likely mean disagreement between the two readings.

4.3.1.5 Results

A demographic summary of the 10 women with 20 knees from the Y1 visit participating in this pilot study is shown in Table 25. The majority, 17 knees from 18 women, had no RKO with K&L grade 0 or 1, the remaining 3 knees from 2 women had RKO with K&L grade 2.

Table 25: Pilot study 3 demographics

Where BMI=body mass index; IQR=inter-quartile range; K&L=Kellgren & Lawrence.

Y1 demographic	n=20 knees
Age (years) median (IQR)	54 (52-55)
BMI (kg/m ²) median (IQR)	25.1 (22.3-27.4)
K&L grade 0 (%)	80.0
K&L grade 1 (%)	5.0
K&L grade 2 (%)	15.0
K&L grade 3 (%)	0
K&L grade 4 (%)	0

The agreement parameters calculated from the Bland Altman plots (Figure 41a-c) for each of the KJCs are shown below in Table 26.

Table 26: Bland Altman plot agreement parameters for digital v manual readings

Where 1P=one-point; CI=confidence interval; KJC=knee joint centre; KJC1=tibial spine base; KJC2=tibial spine tips; KJC3=tibial plateau centre; LoA=limits of agreement; SD=standard deviation; SE=standard error (all units in degrees).

n=20 KJC	Mean diff.	SD	SE	95% CI	95% LoA
1P KJC1 10	-0.54	1.34	0.30	-1.17, 0.09	-3.17, 2.09
1P KJC2 10	0.29	0.76	0.17	-0.07, 0.65	-1.21, 1.79
1P KJC3 10	-0.27	1.14	0.26	-0.80, 0.27	-2.51, 1.98

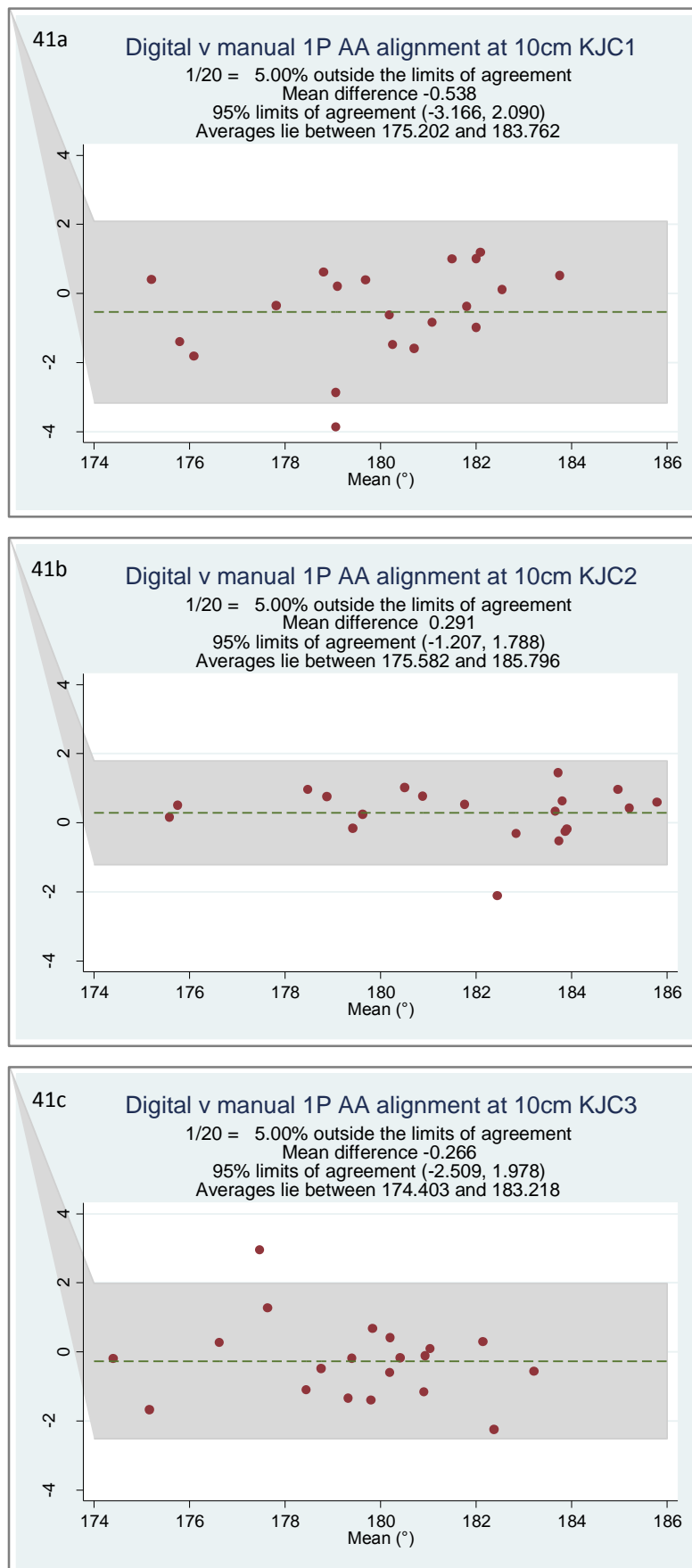
The Bland Altman plots (Figure 41a-c) and Table 26 results show that the mean difference between the digital and manual readings were small at less than 0.6° , which is $<1^\circ$ therefore not clinically significant (Cicuttini et al., 2004). The smallest mean difference was at KJC3 (tibial plateau centre). The Bland Altman plots (Figure 41a-c) show no obvious bias between the digital and manual methods, this was also demonstrated by the fact that zero lies within each of the 95% CI for the mean differences in Table 26. In addition, almost all of the 20 measurements were within the upper and lower LoA (two SDs either side of the mean) on the Bland-Altman plots, indicating overall good agreement between digital and manual readings.

4.3.1.6 Conclusion

Overall there was good agreement between KneeMorf digital and manual goniometer readings for the 1P AA measurement method indicating that these two methods were comparable. The centre of the tibial plateau (KJC3) showed the least mean difference between the digital and manual 1P methods. There were additional advantages to using the digital method over the traditional manual method:

- It is quicker to perform.
- The KneeMorf software is capable of zooming in on parts of the radiograph image allowing more accurate placement of bony landmarks.
- The transparent film that is used during the manual method can on occasions slide on the x-ray box which can affect manual measurement.
- The manual method relies on a goniometer to measure angles this is limited to measuring in 0.5° increments which could also lead to further inaccuracies and reduced reliability.

Figure 41: Bland Altman plots for digital v manual readings



4.3.2 Intra-reader alignment agreement

Intra-reader agreement for AA angle measurement with 10cm shaft length using the KneeMorf software for the author was established. Fifty right knee radiograph images (25 images from Y1 visit and 25 images from Y20 visit) were read for alignment using the KneeMorf software (OxMorf 1.6.21.D4) on two occasions a week apart. Knee AA angles (in degrees) were subsequently calculated using Matlab R2011a program (version 7.12) and exported to an Excel spreadsheet file. Bland-Altman plot parameters were collated and one-way analysis of variance (ANOVA) ICCs (1, 1) were calculated as these data were continuous in nature and supplied by one reader (Shrout and Fleiss, 1979, Rankin and Stokes, 1998).

An ICC ratio of 1 indicates perfect reliability with no measurement error, whilst an ICC of 0 indicates no reliability (Streiner and Norman, 2008). The ICCs and their 95% CI values for each KJC using 1P and 2P methods, and the Bland-Altman plot parameters were calculated using Stata version 13.0 (Stata Corp, College Station, Texas, USA).

Table 27: Intra-reader alignment agreement

Where 1P=one-point; 2P=two-point; CI=confidence interval; ICC=intra-class correlation; KJC=knee joint centre; KJC1=tibial spine base; KJC2=tibial spine tips; KJC3=tibial plateau centre; LoA=limits of agreement; SD=standard deviation; SE=standard error (all units in degrees unless otherwise stated).

n=50 KJC	Mean diff.	SD	SE	95% CI	95% LoA	ICC	95% CI	P value
1P KJC1	0.63	1.10	0.16	0.31, 0.94	-1.52, 2.78	0.97	0.95, 0.98	<0.001
1P KJC2	0.11	0.77	0.11	-0.11, 0.33	-1.40, 1.63	0.99	0.98, 0.99	<0.001
1P KJC3	0.11	0.67	0.09	-0.08, 0.30	-1.20, 1.42	0.99	0.98, 0.99	<0.001
2P KJC1	0.35	0.68	0.10	0.16, 0.54	-0.98, 1.67	0.98	0.97, 0.99	<0.001
2P KJC2	0.10	0.54	0.08	-0.06, 0.25	-0.96, 1.16	0.99	0.98, 0.99	<0.001
2P KJC3	0.09	0.56	0.08	-0.06, 0.26	-1.01, 1.21	0.99	0.98, 0.99	<0.001

The Bland-Altman parameters in Table 27 show small mean differences at less than 1° for all measurements and tight 95% LoA. The 2P method showed the least differences with the smallest being 0.09° for 2P KJC3. Subsequently there was high intra-reader agreement with ICCs ranging from 0.97 to 0.99 for all the KJCs, with KJC2 and KJC3 being the greatest at ICCs of 0.99. Overall good intra-reader agreement was shown, although a limitation is that only right knees were assessed in this agreement study. Biologically a difference in

alignment between left and right knees is not expected however this is a small caveat for the main alignment studies that follow.

4.3.3 Inter-reader alignment agreement

The same fifty right knee radiograph images (25 images from Y1 visit and 25 images from Y20 visit) were read for alignment with 10cm shaft length using the KneeMorf software (OxMorf 1.6.21.D4) by an orthopaedic clinical research fellow (SJ) to establish inter-reader agreement between readers LG and SJ.

Knee AA angles (in degrees) were subsequently calculated using Matlab R2011a program (version 7.12) and exported to an Excel spreadsheet file.

Bland-Altman plot parameters were collated and two-way ANOVA ICCs (3, 1) were calculated as this data was continuous in nature and supplied by two readers (LG & SJ) (Shrout and Fleiss, 1979, Rankin and Stokes, 1998). The ICCs and their 95% CI values for each KJC using each method and the Bland-Altman plot parameters were calculated using Stata version 13.0 (Stata Corp, College Station, Texas, USA).

Table 28: Inter-reader alignment agreement

Where 1P=one-point; 2P=two-point; CI=confidence interval; ICC=intra-class correlation; KJC=knee joint centre; KJC1=tibial spine base; KJC2=tibial spine tips; KJC3=tibial plateau centre; LoA=limits of agreement; SD=standard deviation; SE=standard error (all units in degrees unless otherwise stated).

n=50 KJC	Mean diff.	SD	SE	95% CI	95% LoA	ICC	95% CI	P value
1P KJC1	1.58	1.42	0.20	1.17, 1.98	-1.20, 4.35	0.96	0.94, 0.98	<0.001
1P KJC2	-0.14	0.78	0.11	-0.36, 0.08	-1.66, 1.38	0.99	0.98, 0.99	<0.001
1P KJC3	-0.07	0.73	0.10	-0.27, 0.14	-1.49, 1.36	0.99	0.97, 0.99	<0.001
2P KJC1	0.63	0.94	0.13	0.36, 0.90	-1.21, 2.47	0.98	0.96, 0.99	<0.001
2P KJC2	-0.22	0.64	0.09	-0.40, -0.04	-1.48, 1.03	0.99	0.98, 0.99	<0.001
2P KJC3	-0.19	0.66	0.09	-0.38, -0.01	-1.48, 1.10	0.98	0.97, 0.99	<0.001

The Bland-Altman parameters in Table 28 show larger mean differences between the two readers for KJC1 (tibial spine base) which is clinically significant ($\geq 1^\circ$) for the 1P method and less so for the 2P method. In comparison, the mean differences for KJC2 and KJC3 were much smaller for both the 1P and 2P methods, with the smallest being -0.07° and -0.19° at KJC3 for both 1P and 2P methods. Subsequently there were higher ICCs 0.98 or 0.99 with tighter 95% CIs for KJC2 and KJC3. Overall this shows good inter-

reader agreement between the two readers, although as discussed previously, a limitation is that only right knees were assessed in this agreement study.

4.4 Chapter summary

4.4.1 Pilot study 1 key points

- Overall mean differences between the standard 10cm shaft length and 9, 9.5, 10.5 and 11cm shaft lengths were small (approximately $\leq \pm 0.5^\circ$) and not clinically significant, therefore it is acceptable to use 10cm as a standard shaft length in future AA analysis in this thesis.
- Good agreement at all three KJCs when 11cm v 9cm shaft lengths were compared – KJC2 (tibial spine tips) showed the least difference and 2P methods showed smaller mean differences than 1P methods, though the sample size was too small to definitively pick one method or one KJC.
- The number of knees classified in each alignment category as either varus, neutral or valgus was dependent on the KJC and the method (1P or 2P) used.

4.4.2 Pilot study 2 key points

- Agreement between 7cm and 10cm shaft length AA angles was poor.
- Similar to the previous pilot study, 2P methods continue to show less variation than 1P methods.
- KJC3 (tibial plateau centre) displays the narrowest LoA overall and was less prone to systematic bias than the other KJCs.
- Consistent overestimation of varus and neutral knees with shaft lengths <10cm using 1P method, and to a lesser extent in neutral knees using 2P method.
- Shorter shaft lengths reduced the AA angle precision on AP view SLRs in full extension compared to using a 10cm shaft length.
- Future AA analyses will be based on a 10cm shaft length and knees without 10cm will be excluded.
- To assess whether this potentially introduces a bias, alignment measurements will be collected at 7cm and 10cm shaft lengths for further comparison in a larger sample.

4.4.3 Pilot study 3 key points

- Good agreement between KneeMorf digital and manual goniometer readings for 1P AA measurement method showing the two methods were comparable and KJC3 (tibial plateau centre) showed the least mean difference.
- High intra- and inter-reader agreement with KJC2 (tibial spine tips) and KJC3 (tibial plateau centre) displaying least mean differences and greatest ICCs.

4.4.4 Final summary

- A 10cm shaft length will be used in all future alignment analyses in this thesis as use of shorter shaft lengths affects angle measurement.
- Measuring alignment digitally with the KneeMorf software was comparable to the manual method.
- Good intra- and inter-reader agreement was shown for KneeMorf alignment measurements.
- 2P methods may be more accurate as they display less variation than 1P methods, however the alignment literature contains a mix of 1P and 2P methods therefore for comparative purpose both methods will be presented in this thesis.
- Alignment category classification was dependent on whether a 1P or 2P method was used indicating method specific alignment categories are required.
- In these small pilot studies KJC2 (tibial spine tips) and KJC3 (tibial plateau centre) display least mean differences, greatest reproducibility and least systematic bias (for KJC3) however further data is required in order to make a definitive KJC choice.

5. Chapter 5: Knee alignment cross-sectional associations with knee osteoarthritis

5.1 Background

Knee mal-alignment is a common clinical sign of KOA. Mal-alignment in either a varus (bow leg) or valgus (knock knee) direction influences the load distribution across the knee joint, leading to subsequent degenerative changes (Tetsworth and Paley, 1994). The gold standard measurement of alignment is the MA measuring the HKA angle on a FLR (14 x 51 inch) (Tetsworth and Paley, 1994, Hsu et al., 1990). However, as discussed previously in the literature review (section 2.6.1) the main drawbacks associated with this MA alignment method are greater radiation exposure and the requirement for specialist radiography equipment and expertise making it costly both in regards to resources and radiation, and so the availability of FLRs in epidemiological studies is limited. MA mal-alignment has been shown to be a potent risk factor for KOA progression (Sharma et al., 2001, Cerejo et al., 2002, Felson et al., 2003, Felson et al., 2004, Sharma et al., 2008, Sharma et al., 2010) and a predictor of functional decline (Sharma et al., 2001). Its role in the incidence of KOA is less proven with only one study demonstrating varus MA alignment (Sharma et al., 2010) and one study demonstrating valgus MA alignment (Felson et al., 2013) increase the risk of the initial development of KOA.

An alternative knee alignment measurement known as the AA alignment method was first reported comparable to the MA alignment method by Kraus in 2005 (Kraus et al., 2005) and then subsequently by other study groups (Hinman et al., 2006, Issa et al., 2007, Colebatch et al., 2009, Felson et al., 2009, Chang et al., 2010). The AA alignment method measures the FTA on SLRs (14 x 17 inch) which are typically obtained in regular clinical practice, unlike FLRs which are generally not routine. Less radiation exposure is received from SLRs, making them safer, more convenient and more cost-effective than FLRs. AA mal-alignment has been shown to be a risk factor for KOA progression (Brouwer et al., 2007, Felson et al., 2009) and conflicting results have been reported for KOA incidence. Varus AA alignment has been

associated with incident RKOA in one cohort study by Brouwer and colleagues (Brouwer et al., 2007), but this was not evident in a case-control study by Hunter and colleagues (Hunter et al., 2007), indicating further research using the AA alignment method was required. However, consensus defining the optimal AA alignment method has not yet been reached (McDaniel et al., 2010), due to the variation in measurement technique in the current AA alignment literature. A range of different KJC locations have been used. One study uses the base of tibial spines mid-point (Brouwer et al., 2007), other studies use the tips of the tibial spine mid-point (Hunter et al., 2007, Wong et al., 2009, Zhai et al., 2007, Colebatch et al., 2009, Kraus et al., 2005), while the majority of studies simply use the centre of the tibial spines specifying neither the tips nor the base (Felson et al., 2002, Harvey et al., 2008, Janakiramanan et al., 2008, Nelson et al., 2009, Cicuttini et al., 2004, Lim et al., 2008a, Mazzuca et al., 2010, Teichtahl et al., 2006, Teichtahl et al., 2009b, Hinman et al., 2006, Issa et al., 2007).

Another variation in technique is that the majority of AA alignment publications to date predominantly use a 1P AA alignment method that measures the AA angle formed between the FAA and the TAA based on a single 1P KJC location. However, most of the MA alignment publications actually use a 2P method where the angle measured is formed by two separate axes: the femoral axis originating from the centre of the femoral head to the femoral inter-condylar notch point, and the tibial axis originating from the KJC location to the mid-point of the tibial plafond at the ankle. The more recently published MA v AA alignment comparative studies from Felson (Felson et al., 2009), Chang (Chang et al., 2010) and Sheehy (Sheehy et al., 2011) have used a 2P AA method compared to a 2P MA method, but it is not clear in the current literature if using a 1P AA method or 2P AA method is optimum and whether there are any differences between these methods.

As discussed in section 2.6.3.3, McDaniel and colleagues have been the only group to date to investigate the performance metrics of methods of AA alignment measurement using different KJCs against the gold standard MA alignment method (McDaniel et al., 2010). Although there was not a clearly preferred individual AA alignment method, their study results recommended standardising AA measurements using either method B (base of the tibial spine

mid-point) or method C (centre of the tibia) and suggested comparing 1P and 2P methods in larger studies.

These results form the basis of this cross-sectional AA alignment study in the Chingford cohort. AA alignment data was collected using the KneeMorf software program for 1P and 2P methods, at both the KJCs (base of the tibial spines mid-point and centre of the tibial plateau) recommended by McDaniel's study and a third KJC was also included using the tips of the tibial spine mid-point as this KJC is commonly reported in the AA alignment literature. There are no FLRs in the Chingford cohort available for AA alignment comparison against the gold standard, although substantial clinical outcome data has been collected, and so cross-sectional associations with SRKOA, RKOAs and knee pain were assessed.

5.2 Aim

The main aims of this study were:

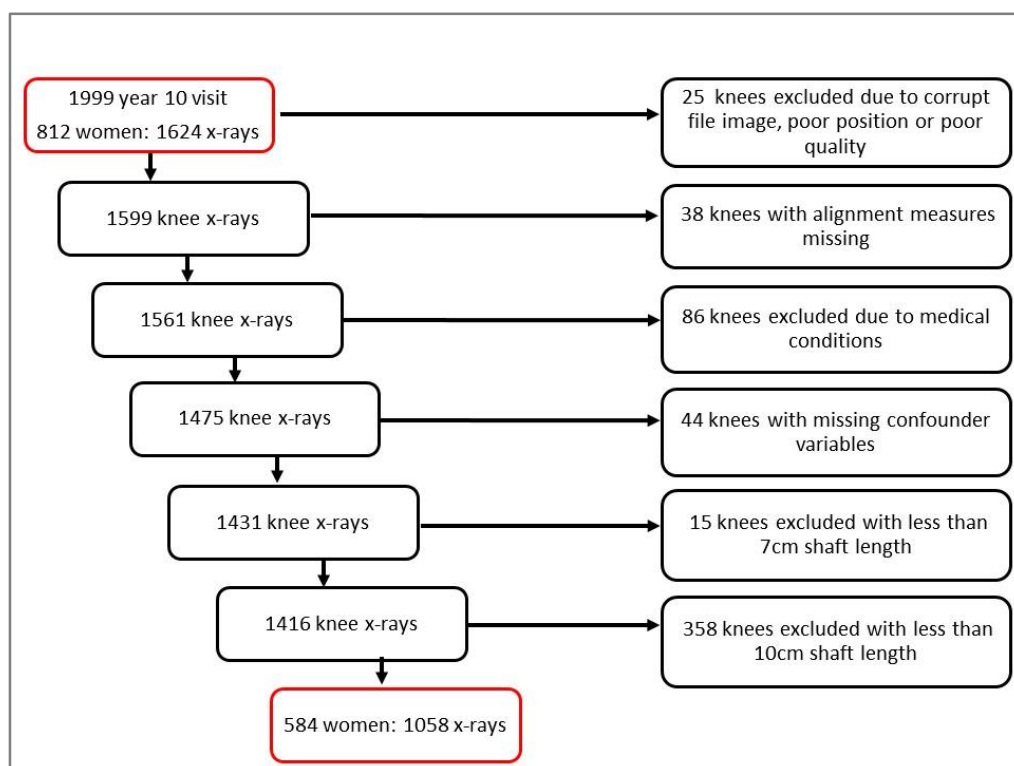
- 1) To determine the optimal 1P and 2P AA method based on reproducibility and cross-sectional associations with clinical outcomes.
- 2) To define appropriate varus, neutral, valgus alignment categories for the chosen optimal 1P and 2P AA method.
- 3) To describe cross-sectional associations of chosen alignment categories for optimal 1P and 2P AA methods with SRKOA, RKOAs and knee pain.

5.3 Method

5.3.1 Study population

Participants included in this study were Chingford cohort women attending the Y10 clinical visit with accompanying Y10 knee SLRs and confounder variable data, who did not report an inflammatory or neurological medical condition. The derivation of the study population is shown in Figure 42 and at the outset 812 women attended the Y10 visit with a possible 1624 knee SLRs.

Figure 42: Derivation of cross-sectional analysis sample of 1058 knees



A total of 25 knee images were excluded due to either: corrupt scanned file images, poor positioning on the radiograph or poor image quality thereby resulting in AA alignment not being measured. This left a total of 1599 knee images, 38 knee images were excluded as they had one or more of the alignment measurements missing, leaving 1561 knee images. A total of 86 knee images were excluded due to 43 women having one of the medical conditions listed in the exclusion criteria (section 3.4.2). A further 22 women (44 knees) were excluded as they were missing confounder variable data of either: age, BMI, or presence of knee injury. Finally a total of 373 knees were excluded as they had either a femoral, or tibial, or both femoral and tibial shaft length of less than 10cm and previous pilot study results (section 4.4.4) have concluded that a 10cm shaft length is optimum for measuring AA alignment. This left a final total of 1058 ‘perfect’ knees, from 584 women, available for inclusion in this cross-sectional analysis.

5.3.2 Imaging

AP fully-extended weight bearing bilateral knee SLRs were taken at the Y10 clinic visit using a standardised protocol, that was established at the Y1 baseline visit and repeated for all subsequent radiograph clinic visits (Hart et al., 1999) as previously described in section 3.5.3.

All Y10 radiographs were graded for K&L, osteophytes and JSN by DH, further details and intra-observer reproducibility are reported in section 3.5.3. All knees with TKRs and UKRs were excluded from analysis as AA alignment measurements were unobtainable with a prosthesis in situ (n=8 knees at the Y10 clinic visit).

5.3.3 Alignment measurement

AA alignment was measured by the author manually placing alignment points on each digitised SLR image with a computer mouse using the KneeMorf software program as described in section 3.5.4.2 and further detail of point placement is provided in the KneeMorf alignment manual in appendix 19. As there is currently no gold standard method for measuring AA alignment on a SLR, a total of six, three 1P (Figure 28a-c) and three 2P (Figure 28d-f) methods of measuring AA were tested using three tibial KJCs:

- a) tibial spine base mid-point (KJC1)
- b) tibial spine tips mid-point (KJC2)
- c) tibial plateau centre (KJC3)

For both 1P (Figure 27) and 2P (Figure 31) methods the AA angle created by the intersection of the FAA and the TAA was measured medially.

All Y10 SLRs were measured for alignment in batches of 50 images by the author. They were read individually, in a random order and blinded to all clinical information. All measurements were performed on one SLR before beginning measurements on another. The ICCs for intra-reader reproducibility for one set of 50 images (read twice by the author one week apart) for all six AA measurements were high between 0.97 - 0.99. All the 95% LoA were similar although 1P KJC1 (-1.52, 2.78) and 2P KJC1 (-0.98, 1.67) were greatest (Table 27, section 4.3.2).

All angles were measured to within 0.01° by the KneeMorf software program. Usually angles less than 180° are considered varus and angles greater than

180° are considered valgus. As associations between AA alignment and clinical outcomes were non-linear it was not possible to use AA alignment as a continuous measure for analysis, therefore AA alignment categories were required. Previous pilot studies (section 4.4) identified that the varus (<178°), neutral (178-182°) and valgus (>182°) alignment categories defined by Colebatch and colleagues (Colebatch et al., 2009) for AP SLRs taken in full extension, are not necessarily appropriate to apply to both 1P and 2P AA methods therefore new alignment categories will be defined using associations with clinical outcomes.

5.3.4 Outcome variables

All outcomes were knee-based. The primary outcome variable was Y10 SRKOA; RKOAs and knee pain were secondary outcomes as defined in section 3.6.

5.3.5 Confounding variables

Adjustments were made for Y10 age, BMI and knee injury confounding variables as defined in section 3.7.

5.4 Analysis

All analysis was completed using Stata version 13.0 (Stata Corp, College Station, Texas, USA). Prior to analysis, data distribution was checked using histograms and scatter plots for inconsistencies, outliers, and to assess whether normal distributions existed. Where possible both knees from each woman were included in cross-sectional analyses.

The demographic and clinical characteristics of the study population were presented for the included and excluded Y10 cohort as the median with IQR for non-normally distributed continuous variables, and mean with SD for normally distributed continuous variables. Categorical variables were presented as a number and a percentage. Statistically significant differences in measured variables between the included and excluded cohort were examined using Kruskal Wallis test for age; two independent samples t-test for BMI, and chi-square tests for knee injury, knee pain, RKOAs and SRKOAs. Comparisons were also made between women with knees 10cm or more in shaft length, to those excluded knees with a shaft length of less than 10cm and to those with a shaft length of less than 7cm.

Bland-Altman plot parameters and ICCs for intra-reader and inter-reader reproducibility were calculated previously (see Table 27 section 4.3.2 and Table 28 section 4.3.3 respectively).

Pearson correlation coefficients were completed to determine the statistical significance of associations between each of the six AA alignment methods.

Cross-sectional associations between each of the six AA methods and the three clinical outcomes were examined using clustered t-tests to account for correlated knees. Statistically significant differences between knees with and without the clinical outcome were identified at the p value <0.05 level, however AA mean angle differences were only considered to be clinically significant if greater than 1° (Cicuttini et al., 2004).

Histograms of the chosen 1P and 2P methods were plotted which identified that alternative alignment category cut-off points to the varus <178°, neutral 178-182° and valgus >182° would be required for the 2P method as the mean values for each method differ by more than 2°. New alignment category cut-off points were based on the association with SRKOA clinical outcome, rather than on the association with MA alignment as FLRs were not available in the Chingford cohort. The following technique from Heim and colleagues (Heim et al., 2011), who determined optimal cut-off values for waist circumference in 70+ year old cohort, was adapted to establish appropriate alignment category cut-off points:

- a) 1P and 2P AA angles were plotted against the SRKOA outcome using restricted cubic spline regression functions with 5 knots (restricted cubic spline instead of linear spline was chosen as it provided a more conservative estimate of the association where data are often sparse).
- b) Optimal cut-off values for varus / neutral / valgus knee alignment with SRKOA were assessed visually by 3 independent readers (NA = reader 1, LG = reader 2 & MS = reader 3). A priori, the consensus for optimal alignment cut-off values was set where the probability of SRKOA outcome starts to decrease more rapidly for varus and increase more rapidly for valgus.
- c) The mean of the three values were calculated to the nearest degree to generate the appropriate varus / neutral / valgus cut-off values for both methods.

- d) AA knee alignment was then divided into the new varus / neutral / valgus categories and cross-sectional associations with SRKOA outcome controlling for confounders (age, BMI & knee injury) by GEE analysis was performed.
- e) Model fit using the original and new alignment category cut-off values was assessed using the Quasi-likelihood under the Independence Criterion (QIC) (Pan, 2001). A lower QIC value indicates a better model fit.

GEE was used to take into account the correlation between left and right knees in one individual. These analyses were executed for varus and valgus alignment, with neutral alignment as the reference group. GEE analyses were repeated for RKOAs and knee pain outcomes, and sensitivity analyses were completed for SRKOA and knee pain outcomes. SRKOA positive knees were compared to RKOAs negative (K&L grades 0 or 1) and knee pain negative (no pain in the preceding month); and knee pain positive knees were compared to knee pain negative knees. A further sensitivity analysis was completed to examine associations between medial and lateral JSN for RKOAs risk in varus and valgus knees respectively.

5.5 Results

5.5.1 Study population

A total of 1058 knees from 584 women were included in this cross-sectional study. Table 29 shows clinical characteristics for included and excluded women attending the Y10 Chingford study visit. Although the included women were slightly younger this difference was not clinically significant and all other characteristics were similar.

Table 29: Y10 clinical characteristics

Where AA=anatomic axis; BMI=body mass index; IQR=inter-quartile range; KJC=knee joint centre; K&L=Kellgren & Lawrence grade; n=number; RKOA=radiographic knee osteoarthritis; SD=standard deviation; SRKOA=symptomatic radiographic knee osteoarthritis; 1P=one point; 2P=two point.

Characteristic	Included Y10 cohort (n=1058 knees)	Excluded Y10 cohort (n=566 knees)	P value*
Age, median (IQR) years	62 (57-67)	63 (57-69)	0.004
BMI, mean (\pm SD) kg/m ²	26.7 (4.6)	26.8 (4.8)	0.67
Knee injury, %	16.5	15.9	0.78
Knee pain \geq 15 days, %	13.4	15.4	0.28
RKOA \geq 2 K&L grade, % (n)	27.9	27.9 (n=544)	0.98
SRKOA, % (n)	6.1	8.3 (n=544)	0.09
Mean AA angle° (\pm SD)			
1P KJC1	180.23 (3.70)	-	-
1P KJC2	182.72 (3.40)	-	-
1P KJC3	180.11 (2.93)	-	-
2P KJC1	182.47 (2.78)	-	-
2P KJC2	183.64 (2.66)	-	-
2P KJC3	182.53 (2.51)	-	-

*P values compare age using Kruskal Wallis test; BMI using two sample t-test; injury, knee pain, RKOA & SRKOA using Chi-square test.

To see if there were any differences in clinical characteristics based on the shaft length available on the knee SLRs, comparisons were made between women with the 1058 knees with a shaft length of 10cm or more, to the women with 358 knees excluded with a shaft length of less than 10cm and to the women with 15 knees excluded with a shaft length of less than 7cm. Results were identical for both the 1P and 2P methods at all 3 KJCs, therefore a summary is presented in Table 30. Similar to Table 29, the women with knees 10cm or more in shaft length in the included cohort were slightly younger ($p=0.02$) although this was not clinically significant, than women with knees less than 10cm. All other comparisons between these two groups were similar. Women with knees 10cm or more in shaft length had a greater mean BMI 26.7 kg/m² (\pm SD 4.6) versus 23.8kg/m² (\pm SD 3.8) ($p=0.01$), than women with knees less than 7cm shaft length, however the remaining comparisons between these two groups were similar.

Table 30: Y10 clinical characteristics for different shaft lengths

Where BMI=body mass index; IQR=inter-quartile range; K&L=Kellgren & Lawrence grade; n=number; RKO=radiographic knee osteoarthritis; SRKO=symptomatic radiographic knee osteoarthritis.

Characteristic	Included Y10 knees (≥ 10 cm) (n=1058)	Knees < 10 cm (n=358)	P value* (< 10 v ≥ 10)	Knees < 7 cm (n=15)	P value* (< 7 v ≥ 10)
Age, median (IQR) years	62 (57-67)	63 (58-68)	0.02	60 (57-65)	0.60
BMI, mean (\pm SD) kg/m ²	26.7 (4.6)	26.9 (4.8)	0.61	23.8 (3.8)	0.01
Knee injury, %	16.5	13.7	0.22	6.7	0.31
Knee pain ≥ 15 days, %	13.4	15.4	0.36	20.0	0.46
RKO ≥ 2 K&L grade, %	27.9	28.5	0.83	26.7	0.92
SRKO, %	6.1	7.3	0.42	13.3	0.24

*P values compare age using Kruskal Wallis test; BMI using two sample t-test; injury, knee pain, RKO & SRKO using Chi-square test.

5.5.2 Correlation between methods

All 6 alternative AA methods were highly correlated with each other and statistically significant at $p < 0.001$ (Table 31). All 1P methods were correlated with each other $r = 0.84 - 0.91$. The 2P methods were more strongly correlated with each other $r = 0.93 - 0.96$. The 1P and 2P methods with the same KJC were correlated ranging from 0.87 (1P KJC3 v 2P KJC3) to 0.91 (1P KJC2 v 2P KJC2). The remaining 1P and 2P methods with different KJCs were less strongly correlated ranging from 0.77 (1P KJC1 v 2P KJC3) to 0.88 (1P KJC2 v 2P KJC1).

Table 31: Y10 Pearson correlation coefficients for alternative methods

Where 1P=one point; 2P=two point; KJC=knee joint centre.

n=1058 Method	1P KJC1	1P KJC2	1P KJC3	2P KJC1	2P KJC2	2P KJC3
1P KJC1	1					
1P KJC2	0.91	1				
1P KJC3	0.84	0.89	1			
2P KJC1	0.90	0.88	0.80	1		
2P KJC2	0.82	0.91	0.81	0.96	1	
2P KJC3	0.77	0.84	0.87	0.93	0.96	1

All results significant at $p < 0.001$

5.5.3 Cross-sectional associations with clinical outcomes

Table 32 shows the cross-sectional associations calculated using clustered t-tests (to account for correlated knees) between each AA alignment method and SRKOA, RKOAs and knee pain clinical outcomes. These results focus predominantly on SRKOA, as this was the primary clinical outcome in this study.

KJC

When examining the mean AA angles between each of the KJCs for SRKOA, it appears that mean AA angles calculated using KJC2 are greater (i.e. more valgus) by at least 2° for 1P, and by at least 1° for 2P methods compared to means AA angles from KJC1 and KJC3 in knees with and without SRKOA. These differences in mean AA angles measured using KJC2 also apply to RKOAs and knee pain outcomes which indicate a consistent difference in AA angle when it was measured at the tibial spine tips, whereas the mean AA angles measured at KJC1 and KJC3 were similar within 1P and 2P methods across all three of the clinical outcomes.

None of the three 1P KJCs were significantly different, although KJC3 has the greatest mean difference (0.63°) in knees with and without SRKOA. For the 2P method KJC3 had the greatest mean difference (1.02°) being statistically ($p=0.01$) and clinically significantly associated with SRKOA. This association also remained significant for 2P KJC3 ($p=0.02$) when the SRKOA sensitivity analysis comparing RKOAs negative (K&L 0 or 1) and pain negative (0 days pain) knees against RKOAs positive (K&L ≥ 2) and pain positive knees (≥ 15 days pain), was completed (Table 34).

1P v 2P method

Table 32 also highlights that the mean AA angles at all three KJCs calculated using a 2P method were all greater (i.e. more valgus) than the same angles calculated using a 1P method across all three clinical outcomes. This means that when the alignment category cut-off points were applied to the 2P method AA angles in the alignment classification Table 33, there were large differences in the number of knees classified into varus / neutral / valgus groups when compared to the 1P method, e.g. 1P KJC1 shows 301 knees were classified as varus ($<178^\circ$), whereas in the same knees only 45 were classified as varus if the 2P method is used. This indicated that alternative alignment category cut-off

points were required depending on whether a 1P or a 2P method was used (this is discussed further in section 5.5.5).

5.5.4 Choosing optimal 1P & 2P method

Based on the results shown in Table 32 and Table 34, and the previous KneeMorf pilot studies (section 4.4), it was now possible to decide which 1P and 2P method to carry forward for future alignment analyses. 1P KJC3 and 2P KJC3 were chosen for the following reasons:

Identification of KJC location

There are often difficulties in identifying the base of the tibial spine mid-point (KJC1) and tips of the tibial spines (KJC2) due to indistinct tibial spines and/or tibial spine osteophytes. Although KJC3 requires the exclusion of marginal tibial osteophytes on the tibial plateau, if these were present they were often easily identifiable for exclusion compared to osteophytes located on or around the tibial spines which create added difficulty locating the inter-spine mid-points required for KJC1 and KJC2.

Association with SRKOA clinical outcome

KJC3 showed the greatest association with the primary SRKOA outcome for both 1P and 2P methods in Table 32.

Digital v manual image agreement

The digital v manual AA angle comparison for 1P KJC3 showed good agreement (section 4.3.1.5) with a small mean difference of -0.27° (95% CI -0.80, 0.27). Unfortunately 2P method data was not available as it was not possible to manually measure these angles with a goniometer as the intersection of the independent femoral and tibial axes often occurred outside of the knee (McDaniel et al., 2010).

Intra-reader reproducibility

Intra-reader reproducibility was joint highest with KJC2 (section 4.3.2) for both the 1P and 2P KJC3 with ICCs at 0.99 (95% CI 0.98, 0.99) and p values <0.001 . Mean differences on Bland-Altman plots were smallest for KJC3 at 0.11° (95% LoA -1.20, 1.42) for 1P and 0.09° (95% LoA -1.01, 1.21) for the 2P method.

Inter-reader reproducibility

Although not required for this thesis as all alignment readings were performed by the author, the inter-reader reproducibility was also high for both 1P and 2P

KJC3 (section 4.3.3) with ICCs at 0.98 (95% CI 0.97, 0.99) and p values <0.001. Mean differences on Bland-Altman plots were smallest for KJC3 at -0.07 (95% LoA -1.49, 1.36) for 1P and -0.19 (95% LoA -1.48, 1.10) for 2P method.

On the basis of all these results, both the 1P and 2P KJC3 methods will be used in future alignment analyses in this thesis, however current results show that alternative alignment category cut-off points are required depending on which method is used so this is now examined.

Table 32: Y10 clustered t-test cross-sectional associations with clinical outcomes

Where 1P=one-point; 2P=two-point; CI=confidence interval; K&L=Kellgren & Lawrence grade; KJC=knee joint centre; KJC1=tibial spine base; KJC2=tibial spine tips; KJC3=tibial plateau centre; RKOA=radiographic knee osteoarthritis; SD=standard deviation; SRKOA=symptomatic radiographic knee osteoarthritis. All values shown are in degrees unless otherwise stated.

(n=1058) Method	Knee pain			RKOA			SRKOA		
	-(n=916) Mean (\pm SD) (95% CI)	+(n=142) Mean (\pm SD) (95% CI)	P value	-(n=763) Mean (\pm SD) (95% CI)	+(n=295) Mean (\pm SD) (95% CI)	P value	-(n=994) Mean (\pm SD) (95% CI)	+(n=64) Mean (\pm SD) (95% CI)	P value
1P KJC1	180.18 (4.62) (179.88,180.48)	180.55 (4.57) (179.78,181.31)	0.38	180.07 (4.60) (179.75,180.40)	180.65 (4.62) (180.12,181.18)	0.07	180.23 (4.61) (179.94,180.52)	180.26 (4.61) (179.10,181.42)	0.96
1P KJC2	182.68 (4.28) (182.40,182.95)	182.97 (4.24) (182.26,183.67)	0.45	182.57 (4.27) (182.27,182.87)	183.09 (4.28) (182.60,183.59)	0.07	182.73 (4.28) (182.47,183.00)	182.46 (4.27) (181.39,183.54)	0.63
1P KJC3	180.11 (3.63) (179.87,180.34)	180.12 (3.59) (179.52,180.72)	0.98	180.07 (3.62) (179.81,180.32)	180.23 (3.63) (179.81,180.64)	0.52	180.15 (3.62) (179.92,180.37)	179.52 (3.61) (178.61,180.43)	0.18
2P KJC1	182.47 (3.52) (182.24,182.70)	182.44 (3.49) (181.86,183.03)	0.94	182.43 (3.52) (182.18,182.68)	182.57 (3.53) (182.16,182.97)	0.55	182.50 (3.51) (182.28,182.72)	181.88 (3.51) (181.00,182.77)	0.17
2P KJC2	183.65 (3.39) (183.43,183.87)	183.60 (3.35) (183.04,184.15)	0.87	183.61 (3.38) (183.37,183.85)	183.72 (3.39) (183.33,184.11)	0.62	183.68 (3.37) (183.48,183.89)	182.94 (3.36) (182.10,183.79)	0.09
2P KJC3	182.56 (3.17) (182.35,182.76)	182.34 (3.13) (181.82,182.87)	0.45	182.55 (3.16) (182.33,182.78)	182.46 (3.17) (182.10,182.83)	0.67	182.59 (3.15) (182.39,182.79)	181.57 (3.14) (180.78,182.37)	0.01

Table 33: Y10 alignment category classification

Where 1P=one-point; 2P=two-point; KJC=knee joint centre; KJC1=tibial spine base; KJC2=tibial spine tips; KJC3=tibial plateau centre. All values shown are mean (\pm SD) in degrees unless otherwise stated.

(n=1058) Method	Alignment classification		
	Varus <178°	Neutral 178-182°	Valgus >182°
1P KJC1	175.93 (1.73) n=301	180.03 (1.11) n=431	184.47 (2.19) n=326
1P KJC2	176.53 (1.56) n=72	180.33 (1.13) n=394	185.05 (2.37) n=592
1P KJC3	176.40 (1.41) n=245	179.97 (1.14) n=555	183.93 (1.71) n=258
2P KJC1	176.27 (1.87) n=45	180.51 (1.05) n=422	184.33 (1.90) n=591
2P KJC2	176.23 (2.25) n=20	180.74 (0.99) n=238	184.69 (2.00) n=800
2P KJC3	176.23 (2.09) n=37	180.69 (0.97) n=408	184.13 (1.67) n=613

Table 34: Y10 clustered t-test sensitivity analysis cross-sectional associations with clinical outcomes

Where 1P=one-point; 2P=two-point; KJC=knee joint centre; KJC1=tibial spine base; KJC2=tibial spine tips; KJC3=tibial plateau centre; SA=sensitivity analysis; SRKOA= symptomatic radiographic knee osteoarthritis; K&L=Kellgren & Lawrence grade. All values shown are mean (\pm SD) in degrees unless otherwise stated.

Method	SA knee pain			SA SRKOA		
	-(n=734) Mean (\pm SD) (95% CI)	+(n=142) Mean (\pm SD) (95% CI)	P value	-(n=562) Mean (\pm SD) (95% CI)	+(n=64) Mean (\pm SD) (95% CI)	P value
1P KJC1	180.14 (4.43) (179.82,180.46)	180.55 (4.43) (179.81,181.29)	0.32	180.01 (4.30) (179.66,180.37)	180.26 (4.30) (179.18,181.34)	0.66
1P KJC2	182.63 (4.18) (182.32,182.93)	182.97 (4.18) (182.27,183.66)	0.34	182.48 (4.00) (182.14,182.81)	182.46 (4.00) (181.45,183.47)	0.98
1P KJC3	180.13 (3.61) (179.86,180.39)	180.12 (3.61) (179.52,180.72)	0.98	180.03 (3.44) (179.74,180.31)	179.52 (3.44) (178.65,180.39)	0.26
2P KJC1	182.45 (3.39) (182.20,182.69)	182.45 (3.39) (181.88,183.01)	0.99	182.37 (3.25) (182.11,182.64)	181.88 (3.25) (181.06,182.70)	0.25
2P KJC2	183.62 (3.29) (183.38,183.86)	183.60 (3.29) (183.05,184.14)	0.93	183.54 (3.13) (183.28,183.80)	182.94 (3.13) (182.15,183.73)	0.15
2P KJC3	182.57 (3.12) (182.34,182.80)	182.34 (3.12) (181.82,182.86)	0.43	182.51 (2.96) (182.27,182.76)	181.58 (3.14) (180.83,182.32)	0.02

5.5.5 Choosing optimal alignment categories

Figure 43 shows histograms of the chosen 1P and 2P methods for KJC3. Normal distributions are shown for both methods, but from these histograms the 2P method measurements are tighter, showing less variation (2P SD $\pm 2.51^\circ$ v 1P SD $\pm 2.93^\circ$) and indicating less measurement error with the 2P method as also previously shown in the KneeMorf pilot studies (section 4.4). Since the mean values between 1P and 2P methods differ by more than 2° , the varus ($<178^\circ$), neutral ($178-182^\circ$) and valgus ($>182^\circ$) alignment categories adopted from Colebatch and colleagues (Colebatch et al., 2009) (who studied AA versus MA alignment in a female only healthy population with AP FLRs images) applied to the 1P method would not be appropriate for the 2P method. As there were no pre-defined alignment categories in the current literature for an AA alignment 2P method, the technique described in the analysis section (5.4) was used to determine new appropriate alignment cut-off values for varus / neutral / valgus knees for both 1P and 2P methods. This was based on the association with SRKOA clinical outcome rather than on the association with MA alignment, since FLRs were not available in the Chingford cohort. As there was no gold standard to follow, a certain degree of arbitrariness is recognised with these categorisations and cut point positions. Figure 44 shows the new cut-point values generated for the 1P and 2P methods. For the 1P method the cut-point values remain the same as used previously varus $<178^\circ$, neutral $178-182^\circ$ and valgus $>182^\circ$. For the 2P method the new suggested cut-point values were varus $<180^\circ$, neutral $180-185^\circ$ and valgus $>185^\circ$. These new alignment categories were used in the GEE analysis in Table 35 and Table 36 to examine cross-sectional associations between the proposed cut-point values and SRKOA, RKOA and knee pain clinical outcomes.

Figure 43: Histograms of chosen methods

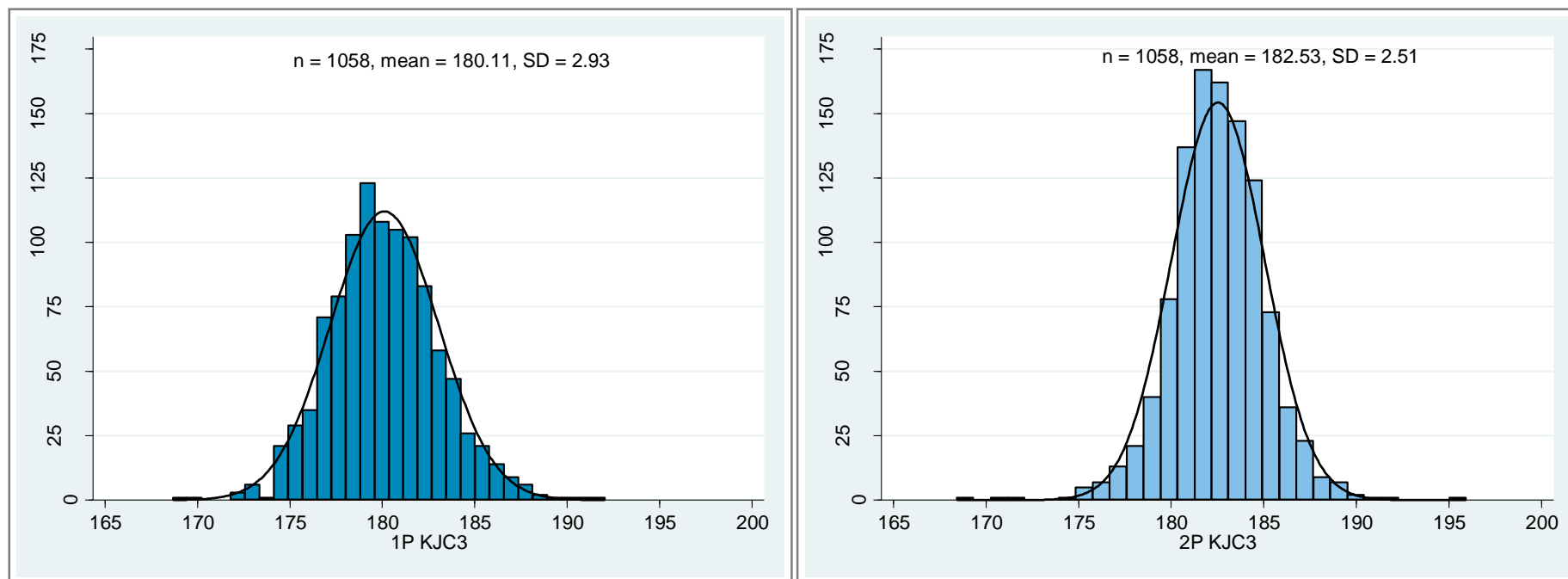
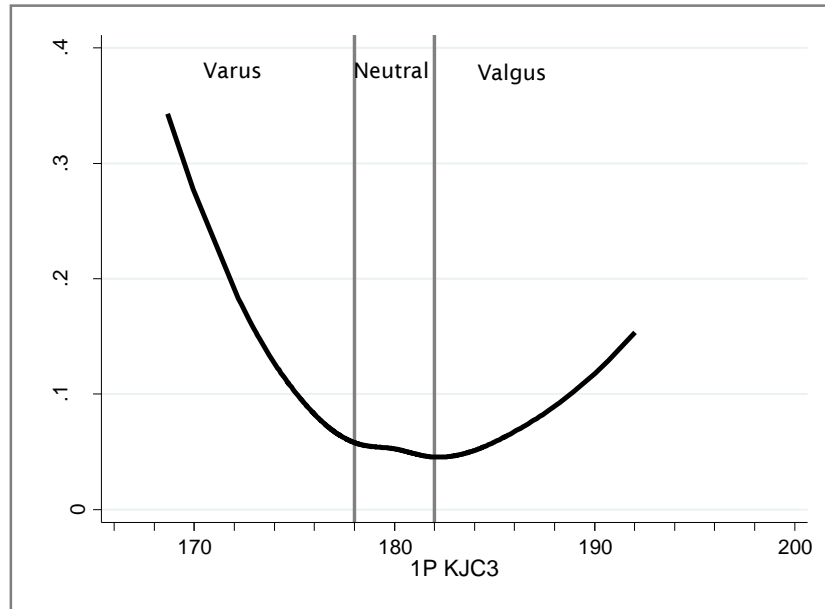


Figure 44: Cubic spline regression graphs with chosen cut-off values



1P KJC3

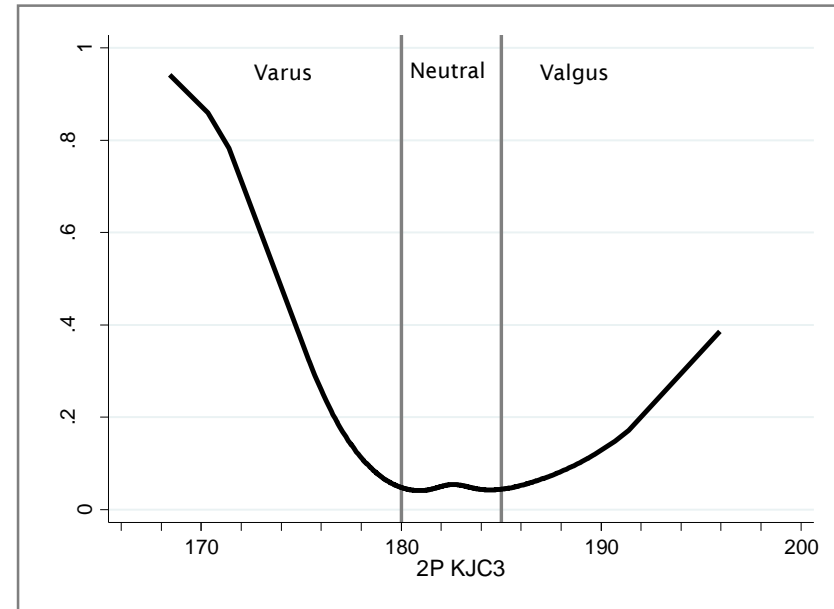
Reader 1: 178.0 – 182.5°

Reader 2: 177.5 – 182.5°

Reader 3: 178.0 – 182.0°

Mean: 177.8 – 182.3°

Rounded to: 178.0 – 182.0°



2P KJC3

Reader 1: 180.5 – 184.5°

Reader 2: 180.5 – 185.5°

Reader 3: 180.0 – 185.5°

Mean: 180.3 – 185.0°

Rounded to: 180.0 – 185.0°

NB: please note different scales on y axes.

5.5.6 GEE cross-sectional associations with clinical outcomes

Alignment categories

The GEE logistic regression analyses in Table 35 show that the new cut-off alignment categories (neutral 180-185°, varus <180° and valgus >185°) for 2P KJC3 provide slightly lower odds ratios with tighter 95% CIs for all three outcomes than the previous alignment categories shown (neutral 178-182°, varus <178° and valgus >182°) in the final shaded row of Table 35. The QIC values give an indication of model fit with a lower QIC value indicating a better model fit. For SRKOA outcome, the QIC values between the new and previous alignment categories are identical at 758 in the unadjusted model and slightly lower at 723 in the adjusted model for the new categories compared to 724 for the previous categories. For RKOA outcome, the new categories show a better fit with lower QIC values in both the unadjusted (1822) and adjusted (1612) models compared to the equivalent unadjusted (1849) and adjusted (1624) for the previous categories. The reverse is true when it comes to knee pain outcome with slightly lower values seen for the previous categories (1243 unadjusted and 1236 adjusted) than the newly defined categories (1248 unadjusted and 1241 adjusted). Overall, the new cut-off alignment categories for 2P KJC3 are a better fit for the SRKOA and RKOA clinical outcomes and there is an improvement in the distribution of varus (n=134 v n=37) and valgus (n=146 v n=613) knees therefore the previous alignment categories are now dropped and all further results will focus on the 2P KJC3 using the new cut-off alignment categories.

SRKOA outcome

Varus versus neutral alignment was associated with increased risk of SRKOA outcome using the 2P method and this association remained significant (OR 1.86, 95% CI 1.10, 3.15) when adjusted for Y10 age, BMI and knee injury (second row Table 35). A similar, but non-significant trend was seen for the 1P method (adjusted OR 1.57, 95% CI 0.97, 2.54) in the first row Table 35. The varus versus neutral alignment results for the 2P method also remained significant (OR 1.83, 95%CI 1.07, 3.12) in the unadjusted 2P KJC3 sensitivity analysis SRKOA (Table 36), however full adjustment was not possible in this model due to reduced statistical power.

Across the three clinical outcomes in Table 35, the greatest associations between varus versus neutral alignment were demonstrated with SRKOA for both the 1P and 2P methods.

Valgus versus neutral alignment was not significantly associated with increased risk of SRKOA using either the 2P (adjusted OR 1.15, 95% CI 0.64, 2.08) or the 1P (adjusted OR 1.04, 95% CI 0.64, 1.71) KJC3 method.

RKOA outcome

Varus versus neutral alignment was also associated with increased risk of RKOA for the 2P method, but to a slightly lesser extent than SRKOA, with an adjusted OR 1.81 (95% CI 1.20, 2.73). Valgus versus neutral alignment was significantly associated with RKOA for the 2P method with an adjusted OR 1.79 (95% CI 1.20, 2.66), which was the greatest 2P valgus association across all three clinical outcomes.

For the 1P method, varus versus neutral alignment demonstrated greater association with RKOA (adjusted OR 1.13, 95% CI 0.79, 1.61) than valgus versus neutral alignment (adjusted OR 0.88, 95% CI 0.63, 1.25) but neither association was significant.

Knee pain outcome

There was greater association for valgus versus neutral knees compared to varus versus neutral knees for knee pain, although neither the 2P (OR 1.14, 95% CI 0.78, 1.66) nor 1P (OR 1.14, 95% CI 0.84, 1.56) associations were significant. These greater associations for valgus knees were maintained in the adjusted sensitivity analysis for knee pain in Table 36, but results remained non-significant.

Joint space narrowing

Due to the significant findings reported for varus and valgus alignment categories with RKOA in Table 35, an additional GEE analysis, was completed to examine if the varus and valgus associations with RKOA were related to medial and lateral JSN respectively (see Table 37). JSN was graded 0-3 (section 3.5.3) and was considered present in this analysis in knees graded 1 or above.

Table 35: Y10 cross-sectional GEE associations with clinical outcomes by alignment classification for chosen methods

Where 1P=one-point; 2P=two-point; KJC=knee joint centre; KJC3=tibial plateau centre; RKOA=radiographic knee osteoarthritis; K&L=Kellgren & Lawrence grade; SRKOA=symptomatic radiographic knee osteoarthritis; SD=standard deviation. *Adjusted for Y10 age, bmi and knee injury.

Method (n=1058 knees)		Knee pain			RKOA			SRKOA		
		- (n=916)	+ (n=142)	QIC	-(n=763)	+(n=295)	QIC	-(n=994)	+(n=64)	QIC
		OR (95% CI)	P value		OR (95% CI)	P value		OR (95% CI)	P value	
1P KJC3	Neutral 178-182° Reference	n=488 1.0 (-)	n=67 -	1248 1240	n=414 1.0 (-)	n=141 -	1869 1636	n=529 1.0 (-)	n=26 -	776 735
	Varus <178° Unadjusted	n=213 0.99 (0.70,1.39)	n=32 0.95		n=172 1.08 (0.79,1.48)	n=73 0.62		n=225 1.59 (0.96,2.63)	n=20 0.07	
	Adjusted*	0.98 (0.70,1.37)	0.90		1.13 (0.79,1.61)	0.49		1.57 (0.97,2.54)	0.07	
	Valgus >182° Unadjusted	n=215 1.19 (0.87,1.63)	n=43 0.26		n=177 1.01 (0.74,1.38)	n=81 0.93		n=240 1.17 (0.69,1.98)	n=18 0.56	
	Adjusted*	1.14 (0.84,1.56)	0.39		0.88 (0.63,1.25)	0.48		1.04 (0.64,1.71)	0.86	
NEW 2P KJC3	Neutral 180-185° Reference	n=682 1.0 (-)	n=96 -	1248 1241	n=602 1.0 (-)	n=176 -	1822 1612	n=746 1.0 (-)	n=32 -	758 723
	Varus <180° Unadjusted	n=113 0.98 (0.64,1.48)	n=21 0.92		n = 78 1.82 (1.26,2.64)	n=56 0.002		n=116 2.24 (1.28,3.93)	n=18 0.005	
	Adjusted*	0.92 (0.62,1.39)	0.70		1.81 (1.20,2.73)	0.005		1.86 (1.10,3.15)	0.02	
	Valgus >185° Unadjusted	n=121 1.21 (0.82,1.77)	n=25 0.33		n=83 2.01 (1.26,2.64)	n=63 <0.001		n=132 1.40 (0.74,2.64)	n=14 0.30	
	Adjusted*	1.14 (0.78,1.66)	0.49		1.79 (1.20,2.66)	0.004		1.15 (0.64,2.08)	0.64	
OLD 2P KJC3	Neutral 178-182° Reference	n=360 1.0 (-)	n=48 -	1243 1236	n=294 1.0 (-)	n=114 -	1849 1624	n=386 1.0 (-)	n=22 -	758 724
	Varus <178° Unadjusted	n=27 2.40 (1.21,4.79)	n=10 0.01		n = 16 2.12 (1.07,4.20)	n=21 0.03		n=27 4.86 (2.09,11.28)	n=10 <0.001	
	Adjusted*	2.03 (1.03,4.02)	0.04		1.96 (0.91,4.19)	0.08		3.25 (1.43,7.37)	0.005	
	Valgus >182° Unadjusted	n=529 1.25 (0.92,1.70)	n=84 0.15		n=453 0.83 (0.63,1.09)	n=160 0.17		n=581 1.09 (0.66,1.80)	n=32 0.74	
	Adjusted*	1.25 (0.92,1.70)	0.15		0.78 (0.58,1.06)	0.12		1.08 (0.67,1.76)	0.74	

Table 36: Y10 sensitivity analysis cross-sectional GEE associations by alignment classification for chosen methods

Where 1P=one-point, 2P=two-point, KJC=knee joint centre, KJC3=tibial plateau centre, SA=sensitivity analysis, K&L=Kellgren & Lawrence grade, SRKOA=symptomatic radiographic knee osteoarthritis.

*Adjusted for Y10 age, bmi and knee injury. ^adjusted for age & BMI only, unable to adjust for knee injury due to reduced power.

Method		SA knee pain		SA SRKOA	
		- (n=734)	+ (n=142)	-(n=562)	+(n=64)
		OR (95% CI)	P value	OR (95% CI)	P value
1P KJC	Neutral 178-182° Reference	n=394 1.0 (-)	n=67 -	n=307 1.0 (-)	n=26 -
	Varus <178° Unadjusted	n=166 1.05 (0.75,1.47)	n=32 0.76	n=128 1.23 (0.80,1.88)	n=20 0.35
	Adjusted*	1.04 (0.74,1.45)	0.82	1.12 (0.79,1.59)^	0.52^
	Valgus >182° Unadjusted	n=174 1.18 (0.87,1.59)	n=43 0.29	n=127 1.11 (0.73,1.69)	n=18 0.63
	Adjusted*	1.14 (0.84,1.53)	0.40	0.99 (0.74,1.35)^	0.98^
NEW 2P KJC3	Neutral 180-185° Reference	n=551 1.0 (-)	n=96 -	n=441 1.0 (-)	n=32 -
	Varus <180° Unadjusted	n=88 1.03 (0.69,1.56)	n=21 0.87	n=62 1.83 (1.07,3.12)	n=18 0.03
	Adjusted*	0.98 (0.65,1.47)	0.91	1.33 (0.88,2.03)^	0.18^
	Valgus >185° Unadjusted	n=95 1.21 (0.83,1.74)	n=25 0.32	n=59 1.59 (0.93,2.72)	n=14 0.09
	Adjusted*	1.16 (0.81,1.65)	0.43	1.37 (0.94,1.98)^	0.10^
OLD 2P KJC3	Neutral 178-182° Reference	n=285 1.0 (-)	n=48 -	n=220 1.0 (-)	n=22 -
	Varus <178° Unadjusted	n=23 2.24 (1.15,4.37)	n=10 0.02	n=14 2.99 (1.26,7.10)	n=10 0.01
	Adjusted*	1.84 (0.95,3.57)	0.07	1.39 (0.73,2.64)^	0.32^
	Valgus >182° Unadjusted	n=426 1.21 (0.89,1.63)	n=84 0.22	n=328 1.11 (0.73,1.67)	n=32 0.63
	Adjusted*	1.21 (0.89,1.64)	0.22	1.23 (0.93,1.62)^	0.15^

Chapter 5: Cross-sectional alignment

Table 37: Y10 cross-sectional RKOA GEE associations by joint space narrowing for chosen methods

Where 1P=one-point; 2P=two-point; JSN=joint space narrowing; KJC=knee joint centre; KJC3=tibial plateau centre; RKOA=radiographic knee osteoarthritis; K&L=Kellgren & Lawrence grade; SD=standard deviation. *Adjusted for Y10 age, bmi and knee injury. ~ data missing for 3 knees.

Method		RKOA		Medial JSN		Lateral JSN ~		Medial JSN (n=216)		Lateral JSN ~ (n=65)	
		- (n=763)	+ (n=295)	- (n=842)	+ (n=216)	- (n=990)	+ (n=65)	RKOA - (n=130)	RKOA + (n=86)	RKOA - (n=33)	RKOA + (n=32)
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
1P KJC3	Neutral 178-182° Reference	n=414 1.0 (-)	n=141 -	n=441 1.0 (-)	n=114 -	n=533 1.0 (-)	n=21 -	n=80 1.0 (-)	n=34 -	n=14 1.0 (-)	n=7 -
	Varus <178° Unadjusted	n=172 1.08 (0.79,1.48)	n=73 0.62	n=198 1.01 (0.77,1.33)	n=47 0.96	n=228 1.16 (0.70,1.93)	n=16 0.57	n=17 2.54 (1.36,4.72)	n=30 0.003	n=8 1.58 (0.52,4.83)	n=8 0.42
	Adjusted*	1.13 (0.79,1.61)	0.49	1.00 (0.76,1.31)	0.99	1.18 (0.69,2.01)	0.54	3.69 (1.66,8.21)	0.001	1.86 (0.37,9.40)	0.45
2P KJC3	Valgus >182° Unadjusted	n=177 1.01 (0.74,1.38)	n=81 0.93	n=203 0.89 (0.68,1.17)	n=55 0.42	n=229 1.87 (1.21,2.89)	n=28 0.005	n=33 1.27 (0.70,2.30)	n=22 0.44	n=11 1.98 (0.81,4.84)	n=17 0.13
	Adjusted*	0.88 (0.63,1.25)	0.48	0.88 (0.67,1.15)	0.34	1.88 (1.19,2.97)	0.007	1.15 (0.53,2.49)	0.72	2.53 (0.58,11.03)	0.22
	Neutral 180-185° Reference	n=602 1.0 (-)	n=176 -	n=628 1.0 (-)	n=150 -	n=744 1.0 (-)	n=32 -	n=109 1.0 (-)	n=41 -	n=22 1.0 (-)	n=10 -
2P KJC3	Varus <180° Unadjusted	n=78 1.82 (1.26,2.64)	n=56 0.002	n=97 1.33 (0.96,1.83)	n=37 0.09	n=126 0.85 (0.43,1.69)	n=7 0.65	n=6 5.38 (2.63,11.00)	n=31 <0.001	n=3 2.30 (0.71,7.44)	n=4 0.17
	Adjusted*	1.81 (1.20,2.73)	0.005	1.29 (0.94,1.78)	0.12	0.84 (0.42,1.68)	0.62	5.90 (2.44,14.26)	<0.001	2.76 (0.52,14.69)	0.23
	Valgus >185° Unadjusted	n=83 2.01 (1.26,2.64)	n=63 <0.001	n=117 1.06 (0.76,1.47)	n=29 0.74	n=120 2.54 (1.59,4.06)	n=26 <0.001	n=15 1.86 (0.88,3.92)	n=14 0.10	n=8 3.48 (1.40,8.67)	n=18 0.007
	Adjusted*	1.79 (1.20,2.66)	0.004	1.03 (0.74,1.43)	0.87	2.53 (1.55,4.13)	<0.001	1.55 (0.59,4.08)	0.38	5.11 (1.24,21.08)	0.02

Medial JSN

Out of the total 1058 knees in Table 37, 216 knees had a score of ≥ 1 medial JSN. When knees with medial JSN grade 1 or above ($n=216$) were compared to knees without medial JSN ($n=842$), there were stronger associations with varus versus neutral, than valgus versus neutral alignment for both the 2P and 1P method although neither were significantly associated. Of the 216 knees with medial JSN, 130 (60.2%) had a K&L grade 0 or 1, and 86 knees (39.8%) had K&L grade ≥ 2 . In knees with medial JSN, varus versus neutral alignment was significantly associated with increased risk of RKO for the 2P method with an adjusted OR 5.90 (95% CI 2.44, 14.26). A similar, but weaker association was seen for the 1P method with an adjusted OR of 3.69 (95% CI 1.66, 8.21). In knees with medial JSN, valgus versus neutral alignment was not significantly associated with RKO for either the 2P or the 1P method.

Lateral JSN

Out of the 1058 knees in total, only 65 knees had a score of ≥ 1 lateral JSN. When knees with lateral JSN grade 1 or above ($n=65$) were compared to knees without lateral JSN ($n=990$), strong associations were found when valgus was compared to neutral for both the 2P method (adjusted OR 2.53 (95% CI 1.55, 4.13)) and 1P method (adjusted OR 1.88 (95% CI 1.19, 2.97)), but not when varus was compared to neutral alignment. Of the 65 knees with lateral JSN, 33 knees (50.8%) had a K&L grade of 0 or 1, and 32 knees (49.2%) had a K&L grade ≥ 2 . In knees with lateral JSN, valgus versus neutral alignment was significantly associated with increased risk of RKO for the 2P method with an adjusted OR of 5.11 (95% CI 1.24, 21.08). A less strong and non-significant association was seen for the 1P method with an adjusted OR of 2.53 (95% CI 0.58, 11.03). In knees with lateral JSN, varus versus neutral alignment was not significantly associated with RKO for either the 2P or the 1P method.

Overall therefore, the significantly increased risk of RKO with the 2P method for varus versus neutral alignment may in part be explained by the association with medial JSN, and subsequent increased risk of RKO for valgus versus neutral alignment may in part be explained by lateral JSN. Unfortunately there was insufficient statistical power to focus this analysis solely on knees with K&L grade 2 or more.

5.6 Discussion

Aim 1: To determine the optimal 1P and 2P AA method

This study and the previous pilot study work (chapter 4) has identified KJC3 as the optimal 1P and 2P AA method to take forward for future alignment analyses. This recommendation is based on:

- a) Ease of identification of the tibial plateau KJC location compared with base of tibial spine (KJC1) or tips of tibial spine (KJC2) mid-points either due to indistinct tibial spines and/or tibial spine osteophytes.
- b) KJC3 showed the greatest statistical and clinical significant association with the primary SRKOA outcome for both 1P and 2P methods (Table 32).
- c) Good agreement for 1P KJC3 between digital versus manual image AA angle comparison (section 4.3.1).
- d) High intra- and inter-reader (section 4.3.2 and 4.3.3 respectively) reproducibility for both 1P and 2P KJC3 methods.

The choice to use 1P and 2P KJC3 is also further justified by the recommendation from McDaniel and colleagues (McDaniel et al., 2010). It is the only group to date to compare AA alignment performance metrics using different KJCs against the gold standard MA alignment method. Although posterior-anterior view SLRs in fixed flexion with a positioning frame were used, which is a different view and position to the anterior-posterior view in full extension SLRs taken in the Chingford Study, they recommended standardising AA measurements using either the base of the tibial spine mid-point (KJC1) or the centre of the tibial plateau (KJC3) and suggested comparing 1P and 2P methods in larger studies. These results therefore formed the basis of this cross-sectional AA alignment study in the Chingford cohort and this is one of the first studies to extensively compare the 1P method with the 2P method for AA alignment.

It is clear from this study that there is a difference in AA alignment angles measured between a 1P and a 2P method. In this study this difference was more than 2° as shown in Figure 43:

1P KJC3 mean 180.11° (SD ±2.93°) and 2P KJC3 mean 182.53° (SD ±2.51°).

For the alternative KJC landmarks, KJC1 showed a similar 2° difference between the methods, whereas the difference was less than 1° for KJC2:

1P KJC1 mean 180.23° (SD $\pm 3.70^{\circ}$) and 2P KJC1 mean 182.47° (SD $\pm 2.77^{\circ}$).

1P KJC2 mean 182.71° (SD $\pm 3.40^{\circ}$) and 2P KJC2 mean 183.64° (SD $\pm 2.66^{\circ}$).

It is not clear where these differences between the 1P and 2P methods arise, and since there are no other studies comparing these differences, it is hard to know which method (1P or 2P) to choose overall. However, in this study and the previous KneeMorf pilot studies (chapter 4) the 2P method has consistently displayed tighter measurements showing less variation with smaller SDs indicating less measurement error than the 1P method. A MA alignment study by Goker & Block also reported improved precision with CAA permitting detection of differences less than 1° when comparing a 2P digital method (using KJC3) with a 2P manual method (using KJC2) on FLRs in 28 OA knees (Goker and Block, 2007). Unfortunately there have been no CAA AA alignment studies using KJC3 published to date for comparison.

Aim 2: To define appropriate alignment categories for chosen optimal 1P and 2P AA methods

Previous comparative AA versus MA alignment studies have used AA alignment as a continuous measurement in their analyses, with angles less than 180° considered varus and angles greater than 180° considered valgus (Kraus et al., 2005, Hinman et al., 2006, Chang et al., 2010, McDaniel et al., 2010).

However, as there were no FLRs available for comparison in the Chingford cohort, cross-sectional associations with SRKOA, RKOAs and knee pain clinical outcomes were assessed, and as all associations with clinical outcomes were non-linear it was not possible to use AA alignment as a continuous measure for these analyses. Therefore AA alignment categories were required. As the mean values between 1P and 2P methods differed by more than 2° , it was clear that the varus ($<178^{\circ}$), neutral ($178-182^{\circ}$) and valgus ($>182^{\circ}$) alignment categories adopted from Colebatch and colleagues (Colebatch et al., 2009) applied to the 1P method would not be appropriate for the 2P method. Some of the AA alignment studies that have used alignment categories in their analyses (Brouwer et al., 2007, Zhai et al., 2007, Wong et al., 2009, Mazzuca et al., 2010) have applied a valgus offset angle to the varus $<178.5^{\circ}$, neutral $178.5-180^{\circ}$ and valgus $>180^{\circ}$ categories described in Moreland's seminal paper published in 1987 (Moreland et al., 1987) which examined MA alignment in 25

healthy male participants with a mean age of 30 years but this was not deemed applicable to a female only cohort population with a median age of 62 years containing AA alignment measurements. The AA alignment cohort study of Hunter and colleagues (Hunter et al., 2007) was a case-control study using 1P KJC2 on AP full extension SLRs in a KOA population which categorised their AA alignment variable into quartiles with 5-10° valgus as the reference group. Due to the difference in study design nor was this applicable to this dataset.

As there was a distinct lack of appropriate pre-defined categories in the current literature for AA alignment, the technique previously described in the analysis section (5.4) and reported in a waist-circumference measurement study by Heim and colleagues (Heim et al., 2011), determined new appropriate alignment cut-off values for varus / neutral / valgus knees for both 1P and 2P methods based on the association with the SRKOA primary clinical outcome (Figure 44). For the 1P method the cut-point values remained the same, as Colebatch's study: varus <178°, neutral 178 -182° and valgus >182°. For the 2P method the new suggested cut-point values were varus <180°, neutral 180 - 185° and valgus >185°. The lower QIC values in Table 35 indicated that the new cut-point values were a better fit for the SRKOA and RKOA clinical outcomes and have therefore been adopted for future analyses.

Although the previous alignment categories displayed stronger ORs for varus knees for all three outcomes, fewer but a greater number of more severe knees were identified. In comparison the new alignment categories displayed slightly weaker ORs for varus and stronger ORs for valgus, however identified more varus and valgus knees overall based on the association with SRKOA outcome. This is considered more clinically relevant than comparing or trying to reproduce MA alignment, which was originally based on Moreland's study of 25 healthy male participants with a mean age of 30 years (Moreland et al., 1987).

Aim 3: To describe cross-sectional associations for chosen optimal 1P and 2P AA methods with SRKOA, RKOA and knee pain clinical outcomes

This study examined AA alignment cross-sectional associations with SRKOA, RKOA and knee pain clinical outcomes, which is novel as previous cross-sectional AA alignment studies have reported associations with RKOA only, and

used AA alignment as a continuous measurement in their analyses (Teichtahl et al., 2006, Janakiraman et al., 2008, Laxafoss et al., 2013).

Varus knees compared to neutral knees were associated with significantly increased risk of SRKOA by the 2P method, with a similar but non-significant trend for the 1P method. Valgus knees versus neutral knees were not significantly associated with increased risk of SRKOA using either the 2P or 1P method. For RKO, the 2P method showed significantly increased risk for varus and valgus knees compared with neutral knees, and a similar but non-significant trend was seen for the 1P method. To explore the increased risk of RKO for varus and valgus knees further, associations with medial and lateral JSN were examined. The significant associations with RKO (and possibly with SRKOA) using the 2P method may in part be explained by the associations seen between medial JSN for varus knees and lateral JSN for valgus knees, although there was insufficient statistical power in this study to focus solely on knees with K&L grade 2 or more. However, this would agree with Sharma (Sharma et al., 2001) who first demonstrated that varus MA alignment was associated with medial JSN progression and valgus MA alignment with lateral JSN progression in a KOA population. It would also agree with Teichtahl (Teichtahl et al., 2006) who reported cross-sectional AA alignment (measured as a continuous variable) being associated with the risk of compartment-specific JSN in a KOA cohort. The load transmitted through the neutrally aligned knee is distributed unequally between the medial and lateral compartments (Hsu et al., 1990, Harrington, 1983, Johnson et al., 1980), with up to 70% of the load going through the medial compartment (Schipplein and Andriacchi, 1991). This disproportionate transmission to the medial compartment in the normally aligned ambulating knee was first reported by Morrison in 1970 (Morrison, 1970). Knee alignment therefore influences the medial to lateral compartment load distribution, with any shift from neutral alignment of the hip, knee and ankle affecting the load distribution at the knee joint (Tetsworth and Paley, 1994). With just 4 - 6° of varus alignment, the load through the medial compartment can be increased by up to 90% (Hsu et al., 1990). Valgus alignment is associated with an increase in lateral compartment loading (Bruns et al., 1993), although greater load is taken through the medial compartment until a more severe valgus deformity is present (Harrington, 1983, Johnson et al., 1980). This may explain the non-significant association between valgus versus neutral knees and SRKOA. It is these increases in compartment loading

that are thought to increase stress on articular cartilage and surrounding knee joint structures that subsequently lead to degenerative KOA changes.

Greater associations were present for valgus versus neutral knees compared to varus versus neutral knees for knee pain outcome, and these associations were maintained in the adjusted sensitivity analysis, although neither the 2P or 1P associations were significant in either model. The reasons why knee pain should behave differently to RKOA and SRKOA outcomes are not clear and further studies in this area are required. It could be related to the multi-dimensional aspects of pain and that more than just OA knee pain was being measured here, although women with inflammatory, neurological and fibromyalgia type conditions were excluded from this study. Alternatively, it may be due to knee pain originating from knee soft tissue structures such as ligaments, menisci and/or possibly due to the involvement of the patella-femoral joint which was not assessed in this study as skyline radiographs were not available.

5.6.1 Study strengths

This study has a number of benefits, as having uniquely compared six alternative AA alignment measures using three different KJCs, it is one of the first studies to compare 1P versus 2P method alignment measurement. This has been carried out using a large sample of over 1000 knees from 584 women who are known to be representative of a normal, predominantly Caucasian, female population (Hart and Spector, 1993a, Hart et al., 1994). Cross-sectional associations have been assessed with SRKOA, RKOA and knee pain clinical outcomes, which is not only novel as previous cross-sectional AA alignment studies have reported associations with RKOA only, but also clinically relevant as the discordant relationship between RKOA and reported knee pain is well known (Bedson and Croft, 2008). A further strength of this study is the use of the KneeMorf software program to collect the AA alignment measurements. Previous pilot study work (in chapter 4) has shown that this is a reliable and valid automatic alignment measurement tool. As angles can be measured to within 0.01° using KneeMorf the accuracy is far greater than any manual measurement with a goniometer which only allows 0.5° accuracy at best.

5.6.2 Study limitations

Due to the original cohort study design, the results of this study are restricted to middle-aged women who are predominantly Caucasian. While there were no clinically significant differences between the included and excluded cohorts in this study, it is important to remember that these cross-sectional data are taken from a longitudinal cohort study therefore there is potential for study bias as a result of loss to follow-up due to deaths, withdrawal due to illness and/or disability leading to a generally healthier cohort attending the follow-up visits. The possibility remains, that for whatever reason, subjects lost to follow-up could therefore have significantly worse SRKOA and/or knee mal-alignment than those included in this analysis. If this is the case it could alter the prevalence, although the reported associations would not be affected.

Analysis was restricted to women with knee SLRs that had femoral and tibial shaft lengths of 10cm or more as previous pilot study results (section 4.4) concluded that a 10cm shaft length was optimum for measuring AA alignment. Comparisons between this group of women and those with less than 10cm or with less than 7cm shaft lengths, showed no statistically significant differences between the three clinical outcomes, therefore this should not affect the associations reported. The 15 knees with a shaft length less than 7cm had statistically and clinically significant reduced BMI than knees with 10cm or more, why this should be the case is not clear.

When the Chingford study started in 1989, the standard view for knee SLR was AP, weight-bearing in full knee extension. However, due to underestimation of JSN in fully extended views, current practice now prefers semi-flexed views (Buckland-Wright et al., 1999) and the more rigorous fluoroscopy-assisted positioning (Mazzuca et al., 1997). To accurately evaluate change over time, long-term cohort studies often continue using the same radiographic protocol as used at the baseline visit, which is the situation in the Chingford study. It is not always possible to acquire a fully extended knee position on a radiograph. Pain, stiffness and fixed flexion deformities of the knee joint may prevent full extension, and/or possible limb rotation can occur. Both of these could affect alignment measurement, JSN and K&L grading, which is a limitation to this study. In more recent studies that use semi-flexed views these issues are overcome by use of a positioning device that standardises knee flexion and limb rotation (Kraus et al., 2005, Felson et al., 2009, McDaniel et al., 2010).

This was not available for use in the Chingford cohort or in the previous AA alignment cohort studies using full extension AP knee SLRs (Hunter et al., 2007, Brouwer et al., 2007) therefore this same limitation applies across all of these studies.

A clear limitation to this study is the lack of FLRs in the Chingford cohort for measurement of MA alignment. Recent studies have demonstrated strong correlation (from 0.75 to 0.88) in KOA populations between MA alignment on FLRs and AA alignment measured on SLRs (Kraus et al., 2005, Hinman et al., 2006, Issa et al., 2007). Alignment measurements on SLRs do not capture the distal tibial or proximal femoral anatomy. The part of the femoral shaft used to determine AA alignment does not include the femoral neck that protrudes medially from the upper femoral shaft which is used in determining MA alignment, therefore use of a valgus offset correction angle is suggested to account for the difference between AA and MA alignment. Kraus and colleagues recommend a mean valgus offset of 4.0° (3.3° for women and 5.9° for men) for AA alignment measurement on fixed flexion PA SLRs (Kraus et al., 2005). Issa and colleagues recommend a mean valgus offset 3.4° (3.1° for women and 4.7° for men) for AA alignment measurement on semi-flexed AP SLRs (Issa et al., 2007), and Hinman and colleagues did not report using a valgus offset on fully extended AP SLRs (Hinman et al., 2006). A point to note is that all three of these studies measured their AA alignment using their FLR images as opposed to measuring AA alignment on a separate SLR, whether this has any bearing on the accuracy of these measurements, can only be explained by further studies.

A more recent study by Colebatch and colleagues, that compared fully extended AP SLRs with FLRs (correlation $r=0.81$) in a healthy all female population, found no evidence of needing to apply an offset correction angle in terms of the mean alignment or those classified as valgus (Colebatch et al., 2009). This difference could be a result of studying a healthy all female population in comparison to the studies by Kraus (Kraus et al., 2005), Hinman (Hinman et al., 2006), and Issa (Issa et al., 2007) who used RKO populations containing males and females, and/or a result of using a fully extended knee position compared to fixed-flexion or semi-flexed radiographic views. As the Chingford study is a female only cohort containing a mix of healthy and KOA

participants with fully-extended SLR images an offset correction has not been used in this study.

5.6.3 Conclusion

This study has uniquely compared AA alignment measurements using 1P and 2P methods at 3 different KJC landmarks and identified KJC3, at the centre of the tibial plateau, as the optimal KJC to take forward for future alignment analyses in this cohort. Based on cross-sectional associations with SRKOA this study has also identified appropriate varus / neutral / valgus alignment categories to be used for 1P and 2P methods. Further replication and validation with MA alignment comparison is required. Finally novel cross-sectional associations with SRKOA, RKOAs and knee pain clinical outcomes have been described, and future research regarding longitudinal associations with these clinical outcomes is warranted.

5.6.4 Final summary

- KJC3 at the tibial plateau centre will be used for future alignment analyses in this thesis.
- There are differences between 1P and 2P AA methods therefore method specific alignment categories are required and the following are recommended:
1P method: varus $<178^\circ$, neutral $178 - 182^\circ$ and valgus $>182^\circ$
2P method: varus $<180^\circ$, neutral $180 - 185^\circ$ and valgus $>185^\circ$
- Cross-sectional associations demonstrated increased risk of SRKOA for varus knees and increased risk of RKOAs for varus and valgus knees, which may partly be explained by associations between medial JSN for varus and lateral JSN for valgus knees. However for knee pain, greater associations were present for valgus knees.

6. Chapter 6: The natural history of knee alignment and longitudinal associations with knee osteoarthritis

6.1 Background

A systematic review by Tanamas and colleagues (Tanamas et al., 2009) reported that there are now a number of epidemiological studies identifying severity of mal-alignment as a predictor of KOA progression (Cerejo et al., 2002, Felson et al., 2003, Felson et al., 2004, Cicuttini et al., 2004, Brouwer et al., 2007, Janakiramanan et al., 2008, Sharma et al., 2008, Teichtahl et al., 2009a, Sharma et al., 2010, Sharma et al., 2001) however there is still some debate about the role knee alignment plays with regard to the incidence of KOA. Varus alignment has been associated with incident RKOA in two cohort studies (Brouwer et al., 2007, Sharma et al., 2010) but this was not evident in a case-control study (Hunter et al., 2007). The association between valgus alignment and incident RKOA was either borderline (Brouwer et al., 2007) or not evident (Sharma et al., 2010); although a more recent study by Felson and colleagues reported valgus mal-alignment increases the risk of RKOA incidence and progression as well as the risk of lateral cartilage damage (Felson et al., 2013). Due to the limited number of studies and conflicting findings on the relationship between knee alignment and incident KOA, further research is required to clarify the role alignment has in the development of KOA. More studies are also required to clarify the relationship between alignment and SRKOA as opposed to RKOA, which is not clear as it has been examined less frequently.

The longitudinal cohort studies examining KOA incidence and progression to date have used mean follow-up periods ranging from 18 months (Sharma et al., 2001, Cerejo et al., 2002) to 6 years (Miyazaki et al., 2002) for MA alignment studies, and from 2 years (Teichtahl et al., 2009a) to 8.7 years (Hunter et al., 2007) for AA alignment studies. Data from the Chingford cohort allows examination of the natural history of AA alignment in women with and without knee osteoarthritis over a 10 year period, the longest period of follow-up to date.

6.2 Aim

The main aims of this study were:

- 1) To describe the natural history of AA alignment in a female general population over a 10 year period.
- 2) To describe longitudinal associations of AA alignment at Y10 with SRKOA, RKOAs and knee pain incidence at Y20 in the same population.

6.3 Method

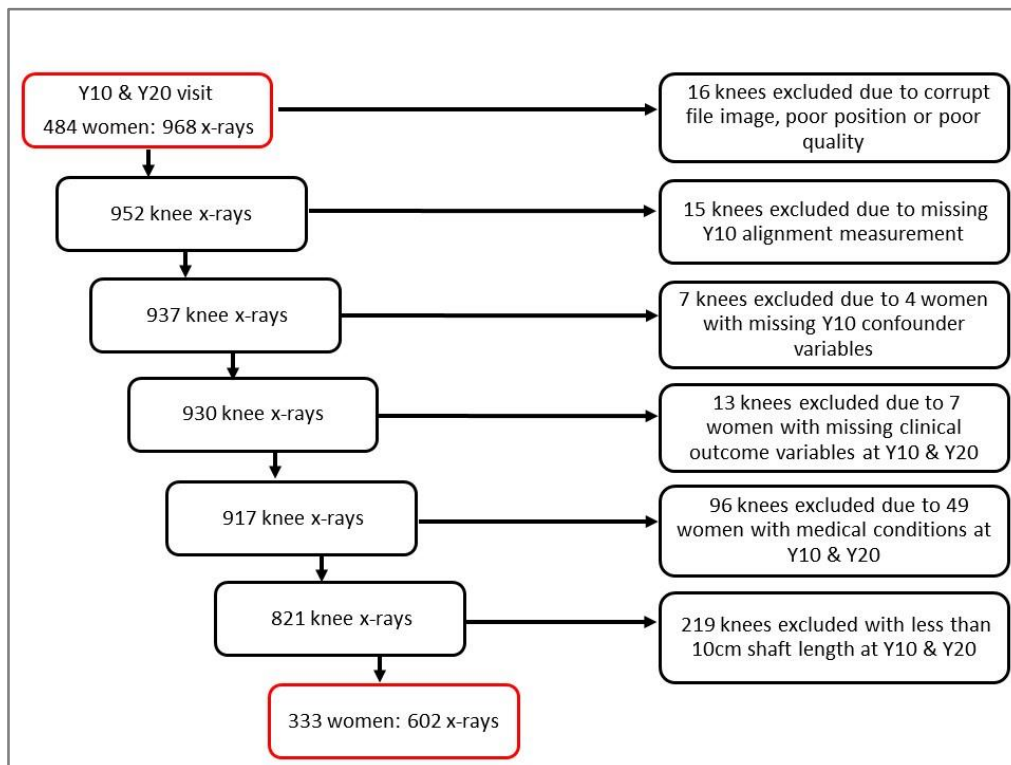
6.3.1 Study population

Participants included in this study were Chingford cohort women attending both the Y10 and Y20 clinical visits with: accompanying Y10 and Y20 knee SLRs; confounder variable data present at Y10; clinical outcome data present at Y10 and Y20; and women who did not report an inflammatory or neurological medical condition listed in the exclusion criteria (section 3.4.2) at either Y10 or Y20. The derivation of the study population is shown in Figure 45 and at the outset 484 women attended both the Y10 and Y20 visits with a possible 968 knee SLRs.

A total of 16 knees were excluded due to either: corrupt scanned file images, poor positioning on the radiograph or poor image quality thereby resulting in AA alignment not being measured. This left a total of 952 knee images, 15 images were excluded due to missing Y10 alignment measurements leaving 937 knee images. There were missing Y10 confounder variable data of either: age, BMI or presence of knee injury, for 4 women (7 knees) leaving 930 knee images. A further 7 women (13 knees) were excluded due to missing clinical outcome variable data (K&L grade and/or knee pain) at Y10 and Y20 leaving 917 knee images. A total of 96 knee images were excluded due to 49 women having one of the medical conditions listed in the exclusion criteria (section 3.4.2) at Y10 and/or Y20 leaving 821 knee images.

Finally a total of 219 knees were excluded as they had either a femoral, or tibial, or both femoral and tibial shaft length of less than 10cm as previous pilot study results (section 4.4) concluded that a 10cm shaft length is optimum for measuring AA alignment. This left a final total of 602 'perfect' knees from 333 women, available for longitudinal analysis.

Figure 45: Derivation of longitudinal analysis sample of 602 knees



These 602 knees were compared to the 366 knees from the 151 women who were excluded from the longitudinal analysis as shown in Table 38. This table shows that those excluded were slightly older ($p=0.05$) although this one year age difference was not clinically significant. All other Y10 characteristics were similar apart from an approximate 0.5° alignment difference between included and excluded knees. Although statistically significant, as this was less than 1° it was not considered clinically significant (Cicuttini et al., 2004).

Table 38: Baseline Y10 clinical characteristics

Where 1P=one-point method; 2P=two-point method; AA=anatomic axis; BMI=body mass index; IQR=inter-quartile range; KJC=knee joint centre; K&L=Kellgren & Lawrence grade; RKOA=radiographic knee osteoarthritis; SRKOA=symptomatic radiographic knee osteoarthritis; SD=standard deviation.

Y10 characteristic	All available knees (n=968 knees)	Excluded cohort (n=366 knees)	Included cohort (n=602 knees)	P value ^a
Age, median (IQR) years	61 (56,65) (n=960)	61 (57,67) (n=358)	60 (56,65)	0.05
BMI, mean (\pm SD) kg/m ²	26.6 (4.4) (n=960)	26.7 (4.2) (n=358)	26.5 (4.5)	0.54
Knee injury, %	14.9	15.9	14.3	0.51
Knee pain \geq 15 days, %	12.6 (n=960)	13.1 (n=358)	12.3	0.71
RKOA \geq 2 K&L grade, %	26.7 (n=962)	26.4 (n=360)	26.9	0.86
SRKOA, %	6.0 (n=956)	6.5 (n=354)	5.7	0.59
Mean AA angle (\pm SD) ^o				
1P KJC3	179.93 (3.66) (n=938)	179.58 (3.54) (n=336)	180.13 (3.40)	0.02
2P KJC3	182.37 (3.09) (n=937)	182.06 (3.03) (n=335)	182.54 (3.03)	0.02

^a P values comparing included to excluded knees using Kruskal Wallis test for age; two sample t-test for BMI; Chi-square test for injury, knee pain, RKOA & SRKOA; and clustered t-tests for AA angle comparison.

6.3.2 Imaging

AP fully-extended weight bearing bilateral knee SLRs were taken at the Y10 and Y20 clinic visits using a standardised protocol that was established at the Y1 baseline visit and repeated for all subsequent radiograph clinic visits (Hart et al., 1999) as described previously in section 3.5.3. Y10 images were plain film SLRs that were scanned on a digital scanner at 600 dpi with a grey scale pixel depth of 16 bits. At Y20 digital images were taken, with inclusion of a KIDA wedge calibration object (Marijnissen et al., 2008). Pixel size for the digital images was determined using embedded DICOM information.

All Y10 radiographs were graded by DH and Y20 radiographs were graded by KL using the K&L global score (Kellgren and Lawrence, 1957) as described in section 3.5.3.

TKRs and UKRs were identified by a combination of self-report and GP records, and further confirmation obtained on review of the radiograph. By Y20 there were 19 knees from 15 women with knee arthroplasties, 4 women with bilateral TKRs (n=8 knees), 10 women with unilateral TKRs (n=10 knees) and 1 woman with a medial UKR (n=1 knee).

6.3.3 Alignment measurement

1P and 2P AA alignment based at KJC 3 (the tibial plateau centre) were measured by the author on all Y10 and Y20 radiographs using KneeMorf as described previously in section 3.5.4.2.

6.3.4 Outcome variables

All outcomes were knee-based. The primary outcome variable was Y20 SRKOA; RKOAs and knee pain were secondary outcomes as defined in section 3.6.

6.3.5 Confounding variables

Adjustments were made for Y10 age, BMI and knee injury confounding variables as defined in section 3.7.

6.4 Analysis

All analyses were completed using Stata version 13.0 (Stata Corp, College Station, Texas, USA). Prior to analysis, data distribution was checked using histograms and scatter plots for inconsistencies, outliers and to assess whether normal distributions existed. Where possible both knees from each woman were included in longitudinal analyses, with 269 women supplying two knees and 64 women supplying one knee resulting in a total of 333 women with 602 knees (Figure 45).

For the natural history analysis (aim 1), the 19 knees from 15 women with TKRs at Y20 were excluded as it was not possible to measure Y20 AA alignment with a prosthesis in situ so this left a total of 583 knees from 327 women with alignment measurements at Y10 and Y20.

For the incidence analysis (aim 2), the 19 knees with TKRs at Y20 were included and re-coded positive (if not already coded positive) for SRKOA and RKOAs clinical outcomes. The excluded cohort in this analysis comprised 34 knees which were SRKOA incidence positive at Y10, leaving a total of 568 knees from 319 women for the incidence analysis.

Within these 568 knees there were 400 knees that were Y10 RKOAs negative and Y10 knee pain negative, 40 knees that were Y10 RKOAs negative and Y10 knee pain positive and 128 knees that were Y10 RKOAs positive and Y10 knee pain negative. Therefore for the Y20 RKOAs incidence analysis there were a total of 440 knees (400 + 40) and for the Y20 knee pain incidence analysis there were a total of 528 knees (400 + 128).

The demographic and clinical characteristics of the study population are presented for the included and excluded cohort as the median with IQR for non-normally distributed continuous variables, and mean with SD for normally distributed continuous variables. Categorical variables are presented as a number and a percentage. Statistically significant differences (with p values <0.05) in measured variables between the included and excluded cohorts were examined using clustered t -tests for normal continuous alignment variables, two independent samples t -test for normal continuous variables, Kruskal Wallis test for non-normal continuous variables and chi-square test for categorical variables.

To check distributions, histograms of the 1P and 2P alignment methods for Y10 and Y20 were plotted and differences between means were examined using t-tests adjusted for correlated data.

Change in AA alignment was calculated by subtracting Y10 from Y20 alignment measurements and the mean (\pm SD) alignment change in degrees for all / neutral / varus / valgus knees (using alignment categories identified in the cross-sectional analysis section 5.5.5) was tabulated, highlighting less than 1° change, more than 1° change varus and more than 1° change valgus. AA mean angle differences were considered to be clinically significant if greater than 1° (Cicuttini et al., 2004). Categorical change in AA alignment was also calculated to examine percentage of knees that remained within the same neutral / varus / valgus alignment categories or change categories from Y10 to Y20. Box plots were drawn to describe the natural history of AA alignment with SRKOA, RKOA and knee pain over a 10 year period.

Longitudinal associations between Y10 1P and 2P alignment measurements and Y20 SRKOA, RKOA and knee pain incidence were completed using GEE to account for the correlation between left and right knees in one individual. These analyses were executed for varus and valgus alignment, with neutral alignment as the reference group using the alignment categories based on the association with SRKOA clinical outcome defined in the Y10 cross-sectional analysis section 5.5.5. ORs and their 95% CIs were calculated and analyses were adjusted for Y10 age, BMI and presence of knee injury.

Sensitivity analyses for longitudinal associations between Y10 1P and 2P alignment measurements and Y20 SRKOA incidence were also completed. The first sensitivity analysis compared Y20 SRKOA incidence using only Y10 RKOA negative knees, thereby excluding 10 RKOA positive and Y10 knee pain negative knees from the original Y20 SRKOA incidence analysis. A second sensitivity analysis compared Y20 SRKOA incidence specifically to Y10 super-control knees which were RKOA negative (K&L grades 0 or 1) and knee pain negative (no pain in the preceding month). Previous comparisons included K&L grades 0 or 1 with less than or equal to 14 days knee pain in addition to knee pain negative knees.

6.5 Results

6.5.1 Natural history study population

A total of 602 knees from 333 women were present for the alignment natural history longitudinal analysis. Table 39 shows the baseline clinical characteristics at Y10 of the included and excluded cohort of women for this analysis. As some AA alignment measurements at Y20 were unobtainable due to the presence of TKR prostheses, the excluded cohort comprised the 19 TKR positive knees at Y20 which were from 15 women (4 women with bilateral TKRs, 10 women with unilateral TKRs and 1 woman with a medial UKR). As expected these excluded women with Y20 TKRs had significantly greater knee pain, RKOAs and SRKOAs. Their presence of knee injury was also greater than the 327 women supplying 583 knees free from TKR at Y20 in the included cohort. In addition, the excluded knees were more varus in their mean 1P and 2P AA alignment angle than the included knees. The remaining 583 knees were divided into three alignment categories (identified in the cross-sectional alignment section 5.5.5). Using the 1P alignment method 309 knees (53%) were considered to have neutral alignment (178° - 182°), 131 knees (22%) had varus alignment ($<178^{\circ}$) and 143 knees (25%) had valgus alignment ($>182^{\circ}$). Using the 2P alignment method 448 knees (77%) were considered to have neutral alignment (180° - 185°), 60 knees (10%) had varus alignment ($<180^{\circ}$) and 75 knees (13%) had valgus alignment ($>185^{\circ}$).

6.5.2 Calculating alignment change over 10 years

Figure 46 shows the AA alignment variables at Y10 (Figure 46a for 1P and Figure 46b for 2P method) and Y20 (Figure 46c for 1P and Figure 46d for 2P method) for the included knees ($n=583$) were normally distributed at both time points for each method. The Y10 1P method had a mean of 180.17° (\pm SD 2.86) with a 20° AA range from 172° - 192° . The same knees at Y10 measured with the 2P method had a greater mean of 182.60° (\pm 2.32) with a slightly smaller 18° AA range from 174° - 192° . Using an unpaired t-test adjusted for correlated data, the difference between Y10 1P and 2P means was clinically significant (mean difference is 2.42° , therefore greater than 1°) (Cicuttini et al., 2004) and statistically significant at $p<0.0001$.

By Y20 the 1P method mean had increased slightly to 180.54° (± 3.66) with a larger 27° AA range from $169 - 196^{\circ}$, although the 2P method mean still remained greater than the 1P method at 182.66° (± 3.20) it had more or less stayed the same compared to the Y10 2P mean, however the range has widened to 29° from $170 - 199^{\circ}$. The 2.12° difference between Y20 1P and 2P means was also clinically and statistically significant at $p < 0.0001$ with an unpaired t-test adjusted for correlated data. Using paired t-tests adjusted for correlated data, the difference between Y10 1P v Y20 1P means was statistically significant at $p = 0.009$ but not clinically significant at less than 0.36° , and the 0.06° difference between Y10 2P v Y20 2P means was neither clinically or statistically significant at $p = 0.54$.

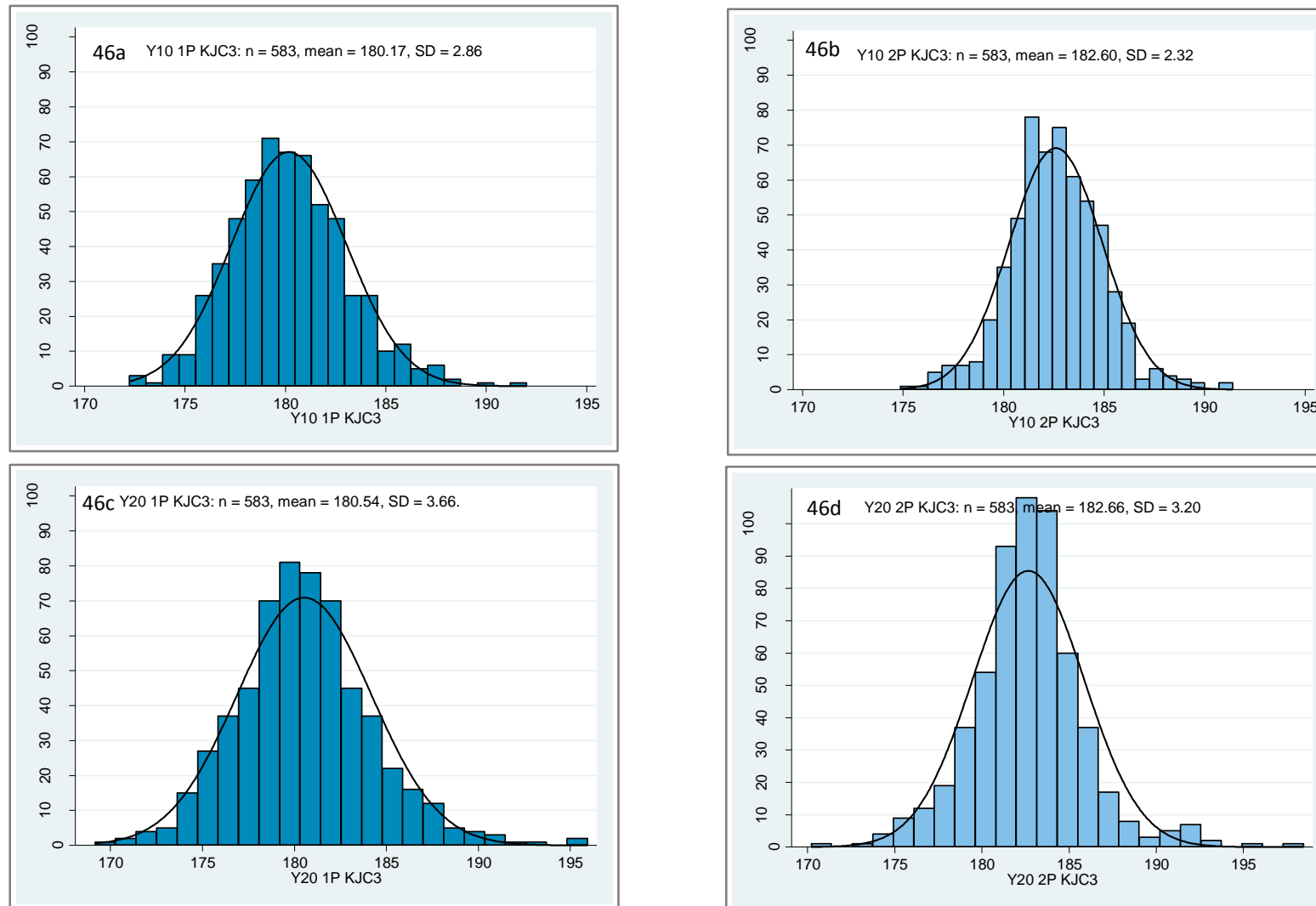
Table 39: Baseline clinical characteristics for Y10 to Y20 AA alignment natural history analysis

Where AA=anatomic axis; BMI=body mass index; IQR=inter-quartile range; KJC=knee joint centre; K&L=Kellgren & Lawrence grade; RKOA=radiographic knee osteoarthritis; SRKOA=symptomatic radiographic knee osteoarthritis; SD=standard deviation; 1P=one-point; 2P=two-point.

Y10 characteristic	Full cohort (n=602 knees)	Excluded cohort (n=19 knees)	Included cohort (n=583 knees)	P value ^a
Age, median (IQR) years	60 (56,65)	61 (57,65)	60 (56,65)	0.48
BMI, mean (\pm SD) kg/m ²	26.5 (4.5)	27.5 (3.5)	26.5 (4.6)	0.32
Knee injury, %	14.3	52.6	13.0	<0.001
Knee pain \geq 15 days, %	12.3	57.9	10.8	<0.001
RKOA \geq 2 K&L grade, %	26.9	73.7	25.4	<0.001
SRKOA, %	5.7	52.6	4.1	<0.001
AA angle:				
1P KJC3, mean (\pm SD) ^o	180.13 (3.54)	178.67 (3.63)	180.17 (3.63)	0.08
1P neutral 178-182 ^o , %	52.5	36.8	53.0	
1P varus <178 ^o , %	23.1	42.1	22.5	
1P valgus >182 ^o , %	24.4	21.1	24.5	
2P KJC3, mean (\pm SD) ^o	182.54 (3.03)	180.72 (3.01)	182.60 (3.00)	0.008
2P neutral 180-185 ^o , %	75.7	42.1	76.8	
2P varus <180 ^o , %	11.3	42.1	10.3	
2P valgus >185 ^o , %	13.0	15.8	12.9	

^a P values comparing included (Y20 TKR negative) to excluded (Y20 TKR positive) cohort using: Kruskal Wallis test for age; two sample t-test for BMI; Chi-square test for injury, knee pain, RKOA & SRKOA; clustered t-tests for mean AA angle.

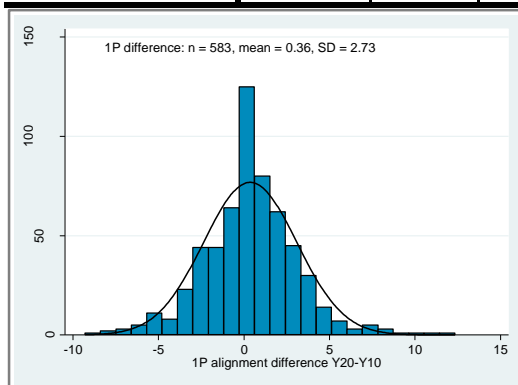
Figure 46: AA alignment distributions for included cohort knees at Y10 & Y20 for 1P & 2P methods



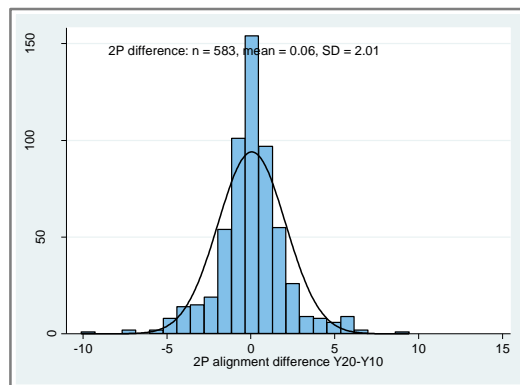
Change in AA alignment was calculated by subtracting Y10 from Y20 alignment measurements. The mean (\pm SD) alignment change in degrees for all / neutral / varus / valgus knees (using alignment categories identified in the cross-sectional alignment section 5.5.5) is shown in Table 40a for 1P method and Table 40b for 2P method (negative values represent a varus change, positive value represent a valgus change).

Table 40: Change in alignment from Y20 to Y10

40a: Y10 1P alignment	Mean change° (\pm SD)	<1° change n (%)	>+1° change n (%)	>-1° change n (%)
All knees (n=583)	0.36 (2.73)	208 (35.7)	217 (37.2)	158 (27.1)
Neutral knees (n=309) 178-182°	0.25 (2.53)	112 (36.3)	116 (37.5)	81 (26.2)
Varus knees (n=131) <178°	1.13 (2.63)	51 (38.9)	60 (45.8)	20 (15.3)
Valgus knees (n=143) >182°	-0.11 (3.08)	45 (31.5)	41 (28.7)	57 (39.9)



40b: Y10 2P alignment	Mean change° (±SD)	<1° change n (%)	>+1° change n (%)	>-1° change n (%)
All knees (n=583)	0.06 (2.01)	307 (52.7)	142 (24.4)	134 (23.0)
Neutral knees (n=448) 180-185°	-0.04 (1.92)	244 (54.5)	104 (23.2)	100 (22.3)
Varus knees (n=60) <180°	-0.05 (2.06)	29 (48.3)	14 (23.3)	17 (28.3)
Valgus knees (n=75) >185°	0.77 (2.37)	34 (45.3)	24 (32.0)	17 (22.7)



The overall mean angle change over ten years in all 583 knees was small at $0.36^\circ (\pm 2.73)$ for 1P method and even smaller at $0.06^\circ (\pm 2.01)$ for the 2P method. Mean angle differences greater than 1° were considered to be clinically significant (Cicuttini et al., 2004), so for the 1P method, 37% of all knees showed a more than 1° valgus (positive angle) change and 27% showed a more than 1° varus (negative angle) change. The largest mean change of $1.13^\circ (\pm 2.63)$ in a valgus direction was seen in 1P varus knees (Table 40a) which was clinically surprising as it is more biologically intuitive that varus knees at baseline would become more varus at follow-up (this was seen with the 2P varus knees in Table 40b) rather than valgus. A similar pattern was seen with 1P valgus knees with 40% of valgus knees displaying a more than 1° varus change (Table 40a), whereas 32% of 2P valgus knees display a more than 1° valgus change (Table 40b). To explore these clinical anomalies with the 1P method further, categorical change in AA alignment was also calculated to examine percentage of knees that remain within the same neutral / varus /

valgus alignment categories or change categories from Y10 to Y20 as shown in Table 41a for 1P method and Table 41b for 2P method.

Table 41: Change in alignment categories

41a: Y20 1P alignment		Neutral (178-182°)	Varus (<178°)	Valgus (>182°)	Total
Y10 1P alignment	Neutral (178-182°)	181 (58.6)	55 (17.8)	73 (23.6)	309 (100)
	Varus (<178°)	56 (42.7)	69 (52.7)	6 (4.6)	131 (100)
Valgus (>182°)	Valgus (>182°)	32 (22.4)	7 (4.9)	104 (72.7)	143 (100)
	Total	269 (46.1)	131 (22.5)	183 (31.4)	583 (100)

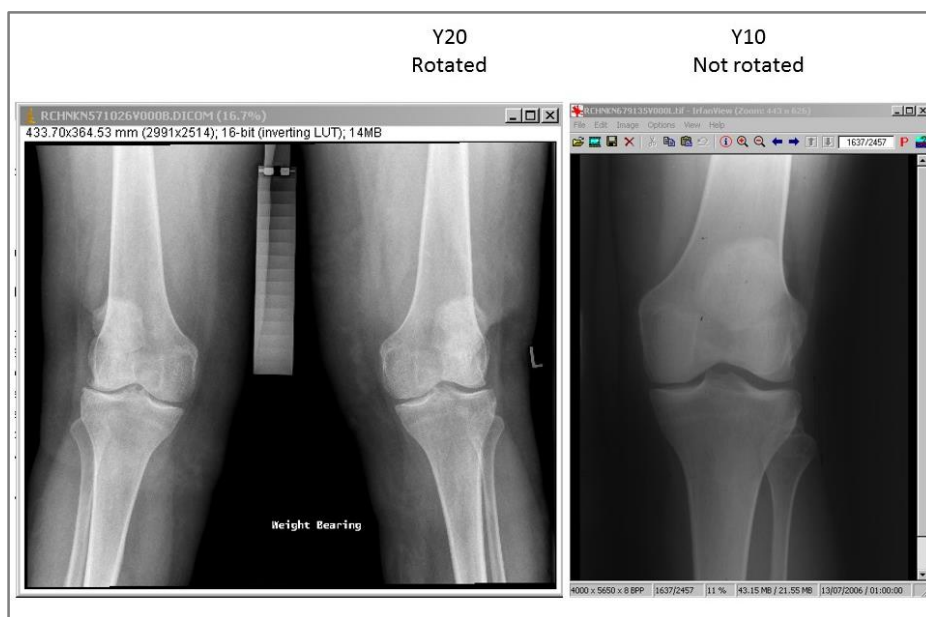
41b: Y20 2P alignment		Neutral (180-185°)	Varus (<180°)	Valgus (>185°)	Total
Y10 2P alignment	Neutral (180-185°)	344 (76.8)	53 (11.8)	51 (11.4)	448 (100)
	Varus (<180°)	16 (26.7)	44 (73.3)	0 (0)	60 (100)
Valgus (>185°)	Valgus (>185°)	17 (22.7)	0 (0)	58 (77.3)	75 (100)
	Total	377 (64.7)	97 (16.6)	109 (18.7)	583 (100)

After 10 years the majority of knees stay within the same alignment category: 59% neutral, 53% varus and 73% valgus for the 1P method (Table 41a), and these numbers were greater for the 2P method (Table 41b): 77% neutral, 73% varus and 77% valgus. The figures highlighted in red in Table 41a show a 5% minority of knees that started as varus at Y10 and moved to valgus by Y20, or started as valgus at Y10 and moved to varus by Y20. These clinical anomalies were not evident with the 2P method (Table 41b), i.e. no knees moved from Y10 varus to Y20 valgus category or vice versa, possibly indicating that the 2P AA alignment method may be more robust and less susceptible to positioning error than the 1P method and/or this may be due to the slightly wider alignment category cut-off points used for the 2P method.

Due to the clinical alignment anomalies highlighted by Table 40a and Table 41a, Y10 and Y20 paired digital radiograph images with the most extreme

mean alignment change e.g. more than $+5^\circ$ valgus ($n=23$) and less than -5° varus ($n=21$) identified from the alignment change histogram associated with Table 40a and the 5% minority knees ($n=13$) from Table 41a were identified for review by the author. It was clear that some of these alignment anomalies were associated with rotated knee images that were identified based either on the position of the patella located outside of the trochlear groove and/or on the degree of overlap between the fibula head and tibia (see Figure 47 rotated Y20 left knee image).

Figure 47: Identifying rotated images



On review of the 57 outlier paired Y10 and Y20 digital radiograph images identified from Table 40a and Table 41a, 44 knees were identified as rotated; of these 12 knees were rotated at Y10, 25 knees were rotated at Y20 and 7 knees were rotated at both Y10 and Y20. To examine differences in baseline clinical characteristics, these 44 rotated knees were compared to the remaining 539 non-rotated knees (Table 42).

Table 42 shows that the 44 rotated knees had a significantly greater BMI than the 539 non-rotated knees ($p < 0.001$), however knee pain which could also contribute to adopting a rotated knee position during imaging was not significantly different ($p=0.16$)

Table 42: Clinical characteristics comparing rotated and non-rotated knees

Where AA=anatomic axis; BMI=body mass index; IQR=inter-quartile range; KJC=knee joint centre; K&L=Kellgren & Lawrence grade; RKO = radiographic knee osteoarthritis; SRKOA=symptomatic radiographic knee osteoarthritis; SD=standard deviation; 1P=one point; 2P=two-point.

Y10 characteristic	Non-rotated knees (n=539)	Rotated knees (n=44)	P value ^a	Y10 rotated knees (n=12)	Y20 rotated knees (n=25)	Y10 & Y20 rotated knees (n=7)
Age, median (IQR) years	60 (56,65)	61.5 (56,66.5)	0.41	60.5 (56,64)	63 (56,67)	65 (55,67)
BMI, mean (\pm SD) kg/m ²	26.2 (4.3)	30.5 (5.7)	<0.001	31.7 (6.1)	29.4 (5.3)	32.4 (6.4)
Knee injury, %	12.6	18.2	0.29	8.3	16.0	42.9
Knee pain \geq 15 days, %	11.3	4.5	0.16	0	8.0	0
RKO \geq 2 K&L grade, %	25.2	27.3	0.77	41.7	24.0	14.3
SRKOA, %	4.3	2.3	0.52	0	4.0	0
Mean AA angle (\pm SD) ^o						
1P KJC3	180.02 (3.52)	182.05 (3.53)	<0.001	183.03 (4.66)	180.56 (3.36)	185.69 (1.84)
2P KJC3	182.50 (2.86)	183.83 (2.86)	0.003	183.72 (2.75)	183.01 (2.24)	186.95 (1.82)
1P change Y20 to Y10 ^b	0.19 (3.38)	2.46 (3.39)	<0.001	-1.36 (3.83)	4.59 (4.35)	1.42 (3.49)
2P change Y20 to Y10 ^b	-0.06 (2.44)	1.52 (2.45)	<0.001	-0.47 (2.97)	2.82 (2.63)	0.31 (2.65)

^a P values comparing rotated (n=44) to non-rotated (n=539) knees using Kruskal Wallis test for age; two-sample t-test for BMI; Chi-square test for injury, knee pain, RKO & SRKOA; clustered t-tests for AA angle comparison; ^b negative change=varus, positive change=valgus.

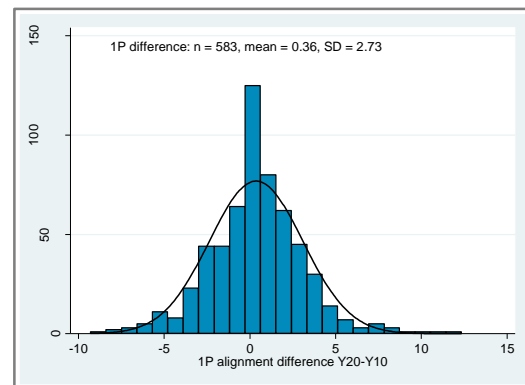
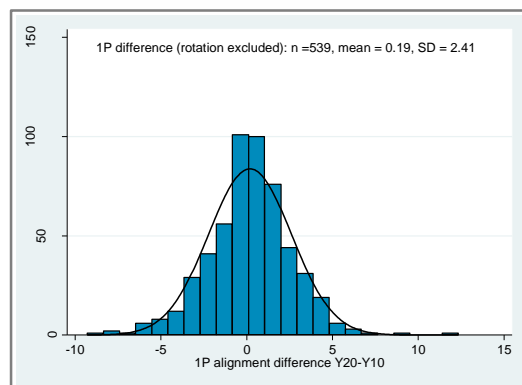
The mean AA angles for the 1P and 2P method and the mean change in AA angle were also significantly greater in rotated knees, which was expected as these knees were identified as outliers. All other characteristics between the two groups were similar. When clinical characteristics between Y10 rotated knees, Y20 rotated knees and the combined Y10 and Y20 rotated knees were examined in Table 42 it is clear that Y10 and Y20 rotated knees had the greatest mean BMI at 32.4 kg/m² (SD \pm 6.4). There were also differences in magnitude and direction for 1P and 2P AA angle change with Y20 rotated knees showing the greatest mean change in a positive valgus direction of 4.59° (SD \pm 4.35) for 1P and 2.82° (SD \pm 2.63) for 2P method. Y10 rotated knees show a smaller change but in a varus direction of -1.36° (SD \pm 3.83) for 1P and -0.47° (SD \pm 2.97) for 2P method, and the combined Y10 and Y20 knees show change in a valgus direction with 1.42° (SD \pm 3.49) for 1P and 0.31° (SD \pm 2.65) for 2P method.

Overall the results from Table 42 suggest that knees were not rotated at random. The 44 rotated knees from Table 42 were removed from the 583 knee sample, leaving 539 non-rotated knees and Table 40 and Table 41 were repeated without the rotated knees (Table 43 and Table 44, Table 45 and Table 46 respectively) for comparison (negative values represent a varus change, positive values represent a valgus change).

Table 43 shows other than a reduction in mean change for varus knees from 1.13° (\pm 2.63) to 0.66° (\pm 2.02) in a valgus direction, removing the outlier rotated knees from the sample had little effect on the 1P AA alignment when compared with Table 40a, and the effect was even less for the 2P AA alignment as shown in Table 44 and Table 40b.

Table 43: Change in 1P alignment with rotation excluded

Y10 1P alignment category	Mean ° change ^a (±SD)	<1° change n (%)	>+1° change n (%)	>-1° change n (%)
All knees (n=539)	0.19 (2.41)	204 (37.8)	187 (34.7)	148 (27.5)
Neutral knees (n=302) 178-182°	0.19 (2.43)	111 (36.7)	112 (37.1)	79 (26.2)
Varus knees (n=121) <178°	0.66 (2.02)	51 (42.1)	50 (41.3)	20 (16.5)
Valgus knees (n=116) >182°	-0.31 (2.65)	42 (36.2)	25 (21.6)	49 (42.2)

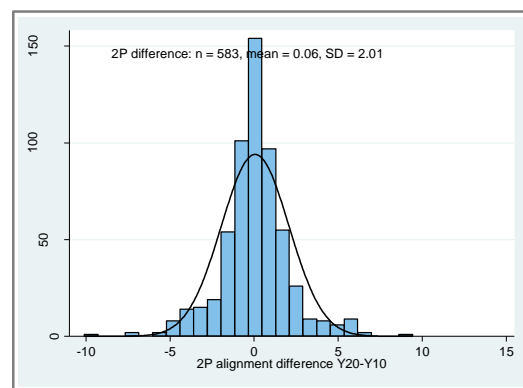
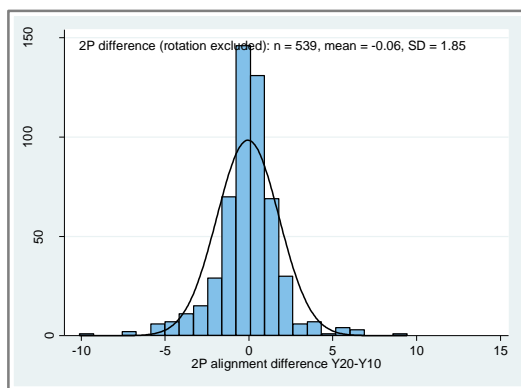


40a: rotation included Y10 1P alignment category	Mean ° change ^a (±SD)	<1° change n (%)	>+1° change n (%)	>-1° change n (%)
All knees (n=583)	0.36 (2.73)	208 (35.7)	217 (37.2)	158 (27.1)
Neutral knees (n=309) 178-182°	0.25 (2.53)	112 (36.3)	116 (37.5)	81 (26.2)
Varus knees (n=131) <178°	1.13 (2.63)	51 (38.9)	60 (45.8)	20 (15.3)
Valgus knees (n=143) >182°	-0.11 (3.08)	45 (31.5)	41 (28.7)	57 (39.9)

^a negative value is a varus change; positive value is a valgus change.

Table 44: Change in 2P alignment with rotation excluded

Y10 2P alignment category	Mean change ^a ° (±SD)	<1° change n (%)	>+1° change n (%)	>-1° change n (%)
All knees (n=539)	-0.06 (1.85)	301 (55.8)	116 (21.5)	122 (22.6)
Neutral knees (n=419) 180-185°	-0.12 (1.77)	241 (57.5)	88 (21.0)	90 (21.5)
Varus knees (n=57) <180°	-0.25 (1.88)	29 (50.9)	11 (19.3)	17 (29.8)
Valgus knees (n=63) >185°	0.54 (2.23)	31 (49.2)	17 (27.0)	15 (23.8)



40b: rotation included Y10 2P alignment category	Mean change ^a ° (±SD)	<1° change n (%)	>+1° change n (%)	>-1° change n (%)
All knees (n=583)	0.06 (2.01)	307 (52.7)	142 (24.4)	134 (23.0)
Neutral knees (n=448) 180-185°	-0.04 (1.92)	244 (54.5)	104 (23.2)	100 (22.3)
Varus knees (n=60) <180°	-0.05 (2.06)	29 (48.3)	14 (23.3)	17 (28.3)
Valgus knees (n=75) >185°	0.77 (2.37)	34 (45.3)	24 (32.0)	17 (22.7)

^a negative value is a varus change; positive value is a valgus change.

Table 45: Change in 1P alignment categories with rotation excluded

Y10 1P alignment \ Y20 1P alignment		Neutral (178-182°)	Varus (<178°)	Valgus (>182°)	Total
Neutral (178-182°)	(n) (%)	180 (59.6)	54 (17.9)	68 (22.5)	302 (100)
Varus (<178°)	(n) (%)	52 (43.0)	69 (57.0)	0 (0)	121 (100)
Valgus (>182°)	(n) (%)	32 (27.6)	2 (1.7)	82 (70.7)	116 (100)
Total	(n) (%)	264 (49.0)	125 (23.2)	150 (27.8)	538 (100)

41a: rot. included Y10 1P alignment \ Y20 1P alignment		Neutral (178-182°)	Varus (<178°)	Valgus (>182°)	Total
Neutral (178-182°)	(n) (%)	181 (58.6)	55 (17.8)	73 (23.6)	309 (100)
Varus (<178°)	(n) (%)	56 (42.7)	69 (52.7)	6 (4.6)	131 (100)
Valgus (>182°)	(n) (%)	32 (22.4)	7 (4.9)	104 (72.7)	143 (100)
Total	(n) (%)	269 (46.1)	131 (22.5)	183 (31.4)	583 (100)

Table 46: Change in 2P alignment categories with rotation excluded

Y10 2P alignment \ Y20 2P alignment		Neutral (180-185°)	Varus (<180°)	Valgus (>185°)	Total
Neutral (180-185°)	(n) (%)	332 (79.2)	51 (12.2)	36 (8.6)	419 (100)
Varus (<180°)	(n) (%)	13 (22.8)	44 (77.2)	0 (0)	57 (100)
Valgus (>185°)	(n) (%)	16 (25.4)	0 (0)	47 (74.6)	63 (100)
Total	(n) (%)	361 (67.0)	95 (17.6)	83 (15.4)	539 (100)

41b: rot. included Y10 2P alignment \ Y20 2P alignment		Neutral (180-185°)	Varus (<180°)	Valgus (>185°)	Total
Neutral (180-185°)	(n) (%)	344 (76.8)	53 (11.8)	51 (11.4)	448 (100)
Varus (<180°)	(n) (%)	16 (26.7)	44 (73.3)	0 (0)	60 (100)
Valgus (>185°)	(n) (%)	17 (22.7)	0 (0)	58 (77.3)	75 (100)
Total	(n) (%)	377 (64.7)	97 (16.6)	109 (18.7)	583 (100)

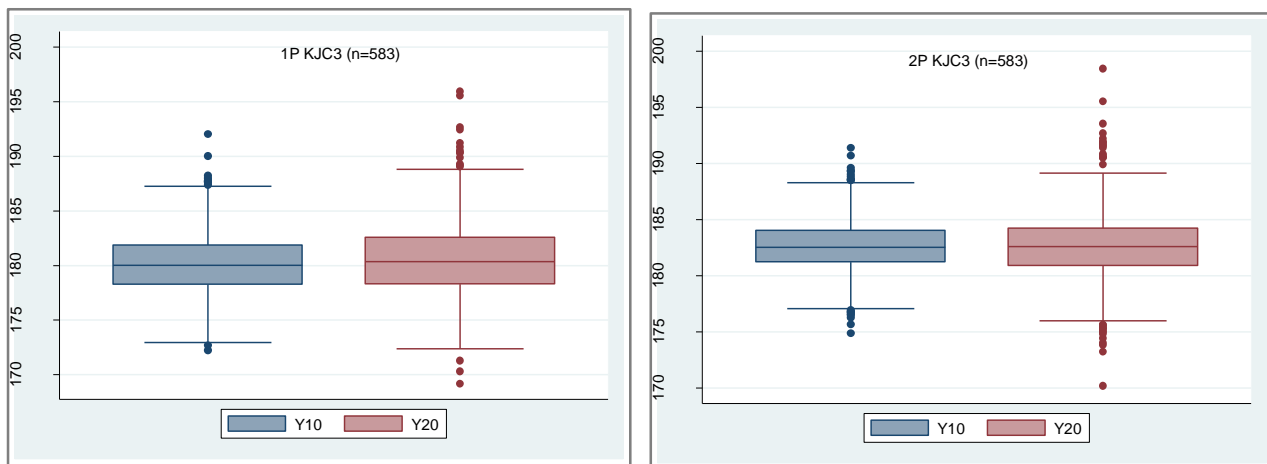
When the 44 rotated knees were removed from the alignment category tables there was little change in the 1P (Table 45) and 2P (Table 46) AA alignment categories compared to Table 41a and Table 41b respectively.

Table 43, Table 44, Table 45 and Table 46 show that removing the rotated outlier images had little bearing on the current alignment results. It was therefore likely that there were still rotated images contained within the main sample that could affect alignment measurement. Further development work is planned for the next phase of KneeMorf software to allow automatic identification of rotated images so that an appropriate correction factor to the AA alignment measurement can be applied. In the meantime, in order to preserve sample size these rotated images were included in the preceding analyses and this limitation to using the current version of KneeMorf alignment software was acknowledged.

6.5.3 Natural history of AA alignment over 10 years

This natural history analysis utilises all 583 knees. The box and whisker plots in Figure 48 show normally distributed AA alignment measurements with a greater spread in ranges at Y20 for both methods. Overall there is a negligible mean difference in a very slight valgus direction in both the 1P (0.36° , $SD \pm 2.73^\circ$) and 2P (0.06° , $SD \pm 2.01^\circ$) AA alignment methods over this ten year period. Although the 1P method difference between Y10 and Y20 is statistically significant ($p=0.009$), at 0.36° the change is less than 1° and therefore not regarded as clinically significant (Cicuttini et al., 2004).

Figure 48: Box plots for all knees



Alignment (n=583)	Y10	Y20	Mean difference ^a ° (±SD)	P value ^b
1P mean AA angle ° (±SD)	180.17 (2.86)	180.54 (3.66)	0.36 (2.73)	0.009
2P mean AA angle ° (±SD)	182.60 (2.33)	182.66 (3.20)	0.06 (2.01)	0.54

^a Mean difference: negative=varus, positive=valgus; ^b P value comparing Y10 with Y20 knees using t-test adjusted for correlated data.

Box and whisker plots also examined the change in AA alignment over ten years in Y10 SRKOA negative knees (n=559) compared to Y10 SRKOA positive knees (n=24) for 1P and 2P methods in Figure 49.

For SRKOA negative knees the Y10 1P mean was 180.16° (SD ±3.57) and Y20 1P mean was 180.52° (SD ±4.66), with a mean difference in AA alignment of 0.36° (SD ±2.60) in a slight valgus direction which although statistically significant at p=0.008, was not regarded as clinically significant, being less than 1° it was not regarded as clinically significant (Cicuttini et al., 2004). For 1P SRKOA positive knees, the Y10 mean was 180.51° (SD ± 3.50°), and the Y20 1P mean was slightly greater at 180.96° (SD ±4.57°) with a slight valgus mean difference of 0.45° (SD ±4.88°), with a p value = 0.71.

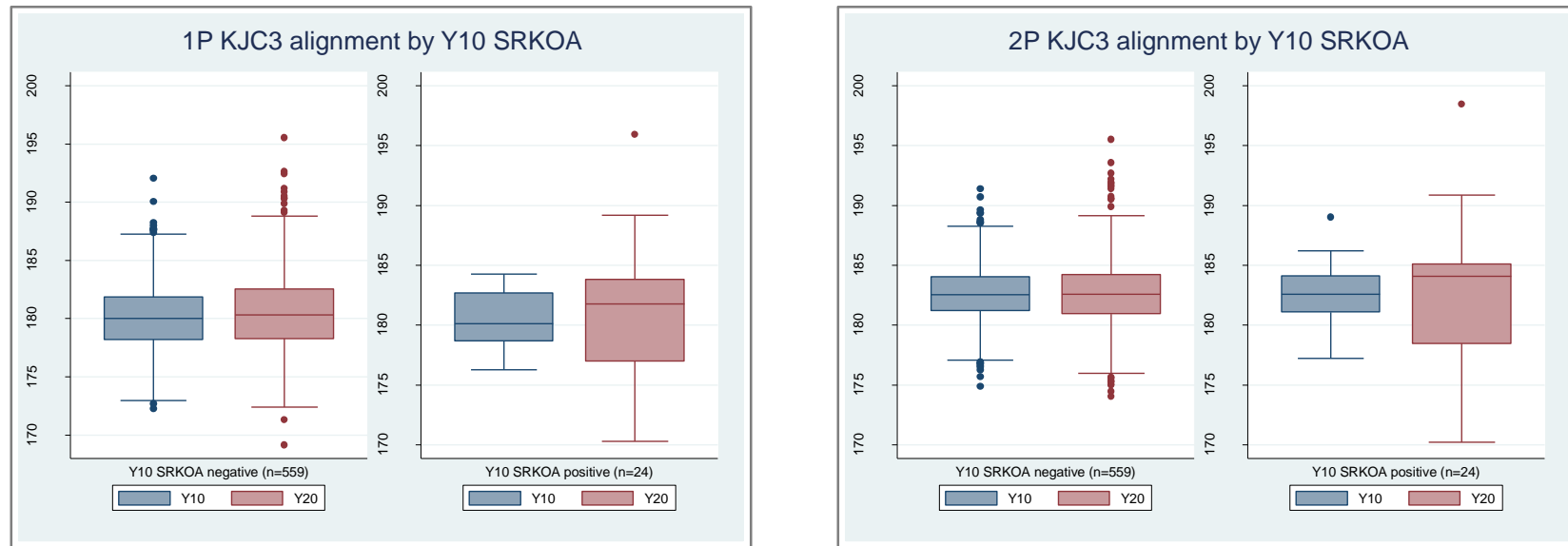
For the 2P methods the mean differences were very small with 0.07° (SD ±1.88°) in a valgus direction for SRKOA negative knees and -0.01° (SD ±4.04°) in a negligible varus direction for SRKOA positive knees over this 10 year period.

The box and whisker plots in Figure 50 examine the change in AA alignment over ten years in Y10 RKOAs negative knees (n=435) compared to Y10 RKOAs positive knees (n=148) for 1P and 2P methods. For the 1P method the mean change in AA alignment over this ten year period for RKOAs negative and RKOAs

positive knees was less than 0.4° valgus which although statistically significant ($p=0.012$) for RKOA negative knees, overall neither differences were clinically significant.

For the 2P method the mean change in AA alignment over ten years for RKOA negative knees was very small at 0.08° (SD ± 1.77) and even smaller at 0.02° (SD ± 2.59) for RKOA positive knees, neither difference was statistically or clinically significant.

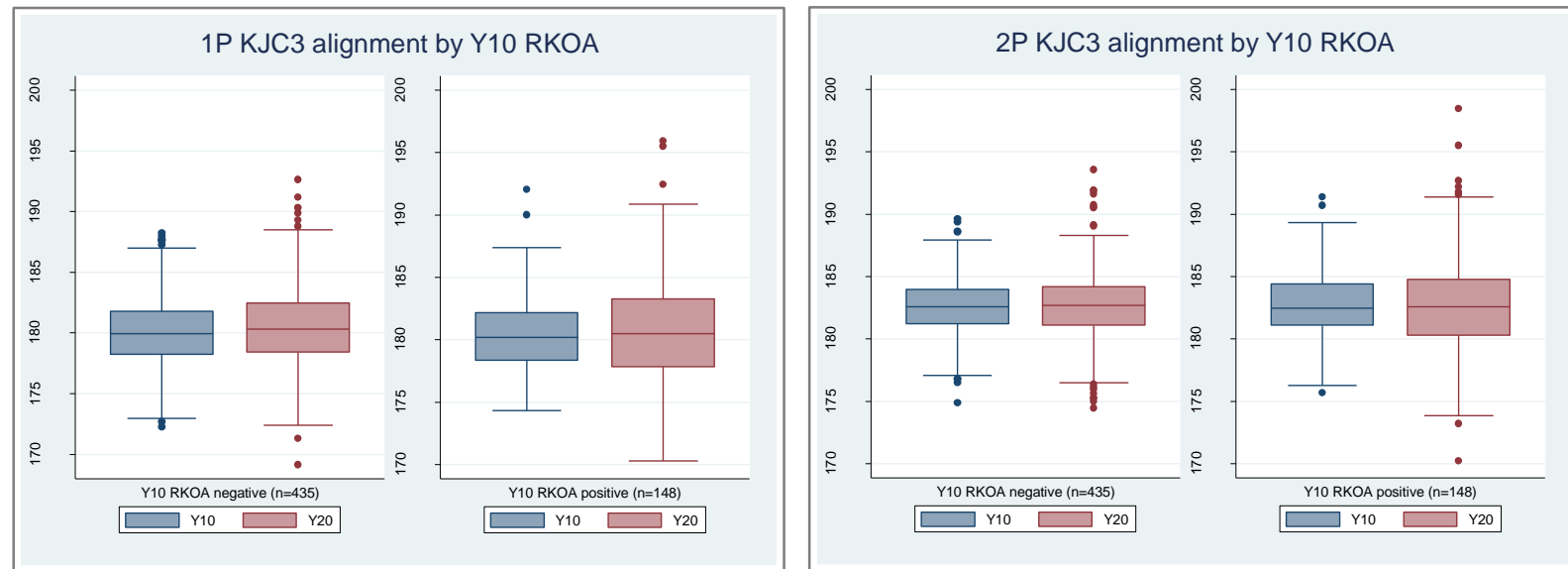
Figure 49: Box plots for all knees by Y10 SRKOA



Alignment	Y10 SRKOA - Y10 (n=559 knees)	Y10 SRKOA - Y20 (n=559 knees)	SRKOA – mean difference ^a ° (±SD)	P value ^b	Y10 SRKOA + Y10 (n=24 knees)	Y10 SRKOA + Y20 (n=24 knees)	SRKOA + mean difference ^a ° (±SD)	P value ^b
1P mean AA angle ° (±SD)	180.16 (3.57)	180.52 (4.66)	0.36 (2.60)	0.008	180.51 (3.50)	180.96 (4.57)	0.45 (4.88)	0.71
2P mean AA angle ° (±SD)	182.60 (2.91)	182.67 (4.11)	0.07 (1.88)	0.49	182.49 (2.86)	182.48 (4.03)	-0.01 (4.04)	0.99

^a Mean difference: negative=varus, positive=valgus; ^b P value comparing Y10 with Y20 knees using t-test adjusted for correlated data.

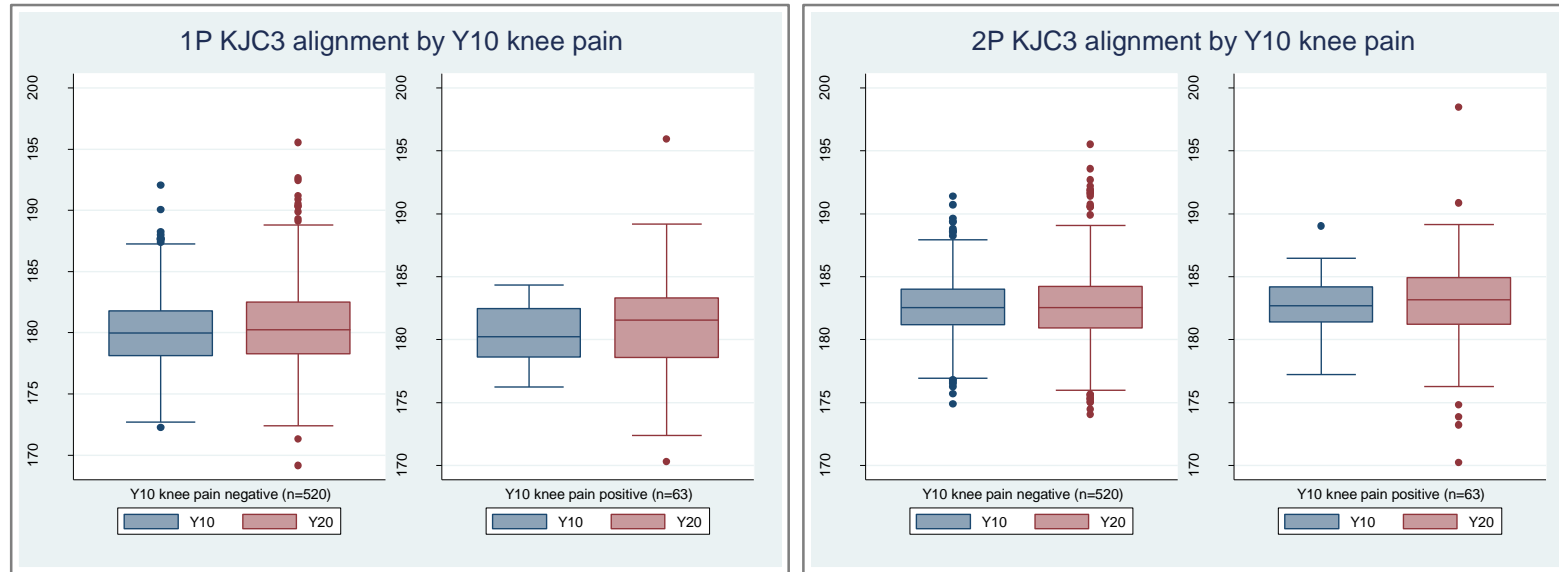
Figure 50: Box plots for all knees by Y10 RKO



Alignment	Y10 RKO - Y10 (n=435 knees)	Y10 RKO - Y20 (n=435 knees)	RKO - mean difference ^a ° (±SD)	P value ^b	Y10 RKO + Y10 (n=148 knees)	Y10 RKO + Y20 (n=148 knees)	RKO + mean difference ^a ° (±SD)	P value ^b
1P mean AA angle ° (±SD)	180.11 (3.58)	180.46 (4.67)	0.36 (2.50)	0.012	180.37 (3.58)	180.75 (4.67)	0.37 (3.33)	0.25
2P mean AA angle ° (±SD)	182.59 (2.91)	182.66 (4.11)	0.08 (1.77)	0.43	182.64 (2.92)	182.65 (4.11)	0.02 (2.59)	0.95

^a Mean difference: negative=varus, positive=valgus; ^b P value comparing Y10 with Y20 knees using t-test adjusted for correlated data.

Figure 51: Box plots for all knees by Y10 knee pain



Alignment	Y10 KP - Y10 (n=520 knees)	Y10 KP - Y20 (n=520 knees)	KP – mean difference ^a ° (±SD)	P value ^b	Y10 KP + Y10 (n=63 knees)	Y10 KP + Y20 (n=63 knees)	KP + mean difference ^a ° (±SD)	P value ^b
1P mean AA angle ° (±SD)	180.14 (3.57)	180.48 (4.67)	0.34 (2.63)	0.02	180.47 (3.50)	181.02 (4.58)	0.55 (3.45)	0.27
2P mean AA angle ° (±SD)	182.58 (2.92)	182.64 (4.11)	0.06 (1.90)	0.58	182.76 (2.86)	182.87 (4.02)	0.11 (2.76)	0.79

^a Mean difference: negative=varus, positive=valgus; ^b P value comparing Y10 with Y20 knees using t-test adjusted for correlated data.

Finally the box and whisker plots in Figure 51 examine the change in AA alignment over ten years in Y10 knee pain negative knees (n=520) compared to Y10 knee pain positive knees (n=63) for 1P and 2P methods. For the 1P method the mean change in AA alignment over this ten year period was 0.34° (± 2.63) for knee pain negative knees and a larger mean change of 0.55° (± 3.45) for knee pain positive knees, both in a slight valgus direction, although the knee pain negative change was statistically significant at $p=0.02$, neither of these changes were clinically significant.

For the 2P method, smaller mean changes were present at 0.06° (± 1.90) for knee pain negative knees and 0.11° (± 2.76) for knee pain positive knees, neither were statistically or clinically significant.

Natural history of alignment results summary

- The change in alignment seen in these 583 knees over 10 years was small and limited by the identification of rotated knees.
- The majority of knees (over 50% for the 1P method and over 70% for the 2P method) stay within the same alignment category: 59% neutral, 53% varus and 73% valgus for the 1P method (Table 41a), and 77% neutral, 73% varus and 77% valgus for the 2P method (Table 41b).
- Overall there was a negligible change in AA alignment angle in a very slight valgus direction in both the 1P (0.36° , $SD \pm 2.73^{\circ}$) and 2P (0.06° , $SD \pm 2.01^{\circ}$) AA alignment methods over this ten year period (Figure 48).
- These alignment changes remained similar in size and direction between comparisons of SRKOA, RKOAs and knee pain positive and negative knees for 1P and 2P methods.

6.5.4 Incidence study population

The clinical characteristics of the knees from the women participating in the longitudinal incidence analysis are shown in Table 47.

Table 47: Baseline clinical characteristics for Y10 to Y20 AA incidence analysis

Where AA=anatomic axis; BMI=body mass index; IQR=inter-quartile range; KJC=knee joint centre; K&L=Kellgren & Lawrence grade; n/a=not applicable; RKOA=radiographic knee osteoarthritis; SRKOA=symptomatic radiographic knee osteoarthritis; SD=standard deviation.

Y10 characteristic	Full cohort (n=602 knees)	Excluded cohort (n=34 knees)	Included cohort (n=568 knees)	P value ^a
Age, median (IQR) years	60 (56,65)	61.5 (56,66)	60 (56,65)	0.33
BMI, mean (\pm SD) kg/m ²	26.5 (4.5)	28.5 (4.0)	26.4 (4.5)	0.009
Knee injury, %	14.3	32.4	13.2	0.002
Knee pain \geq 15 days, %	12.3	100.00	7.0	n/a
RKOA \geq 2 K&L grade, %	26.9	100.00	22.5	n/a
SRKOA, %	5.7	100.00	0	n/a
AA angle:				
1P KJC3, mean $^{\circ}$ (\pm SD)	180.13 (3.54)	179.53 (3.66)	180.16 (3.65)	0.33
1P neutral 178-182 $^{\circ}$, %	52.5	53.0	52.5	
1P varus <178 $^{\circ}$, %	23.1	23.5	23.0	
1P valgus >182 $^{\circ}$, %	24.4	23.5	24.5	
2P KJC3, mean $^{\circ}$ (\pm SD)	182.54 (3.03)	181.60 (3.05)	182.60 (3.04)	0.06
2P neutral 180-185 $^{\circ}$, %	75.7	58.8	76.8	
2P varus <180 $^{\circ}$, %	11.3	23.5	10.5	
2P valgus >185 $^{\circ}$, %	12.0	17.7	12.7	

^a P values comparing included (Y10 SRKOA incidence negative) to excluded (Y10 SRKOA incidence positive) cohort using: Kruskal Wallis test for age; two-sample t-test for BMI; Chi-square test for injury; clustered t-tests for mean AA angle.

The 19 knees from 15 women with TKRs at Y20 (4 women with bilateral and 11 women with unilateral TKRs) were included in this analysis and coded positive for clinical outcomes SRKOA and RKOA. The excluded cohort in this analysis comprised 34 knees from 23 women (11 bilateral and 12 single knees) that were SRKOA positive at Y10, 10 of these knees (3 women with bilateral and 4 women with unilateral) had a TKR by Y20. As expected these excluded knees had more knee pain, RKOA and SRKOA; greater BMI ($p=0.009$) and presence of knee injury ($p=0.002$), and were slightly more varus in 1P and 2P alignment than the 568 knees from 319 women in the included cohort. Of the 568 knees in the included cohort using the 1P alignment method 298 knees (52%) had neutral alignment (178-182 $^{\circ}$), 131 knees (23%) had varus alignment (<178 $^{\circ}$) and 139 knees (25%) had valgus alignment (>182 $^{\circ}$). Using the 2P alignment

method 436 knees (77%) were considered to have neutral alignment (180-185°), 60 knees (10%) had varus alignment (<180°) and 72 knees (13%) had valgus alignment (>185°).

There were 9 knees from 9 women in the included cohort who had a TKR by Y20, and therefore Y20 alignment data is not available for these knees resulting in a total of 559 knees from 310 women with complete alignment data at Y10 and Y20.

6.5.5 Incidence longitudinal associations

Longitudinal associations between Y10 1P and 2P alignment measurements and Y20 SRKOA, RKOAs and knee pain incidence were examined using GEE analysis with results shown in Table 48. These analyses were executed for varus and valgus alignment, with neutral alignment as the reference group using the alignment categories based on the association with SRKOA clinical outcome defined in the Y10 cross-sectional section 5.5.5. Analyses were adjusted for Y10 age, BMI and presence of knee injury.

SRKOA incidence

Among 568 knees without SRKOA (K&L grade 0 or 1 without knee pain or with less than 14 days pain) at baseline (Y10), SRKOA (K&L grade ≥ 2 with ≥ 15 days knee pain) had developed at follow-up (Y20) in a total of 83 knees (15% SRKOA incidence). Of these 83 knees using the 1P alignment method, 44% (n=36) were neutrally aligned, 26% (n=22) were varus and 30% (n=25) were valgus. For SRKOA incidence at Y20, slightly greater associations were seen for varus knees (OR 1.36, 95% CI 0.75, 2.47) versus neutral alignment compared to valgus knees (OR 1.26, 95% CI 0.70, 2.26) for the 1P method but neither the crude nor adjusted models were statistically significantly associated.

Using the 2P method of the 83 SRKOA positive knees, 71% (n=59) were neutral, 12% (n=10) were varus and 17% (n=14) were valgus aligned. Slightly greater associations were seen for valgus knees (OR 1.07, 95% CI 0.54, 2.14) versus neutral knees compared to varus knees (OR 0.97, 95% CI 0.44, 2.12) although again neither model was statistically significantly associated.

RKOA incidence

Among the 440 knees without RKOAs (K&L grade 0 or 1) at Y10 baseline, RKOAs (K&L grade ≥ 2) had developed at Y20 follow-up in a total of 295 knees (67%

RKOA incidence). Using the 1P alignment method, of these 295 knees, 51% (n=151) were neutral, 22% (n=65) were varus and 27% (n=79) were valgus. Greater associations for increased risk of RKOA incidence at Y20 were seen for valgus versus neutral compared to varus knees for the 1P method. The crude model was not significantly associated (OR 1.58, 95% CI 0.95, 2.62) and the association was further attenuated (OR 1.41, 95% CI 0.83, 2.38) on adjustment for Y10 age, BMI and knee injury.

Using the 2P method on the 295 RKOA positive knees, 78% (n=230) were neutral, 10% were varus and 12% were valgus knees. With the 2P method there were slightly greater associations for the adjusted model with varus knees (OR 1.38, 95% CI 0.67, 2.85) versus neutral alignment rather than valgus knees (OR 1.21, 95% CI 0.59, 2.46) but neither the crude nor adjusted models were statistically significantly associated.

Knee pain incidence

Among the 528 knees without knee pain (knees with no knee pain or knees with ≤ 14 days pain) at Y10 baseline, knee pain (knees with ≥ 15 days knee pain) had developed at Y20 follow-up in a total of 77 knees (15% knee pain incidence). Using the 1P alignment method, of these 77 knees, 44% (n=34) were neutral, 30% (n=23) were varus and 26% (n=20) were valgus. Greater associations for increased risk of knee pain incidence at Y20 were seen for varus knees (OR 1.45, 95% CI 0.79, 2.65) versus neutral alignment rather than valgus knees (which showed a reduction in risk in the adjusted model (OR 0.97, 95% CI 0.51, 1.84) due to the association with Y10 BMI and knee injury), but neither the crude nor adjusted models were statistically significantly associated.

Using the 2P method of the 77 knee pain positive knees, 72% (n=55) were neutral, 14% (n=11) were varus and 14% (n=11) were valgus knees. Similar to the 1P model, greater associations for increased risk of knee pain incidence at Y20 were seen for varus knees (OR 1.16, 95% CI 0.54, 1.84) versus neutral alignment rather than valgus knees (which again showed a reduction in risk in the adjusted model (OR 0.75, 95% CI 0.35, 1.65) again due to the association with Y10 BMI and knee injury), but neither the crude nor adjusted models were statistically significantly associated.

Sensitivity analyses

Sensitivity analyses for longitudinal associations between Y10 1P and 2P alignment measurements and Y20 SRKOA incidence were completed in Table 49. Sensitivity analysis 1 (SA1) compares Y20 SRKOA incidence using only Y10 RKOA negative knees (n=440), thereby excluding the 128 Y10 RKOA positive and Y10 knee pain negative knees from the original Y20 SRKOA analysis (n=568 knees) in Table 48. Sensitivity analysis 2 (SA2) using a population of 115 knees compares Y20 SRKOA incidence specifically to Y10 super-control knees which were RKOA negative (K&L grades 0 or 1) and knee pain negative (no pain in the preceding month).

Sensitivity analysis 1

When Y20 SRKOA incidence using only Y10 RKOA negative knees (n=440) in Table 49 was compared to Y20 SRKOA incidence using n=568 in Table 48 (the 128 knees that were Y10 RKOA positive and Y10 knee pain negative were removed), the results show that for the 1P method the association with varus alignment was reduced in the adjusted model from 1.36 (95% CI 0.75, 2.47) (Table 48) to 0.90 (95% CI 0.42, 1.95) (Table 49), but the association with valgus alignment remained more or less the same from 1.26 (95% CI 0.70, 2.26) (Table 48) to 1.31 (95% CI 0.66, 2.60) (Table 49), although neither the crude nor adjusted models were significantly associated in either table. For the 2P method, again associations with varus alignment were further reduced in Table 49, but the association with valgus alignment was increased to 1.47 (95% CI 0.64, 3.36) in the adjusted model although again this was not significantly associated.

Table 48: Longitudinal GEE associations for Y20 SRKOA, RKO A & knee pain incidence based on association with Y10 alignment.

Where 1P=one-point; 2P=two-point; KJC=knee joint centre; KJC3=tibial plateau centre; RKO A=radiographic knee osteoarthritis; K&L=Kellgren & Lawrence grade; SRKOA=symptomatic radiographic knee osteoarthritis. *Adjusted for Y10 age, bmi and knee injury.

Method		Y20 knee pain (n=528)		Y20 RKO A (n=440)		Y20 SRKOA (n=568) ^a	
		- (n=451)	+ (n=77)	- (n=145)	+ (n=295)	- (n=485)	+ (n=83)
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Y10 1P KJC3	Neutral 178-182° Reference	n=245 1.0 (-)	n=34 -	n=83 1.0 (-)	n=151 -	n=262 1.0 (-)	n=36 -
	Varus <178°	n=102	n=23	n=35	n=65	n=109	n=22
	Crude	1.51 (0.86,2.67)	0.15	1.10 (0.67,1.80)	0.70	1.42 (0.80,2.50)	0.23
	Adjusted*	1.45 (0.79,2.65)	0.23	1.16 (0.70,1.91)	0.56	1.36 (0.75,2.47)	0.32
	Valgus >182°	n=104	n=20	n=27	n=79	n=114	n=25
	Crude	1.22 (0.67,2.23)	0.51	1.58 (0.95,2.63)	0.08	1.51 (0.87,2.63)	0.14
	Adjusted*	0.97 (0.51,1.84)	0.92	1.41 (0.83,2.38)	0.20	1.26 (0.70,2.26)	0.44
Y10 2P KJC3	Neutral 180-185° Reference	n=348 1.0 (-)	n=55 -	n=120 1.0 (-)	n=230 -	n=377 1.0 (-)	n=59 -
	Varus <180°	n=48	n=11	n=12	n=29	n=50	n=10
	Crude	1.26 (0.61,2.62)	0.53	1.35 (0.66,2.77)	0.41	1.08 (0.51,2.30)	0.84
	Adjusted*	1.16 (0.54,2.49)	0.71	1.38 (0.67,2.85)	0.39	0.97 (0.44,2.12)	0.94
	Valgus >185°	n=55	n=11	n=13	n=36	n=58	n=14
	Crude	1.09 (0.52,2.28)	0.82	1.41 (0.72,2.76)	0.32	1.48 (0.77,2.82)	0.24
	Adjusted*	0.75 (0.35,1.65)	0.48	1.21 (0.59,2.46)	0.60	1.07 (0.54,2.14)	0.85

^a SRKOA incidence: SRKOA negative (K&L 0 or 1 & ≤14 days or no pain) at Y10, SRKOA positive (K&L ≥2 & L ≥15+ days pain) at Y20; SRKOA sample also includes 128 Y10 RKO A positive & Y10 knee pain negative knees on top of 440 knees from RKO A sample.

Table 49: Sensitivity analysis for SRKOA incidence longitudinal GEE associations.

Where 1P=one-point; 2P=two-point; KJC=knee joint centre; SRKOA=symptomatic radiographic knee osteoarthritis; SA=sensitivity analysis.*Adjusted for Y10 age, bmi & knee injury.

Method		Y20 SA1 SRKOA (n=440) ^a		Y20 SA2 SRKOA (n=115) ^b	
		- (n=385)	+ (n=55)	- (n=90)	+ (n=25)
		OR (95% CI)	P value	OR (95% CI)	P value
Y10 1P KJC	Neutral 178-182°	n=206	n=28	n=59	n=13
	Reference	1.0 (-)	-	1.0 (-)	-
	Varus <178°	n=90	n=10	n=19	n=5
	Crude	0.84 (0.39, 1.81)	0.66	1.22 (0.39, 3.78)	0.74
	Adjusted*	0.90 (0.42, 1.95)	0.69	1.01 (0.29, 3.49)	0.99
	Valgus >182°	n=89	n=17	n=12	n=7
Y10 2P KJC	Crude	1.46 (0.76, 2.79)	0.26	2.53 (0.85, 7.49)	0.09
	Adjusted*	1.31 (0.66, 2.60)	0.49	1.46 (0.40, 5.26)	0.57
	Neutral 180-185°	n=308	n=42	n=73	n=19
	Reference	1.0 (-)	-	1.0 (-)	-
	Varus <180°	n=38	n=3	n=9	n=2
	Crude	0.52 (0.15, 1.87)	0.32	0.89 (0.19, 4.24)	0.88
Y10 2P KJC	Adjusted*	0.52 (0.15, 1.84)	0.31	0.92 (0.18, 4.65)	0.92
	Valgus >185°	n=39	n=10	n=8	n=4
	Crude	2.03 (0.95, 4.35)	0.07	1.86 (0.52, 6.67)	0.34
	Adjusted*	1.47 (0.64, 3.36)	0.36	0.80 (0.15, 6.54)	0.81

^a Y20 SA1 SRKOA incidence using SRKOA negative (K&L 0 or 1 & ≤14 days or no pain) at Y10, SRKOA positive (K&L ≥2 & ≥15+ days pain) at Y20 from Y10 RKO negative knees (n=440).

^b Y20 SA2 SRKOA incidence using Y10 super control SRKOA negative (K&L 0 or 1 & no knee pain) knees only.

Sensitivity analysis 2

When Y20 SRKOA incidence was compared using only Y10 RKO negative (K&L grades 0 or 1) and knee pain negative super-control knees (no pain in the preceding month) (n=115) (Table 49), there was a suggestion of valgus knees being more strongly associated with Y20 SRKOA incidence particularly for the 1P method where the crude model was near to being significantly associated (OR 2.53, 95% CI 0.85, 7.49) however this association was attenuated in the adjusted model (OR 1.46, 95% CI 0.40, 5.26). For the 2P method, associations with varus alignment were further reduced in Table 49, but the association with valgus alignment is increased to 1.86 (95% CI 0.52, 6.67) in the crude model although this was also attenuated in the adjusted model to 0.80 (0.15, 6.54) due to the association with knee injury.

Longitudinal incidence results summary

SRKOA incidence:

- Neither crude nor adjusted models were significantly associated for either method. Slighter greater associations were seen for varus versus neutral knees compared to valgus knees for the 1P method, whereas slightly greater associations were seen for valgus versus neutral knees compared to varus knees for the 2P method.
- When compared only against Y10 RKOAs, the association with varus alignment was reduced, but the association with valgus alignment remained the same for 1P and increased for 2P method.
- When compared only against Y10 super-control knees, there was a suggestion of valgus versus neutral compared to varus knees being more strongly associated with Y20 SRKOA incidence for both methods, though these associations were approximately halved when adjusted.

RKOA incidence:

- Greater associations for increased risk of Y20 RKOAs were seen for valgus versus neutral compared to varus knee for 1P method, with the crude model nearing statistical significance, although this association was attenuated on adjustment.
- Alternatively for the 2P method, there were slightly greater associations present for the varus versus neutral alignment rather than valgus knees but neither crude nor adjusted models were statistically significant.

Knee pain incidence:

- Neither crude nor adjusted models were significantly associated for either method, however consistent associations with Y20 knee pain incidence were seen for 1P and 2P methods with greater associations for increased risk for varus versus neutral rather than valgus knees.

Overall:

- It is very difficult to interpret these findings given the limitations caused by rotation and reduced statistical power (particularly for the SRKOA outcome) as discussed further in section 6.6.

6.6 Discussion

Aim 1: The natural history of AA alignment over 10 years

Considering the limitations, this study uniquely describes the natural history of knee alignment using 1P and 2P AA alignment methods over a 10 year period in 583 knees from a general female population. The majority of knees (over 50% for the 1P method and over 70% for the 2P method), stay within the same alignment category after 10 years: 59% neutral, 53% varus and 73% valgus for the 1P method (Table 41a), and 77% neutral, 73% varus and 77% valgus for the 2P method (Table 41b). Overall there was a very slight but non-statistical mean difference in a valgus direction in both the 1P (0.36° , \pm SD 2.73°) and 2P (0.06° , \pm SD 2.01°) AA alignment methods over this 10 year period (Figure 48). These alignment changes remain similar in size and direction when comparisons between positive and negative SRKOA, RKOAs, and knee pain knees were made.

However due to the identification of rotated knee images within this sample these results must be interpreted with caution. The change in AA alignment calculated for the 583 knees, by subtracting Y10 from Y20 alignment measurements, gave unusual results with the largest mean change of 1.13° (\pm SD 2.63°) in a valgus direction seen in 1P varus knees (Table 40a). This was clinically surprising as varus knees at baseline would be expected to become more varus at follow-up rather than valgus. A similar pattern was noted in 1P valgus knees where a smaller mean change of -0.11° (\pm SD 3.08°) in a varus direction was seen (Table 40a). Categorical change in 1P and 2P (Table 41a and b) AA alignment showed a 5% minority of knees using the 1P method were identified as unusual in that they started as varus at Y10 and moved to valgus alignment by Y20 ($n=6$ knees), or started as valgus at Y10 and moved to varus alignment by Y20 ($n=7$ knees). These 13 knees and those identified with more than 5° of valgus change ($n=23$) or more than 5° of varus change ($n=21$) were highlighted as outlier knees and their Y10 and Y20 paired digital radiograph images were re-examined to see if these outliers were in fact real or whether they could be explained by some other factor. A total of 44 (12 knees rotated at Y10, 25 knees rotated at Y20 and 7 knees rotated at both Y10 and Y20) out of the 57 outlier paired radiograph images were identified visually as being rotated, as a result of the patella being positioned outside of the trochlear groove and/or due to the degree of overlap between the fibula head and tibia

as shown in Figure 47. Therefore despite applying the same positioning protocol (where the back of the knee was kept in contact with the cassette, the patella was centred over the lower portion of the femur and the tibial tubercles faced forward) during the acquisition of all knee radiograph images taken at Chingford cohort study visits, it is clear that this was in some cases inadequate in controlling knee rotation. Use of a standardised positioning frame during radiograph imaging would have been beneficial but unfortunately this was not available during the cohort study period.

When the rotated outlier knees were compared to the non-rotated knees in Table 42, the 44 rotated knees had a significantly greater BMI than the 539 non-rotated knees ($p=0.0001$), however knee pain which could also contribute to adopting a rotated knee position during imaging was not significantly different ($p=0.16$). When the 44 rotated knees were excluded from the change in alignment analysis (Table 43 and Table 44), only a small effect on the unusual results from Table 40a was seen. Varus 1P knees showed a lesser, but still in a valgus direction, mean change of 0.66° (\pm SD 2.02°), and valgus knees showed a greater, but still in a varus direction, mean change of -0.31° (\pm SD 2.65°). Therefore, as excluding the 44 identified outlier rotated knees did not completely resolve the varus/valgus direction anomalies identified in Table 40a, this suggested that there were probably still a degree of mildly rotated images contained within the main sample that could affect overall alignment measurement. However, it would not be practical to exclude all the mildly rotated knees in this analysis due to:

- a) reduced power from a smaller sample size (further details below), and
- b) the possibility of introducing a potential bias as rotated knees displayed a greater BMI.

Power calculations for the 1P method identified sufficient power to find a statistically significant difference ($p = 0.009$) by accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 452 knees were required to recognise a statistically significant difference using a minimum expected difference of 0.36° , a standard deviation of $\pm 2.73^\circ$, and a drop-out rate of 0%. However, the 2P method was under-powered to find a statistically significant difference ($p = 0.54$) by accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 8809 knees were necessary to recognise a statistically

significant difference, using a minimum expected difference of 0.06° , a standard deviation of 2.01° , and a drop-out rate of 0%. If the minimum expected difference was increased from 0.06° to 0.24° then there would have been sufficient power to find a statistically significant difference with 551 knees. Despite having sufficient power to detect a statistically significant difference for the 1P method, the 0.36° minimum expected difference is below 1° and therefore not considered clinically significant.

As removal of the identified rotated outlier images had little bearing on the alignment results in this analysis, it was probable there were still mildly rotated images contained within the main sample that affected alignment measurement. In order to preserve sample size and reduce bias these remained included in the analyses which is a limitation to this study and so results must be interpreted with caution. It is more plausible that this small valgus change in alignment is a consequence of measurement error due to rotated images contained within this study population as opposed to a true biological finding. An adjustment for knee rotation would address this issue. Further development work of the KneeMorf software is planned over the next 2 years through automatic identification of rotated images to apply an appropriate correction factor to the AA alignment measurement in order to correct this issue.

There are very few studies to which these natural history results can be compared, as the majority of AA knee alignment studies to date have measured knee alignment at the baseline time point only (Cicuttini et al., 2004, Brouwer et al., 2007, Hunter et al., 2007, Zhai et al., 2007). There is one study by Teichtahl and colleagues that examines whether change in AA knee alignment between baseline and 2 years is associated with a change in knee cartilage volume (measured via MRI) in the subsequent 2.5 years in the symptomatic index knee of a mixed gender KOA population ($n=78$) (Teichtahl et al., 2009a). The mean change in AA knee alignment in Teichtahl's study was also small at 0.22° (\pm SD 0.35°). This was measured using an alternative 1P method based on the centre of the tibial spines (indicating neither the tips nor the base) and so it is not directly comparable to the 1P method results shown here which used the centre of the tibial plateau. There is a lack of descriptive knee alignment natural history studies in the current literature. Once the rotation limitation of this Chingford cohort alignment data is appropriately

addressed (which is outside the scope of this thesis), this will be a valuable resource to describe the natural knee alignment patterns associated with three clinically important outcomes of SRKOA, RKOA and knee pain in a general female population spanning ten years, the longest period of follow-up.

Aim 2: Longitudinal associations of AA alignment at Y10 with KOA incidence at Y20

This study describes the longitudinal association between Y10 1P and 2P AA alignment measurements and Y20 SRKOA, RKOA and knee pain incidence, which is unique for the following reasons:

- 1) Firstly, for using SRKOA as the main outcome as previous AA alignment studies do not take reported knee pain symptoms into consideration using only RKOA incidence as their outcome (Brouwer et al., 2007, Hunter et al., 2007).
- 2) Secondly, for providing the longest period of follow-up spanning 10 years. Previous AA alignment incidence studies have had mean follow-ups of 6.6 and 8.7 years respectively (Hunter et al., 2007, Brouwer et al., 2007).
- 3) Thirdly, for providing a comparison between the 1P and 2P method of measuring AA alignment – previous AA alignment studies have used the 1P method only using two different KJCs, the tibial spine tips knee joint centre (Hunter et al., 2007) and the tibial spine base knee joint centre (Brouwer et al., 2007).

However, there was insufficient power in this incidence analysis to acquire statistically significant differences for either the 1P or 2P method. For the 1P method a difference of at least 11% (which was approximately double the reported difference in Table 48) was required between the proportion of knees that developed Y20 SRKOA with neutral alignment at Y10 and the proportion of knees that developed Y20 SRKOA with varus or valgus alignment at Y10. A difference of at least 9% (again approximately double the reported difference in Table 48) was required for the 2P method.

Unfortunately there were no SRKOA incidence AA alignment studies available for comparison as previous AA alignment studies did not take reported knee pain symptoms into consideration, and used only RKOA incidence as their

outcome (Brouwer et al., 2007, Hunter et al., 2007). The GEE analysis results for RKOA incidence from this study (Table 48) showed that greater associations for increased risk of RKOA incidence at Y20 were seen for valgus versus neutral alignment compared to varus knees for the 1P method. The unadjusted model was near to being significantly associated (OR 1.58, 95% CI 0.95, 2.63) however this association was attenuated (OR 1.41, 95% CI 0.83, 2.38) on adjustment for Y10 age, BMI and knee injury. These 1P method results agree with Hunter and colleagues, who in their case-control study with 8.75 years mean follow-up demonstrated baseline AA alignment was not associated with incident RKOA (Hunter et al., 2007). In comparison Brouwer and colleagues reported increasing varus alignment was associated with RKOA incidence (OR 2.06, 95% CI 1.28, 3.32), and valgus alignment was associated with a borderline significant increase in RKOA incidence (OR 1.54, 95% 0.97, 2.44) after a mean follow-up of 6.6 years (Brouwer et al., 2007). These different findings may partly be explained by the fact that these studies used different KJCs for their AA alignment measurements: Hunter used the tibial spine tips and Brouwer used the tibial spine base, whereas this study used the centre of the tibial plateau.

For the 2P method there were no other RKOA incidence AA alignment studies available for comparison using this method. These results showed slightly greater associations present for the RKOA incidence adjusted model with varus knees (OR 1.38, 95% CI 0.67, 2.85) versus neutral alignment rather than valgus knees (OR 1.21, 95% CI 0.59, 2.46) but neither the unadjusted nor adjusted models were statistically significantly associated possibly as a result of being under-powered.

Similar to SRKOA, there were no knee pain AA alignment studies available for comparison of the results shown in Table 48 for knee pain incidence. These results showed consistent associations for 1P and 2P methods with greater associations for increased risk of Y20 knee pain incidence for varus versus neutral rather than valgus knees. However as discussed previously a degree of caution is required with interpretation of all these results due to issues identified with rotated images and lack of power. It is therefore difficult at this time to draw valid conclusions in terms of the overall association between AA alignment with incidence of SRKOA, RKOA and knee pain over this ten year period.

6.6.1 Conclusion

This chapter has provided a unique longitudinal analysis of 1P and 2P AA alignment in a general female population using three clinically important outcomes of SRKOA, RKOAs and knee pain spanning a 10 year period, which is the longest available follow-up period for an alignment study. Due to the issue of rotated images within this sample, it is sensible to delay full judgement of these results until automatic identification of rotated images is available in the next development phase of KneeMorf software, thereby allowing an appropriate correction factor to be applied to AA alignment measurement.

6.6.2 Final summary

- The majority of knees stayed within the same alignment category after 10 years.
- Overall negligible change in AA alignment angle in a very slight valgus direction over ten years which remained similar in size and direction between positive and negative SRKOA, RKOAs and knee pain knees.
- The longitudinal associations with Y20 SRKOA, RKOAs and knee pain incidence were limited by insufficient power to acquire statistically significant differences for either the 1P or 2P method, and the identification of rotated images within the sample means it is difficult to draw valid conclusions at this time.

7. Chapter 7: The natural history, cross-sectional and longitudinal associations of body mass with knee osteoarthritis

7.1 Background

The current obesity epidemic is leading to a rise in a range of NCDs such as type 2 diabetes, hypertension, CVD, cancer and musculoskeletal conditions such as OA (World Health Organization, 2015). BMI is known to be strongly and positively associated with KOA, mainly defined as RKOA. This is irrespective of study design, whether cross-sectional, case-control or prospective cohort. However, the majority of research in this area is predominantly cross-sectional in design (Hart and Spector, 1993b, Cooper et al., 1994b, Hochberg et al., 1995, Rogers and Wilder, 2008); uses body weight measurements taken at baseline but not at follow-up visits (Reijman et al., 2007, Lohmander et al., 2009), or uses self-reported body weight and height measurements (Gelber et al., 1999, Grotle et al., 2008, Adamson et al., 2006), which could have a potential for bias. There are few longitudinal cohorts examining the true change in body weight over time, and the long-term impact of obesity on knee joints. There are fewer still that consider the associations between obesity and a range of KOA outcomes including SRKOA, RKOA and knee pain that this study will examine.

Although BMI is the most useful population-level measure of overweight and obesity (World Health Organization, 2015) it gives little indication as to body composition or fat distribution. As a result BMI can overestimate body fat in athletes and others with a lean body mass or muscular build, and it may equally underestimate body fat in those with less lean body mass such as older people and others who have lost muscle bulk. For this reason, WC is included in this study thereby allowing body shape and subsequent fat distribution to be considered. A large WC indicates an android fat distribution with greater amounts of fat tissue around the trunk and abdomen, known as central obesity or 'apple shape' which is directly related to an increase in CVD (Donahue et al., 1987, de Koning et al., 2007). Whether this is directly linked to increases in SRKOA, RKOA and knee pain is not clear. This study also explores these

associations, and examines whether there is any advantage to using WC over BMI measurements.

7.2 Aim

The main aims of this study were to examine the following in a general female cohort population:

- 1) To describe the natural history of BMI at 5 yearly intervals over a 19 year period.
- 2) To describe the natural history of BMI and its associations with SRKOA, RKOAs and knee pain at 5 yearly intervals over a 19 year period.
- 3) To describe the natural history of WC and its association with BMI, SRKOA, RKOAs and knee pain over a 19 year period.
- 4) To describe cross-sectional associations between BMI and WC with SRKOA, RKOAs and knee pain at Y1.
- 5) To describe longitudinal associations for BMI and WC at Y1 with SRKOA, RKOAs and knee pain incidence at Y10.

7.3 Method

7.3.1 Study population

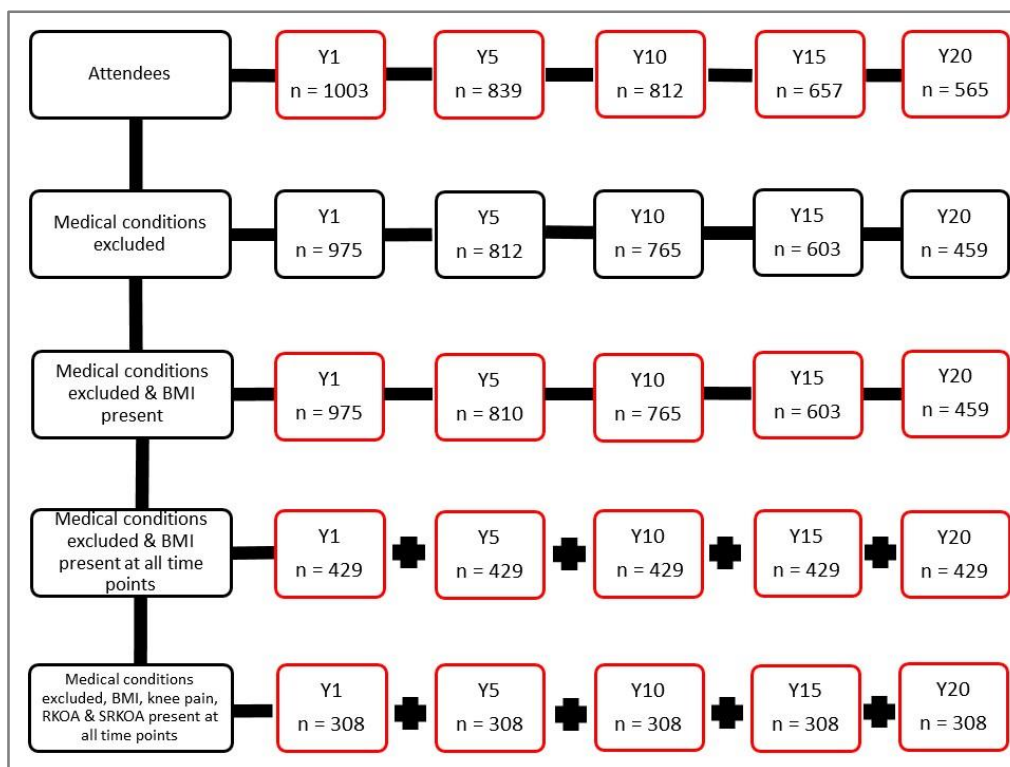
Chingford cohort women with the following measurements present were included in this study:

- 1) BMI at each of the following time points Y1, Y5, Y10, Y15 and Y20 (n=429).
- 2) BMI, SRKOA, RKOAs and knee pain at each of the following time points Y1, Y5, Y10, Y15 and Y20 (n=308).
- 3) WC and BMI at Y1 and Y20 (n=457).
- 4) BMI, WC, SRKOA, RKOAs and knee pain at Y1 (n=823).
- 5) BMI and WC at Y1, and SRKOA, RKOAs and knee pain at Y10 (n=646).

Women with any of the medical conditions listed in the exclusion criteria (section 3.4.2) at either Y1, Y5, Y10, Y15 or Y20 time points were excluded. Women with TKRs were included and re-coded positive for knee pain, RKOAs and SRKOA outcomes if not already coded so (Y1 n=3, Y5 n=2, Y10 n=6, Y15

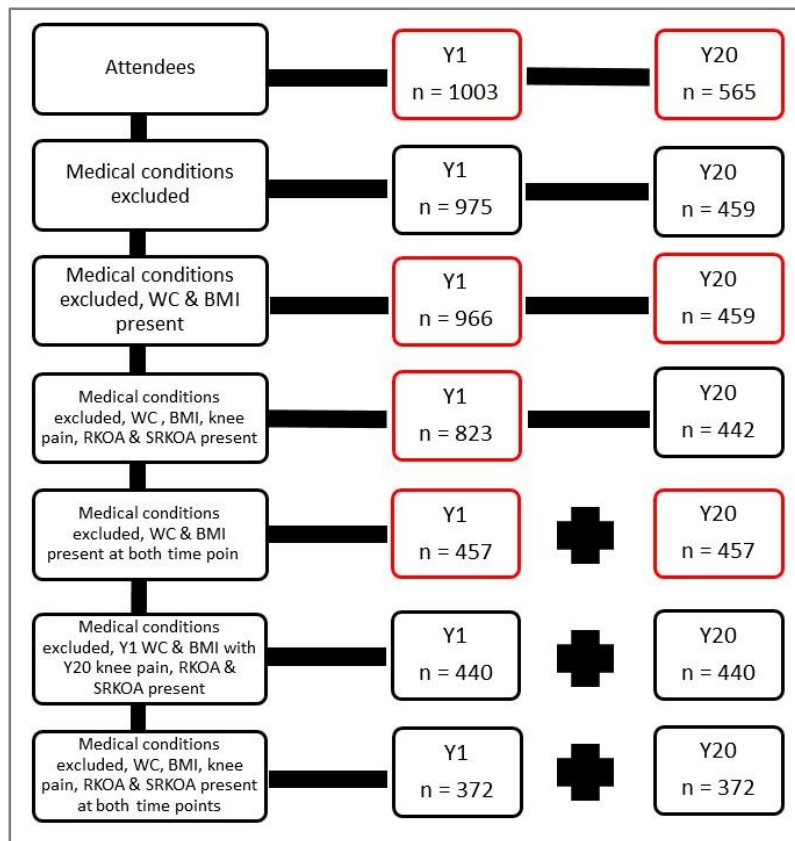
n=20 & Y20 n=35 TKRs). The derivation of the different study populations are shown in Figure 52, 53 and 54.

Figure 52: Derivation of BMI natural history analysis study population



For aim 1, to describe the BMI natural history at 5 yearly intervals over the 19 year period, Figure 52 details the number of women available at each of the five time points for this BMI natural history analysis. Excluding medical conditions there were 975 women at Y1, 810 women at Y5, 765 women at Y10, 603 women at Y15 and 459 women at Y20 with BMI recorded. There were a total of 429 women attending all the time points with BMI recorded, and out of these there were 308 women who attended all five visits with BMI, SRKO, RKO & knee pain variables recorded who will therefore be included in aim 2 which describes the natural history of BMI with SRKO, RKO and knee pain.

Figure 53: Derivation of WC natural history analysis study population

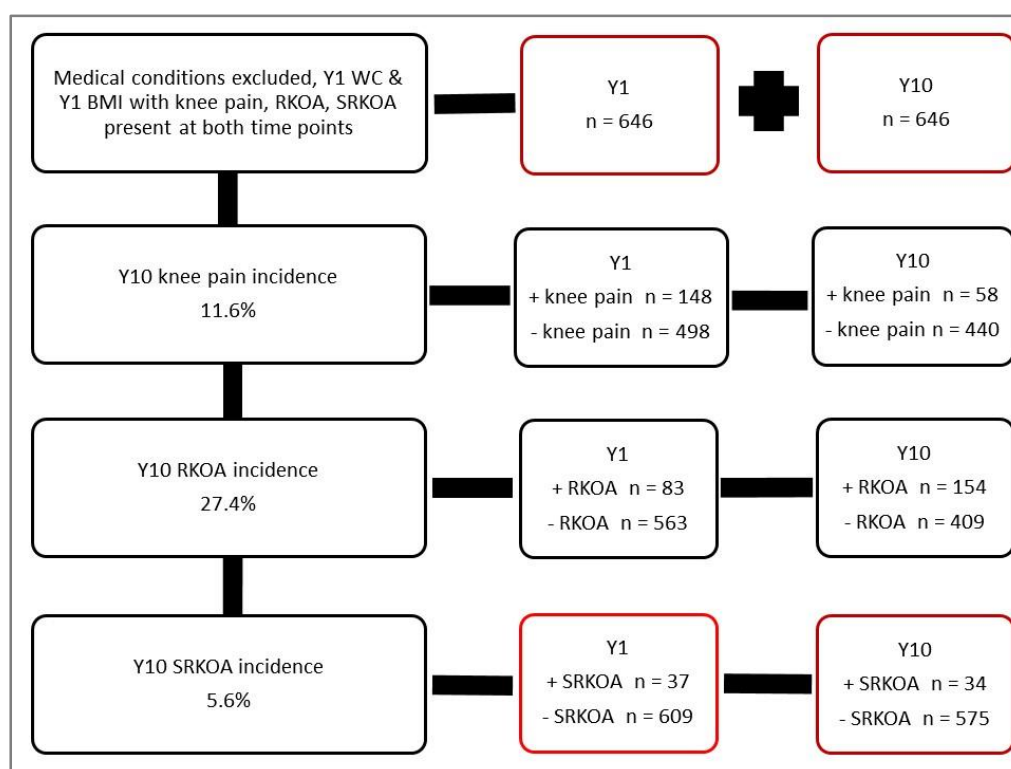


For aim 3 which describes the natural history of WC and its association with BMI over the 19 year period, Figure 53 details the number of women available at Y1 (n=966) and Y20 (n=459) with WC and BMI measurements available. A total of 457 women attended both Y1 and Y20 visits with WC and BMI measurements.

For aim 4, to describe cross-sectional associations between BMI and WC with SRKOA, RKOA and knee pain at Y1, a total of 823 women with these variables available at the Y1 baseline visit as shown in Figure 53.

For aim 5, to describe longitudinal associations for BMI and WC at Y1 with SRKOA, RKOA and knee pain incidence at Y10, there were 646 women with Y1 BMI and WC with SRKOA, RKOA and knee pain variables present at Y1 and Y10 (Figure 54). Incident cases for SRKOA (6%), RKOA (27%) and knee pain (12%) were calculated by identifying the new cases developed at Y10 following removal of Y1 positive cases.

Figure 54: Derivation of longitudinal incidence analysis study population



7.3.2 Exposure variables

Body mass index

Height measured in centimetres and body weight measured in kilograms were collected at the five clinic visits Y1, Y5, Y10, Y15 and Y20 following the SOP located in appendix A15. Further details of the methodology of these measurements can be found in section 3.5.1. BMI was subsequently determined using the WHO standard calculation (World Health Organization, 1995) listed in section 2.5.5.1 and was used as a continuous variable in these analyses. BMI was also stratified according to the WHO international adult BMI classification (Table 7 in section 2.5.5.1) into underweight $< 18.50 \text{ kg/m}^2$, normal $18.50 - 24.99 \text{ kg/m}^2$, overweight $25.0 - 29.99 \text{ kg/m}^2$ and obese $\geq 30.00 \text{ kg/m}^2$ (World Health Organization, 1995) to examine BMI changes in WHO categories over time.

Waist circumference

WC measured in centimetres was collected at the Y1 and Y20 clinic visits following the SOP (appendix A17) at both time points. Further details of this methodology is in the methods section 3.5.1.3. WC was used as a continuous

variable in these analyses and a WC of ≥ 80 cm defines central obesity in European women as stated by the International Diabetes Federation (International Diabetes Federation, 2006) and WHO (World Health Organization, 2011).

7.3.3 Outcome variables

The primary outcome variable was SRKOA, with RKOAs and knee pain as secondary outcomes as defined in section 3.6. Outcomes were categorised into none, unilateral, bilateral or any (unilateral + bilateral) for analyses.

7.3.4 Confounding variables

Analyses were adjusted for age and knee injury at Y1 as defined in section 3.7.

7.4 Analysis

All analyses were completed using Stata version 13.0 (Stata Corp, College Station, Texas, USA). Prior to analysis, data distribution was checked using histograms and scatter plots for inconsistencies, outliers and to assess whether normal distributions existed.

The demographic and clinical characteristics of each study population were presented for the included and excluded cohorts as the median with IQR for non-normally distributed continuous variables, and mean with SD for normally distributed continuous variables. Categorical variables were presented as a number and a percentage. Statistically significant differences (with p values < 0.05) in measured variables between the included and excluded cohorts were examined using two independent sample t -tests for normal continuous variables, Kruskal Wallis test for non-normal continuous variables and chi-square test for categorical variables.

For aim 1, the natural history of BMI was examined at 5 year intervals from Y1 to Y20 using the mean (\pm SD). Stratification into the WHO BMI categories allowed cross-tabulation and stacked bar graphs were plotted for complete attendees and all attendees for comparison.

For aim 2, the percentage of women reporting each outcome (unilateral or bilateral) by clinic visit was calculated, then the mean BMI (\pm SD) for none, unilateral and bilateral outcome by clinic visit was tabulated. A one-way

ANOVA test (with a Bonferroni correction) provided an associated p value for the difference between the three groups. A Bonferroni correction was included to account for multiple testing and to establish where, if any, the significant difference between the groups was e.g. unilateral v none, bilateral v none or unilateral v bilateral. Stacked bar graphs stratified by WHO BMI categories and by none / unilateral / bilateral outcomes for complete attendees and all attendees were plotted for comparison.

For aim 3, the natural history of WC was examined at Y1 and Y20 using the mean (\pm SD), and the mean WC (\pm SD) for none, unilateral and bilateral outcome by each clinic visit was tabulated. Similar to aim 2, a one-way ANOVA test with Bonferroni correction provided an associated p value for the difference between the three groups. Scatter plots examined the association between WC and BMI. Pearson correlation coefficients were calculated to assess strength of association and r^2 values to assess the variability explained by each model between complete attendees and all attendees for comparison.

For aim 4, Y1 cross-sectional associations between BMI and WC with SRKOA, RKO and knee pain, the exposure variables (BMI and WC) were continuous and the outcomes were categorical (none / unilateral / bilateral / any) therefore logistic regression analyses at the subject-level were performed and expressed as ORs with 95% CIs. The crude model and the adjusted model adjusted for Y1 age and knee injury were presented. Pseudo R^2 was provided to allow comparison, since the different units of measurement kg/m^2 for BMI and cm for WC make direct comparisons based on effect sizes difficult to justify. BMI and WC were examined separately first and then combined in a second model and presented graphically for the main outcome SRKOA.

For aim 5 longitudinal associations, similar logistic regression analyses to aim 4 were repeated using Y1 BMI and WC measurements for Y10 incident SRKOA, RKO and knee pain outcomes as described in Figure 54.

7.5 Results

7.5.1 Aim 1: Natural history of BMI

A total of 429 women were included in the BMI natural history population as shown in Figure 52. Table 50 shows the baseline Y1 characteristics of the 429 women who attended all five clinic visits with BMI measurements recorded at

Y1, Y5, Y10, Y15 and Y20, known as the included cohort, against the remaining 574 women who were excluded. This table shows that excluded women were significantly older ($p < 0.001$), slightly heavier with a greater BMI ($p < 0.001$), and suffered greater knee pain ($p < 0.01$) than the women attending all five time points, indicating that the included cohort were a younger and possibly healthier group of women.

Table 50: Baseline clinical characteristics for attendees with BMI recorded at Y1, Y5, Y10, Y15 and Y20

Where BMI=body mass index; IQR=inter-quartile range; K&L=Kellgren & Lawrence grade; RKOA=radiographic knee osteoarthritis; SRKO=symptomatic radiographic knee osteoarthritis; SD=standard deviation.

Y1 characteristic	Full cohort (n=1003 women)	Excluded cohort (n=574 women)	Included cohort (n=429 women)	P value ^a
Age, median (IQR) years	54 (49,60)	56 (50,61)	51 (48,56)	<0.001
BMI, mean (SD) kg/m ²	25.6 (4.3)	26.0 (4.7)	25.1(3.7)	<0.001
Knee pain* ≥ 1 month, %	25.1 (n=880)	28.5 (n=505)	20.5 (n=375)	<0.01
RKO ≥ 2 K&L grade, %	14.7 (n=970)	16.2 (n=551)	12.9 (n=419)	0.26
SRKO, %	6.8 (n=855)	8.2 (n=490)	4.9 (n=365)	0.18

^a P values comparing included to excluded cohort using Kruskal Wallis test for age, two sample t-test for BMI; Chi-square test for knee pain, RKO & SRKO. * Person-level knee pain available only.

The 429 women included in the BMI natural history analysis demonstrate that the mean BMI (\pm SD) gradually increases over 19 years from a borderline normal BMI at Y1 to an overweight BMI by Y20:

- 25.1 kg/m² (\pm 3.7) at Y1,
- to 26.0 kg/m² (\pm 4.1) at Y5,
- to 26.4 kg/m² (\pm 4.3) at Y10,
- to 27.0 kg/m² (\pm 4.6) at Y15,
- to 27.7 kg/m² (\pm 5.0) at Y20.

With stratification of these continuous BMI variables into the WHO BMI categories of underweight < 18.50 kg/m², normal $18.50 - 24.99$ kg/m², overweight $25.00 - 29.99$ kg/m² and obese ≥ 30.00 kg/m² (World Health Organization, 1995) it was possible to clearly examine BMI changes over 19 years in this cohort. Table 51 shows the changes in WHO BMI categories from Y1 baseline to Y20. Only 27% of women remained in the normal BMI category throughout the study period. At Y1, the majority (56%) of women were in the

normal BMI range, with 33% in overweight and 11% in obese categories. By Y20, the percentage of women in the normal BMI range had dropped to 30%, resulting in subsequent increases to 40% in the overweight category and the largest increase seen in the obese category with a near tripling up to 30% of women.

Table 51: Cross tabulation of Y1 and Y20 WHO BMI categories

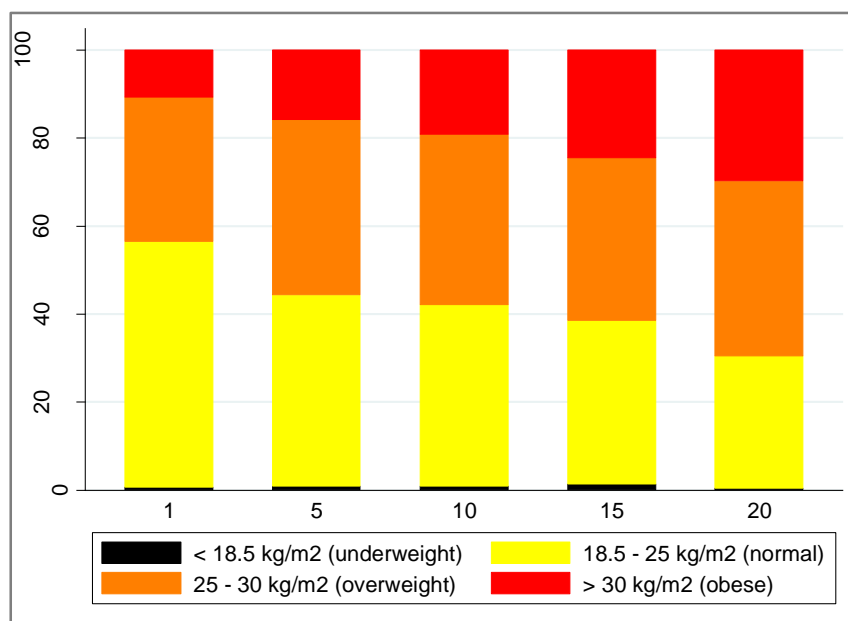
Results displayed as n out of a total n=429 (%)

Y1 \ Y20	Underweight	Normal	Overweight	Obese	Total n (%)
Underweight	0 (0)	3 (0.7)	0 (0)	0 (0)	3 (0.7)
Normal	2 (0.5)	115 (26.8)	106 (24.7)	16 (3.7)	239 (55.7)
Overweight	0 (0)	11 (2.6)	61 (14.2)	69 (16.1)	141 (32.9)
Obese	0 (0)	0 (0)	3 (0.7)	43 (10.0)	46 (10.7)
Total n (%)	2 (0.5)	129 (30.1)	170 (39.6)	128 (29.8)	429 (100)

The stacked bar graphs in Figure 55 show the natural history of BMI by WHO BMI categories for the 429 women attending all of the five clinics visits in Figure 55a, and for the total amount of women attending each clinic visit with BMI measurements present in Figure 55b. Overall both bar graphs show a similar pattern. Figure 55a shows the approximate 25% reduction in percentage of women in the normal BMI (yellow) category range from Y1 to Y20 starting as a rapid drop by approximately 15% by Y5 and then continuing to gradually decrease over the remaining 5 yearly time points that have been measured. Consequentially there were gradual increases from Y1 in the percentage of women in the overweight (orange) and obese (red) categories up to Y10, and then normal and overweight categories level out slightly and the obese category increases rapidly to around 30% by Y20. Figure 55b shows a similar pattern albeit with more gradual decreases in normal and increases in overweight and obese categories over the same time period.

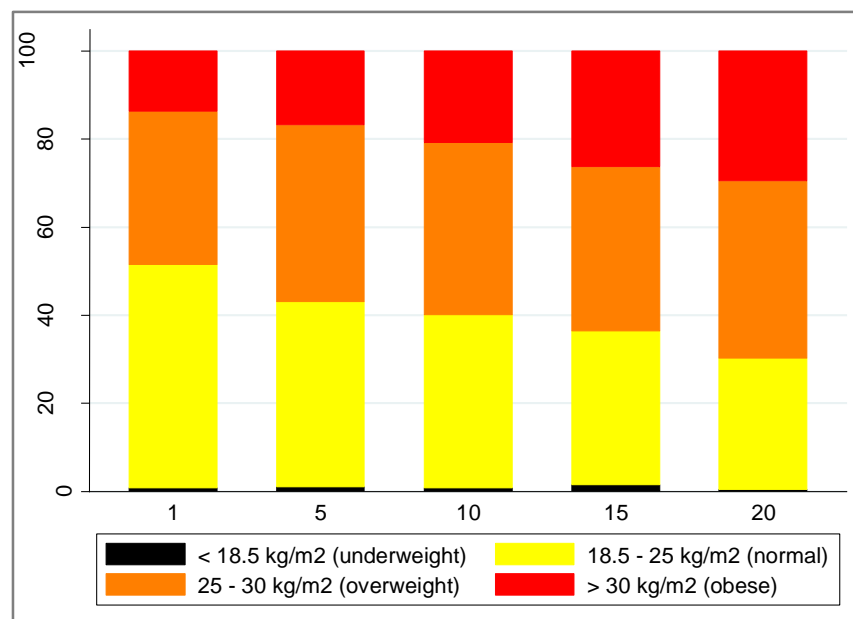
Figure 55: Natural history of BMI

55a: BMI only at each time point (n=429)



55b: BMI in all attendees

(Y1 n=975, Y5 n=810, Y10 n=765, Y15 n=603, Y20 n=459)



7.5.1.1 Aim 1 results summary

- Over a 19 year period BMI increased gradually from a normal BMI of 25.1 kg/m² to an overweight BMI of 27.7 kg/m².
- Only 27% of women remained in the normal BMI category throughout the 19 years.
- By Y20 there was a near tripling of obese women to 30%.

7.5.2 Aim 2: Natural history of BMI and its association with SRKOA, RKOA and knee pain

There were a total of 308 women with BMI, knee pain, RKOA and SRKOA variables recorded at each of the five time points over the 19 year period as shown in Figure 52. Table 52 shows the baseline Y1 characteristics of the 308 women who attended all five clinic visits with all variables present at Y1, Y5, Y10, Y15 and Y20, known as the included cohort, against the remaining 695 excluded women. This table shows that excluded women were significantly older ($p < 0.001$), slightly heavier with a greater BMI ($p < 0.05$) and suffered greater knee pain ($p < 0.05$) than the women attending all five time points indicating that the included cohort were a younger and possibly healthier group of women.

Table 52: Baseline clinical characteristics for complete attendees at Y1, Y5, Y10, Y15 and Y20

Where BMI=body mass index; IQR=inter-quartile range; K&L=Kellgren & Lawrence grade; RKOA=radiographic knee osteoarthritis; SRKOA=symptomatic radiographic knee osteoarthritis; SD=standard deviation.

Y1 characteristic	Full cohort (n=1003 women)	Excluded cohort (n=695 women)	Included cohort (n=308 women)	P value ^a
Age, median (IQR) years	54 (49,60)	55 (50,60)	51 (47,56)	<0.001
BMI, mean (SD) kg/m ²	25.6 (4.3)	25.8 (4.5)	25.1 (3.8)	<0.05
Knee pain* ≥ 1 month, %	25.1 (n=880)	27.6 (n=572)	20.5	<0.05
RKOA ≥ 2 K&L grade, %	14.7 (n=970)	16.0 (n=662)	12.0	0.14
SRKOA*, %	6.8 (n=855)	8.0 (n=547)	4.5	0.13

^a P values comparing included to excluded cohort using Kruskal Wallis test for age, two sample t-test for BMI; Chi-square test for knee pain, RKOA & SRKOA. * Person-level knee pain available only.

Natural history of BMI with SRKOA

During 19 years there was a small reduction first (this may be a result of over-reporting from the person-level knee pain being available at Y1) then from Y10 onwards, there was a slow increase in percentage of women reporting SRKOA (unilateral or bilateral) from:

- 4% (14/308) at Y1,
- to 3% (10/308) at Y5,
- to 7% (21/308) at Y10,
- to 13% (41/308) at Y15,
- to 23% (70/308) at Y20.

Table 53: Mean BMI (\pm SD) for SRKOA by clinic visit

Where BMI=body mass index; SRKOA=symptomatic radiographic knee osteoarthritis; SD=standard deviation.

Clinic visit (n=308)	No SRKOA	Unilateral SRKOA	Bilateral SRKOA	P value
Y1 *	25.0 (3.7) (n=294)	28.2 (5.7) (n=7)	26.5 (3.6) (n=7)	0.06
Y5	26.0 (4.1) (n=298)	27.8 (4.7) (n=6)	30.5 (2.6) (n=4)	0.06
Y10	26.3 (4.3) (n=287)	31.5 (3.8) (n=10)	27.9 (3.6) (n=11)	<0.001
Y15	26.7 (4.4) (n=267)	30.1 (5.3) (n=31)	30.6 (3.9) (n=10)	<0.001
Y20	27.1 (4.4) (n=238)	29.9 (5.4) (n=43)	31.2 (6.3) (n=27)	<0.001

*Person-level knee pain available only but unilateral / bilateral RKOA present.

Table 53 shows that women with unilateral or bilateral SRKOA had a higher mean BMI than those without SRKOA which was statistically significant at Y10, Y15 and Y20. At some visits (Y5, Y15 and Y20), women with bilateral SRKOA had a greater BMI than those with unilateral SRKOA indicating a possible dose-response association (though the differences between unilateral and bilateral were not statistically significant). However the reverse was shown at Y1 and Y10 which could be due to fluctuating KOA pain patterns.

Natural history of BMI with RKO

Increasing percentages of women reported RKO (unilateral or bilateral) over the 19 year study period from:

- 12% (37/308) at Y1,
- to 22% (68/308) at Y5,
- to 34% (104/308) at Y10,
- to 44% (135/308) at Y15,
- to 85% (263/308) at Y20.

The large increase to 85% at Y20 was possibly a result of over-reporting due to the collection of digital knee radiograph images at Y20 which allowed the zoom in/out features of the KneeMorf software that may have made identification of K&L grading criteria easier.

Table 54 shows that women with unilateral or bilateral RKO have statistically significantly greater mean BMIs than those without RKO. As time progresses the women with the greatest mean BMI have bilateral RKO, indicating a possible dose-response association (though the only statistically significant difference between unilateral and bilateral was at Y20 $p=0.006$).

Table 54: Mean BMI (\pm SD) for RKO by clinic visit

Where BMI=body mass index; RKO=radiographic knee osteoarthritis; SD=standard deviation.

Clinic visit (n=308)	No RKO	Unilateral RKO	Bilateral RKO	P value
Y1	24.9 (3.6) (n=271)	27.4 (4.6) (n=26)	27.0 (3.4) (n=11)	0.001
Y5	25.6 (3.8) (n=240)	27.2 (4.5) (n=37)	29.1 (4.9) (n=31)	<0.001
Y10	25.6 (3.8) (n=204)	27.6 (3.9) (n=54)	29.0 (5.4) (n=50)	<0.001
Y15	26.3 (4.3) (n=173)	27.2 (4.1) (n=54)	28.8 (5.3) (n=81)	<0.001
Y20	25.4 (3.7) (n=45)	26.6 (4.7) (n=62)	28.8 (5.0) (n=201)	<0.001

Natural history of BMI with knee pain

During 19 years there was a steady increase in the percentage of women reporting knee pain (unilateral or bilateral) from Y5 onwards (only person-level knee pain was available at Y1, therefore over-reporting was likely):

- 20% (63/308) at Y1,
- to 7% (20/308) at Y5,
- to 13% (40/308) at Y10,
- to 21% (65/308) at Y15,
- to 25% (78/308) at Y20.

Table 55: Mean BMI (\pm SD) for knee pain by clinic visit

Where BMI=body mass index; N/A=not available; SD=standard deviation.

Clinic visit (n=308)	No knee pain	Unilateral knee pain	Bilateral knee pain	P value
Y1*	24.9 (3.7) (n=245)	N/A *	25.9 (4.1) (n=63)	0.06
Y5	26.0 (4.1) (n=288)	27.5 (5.3) (n=11)	27.3 (3.5) (n=9)	0.35
Y10	26.3 (4.3) (n=268)	27.6 (5.0) (n=14)	27.8 (3.8) (n=26)	0.17
Y15	26.7 (4.4) (n=243)	28.6 (5.5) (n=40)	29.0 (4.5) (n=25)	<0.01
Y20	27.1 (4.5) (n=230)	29.5 (5.6) (n=46)	30.4 (6.2) (n=32)	<0.001

*Person-level knee pain available only.

Table 55 shows a general trend that women with unilateral or bilateral knee pain had a greater mean BMI than those without knee pain which was statistically significant at Y15 and Y20. Over time there was little difference in BMI between women with unilateral and bilateral knee pain.

For the 308 women attending each clinic visit over this 19 year period, the stacked bar graphs in Figure 56 display the natural history of: BMI by WHO category (Figure 56a), BMI by SRKOA (Figure 56b), BMI by RKOA (Figure 56c) and BMI by knee pain (Figure 56d).

Figure 56a shows a similar BMI pattern as described earlier for Figure 55 with a rapid decrease in normal BMI by approximately 15% by Y5 and then gradually decreasing over the remaining 5 yearly time points. There was then a rapid increase in overweight BMI by approximately 10% by Y5 which levels off, whilst a steady increase from 12% at Y1 to 30% by Y20 was seen in the obese BMI category.

Figure 56b displays WHO BMI categories stratified by SRKOA and shows a greater proportion of overweight and obese women suffer with unilateral and/or bilateral SRKOA. As time progresses the proportion of obese women with SRKOA increases from Y1 to Y20 more uniformly for bilateral than unilateral symptoms. The unusual representation at Y5 was due to only 2 overweight and 2 obese women with bilateral SRKOA.

Figure 56c displays WHO BMI categories stratified by RKOAs and shows a uniform reduction in normal BMI across the time points up to Y15 for none, unilateral and bilateral RKOAs. The percentage of overweight women remains fairly consistent over the years, but the number of obese women seems to increase initially by Y5 and then level off from Y10 onwards with the largest percentages in the bilateral RKOAs categories.

Figure 56d displays WHO BMI categories stratified by knee pain and shows a gradual reduction in normal BMI across none, unilateral and bilateral knee pain over the years. There were similar percentages of overweight women reporting none, unilateral and bilateral knee pain at Y5 and Y10. These then decrease for Y15 and Y20, with subsequent increases in obese women for unilateral and bilateral knee pain with the largest percentages in the bilateral categories.

Figure 57 bar graphs are a repeat of Figure 56 bar graphs but with all available women attending at each time point to check for any differences between the 308 complete attendees and those women not included. Graphs 56a, 56b 56c and 56d show very similar patterns to those reported for their counterpart 55a, 55b, 55c and 55d graphs so no obvious bias was identified.

Figure 56: Natural history of BMI and associations with SRKOA, RKOA & knee pain in 308 complete attendees

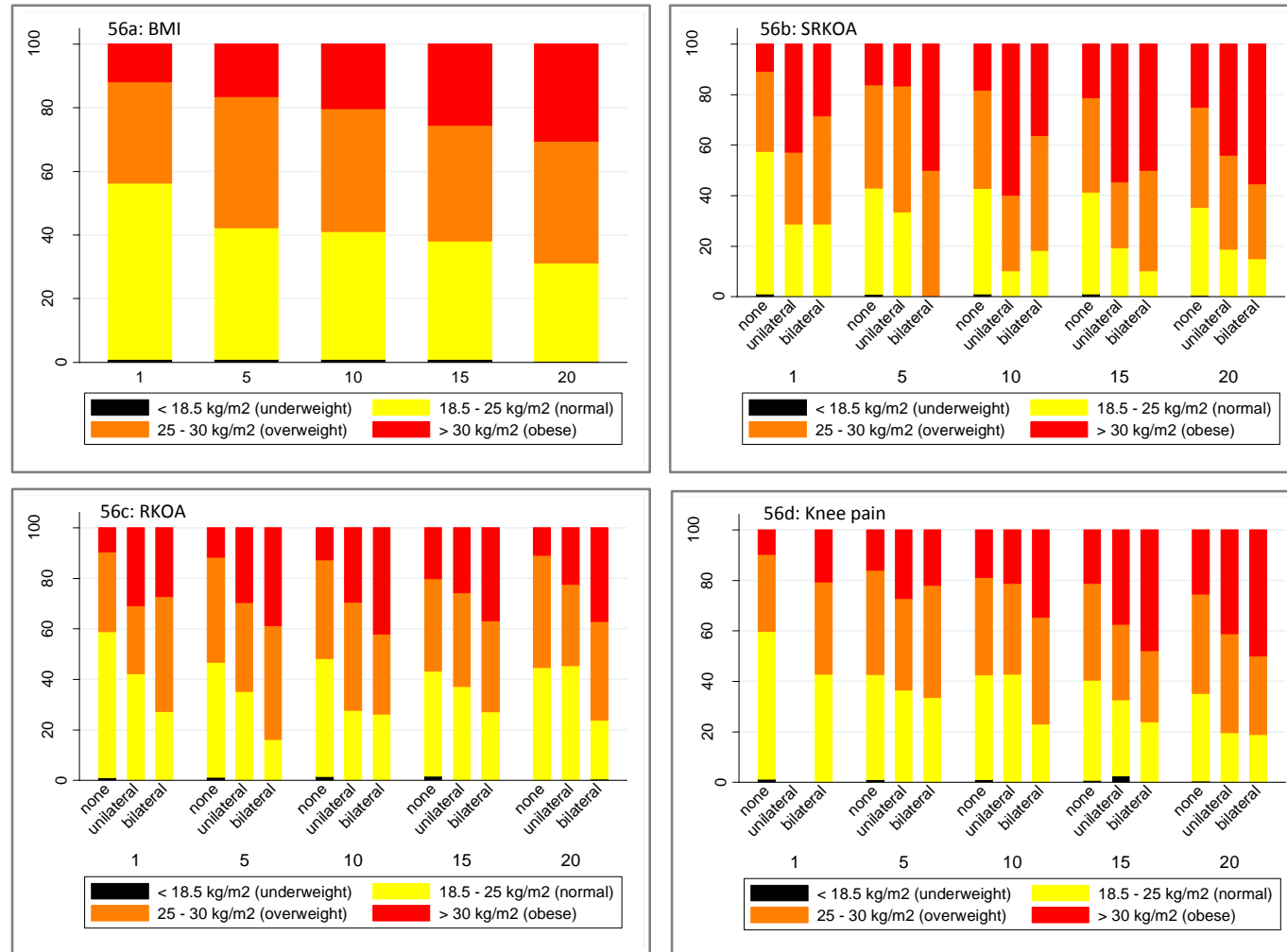
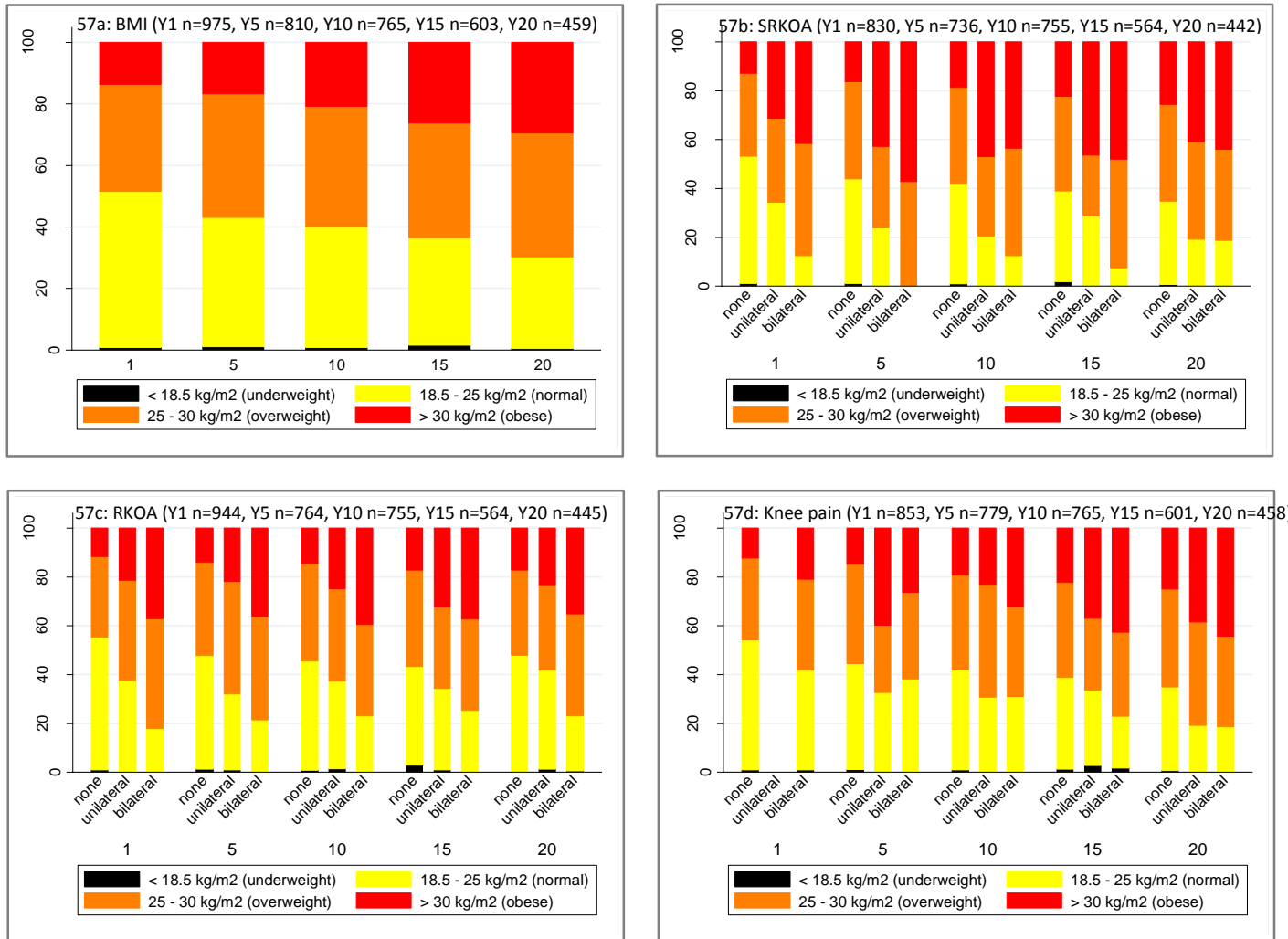


Figure 57: Natural history of BMI and associations with SRKOA, RKOA & knee pain in all attendees



7.5.2.1 Aim 2 results summary

- Women with unilateral or bilateral SRKOA have a higher and increasing BMI than those without SRKOA over 19 years. On occasions women with bilateral SRKOA have a greater BMI than those with unilateral SRKOA, although over time this pattern was inconsistent, possibly reflecting the fluctuating KOA pain pattern.
- Women with unilateral or bilateral RKOAs have a greater mean BMI than those without RKOAs, and as time progresses the women with the greatest mean BMI have bilateral RKOAs.
- Women with unilateral or bilateral knee pain have a greater and increasing mean BMI than those without knee pain over 19 years. Those with unilateral and bilateral knee pain have similar BMIs.
- Overall the increase in BMI over 19 years is associated with increasing rates of all 3 outcomes, with RKOAs being the strongest, then SRKOAs and then knee pain.
- There were no apparent differences in patterns of associations for all three outcomes shown between complete attendees and non-complete attendees.

7.5.3 Aim 3: Natural history of WC and its association with SRKOA, RKO, knee pain and BMI

A total of 457 women were included in the WC natural history analysis (aim 3) as shown in Figure 53. Table 56 shows the baseline Y1 characteristics of these 457 women who attended both the Y1 and Y20 clinic visits with WC & BMI measurements, against the remaining 546 women who were not included in this analysis. This table shows, similarly to Table 50 and Table 52 previously, that excluded women were significantly older ($p < 0.001$), slightly heavier with a greater BMI ($p < 0.01$) and larger WC ($p < 0.001$) than the women attending both Y1 and Y20 clinic visits indicating again that the included cohort were a slightly younger and slimmer group of women.

Table 56: Baseline clinical characteristics for Y1 and Y20 WC analysis

Where BMI=body mass index; IQR=inter-quartile range; K&L=Kellgren & Lawrence grade; RKO=radiographic knee osteoarthritis; SRKO=symptomatic radiographic knee osteoarthritis; SD=standard deviation; WC=waist circumference.

Y1 characteristic	Full cohort (n=1003 women)	Excluded cohort (n=546 women)	Included cohort (n=457 women)	P value ^a
Age, median (IQR) years	54 (49,60)	57 (50,61)	52 (48,56)	<0.001
BMI, mean (SD) kg/m ²	25.6 (4.3)	26.0 (4.6)	25.2 (3.9)	<0.01
WC, mean (SD)	77.9 (10.0) (n=992)	79.2 (10.4) (n=535)	76.5 (9.3)	<0.001
Knee pain* ≥ 1 month, %	25.1 (n=880)	27.7 (n=481)	22.1 (n=399)	0.06
RKO ≥ 2 K&L grade, %	14.7 (n=970)	15.5 (n=524)	13.9 (n=446)	0.56
SRKO, %	6.8 (n=855)	7.3 (n=467)	6.2 (n=388)	0.77

^a P values comparing included to excluded cohort using Kruskal Wallis test for age; two sample t-test for BMI & WC; Chi-square test for knee pain, RKO & SRKO.* Person-level knee pain available only.

The 457 women included in the WC natural history analysis demonstrated that the mean WC (\pm SD) over 19 years increased on average by 10cm from:

- 76.5cm (\pm 9.3) at Y1
- to 86.6cm (\pm 11.6) at Y20.

Figure 53 shows that out of these 457 women there were 372 women who had WC, BMI, SRKO, RKO and knee pain data at both Y1 and Y20 clinic visits.

Table 57, 58 and 59 show the changes in WC for these 372 women by SRKO, RKO and knee pain outcomes respectively at Y1 and Y20 visits.

Table 57: Mean WC (\pm SD) for SRKOA by clinic visit

Where N/A=not available; RKO=radiographic knee osteoarthritis; SRKOA=symptomatic radiographic knee osteoarthritis; SD=standard deviation; WC=waist circumference.

Clinic visit (n=372)	No SRKOA	Unilateral SRKOA	Bilateral SRKOA	P value
Y1 *	76.1 (9.2) (n=349)	81.8 (13.6) (n=13)	81.7 (5.5) (n=10)	<0.05
Y20	85.4 (11.0) (n=282)	91.4 (12.2) (n=55)	91.2 (11.2) (n=35)	<0.001

*Person-level knee pain available only but unilateral / bilateral RKO present.

Table 58: Mean WC (\pm SD) for RKO by clinic visit

Clinic visit (n=372)	No RKO	Unilateral RKO	Bilateral RKO	P value
Y1	75.7 (9.1) (n=320)	81.2 (11.5) (n=37)	81.1 (5.9) (n=15)	<0.001
Y20	81.7 (9.9) (n=50)	84.4 (11.2) (n=73)	88.5 (11.4) (n=249)	<0.001

Table 59: Mean WC (\pm SD) for knee pain by clinic visit

Clinic visit (n=372)	No knee pain	Unilateral knee pain	Bilateral knee pain	P value
Y1*	76.0 (9.1) (n=291)	N/A *	78.4 (10.4) (n=81)	<0.05
Y20	85.5 (11.0) (n=274)	90.7 (12.4) (n=57)	90.1 (11.2) (n=41)	0.001

*Person-level knee pain available only.

Table 57, 58 and 59 all show that higher WCs were statistically significantly associated with all three SRKOA, RKO and knee pain outcomes. There were little differences between WC for unilateral and bilateral for SRKOA and knee pain, however at Y20 a 4cm difference ($p=0.02$) was significant which could be a true difference or possibly related to over-reporting of Y20 RKO as discussed previously.

Figure 58a, b and c scatter plots show the association between WC and BMI for the 457 included cohort women for Y1, Y20 and change between Y1 and Y20 respectively. The Pearson correlation coefficients and r^2 values are shown in Table 60 for the included cohort and Table 61 for the full attendees.

Figure 58: WC and its association with BMI in the included cohort

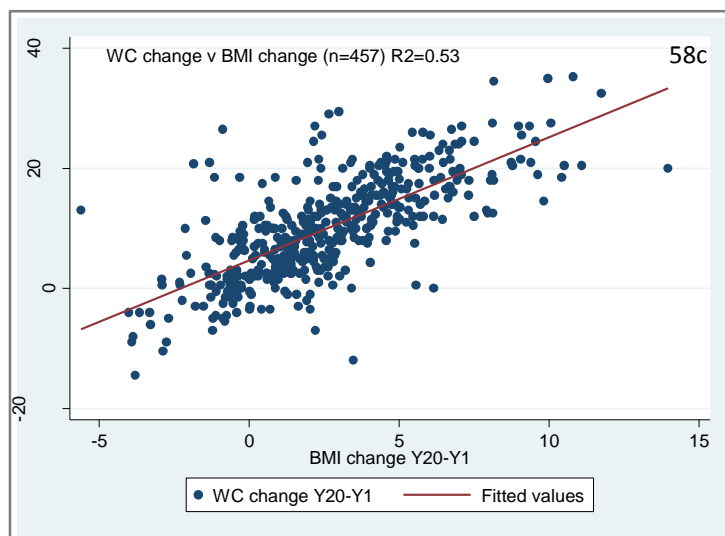
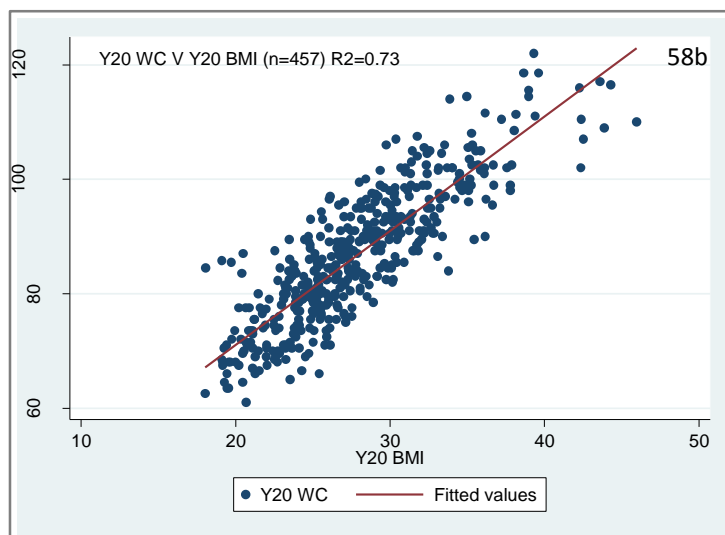
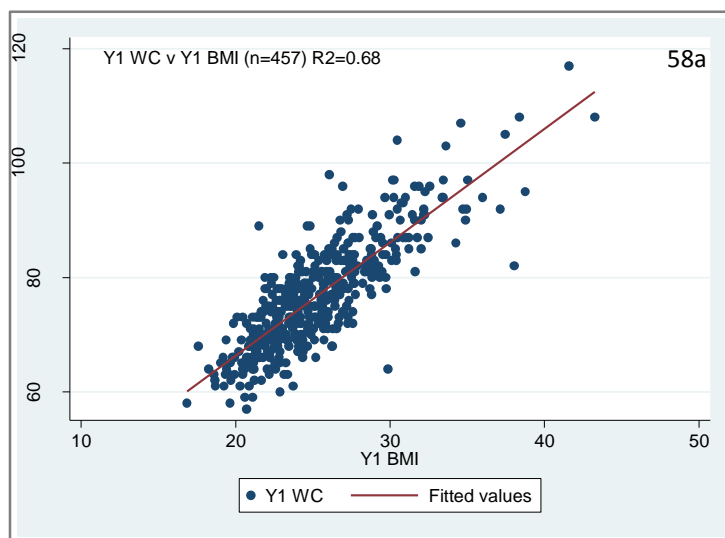


Table 60: WC and BMI correlation coefficients for complete attendees

Where BMI = body mass index; WC = waist circumference.

n=457	Y1 WC	Y20 WC	WC change	Y1 BMI	Y20 BMI	BMI change
Y1 WC	1			0.82 r^2 0.68		
Y20 WC		1			0.86 r^2 0.73	
WC change			1			0.72 r^2 0.53

All results significant at $p < 0.001$

Table 61: WC and BMI correlation coefficients for all attendees

Full attendees	Y1 WC	Y20 WC	WC change	Y1 BMI	Y20 BMI	BMI change
Y1 WC	1			0.83 r^2 0.69 n=992		
Y20 WC		1			0.85 r^2 0.73 n=516	
WC change			1			0.72 r^2 0.52 n=513

All results significant at $p < 0.001$

The Pearson correlation coefficients and r^2 values are very similar for the 457 women in the included cohort in Table 60 compared to the full attendees in Table 61. Overall the Figure 58 scatter graphs and Table 60 and Table 61 show that WC and BMI were positively strongly correlated with 0.82 at Y1 and 0.86 at Y20, indicating that as WC increases so does BMI. WC and BMI change was slightly less positively correlated at 0.72, however all correlation coefficients were statistically significant ($p < 0.001$). The r^2 values were also high and statistically significant ($p < 0.001$) with 68% of the variability explained by the model for Y1, 73% explained by the model for Y20 and 53% of the variability explained in WC and BMI change.

7.5.3.1 Aim 3 results summary

- WC increased on average by 10cm over the 19 year period.
- Higher WCs were significantly associated with all three SRKOA, RKO and knee pain outcomes.
- WC and BMI were significantly positively strongly correlated, indicating that women with a greater WC have a greater BMI.

7.5.4 Aim 4: Cross-sectional associations between BMI and WC with SRKOA, RKO and knee pain at Y1

A total of 823 women were included in the Y1 cross-sectional analysis examining associations between BMI and WC with SRKOA, RKO and knee pain (Figure 53). Table 62 shows the baseline characteristics of the 823 included women with BMI, WC, SRKOA, RKO and knee pain variables recorded at Y1, against the remaining 180 women who were not included in this analysis. This table shows that excluded women were significantly older ($p < 0.001$) with more RKO ($p < 0.05$) than the included cohort.

Table 62: Baseline clinical characteristics for Y1 attendees

Where BMI=body mass index; IQR=inter-quartile range; K&L=Kellgren & Lawrence grade; RKO=radiographic knee osteoarthritis; SRKOA=symptomatic radiographic knee osteoarthritis; SD=standard deviation; WC=waist circumference.

Y1 characteristic	Full cohort (n=1003 women)	Excluded cohort (n=180 women)	Included cohort (n=823 women)	P value ^a
Age, median (IQR) years	54 (49,60)	56 (51.5,60)	53 (48,59)	<0.001
BMI, mean (SD) kg/m ²	25.6 (4.3)	25.3 (3.9)	25.7 (4.4)	0.31
WC, mean (SD)	77.9 (10.0) (n=992)	78.4 (9.2) (n=169)	77.9 (10.2)	0.50
Knee pain* ≥ 1 month, %	25.1 (n=880)	31.6 (n=57)	24.7	0.24
RKO ≥ 2 K&L grade, %	14.7 (n=970)	20.4 (n=147)	13.7	0.05
SRKOA*, %	6.8 (n=855)	6.3 (n=32)	6.8	0.97

^a P values comparing included to excluded cohort using Kruskal Wallis test for age, two sample t-test for BMI & WC; Chi-square test for knee pain, RKO & SRKOA.* Person-level knee pain available only.

Table 63 shows separate logistic regression analyses for BMI and WC at the subject-level for Y1 cross-sectional associations with SRKOA, RKO and knee pain. The ORs and their 95% CIs for the crude and the adjusted models (adjusted for Y1 age and knee injury) were presented and the pseudo R^2 was included to allow direct comparisons.

For the main outcome, SRKOA, in the crude model Y1 BMI was significantly associated with all SRKOA outcomes (unilateral, bilateral and any). On adjustment for Y1 age and knee injury, the association for unilateral SRKOA was attenuated, but the association with bilateral SRKOA remained the strongest (OR 1.15, 95% CI 1.07, 1.24). Therefore for every unit of BMI, there was a 15% compound increase in the odds of reporting bilateral SRKOA at Y1 compared to those women without SRKOA. The pseudo R^2 shows very similar but slightly weaker associations for Y1 WC in the crude and adjusted SRKOA models as the adjusted bilateral SRKOA for WC was 0.08 compared to 0.10 for BMI. The differences in pseudo R^2 between BMI and WC were small within each of the three outcomes in Table 63, which indicate that BMI and WC were showing very similar associations.

Similar associations to those described above for SRKOA were also seen in the RKOA crude and adjusted models for BMI and WC. The greatest pseudo R^2 values were for bilateral RKOA with 0.16 for BMI and 0.12 for the WC equivalent.

Associations for knee pain were limited to bilateral knees as only person-level pain was reported at Y1. The ORs show the weakest significant associations for bilateral knee pain across all three of the outcomes and the pseudo R^2 shows no difference between BMI and WC at 0.01 and 0.05 for crude and adjusted knee pain respectively.

The graphs in Figure 59 display the ORs and 95% CI for unilateral / bilateral / any SRKOA outcome with BMI crude, WC crude, BMI & WC crude (mutually adjusted for each other) and BMI & WC fully adjusted (mutually adjusted for each other and adjusted for Y1 age and knee injury) models. It is clear from these graphs that WC as a measurement on its own is similar in its association with the SRKOA outcome as BMI is on its own, therefore if measuring BMI in clinic was difficult then WC could be used as an alternative measurement. However when BMI and WC were combined in the same model, little extra information on the association with SRKOA was provided as the pseudo R^2 values remained similar for the singular and combined models. These graphs also reinforce that associations were stronger for bilateral SRKOA than unilateral SRKOA. In addition, for the bilateral and any SRKOA models the association with Y1 BMI remains significant and consistent (albeit with wider

confidence intervals) compared to the reducing association with Y1 WC which attenuates in the combined crude and adjusted models.

7.5.4.1 Aim 4 results summary

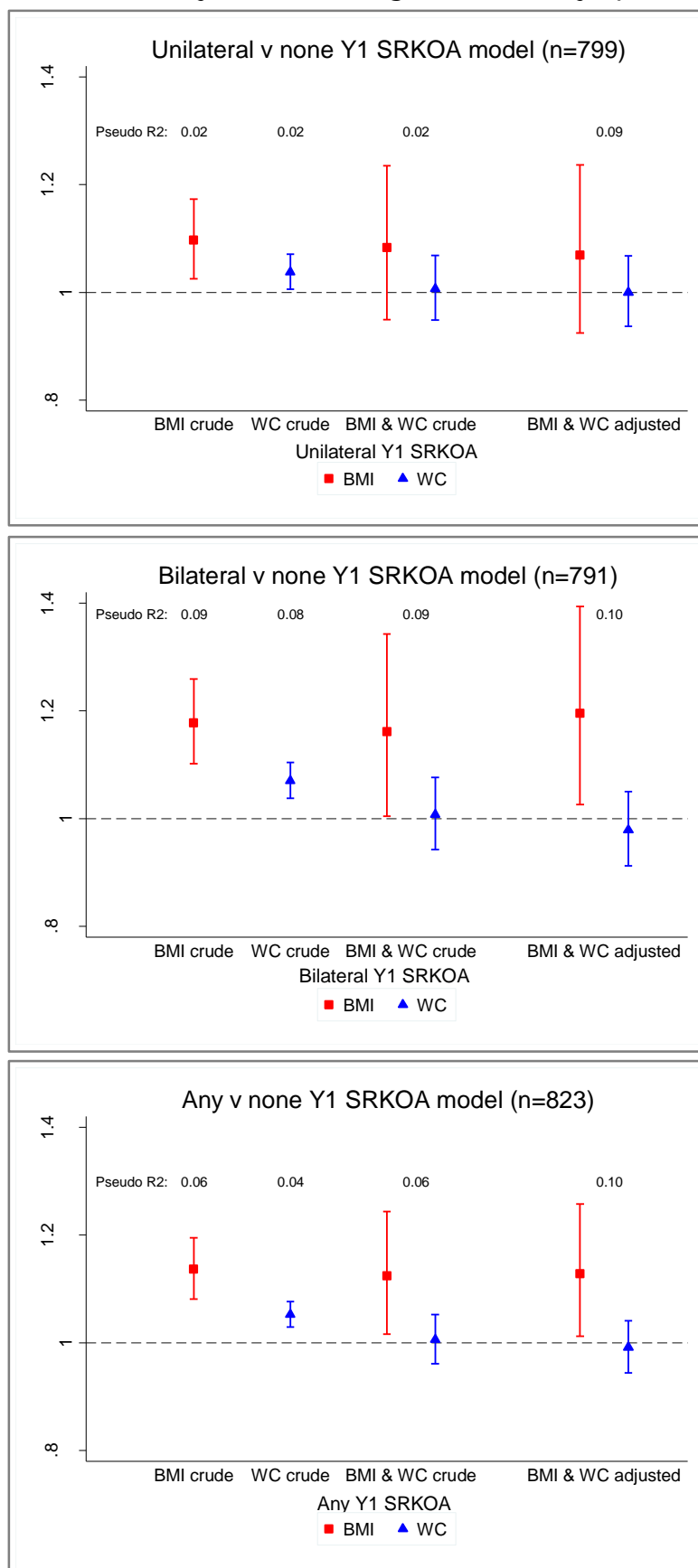
- Similar associations were shown between Y1 BMI and Y1 WC across all three outcomes, with bilateral associations being the strongest.
- No additional information was provided when both BMI and WC were combined, therefore use of one measurement was sufficient.
- BMI would be the suggested measure of choice as unlike WC it maintained significant associations with bilateral and any SRKOA.
- However, WC could be used as an alternative measurement if measuring BMI was difficult.
- Associations were greatest for bilateral over unilateral SRKOA and RKOAs which suggests alternative pathological mechanisms might exist.

Table 63: Cross-sectional associations between BMI and WC with SRKOA, RKOA and knee pain at Y1

Where BMI=body mass index; K&L=Kellgren & Lawrence grade; N/A=not available; RKOA=radiographic knee osteoarthritis; SRKOA=symptomatic radiographic knee osteoarthritis; WC=waist circumference; * Person-level knee pain available only; ^a adjusted for Y1 age and knee injury.

Y1 outcome (n=823) Y1 exposure		Y1 knee pain *			Y1 RKOA			Y1 SRKOA *		
		+ (n=203)	- (n=620)	Pseudo R ²	+ (n=113)	- (n=710)	Pseudo R ²	+ (n=56)	- (n=767)	Pseudo R ²
		OR (95% CI) (n)	P value		OR (95% CI) (n)	P value		OR (95% CI) (n)	P value	
Y1 BMI	Unilateral v none				n=73	n=710		n=32	n=767	
	Crude	N/A	N/A	N/A	1.10 (1.04,1.15) (n=783)	<0.001	0.03	1.10 (1.03,1.17) (n=799)	0.007	0.02
	Adjusted ^a	N/A	N/A	N/A	1.09 (1.03,1.15) (n=770)	0.001	0.08	1.07 (0.99,1.15) (n=785)	0.07	0.09
	Bilateral v none	n=203	n=620		n=40	n=710		n=24	n=767	
	Crude	1.05 (1.02,1.09) (n=823)	0.004	0.01	1.18 (1.12,1.25) (n=750)	<0.001	0.10	1.18 (1.10,1.26) (n=791)	<0.001	0.09
	Adjusted ^a	1.04 (1.00,1.07) (n=807)	0.03	0.05	1.17 (1.10,1.24) (n=735)	<0.001	0.16	1.15 (1.07,1.24) (n=776)	<0.001	0.10
Y1 WC	Any v none				n=113	n=710		n=56	n=767	
	Crude	N/A	N/A	N/A	1.14 (1.09,1.18) (n=823)	<0.001	0.06	1.14 (1.08,1.19) (n=823)	<0.001	0.06
	Adjusted ^a	N/A	N/A	N/A	1.12 (1.08,1.17) (n=807)	<0.001	0.12	1.11 (1.05,1.17) (n=807)	<0.001	0.10
	Unilateral v none				n=73	n=710		n=32	n=767	
	Crude	N/A	N/A	N/A	1.03 (1.02,1.06) (n=783)	0.001	0.02	1.04 (1.01,1.07) (n=799)	0.02	0.02
	Adjusted ^a	N/A	N/A	N/A	1.03 (1.01,1.06) (n=770)	0.01	0.07	1.03 (0.99,1.06) (n=785)	0.13	0.09
Y1 WC	Bilateral v none	n=203	n=620		n=40	n=710		n=24	n=767	
	Crude	1.02 (1.00,1.04) (n=823)	0.009	0.01	1.07 (1.04, 1.10) (n=750)	<0.001	0.07	1.07 (1.04,1.10) (n=791)	<0.001	0.08
	Adjusted ^a	1.01 (0.99,1.03) (n=807)	0.07	0.05	1.05 (1.02, 1.08) (n=735)	0.001	0.12	1.05 (1.02,1.09) (n=776)	0.005	0.08
	Any v none				n=113	n=710		n=56	n=767	
	Crude	N/A	N/A	N/A	1.05 (1.03, 1.07) (n=823)	<0.001	0.04	1.05 (1.03,1.08) (n=823)	<0.001	0.04
	Adjusted ^a	N/A	N/A	N/A	1.04 (1.02, 1.06) (n=807)	<0.001	0.10	1.04 (1.01,1.07) (n=807)	0.003	0.09

Figure 59: Y1 cross-sectional associations between BMI and WC for SRKOA
(BMI & WC adjusted for Y1 age and knee injury)



7.5.5 Aim 5: Longitudinal associations between Y1 BMI and WC with Y10 knee pain, RKOA and SRKOA

For the longitudinal analysis there were a total of 646 women included as shown in Figure 54. Table 64 shows the baseline characteristics of the 646 women who had BMI and WC at Y1 in addition to SRKOA, RKOA and knee pain variables at Y1 and Y10, against the remaining 357 women excluded from this analysis. The excluded women were significantly older ($p < 0.001$), with larger WCs ($p < 0.01$) and greater level of knee pain ($p < 0.01$) and RKOA ($p < 0.01$), indicating that the included women may be a younger, slimmer and less symptomatic group.

Table 64: Baseline clinical characteristics for Y10 longitudinal analysis

Where BMI=body mass index; IQR=inter-quartile range; K&L=Kellgren & Lawrence grade; RKOA=radiographic knee osteoarthritis; SRKOA=symptomatic radiographic knee osteoarthritis; SD=standard deviation; WC=waist circumference.

Y1 characteristic	Full cohort (n=1003 women)	Excluded cohort (n=357 women)	Included cohort (n=646 women)	P value ^a
Age, median (IQR) years	54 (49,60)	57 (50,61)	53 (48,58)	<0.001
BMI, mean (SD) kg/m ²	25.6 (4.3)	25.9 (4.7)	25.4 (4.1)	0.08
WC, mean (SD)	77.9 (10.0) (n=992)	79.2 (10.6) (n=346)	77.3 (9.6)	<0.01
Knee pain* ≥ 1 month, %	25.1 (n=880)	31.2 (n=234)	22.9	0.01
RKOA ≥ 2 K&L grade, %	14.7 (n=970)	18.5 (n=324)	12.8	<0.01
SRKOA*, %	6.8 (n=855)	10.0 (n=209)	5.7	0.08

^a P values comparing included to excluded cohort using Kruskal Wallis test for age, two sample t-test for BMI & WC; Chi-square test for knee pain, RKOA & SRKOA. * Person-level knee pain available only.

The incident cases of the three outcomes were established by removing the Y1 positive cases (n=37 for SRKOA, n=83 for RKOA and n=148 women for knee pain) from the 646 included women then identifying women that by Y10 had developed incident cases for SRKOA (34 women out of 609 = 6%), RKOA (154 women out of 563 = 27%) and knee pain (58 women out of 498 = 12%) as shown in Figure 54.

Table 65 shows separate logistic regression analyses for BMI and WC at the subject-level for longitudinal associations with Y10 SRKOA, RKOA and knee pain incidence. The ORs and their 95% CIs for the crude and adjusted models (adjusted for Y1 age and knee injury) were presented and the pseudo R^2 was included to allow direct comparisons.

For the main outcome SRKOA, in the crude and adjusted models Y1 BMI was significantly associated with very similar sized ORs across unilateral, bilateral and any SRKOA. The same was seen for Y1 WC although the association with bilateral SRKOA was slightly attenuated. The differences in pseudo R^2 between the crude and adjusted SRKOA models for Y1 BMI and WC were extremely small demonstrating that Y1 BMI and Y1 WC were very similar predictors of unilateral, bilateral or any SRKOA.

For RKOAs, in the crude and adjusted models Y1 BMI was significantly associated with bilateral and any RKOAs. The strongest association was with bilateral RKOAs (OR 1.20, 95% CI 1.12, 1.28) showing that for every unit of BMI, there was a 20% compound increase in the odds of reporting bilateral RKOAs at Y10 compared to those women without RKOAs. Y1 BMI was not significantly associated with Y10 unilateral RKOAs. Similar but less strong associations were seen for Y1 WC across unilateral, bilateral and any RKOAs. The pseudo R^2 was greatest in the adjusted bilateral RKOAs at 0.13 for BMI and 0.11 for WC, the remaining pseudo R^2 values were very similar between BMI and WC showing that Y1 BMI and Y1 WC were similar predictors of unilateral, bilateral or any RKOAs.

Associations were weakest for knee pain. Y1 BMI was a weak predictor of Y10 bilateral knee pain (OR 1.07, 95% CI 1.00, 1.15) but not a predictor of unilateral or any knee pain. Y1 WC was a weak predictor of Y10 bilateral knee pain (OR 1.04, 95% CI 1.00, 1.07) but also of any knee pain (OR 1.03, 95% CI 1.00, 1.06). The pseudo R^2 values for Y1 BMI and Y1 WC were again very similar and small (<0.02) in comparison to the pseudo R^2 values seen in the RKOAs and SRKOAs models.

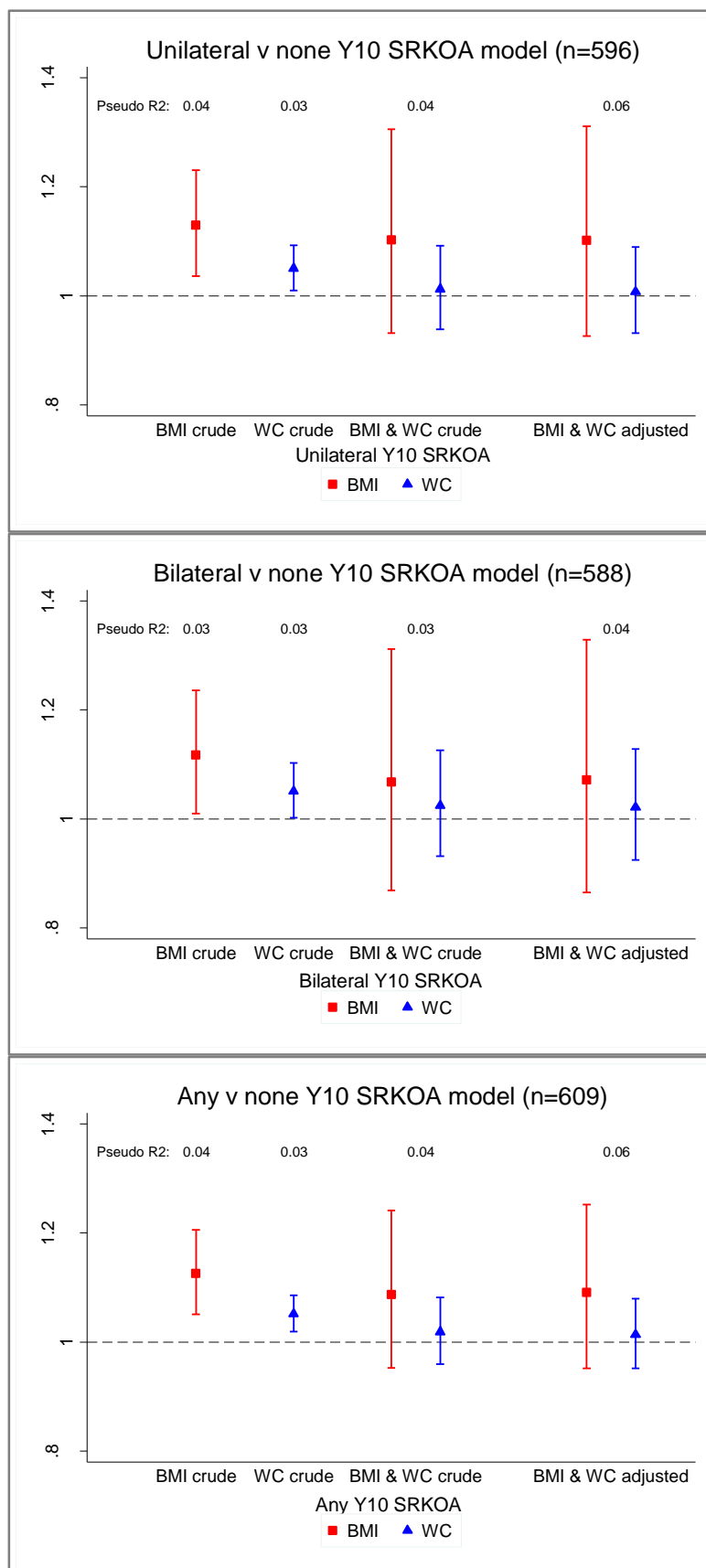
Table 65: Longitudinal associations between Y1 BMI and WC with Y10 SRKOA, RKOA and knee pain incidence

Where BMI=body mass index; RKOA=radiographic knee osteoarthritis; SRKOA=symptomatic radiographic knee osteoarthritis; WC=waist circumference; ^a adjusted for Y1 age and knee injury.

Y10 outcome Y1 exposure (n=646)		Y10 knee pain incidence (n=498)			Y10 RKOA incidence (n=563)			Y10 SRKOA incidence (n=609)		
		+	-	Pseudo R ²	+	-	Pseudo R ²	+	-	Pseudo R ²
		(n=58)	(n=440)		(n=154)	(n=409)		(n=34)	(n=575)	
		OR (95% CI) (n)	P value		OR (95% CI) (n)	P value		OR (95% CI) (n)	P value	
Y1 BMI	Unilateral v none	n=20	n=440		n=96	n=409		n=21	n=575	
	Crude	1.00 (0.90,1.12) (n=460)	0.93	0.00	1.05 (0.98,1.11) (n=505)	0.15	0.00	1.13 (1.04,1.23) (n=596)	0.006	0.04
	Adjusted ^a	1.01 (0.90,1.13) (n=452)	0.84	0.00	1.04 (0.97,1.10) (n=499)	0.26	0.03	1.12 (1.02,1.22) (n=587)	0.01	0.06
	Bilateral v none	n=38	n=440		n=58	n=409		n=13	n=575	
	Crude	1.07 (1.00,1.15) (n=478)	0.05	0.01	1.21 (1.14,1.30) (n=467)	<0.001	0.11	1.12 (1.01,1.24) (n=588)	0.03	0.03
	Adjusted ^a	1.07 (1.00,1.15) (n=469)	0.05	0.01	1.20 (1.12,1.28) (n=459)	<0.001	0.13	1.11 (1.00,1.24) (n=578)	0.05	0.04
	Any v none	n=58	n=440		n=154	n=409		n=34	n=575	
	Crude	1.05 (0.99,1.12) (n=498)	0.10	0.01	1.12 (1.07,1.17) (n=563)	<0.001	0.03	1.13 (1.05,1.21) (n=609)	0.001	0.04
	Adjusted ^a	1.05 (0.99,1.12) (n=489)	0.10	0.01	1.11 (1.05,1.16) (n=554)	<0.001	0.06	1.12 (1.04,1.20) (n=599)	0.002	0.06
Y1 WC	Unilateral v none	n=20	n=440		n=96	n=409		n=21	n=575	
	Crude	1.01 (0.96,1.05) (n=460)	0.79	0.00	1.02 (0.99,1.04) (n=505)	0.17	0.00	1.05 (1.01,1.09) (n=596)	0.01	0.03
	Adjusted ^a	1.01 (0.96,1.06) (n=452)	0.72	0.00	1.01 (0.98,1.04) (n=499)	0.47	0.02	1.05 (1.00,1.09) (n=587)	0.03	0.06
	Bilateral v none	n=38	n=440		n=58	n=409		n=13	n=575	
	Crude	1.03 (1.00,1.07) (n=478)	0.03	0.02	1.08 (1.05,1.11) (n=467)	<0.001	0.09	1.05 (1.00,1.10) (n=588)	0.04	0.03
	Adjusted ^a	1.04 (1.00,1.07) (n=469)	0.03	0.02	1.07 (1.04,1.10) (n=459)	<0.001	0.11	1.05 (1.00,1.10) (n=578)	0.06	0.04
	Any v none	n=58	n=440		n=154	n=409		n=34	n=575	
	Crude	1.03 (1.00,1.05) (n=498)	0.05	0.01	1.04 (1.02,1.07) (n=563)	<0.001	0.03	1.05 (1.02,1.09) (n=609)	0.002	0.03
	Adjusted ^a	1.03 (1.00,1.06) (n=489)	0.05	0.01	1.04 (1.01,1.06) (n=554)	0.001	0.05	1.05 (1.01,1.08) (n=599)	0.006	0.05

Figure 60: Associations between Y1 BMI & WC for Y10 SRKOA incidence

(BMI & WC adjusted for Y1 age and knee injury)



The graphs in Figure 60 display the ORs and 95% CI for unilateral / bilateral / any Y10 SRKOA incidence with BMI crude, WC crude, BMI & WC crude (mutually adjusted for each other) and BMI & WC fully adjusted (mutually adjusted for each other and adjusted for Y1 age and knee injury) models.

Similar to the graphs in Figure 59, it is clear from the graphs in Figure 60 that WC as a measurement on its own was similar in its predictive value with Y10 SRKOA incidence as BMI was on its own, therefore if measuring BMI in clinic was difficult then measurement of WC could be taken instead to predict later risk of developing SRKOA. However no further value was added to the predictive SRKOA incidence models when BMI and WC were combined as pseudo R^2 values remained similar for singular and combined models. All the significant BMI and WC associations seen in the separate models were attenuated in the combined adjusted models, however associations with BMI remained stronger than WC, across unilateral, bilateral and any SRKOA outcome.

7.5.5.1 Aim 5 results summary

- Similar predictive associations were shown between Y1 BMI and Y1 WC across all three Y10 outcomes.
- No further value was added to the SRKOA predictive model when BMI and WC were combined, therefore use of one measurement was sufficient.
- Again BMI would be the suggested measure of choice as although associations were attenuated with unilateral, bilateral and any SRKOA it remained a stronger predictor than WC.
- However, WC could be used as an alternative measurement to predict Y10 outcome if measuring BMI was difficult.
- Predictive associations for RKOA incidence were strong, weak for SRKOA and very weak for knee pain incidence, suggesting this may be driven by structure.
- Associations were greatest for bilateral over unilateral but only for RKOA which may suggest alternative pathological mechanisms exist for structural KOA compared to SRKOA and knee pain.

7.6 Discussion

The natural history of BMI and WC and their association with three important clinical outcomes: SRKOA, RKOA and knee pain, over a nineteen year period have been described in a well-characterised community based prospective cohort of women based in Chingford, UK. In addition, cross-sectional associations at Y1 and longitudinal associations for Y1 BMI and WC with Y10 incidence of SRKOA, RKOA and knee pain were examined providing a comprehensive overview of the relationship between obesity and a range of KOA outcomes.

Aim 1

The first study aim describing the natural history of BMI over a 19 year period, found that in the 429 participating women the mean BMI increased gradually from a normal BMI of 25.1 kg/m² (± 3.7) to an overweight BMI of 27.7 kg/m² (± 5.0). Within this group, only 27% of women remained in the normal BMI category throughout the 19 years and by Y20 there was a near tripling of obese women to 30%. Previously published data up to Y15 from this cohort (n=594 women) by Goulston and colleagues showed 35% of women remained in the normal BMI category throughout 14 years and by Y15, 26% of women were obese (Goulston et al., 2011), so the growing obese trend continues in this cohort. The increase seen in BMI over time is consistent with the few other long-standing cohorts that have true physical measurements for height and weight collected at numerous time points, the Framingham Study (Felson et al., 1997, Felson et al., 1992) and the NHANES Study (Anderson and Felson, 1988, Davis et al., 1990a).

Aim 2

Overall, the increase in BMI over 19 years was associated with increasing prevalence of all 3 KOA outcomes studied in 308 women participating in aim 2 with prevalence for RKOA being the strongest, followed by SRKOA and then knee pain. Women with unilateral or bilateral RKOA had a greater mean BMI than those without RKOA, and as time progressed the women with the greatest mean BMI had bilateral RKOA. This association was similar for SRKOA, although only on occasions did women with bilateral SRKOA have a greater BMI than those with unilateral SRKOA over the 19 years. The pattern was inconsistent, possibly reflecting the fluctuating pain patterns that can occur

with KOA (Soni et al., 2012) and the likely over-reporting of Y1 knee pain (discussed further in section 7.6.2) may contribute to this fluctuation. Similarly, women with unilateral or bilateral knee pain had greater and increasing mean BMI than those without knee pain over the 19 years. There was little difference in BMI between women with unilateral and bilateral knee pain. There were signs shown of differences existing between bilateral and unilateral RKOAs and possibly SRKOAs outcomes, which could be suggestive of alternative pathological mechanisms, this will be discussed further under aims 4 and 5.

Aim 3

The 457 women participating in aim 3, displayed a mean average increase of 10cm in WC from 76.5cm (SD ± 9.3) at Y1 which was normal, to 86.6cm (SD ± 9.3) at Y20, categorised as central obesity (International Diabetes Federation, 2006, World Health Organization, 2011). Higher WCs were significantly associated with all three SRKOAs, RKOAs and knee pain outcomes at Y1 and Y20. There were little differences between WC for unilateral and bilateral SRKOAs and knee pain, however at Y20 a significant 4cm difference ($p=0.02$) was present which may be a true difference or may be related to the increased prevalence of RKOAs at Y20 (discussed further in section 7.6.2). Previous KOA studies that include WC measurements have only measured WC at one time point (Abbate et al., 2006, Engstrom et al., 2009, Holliday et al., 2011, Han et al., 2013, Lohmander et al., 2009, Monira et al., 2014, Wang et al., 2009, Yoshimura et al., 2011, Janssen and Mark, 2006) and predominantly use RKOAs or TKRs as their outcome. There were no studies for comparison of change in WC across the three outcomes examined here. WC and BMI were found to be significantly positively correlated, indicating that women with a greater WC have a greater BMI, which was also reported by Abbate and colleagues (Abbate et al., 2006).

Aim 4

The Y1 cross-sectional associations completed for the 823 women participating in aim 4 showed very similar significant associations for BMI and for WC with SRKOAs and RKOAs. Knee pain associations were smaller and limited solely to bilateral associations due to only having person-level knee pain present at Y1 (discussed further in section 7.6.2). Pseudo R^2 was provided to allow comparison since the different units of measurement, kg/m^2 for BMI and cm for WC, make direct comparisons based on effect sizes difficult to justify. The

pseudo R^2 in Table 63, showed that BMI and WC associations between SRKOA and RKOAs were very similar and significantly associated, with bilateral associations for the RKOAs adjusted model being the strongest at 0.16. These results agree (although the principal outcomes were not SRKOA) with Han and colleagues who reported that WC was associated with self-reported RKOAs in the Korean NHANES study (Han et al., 2013), and with Holliday and colleagues who showed a greater WC was associated with increased TKR risk, but the WC association was weaker than that with BMI in the Genetics of Osteoarthritis And Lifestyle (GOAL) study (Holliday et al., 2011).

However, when BMI and WC were combined and mutually adjusted, and then fully adjusted (for Y1 age and knee injury) in the Figure 59 graphs, no further additional information was provided in terms of predicting the main SRKOA outcome in the combined models compared to the singular crude models for BMI and WC. This suggests use of one measurement was sufficient for predicting SRKOA outcome. BMI would be the preferred measure as unlike WC, it maintains significant associations with bilateral and any SRKOA on adjustment. Abbate and colleagues who studied a similar relationship in the Johnston County OA project suggested that measures of fat distribution such as WC and WHR offer no advantage over the simple measure of BMI in assessment of RKOAs risk (Abbate et al., 2006), which is in agreement with the results in Figure 59 for SRKOA outcome. However, Janssen and colleagues reported that when BMI and WC were used as continuous variables to predict self-report arthritis and RKOAs in the NHANES study they did not have independent effects on either, but when BMI and WC were categorised into tertiles, independent effects were observed on both outcomes (Janssen and Mark, 2006). Therefore their study recommended that WC was measured in conjunction with BMI. There remains continued debate on the contribution of fat distribution to RKOAs outcome, which is possibly a result of the variation in defining RKOAs. All these WC studies used different RKOAs definitions: self-report (Han et al., 2013), TKR risk (Holliday et al., 2011), K&L ≥ 2 on AP view weight bearing radiographs (Abbate et al., 2006) and K&L ≥ 2 on AP view non-weight bearing radiographs (Janssen and Mark, 2006).

The cross-sectional results presented here were in agreement with those presented previously for RKOAs from the Chingford study by Hart (Hart and Spector, 1993b) confirming that obesity was strongly associated with RKOAs,

particularly for bilateral disease, and suggestive that body fat distributed around the waist is less important. This is true for both SRKOA and RKOAs. These new results show in addition that the singular crude models for BMI and WC displayed similar pseudo R^2 values for SRKOA indicating that it would be acceptable to substitute BMI with WC measurement on the occasions when it might be difficult to measure weight or height in a clinical situation. For example when a patient has mobility problems it might be easier to measure WC.

These results also suggest that alternative pathological mechanisms may exist, as greater associations for bilateral over unilateral were present for SRKOA and RKOAs. This may support the theory that, similar to hand OA, bilateral SRKOA and RKOAs may be linked to an important systemic metabolic component and not only as a result of mechanical loading. This will be discussed further under the aim 5 longitudinal analysis.

Aim 5

For the 646 women participating in the longitudinal analysis the differences in pseudo R^2 between the crude and adjusted models across all three outcomes were very small for the univariate Y1 BMI and WC analyses in Table 65. Y1 BMI and Y1 WC were very similar predictors of unilateral, bilateral or any SRKOA / RKOAs / knee pain incidence at Y10. The strongest predictive association was seen for Y10 bilateral RKOAs incidence (adjusted pseudo $R^2 = 0.13$ for Y1 BMI and 0.11 for Y1 WC); weak associations were seen across unilateral / bilateral / any Y10 SRKOA incidence and very weak associations across all the groups for Y10 knee pain incidence, suggesting that the association for incident RKOAs may be driven by structure.

The results for RKOAs agree with other incidence studies: Lohmander and colleagues reported all measures of overweight including BMI and WC were associated with incidence of TKR, with BMI being the strongest, after 11 years follow up in the Malmo Diet and Cancer study (Lohmander et al., 2009). A second study with this cohort by Engstrom and colleagues reported that the increased incidence of TKR in participants with metabolic syndrome (MetS) which includes central obesity, hypertension, dyslipidaemia, diabetes and insulin resistance, was largely explained by increased BMI (Engstrom et al., 2009). A more recent study by Monira Hussain and colleagues using the Melbourne Collaborative Cohort Study reported that the cumulative number of

MetS components were associated with increased risk of TKR after 6.8 years, independent of BMI, indicating the additive effect of MetS components may be where the cause lies (Monira et al., 2014). Yoshimura and colleagues also reported the accumulation of MetS components was significantly related to the presence of RKOA in the Research on Osteoarthritis Against Disability (ROAD) cohort in Japan (Yoshimura et al., 2011). There have not been any further studies comparing BMI and WC with SRKOA or knee pain for comparison of the other outcomes used in this study. However, the fact that osteoarthritic knee pain can be fluctuating (Soni et al., 2012) may be a contributing factor to the weaker associations present for SRKOA and knee pain incidence.

Similar to the cross-sectional study, associations were greatest for bilateral over unilateral, but only for Y10 RKOA incidence, which may suggest alternative pathological mechanisms exist for structural RKOA compared to SRKOA and knee pain. Traditionally the mechanism of association between BMI and KOA was thought to be purely biomechanical, with excess body weight having a detrimental loading effect on weight bearing joints. However, studies examining obesity and hip OA reported no associations (Gelber et al., 1999, Grotle et al., 2008), whereas associations were reported between obesity and hand OA (Carman et al., 1994, Cicuttini et al., 1996) indicating that the mechanism of association cannot be purely mechanical, and in fact contains a metabolic component. Adipose tissue, previously considered to be a passive energy store, is now recognised as being a highly active metabolic endocrine organ secreting chemical messengers known as adipocytokines (Sowers and Karvonen-Gutierrez, 2010). Leptin is an adipocytokine involved in the metabolic syndrome which also has a direct effect on chondrocytes (Dumond et al., 2003). The role of obesity-related inflammatory processes via adipocytokines is a suggested pathological pathway that is currently being investigated (Wang et al., 2015, de Lange-Brokaar et al., 2012).

When BMI and WC were combined and mutually adjusted for each other and then fully adjusted (for Y1 age and knee injury) in the Figure 60 graphs, similar to the cross-sectional study no further additional information was provided in terms of predicting Y10 SRKOA incidence in the combined models compared to the singular crude models for BMI and WC. This again suggests use of one measurement was sufficient for predicting Y10 SRKOA incidence, and BMI would continue to be the measure of choice. Even though BMI associations

were attenuated with unilateral, bilateral and any SRKOA, it still remained a stronger predictor than WC.

7.6.1 Study strengths

There are very few longitudinal studies with true physical measurements for height and weight data collected at different time points as achieved in the Chingford cohort. This is a real strength making the Chingford cohort study an extremely valuable data set. Most other cohorts studying obesity and KOA have examined height and weight measurements at baseline only (Lohmander et al., 2009, Hochberg et al., 1995, Reijman et al., 2007, Cooper et al., 1994b, Felson et al., 1988, Schouten et al., 1992, Anderson and Felson, 1988) and some rely on self-reported figures, which have a great potential for recall bias thereby questioning their reliability (Gelber et al., 1999, Jinks et al., 2006, Grotle et al., 2008, Holliday et al., 2011).

The same applies to physical measurements of WC, although only measured at two time points (Y1 and Y20) in this cohort, it has provided the longest WC natural history with KOA as previous KOA studies measured WC at baseline only (Abbate et al., 2006, Engstrom et al., 2009, Holliday et al., 2011, Han et al., 2013, Lohmander et al., 2009, Monira et al., 2014, Wang et al., 2009, Yoshimura et al., 2011, Janssen and Mark, 2006).

Overall this study provides valuable information on the change in BMI and WC over a 19 year period and is the longest natural history of BMI and WC with KOA outcomes to date. This was achieved by the good attendance rate at subsequent clinic visits. Over 50% (n=516) of the original 1,003 women attended the Y20 clinic visit. The fact that the cohort study retained the majority of the same staff throughout its course was a real strength in terms of maintaining excellent attendance rates and rapport with the study participants.

A further strength is that BMI and WC associations were described across three clinically important outcomes SRKOA, RKOA and knee pain. The majority of previous longitudinal studies focus on structural RKOA (Cooper et al., 2000, Schouten et al., 1992, Anderson and Felson, 1988, Felson et al., 1988, Reijman et al., 2007). More recently there have been some longitudinal obesity studies that focus on knee pain (Jinks et al., 2006, Macfarlane et al., 2011). However there are few longitudinal studies that examine SRKOA (RKOA combined with knee pain) which is now more clinically relevant, or that have the capacity to

compare across all three outcomes of SRKOA, RKOAs and knee pain as this study has done.

7.6.2 Study limitations

In epidemiology studies, bias is often an issue (Silman and Macfarlane, 2002). Participants lost to follow-up are a major limitation of all long-term cohort studies, and the Chingford study is no exception. The 39% drop-out rate (329/845 adjusted for 158 deaths by Y20) for the Y20 visit was an unavoidable limitation. However to have 516 women out of the original 1,003 still attending after 19 years was an excellent attendance rate. There was a potential for study bias due to deaths, participants dropping out because of disability and illness, and generally a healthier cohort attending the follow-up visits as highlighted by the significant baseline characteristic differences between included women and those excluded across all five aims of this study. These significant differences suggested that the included women were generally younger, slimmer and less symptomatic with reduced levels of knee pain and/or RKOAs. Whilst these differences were similar enough not to imply a severe bias, the unknown possibility remains that for whatever reason, the participants lost to follow-up, could have had significantly worse knee pain, RKOAs and/or a greater BMI than those included in the analysis. There is no way of knowing the potential effect of this type of bias on any study design. The use of complete-case analysis could add further bias due to the removal of participants not present for intermediate visits. However when the complete-case analyses were compared to all attending women analyses for aims 1 (BMI), 2 (BMI with SRKOA, RKOAs and knee pain) and 3 (WC with SRKOA, RKOAs, knee pain and BMI), the corresponding bar graphs and scatter graphs all displayed very similar patterns indicating no obvious identifiable bias was present.

There were further limitations with some of the variables collected at the baseline Y1 visit. Both knee pain and knee injury variables collected by a self-administered questionnaire, were person-level questions in comparison to the knee-specific questions that were asked at subsequent study clinic visits. If a positive answer was provided to either Y1 question then both right and left knees were considered positive. Therefore there is an element of over-reporting of knee pain and knee injury at Y1. As a consequence, the prevalence of knee pain and subsequently derived SRKOA outcome at Y1 was

higher (20% for knee pain and 4% for SRKOA) than the Y5 prevalence (7% for knee pain and 3% for SRKOA) displayed in the aim 2 analysis (section 7.5.2). This also may have affected the aim 4 cross-sectional analysis with possibly greater associations being reported for SRKOA and knee pain. Also adjustment for Y1 knee injury could have affected the associations reported in the cross-sectional analysis in aim 4 and the longitudinal analysis in aim 5.

At the Y20 clinic visit, digital knee radiograph DICOM images were collected and graded for K&L global score by Dr Kirsten Leyland using KneeMorf software (described in section 3.5.4.2). The benefits of using digital images meant that the zoom in/out features of the KneeMorf software may have allowed for easier identification of K&L grading parameters such as osteophytes and joint space narrowing. This may have contributed to the large increase in RKOA prevalence from 44% at Y15 to 85% at Y20 as displayed in the aim 2 analysis (section 7.5.2).

Analyses in this study were adjusted for baseline age and knee injury. It is possible that there are other potential confounder variables that could be associated with the exposure and outcomes in this study such as physical activity, smoking and alcohol. Whilst some of these were available at the Y1 baseline visit, they were not all available at the Y10 clinic visit which was the other time point used as a baseline in this thesis, therefore for consistency across study visits confounding variables were limited to age and knee injury.

7.6.3 Clinical implications

Obesity is a well-known risk factor for KOA (Sowers and Karvonen-Gutierrez, 2010). In line with near tripling of obese women to 30% over 19 years in this cohort, the prevalence of KOA also increased. As BMI increases, the lifetime risk of KOA increases with 2 in 3 obese adults developing symptomatic KOA in their lifetime (Murphy et al., 2008). Results from this study therefore reinforce the benefits of preventing weight gain in middle-aged women as this will reduce the incidence of SRKOA, RKOA and knee pain in later life.

It seems that measures of fat distribution by WC offer no advantage over the simple measure of BMI in predicting SRKOA. However these results show that it would be acceptable to substitute BMI with WC measurement on occasions when it might be difficult to measure weight or height in a clinical situation.

For example for patients with mobility problems it might be easier to measure WC.

7.6.4 Conclusion

This study has detailed the natural history of BMI and WC over 19 years, and has showed a marked increase in both measurements over this period. Fewer women remained in the normal BMI category and a substantial number of women moved into the obese BMI category. Cross-sectional analysis identified similar associations between BMI and WC across SRKOA, RKOA and knee pain outcomes, with bilateral associations being the strongest for SRKOA and RKOA. This is maintained longitudinally only for RKOA, indicating that the bilateral association may be driven by structure.

No further value was added to the SRKOA predictive model when BMI and WC were combined, and so use of one measurement, preferably BMI, is suggested. However WC could be substituted where measuring BMI is difficult.

Results from this study therefore reinforce the benefits of preventing weight gain in middle-aged women as this will reduce the incidence of SRKOA, RKOA and knee pain in later life.

7.6.5 Final summary

- After 19 years there was a near tripling of the number of obese women.
- Increases in BMI over 19 years were associated with increased rates of all 3 outcomes with prevalence for RKOA being the strongest, then SRKOA and then knee pain.
- Predictive associations for Y1 BMI and WC for Y10 RKOA incidence were strong, but weaker for SRKOA incidence and very weak for knee pain incidence, suggesting this association may be driven by structure.
- Longitudinal associations were greater with bilateral than with unilateral RKOA incidence, suggesting that alternative pathological mechanisms may exist for structural RKOA compared to SRKOA and knee pain.
- Measures of fat distribution by WC offer no advantage over the simple measure of BMI in predicting SRKOA, although WC could be substituted if measuring BMI was difficult.

8. Chapter 8: The cross-sectional interaction between knee alignment and body mass on knee osteoarthritis

8.1 Background

Previous thoughts of OA being primarily a disease affecting articular cartilage have been overtaken by the concept that OA now involves all of the tissues surrounding a joint (articular cartilage, synovium, sub-chondral bone, peri-articular muscle, ligaments, sensory nerves) interacting in a way that ultimately represents 'failure of the joint as an organ' (Arden and Cooper, 2006). How risk factors play a part in these tissues reaching the point of failure is of great interest. Excess body weight and mal-alignment of the lower limb are both known risk factors for KOA, due to the fact that they both contribute to increased joint loading (Felson et al., 2004, Sharma et al., 2001, Reijman et al., 2007, Sharma et al., 2000, Niu et al., 2009, Brouwer et al., 2007). Varus alignment is strongly associated with KOA progression (Sharma et al., 2001, Brouwer et al., 2007, Sharma et al., 2010, Tanamas et al., 2009) but the effect on KOA incidence is less clear (Tanamas et al., 2009, Brouwer et al., 2007, Hunter et al., 2007, Sharma et al., 2010). The effect of body weight as a risk factor for KOA incidence is more defined (Cooper et al., 2000, Coggon et al., 2001, Felson et al., 1988, Reijman et al., 2007, Spector et al., 1994) but its role in KOA progression may be dependent on knee mal-alignment (Felson et al., 2004, Niu et al., 2009). The combined effect of obesity and mal-alignment is less known as interactions between risk factors for OA are not yet fully understood (Lohmander and Felson, 2004).

With a general population that is ageing and growing increasingly heavier, the risk of developing KOA is on the increase but what are the combined effects of having specific risk factors such as obesity and knee mal-alignment presenting together, and at what point in the disease process is this of relevance? There is a critical gap in the knowledge of understanding risk factors and their inter-relationships, so further research on risk factor interaction is vital for developing effective ways of treating and managing

OA. This chapter examines the interaction of BMI and knee alignment on SRKOA, RKOAs and knee pain from a cross-sectional perspective.

8.2 Aim

The main aim of this study was:

- To describe the interaction of BMI and knee alignment on cross-sectional associations with SRKOA, RKOAs and knee pain in a general female population.

8.3 Method

8.3.1 Study population

Participants included in this study were women with BMI, knee alignment, SRKOA, RKOAs and knee pain variables at Y10. Women with any of the medical conditions listed in the exclusion criteria (section 3.4.2) at Y10 were excluded. This left a total of 1058 knees from 584 women available for the cross-sectional interaction analysis (Figure 42, section 5.3 for 1058 sample derivation).

8.3.2 Exposure variables

Body mass index

Height measured in centimetres and body weight measured in kilograms were collected at the Y10 clinic visits following the SOP located in appendix A15. Further details of the methodology is in section 3.5.1. BMI was subsequently determined using the WHO standard calculation (World Health Organization, 1995) listed in section 2.5.5.1. BMI was stratified according to the WHO international adult BMI classification (Table 7, section 2.5.5.1) into underweight $< 18.50 \text{ kg/m}^2$, normal $18.50 - 24.99 \text{ kg/m}^2$, overweight $25.0 - 29.99 \text{ kg/m}^2$ and obese $\geq 30.00 \text{ kg/m}^2$. Due to small numbers of underweight knees ($n=13$), the underweight and normal BMI categories were merged together and used as the reference category.

Knee alignment

1P and 2P AA alignment based at KJC 3 (the tibial plateau centre) were measured by the author on all Y10 radiographs using KneeMorf as described previously in section 3.5.4.2. 1P and 2P alignment was categorised into neutral / varus / valgus alignment categories as defined in section 5.5.5, with the neutral category used as the referent category.

8.3.3 Outcome variables

All outcomes were knee-based. The primary outcome variable was Y10 SRKOA, RKOAs and knee pain were secondary outcomes as defined in section 3.6.

8.3.4 Confounding variables

Adjustments were made for age and knee injury data collected at the Y10 clinic visit as defined in section 3.7. Age was used as a continuous variable and knee injury was used as a categorical yes/no variable in these analyses.

8.4 Analysis

All analysis was completed using Stata version 13.0 (Stata Corp, College Station, Texas, USA). Prior to analysis, data distribution was checked using histograms and scatter plots for inconsistencies, outliers and to assess whether normal distributions existed. Where possible both knees from each woman were included. There were 474 women supplying two knees and 110 women supplying one knee resulting in a total of 584 women with 1058 knees. The 8 knees with TKRs at Y10 were excluded from the analysis as AA alignment measurements were unobtainable with a prosthesis in situ.

The demographic and clinical characteristics for the included and excluded cohorts were presented as the median with IQR for non-normally distributed variables, and mean with SD for normally distributed variables. Categorical variables were presented as a number and a percentage. Statistically significant differences (with p values <0.05) in measured variables between the included and excluded cohort were examined using two independent sample t-tests for normal variables, Kruskal Wallis test for non-normal variables and chi-square test for categorical variables.

Firstly for this cross-sectional analysis, bar graphs stratified by alignment (varus/neutral/valgus) and BMI (normal/overweight/obese) for each outcome were plotted to show percentage distributions of the included 1058 knees.

Secondly, cross-sectional associations were completed between Y10 alignment measurements stratified by the three BMI categories (normal, overweight and obese) and Y10 SRKOA, RKOAs and knee pain outcomes using GEE to account for the correlation between left and right knees in one individual. Normal, overweight and obese BMI category knees were analysed for varus and valgus alignment (based on the association with SRKOA clinical outcome defined in the Y10 cross-sectional analysis section 5.5.5) and calculated relative to neutrally aligned knees as reference. ORs and their 95% CIs were calculated and analyses were adjusted for Y10 age and presence of knee injury. There were clearly insufficient knees present in some of the normal BMI stratifications for a meaningful interaction analysis to be completed. It was therefore decided to merge normal and overweight knees together for comparison against obese knees. The ORs from the adjusted models were plotted. Analysis was stratified by BMI category (knees from normal or overweight BMI versus knees from obese BMI) then tested for interaction between BMI category and alignment. The interaction p value was presented in each graph.

Thirdly, due to limited data in some cells and because testing interaction is data hungry, BMI and alignment variables were merged from three categories into two clinically important categories. BMI was categorised into normal (≤ 25 kg/m²) and overweight (> 25 kg/m²), and alignment categorised into neutral (178-182° for 1P and 180-185° for 2P) and mal-alignment ($< 178^\circ$ or $> 184^\circ$ for 1P and $< 180^\circ$ or $> 185^\circ$ for 2P). Using neutral alignment with normal BMI knees as referent, a two by two table was constructed showing the OR for mal-aligned normal BMI knees and neutral aligned knees with overweight BMI. The sum of these increases together with the background effect of neutral aligned normal BMI knees was then compared to the combined joint effect of mal-aligned overweight knees. This represented the additive effect when BMI and mal-alignment were present together, using an additive effect method reported by Rothman (Rothman, 2002). The interaction between two category BMI and two category alignment was tested and the interaction p value presented under each 2x2 table.

All cross-sectional analyses were repeated for both 1P and 2P alignment methods.

8.5 Results

8.5.1 Cross-sectional interaction study population

A total of 1058 knees from 584 women were included in this cross-sectional interaction analysis. Table 66 shows the clinical characteristics from the full cohort (n=1624), the excluded cohort (n=566) and the included cohort (n=1058) women attending the Y10 study visit. Although the included women were slightly younger this difference was not clinically significant and all other characteristics were similar.

Table 66: Clinical characteristics for cross-sectional interaction analysis

Where 1P=one-point; 2P=two-point; AA=anatomic axis; BMI=body mass index; IQR=inter-quartile range; KJC=knee joint centre; K&L=Kellgren & Lawrence grade; RKOA=radiographic knee osteoarthritis; SRKOA=symptomatic radiographic knee osteoarthritis; SD=standard deviation.

Y10 characteristic	Full Y10 cohort (n=1624 knees)	Excluded Y10 cohort (n=566 knees)	Included Y10 cohort (n=1058 knees)	P value ^a
Age, median (IQR) years	62 (57-68)	63 (57-69)	62 (57-67)	0.004
BMI, mean (\pm SD) kg/m ²	26.8 (4.7)	26.9 (4.8)	26.7 (4.6)	0.67
Knee injury, %	16.3	15.9	16.5	0.78
Knee pain \geq 15 days, %	14.1	15.4	13.4	0.28
RKOA \geq 2 K&L grade, %	27.9 (n=1602)	27.9 (n=544)	27.9	0.98
SRKOA, %	6.8 (n=1602)	8.3 (n=544)	6.1	0.09
AA angle:				
1P KJC3, mean (\pm SD)°	-	-	180.11 (2.93)	-
1P neutral 178-182°, %	-	-	52.5 (n=555)	-
1P varus <178°, %	-	-	23.2 (n=245)	-
1P valgus >182°, %	-	-	24.4 (n=258)	-
2P KJC3, mean (\pm SD)°	-	-	182.53 (2.51)	-
2P neutral 180-185°, %	-	-	73.5 (n=778)	-
2P varus <180°, %	-	-	12.7 (n=134)	-
2P valgus >185°, %	-	-	13.8 (n=146)	-

^a P values comparing included to excluded cohort using: Kruskal Wallis test for age; two sample t-test for BMI; Chi-square test for injury, knee pain, RKOA & SRKOA.

8.5.2 1P alignment Y10 cross-sectional interaction

Figure 61 displays bar graphs stratified by Y10 1P alignment (varus <178°, neutral 178-182°, valgus >182°) and Y10 BMI (normal <25 kg/m², overweight 25-30 kg/m², obese >30 kg/m²) for each of the Y10 outcomes

SRKOA, RKOAs and knee pain. The left hand side shows knees positive for each outcome versus knees negative for each outcome on the right hand side. Similar patterns were shown between positive and negative knees for RKOAs and knee pain outcomes for all BMI and 1P alignment categories. Neutral alignment was the most common with few differences in varus and valgus distribution between positive and negative knees. For the Y10 SRKOA outcome, there was a levelling of the number of overweight and obese SRKOA positive knees when compared to SRKOA negative knees. For SRKOA positive normal BMI knees there were more neutral knees and no varus aligned knees which may indicate a weak interaction, but also indicates there was an empty data cell which affects future analysis hence the requirement to merge normal and overweight BMI categories.

Table 67 shows the GEE cross-sectional associations between Y10 1P alignment measurements stratified by the three BMI categories for each of the Y10 outcomes. The ORs and their 95% CIs for the crude models were shown first followed by the model adjusted for Y10 age and presence of knee injury.

For SRKOA and RKOAs outcomes an increase in association was seen for varus 1P alignment for overweight and obese knees. Varus knees carrying the most weight had nearly three times the odds of SRKOA (OR 2.83, 95% CI 1.15, 6.95) and twice the odds of RKOAs (OR 2.03, 95% CI 1.04, 3.95) compared to neutral obese knees. This association was not present for knee pain, neither was it seen in valgus knees for any outcome, although valgus normal BMI knees displayed a tendency to be associated with knee pain in the adjusted model (OR 1.68, 95% CI 1.00, 2.83).

As the overall number of Y10 SRKOA positive knees was small at 64, for the normal BMI category there were some alignment categories (highlighted in Table 67) where no knees (varus) or only 1 knee (valgus) were present. This limits the proposed interaction analyses so it was decided to merge normal and overweight knees together for comparison against obese knees for future analyses.

Figure 61: Y10 BMI by Y10 1P alignment for all Y10 outcomes

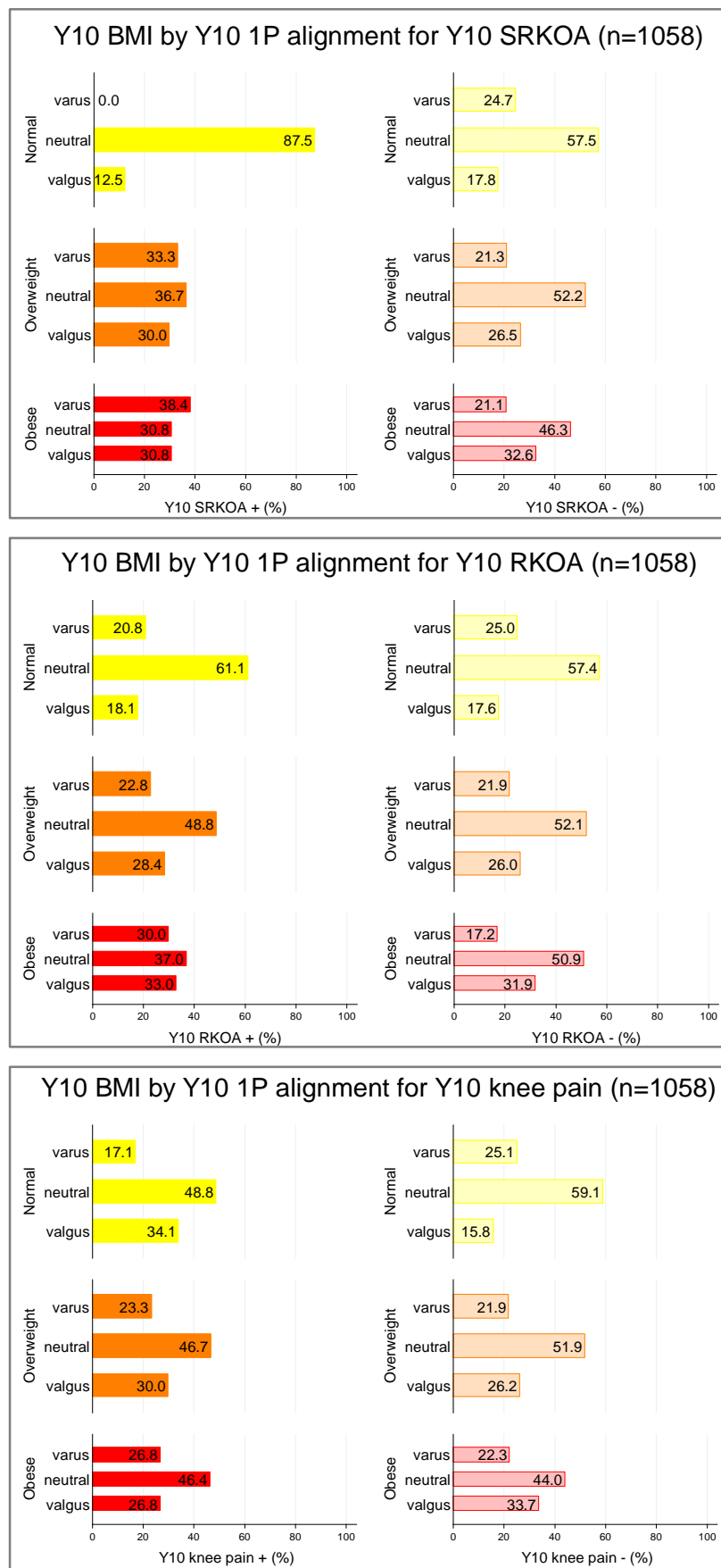


Table 67: Cross-sectional associations with Y10 outcomes by BMI categories and 1P alignment

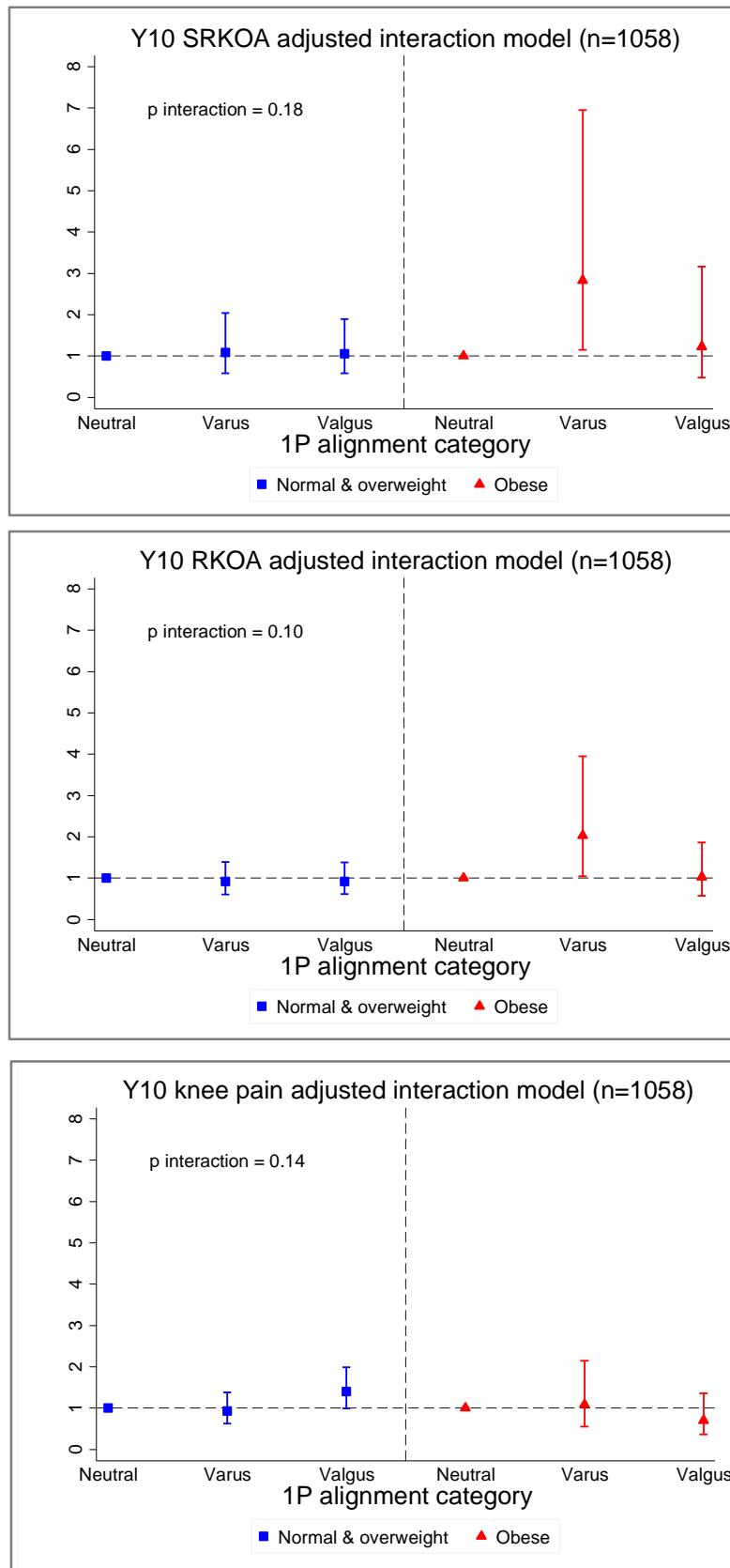
Where 1P=one-point; KJC=knee joint centre; KJC3=tibial plateau centre; K&L=Kellgren & Lawrence grade; N/A=not available; RKOA=radiographic knee osteoarthritis; SRKOA=symptomatic radiographic knee osteoarthritis; ^a adjusted for Y10 age and knee injury.

Y10 1P alignment (°) by BMI (kg/m ²)		Y10 knee pain (≥15+ days)		Y10 RKOA (≥2 K&L)		Y10 SRKOA (≥2 K&L & ≥15+ days)	
		- (n=916)	+ (n=142)	- (n=763)	+ (n=295)	- (n=994)	+ (n=64)
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Normal ≤24.99 (n=408)	Neutral 178-182° Reference	n=217 1.0 (-)	n=20 -	n=193 1.0 (-)	n=44 -	n=230 1.0 (-)	n=7 -
	Varus <178° Crude	n=92 0.63 (0.35,1.11)	n=7 0.11	n=84 0.61 (0.32,1.16)	n=15 0.13	n=99 N/A	n=0 N/A
	Adjusted ^a	0.62 (0.33,1.15)	0.13	0.62 (0.31,1.23)	0.29	N/A	N/A
	Valgus >182° Crude	n=58 1.52 (0.96,2.40)	n=14 0.07	n=59 0.83 (0.44,1.59)	n=13 0.58	n=71 N/A	n=1 N/A
	Adjusted ^a	1.68 (1.00,2.83)	0.05	0.68 (0.33,1.39)	0.29	N/A	N/A
Overweight 25-29.99 (n=434)	Neutral 178-182° Reference	n=194 1.0 (-)	n=28 -	n=162 1.0 (-)	n=60	n=211 1.0 (-)	n=11 -
	Varus <178° Crude	n=82 1.30 (0.78,2.16)	n=14 0.32	n=68 1.10 (0.66,1.81)	n=28 0.72	n=86 1.80 (0.84,3.84)	n=10 0.13
	Adjusted ^a	1.33 (0.81,2.21)	0.26	1.23 (0.72,2.11)	0.45	2.06 (0.92,4.63)	0.08
	Valgus >182° Crude	n=98 1.21 (0.75,1.96)	n=18 0.43	n=81 0.94 (0.58,1.51)	n=35 0.79	n=107 1.42 (0.67,2.99)	n=9 0.36
	Adjusted ^a	1.21 (0.77,1.93)	0.41	0.99 (0.60,1.63)	0.96	1.45 (0.69,3.07)	0.33
Obese ≥30.00 (n=216)	Neutral 178-182° Reference	n=77 1.0 (-)	n=19 -	n=59 1.0 (-)	n=37	n=88 1.0 (-)	n=8 -
	Varus <178° Crude	n=39 1.09 (0.55,2.16)	n=11 0.82	n=20 2.02 (1.06,3.86)	n=30 0.03	n=40 2.85 (1.16,7.00)	n=10 0.02
	Adjusted ^a	1.09 (0.55,2.15)	0.82	2.03 (1.04,3.95)	0.04	2.83 (1.15,6.95)	0.02
	Valgus >182° Crude	n=59 0.72 (0.37,1.39)	n=11 0.32	n=37 1.07 (0.60, 1.89)	n=33 0.82	n=62 1.26 (0.49,3.21)	n=8 0.63
	Adjusted ^a	0.70 (0.36,1.36)	0.29	1.03 (0.57,1.86)	0.93	1.23 (0.48,3.16)	0.67

Figure 62 graphs plot the ORs and associated 95% CIs from the adjusted models, stratified by 1P alignment and the merged BMI categories normal/overweight versus obese knees for each of the Y10 outcomes. The interaction between BMI category and 1P alignment was tested and the interaction p value presented on each graph.

Obesity appeared to modify the effect on 1P varus alignment knees for both SRKOA and RKOAs outcomes. There was increased obese varus risk compared to the flat normal/overweight alignment categories on both Figure 62 SRKOA and RKOAs graphs. For knee pain there were no significant differences as both the normal/overweight and obese alignment categories display a flatter pattern. Although visually an obese varus 1P alignment interaction was presented for SRKOA and RKOAs neither outcome was statistically significant at the $p < 0.05$ level ($p = 0.18$ and $p = 0.10$ respectively).

Figure 62: Interaction between BMI and 1P alignment on Y10 outcomes
(adjusted for Y10 age and knee injury)



The 2 x 2 tables Table 68, 69 and 70 show crude and adjusted interaction between BMI (overweight and obese BMI merged together now termed overweight versus normal BMI) and 1P alignment (varus and valgus alignment merged together now termed mal-alignment versus neutral alignment) on the three Y10 outcomes. Neutral alignment normal BMI knees were used as referent.

For Y10 SRKOA in Table 68, the observed adjusted OR for knees with mal-alignment and overweight was significant at 4.54 (95% CI 1.77, 11.64) which was nearly double the odds of neutral alignment overweight knees at 2.68 (95% CI 1.00, 7.15). Among knees from women with normal BMI, mal-alignment reduced OR by 0.78 to 0.22 (95% CI 0.04, 1.15) for SRKOA relative to neutral alignment. Clinically this was not expected and possibly explained by the reduced number of positive SRKOA normal BMI knees with mal-alignment (n=0 varus and n=1 valgus) as previously highlighted in Table 67. The increase in OR of overweight with neutral alignment was 1.68 and the increase in OR of overweight with mal-alignment was 3.54, indicating a statistically significant ($p=0.02$) biological interaction between BMI and 1P alignment on SRKOA.

For Y10 RKOAs in Table 69, the observed adjusted OR for knees with mal-alignment and overweight was significant at 2.38 (95% CI 1.54, 3.68) which demonstrated a stronger association than neutral alignment and overweight at 1.93 (95% CI 1.24, 3.00). These associations for Y10 RKOAs were approximately half as strong as the associations shown for Y10 SRKOA. Among knees from women with normal BMI, mal-alignment also reduced OR by 0.35 to 0.65 (95% CI 0.39, 1.08) for RKOAs relative to neutral alignment. Again clinically this was not expected. The increase in OR from being overweight in knees with neutral alignment was 0.93 and the increase in OR of being overweight with mal-alignment was 1.38. This again indicated a biological interaction between BMI and 1P alignment on RKOAs which was also statistically significant ($p=0.04$).

For Y10 knee pain in Table 70, the observed adjusted OR for knees with 1P mal-alignment and overweight was significant at 1.82 (95% CI 1.05, 3.16). Among knees from women with normal BMI, mal-alignment increased the OR slightly by 0.07 to 1.07 (95% CI 0.69, 1.68) for knee pain relative to neutral alignment. The increase in OR of being overweight in knees with

neutral alignment was 0.69 and the increase in OR of being overweight with mal-alignment was not much greater at 0.82. This indicated that the biological interaction between BMI and 1P alignment on knee pain was small (i.e. less than 1) in comparison to SRKOA and RKOAs and was not statistically significant ($p=0.99$).

1P alignment cross-sectional results summary

- This interaction analysis was limited by reduced number of 1P varus ($n=0$) and valgus ($n=1$) normal BMI SRKOA positive knees, therefore stratification of 1P alignment and BMI into 3 categories was not possible.
- When 1P alignment was split into 3 categories (neutral, varus and valgus) and BMI was split into 2 categories (normal/overweight and obese), obesity appeared to modify the effect on 1P varus alignment knees for both Y10 SRKOA and RKOAs (although interactions were not statistically significant at the $p < 0.05$ level). This effect was not present for knee pain.
- When 1P alignment and BMI were split into 2 categories (neutral and mal-alignment with normal and overweight respectively) there were biological and statistically significant cross-sectional interactions for Y10 SRKOA and RKOAs, but not Y10 knee pain indicating these interactions may be driven by structure.

Table 68: Y10 SRKOA cross-sectional associations between combined BMI and 1P alignment

Where 1P=one-point; BMI=body mass index; ^a adjusted for Y10 age and knee injury (OR with 95% CI shown).

(Total n=1058) 1P alignment	BMI	Normal (<25 kg/m²) n=408	Overweight (≥25 kg/m²) n=650
Neutral (178-182°) n=555		n=237	n=318
Crude		1.0	2.65 (1.00,7.03)
Adjusted ^a		1.0	2.68 (1.00,7.15)
Mal-alignment (<178 or >182°) n=503		n=171	n=332
Crude		0.23 (0.04,1.26)	4.48 (1.76,11.39)
Adjusted ^a		0.22 (0.04,1.15)	4.54 (1.77,11.64)

p interaction = **0.02**

Table 69: Y10 RKOA cross-sectional associations between combined BMI and 1P alignment

(Total n=1058) 1P alignment	BMI	Normal (<25 kg/m²) n=408	Overweight (≥25 kg/m²) n=650
Neutral (178-182°) n=555		n=237	n=318
Crude		1.0	1.97 (1.28,3.02)
Adjusted ^a		1.0	1.93 (1.24,3.00)
Mal-alignment (<178 or >182°) n=503		n=171	n=332
Crude		0.70 (0.43,1.13)	2.32 (1.52,3.54)
Adjusted ^a		0.65 (0.39,1.08)	2.38 (1.54,3.68)

p interaction = **0.04**

Table 70: Y10 knee pain cross-sectional associations between combined BMI and 1P alignment

(Total n=1058) 1P alignment	BMI	Normal (<25 kg/m²) n=408	Overweight (≥25 kg/m²) n=650
Neutral (178-182°) n=555		n=237	n=318
Crude		1.0	1.69 (0.97,2.94)
Adjusted ^a		1.0	1.69 (0.97,2.94)
Mal-alignment (<178 or >182°) n=503		n=171	n=332
Crude		1.08 (0.69,1.69)	1.83 (1.06,3.16)
Adjusted ^a		1.07 (0.69,1.68)	1.82 (1.05,3.16)

p interaction = 0.99

8.5.3 2P alignment Y10 cross-sectional interaction

All Y10 cross-sectional analyses were repeated for the 2P alignment method.

Figure 63 displays bar graphs stratified by Y10 2P alignment (varus $<180^\circ$, neutral $180-185^\circ$, valgus $>185^\circ$) and Y10 BMI (normal $<25 \text{ kg/m}^2$, overweight $25-30 \text{ kg/m}^2$, obese $>30 \text{ kg/m}^2$) for each of the Y10 outcomes SRKOA, RKOAs and knee pain. Similar patterns were shown between positive and negative knees for RKOAs and knee pain outcomes for all BMI and 2P alignment categories. Neutral alignment contained the largest percentage of knees (and greater percentages than 1P neutral alignment) with few differences in varus and valgus distribution between positive and negative knees. For the Y10 SRKOA positive outcome, there was the same lack of varus aligned normal BMI knees as the 1P method. In addition Y10 knee pain positive knees were also lacking, which together would affect future analysis. In the SRKOA positive obese category there were more varus aligned knees than neutral. This was a different pattern to SRKOA negative knees, where there were more neutral aligned knees.

Table 71 shows the GEE cross-sectional associations between Y10 2P alignment measurements stratified by the three BMI categories for each of the Y10 outcomes. Similar to Table 67 for 1P alignment, an increase in association was seen for varus 2P alignment for overweight and obese knees for SRKOA and RKOAs in Table 71. This again indicates that varus knees carrying the most weight have over 3 times the odds of SRKOA (OR 3.68, 95% CI 1.45, 9.38) and over twice the odds of RKOAs (OR 2.69, 95% CI 1.32, 5.52) compared to neutral obese knees. Similarly, a less strong and non-significant association was seen for knee pain (OR 1.16, 95% CI 0.65, 2.08 for overweight varus knees and OR 1.63, 95% CI 0.80, 3.29 for obese varus knees), which was not seen in Table 70 for 1P alignment. In addition, a significant association was seen for valgus 2P alignment for overweight BMI knees but only for RKOAs (OR 2.07, 95% CI 1.16, 3.68), which was reduced making it non-significant in RKOAs obese BMI knees (OR 1.84, 95% CI 0.92, 3.70).

Figure 63: Y10 BMI by Y10 2P alignment for all Y10 outcomes

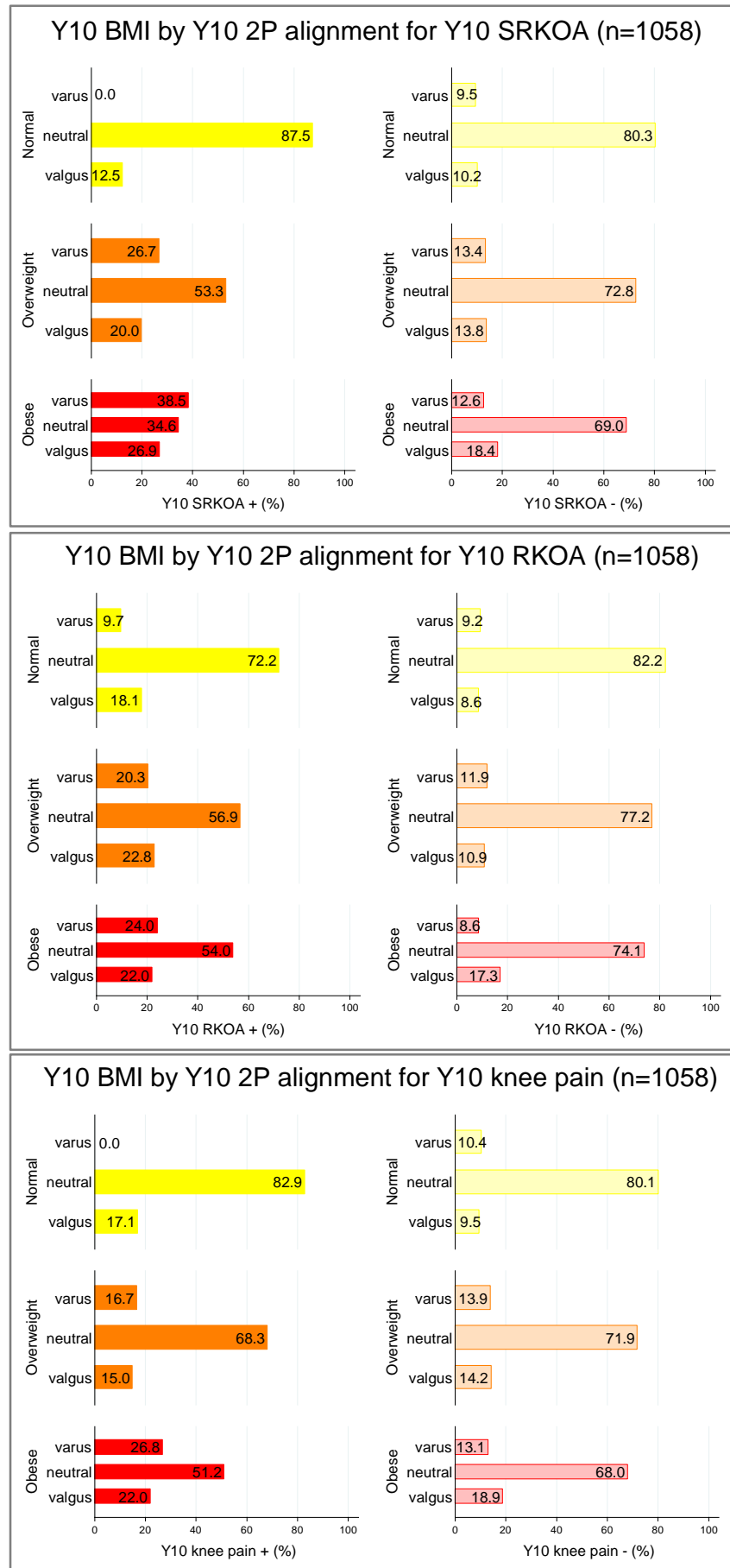


Table 71: Y10 cross-sectional associations by BMI categories for 2P alignment

Where 2P=two-point; KJC=knee joint centre; KJC3=tibial plateau centre; K&L=Kellgren & Lawrence grade; RKOA=radiographic knee osteoarthritis; SRKOA=symptomatic radiographic knee osteoarthritis. ^a adjusted for Y10 age and knee injury.

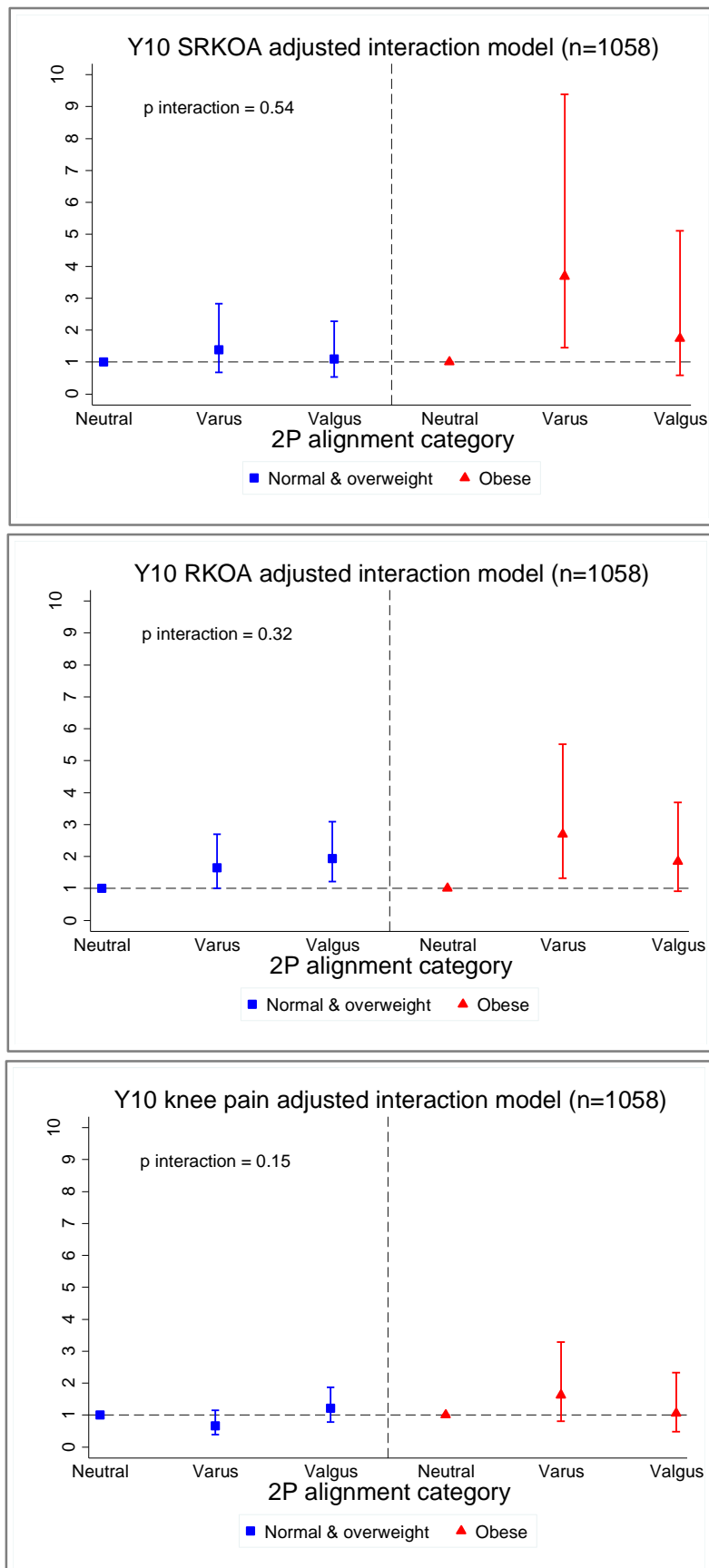
Y10 outcome Y10 2P (n=1058 knees) alignment (°) by BMI (kg/m ²)		Y10 knee pain (≥15+ days)		Y10 RKOA (≥2 K&L)		Y10 SRKOA (≥2 K&L & ≥15+ days)	
		- (n=916)	+ (n=142)	- (n=763)	+ (n=295)	- (n=994)	+ (n=64)
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Normal ≤24.99 (n=408)	Neutral 180-185° Reference	n=294 1.0 (-)	n=34 -	n=276 1.0 (-)	n=52 -	n=321 1.0 (-)	n=7 -
	Varus <180° Crude	n=38 N/A	n=0 N/A	n=31 0.76 (0.29,1.99)	n=7 0.58	n=38 N/A	n=0 N/A
	Adjusted ^a	N/A	N/A	0.78 (0.29,2.10)	0.62	N/A	N/A
	Valgus >185° Crude	n=35 1.20 (0.66,2.16)	n=7 0.55	n=29 1.82 (0.87,3.81)	n=13 0.11	n=41 N/A	n=1 N/A
	Adjusted ^a	1.27 (0.64,2.53)	0.49	1.55 (0.69,3.49)	0.29	N/A	N/A
Overweight 25-29.99 (n=434)	Neutral 180-185° Reference	n=269 1.0 (-)	n=41 -	n=240 1.0 (-)	n=70	n=294 1.0 (-)	n=16 -
	Varus <180° Crude	n=52 1.16 (0.64,2.09)	n=10 0.62	n=37 1.90 (1.08,3.34)	n=25 0.03	n=54 2.25 (1.02,4.98)	n=8 0.04
	Adjusted ^a	1.16 (0.65, 2.08)	0.61	2.11 (1.17,3.83)	0.01	2.38 (1.05,5.37)	0.04
	Valgus >185° Crude	n=53 1.17 (0.68,2.03)	n=9 0.56	n=34 2.06 (1.20,3.55)	n=28 0.009	n=56 1.60 (0.70, 3.65)	n=6 0.26
	Adjusted ^a	1.15 (0.68, 1.96)	0.60	2.07 (1.16,3.68)	0.01	1.49 (0.66,3.38)	0.34
Obese ≥30.00 (n=216)	Neutral 180-185° Reference	n=119 1.0 (-)	n=21 -	n=86 1.0 (-)	n=54	n=131 1.0 (-)	n=9 -
	Varus <180° Crude	n=23 1.65 (0.81,3.34)	n=11 0.17	n=10 2.74 (1.36,5.50)	n=24 0.005	n=24 3.79 (1.49,9.63)	n=10 0.005
	Adjusted ^a	1.63 (0.80,3.29)	0.18	2.69 (1.32,5.52)	0.007	3.68 (1.45,9.38)	0.006
	Valgus >185° Crude	n=33 1.07 (0.49,2.37)	n=9 0.86	n=20 1.94 (0.98,3.84)	n=22 0.06	n=35 1.80 (0.61,5.27)	n=7 0.28
	Adjusted ^a	1.05 (0.48,2.32)	0.90	1.84 (0.92,3.70)	0.09	1.74 (0.59, 5.12)	0.32

Similar to the 1P alignment method, for the normal BMI category there were no varus knees and only 1 valgus knee present (highlighted in Table 71). In addition there was a lack of 2P varus normal BMI knee pain positive knees, therefore as previously discussed normal and overweight BMI knees were merged for comparison with obese BMI knees.

Figure 64 graphs plot the ORs and associated 95% CIs from the adjusted models, stratified by 2P alignment and the merged BMI categories normal/overweight versus obese knees for each of the Y10 outcomes, with their interaction p values.

Similar to 1P alignment in Figure 62, the graphs in Figure 64 show that obesity appears to modify the effect on 2P varus alignment knees for both SRKOA and RKOA outcomes as shown by increased obese varus risk compared to the flat normal/overweight alignment categories on both Figure 64 SRKOA and RKOA graphs. This increased obese varus risk is not so prominent on the knee pain graph and overall confidence intervals are wider for 2P than 1P alignment. Although visually an obese varus 2P alignment interaction was presented for both SRKOA and RKOA outcomes, neither were statistically significant ($p=0.54$ and $p=0.32$ respectively).

Figure 64: Interaction between BMI and 2P alignment on Y10 outcomes
(adjusted for Y10 age and knee injury)



The 2 x 2 Table 72, 73 and 74 for 2P alignment show a similar pattern of associations to the 1P alignment Table 68, 69 and 70. However in Table 72, neither the crude nor adjusted SRKOA model achieved full convergence (possibly due to the absence of varus and valgus normal BMI SRKOA positive knees). These results show larger ORs and wider 95% CIs than the equivalent 1P alignment Table 68 and need to be interpreted with caution. The observed adjusted OR for knees with mal-alignment and overweight was significant at 6.23 (95% CI 2.36, 16.46) which was double the odds of neutral alignment overweight knees at 3.27 (95% CI 1.23, 8.68). Among knees from women with normal BMI, mal-alignment reduced OR by 0.48 to 0.52 (95% CI 0.09, 3.06) for SRKOA relative to neutral alignment. Clinically this was not expected and likely a result of reduced number of positive SRKOA normal BMI knees with mal-alignment (n=0 varus and n=1 valgus) as previously highlighted in Table 71. The increase in OR from being overweight in knees with neutral alignment was 2.27 and with mal-alignment was 5.23. This indicated a biological interaction between BMI and 2P alignment on SRKOA that was not statistically significant (p=0.16), but full model convergence was not achieved which could affect the interaction test result and overall interpretation.

For Y10 RKOAs in Table 73, the observed adjusted OR for knees with mal-alignment and overweight was significant at 4.35 (95% CI 2.77, 6.83) which demonstrates a stronger association than neutral alignment overweight knees at 2.05 (95% CI 1.36, 3.10). These associations for 2P Y10 RKOAs were stronger than the equivalent 1P alignment associations in Table 69. Among knees from women with normal BMI, mal-alignment slightly increased the OR by 0.12 to 1.12 (95% CI 0.60, 2.08) for RKOAs relative to neutral alignment. This was more clinically relevant than the reduction shown with the equivalent 1P alignment model in Table 69. The increase in OR from being overweight in knees with neutral alignment was 1.05; the increase in OR from being overweight with mal-alignment was 3.35, indicating a biological interaction between BMI and 2P alignment on RKOAs which was approaching statistical significance (p=0.08).

For Y10 knee pain in Table 74, the observed adjusted OR for knees with 2P mal-alignment and overweight was significant at 1.77 (95% CI 1.04, 3.02). Among knees from women with normal BMI, mal-alignment reduced the OR

by 0.33 to 0.67 (95% CI 0.34, 1.33) for knee pain relative to neutral alignment. Again clinically this was not expected and most likely due to $n=0$ 2P varus normal BMI knee pain positive knees as previously highlighted in Table 71. The increase in OR from being overweight in knees with neutral alignment was 0.47 and in knees with mal-alignment was only 0.77 therefore the biological interaction between BMI and 2P alignment on knee pain was small and was not statistically significant ($p=0.13$).

2P alignment results summary

- This interaction analysis was limited by reduced number of 2P varus ($n=0$) and valgus ($n=1$) normal BMI SRKOA positive knees, and varus ($n=0$) normal BMI knee pain positive knees therefore stratification of 2P alignment and BMI into 3 categories was not possible.
- When 2P alignment was split into 3 categories (neutral, varus and valgus) and BMI was split into 2 categories (normal/overweight and obese), obesity appeared to modify the effect on 2P varus alignment knees for both Y10 SRKOA and RKOAs (although interactions were not statistically significant). This association was less for knee pain.
- When 2P alignment and BMI were split into 2 categories (neutral and mal-alignment with normal and overweight respectively) greater associations were seen for mal-aligned overweight knees for all three outcomes and for neutral aligned overweight knees for SRKOA and RKOAs. Unlike the 1P alignment models, the 2P interactions were not statistically significant for SRKOA (but this model was not fully converged) nor for RKOAs (although this was approaching significance).

Table 72: Y10 SRKOA cross-sectional associations between combined BMI and 2P alignment

Where 2P=two-point; BMI=body mass index; ^a adjusted for Y10 age and knee injury (OR with 95% CI shown).

(Total n=1058) 2P alignment	BMI	Normal (<25 kg/m²) n=408	Overweight (≥25 kg/m²) n=650
Neutral (180-185°) n=778		n=328	n=450
Crude		1.0	3.19 (1.22,8.36)*
Adjusted ^a		1.0	3.27 (1.23,8.68)*
Mal-alignment (<180 or >185°) n=280		n=80	n=200
Crude		0.48 (0.07,3.26)*	6.46 (2.48,16.84)*
Adjusted ^a		0.52 (0.09,3.06)*	6.23 (2.36,16.46)*

*full convergence not achieved.

p interaction = 0.16

Table 73: Y10 RKOAs cross-sectional associations between combined BMI and 2P alignment

(Total n=1058) 2P alignment	BMI	Normal (<25 kg/m²) n=408	Overweight (≥25 kg/m²) n=650
Neutral (180-185°) n=778		n=328	n=450
Crude		1.0	2.03 (1.35,3.04)
Adjusted ^a		1.0	2.05 (1.36,3.10)
Mal-alignment (<180 or >185°) n=280		n=80	n=200
Crude		1.21 (0.67,2.20)	4.26 (2.75,6.60)
Adjusted ^a		1.12 (0.60,2.08)	4.35 (2.77,6.83)

p interaction = 0.08

Table 74: Y10 knee pain cross-sectional associations between combined BMI and 2P alignment

(Total n=1058) 2P alignment	BMI	Normal (<25 kg/m²) n=408	Overweight (≥25 kg/m²) n=650
Neutral (180-185°) n=778		n=328	n=450
Crude		1.0	1.47 (0.88,2.44)
Adjusted ^a		1.0	1.47 (0.88,2.44)
Mal-alignment (<180 or >185°) n=280		n=80	n=200
Crude		0.69 (0.35,1.37)	1.80 (1.06,3.07)
Adjusted ^a		0.67 (0.34,1.33)	1.77 (1.04,3.02)

p interaction = 0.13

8.6 Discussion

This study uniquely examines the interaction effect of BMI and knee alignment on cross-sectional associations with SRKOA, RKOAs and knee pain in 1058 knees from a general female population using both 1P and 2P alignment methods.

Due to reduced numbers of varus and valgus normal BMI SRKOA positive knees for both 1P and 2P alignment methods, and reduced 2P varus normal BMI knee pain positive knees (Table 67 for 1P and Table 71 for 2P alignment) stratification into the 3 categories of alignment (neutral / varus / valgus) and the 3 categories of BMI (normal / overweight / obese) was not possible for this interaction study. Therefore normal and overweight BMI categories were merged and compared to obese BMI. In this 3 alignment x 2 BMI category analysis, obesity appeared to modify the effect on 1P (Figure 62) and 2P (Figure 64) varus alignment knees for both Y10 SRKOA and RKOAs (although interactions were not statistically significant at the $p < 0.05$ level). This effect was not seen for knee pain, indicating that this biological interaction may be driven by structure rather than pain.

Similarly, when the 2 x 2 category analysis (neutral and mal-alignment with normal and overweight BMI) was performed there were stronger indications that these interactions were driven by structure. In the 1P alignment SRKOA model in Table 68 normal BMI mal-aligned knees were not at SRKOA risk. Although reduced odds were shown they were not significant (and most likely explained by too few normal BMI neutral aligned knees in this category), but for overweight knees with neutral alignment, the risk of SRKOA more than doubled, and the risk nearly doubled again for overweight mal-aligned knees. This interaction was statistically significant, but the wide confidence intervals for overweight knees should be noted and for neutrally aligned overweight knees the ORs were only just significant.

A similar but weaker association was seen for RKOAs in Table 69 with a near doubling of risk for RKOAs for 1P neutral aligned overweight knees, which was slightly further increased for mal-aligned overweight knees. This interaction was also statistically significant with tighter confidence intervals than the equivalent SRKOA.

Although a similar association was seen for knee pain in overweight neutral and mal-aligned knees in Table 70, the association was weaker and the interaction was not statistically significant.

For 2P alignment, overall associations were comparable but greater in strength to 1P alignment for SRKOA and RKOAs in mal-aligned overweight and neutrally aligned overweight knees. Unfortunately the 2P SRKOA model in Table 72 did not fully converge (most likely due to reduced statistical power), and so these results must be interpreted with caution. For RKOAs there was a clear doubling of RKOAs risk in neutrally aligned overweight knees which then doubles again for mal-aligned overweight knees in Table 73. Although not significant this interaction was approaching statistical significance. The associations for knee pain for overweight neutral and mal-aligned knees in Table 74 were much weaker and comparable with 1P alignment, indicating again that this interaction was primarily driven by structure rather than pain.

The discordance between structural RKOAs and knee pain is well known (Bedson and Croft, 2008) and remains a focus for current research. There are few comparable studies on interaction in the literature and these predominantly use MA alignment obtained from FLRs which are not directly comparable to the AA alignment methods used in this study. However, other cross-sectional interaction studies have found that BMI was related to OA severity in varus but not valgus knees (Sharma et al., 2000). The association between MA alignment and dynamic knee joint loading was found to be highest in those with the highest body mass (Moyer et al., 2010). Messier and colleagues in 2014 identified that MA alignment and BMI were associated with different measures of KOA joint loads: alignment was associated with external KAM and BMI with knee compressive and shear forces (Messier et al., 2014). All of these studies used MA alignment and RKOAs as their main outcome. There appear to be no other studies that compare the associations across other outcomes that were examined in this study.

There are two AA alignment interaction studies that examine incidence of RKOAs in female cohorts. Mazzuca and colleagues published results that are suggestive that the risk of developing bilateral tibio-femoral RKOAs in overweight/obese women may be mediated by varus mal-alignment after 2.5

years follow up (Mazzuca et al., 2011). After a similar follow up period, Runhaar and colleagues reported that varus and valgus alignment increased the risk of incident RKOA in middle aged overweight/obese women (Runhaar et al., 2014). Although these were both longitudinal studies using a population of women who were at risk of developing KOA, their results do agree with the results from this cross-sectional study of obesity modifying the effect on varus aligned knees for SRKOA and RKOA in a general female population. It was not possible to examine incidence in this study as this would have reduced the sample from 1058 knees to approximately 600 knees present at Y10 and Y20 visits. This would not have achieved any meaningful longitudinal results as results were already limited by power in the cross-sectional analysis.

8.6.1 Study strengths

This study has a number of strengths having described the interaction of BMI and knee alignment on cross-sectional associations with SRKOA, RKOA and knee pain using both 1P and 2P alignment methods. This was carried out using a large sample of over 1000 knees from 584 women, representative of a normal, predominantly Caucasian, female population (Hart and Spector, 1993a, Hart et al., 1994). Cross-sectional associations with SRKOA, RKOA and knee pain clinical outcomes were assessed. This is not only novel, as previous interaction studies report associations with RKOA only, but also clinically relevant as the discordant relationship between RKOA and reported knee pain is well known (Bedson and Croft, 2008).

8.6.2 Study limitations

Although there was a large sample of over 1000 knees in this study, interaction analyses are extremely data hungry as they require the division of the study population into smaller sub-groups for comparison (Rothman et al., 2008). Regarding the power of an interaction test, it has been suggested that studies with 80% power for the overall effect have only 29% power to detect a similar sized interaction effect. To compensate for this reduction in power, sample size should be inflated fourfold (Brookes et al., 2004) for interaction analyses. This current cross-sectional analysis was

limited by power, with low numbers of knees in certain sub-groups. It is the likely cause for some models producing clinically unexpected results with reduced outcome risk for normal BMI mal-aligned knees (Table 68, 69, 70 and 74) and worse for the 2P SRKOA model (Table 72) which did not fully converge. As a result these cross-sectional results must be interpreted with a degree of caution. There was insufficient power to examine the interaction of BMI and alignment from a longitudinal perspective, and so comments on the possible causal pathway cannot be provided.

Contrary to previous AA alignment interaction studies that have recruited their study populations based on OA and/or obesity (Mazzuca et al., 2011, Runhaar et al., 2014), the Chingford Women's study cohort population was recruited from the general population of a large general practice register in Chingford, North London, UK. The original overall study aim was to study osteoporosis, but it was not a requirement of the study to be osteoporotic. There was no inherent bias at the start of the study towards an OA population and it is not thought to be a major factor for this cross-sectional analysis. There were no clinically significant differences between the included and excluded cohorts in this study as shown in Table 66. The results of this study are restricted to middle-aged women who are predominantly Caucasian, and should not be extrapolated to other ethnicities or males.

In this study knee alignment was measured on SLRs. Gold standard FLRs were not available in this cohort which was a limitation. Alignment measured on SLRs has been previously validated (Kraus et al., 2005), and although suggestions have been made to compare 1P and 2P alignment methods (McDaniel et al., 2010), this is one of the first studies to do so. Alignment measured on radiographs is only a static representation of what is happening at the tibio-femoral joint and this was another limitation of this study. It does not consider the dynamic loads these joints are under, which may give a truer picture of the additional biomechanical loading experienced in an overweight mal-aligned weight bearing knee.

8.6.3 Clinical implications

Although this cross-sectional analysis was limited by power, there was a suggestion that a biological interaction exists between BMI and knee

alignment so that overweight mal-aligned knees display greater risks of SRKOA and RKO. Clinically this is important as both mal-alignment and obesity are modifiable risk factors, and targeting these risk factors with possible treatments in a timely manner, preferably before both risk factors appear together in the same knee, is paramount. For example patients presenting in clinic with increased weight should not only be targeted with weight management advice (Christensen et al., 2007) alongside the other standard core KOA treatments such as access to appropriate information, activity and exercise including muscle strengthening and general aerobic fitness as recommended by NICE 2014 guidelines (National Institute for Health and Care Excellence, 2014b) and OARSI guidelines (McAlindon et al., 2014). They should also be provided with conservative treatment options that could prevent mal-alignment such as bracing (Raja and Dewan, 2011, Segal, 2012), wedged insoles (Raja and Dewan, 2011, Radzimski et al., 2012) and use of assistive devices such as walking aids to reduce weight-bearing loads (Foroughi et al., 2010). Or if the situation was vice-versa in that a patient presents with mal-alignment, then preventative advice on avoiding weight gain or encouraging weight loss as required would also be advised. The results suggested by this cross-sectional study have implications for future clinical trials as patients who were overweight combined with mal-alignment may progress quicker in terms of development (incidence) and progression of SRKOA and RKO. This patient group could be best targeted for recruitment to future trials on conservative treatment options.

8.6.4 Conclusion

This study uniquely examines the interaction of BMI and knee alignment on cross-sectional associations with SRKOA, RKO and knee pain in 1058 knees from a general female population using both 1P and 2P alignment methods. Although limited by low numbers of knees in certain sub-groups, the results suggest that a biological interaction between BMI and knee alignment was present in cross-sectional associations with SRKOA and RKO, but not knee pain, indicating that this interaction may be driven by structure.

8.6.5 Final summary

- Cross-sectional interaction analyses were limited by low numbers of knees in certain sub-groups so overall results must be interpreted with caution.
- Results were suggestive of biological interactions between BMI and knee alignment for SRKOA and RKO, but not knee pain indicating that this interaction may be driven by structure.

9. Chapter 9: Discussion, conclusions & future research

9.1 Introduction

The preceding chapters have presented a series of five studies that explore the associations between alignment and body mass on KOA. Whilst discussions are found at the end of each of the studies, this chapter draws together the main overall findings from these studies, highlighting the knowledge gained and discussing the implications for clinical practice. Limitations of the studies are reviewed and recommendations for future research are proposed.

9.2 Summary of results

9.2.1 Alignment pilot studies

The alignment pilot studies evaluated the performance of the newly designed KneeMorf software and established the alignment measurement technique for femoral and tibial shaft length to be used throughout the alignment studies.

The results of pilot studies 1 and 2 demonstrated that mean differences of shaft lengths at $10\text{cm} \pm 1\text{cm}$ were small, but that use of shaft lengths shorter than this affected the AA angle alignment measurement. As a result a 10cm shaft length for AA alignment measurement was adopted throughout, although measurements at 7cm shaft length were collected for comparison. These pilot studies also indicated that 2P methods may be more accurate as they display less variation than 1P methods. As alignment literature contains a mix of 1P and 2P methods, for comparison both methods were presented in this thesis. It was also clear from these pilot studies that alignment classification into varus, neutral and valgus categories was dependent on whether a 1P or 2P method was used, indicating that method specific alignment categories were required.

Pilot study 3 demonstrated that alignment measured on digitised radiographs with KneeMorf software was comparable to the traditional manual method using a goniometer. Good intra- and inter-reader agreement was shown for KneeMorf measurements.

Overall, these pilot studies showed that measurement of AA angle from KJC2 (tibial spine tips) and KJC3 (tibial plateau centre) displayed the least mean differences and greatest reproducibility. KJC3 displayed the least systematic bias, but further data was required in order to make a definitive KJC choice.

9.2.2 Cross-sectional alignment

The cross-sectional alignment study determined the optimal KJC 1P and 2P AA method for future use in these studies; it defined appropriate varus, neutral and valgus alignment categories for the chosen KJC method and described cross-sectional associations of AA alignment with SRKOA, RKOAs and knee pain.

This study combined with results from the alignment pilot studies (chapter 4) identified KJC3, at the tibial plateau centre, as the optimal 1P and 2P AA method to take forward for future alignment analyses. This recommendation was in agreement with McDaniel and colleagues (McDaniel et al., 2010) and was based on:

- Ease of identification of tibial plateau KJC location compared with base of tibial spine (KJC1) or tips of tibial spine (KJC2) mid-points.
- KJC3 showed the greatest statistically and clinically significant association with the primary SRKOA outcome for both 1P and 2P methods.
- Good agreement for 1P KJC3 between KneeMorf digital versus manual alignment angle comparison.
- High intra- and inter- reader reproducibility for both 1P and 2P KJC3 methods.

Clear differences of approximately 2° were found between 1P and 2P KJC3 methods, inferring that method specific alignment categories were required. Rather than attempting to reproduce MA alignment as in previous studies, it was considered more clinically relevant to recommend the following categories based on their association with the primary outcome SRKOA:

- 1P method: varus <178°, neutral 178 -182° and valgus >182°
- 2P method: varus <180°, neutral 180 - 185° and valgus >185°

These alignment categories were used to examine cross-sectional associations that showed increased risk of SRKOA for varus knees, and increased risk of

RKOA for varus and valgus knees. These may be explained partly by associations between medial JSN for varus and lateral JSN for valgus knees. For knee pain, greater associations were present for valgus knees.

9.2.3 Longitudinal alignment

The longitudinal alignment study described the natural history of AA alignment in this general female population over a 10 year period, and also described the Y10 alignment associations with Y20 SRKOA, RKOA and knee pain incidence. The rotated knee radiograph images are an important limitation of this study and therefore these results, particularly regarding the natural history, must be interpreted cautiously.

Overall mean changes in AA alignment over 10 years were small and in a slight valgus direction for both methods: 1P (0.36° , SD $\pm 2.73^\circ$) and 2P (0.06° , SD $\pm 2.01^\circ$) with most knees remaining within the same alignment category.

The longitudinal associations with Y20 SRKOA, RKOA and knee pain incidence were limited by insufficient statistical power for significant differences for either the 1P or 2P method. The identification of rotated images within the sample made it difficult to draw valid conclusions from these observations. Excluding rotated knees from this study was impractical due to the further reduction in statistical power from the smaller sample size, and also the possibility of introducing a potential bias as rotated knees were associated with a greater BMI.

9.2.4 Cross-sectional and longitudinal body mass

This study examined the natural history of BMI and WC and their cross-sectional and longitudinal association with SRKOA, RKOA and knee pain in this general female population over a 19 year period.

Over 19 years there was a near tripling of the number of obese women. This increase in BMI was associated with increased prevalence of all three outcomes with associations for RKOA being the strongest, then SRKOA and then knee pain.

Cross-sectional analysis identified similar associations between BMI and WC with SRKOA, RKOA and knee pain, with bilateral associations being the strongest for SRKOA and RKOA. This is maintained longitudinally only for

RKOA incidence, indicating that the bilateral association may be driven more by structure than knee pain.

Measure of fat distribution by WC offers no advantage over the measure of BMI in predicting SRKOA, although WC could be substituted when measurement of BMI is difficult.

9.2.5 Cross-sectional interaction

This study examined the interaction of BMI and knee alignment on cross-sectional associations with SRKOA, RKOA and knee pain in this general female population using both 1P and 2P alignment methods.

Although limited by low numbers of knees in certain sub-groups, the results suggest that there was a biological interaction between BMI and knee alignment in cross-sectional associations with SRKOA and RKOA, but not knee pain, indicating that this interaction may be driven by structure.

9.3 Summary of knowledge advancement

Key advances in knowledge from these studies include:

- Using a femoral and tibial shaft length of 10cm \pm 1cm was acceptable to measure AA alignment, but use of shaft lengths shorter than this affected AA angle measurement.
- The cross-sectional alignment study is one of the first to extensively compare 1P versus 2P methods of AA alignment, and to identify clear differences between these two, indicating that each requires method specific alignment categories.
- Although limited by rotated images and by statistical power, the longitudinal alignment study is unique. It provides the longest period (10 years) of alignment follow-up. It uses SRKOA as the main outcome and provides a comparison between 1P and 2P AA alignment methods.
- With obesity a growing problem, a greater BMI and a larger WC is shown here to be associated with increases in SRKOA, RKOA and knee pain prevalence. Predictive associations for Y1 BMI and WC for Y10 RKOA incidence were strong, but weaker for SRKOA incidence and very weak for knee pain incidence, suggesting this association may be driven by structure.

- Although the cross-sectional interaction analysis was limited by statistical power, biological interaction between BMI and knee alignment was suggested so that overweight mal-aligned knees display greater risks of SRKOA and RKO. This is important for targeting timely treatment of these risk factors.

9.4 Implications for research and clinical practice

- Current convention to measure AA alignment uses the maximum femoral or tibial shaft length possible on a radiograph if 10cm is not available. The pilot studies suggests that this might only be acceptable if the shaft length is >9 and <11cm on AP full extension view radiographs. Therefore future studies on AA knee alignment should try to keep within these shaft length boundaries.
- Current alignment literature relies heavily on the methods used in the seminal MA alignment study by Moreland in 1987 (Moreland et al., 1987) that quotes normal alignment values based on 25 healthy males with a mean age of 30. Previous AA alignment studies have applied a valgus offset to their AA angles so that they are comparable to MA alignment, and then have used alignment categories based on Moreland's findings. However, it is questionable whether comparison to MA alignment from 25 young healthy males is appropriate for populations studying AA alignment and osteoarthritis in a variety of age groups across both genders. The cross-sectional alignment study identifies AA alignment categories based on the association with SRKOA outcome. This negates the need to compare to MA alignment and so use of an offset angle would not be required in clinical practice. This study also shows clear differences between results using 1P and 2P AA methods, suggesting that these should not be used inter-changeably in clinical practice, and methodology should be accurately indicated in alignment studies in the literature.
- The near tripling of obese women to 30% over 19 years in this cohort was associated with increased prevalence of SRKOA, RKO and knee pain. Results from this body mass study reinforce the benefits of preventing weight gain in middle-aged women which would reduce the incidence of SRKOA, RKO and knee pain in later life.

- WC as a measure of fat distribution offers no further advantage over the BMI measurement in predicting SRKOA. However, it would be acceptable to substitute BMI with WC measurement where it might be clinically difficult to measure weight or height.
- The suggestion of a biological interaction between BMI and knee alignment, in that overweight mal-aligned knees display greater risks of SRKOA and RKO is clinically important as both obesity and mal-alignment are modifiable risk factors. Targeting these risk factors with possible treatments in a timely manner, preferably before both risk factors appear together in the same knee, is paramount. Weight loss strategies should be provided concurrently with ways of preventing mal-alignment such as bracing, wedged insoles and appropriate use of walking aids to reduce weight bearing loads. More importantly, these results can be used to inform future OA studies to target therapies or prevention strategies on those that are overweight with knee mal-alignment present.

9.5 Limitations

Specific limitations of each study are already highlighted within the discussion section of each study chapter, but further comment here covers limitations that are applicable to the whole thesis.

9.5.1 Cohort design

Due to the original cohort study design, the results of this work are restricted to predominantly Caucasian middle-aged women. Although these women are representative of the general UK female population (Hart et al., 1994, Hart and Spector, 1993a), it would be important to validate findings from this work firstly in another group of similarly aged women, and then of course in men, and in other age groups and ethnicities.

9.5.2 Radiographs

When the Chingford study started in 1989, the standard view for knee SLR was AP, weight bearing in full knee extension. However, due to underestimation of JSN in fully extended view, current practice prefers semi-flexed views (Buckland-Wright et al., 1999). As AP full extension SLRs were taken at years 1,

5, 10 and 15, comparable radiographs were taken at Y20 for consistency. Pain, stiffness and fixed flexion deformities of the knee joint may prevent full extension, and/or possible limb rotation could occur. Both of these could affect alignment measurement, JSN and K&L grading which is a limitation to this work. However, the reported associations are unlikely to be affected as the K&L grade 2 or above criteria to determine positive RKO and SRKO outcomes is based on the presence of a definite osteophyte with possible JSN. The lack of FLRs in this cohort for measurement of MA alignment is a further limitation.

Radiographs from Y1, Y5, Y10 and Y15 visits were plain film SLRs which have subsequently been digitised via a scanner. Y1 and Y5 radiographs were originally graded for K&L (Kellgren and Lawrence, 1957) by the same two observers (TDS and DH), Y10 and Y15 radiographs were read by a single observer (DH). Inter and intra-observer reproducibility was high as reported in section 3.5.3. At Y20, digital images were taken and graded by one observer (KL). As previously reported Y20 intra-observer reproducibility was high (section 3.5.3). Inter-observer reproducibility using Y15 radiographs with original K&L grades from DH showed acceptable agreement, given the different reading conditions. DH was grading plain-film radiographs and KL was grading the same radiographs but digitised, with access to contrast enhancements and zoom via KneeMorf software. This consequently led to increased prevalence of RKO at Y20, although this should not affect the associations reported as it is not thought to be associated with the exposure variables.

9.5.3 Y1 variables

Both knee pain and knee injury variables collected at Y1 by a self-administered questionnaire, were person-level questions in comparison to the knee-specific questions asked at subsequent study clinic visits. If a positive answer was provided to either Y1 question then both right and left knees were considered positive. Therefore there may be an element of over-reporting of knee pain and knee injury at Y1, predominantly affecting results in the body mass study. It is unfortunate that there is no available measure of knee pain severity at any time point. As a result of this limitation it has only been possible to examine associations with incidence of outcomes. It is difficult to define SRKO progression or knee pain progression without a measure of pain severity.

9.5.4 Confounder variables

Possible confounding variables from the literature of similar studies include risk factors such as age, BMI and previous knee injury. These were investigated as part of the statistical analysis for each study. It is possible that there are other potential confounder variables that could be associated with the exposure and outcomes in each study. Whilst other confounding variables such as occupation, physical activity, smoking and alcohol consumption, were available at the Y1 baseline visit, they were not all available at the Y10 visit, the other time baseline time point. For consistency across study visits, confounding variables were limited to those available at both Y1 and Y10 visits.

Multiple imputation, which allows for the uncertainty about missing data by appropriately combining results obtained from several different plausible imputed data sets, may have helped with managing missing values. However, this was not considered appropriate as the limitations with multiple imputation is the assumption that data is missing at random and if the outcome carries information about the missing values of the predictors then this information must be used. Failure to include the outcome and time to this outcome when imputing the missing predictor values would falsely weaken the association. Due to the lack of some key risk factors, for example physical activity, in these analyses it is not possible to deduce causal associations from this work.

9.5.5 Management of bias

Bias is the largest source of uncertainty for epidemiology studies (Silman and Macfarlane, 2002). Bias affects the validity of a study, which may be internal or external. If study results reflect the 'truth' in the study population, the study is internally valid. If the study findings can be generalised to larger populations, the study is externally valid (Silman and Macfarlane, 2002). Potential sources of bias within this thesis are outlined here and have been considered further in each separate study discussion.

Selection bias (internal & external validity)

Selection bias is a systematic error in a study arising from the procedures used to select participants and from factors that may influence study participation (Rothman, 2002). Originally, the entire female population between 45 – 64

years (n=1,353) from a large general practice register of more than 11,000 patients in Chingford were invited to participate in this cohort study. From this available population, 1,003 women agreed to participate. As all females meeting the age criteria on the general practice register had an equal chance to participate in the cohort study then selection bias was not considered present at the outset. This cohort was originally set up to study risk factors for osteoporosis not for OA, but it was not a requirement of the study to be osteoporotic, and so there should be no inherent bias at the start of the study towards an OA population.

Non-response bias (external validity)

Participants lost to follow-up are a major limitation to all long-term cohort studies. There will always be participants who decline to complete a questionnaire or attend an examination, and so it is important to determine if the women who participate are selectively different from those who chose not to. There is a general potential for a healthier cohort to attend the follow-up visits as those less healthy may drop out due to disability, illness or death. At the Y20 visit 49 out of 136 women who were unable physically to attend the clinic, kindly completed the musculoskeletal questionnaire by post, providing a selection of self-reported variables for comparison. Attempts were made in each study to compare the baseline clinical characteristics of included and excluded women. The possibility remains that for whatever reason, participants lost to follow-up, could have had significantly worse outcomes or greater exposures than those included in the analysis. There is no way of knowing the potential effect of this type of bias on any study design. The use of complete-case analysis could add further bias due to the removal of participants not present for intermediate visits.

Subject bias (internal validity)

Study participants reporting for example knee pain, may be subjected to recall bias in that they know they are exposed to the factor of interest (obesity for example) and therefore may be more likely to recall symptoms than those not exposed. To minimize this, participants were asked to report on knee pain experienced within the last month only.

Observer bias (internal validity)

Impartiality of the observer is vital for comparison studies involving interviews, clinical examination and/or measurements. Ideally, the observer should be unaware or blinded to the status of the participant. To limit observer bias in these studies, all knee radiographs were measured for alignment by one observer (the author). This intra-reader agreement was high as examined in section 4.3.2. As the single observer, the author measured alignment for all 4492 radiographs individually, in a random order and blinded to all clinical information, to minimise observer bias. Radiographs were measured in batches of 50 images and all measurements were performed on one radiograph before moving to the next.

9.6 Future research

This thesis has identified several areas for future research that warrant further investigation.

The problem with rotated knee radiographs identified in the longitudinal alignment study is a priority for the next stage of KneeMorf development. To correct this issue automatic identification of rotated images based possibly on patella and/or fibula head placement is proposed, so that in future an appropriate rotation correction factor to the AA alignment measurement maybe applied. With collection of further data on shorter shaft lengths, calculation of a correction factor to apply to shaft lengths less than 10cm should also be possible.

It is important that the differences seen in these studies between 1P and 2P AA alignment methods using KneeMorf are validated in other cohorts with knee SLRs. Validation should be firstly with the similar AP full-extension views, and secondly, in other cohorts using different knee radiograph views such as PA semi-flexed and/or fixed-flexed SLRs. In order to make a definitive choice over use of a 1P or 2P method it may be suggested by the alignment community to validate these methods against MA alignment using FLRs. In addition, condylar and plateau angles have already been measured using KneeMorf, therefore the effect of these on distal femoral alignment and proximal tibial alignment in healthy and OA knees could also be examined.

Radiographs only provide a static representation of knee alignment. There has been no consideration of dynamic loading, for example the KAM, which could give a truer picture of the additional biomechanical loading experienced in an overweight mal-aligned weight bearing knee. This should be examined in future via gait laboratory analyses.

Within the Chingford cohort, hand and patella-femoral radiographs have been taken at alternative time-points to those used in this piece of work. It would therefore be possible to explore further associations with 2D:4D ratio and patella-femoral osteoarthritis.

As mentioned previously, the results from this thesis are applicable to Caucasian middle-aged females from a community population. Follow-up in other females, males, other age groups and ethnicities is required.

9.7 Final summary

- This research has examined knee alignment and body mass as separate risk factors, describing their natural history and their association with prevalence and incidence of SRKOA, RKOA and knee pain, and then examined their cross-sectional interaction on these outcomes in a long-standing female general cohort population. In addition, 1P versus 2P AA knee alignment measurements, and BMI versus WC measurements were compared.
- Differences were found between 1P and 2P measurements indicating method specific alignment categories were required. Based on the centre of the tibial plateau KJC, improvements were identified in the measurement of AA knee alignment, and these require further validation to establish an overall gold standard AA alignment method. Changes in AA alignment over 10 years were small but limited by identification of rotated knees within the population. Improvements to correct this within the KneeMorf software program are required.
- Over 19 years there was a tripling of obese women, which was associated with increased prevalence and incidence of SRKOA, RKOA and knee pain. This reinforces the benefits of preventing weight gain in middle-aged women which would reduce the incidence of SRKOA, RKOA and knee pain in later life. WC measurement offered no further

advantage in predicting SRKOA than BMI, however WC could be substituted if measuring height or weight is difficult.

- Results were suggestive of a cross-sectional biological interaction between BMI and alignment with SRKOA and RKO, but not knee pain, indicating this interaction may be driven by structure. Overweight mal-aligned knees displayed greater risks of SRKOA and RKO, which is particularly useful for informing future studies on which OA population to recruit to clinical trials for example, and is also important for targeting timely treatment of alignment and body mass risk factors.
- Although alignment analyses were limited by identification of rotated images and there was reduced statistical power for longitudinal alignment and cross-sectional interaction analyses, overall results suggest that knee alignment, body mass and their interaction is clinically relevant in KOA which supports the alternative hypothesis and rejects the null hypothesis stated at the outset (section 2.8). This new knowledge should assist in the identification of individuals who would benefit from early intervention and treatment, to reduce the pain, suffering and high future cost of KOA.

Appendices

A1 Phenotypic data list

CHINGFORD STUDY															
		Year													
Parameter		1	2	3	4	5	6	8	9	10	11	13	15		
Non-medical Information															
Date of birth		✓													
Address & phone		✓													
GP		✓													
Hospital number		✓													
Social area number		✓													
Body Measurement															
Weight	current, max, min, age 20	✓	✓	✓	✓	✓	✓	✓	✓	✓					
Height	current, max, loss	✓	✓	✓	✓	✓	✓	✓	✓	✓					
Blood pressure	current measurement	✓	✓	✓	✓	✓	✓	✓	✓	✓					
Waist	"	✓	✓	✓	✓										
Hips	"	✓	✓	✓	✓										
Thighs	"	✓	✓	✓	✓										
Quads	"	✓	✓	✓	✓	✓									
Grip	"	✓	✓	✓	✓										✓
Dolorimeter	"			✓											
Pulse	"				✓										
Sway	"					✓		✓							
Teeth	count, denture count, age					✓									
Spirometry															✓
Cataract & sight test															✓
Get up & Go test															✓
Bone & Joint Data															
DIP, PIP, CMC	duration, stiffness, pain, swelling	✓	✓	✓		✓				✓					✓
Hands	duration, stiffness, pain, current status	✓	✓	✓	✓	✓	✓	✓		✓					✓
Knees	OA, duration, stiffness, pain, swelling, injuries, bending	✓	✓	✓	✓	✓	✓	✓		✓					✓
Hips	BMD, duration, stiffness, pain, current status			✓	✓	✓	✓	✓		✓					✓
Spine	BMD, duration, stiffness, pain, current status, frac grad	✓		✓	✓	✓	✓	✓	✓	✓					✓
Whole body	BMD, body composition							✓		✓					✓
Other joints	OA, general	✓				✓				✓					
Carpal tunnel	symptoms			✓											
Fibromyalgia	"			✓											
Tennis elbow	date					✓									
Frozen shoulder	"					✓									
Other diseases	type			✓											
Hypermobility										✓	✓				
knee radiograph		✓	✓			✓				✓					✓
Hand radiograph		✓	✓	✓							✓				
Spine radiograph		✓			✓				✓						
hip radiograph			✓					✓							
foot radiograph							✓						✓		
Lower limb biomechanics															
MRI Knee														✓	
Chemical Pathology															
Lipids	glucose, cholesterol, triglyceride		✓	✓	✓				✓		✓				
Sex hormones	DHEA, SHBG, oestradiol														
SMAC					✓	✓	✓								
IGG, RF				✓											
Latex															
Serum & Urine		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
DNA					✓				✓	✓		✓		✓	✓

Medical History													
Current medication	type, dose	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Steroids	type, dose, date	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood pressure	date	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Diuretics	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Diabetes	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Thyroid	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cancer	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cardiovascular dis.	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Gastrectomy	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Colecystitis	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ortho operations	"	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fractures	type, date	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Falls	number, type, x-ray						✓	✓	✓	✓	✓	✓	✓
Operations/illnesses	type, date	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Accidents	type, age								✓	✓	✓	✓	✓
Reproductive History													
Menarche	age	✓											
Periods	status, regularity							✓	✓	✓	✓		
Menopause	age	✓	✓	✓	✓								
Hysterectomy	age, indication, ovaries removed	✓	✓	✓	✓			✓	✓	✓	✓		
Births	number, date	✓							✓				
Gynae operations	type	✓	✓										
OCP	age, duration	✓											
HRT	status, age, duration, type	✓	✓	✓	✓			✓	✓	✓	✓		
Family History													
Arthritis	status, joints affected, family occurrence	✓	✓						✓	✓			
Obesity	parental occurrence	✓							✓	✓			
Fractures	family occurrence	✓							✓	✓			
Height loss	"	✓							✓	✓			
General	family details, willingness to join, medical history								✓	✓			
General Health													
SF36, GHQ, HAQ, MRC Back pain													
General well-being	better, same, worse			✓	✓	✓			✓				✓
Sleep	"			✓	✓				✓				✓
Headaches	"			✓	✓				✓				✓
Pain	amount, effect				✓	✓			✓				✓
Dizziness	amount					✓							✓
Emotions	better, same, worse			✓	✓	✓			✓				✓
Decision making	"			✓	✓				✓				✓
Memory	general state									✓			✓
function						✓							✓
Lifestyle													
Hand dominance		✓											
Diet	calcium intake	✓			✓		✓						
Occupation	own, husband	✓	✓				✓						
Activity	ability, type, amount	✓			✓	✓	✓		✓				
Driving	status, age								✓				
Smoking	current status, max, duration	✓							✓	✓	✓		
Alcohol intake	amount	✓											
Footwear	type, duration, injury, bunions									✓			

A2 Substantial amendment application 1



National Patient Safety Agency

National Research Ethics Service

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at <http://eudract.emea.eu.int/document.html#guidance>.

To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available at <http://www.nres.npsa.nhs.uk/applicants/review/after/amendments.htm>.

Details of Chief Investigator:

Name: Alan Hakim
Address: Whipps Cross University Hospital
Whipps Cross Road
Leytonstone
London
E11 1NR
UK
Telephone: 0208 535 6723
Email: alan.hakim@whippsx.nhs.uk
Fax: 0208 535 6504

Full title of study:	Creation Of Chingford Cohort Resource And Maintenance Of Data Collection & Analysis Of A 20-Year Longitudinal Cohort Of Musculo-Skeletal Disease In The General Population: The Chingford Study
Name of main REC:	Redbridge and Waltham Forest Local Research Ethics Committee
REC reference number:	LREC (R&WF) 96
Date study commenced:	July 1989
Protocol reference (if applicable), current version and date:	
Amendment number and date:	2 nd December 2008



National Patient Safety Agency

National Research Ethics Service

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at <http://eudract.emea.eu.int/document.html#guidance>.

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Further guidance is available at <http://www.nres.npsa.nhs.uk/applicants/review/after/amendments.htm>.

Details of Chief Investigator:

Name: Alan Hakim
Address: Whipps Cross University Hospital
Whipps Cross Road
Leytonstone
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E11 1NR
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Email: alan.hakim@whippsx.nhs.uk
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REC reference number:	LREC (R&WF) 96
Date study commenced:	July 1989
Protocol reference (if applicable), current version and date:	
Amendment number and date:	2 nd December 2008

recruit women for repeat investigations at the year 20 visit.

The visit will involve repeat investigations:

- AP weight bearing radiographs of the knee - 2 views
- AP pelvis and hand radiograph
- 20 ml blood & urine collection, DNA collection using a mouth swab to get a small amount of DNA rather than from blood which we have done at previous visits
- Questionnaires on medical history, symptoms, fractures, disability and frailty.
- Measurements including height, weight, blood pressure, grip strength and circumference of waist, hip, thigh and quadriceps.

These measures have been taken before at time points in the study and will be used to measure progression of musculoskeletal diseases and the factors that may be contributing to deterioration or protection of the diseases studied.

The visit will also include some new measurements:

- Hand, hip and knee exam by a physiotherapist as part of a musculo-skeletal assessment to incorporate level of function and associated disability
- Shoulder exam and Shoulder ultrasound by a Doctor
- Sensory Testing and heat pain thresholds

All funds for the radiographs are covered under the Arthritis Research Campaign Grant under the year 20 visit.

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.

List of enclosed documents

Document	Version	Date
Patient Information Sheet	1.0	17.11.2008
Consent Form	1.0	17.11.2008
Year 20 Health Questionnaire	1.0	17.11.2008
Clinic visit sheet	1.0	17.11.2008
Chingford Musculoskeletal Questionnaire	1.0	19.11.2008
Anthropometric Measurements	1.0	17.11.2008

Notice of amendment (non-CTIMP), version 3.1, November 2005

Buccal Smear sample instructions	1.0	17.11.2008
Isohelix brochure including instructions		
Physical examination by physiotherapist	1.0	17.11.2008
Shoulder ultrasound	1.0	17.11.2008
Shoulder constant score technique		
Quantitative Sensory Testing	1.0	17.11.2008
Heat pain protocol	1.0	17.11.2008
Heat pain patient script	1.0	17.11.2008
Smart Tog Study protocol	1.0	17.11.2008
Smart Tog (PIS)	1.0	17.11.2008

Declaration

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.



Signature of Chief Investigator:

Print name: Dr Alan J Hakim

Date of submission: 2.12.2008

A3 Substantial amendment application 2



National Patient Safety Agency

National Research Ethics Service 601-

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at <http://eudract.emea.eu.int/document.html#guidance>.

To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available at <http://www.nres.npsa.nhs.uk/applicants/review/after/amendments.htm>.

Details of Chief Investigator:

Name: Alan Hakim
 Address: Whipps Cross University Hospital
 Whipps Cross Road
 Leytonstone
 London
 E11 1NR
 UK
 Telephone: 0208 535 6723
 Email: alan.hakim@whippsx.nhs.uk
 Fax: 0208 535 6504

Full title of study:	Creation Of Chingford Cohort Resource And Maintenance Of Data Collection & Analysis Of A 20-Year Longitudinal Cohort Of Musculo-Skeletal Disease In The General Population: The Chingford Study
Name of main REC:	Redbridge and Waltham Forest Local Research Ethics Committee
REC reference number:	LREC (R&WF) 96
Date study commenced:	July 1989
Protocol reference (if applicable), current version and date:	
Amendment number and date:	

Type of amendment (indicate all that apply in bold)

(a) Amendment to information previously given on the NRES Application Form

Yes ☒ No

If yes, please refer to relevant sections of the REC application in the "summary of changes" below.

(b) Amendment to the protocol

Yes No ☒

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

Yes ☒ No

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Is this a modified version of an amendment previously notified to the REC and given an unfavourable opinion?

Yes No ☒

Summary of changes

Briefly summarise the main changes proposed in this amendment using language comprehensible to a lay person. Explain the purpose of the changes and their significance for the study. In the case of a modified amendment, highlight the modifications that have been made.

If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

There are 2 parts to this amendment;

1. This is an amendment to the previous application accepted 22/01/2009. Although the current accepted protocol and patient information sheet (version 17/11/08) has information to the patients on a buccal swab DNA collection, we wish to send this collection out as a postal with a newsletter about the 20th year of the study in order to bring the collection forward. The cohort will take 18-24 months to recruit through clinic. Sending out the lengthy PIS, which lists many other investigations to be carried out at the visit, and agreed consent form will contain information about the visit which some patients will not be needing for at least 18 months, and therefore to avoid confusion we wish to send a revised PIS just for the postal collection, explaining the buccal swab collection only, and a separate consent form just for the sample collection.

Type of amendment (indicate all that apply in bold)

(a) Amendment to information previously given on the NRES Application Form

Yes ☒ No

If yes, please refer to relevant sections of the REC application in the "summary of changes" below.

(b) Amendment to the protocol

Yes No ☒

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

Yes ☒ No

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Is this a modified version of an amendment previously notified to the REC and given an unfavourable opinion?

Yes No ☒

Summary of changes

Briefly summarise the main changes proposed in this amendment using language comprehensible to a lay person. Explain the purpose of the changes and their significance for the study. In the case of a modified amendment, highlight the modifications that have been made.

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Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.

List of enclosed documents

<i>Document</i>	<i>Version</i>	<i>Date</i>
Buccal Swab collection PIS	Version 1.0	5/03/2009
Consent form for buccal collection	Version 1.0	5/03/2009
PIS Year 20	Version 2.0	13/03/2009
Consent form with revised PIS version and date	Version 2.0	13/03/2009
Shoulder examination sheet	Version 1.0	26/02/2009
Quantitative Sensory Testing	Version 2.0	13/03/2009
Pain QST DCF Profoma	Version 2.0	13/03/2009
Year 20 Flamingo stand SOP	Version 1.0	17/02/2009
Chingford MSK Questionnaire	Version 2.0	13/03/2009

Declaration

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.



Signature of Chief Investigator:

Dr Alan J Hakim

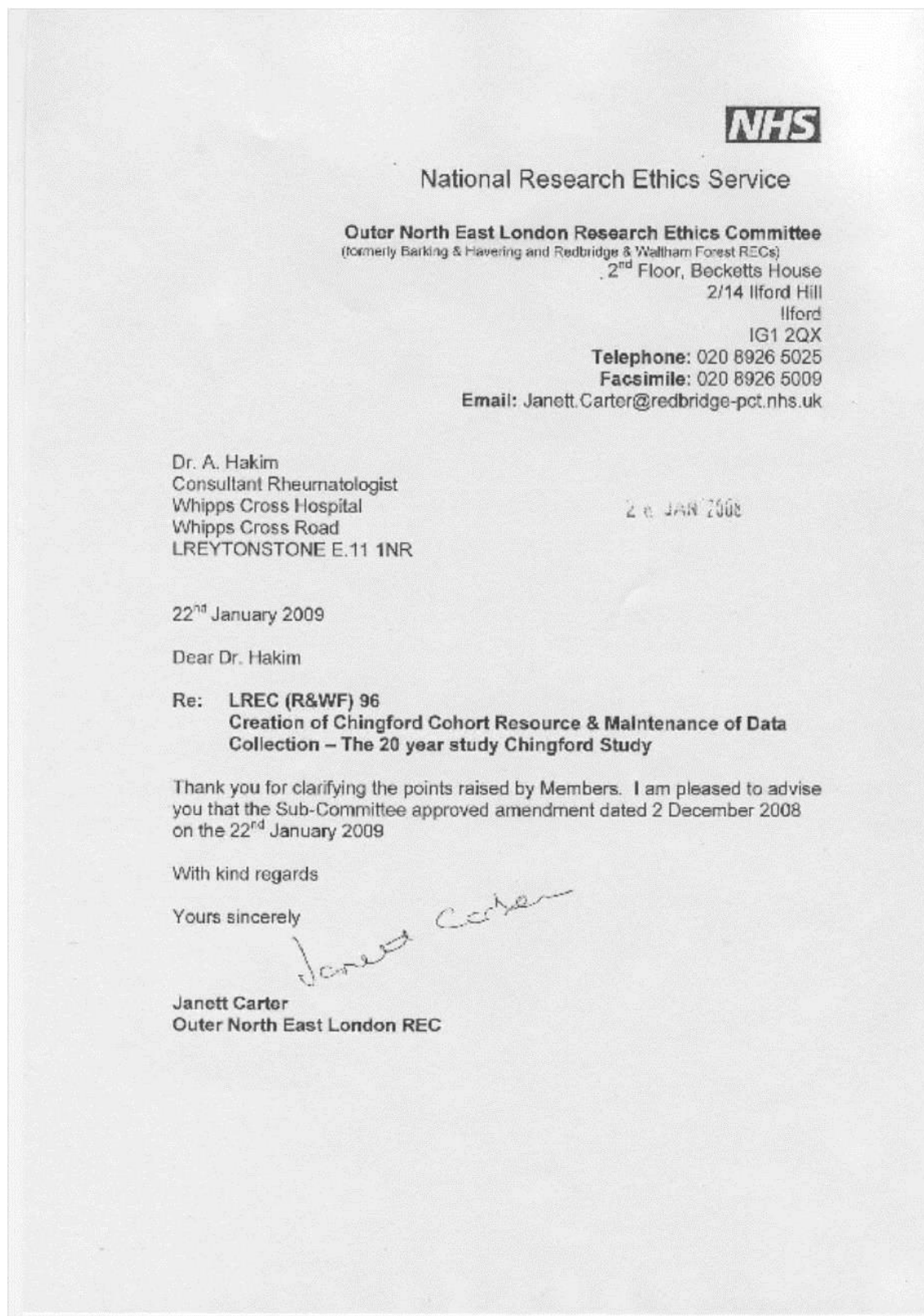
Chair of the Medical Staff Association, Whipps Cross Hospital

Vicechair of the Save Whipps Cross Public Campaign

Print name:

Date of submission:

A4 Ethical approval of substantial amendment 1



A5 Ethical approval of substantial amendment 2



National Research Ethics Service
Outer North East London Research Ethics Committee
2nd Floor, Becketts House
2/14 Ilford Hill
Ilford IG1 2QX
Telephone: 020 8926 5025
Facsimile: 020 8926 5009
Email: Janett.Carter@redbridge-pct.nhs.uk

Dr. Alan Hakim
Consultant Rheumatologist
Whipps Cross Hospital
Leytonstone E.11 1NR

21st May 2009

22 MAY 2009

Dear Dr. Hakim

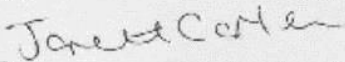
Re: Amendment dated 23 March 2009
Chingford Study
LREC (R&WF) 96

I am pleased to advise you that the Outer North East London Research Ethics Committee approved this amendment on the 14th May 2009

The Committee have asked me to point out that in view of the length of time since this study was first approved, any further amendments will need to be submitted as a new application.


With kind regards

Yours sincerely


Janett Carter
Coordinator

c.c. Maxine Daniels
Liz Clough R&D

A6 R&D approval of substantial amendment 1

Whipps Cross University Hospital 

NHS Trust
 Research & Development Unit

Date: 5th February 2009

Dr Alan Hakim
 Whipps Cross Hospital
 Whipps Cross Road
 Leytonstone
 E11 1NR

Dear Dr Hakim,

Re: Ref 341 Creation of Chingford Cohort Resource And Maintenance of Data Collection and Analysis Of A 20 – Year Longitudinal Cohort Of Musculo-Skeletal Disease In The General Population: The Chingford Study

The Trust Research & Development Committee noted and approved the following amendments for this study:

Amendment		
Patient Information Sheet	Version 1	Date 17/11/08
Patient Consent Form	Version 1	Date 17/11/08

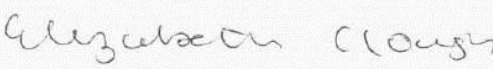
Any further changes to these documents need to be approved by MREC/LREC and the Trust.

It is your responsibility to ensure that all researchers are fully trained in the operation of the approved protocol.

As a researcher with the Trust you are required to adhere to the Research Governance Framework and Trust research monitoring process.

Thank you for your help.

Yours sincerely,






Mr James Green
 Director of Research & Development
 Whipps Cross

Whipps Cross University Hospital
 Whipps Cross Road
 Leytonstone
 London E11 1NR

Tel: 020 8539 5522
 Fax: 020 8558 8115
 www.whippsx.nhs.uk

Direct dial tel:
 Direct dial fax:

Awarded for excellence
to the Orthodontic Department

An Associated University Hospital

Chairman: Stephen Jacobs O.B.E.
 Chief Executive: Dr Lucy Moore

A7 R&D approval of substantial amendment 2

Whipps Cross University Hospital **NHS**

NHS Trust

Whipps Cross University Hospital
Whipps Cross Road
Leytonstone
London E11 1NR

Tel: 020 8539 5522
Fax: 020 8558 8115
www.whippsx.nhs.uk

7/11/2011

Direct dial tel:
Direct dial fax:

FILE NOTE

Chingford 1000 Women study
LREC (R&WF) 96
Whipps Cross R&D REF 341
UKCRN 2453

The Chingford 1000 women study has been running at Whipps Cross for over 20 years and had an amendment approved for the 20 year follow up visits in January 2009 .

Approval was sought for a further second for further changes to the tests to be done simplifying information and altering several tests this gave rise to an amended the PIS and consent.

In addition a separate consent form and PIS was also approved for the Buccal swab test.

These changes were approved by the R&WF REC on 21 May 2009 and by the Whipps Cross R&D committee on 11 May 2009.

The changed documents were:

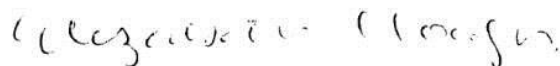
Main study PIS Version 2 :13/03/2009

Main study ICF Version 2 :13/03/2009

Buccal swab test PIS Version 3.0 30/04/2009

Buccal swab test ICF Version 3.0 30/04/2009

A formal letter was not issued for these documents by the Trust but I can confirm that the Trust had no objection to the changes to the study.




Elizabeth Clough
Research & Assurance Manager



Barts and The London
Queen Mary's School of Medicine and Dentistry

Interim Chair: Anne Whitaker
Acting Chief Executive: Cathy Geddes

A8 Whipps Cross University Hospital NHS Trust honorary contract

Whipps Cross University Hospital NHS Trust	
HONORARY CONTRACT Ms Lyndsey Goulston	
1.	You are offered an Honorary Contract as Honorary Research Assistant with Whipps Cross University Hospital NHS Trust ("the Trust").
2.	This appointment will be for a fixed term from 1st December 2008 until 1st December 2009 .
3.	This appointment allows you to undertake the duties outlined in your contract of employment with Southampton NHS Trust on the premises of, and using the facilities of, the Trust.
4.	You will report, on a day to day basis, to Elizabeth Clough, Acting R&D Manager .
5.	In the event of sickness or unavoidable absence you must notify Elizabeth Clough, Acting R&D Manager immediately. Unauthorised absence may be subject to disciplinary action.
6.	You must notify Elizabeth Clough, Acting R&D Manager of any leave that you may be taking, giving reasonable notice where practicable.
7.	You are not required to give, nor are you entitled to receive, any notice in order to terminate this appointment. Where this appointment is terminated by the Trust Southampton NHS Trust , will be notified immediately.
8.	You are required to observe and act in accordance with the Policies and Procedures of the Trust, copies of which are available from your line manager, the Human Resources Department and the Trust's Business Manager.
9.	If you wish to raise concerns or are dissatisfied with any decision of the Trust you should first raise the matter with the Elizabeth Clough, Acting R&D Manager . Should you remain dissatisfied you may take the matter up with management via the Grievance Policy and Procedure as far as a panel of Directors, whose decision is final. Details of the Grievance Policy and Procedure can be obtained from your manager.
10.	If your appointment requires professional or state registration, you must ensure that you remain registered and produce the appropriate evidence on request. Failure to remain registered will result in consensual termination of this appointment without notice.
11.	The Trust manages all research in accordance with the requirements of the Department of Health Research Governance Framework for Health and Social Care (2001). As a contract holder of the Trust you must comply with all reporting requirements, systems and duties of action put in place by the Trust to deliver research governance. If, in the course of your duties, you undertake any form of research you agree to make yourself familiar with the Research Governance Framework and agree to accept the responsibilities associated with your role that are outlined within it.
12.	You and Southampton NHS Trust recognise the Trust's right to benefit from intellectual property arising from work undertaken under this contract in accordance with the Health and Social Care Act 2001. In circumstances where there is potential intellectual property you are required to notify the Trust's Research and Development Department. Specific intellectual property agreements will be negotiated on an individual case by case basis.

13. The Trust accepts liability in respect of your acts and omissions to the degree that those acts and omissions were carried out whilst working on behalf of the Trust and in accordance with your appointment under this contract. You must, however, observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder. You must also act appropriately and responsibly at all times.
14. Whilst undertaking officially sanctioned NHS duties you are covered by the NHS Indemnity Scheme against claims for negligence. In other circumstances (eg when providing services for which you receive a separate fee, or if undertaking research which has not yet received Trust approval) you are not covered by this indemnity. Medical practitioners should ensure that they are covered for any work that does not fall within the scope of the Indemnity Scheme and are therefore strongly advised to subscribe to a medical defence organisation.
15. You must safeguard the confidentiality of all information to which you have access during the course of this appointment. During your appointment with the Trust, or at any time after its termination, you must not disclose to any person or persons, or otherwise make use of, any such information. If you are required to obtain, process or use information, you should do so in a responsible and lawful way. Breaches of confidence in relation to data will result in disciplinary action, not excluding summary dismissal. You are also advised that such breaches may result in civil and/or criminal proceedings.
16. The Trust reserves the right to make amendments to the terms and conditions of your appointment and will give you reasonable notice in the circumstances.

DECLARATION

I confirm that I accept the honorary appointment to the position of **Honorary Research Assistant** and agree to the terms and conditions set out above.

Signature of honorary contract holder: LM Goulston
(Lyndsey Goulston)

Date: 30/3/09

Signed and issued on behalf of Whipps Cross University Hospital NHS Trust by:
(Jackie Essumen)

[Signature]
Date: 05/12/08

Please sign and date and ensure a copy is made available to Liz Clough, R&D Unit, Room 25 Willow Lodge, Whipps Cross University Hospital NHS Trust, Whipps Cross Road, Leytonstone, London E11 1NR.

A9 King's College Hospital London honorary contract

Sir

1st October, 2008

PERSONAL

Ms. L. Goulston,
c/o Ms. Ursula Perks,
Twin Research Unit,
1st Floor, South Wing, Block 4,
St. Thomas' Campus.

Dear Ms. Goulston,

I am pleased to be able to advise you that it has been agreed that you should be accorded the title of Honorary Research Assistant within the Twin Research Unit (St. Thomas' Campus) from 14th July 2008 for a period of two years until 13th July 2010. You will collaborate with the Department in their research work. Whilst working within the Department, you will be accountable to your Head of Department, Professor Tim Spector. This contract does not cover any contact with Guy's and St. Thomas' NHS Foundation Trust patients. An application will have to be made to the Trust if you come into contact with patients or their data.

Please note that whilst on site you are required to be aware and abide by all School, King's College Hospital and Guy's and St. Thomas' Healthcare Codes of Practice as these relate to security and safety. You are also required to comply with the Data Protection Act 1998 which regulates the use of computerised information and should you, in the course of your duties, have access to confidential information you should not disclose it without the express and written permission of your Head of Department. Failure to comply with the above requirements may lead to both the School and yourself being subject to legal action.

In addition, should you, in the course of your School duties and while using School facilities, make any invention or other original work, no arrangements may be made with outside bodies to exploit this invention without the express permission of the School.

Please note that it is a condition of any appointment with the School that Health Clearance is obtained. In connection with this, I have enclosed a staff health questionnaire which should be completed and returned in the envelope provided as soon as possible.

I would be grateful if you could sign and date the duplicate of this letter as acceptance of the above express conditions of this Honorary Research Assistant appointment and return it to me. Please retain the other copy of this letter for your reference.

Entry to the Medical School buildings is restricted by the use of a security system. Please present this contract at the Card Management Centre which is located on the ground floor of Henriette Raphael House (Guy's Campus) immediately next to the reception desk, in order that you can be issued with an ID/swipe card. (Site Services can be contacted on 020-7848-6828 if you need to speak to them regarding retaining your I.D./Swipe Card.) I also enclose a library membership form.

I do hope that you find your time at King's both rewarding and enjoyable.

Yours sincerely,

Susan Rowland (Ms.)
Senior H.R. Administrative Officer

encs.

I, Ms. Lyndsey Goulston, accept the express Conditions of this Honorary Research Assistant appointment as stated in this letter of appointment dated 1st October 2008 and agree to comply with the School's Healthcare Codes of Practice, specifically those which relate to safety, security and confidentiality.

Signed:



Date:

9/4/09

c.c. Professor T. Spector

A10 Participant information sheet



Whipps Cross University Hospital



NHS Trust

Dr AJ Hakim, MA MRCP, Consultant Rheumatologist and Acute Physician
Dr AV Thompson, MB BChir, Associate Specialist
Margaretta Rooney, RGN, Nurse Practitioner

PATIENT INFORMATION SHEET

Creation Of Chingford Cohort Resource And Maintenance Of Data Collection & Analysis Of A 20-Year Longitudinal Cohort Of Musculo-Skeletal Disease In The General Population: The Chingford Study

'You are being invited to come back and take part in the 20th year of this 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. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.'

What is the purpose of the study?

This visit will be part of the ongoing programme of research which you have been part of for 20 years. This visit will provide information on the development of osteoarthritis (OA) in the knee, hip and hand, and by looking at your previous x-rays we can see whether if you have OA it has got worse or stayed the same, or even got better. We will look at what lifestyle factors, such as exercise, diet, medicine, and other diseases may influence OA. We will also look at genes for OA and how much heredity is a factor.

A rheumatology physiotherapist will also be carrying out a short physical examination of your hands, hips and knees so that we are able to compare any physical symptoms you might have with your x-rays that will also be taken as part of this visit. If possible please bring with you a pair of shorts or wear a skirt for the physical examination.

This year we will also be reviewing the prevalence of shoulder disability amongst the entire study group. It is possible that previous shoulder injuries may have passed undetected until now and may be causing you problems with your daily activities. As part of this study we will provide a free, simple and painless ultrasound imaging study of your shoulder, performed by a specialist doctor, that will detect previous shoulder injury and also contribute valuable knowledge about the extent of shoulder dysfunction in our community.

There will also be test to assess each individual's skin sensation. This aims to detect differences in the population in how we experience different symptoms from similar conditions in the shoulder, knee and hip.

We aim to recruit about 600 women who are still in the study. This recruitment will take about 18 months-2 years. The visit will last approximately 1½-2 hours.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. We would like to try and recruit as many of the original cohort as possible. Even if you

think you do not have OA you are still very important to the study, as the information on why you may be protected from disease is just as important to this research.

What will happen to me if I take part?

This visit will be similar to visits you have made in the past for this study. You will have the following investigations;

- *Knee, hip and hand x-ray*
- *Blood sample (a small sample to store frozen blood as we've done on each previous visit)*
- *Urine sample (morning sample which you will bring in to clinic in bottle provided)*
- *Questionnaires*
- *A mouth swab may be used to get a small amount of DNA rather than from blood which we have done at previous visits*
- *Measurements including height, weight, blood pressure, grip strength and circumference of waist, hip, thigh and quadriceps.*
- *Hand, hip and knee exam by a physiotherapist*
- *Shoulder exam, muscle testing and Shoulder ultrasound by a Doctor*
- *Sensory Testing and pain thresholds*

What do I have to do?

Before your visit you can have breakfast or lunch. For your urine sample we need you collect the second sample of the day, so when you first wake up go to the lavatory as normal and collect your second urine of the day in the pot provided. When you come to the unit for your visit please bring your urine sample.

The physiotherapist will carry out an examination of your hands looking for finger nodes (bobbly swellings on the back of the finger joints) – these sometimes relate to arthritis at the hand and other joints.

This will be followed by an examination of your hips to include checks for possible contracture, measuring range of motion, leg length and muscle strength.

The knee examination will include joint palpation, ligament and swelling testing, measuring range of motion, muscle strength and knee alignment.

Finally you will be asked to complete some functional tasks including a short timed walk, timed chair stands and a get up and go test.

As part of your review in our clinic, you will be seen by a doctor who will ask you a short series of questions about your shoulder. There will then be an ultrasound examination of the shoulder. All you will be asked to do during this procedure is to sit comfortably in a chair while a probe is passed over your shoulder joint for several minutes. This is painless, non-invasive and It is the same device used for imaging unborn babies during pregnancy.

You will also have a test to measure muscle strength at the shoulder. This is with a dynamometer which is fixed to a chair or table and you pull against it with the shoulder in different positions. The dynamometer measures the amount of force you are able to pull with. Muscle strength is an important part of shoulder function. We will use the information gathered from patients with and without shoulder problems. We will then be able to tell how much strength is lost due to different shoulder conditions.

The doctor will then conduct a series of sensory testing at the knee, hip and shoulder to determine your ability to detect various stimuli. You will be asked to describe sensations as you feel them. If at any point you experience discomfort this step is ceased immediately.

We will not be doing a bone density scan at this visit as there is now enough information about changes in bone density that take place during the menopause and beyond. As you know, all the past scans have been checked and those of you who need monitoring or treatment have been seen and will be followed up in the clinic.

What are the possible disadvantages and risks of taking part?

Like previous visits, there is no great risk in taking part in this visit. There is a small amount of radiation in the x-rays, but not dissimilar to your exposure from travelling in an aircraft.

When the study is finished we look at the x-rays and will inform you and your GP of any OA you have developed or if your existing OA has worsened. There will be an opportunity for you to speak to staff involved in the study at the study visit if you so wish.

What are the possible benefits of taking part?

The benefits to you from this study will be information given to you on whether you have developed OA, and if you already have OA through the study, has it become more severe or remained the same? The overall benefit from this study will be the identification of factors or genes that may contribute to OA getting more severe and through identifying these we may be able to prevent disability from knee OA in the future.

Since some of the testing we will do involves screening studies, it is possible that we may identify an undiagnosed medical issue. If this is the case we will refer that issue directly to your GP for ongoing management. It might be the case that knowing about such an issue earlier improves the management options that are subsequently available to you.

The more global benefits from this research project will provide unique data on factors that may cause worsening of one of the commonest causes of disability in the community. Few other studies have this amount of information on causes of OA, Osteoporosis and fractures, or have followed patients regularly for so long. Knowledge of preventing progression of these diseases to a severe form will help in planning new treatments and public health services in the future.

Will my taking part in this study be kept confidential?

All information, which is collected, about you during the course of the research will be kept strictly confidential. Any information about you, which leaves the hospital/surgery, will have your name and address removed so that you cannot be recognised from it. The Trust also has strict policies on how we store your data that are adhered to.

What will happen to the results of the research study?

The results from this study will be presented at prestigious national and international meetings. The results will also be written up in high quality medical journals, and may be given press coverage too. At Chingford we hold all papers that have been written about the research from this study, there are about 100 publications in total, which you are welcome to look at.

With the valuable information we collate during this research, our understanding of disease will be enhanced and new treatments can be developed which will benefit all members of our community.

Who is organising and funding the research?

This research is currently funded by the Arthritis Research Campaign. We have been lucky to receive continual funding for this study for 20 years, mostly from the Arthritis Research Campaign (ARC). However we have to continually apply for grants to support our research. Much of the success of our funding has been due to maintaining the women in the study to such high numbers, which is why your previous and future participation is so important to maintain funding.

Who has reviewed the study?

All research methods and studies you participate in have been agreed by Redbridge and Waltham Forest Local Research Ethics Committee.

Contact for Further Information

Thank you for agreeing to take part in this study. Should you require any information about the study please ring Maxine Daniels in the Osteoporosis Unit on 0208 535 6590 (Mon-Fri).

You will be given a copy of the information sheet and a signed consent form to keep.

Osteoporosis Unit, The Silverthorn Centre, 2 Friars Close, Larkshall Road, Chingford E4 6UN e-mail: osteoporosis@whippsx.nhs.uk ; Tel: 020 8535 6590; Fax: 020 8529 9919
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Version 2 :13/03/2009

A11 Participant consent form



Whipps Cross University Hospital
NHS Trust



Dr AJ Hakim, MA MRCP, Consultant Rheumatologist and Acute Physician
Dr AV Thompson, MB BChir, Associate Specialist
Margaretta Rooney, RGN, Nurse Practitioner

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: **Creation Of Chingford Cohort Resource And Maintenance Of Data Collection & Analysis Of A 20-Year Longitudinal Cohort Of Musculo-Skeletal Disease In The General Population: The Chingford Study**

Name of Researcher: **Dr Alan Hakim**

Please initial box

1. I confirm that I have read and understand the information sheet dated ...13 March 2009 for the above study and have had the opportunity to ask questions.

☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

☐

4. I agree to take part in the above study.

☐

Name of Patient

Date

Signature

Name of Person taking consent
(if different from researcher)

Date

Signature

Researcher

Date

Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Osteoporosis Unit, The Silverthorn Centre, 2 Friars Close, Larkshall Road, Chingford E4 6UN
e-mail: osteoporosis@whippsx.nhs.uk; Tel: 020 8535 6590; Fax: 020 8529 9919

Version 2.0: 13/03/09

A12 Participant photograph consent form

Whipps Cross University Hospital **NHS**
NHS Trust

Consent form for filming, recording or photographing patients

Please tick boxes as appropriate.

I _____ (name in block capitals) hereby
give consent for:

☐ myself or my child ☐ (name _____ and age ____)

To be

☐ Photographed ☐ Filmed ☐ Recorded

on _____ (date) for one or more of the purposes listed below (please
mark those applicable):

- research, teaching or training of health care staff ☐
- publication in the Trust's newsletter, promotional literature or website ☐
- broadcast or publication via radio, television or newspapers ☐
- to assist other patients with problems similar to my own / my child's ☐

I understand that I/my child will be recognisable in the photos/ film / recording

Or ☐

I do not wish any recording or image to be used that will identify myself / my child, even when
issued for the purpose agreed above. ☐

I understand that I may withdraw my consent at any stage during filming / recording.

Signed _____

Signed on behalf of Whipps Cross University
Hospital NHS Trust by:

Address _____ Name _____

_____ Dept _____

**FOR PRESS OFFICE: DESCRIPTION OF CLOTHING, LOCATION OF PHOTO,
REASON ETC**



CHINGFORD STUDY

newsletter

January 2010 Number 10

Twenty years on, still going strong - and all down to you!



Reaching the twentieth year of the Chingford Study is a big cause for celebration! So we've put together a special newsletter for you with lots of information that we hope you'll find both interesting and useful.

Party time!

We want to tell you about our plans for our second Chingford Party. For those of you who remember the last party 10 years ago, you'll know what a special event that was. See the back page of this newsletter for details of this latest celebration!

Helping you to help yourself

We have lots of advice for you, from exercises to lifestyle changes, that will help to keep you fit and reduce the risk or effects of osteoarthritis and osteoporosis.

Meet the team

There's news about the people who will be involved in the Study from Year 20 onwards. Maxine Daniels is still setting up clinic appointments and seeing you during your visit but you might like to hear about the other people who are very grateful for your continuing help with this Study.

New tests for Year 20

There's information about your Year 20 tests which are new to us and you.

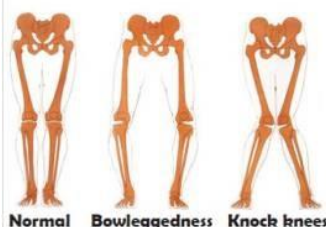
Headline news

We've also got a report on just two of the many research articles that have been published based on the invaluable data that you provide.

New tests for Year 20

As always, we are looking for ways that you can help us increase our knowledge about disease whilst at the same time, keeping tests simple but interesting for you. Here you can read about two new tests for Year 20.

Osteoarthritis (OA) is the most common type of arthritis. It can affect your knees, hips, hands, feet and spine. It is most common among people over the age of 65. Being overweight is one of the strongest risk factors for OA in the knee. Few studies have looked at how body weight throughout life may influence the progress of OA. Studying this potential relationship is important, as obesity is becoming a serious public health problem worldwide.



Knee alignment is thought to play a role in OA. People with knock knees or bow legs can be more at risk of developing OA than people who have straight knees. The usual way of measuring knee alignment is by x-ray, it can also be measured whilst walking in a gait laboratory where movement can be studied electronically using cameras that recognise reflective markers placed on various parts of your legs. As part of your Year 20 clinic visit, we are carrying out repeat knee x-rays, questionnaires and a physical knee examination to look at changes in development or worsening of OA. By collecting information on your body weight and using the body weight data collected on previous visits, we will be able to plot your body weight throughout various time periods in your life, to see what effects this might have on OA.

From this group, a small number of you who have knee pain and knee OA on x-ray, may be asked to visit our new gait lab in Southampton so that we can have a look at your walking patterns. This exciting new technology allows knee alignment whilst moving to be studied very closely and may shed new light on how risk factors such as body weight

and knee alignment, work together in the OA process. By finding out more about the factors that influence the progression of OA we may be able to identify individuals who would benefit from early intervention and treatment, therefore reducing the pain, suffering and the costs of OA in the UK.

.....

A large part of the research we have carried out using the Chingford Study data is in identifying the genes responsible for osteoarthritis. Most of this work was done on the DNA we have collected from you in past clinic visits, where DNA has been collected from blood, but there are much easier ways to collect samples now.

We would like to collect DNA as part Year 20, and you will find accompanying this newsletter, a special kit to collect another DNA sample from you by using a buccal swab (similar to the one below). This is done by simply wiping the swab around your cheek and collecting some cells. The swab is then put back in the tube, labelled and sent back to us. This postal DNA method will also help if we have not been able to collect DNA from you in the past.

Even if you think you do not have OA, your information is just as important to the Study, because we may be able to learn how you are protected from disease. Please do not hesitate to contact Maxine if you would like some more information.



You're headline news!

The Chingford Study data has already proved to be invaluable in helping to make headline news in research journals. We feature just two of the studies here.



References

Richards JB et al. Bone mineral density, osteoporosis, and osteoporotic fractures: a genome-wide association study. *The Lancet* 2008 May 3; 371(9623):1505-12

Valdes AM et al. Genome-wide association scan identifies a prostaglandin-endoperoxide synthase 2 variant involved in risk of knee osteoarthritis. *The American Journal of Human Genetics* 2008; 82:1-10

First large scale gene study of knee osteoarthritis revealed

Scientists, led by a team in the Twin Research Unit, have investigated 500,000 gene markers in women with osteoarthritis (OA) of the knee. The team believe that an examination of these markers will lead to a better understanding of this debilitating condition.

The genome-wide association study appeared in the *American Journal of Human Genetics* 2008. Prof Tim Spector said: "The discovery of these variants highlights the importance of inflammatory pathways in the development of OA and brings us closer to understanding the genetic basis of this common debilitating condition. This gene is hopefully the first of many we will uncover in the next few years."

OA is the most common form of arthritis in elderly people and is the third most common condition causing work disability. Scientists believe that it results from a combination of genetic abnormalities and joint injuries. OA is particularly debilitating in the weight-bearing joints of the knees, and when it reaches a severe stage it can make walking any distance or climbing stairs very difficult.

Genome-wide association studies aim to identify genetic variations among people that can be tied to variations in disease susceptibility, and so find novel genes. In total over 1500 patients and 2600 controls from the US, the UK and the Netherlands were studied. The genetic variant that was found to be involved in all study populations maps close to the gene encoding for the cyclooxygenase-2 enzyme. This enzyme is the target of several anti-inflammatory drugs already used to treat osteoarthritis and other conditions.

Lead author Dr Ana Valdes added: "By finding genes involved in disease risk or

involved in progression we will better understand the molecular pathogenesis of OA and this may open areas for therapeutic intervention. In addition, identifying sets of genetic variants associated with risk of disease or with progression of osteoarthritis, it will be possible to detect individuals at high risk and to better monitor disease progression."

Study identifies genes which increase risk of osteoporosis

Two genetic variants of key biological proteins have been identified which, when present, increase both the risk of osteoporosis and subsequent osteoporotic fractures. Since these variants are present in more than one in five of the population studied, there is a potential role for screening.

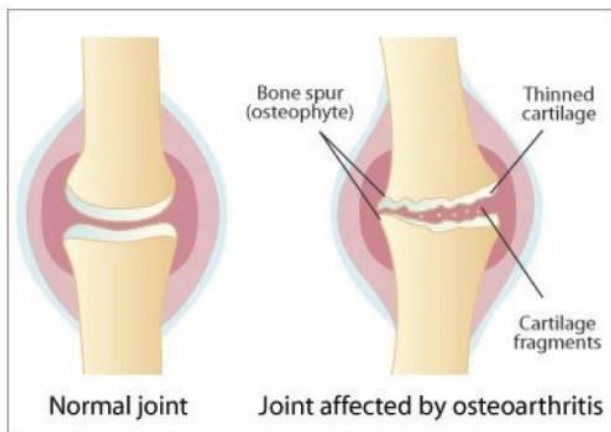
Osteoporosis is defined clinically through the measurement of bone mineral density (BMD), which remains the single best predictor of osteoporotic fractures. BMD is highly heritable.

Prof Tim Spector and colleagues carried out a genome-wide association study, reported in *The Lancet* in 2008, and identified the most promising single nucleotide polymorphisms (SNPs) in their genes, from a total of 314,075 possibilities, which could be responsible for conferring a higher risk of osteoporosis. They identified evidence for an association between BMD and two SNPs - in genes on chromosomes 8 and 11. Both these genes are important targets for bone therapies and drugs are already in development.

The authors say: "These alleles can be measured with near-perfect precision and without bias years before the age at which fractures tend to occur, which could provide ample lead-time for preventive measures."

Look after yourself

While we do all we can to research the causes and symptoms of osteoarthritis and osteoporosis, we can't stop these conditions occurring in you. But there's lots you can do to help yourself, so here we give you our advice!

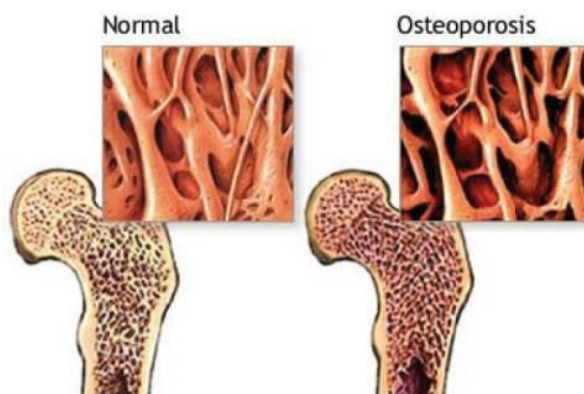


Reduce the risk of osteoarthritis (OA)

- ❑ Avoid over-straining the joints of your hips, knees and hands.
- ❑ Keep your muscles strong to help support your joints (especially if you have early signs of knee OA). Take at least 30 minutes of exercise 5 times a week.
- ❑ Swimming and cycling are great, as is light weights exercise, especially on the thigh muscles, but just regular walking will be beneficial.
- ❑ If you work at a desk, make sure that your chair is at the correct height, and take regular breaks to move around.
- ❑ Maintain a healthy weight. Eat a balanced, healthy diet and keep your weight as close as possible to the ideal for your height and age.

Reduce the risk of osteoporosis (OP)

- ❑ Take regular weight-bearing exercise such as walking or running, keep-fit classes and tennis.
- ❑ Spend time outdoors. Sunlight is great for your bones (but don't get sunburned!).
- ❑ Wear supportive footwear such as trainers.
- ❑ Eat or drink plenty of calcium, for example from milk, cheese, yoghurt, tofu and supplements if needed. A diet rich in oily fish, broccoli and spinach is high in essential vitamin D.
- ❑ Quit smoking and limit alcohol intake.
- ❑ Prevent falls by getting your eyes checked, improving your balance (try Pilates or Tai Chi), and keeping your muscles strong.





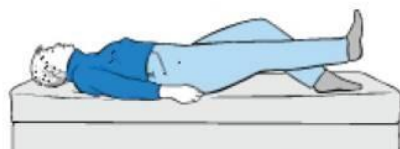
1. Straight-leg raise: sitting

Quadriceps (thigh muscle) exercises

The quadriceps muscle at the front of the thigh becomes weaker in everyone with osteoarthritis of the knee because the normal nerve supply to the muscles is reduced. To overcome this it's essential to exercise the quadriceps muscle as often as possible. It has been proved that strengthening these muscles not only improves your mobility but also reduces pain. The most important thing is to choose exercises that you can do regularly. Try these:

1. Straight-leg raise: sitting

Get into the habit of doing this every time you sit down. Sit back in the chair with a good posture. Straighten and raise one leg, hold it for a slow count to 10, then slowly lower it. Repeat 10 times with each leg. If this is easy, repeat with a weight on the ankle (buy ankle weights from a sports shop or improvise, for example with a tin of peas in a carrier bag wrapped around the ankle).



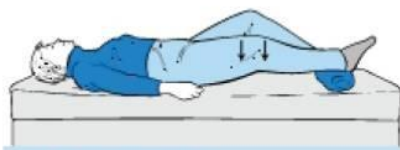
2. Straight-leg raise: lying

2. Straight-leg raise: lying

Get into the habit of doing straight-leg exercises in the morning and at night while lying in bed. With one leg bent at the knee, hold the other leg straight and lift the foot just off the bed. Hold for a slow count of 5 then lower. Repeat with each leg 5 times every morning and evening.

3. Muscle stretch

At least once a day when lying down place a rolled-up towel under one ankle, then bend the other leg at the knee. With the straight leg, use your leg muscles to push the back of the knee firmly towards the bed or the floor. Hold for a slow count of 5. Repeat with each leg 5 times.



3. Muscle stretch

4. Clenching exercises

During the day, whether standing or sitting, get into the habit of clenching and releasing the quadriceps muscle. By constantly stimulating the muscles, they become stronger.

Motion is Lotion!

In healthy adults, moveable joints such as the fingers, wrists, knees, shoulders and elbows like to be moved and when we move them we bathe them in their own natural lotion. This lotion is called synovial fluid and it's produced in the synovial membrane that the joint sits in. It is a little like egg white in nature and when the joint moves it is forced to bathe the structures of the joint. Cartilage that sits at the end of the bones relies heavily on the synovial fluid to rid it of toxins and bathe it in nutrients. Any motion of the joint helps this lotion to bathe the cartilage and keep it healthy.

Meet the team!



Prof Nigel Arden

During the last year there have been some significant changes to the research team in the Chingford 1000 Women Study. Previously Professor Tim Spector and Dr Doyle were lead investigators in the Study. Dr Doyle retired in 2007 and Prof Spector has become more involved in the genetics of diseases in the Department of Twin Research at St Thomas' Hospital. His involvement in this study is focusing on the genetics of osteoarthritis. Dr Alan Hakim, Consultant Rheumatologist and Acute Physician, has now taken over the lead at Whipps Cross for the Study, and Prof Nigel Arden from the University of Oxford is going to be leading many of the new research projects.

Professor Nigel Arden

Prof Arden first worked with Prof Tim Spector in the early 1990s using data from the Chingford Study to look at the association between osteoarthritis (OA) and osteoporosis (OP).

Prof Arden continues with his interest in OA and OP by running research programmes incorporating the epidemiology, developmental origins of health and disease, and clinical trials based partly at the Medical Research Council Epidemiology Resource Centre at the University of Southampton, and partly at the Botnar Research Centre at the University of Oxford. He is also interested in the delivery of care for OA and is currently involved with a number of international working parties producing recommendations and guidelines for the management of this common and important condition. Prof Arden's Chingford research team are very interested at looking at osteoarthritis and pain in the shoulders, hips, hands and knees. They are becoming increasingly involved in the design and management of the Year 20 clinic visit. Prof Arden's research team will explore muscle function and mechanics of the knee as well as examining shoulder function using a state-of-the-art shoulder ultrasound machine and looking at musculoskeletal pain using quantitative sensory testing.

Dr Alex Nicholls

Alex is a visiting doctor from Australia who is presently reading for a research Master's degree in Orthopaedic Surgery

at the University of Oxford. As part of this research he will be involved in the Year 20 clinic visit. His main focus areas include community prevalence of shoulder disability and long term predictors of OA in the hip and knee joints. The size and ongoing duration of the Chingford 1000 Women Study provides a rich source of opportunity for further advancing medical knowledge in these areas.

Dr Michael Daines

Michael is a visiting orthopaedic surgeon from the USA who presently holds the prestigious Girdlestone Fellowship at the Nuffield Department of Orthopaedic Surgery in Oxford. Whilst in the UK he is helping to lead ongoing research at the University of Oxford into a variety of shoulder injuries and conditions. He is particularly interested in the use of ultrasound as a diagnostic tool in the pre-surgical setting so will be involved in the Year 20 clinic, looking at the prevalence of shoulder disability.

Dr Anushka Soni

Anushka is the University of Oxford Clinical Lecturer in Rheumatology and currently combines research with her clinical duties as well as teaching Oxford clinical medical students. Her main research interest is musculoskeletal pain. As part of her current research duties, she performs Quantitative Sensory Testing (QST) for the Year 20 Chingford visit. This is a technique that allows us to test how sensitive people are to pain. Anushka



Dr Alex Nicholls



Dr Anushka Soni



Lyndsey Goulston

will be looking to see if there are any relationships between the sensory thresholds and the related information gained from the x-rays, ultrasound and questionnaire. Musculoskeletal pain is the most common cause of disability worldwide and the Chingford Study provides a unique opportunity to answer a number of questions regarding the nature and mechanisms of this pain. In time this will hopefully help to develop future treatments.

Miss Lyndsey Goulston

Lyndsey is a rheumatology research physiotherapist based at the MRC in Southampton. She qualified as a physiotherapist at the University of Liverpool in 1999, worked as a junior physiotherapist at Hammersmith Hospitals NHS Trust in London until 2003, then worked in Gibraltar as a musculoskeletal physiotherapist for one year. During this time she developed a special interest in rheumatology, in particular OA, and she is now working towards a PhD in OA of the knee.

Miss Kirsten White

Kirsten is a PhD student working towards a degree in Musculoskeletal Science at the University of Oxford. In 2007 she completed her Master's degree at University College London, where her dissertation focused on diagnosing OA in medieval skeletons. She is continuing her interest in the effects of OA on bone by analysing the knee radiographs from the Chingford Study. Kirsten is hoping that her research will provide a better understanding of the relationship between bony changes that occur and the pain that is often associated with knee OA.

Dr Ana Valdes

Ana is a senior lecturer in Department of Twin Research focusing on the genetics of ageing and OA. She trained in population genetics and genetic epidemiology at the University of California Berkeley before joining the Twin Research Unit in 2004. She has been using the valuable X-ray and DNA

data collected in the Chingford Study to understand how genetic factors influence risk of knee and hip OA. Recently, she used the Chingford data to discover that genetic variants of an enzyme involved in inflammation, COX-2, increase risk of osteoarthritis of the knee. Currently she is leading a study to determine combinations of genetic variants that can be used to predict a person's risk for OA. Dr Valdes says: "I am extremely grateful to all the women who have so faithfully participated in this study for twenty years now. It is thanks to your time and energy that we can uncover the risk factors associated with ageing and disease".

Dr Feng Zhang

Feng has been a genetic epidemiologist in the Department of Twin Research for the past three years. She trained in clinical medicine in China and finished her MSc and PhD on genetic epidemiology in the UK. Since joining the Department in 2005, she has used Chingford data to search for risk factors from both genetics and the environment for OA, OP and fractures. The results have been presented at scientific meetings and international congresses. She says: "Thank you to all participants of the Chingford Study. It is your continuous support and participation over the years that make our research possible!"

Dr Guangju Zhai

Guangju is an active medical researcher focusing on musculoskeletal diseases. He trained in medicine and epidemiology in China and Australia and joined the Department of Twin Research in 2005 as a senior genetic epidemiologist. He has been using Chingford Study data to answer important questions related to our health, for example, recently, he examined the natural history of bone loss in postmenopausal women. He confirmed the protective role of HRT, increasing weight, and lean mass in long-term bone loss. He says: "Thank you to all involved in the Study. Your support and every contribution you make has a vital impact on our research".



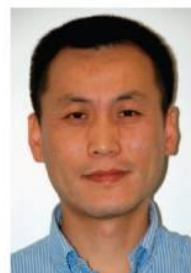
Kirsten White



Dr Ana Valdes



Dr Feng Zhang



Dr Guangju Zhai

Party time again!



Most of you will fondly recall the party celebrating the 10th Anniversary of the Study's inception (pictured below). Well now we are happy to announce another party commemorating the achievement of the Study reaching its 20th year - thanks to the support of all our wonderful women!

We are therefore delighted to invite you to celebrate the 20th Anniversary of the Study at the Sir James Hawkey Hall in Woodford Green, Essex on Thursday 24th June 2010. This will certainly be an afternoon to remember, with an extra special tea, gifts, raffle and speakers, plus a surprise celebrity guest to be announced very soon! All the Chingford 1000 Women are welcome, even if you have not participated in the Year 20 visit. Invitations will be sent out in the New Year.

We are extremely grateful for all the support we have received in the past and any additional funding towards the venue, catering, etc., would be much appreciated. We welcome support from other organisations such as Rotary, sports and friendship clubs, etc. Any other donations such as raffle prizes from businesses and individuals will also be gratefully received and will help us to make this the greatest party ever!



Famous women

The following famous women were born during the same years as our Chingford 1000 Women.

1924: Gloria Vanderbilt, US designer & poet
 1925: Margaret Thatcher, first woman Prime Minister
 1926: Queen Elizabeth II
 1927: Honor Blackman, actress
 1928: Shirley Temple, actress & diplomat
 1929: Patricia Routledge, actress
 1930: Ruth Rendell, novelist
 1931: Claire Rayner, agony aunt & journalist
 1932: Elizabeth Taylor, actress
 1933: Sheila Hancock, actress
 1934: Mary Quant, fashion designer
 1935: Julie Andrews, actress & singer
 1936: Glenda Jackson, actress & MP
 1937: Jackie Collins, author
 1938: Tina Turner, singer
 1939: Dame Mary Peters, pentathlete
 1940: Esther Rantzen, journalist & TV presenter
 1941: Delia Smith, author of cookery books & TV presenter
 1942: Barbra Streisand, singer & actress
 1943: Billie Jean King, Tennis Player
 1944: Janet Street-Porter, journalist
 1945: Virginia Wade, tennis player

Please keep in touch

If you can't now attend clinics, we would be grateful if you could still fill in postal questionnaires and remain in the Study. If you need to contact us please ring Maxine Daniels on 0208 535 6590. Don't forget to let us know your contact details if you move too!

A14A Y20 party poster - in the beginning



In the beginning....

The Chingford 1,000 Women Study was established in 1989 as a joint project between Professor Tim Spector and Dr David Doyle.



The aim of the study:

The object was to invite 1,000 women to take part in a study, throughout which they would all be screened for bone and joint disease and monitored for osteoarthritis & osteoporosis over an extended period of time.

The aim being to discover:

- a) How many within the group might be or become affected.
- b) Establish any risk factors.
- c) Monitor any progression of the disease.
- d) Identify any specific high risk sector within the group.
- e) To discover a means of preventing the disease.
- f) To discover a cure for the disease.

The search for volunteers:

Using the age/sex register of the Handsworth Avenue General Practice in Highams Park, Chingford, 1,353 women aged 45 - 64 years of age were identified as possible volunteers.

Why only 1,000?:

Of the 1,353 women initially identified, it was subsequently discovered that:

66 had moved away from the Chingford area.

278 declined participation.

.... and sadly, 6 had passed away.

Finally, 1003 Chingford Women were recruited to the study.

Who are you?:

It may be of interest to you to learn that 98% of Chingford Women recruited are caucasian and predominantly of a middle class social background.

Acknowledgements

We would like to extend our acknowledgements to the following:
The 1003 Chingford Women for participating.
The rest of the Chingford Research team.
Arthritis Research UK for funding contributions.



Whipps Cross University Hospital **NHS**
NHS Trust



A14B Y20 party poster - meet the team



Meet the team



Prof. Tim Spector:
Based at the Department
of Twin Research
at Kings College, London.



Dr. Alan Hakim:
Consultant Rheumatologist
and Acute Physician, based
at Whips Cross Hospital
and Silverthorn Centre.



Prof. Nigel Arden:
Based at the Botnar
Research Centre, University
of Oxford and University
of Southampton.



Dr. Deborah Hart:
Research Epidemiologist,
based at Department
of Twin Research,
King's College, London.



Dr. Vicky Thompson:
Associate Specialist,
based at the
Silverthorn Centre.



Dr. Anushka Soni:
Rheumatologist,
based at
University of Oxford.



Miss Hannah Oag:
Orthopaedic Surgeon,
based at
University of Oxford.



Lindsey Goulston:
Rheumatology Research
Physiotherapist based at
University of Southampton.



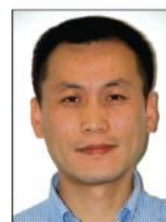
Mr. Nick Bottomley:
Orthopaedic Surgeon,
based at
University of Oxford.



Dr. Ana Valdes:
Epidemiologist,
based at Department
of Twin Research,
King's College, London.



Dr. Feng Zhang:
Epidemiologist, based
at Department
of Twin Research,
King's College, London.



Dr. Guangju Zhai:
Epidemiologist, based
at Department
of Twin Research,
King's College, London.



Gabriela Surdulescu:
Laboratory Manager,
based at Department
of Twin Research,
King's College, London.



Kirsten White:
PHD Student,
based at
University of Oxford.



Mei Lau:
Data Manager,
based at
University of Oxford.



Maxine Daniels:
Study Co-ordinator, based
at the Silverthorn Centre and
Department of Twin Research,
King's College, London.



Tracey Chapman:
Administrative Assistant,
based at the
Silverthorn Centre.



Eileen Salman:
Phlebotomist,
based at the
Silverthorn Centre

Acknowledgements

We would like to extend our
acknowledgements to the following:
The 1003 Chingford Women for participating.
The rest of the Chingford Research team.
Arthritis Research UK for funding contributions
and June Andrew for being our model
in the above pictures.



A14C Y20 party poster – taking measurements



Year 20 visit: taking measurements and blood pressure

By Maxine Daniels:
Study Co-ordinator
Silverthorn Centre.

You will be seen by Maxine, the study co-ordinator, who will carry out a grip test and take a variety of measurements:



Grip Test:
Measured in kilograms, the average grip strength is 15 kg (approximately 33 lbs).



Height:
The average height measures 158.2 cm (5ft, 2 1/4 inches).



Weight:
The average weight measures 70.01 kg (approximately 11 stone).



Waist, hips, thighs and quad muscle measurements:
The average waist measures 86.9cm (34 1/4 inches)
The average hips measure 104.9cm (41 1/4 inches)
The average thigh measures 54.6cm (21 1/2 inches)
The average quad muscle measures 44.4cm (17 1/2 inches).

Eileen Salman, phlebotomist:
Taking samples of serum and plasma, also processing urine samples.



Taking blood pressure:
is another stage in the visit.



By checking your body shape, we can determine whether you are an 'apple' or a 'pear'.

If you carry excess weight around your abdomen, this means you are an 'apple' shape.

If you carry excess weight around your bottom and thighs, this means you are a 'pear' shape.

Of the 2 shapes, 'pears' run less risk of serious conditions such as heart disease, raised blood pressure, type 2 diabetes and some forms of cancer.

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Whipps Cross University Hospital
NHS Trust



A14D Y20 party poster - joint examinations



Year 20 visit: looking at your joints

By Lyndsey Goulston

Rheumatology research physiotherapist
University of Southampton

What does this station of the year 20 visit involve?

- Being seen by Lyndsey the research physiotherapist
- Lyndsey looks at your knees, hips and hands and carries out some simple tests of function

Looking at your knee joints

- This involves checking your knee movement, muscle strength, ligaments, identifying any swelling or painful areas



Looking at your hip joints

- This involves checking your hip movement & measuring the length of your legs



Looking at your hands

- This involves looking for any bumps on your fingers and thumbs



Looking at your function

- Chair rises – to see how strong your legs are
- One leg stand – to check your balance
- Get up & go test and timed walk – to check your mobility



A big thank you to all of you that have attended the year 20 visit so far

If we haven't seen you yet then please do come along – we would love to see you!

Acknowledgements

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A14E Y20 party poster – studying body weight

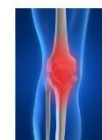


Studying your body weight

By Lyndsey Goulston
Rheumatology research physiotherapist
University of Southampton



- In the UK there are over 6 million people with knee pain
- There is a rising obesity epidemic
- We have looked at how your weight over time may influence your knee pain

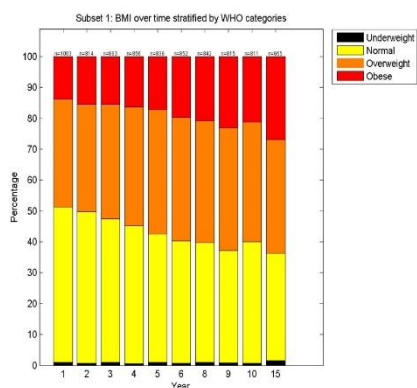
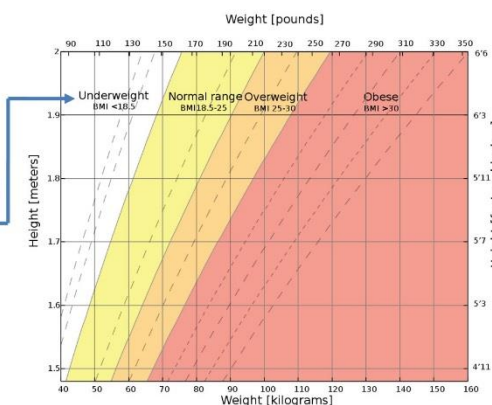


Height & weight measurements



- Your height & weight have been measured at **10** time points
- This is valuable information to see what has happened over time
- We have used your height & weight (from years 1, 5, 10, 15) and compared it to your knee pain at year 15

- Using your height & weight measurements we are able to calculate your **Body Mass Index (BMI)**
- BMI is a measure of body fat calculated by: $\frac{\text{mass (kg)}}{(\text{height (m)})^2}$
- You can check this chart to work out your current BMI and see which BMI category you are



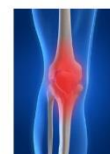
- This chart shows all of your BMI measurements over 15 years grouped by the BMI categories shown on the graph above
- Its interesting to see that some of you are gradually getting heavier!

We looked at the change in your BMI over the 15 years and found:

- **49%** of you remained **stable** within the same BMI category
- **34%** of you **increased** by at least one BMI category
- **12%** of you **fluctuated** with a rise and a fall of at least one BMI category
- **5%** of you **decreased** by at least one BMI category

What does this mean for your knee pain?

- Your BMI at the beginning and after 15 years is linked to your knee pain at year 15, so the **heavier** you are the **more** likely you are to have **knee pain**
- The heavier you are the more likely you are to have pain in **both knees** rather than just one knee
- The change in BMI category is **not** linked to your knee pain



Acknowledgements

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A14F Y20 party poster – studying knee alignment



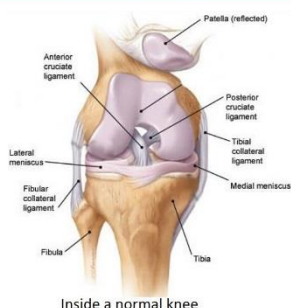
Studying your knee alignment

By Lyndsey Goulston

Rheumatology research physiotherapist
University of Southampton

What is knee alignment?

- Knee alignment refers to how straight or not your knees are when you are standing

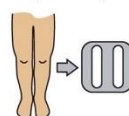


Inside a normal knee

Types of knee alignment

- Knee alignment can be either:

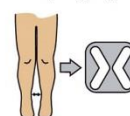
normal
(neutral)



bow leg
(varus)



knock knee
(valgus)



Why is knee alignment important?

- Knee alignment is thought to play a role in osteoarthritis (OA)
- People with knock knees or bow legs are more at risk of developing OA than people who have straight knees
- By finding out more about the factors that influence OA we are able to identify people who would benefit from early intervention and treatment, therefore reducing the pain, suffering and the high costs of OA in the UK



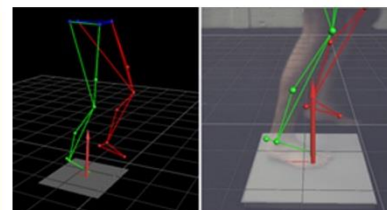
Inside an OA knee



How is knee alignment measured?

- Usually by x-ray
- We will be looking at all your knee x-rays that have been taken over the years to see if your knee alignment has changed
- Knee alignment can also be measured electronically whilst walking in a gait laboratory using cameras that recognise reflective markers placed on various parts of your legs

- As part of your year 20 visit, a small number of you with knee pain and knee OA on x-ray, may be asked to visit our gait lab so we can look at your walking patterns
- This technology allows knee alignment whilst walking to be studied very closely and may shed new light on how factors such as body weight and knee alignment, work together in the OA process



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A15 Height & weight SOP

Chingford Women Study Year 20 visit

Height measurement SOP

- Stand the participant to be measured barefoot against the wall-mounted stadiometer (Leicester Height Measure, SECA).
- Check that the legs are straight and position the buttocks and shoulder blades touching the uprights. The shoulders should be relaxed and arms placed to the side. Remove headgear where appropriate. Ensure patient is looking straight ahead and not down.
- Position the head in the Frankfurt Plane (an imaginary horizontal line running between the ear hole and the lower border of the eye), then with both hands lower the measuring arm firmly onto the participant's head.
- Read off the height to the nearest 0.1 centimetre at the red arrow pointing to the metric scale. Record height in centimetres on the data collection form.

Weight measurement SOP

- Remove outer and any heavy clothing.
- Remove shoes.
- Check seated scales are functioning correctly and registered at '0'.
- Sit the participant down on the chair scales ensure the participant is sitting straight.
- Record weight in kilos to the nearest 0.1 kg on the data collection form.

A16 Anthropometry DCF

Chingford Women Study (CWS)
Year 20 visit

ANTHROPOMETRY DATA SHEET

Name _____

Study number

--	--	--	--

Blood pressure (mm/Hg)

			/			
--	--	--	---	--	--	--

Height (cm)

			•	
--	--	--	---	--

Weight (kg)

			•	
--	--	--	---	--

Waist circumference (cm)

			•	
--	--	--	---	--

Hip circumference (cm)

			•	
--	--	--	---	--

Thigh circumference (cm) *(R leg)*

			•	
--	--	--	---	--

Quads circumference (cm) *(R leg)*

			•	
--	--	--	---	--

Grip strength (kg)*3 X on dominant hand (record to nearest 1kg)*Dominant hand **R** **L**

--	--	--

--	--	--

--	--	--

Observer _____ Date _____

A17 Circumferences SOP

Chingford Women Study Year 20 visit

Circumferences SOP

Measurements for body fat circumference with a standard tape measure in a standing position:

Waist = A

Measured to nearest centimetre at the narrowest point between iliac crest and lower edge of ribs.

Hips = B

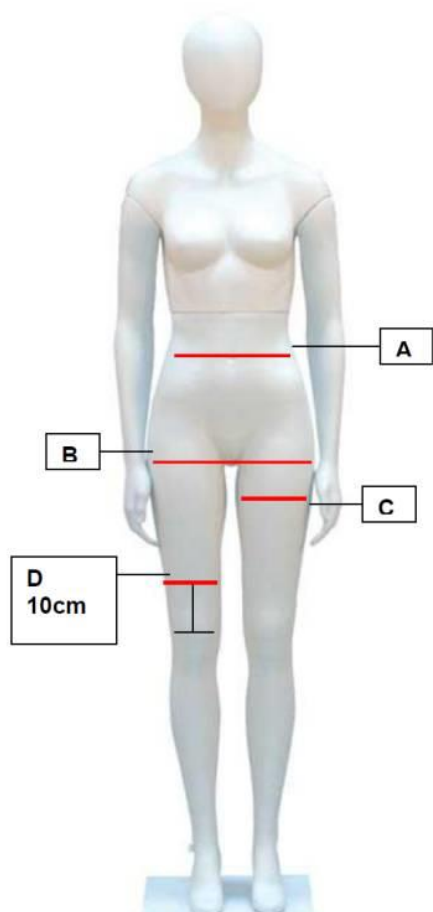
Measured to nearest centimetre at widest point below iliac crest.

Thigh = C

Measured to the nearest centimetre on the right leg directly below the gluteal fold.

Quadriceps = D

Measured to the nearest centimetre around the right quad at 10cm above proximal patella.

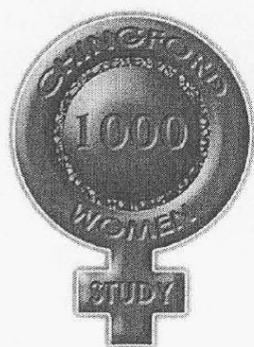


Circumferences SOP, version 2.0, 19/02/09

A18 Musculoskeletal questionnaire

The Chingford Cohort Year 20 follow up visit

Oxford Musculoskeletal Questionnaire



Name _____

Study No.

Date / / .

The Chingford Cohort-Oxford Musculoskeletal Questionnaire

Thank you for agreeing to complete this questionnaire. When you have finished one of our research team will review it with you. If you have any queries please do not hesitate to discuss it with them.

1. Have you ever been told you have osteoarthritis (degeneration / wear & tear) of your knees/hips by a doctor? *(tick all that apply)*

☐ Right knee
☐ Left knee
☐ Right hip
☐ Left hip

2. Do you have any other type of arthritis?

☐ Yes, and it has been diagnosed by a health professional
☐ Yes, but it has *not* been diagnosed by a health professional
☐ No *(if no skip to Q4)*

3. What type of arthritis do you have? *(tick all that apply)*

☐ Rheumatoid
☐ Gout / pseudogout
☐ Psoriatic
☐ Don't know

☐ Other *(eg sero-negative, Lupus)*

4. Please indicate current medications that you take for your joints:

Paracetamol	<input type="checkbox"/> No	<input type="checkbox"/> Yes, taken regularly	<input type="checkbox"/> Yes, taken as needed
Glucosamine sulphate	<input type="checkbox"/> No	<input type="checkbox"/> Yes, taken regularly	<input type="checkbox"/> Yes, taken as needed
Chondroitin sulphate	<input type="checkbox"/> No	<input type="checkbox"/> Yes, taken regularly	<input type="checkbox"/> Yes, taken as needed
Cod liver oil	<input type="checkbox"/> No	<input type="checkbox"/> Yes, taken regularly	<input type="checkbox"/> Yes, taken as needed
Vitamin D supplements	<input type="checkbox"/> No	<input type="checkbox"/> Yes, taken regularly	<input type="checkbox"/> Yes, taken as needed
Anti-inflammatories <i>eg. ibuprofen</i>	<input type="checkbox"/> No	<input type="checkbox"/> Yes, taken regularly	<input type="checkbox"/> Yes, taken as needed
Other <i>(please state)</i> : 			

5. How often do you:

a. Walk outdoors

☐ Never
☐ 1-2 days a week
☐ 3-4 days a week
☐ 5-7 days a week

b. Play light sports? *eg. golf, bowling*

☐ Never
☐ 1-2 days a week
☐ 3-4 days a week
☐ 5-7 days a week

- c. Play moderate sports? *eg. swimming, tennis, badminton*
☐ Never ☐ 1-2 days a week ☐ 3-4 days a week ☐ 5-7 days a week
- d. Play strenuous sports? *eg. jogging, cycling, aerobics, squash*
☐ Never ☐ 1-2 days a week ☐ 3-4 days a week ☐ 5-7 days a week
- e. Do muscle strengthening exercises? *eg. using gym equipment*
☐ Never ☐ 1-2 days a week ☐ 3-4 days a week ☐ 5-7 days a week
6. If you do perform these activities, on average for how long would you do it?
- a. Walk outdoors for?
☐ Less than 1 hour ☐ 1-2 hours ☐ 2-4 hours ☐ +4 hours
- b. Play light sports for?
☐ Less than 1 hour ☐ 1-2 hours ☐ 2-4 hours ☐ +4 hours
- c. Play moderate sports for?
☐ Less than 1 hour ☐ 1-2 hours ☐ 2-4 hours ☐ +4 hours
- d. Play strenuous sports for?
☐ Less than 1 hour ☐ 1-2 hours ☐ 2-4 hours ☐ +4 hours
- e. Do muscle strengthening exercise for?
☐ Less than 1 hour ☐ 1-2 hours ☐ 2-4 hours ☐ +4 hours
7. How many hours per week do you do:
- a. Any work that involves standing or walking? ☐ No ☐ Yes hours
- b. Light housework? *eg. dust, clean kitchen surfaces* ☐ No ☐ Yes hours
- c. Heavy housework? *eg. hoover, wash floors* ☐ No ☐ Yes hours
- d. Home repairs or DIY? ☐ No ☐ Yes hours
- e. Lawn work? *eg. mow grass, rake leaves* ☐ No ☐ Yes hours
- f. General gardening? *eg. planting, weeding* ☐ No ☐ Yes hours
- g. Care for others? *eg. grandchildren, parent, spouse* ☐ No ☐ Yes hours
8. Have you fallen in the last 12 months? ☐ Yes ☐ No (*if no skip to Q13*)
9. If yes, how many times have you fallen in the last 12 months?

10. Did you see a doctor after a fall? ☐ No ☐ Yes
11. Did you break/fracture anything after the fall? ☐ No ☐ Yes
12. If yes, what type of break/fracture was it?
And when was it?
13. Have you ever worn shoes with heels 2 inches or higher?
☐ Yes ☐ No (if no skip to Q16)
14. On average:
- a. What heel height did you wear at what age?
50-60yrs inch 60-70yrs inch 70+yrs inch
- b. How many hours per week did you wear them?
At work/daytime 50-60yrs hrs 60-70yrs hrs 70+yrs hrs
Socially/evening 50-60yrs hrs 60-70yrs hrs 70+yrs hrs
- c. What type of heel did you wear at what age? (*F=fashion, B=block, P=platform, S=stiletto*)
50-60yrs 60-70yrs 70+yrs
15. Have you ever suffered any ankle sprains or other injuries through wearing high heels, which needed resting for more than 24 hours?
☐ No ☐ Yes
16. Do you have bunions?
☐ No ☐ Yes
17. The following questions are designed to help us know how you feel. Read each statement below and tick which one comes closest to how you have been feeling in the past week. Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.
- a. I feel tense or 'wound up'
☐ Most of the time ☐ A lot of the time ☐ From time to time ☐ Not at all
- b. I still enjoy the things I used to enjoy
☐ Definitely as much ☐ Not quite so much ☐ Only a little ☐ Hardly at all

- c. I get a sort of frightened feeling as if something awful is about to happen
☐ Very definitely and quite badly ☐ Yes, but not too badly
☐ A little, but it doesn't worry me ☐ Not at all
- d. I can laugh and see the funny side of things
☐ As much as I always could ☐ Not quite so much
☐ Definitely not so ☐ Not at all
- e. Worrying thoughts go through my mind
☐ A great deal of the time ☐ A lot of the time ☐ Not too often ☐ Very little
- f. I feel cheerful
☐ Never ☐ Not often ☐ Sometimes ☐ Most of the time
- g. I can sit at ease and feel relaxed
☐ Definitely ☐ Usually ☐ Not often ☐ Not at all
- h. I feel as if I am slowed down
☐ Nearly all the time ☐ Very often ☐ Sometimes ☐ Not at all
- i. I get a sort of frightened feeling like 'butterflies' in the stomach
☐ Not at all ☐ Occasionally ☐ Quite often ☐ Very often
- j. I have lost interest in my appearance
☐ Definitely ☐ I don't take as much care as I should
☐ I may not take quite as much care ☐ I take just as much care as ever
- k. I feel restless as if I have to be on the move
☐ Very much indeed ☐ Quite a lot ☐ Not very much ☐ Not at all
- l. I look forward with enjoyment to things
☐ As much as I ever did ☐ Rather less than I used to
☐ Definitely less than I used to ☐ Hardly at all
- m. I get sudden feelings of panic
☐ Very often indeed ☐ Quite often ☐ Not very often ☐ Not at all
- n. I can enjoy a good book or radio or television programme
☐ Often ☐ Sometimes ☐ Not often ☐ Very seldom

18. The following questions ask for **your views about your health**, how you feel and how well you are able to do your usual activities.

If you are unsure about how to answer any questions please tick the best answer you can.

Do not spend too much time in answering, as your immediate answer is likely to be the most accurate.

- a. In general, would you say your health is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

- b. Compared to one year ago, how would you rate your health in general now?

☐ Much better now than one year ago ☐ Somewhat better now than one year ago
☐ About the same as one year ago ☐ Somewhat worse now than one year ago
☐ Much worse now than one year ago

19. The following questions are about activities you might do **during a typical day**. Does your health now limit you in your activities? If so, how much?

- a. Vigorous activities *eg. running, lifting heavy object, strenuous sports?*

☐ Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all

- b. Moderate activities *eg. moving a table, hoovering, bowling, playing golf?*

☐ Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all

- c. Lifting or carrying groceries?

☐ Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all

- d. Climbing one flight of stairs?

☐ Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all

- e. Climbing several flights of stairs?

☐ Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all

- f. Bending, kneeling or stooping?

☐ Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all

- g. Walking 100 yards?

☐ Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all

- h. Walking half a mile?

☐ Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all

- i. Walking more than a mile?

☐ Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all

j. Bathing or dressing yourself?

☐ Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all

20.

During the past four weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

a. Cut down on the amount of time you spent on work or other activities?

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

b. Accomplished less than you would like?

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

c. Were limited in the kind of work or other activities?

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

d. Had difficulty performing the work of other activities ie. it took extra effort?

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

21. **During the past four weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

a. Cut down on the amount of time you spent on work or other activities?

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

b. Accomplished less than you would like?

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

c. Did work or other activities less carefully than usual?

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

22. **During the past four weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?
- ☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely
23. How much bodily pain have you had during the past four weeks?
- ☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe
24. **During the past four weeks**, how much did pain interfere with your normal work? (including work both outside the home and housework)
- ☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely
25. The following questions are about how you feel and how things have been with you **during the past 4 weeks**.
- a. Did you feel full of life?
- ☐ All the time ☐ Most of the time ☐ A good bit of the time
☐ Some of the time ☐ A little of the time ☐ None of the time
- b. Have you been very nervous?
- ☐ All the time ☐ Most of the time ☐ A good bit of the time
☐ Some of the time ☐ A little of the time ☐ None of the time
- c. Have you felt so down in the dumps that nothing could cheer you up?
- ☐ All the time ☐ Most of the time ☐ A good bit of the time
☐ Some of the time ☐ A little of the time ☐ None of the time
- d. Have you felt calm and peaceful?
- ☐ All the time ☐ Most of the time ☐ A good bit of the time
☐ Some of the time ☐ A little of the time ☐ None of the time
- e. Did you have a lot of energy?
- ☐ All the time ☐ Most of the time ☐ A good bit of the time
☐ Some of the time ☐ A little of the time ☐ None of the time
- f. Have you felt downhearted and depressed?
- ☐ All the time ☐ Most of the time ☐ A good bit of the time
☐ Some of the time ☐ A little of the time ☐ None of the time
- g. Did you feel worn out?
- ☐ All the time ☐ Most of the time ☐ A good bit of the time
☐ Some of the time ☐ A little of the time ☐ None of the time

h. Have you been happy?

- | | | |
|---|---|---|
| <input type="checkbox"/> All the time | <input type="checkbox"/> Most of the time | <input type="checkbox"/> A good bit of the time |
| <input type="checkbox"/> Some of the time | <input type="checkbox"/> A little of the time | <input type="checkbox"/> None of the time |

i. Did you feel tired?

- | | | |
|---|---|---|
| <input type="checkbox"/> All the time | <input type="checkbox"/> Most of the time | <input type="checkbox"/> A good bit of the time |
| <input type="checkbox"/> Some of the time | <input type="checkbox"/> A little of the time | <input type="checkbox"/> None of the time |

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

- | | | |
|---|---|---|
| <input type="checkbox"/> All the time | <input type="checkbox"/> Most of the time | <input type="checkbox"/> A good bit of the time |
| <input type="checkbox"/> Some of the time | <input type="checkbox"/> A little of the time | <input type="checkbox"/> None of the time |

27. How **TRUE** or **FALSE** are each of the following statements?

a. I seem to get ill more easily than other people

- ☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

b. I am as healthy as anybody I know

- ☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

c. I expect my health to get worse

- ☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

d. My health is excellent

- ☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

HIPS

28. These questions refer to your hips

a. Did you have pain in your hips in the last year?

- Left:** ☐ No ☐ Yes **Right:** ☐ No ☐ Yes

b. Did you have hip pain in the last month? (*if no skip to Q28e*)

- Left:** ☐ No ☐ Yes **Right:** ☐ No ☐ Yes

c. If yes, on how many days last month did you have hip pain?

- | | | | |
|---------------|-----------------------------------|------------------------------------|-----------------------------------|
| Left: | <input type="checkbox"/> 1-5 days | <input type="checkbox"/> 6-14 days | <input type="checkbox"/> 15+ days |
| Right: | <input type="checkbox"/> 1-5 days | <input type="checkbox"/> 6-14 days | <input type="checkbox"/> 15+ days |

d. If you have hip pain, does it ever wake you at night?

Left: ☐ Never ☐ Occasionally ☐ Most nights
Right: ☐ Never ☐ Occasionally ☐ Most nights

Have you ever had an injury to your hip joint(s) bad enough to impair weight bearing for
 e. a week or more?

Left: ☐ No ☐ Yes **Right:** ☐ No ☐ Yes

29. Have you had pain in or around your *right* hip on most days in the last month?

☐ Yes ☐ No

30. Have you had pain in or around your *left* hip on most days in the last month?

☐ Yes ☐ No

31. Considering the worst hip pain you have had in the last month, how severe was it
 on a scale of 1 - 10?

Left: ☐ 1 no pain ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 worst pain
Right: ☐ 1 no pain ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 worst pain

32. Have you ever had any of the following procedures performed on your hip(s) for
 osteoarthritis? *If YES, please indicate which hip and when (if more than once please
 give first occasion).*

Steroid Injection:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Left	Date	<input type="text"/>
	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Right	Date	<input type="text"/>
Hip washout/ arthroscopy:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Left	Date	<input type="text"/>
	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Right	Date	<input type="text"/>
Total hip replacement:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Left	Date	<input type="text"/>
	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Right	Date	<input type="text"/>
Hip resurfacing:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Left	Date	<input type="text"/>
	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Right	Date	<input type="text"/>

33. Is there any family history of hip arthritis in the following members of your family?

Maternal grandmother:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Maybe	<input type="checkbox"/> Not applicable
Mother:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Maybe	<input type="checkbox"/> Not applicable
Father:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Maybe	<input type="checkbox"/> Not applicable

Aunt:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Maybe	<input type="checkbox"/> Not applicable
Sister:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Maybe	<input type="checkbox"/> Not applicable
Brother:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Maybe	<input type="checkbox"/> Not applicable
Children:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Maybe	<input type="checkbox"/> Not applicable

KNEE

34. These questions refer to your *knees*

a. Did you have pain in your knees in the last year?

Left: ☐ No ☐ Yes Right: ☐ No ☐ Yes

b. Did you have knee pain in the last month? (if no skip to Q34e)

Left: ☐ No ☐ Yes Right: ☐ No ☐ Yes

c. If yes, on how many days last month did you have knee pain?

Left: ☐ 1-5 days ☐ 6-14 days ☐ 15+ days
Right: ☐ 1-5 days ☐ 6-14 days ☐ 15+ days

d. If you have knee pain, does it ever wake you at night?

Left: ☐ Never ☐ Occasionally ☐ Most nights
Right: ☐ Never ☐ Occasionally ☐ Most nights

e. Have you ever had an injury to your knee joint(s) bad enough to impair weight bearing for a week or more?

Left: ☐ No ☐ Yes Right: ☐ No ☐ Yes

f. Do your knees ever swell for more than one month?

Left: ☐ No ☐ Yes Right: ☐ No ☐ Yes

g. Do your knees ever give way?

Left: ☐ No ☐ Yes Right: ☐ No ☐ Yes

h. Do your knees ever feel locked?

Left: ☐ No ☐ Yes Right: ☐ No ☐ Yes

i. Do you get knee pain while walking?

Left: ☐ No ☐ Yes Right: ☐ No ☐ Yes

j. Do you get knee pain while sitting?

Left: ☐ No ☐ Yes

Right: ☐ No ☐ Yes

k. Do you get knee pain while standing?

Left: ☐ No ☐ Yes

Right: ☐ No ☐ Yes

l. Do you get knee pain while lying?

Left: ☐ No ☐ Yes

Right: ☐ No ☐ Yes

m. Do you get knee pain while going up/down stairs?

Left: ☐ No ☐ Yes

Right: ☐ No ☐ Yes

35. Have you had pain in or around your *right* knee on most days in the last month?

☐ Yes ☐ No

36. Have you had pain in or around your *left* knee on most days in the last month?

☐ Yes ☐ No

37. Considering the worst knee pain you have had in the last month, how severe was it on a scale of 1-10?

Left: ☐ 1 no pain ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 worst pain

Right: ☐ 1 no pain ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 worst pain

38. Have you ever had any of the following procedures performed on your knee(s) for osteoarthritis? *If YES, please indicate which knee and when (if more than once please give first occasion).*

Steroid Injection: ☐ No ☐ Yes ☐ Left Date

☐ No ☐ Yes ☐ Right Date

Cartilage operation: ☐ No ☐ Yes ☐ Left Date

☐ No ☐ Yes ☐ Right Date

Knee washout/arthroscopy: ☐ No ☐ Yes ☐ Left Date

☐ No ☐ Yes ☐ Right Date

Total knee replacement: ☐ No ☐ Yes ☐ Left Date

☐ No ☐ Yes ☐ Right Date

Unicondylar knee replacement: ☐ No ☐ Yes ☐ Left Date

☐ No ☐ Yes ☐ Right Date

39. The following questions concern the amount of **pain** you have experienced due to arthritis in your left and right knee. For each situation please indicate the amount of pain experienced in the **last 48 hours** for each knee.

a. Walking on a flat surface

Left: ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
Right: ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

b. Going up or down stairs

Left: ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
Right: ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

c. At night while in bed

Left: ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
Right: ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

d. Sitting or lying

Left: ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
Right: ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

e. Standing upright

Left: ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
Right: ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

40. The following questions concern the amount of **joint stiffness** (not pain) you experience in your left and right knee joints. Stiffness is the sensation of restriction or slowness in the ease with which you move your joints.

For each situation please indicate the amount of stiffness experienced in the **last 48 hours** for each knee.

a. After first wakening in the morning

Left: ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
Right: ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

b. After sitting, lying or resting later in the day

Left: ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
Right: ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

41. The following questions concern your **physical function**. By this we mean your ability to move around and to look after yourself.

For each of the following activities, please indicate the degree of difficulty you have experienced in the **last 48 hours** due to arthritis in both your knee joint(s).

a. Descending stairs

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

b. Ascending stairs

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

c. Rising from sitting

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

d. Standing

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

e. Bending to the floor

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

f. Walking on flat

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

g. Getting in/out of the car

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

h. Going shopping

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

i. Putting on socks/stockings

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

j. Rising from bed

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

k. Taking off socks/stockings

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

l. Lying in bed

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

- m. Getting in/out of the bath
☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
- n. Sitting
☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
- o. Getting on/off the toilet
☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
- p. Doing heavy domestic duties
☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
- q. Doing light domestic duties
☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme
42. These questions are relating to your **knees** during the **past four weeks**. Please answer questions with reference to **both** knees and answer regardless if you have symptoms or not.
- a. How would you describe the pain you usually have from your knee?
Left: ☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe
Right: ☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe
- b. Have you had any trouble with washing and drying yourself (all over) because of your knee?
Left: ☐ No trouble at all ☐ Very little trouble ☐ Moderate trouble
☐ Extreme trouble ☐ Impossible to do
Right: ☐ No trouble at all ☐ Very little trouble ☐ Moderate trouble
☐ Extreme trouble ☐ Impossible to do
- c. Have you had any trouble getting in and out of a car or using public transport because of your knee? (whichever you tend to use)
Left: ☐ No trouble at all ☐ Very little trouble ☐ Moderate trouble
☐ Extreme trouble ☐ Impossible to do
Right: ☐ No trouble at all ☐ Very little trouble ☐ Moderate trouble
☐ Extreme trouble ☐ Impossible to do
- d. For how long have you been able to walk before the pain from your knee becomes severe (with or without a stick)
Left: ☐ No pain / > 30min ☐ 16-30 min ☐ 5-15 min
☐ Around the house only ☐ Not at all - severe on walking
Right: ☐ No pain / > 30min ☐ 16-30 min ☐ 5-15 min
☐ Around the house only ☐ Not at all - severe on walking

e. After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?

Left:	<input type="checkbox"/> Not at all painful	<input type="checkbox"/> Slightly painful	<input type="checkbox"/> Moderately painful
	<input type="checkbox"/> Very painful	<input type="checkbox"/> Unbearable	
Right:	<input type="checkbox"/> Not at all painful	<input type="checkbox"/> Slightly painful	<input type="checkbox"/> Moderately painful
	<input type="checkbox"/> Very painful	<input type="checkbox"/> Unbearable	

f. Have you been limping when walking, because of your knee?

Left:	<input type="checkbox"/> Rarely/never	<input type="checkbox"/> Sometimes or just at first	<input type="checkbox"/> Often, not just at first
	<input type="checkbox"/> Most of the time	<input type="checkbox"/> All of the time	
Right:	<input type="checkbox"/> Rarely/never	<input type="checkbox"/> Sometimes or just at first	<input type="checkbox"/> Often, not just at first
	<input type="checkbox"/> Most of the time	<input type="checkbox"/> All of the time	

g. Could you kneel down and get up again afterwards?

Left:	<input type="checkbox"/> Yes easily	<input type="checkbox"/> With little difficulty	<input type="checkbox"/> With moderate difficulty
	<input type="checkbox"/> With extreme difficulty	<input type="checkbox"/> Impossible to do	
Right:	<input type="checkbox"/> Yes easily	<input type="checkbox"/> With little difficulty	<input type="checkbox"/> With moderate difficulty
	<input type="checkbox"/> With extreme difficulty	<input type="checkbox"/> Impossible to do	

h. Have you been troubled by pain from your knee in bed at night?

Left:	<input type="checkbox"/> No nights	<input type="checkbox"/> Only 1-2 nights	<input type="checkbox"/> Some nights
	<input type="checkbox"/> Most nights	<input type="checkbox"/> Every night	
Right:	<input type="checkbox"/> No nights	<input type="checkbox"/> Only 1-2 nights	<input type="checkbox"/> Some nights
	<input type="checkbox"/> Most nights	<input type="checkbox"/> Every night	

i. How much pain from your knee interfered with your usual work (including housework)?

Left:	<input type="checkbox"/> Not at all	<input type="checkbox"/> A little bit	<input type="checkbox"/> Moderately	<input type="checkbox"/> Greatly	<input type="checkbox"/> Totally
Right:	<input type="checkbox"/> Not at all	<input type="checkbox"/> A little bit	<input type="checkbox"/> Moderately	<input type="checkbox"/> Greatly	<input type="checkbox"/> Totally

j. Have you felt that your knee might suddenly 'give way' or let you down?

Left:	<input type="checkbox"/> Rarely/never	<input type="checkbox"/> Sometimes or just at first	<input type="checkbox"/> Often, not just at first
	<input type="checkbox"/> Most of the time	<input type="checkbox"/> All of the time	
Right:	<input type="checkbox"/> Rarely/never	<input type="checkbox"/> Sometimes or just at first	<input type="checkbox"/> Often, not just at first
	<input type="checkbox"/> Most of the time	<input type="checkbox"/> All of the time	

k. Could you do the household shopping on your own?

Left:	<input type="checkbox"/> Yes easily	<input type="checkbox"/> With little difficulty	<input type="checkbox"/> With moderate difficulty
	<input type="checkbox"/> With extreme difficulty	<input type="checkbox"/> No, impossible	
Right:	<input type="checkbox"/> Yes easily	<input type="checkbox"/> With little difficulty	<input type="checkbox"/> With moderate difficulty
	<input type="checkbox"/> With extreme difficulty	<input type="checkbox"/> No, impossible	

1. Could you walk down a flight of stairs?

- Left:** ☐ Yes easily ☐ With little difficulty ☐ With moderate difficulty
☐ With extreme difficulty ☐ No, impossible
- Right:** ☐ Yes easily ☐ With little difficulty ☐ With moderate difficulty
☐ With extreme difficulty ☐ No, impossible

43. Is there any family history of knee arthritis in the following members of your family?

- Maternal grandmother: ☐ No ☐ Yes ☐ Maybe ☐ Not applicable
 Mother: ☐ No ☐ Yes ☐ Maybe ☐ Not applicable
 Father: ☐ No ☐ Yes ☐ Maybe ☐ Not applicable
 Aunt: ☐ No ☐ Yes ☐ Maybe ☐ Not applicable
 Sister: ☐ No ☐ Yes ☐ Maybe ☐ Not applicable
 Brother: ☐ No ☐ Yes ☐ Maybe ☐ Not applicable
 Children: ☐ No ☐ Yes ☐ Maybe ☐ Not applicable

SHOULDER

44. Shoulder pain history – have you ever had shoulder pain? ☐ No ☐ Yes

45. If no skip to Q46, if yes:

- a. Which shoulder was it? ☐ Left ☐ Right ☐ Both
- b. Considering the worst shoulder pain you have had in the last month, how severe was it on a scale of 1 -
- Left:** ☐ 1 no pain ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 worst pain
Right: ☐ 1 no pain ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 worst pain

46. Have you ever seen your GP about shoulder pain? ☐ No ☐ Yes

47. Have you ever had any of the following treatments for shoulder pain? If yes, how many

- a. Chiropractic therapy
- Left:** ☐ No ☐ Yes ☐ 1 session ☐ 2-5 sessions ☐ 5+ sessions
Right: ☐ No ☐ Yes ☐ 1 session ☐ 2-5 sessions ☐ 5+ sessions
- b. Massage
- Left:** ☐ No ☐ Yes ☐ 1 session ☐ 2-5 sessions ☐ 5+ sessions
Right: ☐ No ☐ Yes ☐ 1 session ☐ 2-5 sessions ☐ 5+ sessions

c. Osteopathy

Left: ☐ No ☐ Yes ☐ 1 session ☐ 2-5 sessions ☐ 5+ sessions
Right: ☐ No ☐ Yes ☐ 1 session ☐ 2-5 sessions ☐ 5+ sessions

d. Physiotherapy

Left: ☐ No ☐ Yes ☐ 1 session ☐ 2-5 sessions ☐ 5+ sessions
Right: ☐ No ☐ Yes ☐ 1 session ☐ 2-5 sessions ☐ 5+ sessions

e. Steroid injection

Left: ☐ No ☐ Yes ☐ 1 session ☐ 2-5 sessions ☐ 5+ sessions
Right: ☐ No ☐ Yes ☐ 1 session ☐ 2-5 sessions ☐ 5+ sessions

f. Surgery

Left: ☐ No ☐ Yes ☐ 1 session ☐ 2-5 sessions ☐ 5+ sessions
Right: ☐ No ☐ Yes ☐ 1 session ☐ 2-5 sessions ☐ 5+ sessions

48. These questions are relating to your **shoulders** during the **past four weeks**. Please answer questions with reference to **both** shoulders and answer regardless if you have symptoms or not.

a. How would you describe the worst pain you had from your shoulder?

Left: ☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe
Right: ☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe

b. Have you had any trouble dressing yourself because of your shoulder?

Left: ☐ No trouble at all ☐ Very little trouble ☐ Moderate trouble
☐ Extreme trouble ☐ Impossible to do
Right: ☐ No trouble at all ☐ Very little trouble ☐ Moderate trouble
☐ Extreme trouble ☐ Impossible to do

c. Have you had any trouble getting in and out of a car or using public transport because of your shoulder?

Left: ☐ No trouble at all ☐ Very little trouble ☐ Moderate trouble
☐ Extreme trouble ☐ Impossible to do
Right: ☐ No trouble at all ☐ Very little trouble ☐ Moderate trouble
☐ Extreme trouble ☐ Impossible to do

d. Have you been able to use a knife and fork – at the same time?

Left: ☐ Yes easily ☐ With little difficulty ☐ With moderate difficulty
☐ With extreme difficulty ☐ No, impossible
Right: ☐ Yes easily ☐ With little difficulty ☐ With moderate difficulty
☐ With extreme difficulty ☐ No, impossible

e. Could you do the household shopping on your own?

Left:	<input type="checkbox"/> Yes easily	<input type="checkbox"/> With little difficulty	<input type="checkbox"/> With moderate difficulty
	<input type="checkbox"/> With extreme difficulty	<input type="checkbox"/> No, impossible	
Right:	<input type="checkbox"/> Yes easily	<input type="checkbox"/> With little difficulty	<input type="checkbox"/> With moderate difficulty
	<input type="checkbox"/> With extreme difficulty	<input type="checkbox"/> No, impossible	

f. Could you carry a tray containing a plate of food across a room?

Left:	<input type="checkbox"/> Yes easily	<input type="checkbox"/> With little difficulty	<input type="checkbox"/> With moderate difficulty
	<input type="checkbox"/> With extreme difficulty	<input type="checkbox"/> No, impossible	
Right:	<input type="checkbox"/> Yes easily	<input type="checkbox"/> With little difficulty	<input type="checkbox"/> With moderate difficulty
	<input type="checkbox"/> With extreme difficulty	<input type="checkbox"/> No, impossible	

g. Could you brush/comb your hair with the affected arm?

Left:	<input type="checkbox"/> Yes easily	<input type="checkbox"/> With little difficulty	<input type="checkbox"/> With moderate difficulty
	<input type="checkbox"/> With extreme difficulty	<input type="checkbox"/> No, impossible	
Right:	<input type="checkbox"/> Yes easily	<input type="checkbox"/> With little difficulty	<input type="checkbox"/> With moderate difficulty
	<input type="checkbox"/> With extreme difficulty	<input type="checkbox"/> No, impossible	

h. How would you describe the pain you usually had from your shoulder?

Left:	<input type="checkbox"/> None	<input type="checkbox"/> Very mild	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe
Right:	<input type="checkbox"/> None	<input type="checkbox"/> Very mild	<input type="checkbox"/> Mild	<input type="checkbox"/> Moderate	<input type="checkbox"/> Severe

i. Could you hang your clothes up in a wardrobe – using the affected arm?

Left:	<input type="checkbox"/> Yes easily	<input type="checkbox"/> With little difficulty	<input type="checkbox"/> With moderate difficulty
	<input type="checkbox"/> With extreme difficulty	<input type="checkbox"/> No, impossible	
Right:	<input type="checkbox"/> Yes easily	<input type="checkbox"/> With little difficulty	<input type="checkbox"/> With moderate difficulty
	<input type="checkbox"/> With extreme difficulty	<input type="checkbox"/> No, impossible	

j. Have you been able to wash and dry yourself under both arms?

Left:	<input type="checkbox"/> Yes easily	<input type="checkbox"/> With little difficulty	<input type="checkbox"/> With moderate difficulty
	<input type="checkbox"/> With extreme difficulty	<input type="checkbox"/> No, impossible	
Right:	<input type="checkbox"/> Yes easily	<input type="checkbox"/> With little difficulty	<input type="checkbox"/> With moderate difficulty
	<input type="checkbox"/> With extreme difficulty	<input type="checkbox"/> No, impossible	

k. How much has pain from your shoulder interfered with your usual work (including housework)?

Left:	<input type="checkbox"/> Not at all	<input type="checkbox"/> A little bit	<input type="checkbox"/> Moderately	<input type="checkbox"/> Greatly	<input type="checkbox"/> Totally
Right:	<input type="checkbox"/> Not at all	<input type="checkbox"/> A little bit	<input type="checkbox"/> Moderately	<input type="checkbox"/> Greatly	<input type="checkbox"/> Totally

I. Have you been troubled by pain from your shoulder in bed at night?

- Left:** ☐ No nights ☐ Only 1-2 nights ☐ Some nights
☐ Most nights ☐ Every night
- Right:** ☐ No nights ☐ Only 1-2 nights ☐ Some nights
☐ Most nights ☐ Every night

49. Is there any family history of shoulder **pain** in the following members of your family?

- | | | | | |
|-----------------------|-----------------------------|------------------------------|--------------------------------|---|
| Maternal grandmother: | <input type="checkbox"/> No | <input type="checkbox"/> Yes | <input type="checkbox"/> Maybe | <input type="checkbox"/> Not applicable |
| Mother: | <input type="checkbox"/> No | <input type="checkbox"/> Yes | <input type="checkbox"/> Maybe | <input type="checkbox"/> Not applicable |
| Father: | <input type="checkbox"/> No | <input type="checkbox"/> Yes | <input type="checkbox"/> Maybe | <input type="checkbox"/> Not applicable |
| Aunt: | <input type="checkbox"/> No | <input type="checkbox"/> Yes | <input type="checkbox"/> Maybe | <input type="checkbox"/> Not applicable |
| Sister: | <input type="checkbox"/> No | <input type="checkbox"/> Yes | <input type="checkbox"/> Maybe | <input type="checkbox"/> Not applicable |
| Brother: | <input type="checkbox"/> No | <input type="checkbox"/> Yes | <input type="checkbox"/> Maybe | <input type="checkbox"/> Not applicable |
| Children: | <input type="checkbox"/> No | <input type="checkbox"/> Yes | <input type="checkbox"/> Maybe | <input type="checkbox"/> Not applicable |

HANDS

50. These questions refer to you *hands*:

a. Did you have pain in your hands in the last year?

- Left:** ☐ No ☐ Yes **Right:** ☐ No ☐ Yes

b. Did you have hand pain in the last month? (*if no skip to Q51*)

- Left:** ☐ No ☐ Yes **Right:** ☐ No ☐ Yes

c. If yes, on how many days last month did you have hand pain?

- Left:** ☐ 1-5 days ☐ 6-14 days ☐ 15+ days
Right: ☐ 1-5 days ☐ 6-14 days ☐ 15+ days

d. If you have hand pain, does it ever wake you at night?

- Left:** ☐ Never ☐ Occasionally ☐ Most nights
Right: ☐ Never ☐ Occasionally ☐ Most nights

51. Considering the worst hand pain you have had in the last month, how severe was it on a scale of 1-10?

- Left:** ☐ 1 no pain ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 worst pain
Right: ☐ 1 no pain ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 worst pain

52. Is there any family history of hand arthritis in the following members of your family?

Maternal grandmother:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Maybe	<input type="checkbox"/> Not applicable
Mother:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Maybe	<input type="checkbox"/> Not applicable
Father:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Maybe	<input type="checkbox"/> Not applicable
Aunt:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Maybe	<input type="checkbox"/> Not applicable
Sister:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Maybe	<input type="checkbox"/> Not applicable
Brother:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Maybe	<input type="checkbox"/> Not applicable
Children:	<input type="checkbox"/> No	<input type="checkbox"/> Yes	<input type="checkbox"/> Maybe	<input type="checkbox"/> Not applicable

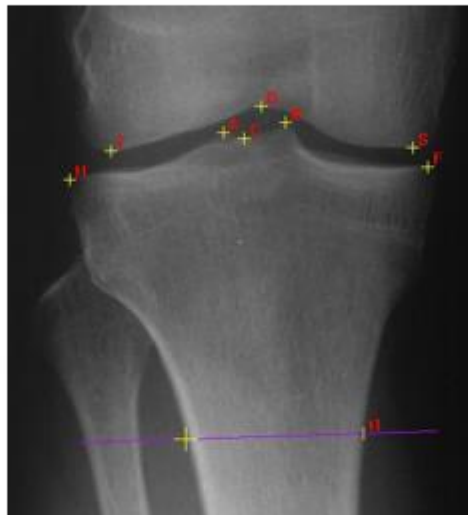
MANY THANKS FOR COMPLETING THIS QUESTIONNAIRE

A19 KneeMorf alignment manual

KneeMorf™ alignment manual

Quick start guide and point placement

Version 1.0



by

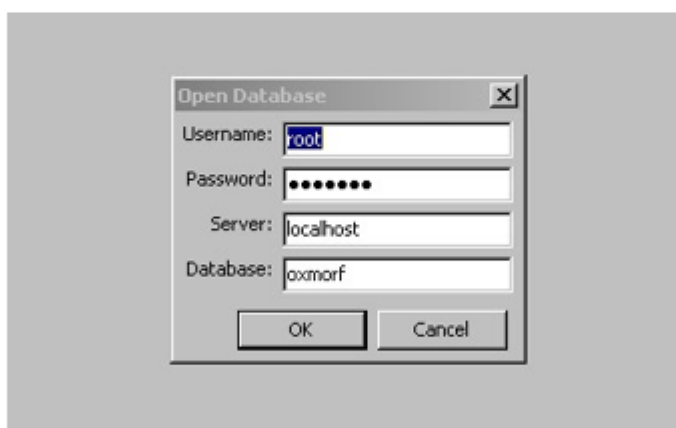
Lyndsey Goulston, Kirsten Leyland

& Dr David Hunter

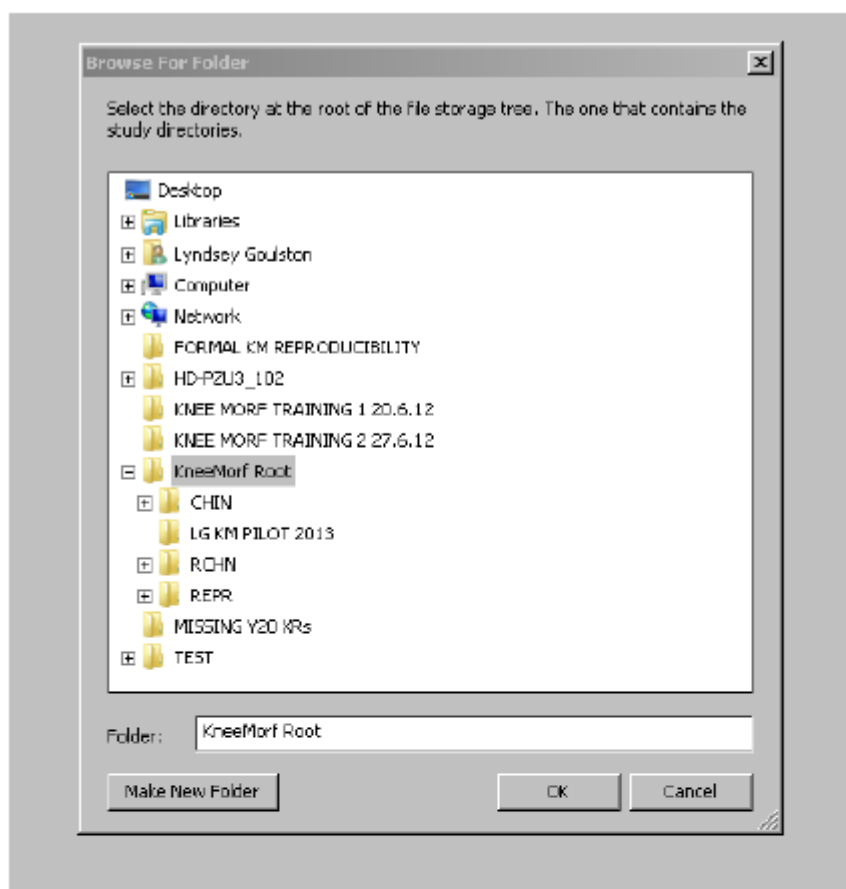
Quick start guide

Set up

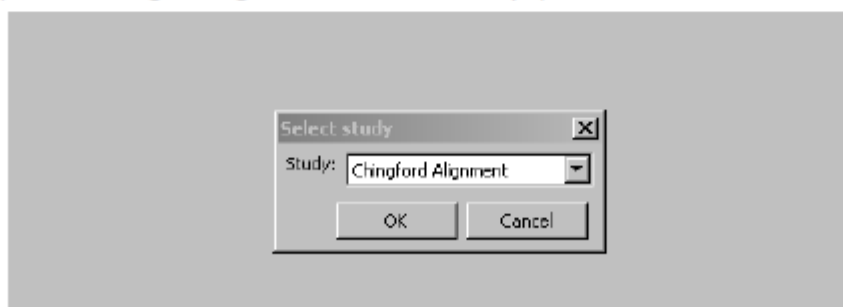
- 1) Plug Samsung high resolution monitor into laptop.
 - 2) Check screen resolution by:
 - a) right click mouse on desktop then select 'screen resolution'.
 - b) ensure Samsung monitor displays a resolution of 1920x 1080 then click on 'ok'.
 - 3) Open KneeMorf software by clicking 'start' on desktop, select 'all programs', scroll down and double click on 'OxMorf 1.6.21.D4-LyndseyMorf-dev (x64)'.
 - 4) The KneeMorf software will open displaying the default 'open database' box below.
- NB: For completion of pilot alignment reading x-rays leave this 'open database' box as it is populated below and click on 'ok', but for reading of randomised Chingford knee x-ray images (RCHN) the 'database' field must be changed from 'oxmorf' to 'alignment'.



- 5) It will then ask you to 'browse for folder', ensure this is set to the 'KneeMorf Root' folder located on the desktop then click 'ok'.

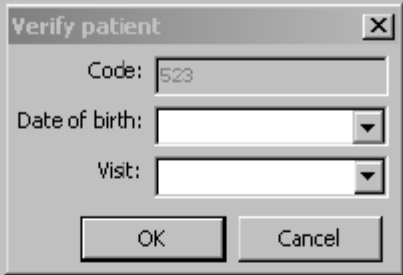


- 6) Ignore the 'select centre' box so click on 'ok'.
- 7) Select 'Chingford alignment' under select study option then click on 'ok'.



- 8) Click on 'select patient' tab in top left hand corner of screen, enter patient study number in the 'select patient code' box e.g. 523 then click on 'ok'.

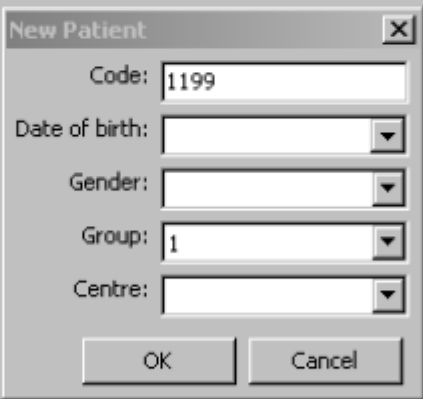
- 9) If the x-ray has been looked at before the 'verify patient' box will appear below:



The 'Verify patient' dialog box has a title bar with a close button (X). It contains three input fields: 'Code' with the value '523', 'Date of birth' with a dropdown arrow, and 'Visit' with a dropdown arrow. At the bottom are two buttons: 'OK' and 'Cancel'.

- Enter e.g. 1st of the month (American format MM/DD/YEAR) in date of birth field.
- Select '0' in visit field, then click 'ok'.

- 10) If the x-ray has not been looked at before the 'new patient' box will appear below:



The 'New Patient' dialog box has a title bar with a close button (X). It contains five input fields: 'Code' with the value '1199', 'Date of birth' with a dropdown arrow, 'Gender' with a dropdown arrow, 'Group' with the value '1', and 'Centre' with a dropdown arrow. At the bottom are two buttons: 'OK' and 'Cancel'.

- Enter e.g. 1st of the month (American format MM/DD/YEAR) in date of birth field.
- Enter female in gender field, then click 'ok'.
- Then the 'visit' box will appear below:

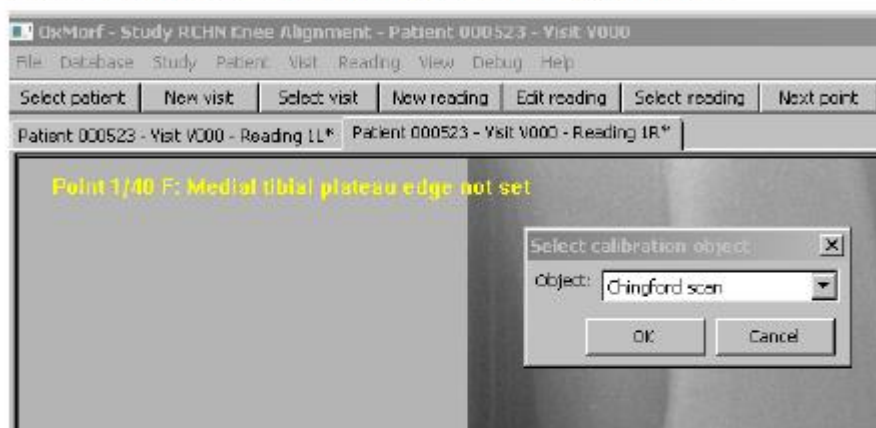
d) Leave the rest of the fields blank and click on 'ok'.

11) Click on 'new reading' tab in top left hand corner of screen to display the 'reading' box below:

- a) **Number/side** field will contain options for unread images. For a new x-ray, the choices will be 1 Both, 1 Left, 1 Right, select which image is required for reading e.g. 1 Both.
- b) The date, user and centre information should already be set and do not need adjusting so click on 'ok' and the x-ray image will appear on the screen.

12) Set calibration object:

- a) For scanned knee x-ray images (tiff images at 600 dpi resolution at Y1, Y5, Y10 and Y15) the calibration object has been pre-determined (by pixel size horizontal 0.042333 x vertical 0.042333) therefore click 'ok' to the 'Chingford scan' option:



- b) For DICOM (digital) knee x-ray images (taken at Y20 identifiable by a central KIDA wedge) select the option 'calibrate from DICOM tag: "Imager Pixel Spacing"' which will automatically be present in the 'select calibration object' box.

NB: do not use the "Pixel Spacing" option as this is incorrect.



13) Keyboard shortcuts

Display options

<i>Option</i>	<i>Command</i>
Zoom in	Ctrl + left drag
Zoom out	Ctrl + A
Adjust contrast	C + left drag (horizontal)
Adjust brightness	C + left drag (vertical)
Scroll around image	Right drag
Toggle point visibility	P
Toggle point label visibility	L

General point placement

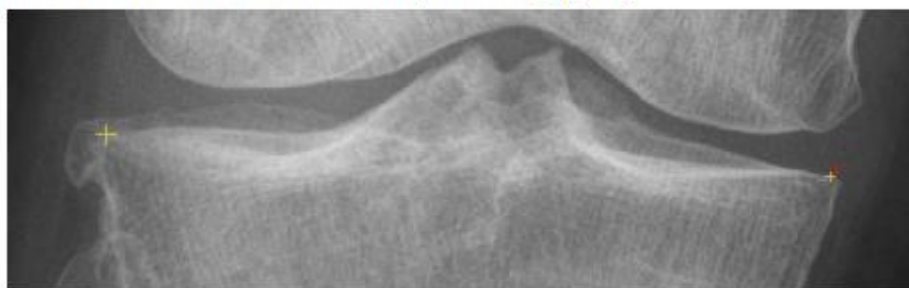
<i>Option</i>	<i>Command</i>
Create current point (if doesn't already exist)	Left click
Move current point	Left drag
Set point and move on to next one	<ol style="list-style-type: none"> 1. Press <enter>, or 2. Press 'Next point' on button bar
Return to previous point	<ol style="list-style-type: none"> 1. Ctrl + Z, or 2. Press 'Previous point' on button bar
Unable to plot point	Press 'Skip point' on button bar (and add comment to comments box)

14) Alignment point placement

Select the knee image for reading e.g. right knee first, then zoom in as far as possible (using Ctrl + left drag) on x-ray image to plot the subsequent 40 points.

NB: If any of the following points are difficult to plot or not able to plot please note the point numbers and appropriate explanation in the 'comments' box on the left hand side of the screen.

Points 1 and 2: medial and lateral tibial plateau edge (point)



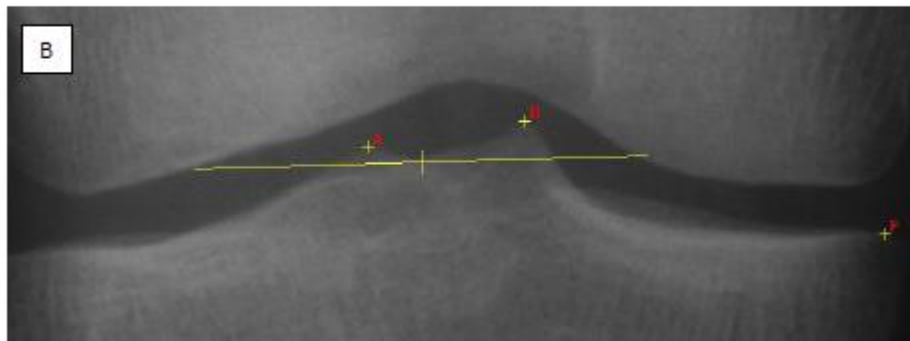
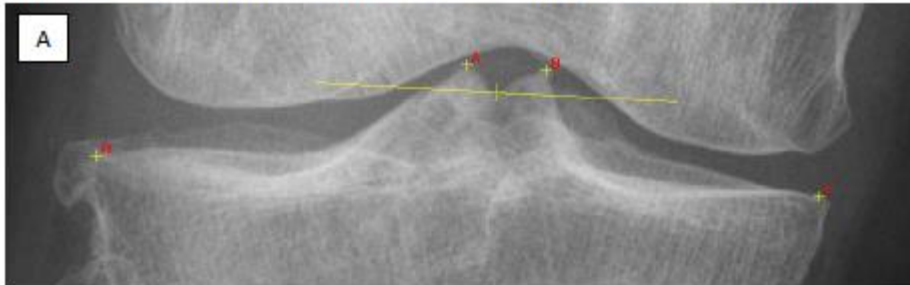
- Place point at the edge of the tibial plateau, in the middle of the sclerotic line (indicating the plateau floor, if present) NOT including marginal osteophytes.
- Ensure medial (non-fibula side) and lateral (on fibula side) are the right way round.

Points 3 and 4: medial and lateral tibial spine (point)



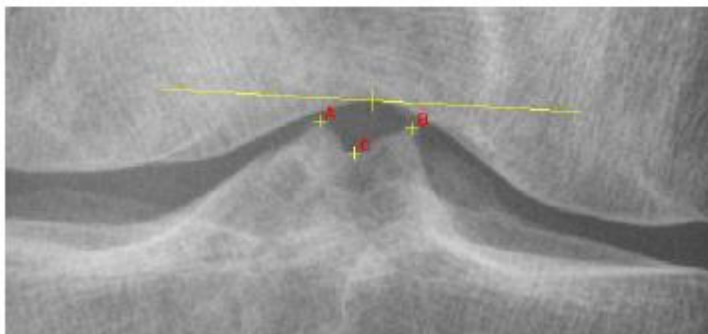
- Click the tip of the medial and lateral spines.
- Some spines may appear taller or split into more than one tip – click on the tallest peak of this type of spine.

Point 5: tibial spine midpoint on tibial bony surface (point with levelling guide)



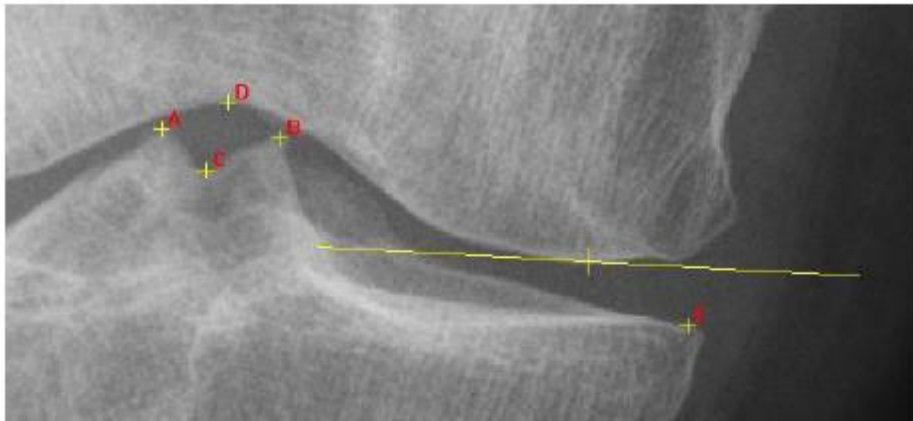
- Use the levelling guide to place the point on the lowest surface of the bone between tibial spines (see A).
- This point may not be perfectly centred between the spines (see B). If this is the case please write 'base TS not centre' in comment box on right hand side of screen.

Point 6: inter condylar notch (point with levelling guide)



- Use the levelling guide to place the point on the highest/deepest surface of the inter condylar notch.
- This point may not be perfectly centred.

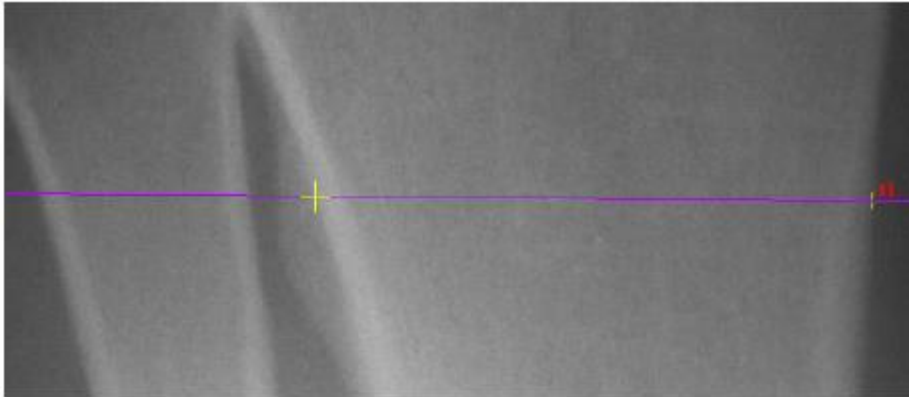
Points 7 and 8: inferior point of medial and lateral femoral condyle (point with levelling guide)



- Use the levelling guide to show the lowest (most distal) edge of the femoral condyle
- If the levelling guide line overlaps bone on either side of the centre point, then the point may not be in the optimal location.

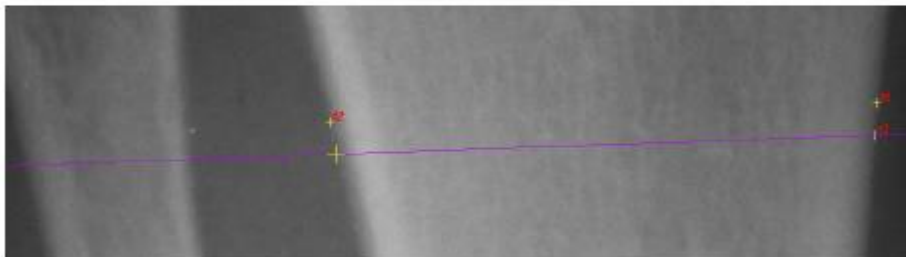
Points 9 and 10: medial and lateral edge of tibial shaft (70mm from KJC 2) (constrained point)





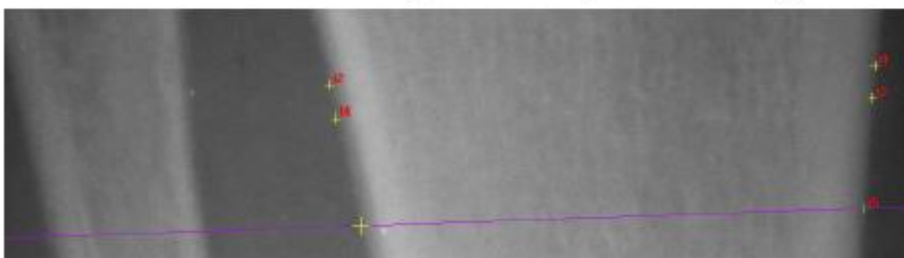
- Place on the outermost edge of the bone NOT on the brightest line, but do not include bulges from the back of the tibia.
- Ensure medial and lateral points are on the correct sides.

Points 11 and 12: medial and lateral edge of tibial shaft (70 mm from KJC 1) (constrained point)



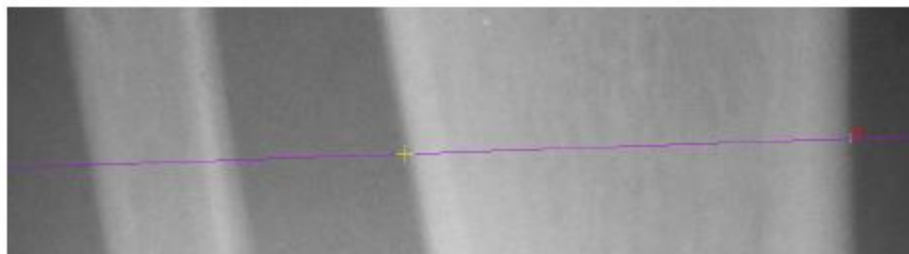
- Place on the outermost edge of the bone NOT on the brightest line.
- Ensure medial and lateral points are on the correct sides.

Points 13 and 14: medial and lateral edge of tibial shaft (70 mm from KJC 3) (constrained point)



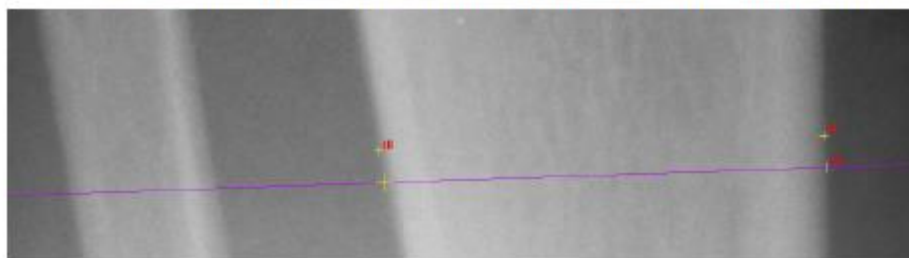
- Place on the outermost edge of the bone NOT on the brightest line.
- Ensure medial and lateral points are on the correct sides.

Points 15 and 16: medial and lateral edge of tibial shaft (100 mm from KJC 2) (constrained point)



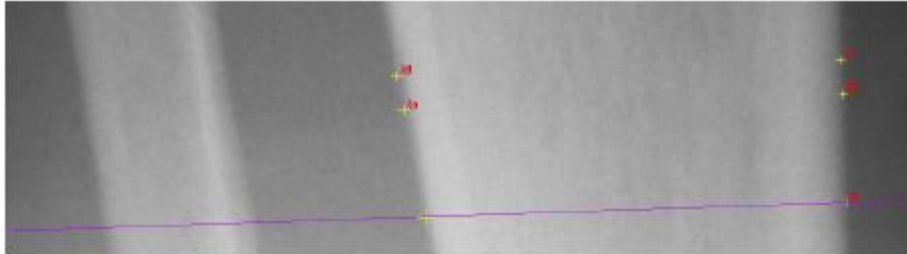
- Place on the outermost edge of the bone NOT on the brightest line.
- Ensure medial and lateral points are on the correct sides.
- If constrained line is off the edge of the x-ray, click 'skip point' tab at top of screen to not place points. Note the point numbers not plotted in the 'comments' box on the right hand side of the screen e.g. tib <10 points 15-16 n/a.

Points 17 and 18: medial edge of tibial shaft (100 mm from KJC 1) (constrained point)



- Place on the outermost edge of the bone NOT on the brightest line.
- Ensure medial and lateral points are on the correct sides.
- If constrained line is off the edge of the x-ray, click 'skip point' tab at top of screen to not place points. Note the point numbers not plotted in the 'comments' box on the right hand side of the screen e.g. tib <10 points 17-18 n/a.

Points 19 and 20: medial and lateral edge of tibial shaft (100 mm from KJC 3) (constrained point)



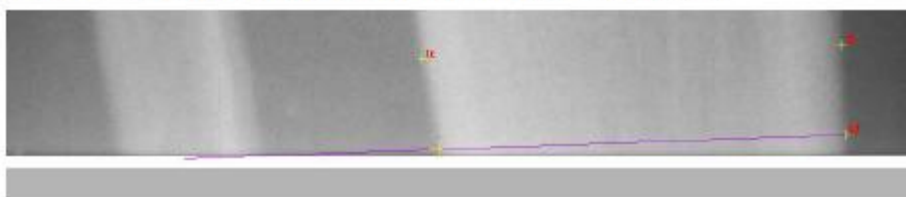
- Place on the outermost edge of the bone NOT on the brightest line.
- Ensure medial and lateral points are on the correct sides.
- If constrained line is off the edge of the x-ray, click 'skip point' tab at top of screen to not place points. Note the point numbers not plotted in the 'comments' box on the right hand side of the screen e.g. tib <10 points 19-20 n/a.

Point 21: most distal medial edge of tibial shaft (point with levelling guide)



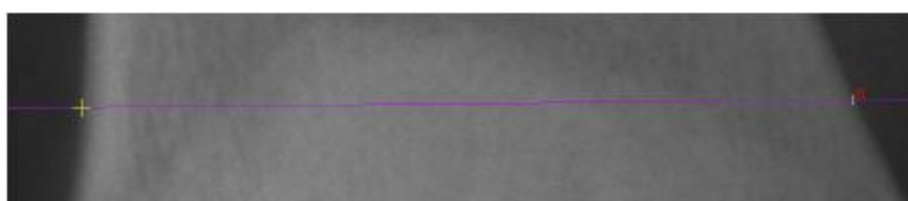
- Make sure the levelling guide line can be clearly seen on both sides of the shaft and is not obscured.
- Place point on the outermost edge (NOT on the brightest line) of the medial tibial shaft as far down as possible (where bone edges are clearly visible).

Points 22: most distal lateral edge of tibial shaft (constrained point)



- Place point on the outermost edge (NOT on the brightest line) of the lateral tibial shaft as far down as possible (where bone edges are clearly visible).

Points 23 and 24: medial edge of femoral shaft (70 mm from KJC 3) (constrained point)



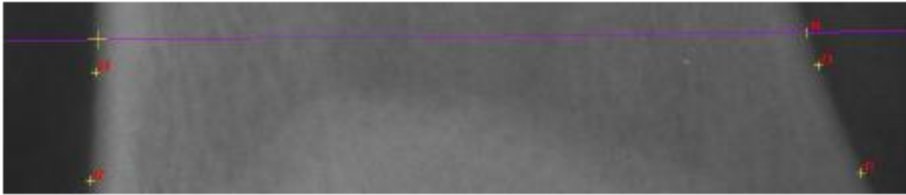
- Place on the outermost edge of the bone NOT on the brightest line.
- Ensure medial and lateral points are on the correct sides.
- Do not include bulges from the back of the femur.

Points 25 and 26: medial and lateral edge of femoral shaft (70 mm from KJC 1) (constrained point)



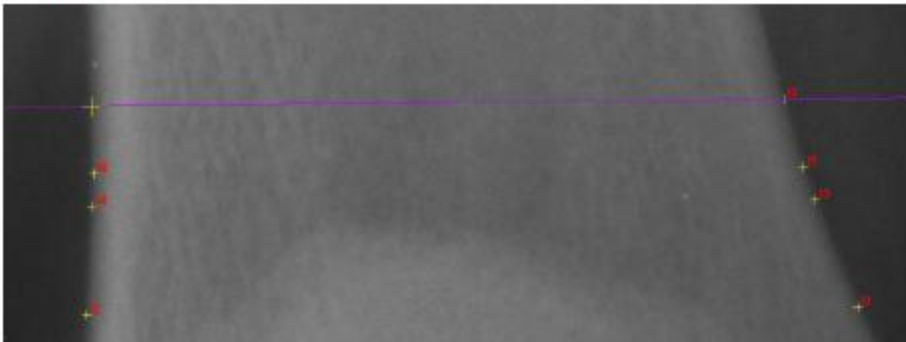
- Place on the outermost edge of the bone NOT on the brightest line.
- Ensure medial and lateral points are on the correct sides.
- Do not include bulges from the back of the femur.

Points 27 and 28: medial and lateral edge of femoral shaft (70 mm from KJC 2) (constrained point)



- Place on the outermost edge of the bone NOT on the brightest line.
- Ensure medial and lateral points are on the correct sides.
- Do not include bulges from the back of the femur.

Points 29 and 30: medial and lateral edge of femoral shaft (70 mm from ICN) (constrained point)



- Place on the outermost edge of the bone NOT on the brightest line.
- Ensure medial and lateral points are on the correct sides.
- Do not include bulges from the back of the femur.

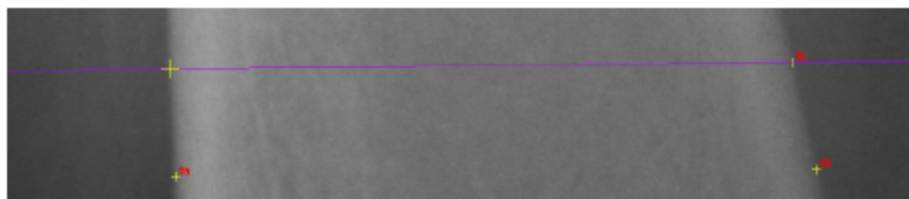
Points 31 and 32: medial edge of femoral shaft (100 mm from KJC 3) (constrained point)



- Place on the outermost edge of the bone NOT on the brightest line.
- Ensure medial and lateral points are on the correct sides.

- If constrained line is off the edge of the x-ray, click 'skip point' tab at top of screen to not place points. Note the point numbers not plotted in the 'comments' box on the right hand side of the screen e.g. fem <10 points 31-32 n/a.

Points 33 and 34: medial and lateral edge of femoral shaft (100 mm from KJC 1) (constrained point)



- Place on the outermost edge of the bone NOT on the brightest line.
- Ensure medial and lateral points are on the correct sides.
- If constrained line is off the edge of the x-ray, click 'skip point' tab at top of screen to not place points. Note the point numbers not plotted in the 'comments' box on the right hand side of the screen e.g. fem <10 points 33-34 n/a.

Points 35 and 36: medial and lateral edge of femoral shaft (100 mm from KJC 2) (constrained point)



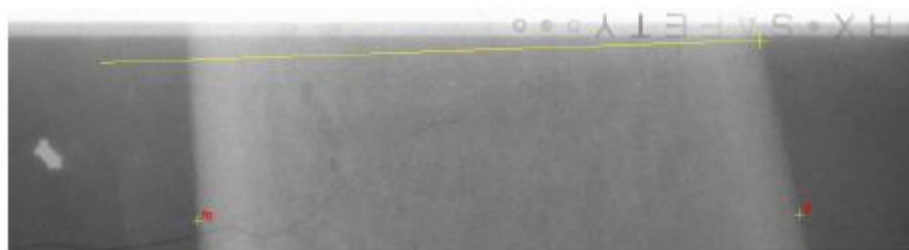
- Place on the outermost edge of the bone NOT on the brightest line.
- Ensure medial and lateral points are on the correct sides.
- If constrained line is off the edge of the x-ray, click 'skip point' tab at top of screen to not place points. Note the point numbers not plotted in the 'comments' box on the right hand side of the screen e.g. fem <10 points 35-36 n/a.

Points 37 and 38: medial and lateral edge of femoral shaft (100 mm from ICN) (constrained point)



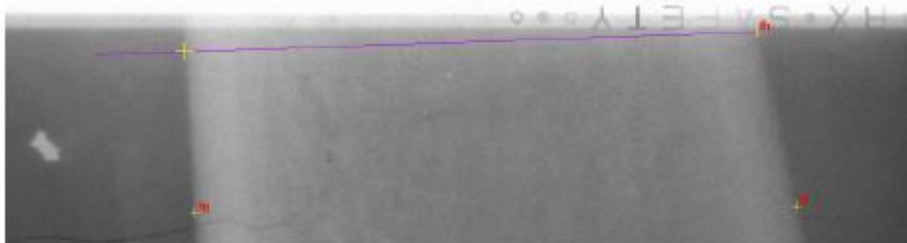
- Place on the outermost edge of the bone NOT on the brightest line.
- Ensure medial and lateral points are on the correct sides.
- If constrained line is off the edge of the x-ray, click 'skip point' tab at top of screen to not place points. Note the point numbers not plotted in the 'comments' box on the right hand side of the screen e.g. fem <10 points 37-38 n/a.

Point 39: most distal medial edge of femoral shaft (point with levelling guide)



- Make sure the levelling guide line can be clearly seen on both sides of the shaft and is not obscured.
- Place point on the outermost edge (NOT on the brightest line) of the medial femoral shaft as far up as possible (where bone edges are clearly visible).

Point 40: most distal lateral edge of femoral shaft (constrained point)



- Place point on the outermost edge (NOT on the brightest line) of the lateral femoral shaft as far up as possible (where bone edges are clearly visible).

15) When all 40 points are plotted, click on 'save reading' tab at top of screen then click on 'close reading' tab.

16) Repeat steps 8-15 until all x-ray images are read.

17) Once all x-ray images are read, click on 'database' drop down box on top of left screen, scroll down to click on 'export all reading to .csv files and dump database' which will save the alignment data into the KneeMorf Root' folder on the desktop. It is a good idea to save readings on a regular basis during the reading period to avoid loss of data.

Creating a new database

- 1) Click on 'file' drop down box in top left hand corner of screen, click on 'create...' to obtain a 'create database' box on screen. Change the 'database' field from 'oxmorf' to 'XXX' eg. 'alignment', then click on 'ok'.

Create Database

Username: root

Password: ••••••••

Server: localhost

Database: alignment

OK Cancel

- 2) Click on 'database' drop down box in top left hand corner of screen, then click on 'create knee alignment tables'.
- 3) Click on 'study' drop down box in top left hand corner of screen, then click on 'new study' to obtain 'study' box below:

Study

Name:

Study Abbreviation (4 Characters):

Joint: Knee Alignment

Principal Investigator:

Start date:

Description:

Funding sources:

Description of visit user1 field:

Description of visit user2 field:

Description of visit user3 field:

Description of visit user4 field:

Description of visit user5 field:

OK Cancel

- a) Ensure the 'joint' field contains 'knee alignment'.
 - b) In the 'name' field enter the study name e.g. 'Chingford alignment'.
 - c) In the 'study abbreviation' field enter the 4 character abbreviation e.g. 'RCHN', then click on 'ok'.
- 4) Click on 'study' drop down box in top left hand corner of screen, then click on 'new group' to obtain 'group' box below:

The 'Group' dialog box contains the following fields:

- Name:
- Number:
- Description:

Buttons: OK, Cancel

- a) In the 'name' field enter '1'.
 - b) In the 'number' field enter '1', then click on 'ok'.
- 5) Click on 'study' drop down box in top left hand corner of screen, then click on 'new proposed visit' to obtain 'proposed visit' box below:

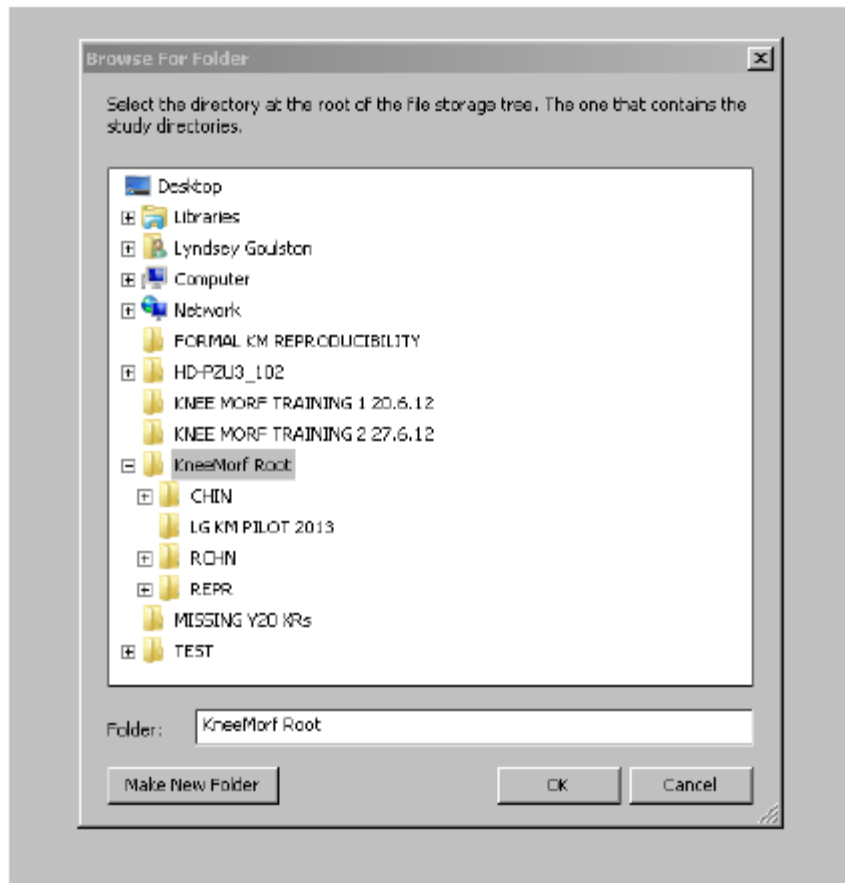
The 'Proposed Visit' dialog box contains the following fields:

- Number:
- Time point (months):
- Description:

Buttons: OK, Cancel

- a) In the 'number' field enter '0'.
- b) In the 'time point' field enter '0', then click on 'ok'.

- 6) Click on 'file' drop down box in top left hand corner of screen, click on 'select file root...' where it will then ask to 'browse for folder', ensure this is set to the 'KneeMorf Root' folder located on the desktop then click 'ok'.



- 7) The new database is now ready to start.

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