KNEE PAIN IN THE COMMUNITY:

RISK FACTORS, INCIDENCE, AND OUTCOME

by

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of Doctor of Philosophy

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Declaration

This is to certify that work submitted in this thesis is the result of original research. It has been conducted substantially by myself with assistance as outlined below. It has not already been accepted for any degree and no publications for this thesis have been undertaken. All authors and works to which reference has been made are fully acknowledged.

Study design, ethical application, data collection, analysis, writing and general administration were conducted primarily by myself with support from Helen Richardson, Eleanor Mitchell and Stevie Short. Sally Doherty provided valuable support as the x-ray reader on the project; and Amy Moody assisted in the clinical assessment/validation stages. Supervision of this thesis was undertaken by Professor Michael Doherty and Dr Weiya Zhang.

Abbreviations

2D:4D	Ring: index finger ratio
aOR	Adjusted odds ratio
BMI	Body mass index
BMD	Bone mineral density
CWP	Chronic widespread pain
CI	Confidence interval
FOD	Female oestrogen deficiency
GP	General Practice
HR	Hazard ratio
HB	Heberden's and Bouchard's nodes
HAD	Hospital Anxiety and Depression Scale
ID	Identification number
ICC	Intra Class Correlation
JSN	Joint space narrowing
κ	Kappa statistic
K/L	Kellgren and Lawrence
LDLDA	Logically Derived Line Drawing Atlas
MRI	Magnetic Resonance Imaging
MVC	Mean maximum voluntary strength
MPC	Mean predicted strength
OR	Odds ratio
ORT	Oestrogen replacement therapy
OA	Osteoarthritis
RR	Relative risk
SF36	Short Form 36 questionnaire
SD	Standard deviation
TKR	Total knee joint replacements
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WHO	World Health Organisation

Abstract

Background: Knee pain affects 1 in 4 people over 55 years, and is a leading cause of disability in the elderly (Peat *et al*, 2001). Whilst the prevalence of knee pain has been examined, the natural history of knee pain and associated risk factors remain unknown (O'Reilly, 1996).

Objectives: to determine in a community sample over a 10 year period: [1] the incidence of knee pain; [2] the outcome of knee pain; and [3] risk factors for both incidence and outcome of knee pain.

Materials and method: This was a retrospective cohort study. Baseline data were collected between 1996-1999, and the cohort was reviewed during 2007-2008. Knee pain was defined as pain around the knee for most days of at least a month. Participants without knee pain at baseline who developed knee pain during the subsequent 10 years were defined as incident cases. Participants with knee pain at baseline who reported worsening of symptoms, improvement of symptoms, no change in symptoms, or who underwent TKR during the past 10 years were defined as outcome cases. Other measures included: age of onset and time from baseline to the first episode of knee pain. Putative risk factors measured at baseline included age, gender and body mass index (BMI); risk factors assessed at follow-up included knee malalignment and foot angulation. Relative risk (RR) was estimated using odds ratio (OR) or hazard ratio (HR) depending on outcomes. Confounding factors were adjusted using logistic regression or COX regression.

Results: 9,429 participants were questioned at baseline (2,868 knee pain positive/6,397 knee pain negative). After 10 years, 5,479 were eligible for follow-up. Of them 3,109 responded and 424 underwent x-rays at both baseline and follow-up. The baseline age of this cohort ranged between 40-83 years, with a mean age of 57 years old; 1,725 (55.5%) were women. The incident rate for knee pain cases during the 10 year follow-up period was 742/2,156 (34.4%); this was similar in men (32%) and women (35%). During the 10 year period 250 (27.4%) of the 914 people with pain at baseline experienced worsening of their symptoms, with 81 (8.9%) requiring total knee joint replacements (TKR). A number of risk factors were explored. Obesity (OR 2.19; 95%CI 1.49, 3.22) and varus malalignment (OR 2.82; 95%CI 1.57, 5.06) significantly associated with incident knee pain, whereas back pain (aOR 1.47; 95%CI 1.02, 2.10) and physical work (aOR 1.88; 95%CI 1.02, 3.50) were related to poor outcome.

Conclusions: For people over the age of 40 years old, 1 in 3 will develop significant knee pain in the next 10 years. Of people with knee pain, 1 in 4 will worsen over a 10 year period and 1 in 11 will require surgery. A number of risk factors were identified including both systemic/constitutional and more local biomechanical factors. This could have practical implications for primary and secondary prevention particularly in relation to modifiable risk factors, such as reduction in BMI, occupational protection of the knees and possible adjustment of knee malalignment.

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I would like to begin by thanking my supervisors Professor Michael Doherty and Dr Weiya Zhang for their constructive comments, and enthusiastic support. I am also indebted to Sally Doherty and Amy Moody (featured in Figures 18, 19, 21, 22, 23, and 25) for their invaluable assistance and expertise with the clinical assessment and study x-rays. Thanks must also be given to Helen Richardson, Eleanor Mitchell and Stevie Short for their administrative assistance.

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Finally, I would like to thank my parents for their unwavering encouragement of my studies, and my friends for their support and patience.

I dedicate this work to my Grandma (Beryl Forrester), who was an academic enthusiast and OA fighter until the end.

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1. Introduction

"Osteoarthritis is a disease of considerable antiquity" (Waldron, 1991). Past studies have shown osteoarthritis (OA) to be one of the most prevalent conditions found in ancient skeletal specimens (Rogers and Dieppe, 1994; Waldron, 1991). OA changes have been seen in skeletons ranging from ancient Peru (Berg, 1972) to Saxon England (Rogers and Dieppe, 1994). Skeletally, OA is recognised by eburnation, osteophytes, pitting of articular surface and deformation of joint contours (Rogers and Dieppe, 1994; Waldon, 1991). Today OA remains a prevalent, chronic, and debilitating condition (Thomas, 2001).

1.1 Characteristics of osteoarthritis

Traditionally named 'hypertrophic arthritis' (Felson *et al*, 2000); classifications of primary (idiopathic) and secondary (traumatic) OA (Altman, 1995) are now regarded as inappropriate. Current consensus describes OA as a dynamic, complex disorder involving both mechanical and biological events (Sharma *et al*, 2006). Ultimately it leads to the alteration of the cells and matrix in articular cartilage and subchondral bone (Sharma *et al*, 2006). In simple terms this results in loss of hyaline cartilage and increased bone growth at the joint margins (osteophytes) (Felson *et al*, 2000). In reality many more tissues are affected, such as the synovium, capsule, and subchondral bone (Figure 1).

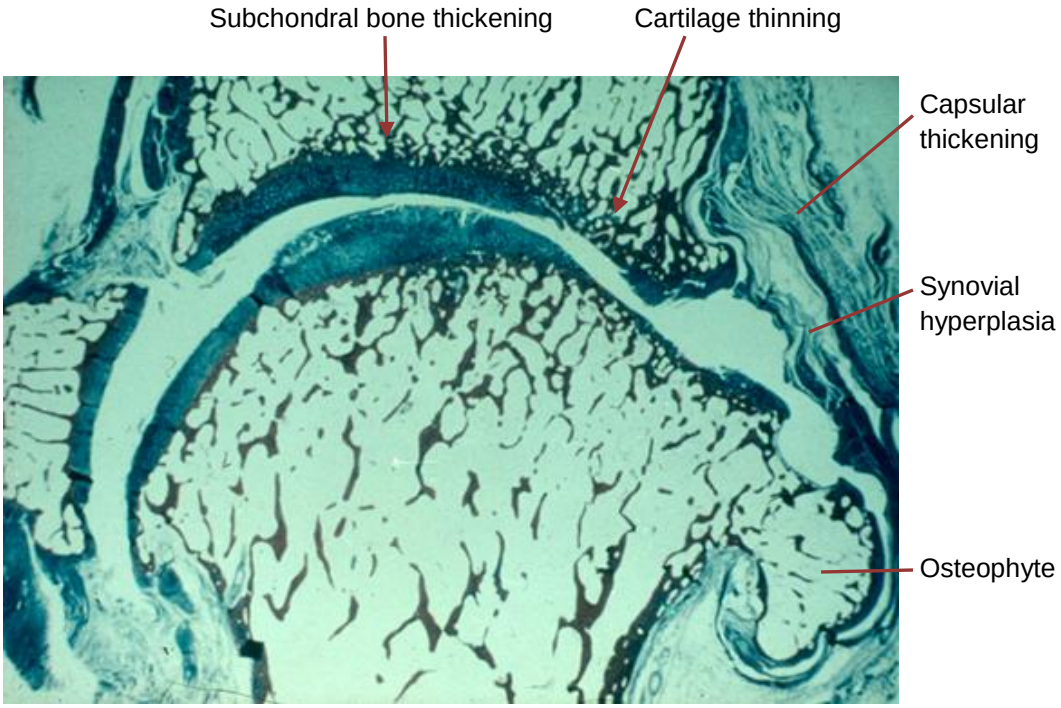

Figure 1. Joint showing histological changes of OA

Classification of OA has been challenging due to the inconsistency of symptoms (Altman, 1995). Although there is some correlation between radiographic and symptomatic presentation it is relatively weak (Sharma *et al*, 2006). The patterning of clinical presentation is thought to be dynamic, and in some respects different depending on the joint involved (Altman, 1995).

As with the clinical symptoms, risk factors for the development and progression of OA are also thought to differ depending on joint site (Felson *et al*, 2000; Sharma *et al*, 2006).

1.2 Epidemiology of osteoarthritis

Over recent decades most epidemiological studies have relied upon prevalence estimates to examine the burden of OA. Rates are thought to vary depending upon the joint examined and the symptoms presented (Thomas, 2001; O'Reilly, 1996). Women have been found to have a significantly higher prevalence for OA than men, particularly at the knee (Thomas, 2001). A 1987 study by Felson *et al* found a higher proportion of women with symptomatic knee OA in comparison to men (p=0.003). In contrast, most studies have found hip OA to be more prevalent in men (Felson *et al*, 2000). Dagenais *et al* (2009) calculated an overall 8.5% prevalence for radiographic hip OA in men, compared to 6.9% in women.

Fewer studies have examined the incidence of OA. The 23-year incidence of hand OA was found to be 40.9% (522/1276) in a population aged 50-74 years (Carman *et al*, 1994), with estimates of yearly incidence ranging from just under 2% to 4% per year (Sharma *et al*, 2006). Similarly the Framingham Osteoarthritis Study showed the incidence of symptomatic knee OA to be approximately 2% per year for women (Felson *et al*, 1995). Epidemiological studies of hip OA yield varying incidence data, though estimates are similar to those of knee and hand OA (Lohmander *et al*; 2009).

1.3 Knee osteoarthritis

Knee OA is a highly prevalent disease among the elderly (≥65-years), and is often considered the largest single cause of lower limb disability in this age group (Brooks, 2006). Felson *et al* (2000) found that approximately 6% of the older population have symptomatic knee OA. The prevalence estimate was slightly higher, at 12.2%, for a Spanish population of a similar age range (Quintana *et al*, 2008).

As with generalised OA, studies of knee OA have often shown an association between gender and prevalence. Quintana *et al* (2008) recorded a significantly higher prevalence of knee OA among women ≥65-years (14.9%). Within this study population only 8.7% of men were found with knee OA (Quintana *et al*, 2008).

Similar results were reported by Felson *et al* (1987), where evidence of radiographic knee OA was found in 52.6% women ≥80-years. A further breakdown of this population focused on the prevalence of knee OA in younger adults (Felson *et al*, 1987). Radiographic OA was found to be more prevalent in men <70-years (30.4%) than women (25.1%) (Figure 2) (Felson *et al*, 1987).

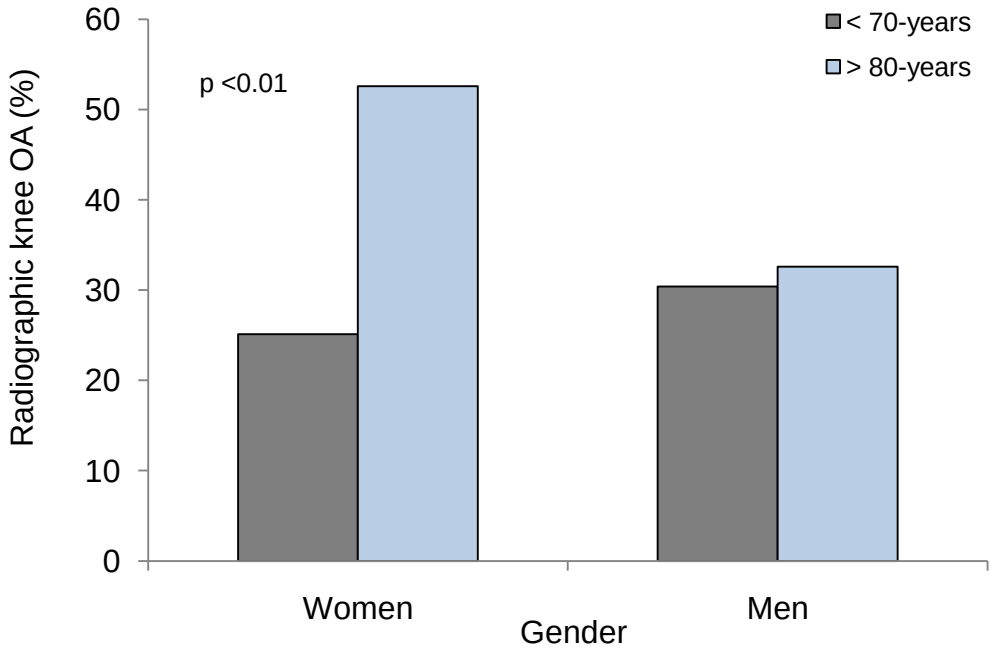

Figure 2. Prevalence of radiographic knee OA according to gender (Felson *et al*, 1987).

1.3.1 Incidence of knee osteoarthritis

Estimates for radiographic incident knee OA vary between 1% and 2% per year (Sharma *et al*, 2006; Felson *et al*, 1995). A 5-year follow-up study by Cooper *et al* (2000) showed an annual incidence of 2.5%, whilst Hart *et al* (1999) reported an incidence rate of approximately 3% per year for middle-aged women (4-year interval). These results are consistent and comparable with the estimates suggested by Sharma *et al* (2006). In support of the prevalence data women were also shown to be 1.7 times more likely to develop incident knee OA than men, with a 95% confidence interval (CI) of 1.0-2.7 (Felson *et al*, 1995).

1.3.2 Radiographic features of knee osteoarthritis

Not all characteristics of knee OA can be distinguished within a clinical setting. The formation of osteophytes (marginal bony growths) and the pathological loss of articular cartilage (Felson *et al*, 2000) can be measured by radiographic or other imaging assessment.

One possible reason for the discordance often noted between clinical and radiographic knee OA diagnosis is that on most occasions only the tibio-femoral compartment is assessed (Duncan *et al*, 2006). Data by Szebenyi *et al* (2006) illustrates the importance of examining changes in both the tibio-femoral and patello-femoral compartments when confirming knee OA. Individuals with Kellgren and Lawrence (K/L) change in either the tibio-femoral or patello-femoral compartment showed no significant difference in pain score compared to those with no K/L change (Szebenyi *et al*, 2006). Conversely, individuals with knee OA in both compartments had significantly more pain than those without K/L changes ($p<0.05$) (Szebenyi *et al*, 2006).

Weight-bearing antero-posterior (tibio-femoral) and skyline (patello-femoral) x-rays are normally recommended to confirm knee OA (Szebenyi *et al*, 2006). Flexed weight bearing views are now considered the most appropriate to allow for any OA change to be seen within the tibio-femoral knee compartments. However, for the current study extended views were used so direct comparisons could be made with the baseline radiographs.

Tibio-femoral OA is identified by the presence of osteophytes at the medial and lateral margins. No osteophytes can be identified at the anterior surface of the tibia or femur on the antero-posterior view since the image is only two dimensional.

Figure 3. Tibio-femoral radiograph showing osteophytes and medial tibio-femoral joint space narrowing (JSN)

Articular cartilage cannot be seen directly on an x-ray. Therefore, loss of cartilage (hyaline and/or fibrocartilage) is noted indirectly by the narrowing of the space between the tibia and the femur (joint space narrowing - JSN).

The patello-femoral compartment is often affected by OA and merits individual radiographic assessment (Nagaosa *et al*, 2000). Locations of

osteophytes for patello-femoral OA are found to be predominantly marginal, specifically at the medial or lateral margins of the patella or femur (Sengupta *et al*, 2006). Again the presence of any JSN (loss of hyaline cartilage) can be assessed between the medial and lateral facets of the patella and the femur.

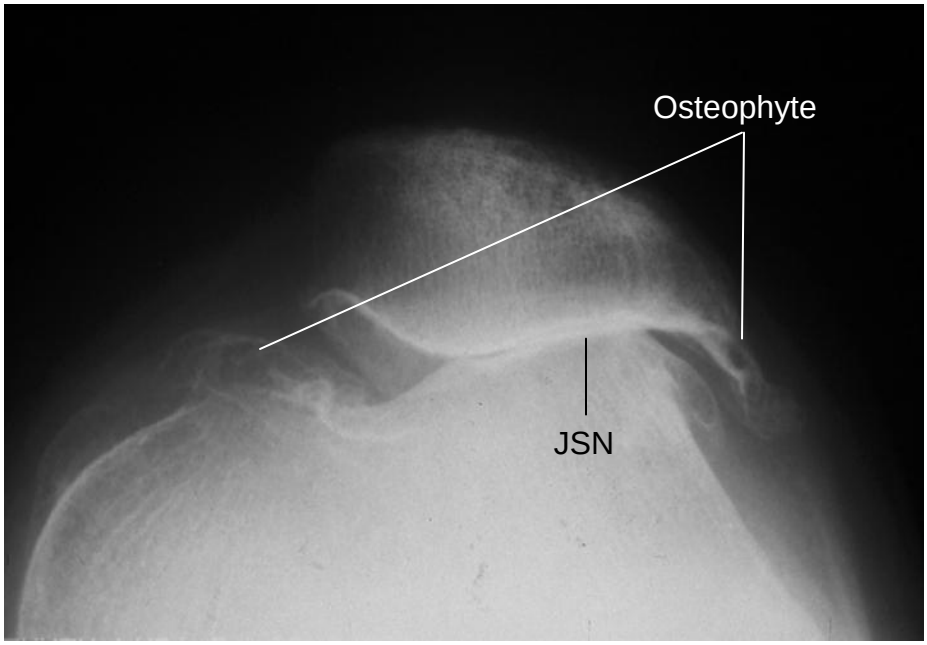

Figure 4. Patello-femoral radiograph showing osteophytes, JSN and lateral subluxation

To describe the association and relevance of osteophytes and JSN, a K/L composite score is often used to grade knee OA. This grading system has for many years been accepted as the gold standard in OA classification (Hart and Spector, 2003). It was adopted in 1961 by The World Health Organisation as their primary standardised method of assessing OA (O'Reilly, 1996).

There are however notable problems with using the K/L classification scale (Hart and Spector, 2003). These include the exclusion or misclassification of the grade one criteria; meaning early signs of OA are often ignored as predictors of disease (Hart and Spector, 2003). The importance of classifying grade 1 K/L as cases rather than controls was shown in the Chingford population (Hart and Spector, 2003). This 10-year cohort study of 1000 women found clear progression of so called “doubtful” grade 1 osteophytes to more definite knee OA in 62% of women (Hart and Spector, 2003). This is compared to only 20% of controls with grade 0 who showed progression to K/L $\geq$2 in the same time period (Hart and Spector, 2003).

Secondly, the K/L scoring system places much greater emphasis on the presence of osteophytes than it does on JSN (Nagaosa *et al*, 2000). This is inconsistent with the findings of several studies, which have suggested that the loss of hyaline cartilage is of particular significance to OA diagnosis (Nagaosa *et al*, 2000). This raises the option of describing and grading individual radiographic features, rather than using a K/L composite score alone (Szebenyi *et al*, 2006). Finally, K/L assumes that individual features progress simultaneously in a fixed fashion, which may not be true.

To try and improve study methodology for assessing knee OA, several groups have developed more sensitive scoring systems (Nagaosa *et al*, 2000). The group in Nottingham created novel line drawings for narrowing

and osteophytes, showing grading in an interval rather than ordinal scale, and providing different atlas drawings of narrowing for men and women (men have wider joint spaces than women). This atlas system also allows for grading of an increase, rather than just a decrease, of joint space.

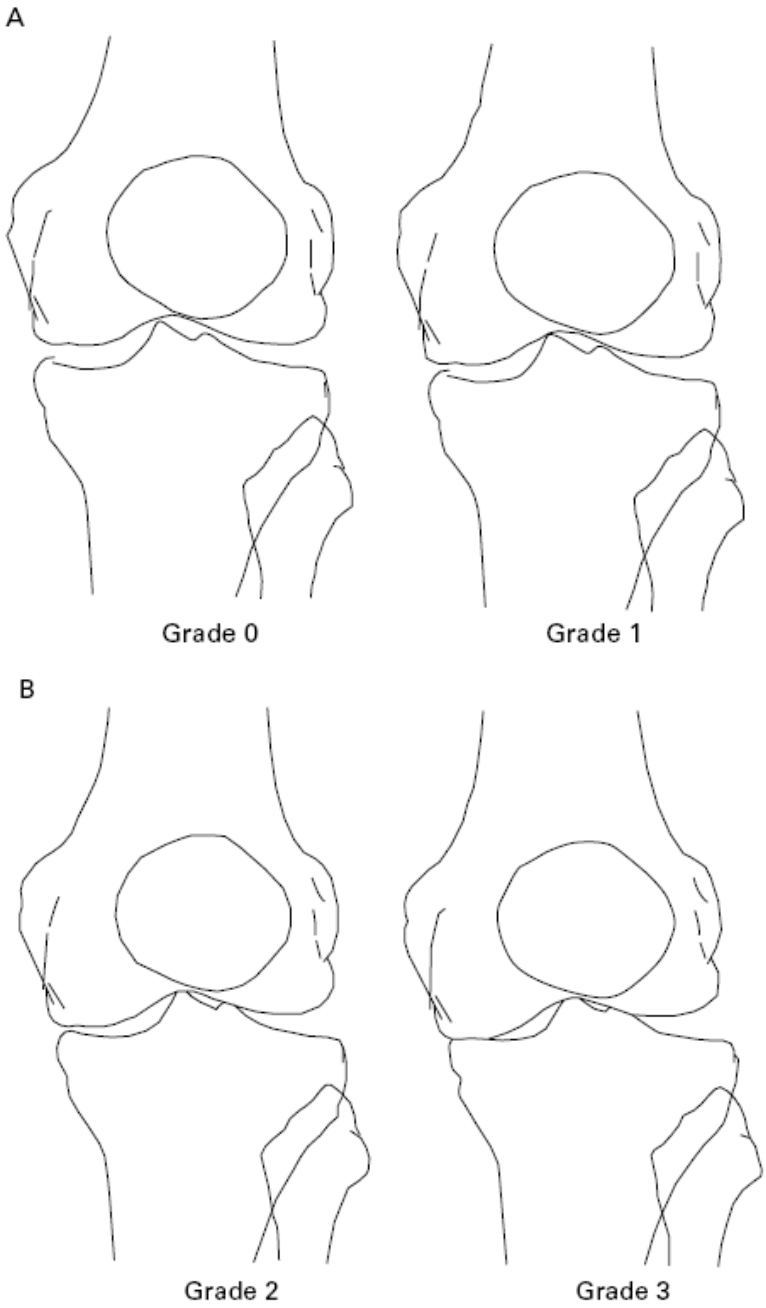

Figure 5. Example from the line drawing atlas of medial tibio-femoral JSN for woman (Nagaosa *et al,* 2000)

Other methods of assessing osteophytes and JSN include ultrasound and Magnetic Resonance Imaging (MRI). However, neither of these techniques is commonly used within a research or clinical setting. Ultrasound is a relatively new method in comparison to radiographic assessment, and as yet the validity of this technique is unknown. In addition, MRI is a very expensive method of analysis and the cost can rarely be justified when assessing OA, especially as x-rays are considered an inexpensive and reasonably efficient imaging technique for assessing large groups of people for clinical or research purposes.

1.4 Knee pain

"knee pain is the malady - not osteoarthritis" (Hadler, 1992).

"Demographically, individuals over 65 years of age are the fastest growing age group" (Dawson *et al*, 2005) and this is a high risk group for knee pain. Contemporary studies have shown knee pain to be a major cause of disability in these adults, often limiting everyday activities (Jordan *et al*, 2006). This in turn can lead to physical isolation and further dependence on the social and health services (Dawson *et al*, 2005). At a population level, such an increase in knee pain cases could lead to dramatic economic consequences for the national health system (Dawson *et al*, 2005; Brooks, 2006).

1.4.1 Relationship between knee OA and knee pain

"Knee pain in older adults is usually attributed to osteoarthritis" (Blagojevic *et al*, 2008). A population based study by Duncan *et al* (2006) found a consistent association between knee pain and radiographic OA, with an adjusted Odds Ratio (aOR) of 3.7 (95%CI 2.0, 6.7). However, the severity and cause of pain can differ between individuals (Creamer *et al*, 1998).

Various studies have reported a direct association between the origins of OA symptoms and pain (Figure 6). It has been suggested that osteophytes may cause ligament straining or capsule pressure (Sengupta *et al*, 2006).

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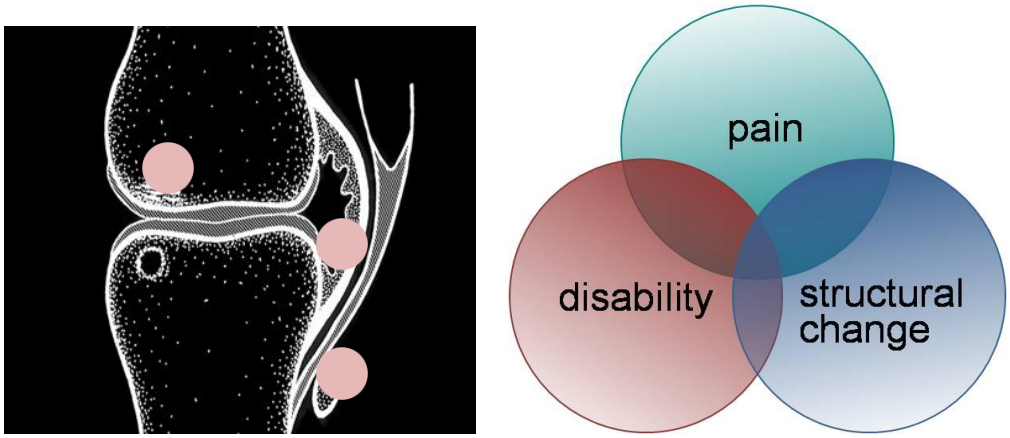


Figure 6. Origin of OA symptoms (bone, synovium/capsule, periarticular) and correlation between pain, disability and structural OA.

Studies have shown discordance between knee pain and the presence of knee OA (Cecchi *et al*, 2008; Duncan *et al*, 2006). Knee pain can be present in the absence of radiographic knee OA change and vice versa

Radiographic OA is therefore not the only possible cause of knee pain. Tears or damage to features such as the meniscus or ligaments can also cause pain at the knee. Alternatively, pain could be due to inflammation of the tendon (tendinitis) or the bursa (bursitis). Secondary bursitis and enthesopathy could be caused by altered joint mechanics. Additionally synovial hyperplasia or collection of fluid in the knee could cause increased pressure on the capsule, which may lead to the development of pain. Pain at the knee could also be referred from other sites, such as the hip, meaning that the source of pain is not the knee joint. Finally, pain at the single regional site of the knee could be linked to fibromyalgia, meaning knee pain may not have a direct cause but be part of an overall pain problem.

1.5 Risk factors for knee OA and knee pain

The identification of genetic, environmental, biochemical and biomechanical risk factors have shown knee OA to be a “common complex disorder” (Doherty, 2001).

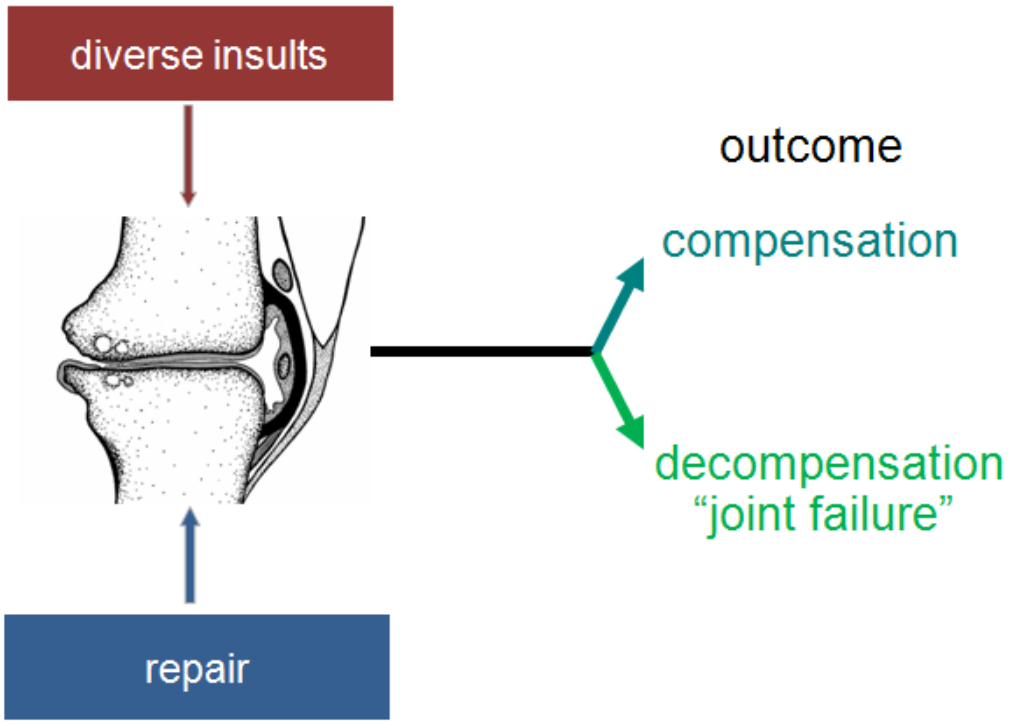


Figure 7. OA as inherent repair

Knee pain also has a number of risk factors, some similar, but some different from those of structural knee OA.

1.5.1 Age

Epidemiological studies show some conflicting evidence as to whether age is an associated risk factor for the incidence or progression of knee OA.

The Framingham OA study found the prevalence of radiographic knee OA to significantly associate with age ($p<0.001$) (Felson *et al*, 1987). A further analysis of the data showed that an increase in age was directly associated with symptomatic OA ($p<0.05$) (Felson *et al*, 1987).

Age has also been associated significantly with incident knee OA. The Chingford Women's Study found age to be significantly higher in those women with radiographically defined osteophytes than those without ($p<0.003$) (Hart *et al*, 1999). However the adjusted risk of incident JSN was not linked to age ($p=0.77$) (Hart *et al*, 1999).

In contrast, a later study by Felson *et al* (1995) showed age (<70, ≥70) not to be a significant risk factor for either incidence or progression of knee OA. One potential explanation is that individuals with OA often die younger (Felson *et al*, 1995). The follow-up participants within this study were on average younger than their counterparts who were deceased (Felson *et al*, 1995). This could be accounted for by left censorship of the data, with only a few individuals with the disorder being available for analysis.

1.5.2 Gender (hormonal status)

It has been suggested that women are two-times more likely to develop incident, radiographic knee OA than men (RR 1.79; 95%CI 1.08, 2.94 (Felson *et al*, 1995). Progression of knee OA was also thought to increase with female gender, RR 1.43, although this was not statistically significant (95%CI 0.80, 2.58) (Felson *et al*, 1995)

The link between female gender and knee OA suggests a possible link with endogenous sex hormones (Hart *et al*, 1995). It has been suggested that oestrogen may slow down bone turnover that is associated with knee OA (Cicuttini *et al*, 1997). In support of this, a 4-year longitudinal study by Hart *et al* (1999) showed a non-significant protective effect of oestrogen replacement therapy (ORT) on incident knee OA in women (OR 0.41; 95%CI 0.12, 1.42). Additional analyses undertaken by Zhang *et al* (1998) used data from the Framingham Osteoarthritis study to report on an 8 year follow up of knee OA individuals. The analysis showed a non-significant protective association between women on ORT and incident knee OA (aOR 0.4; 95%CI 0.1, 3.0). A potential protective effect was also seen for ORT and worsening radiographic knee OA (aOR 0.5; 95%CI 0.1, 2.9) (Zhang *et al*, 1998). One cross sectional study of middle aged women suggested that the effect of oestrogen might be site specific, with benefit from reduced patello-femoral OA but no reduction in tibio-femoral OA (Cicuttini *et al*, 1997).

Severe incident knee pain was also seen to associate with female gender in a 3–year prospective cohort (OR 1.67; 95%CI 1.11, 2.51), though no significant association with knee pain progression was found (OR 1.02; 95%CI 0.67, 1.53) (Jinks *et al*, 2008).

1.5.3 BMI

Several longitudinal cohort studies have investigated the effect of obesity (BMI >30) on knee OA and found positive associations.

The Baltimore Longitudinal Study of Aging (Hochberg *et al*, 1995) showed a significant association between high BMI and knee OA in men (OR 2.40; 95%CI 1.32, 4.35) and women (OR 4.34; 95%CI 1.89, 9.98).

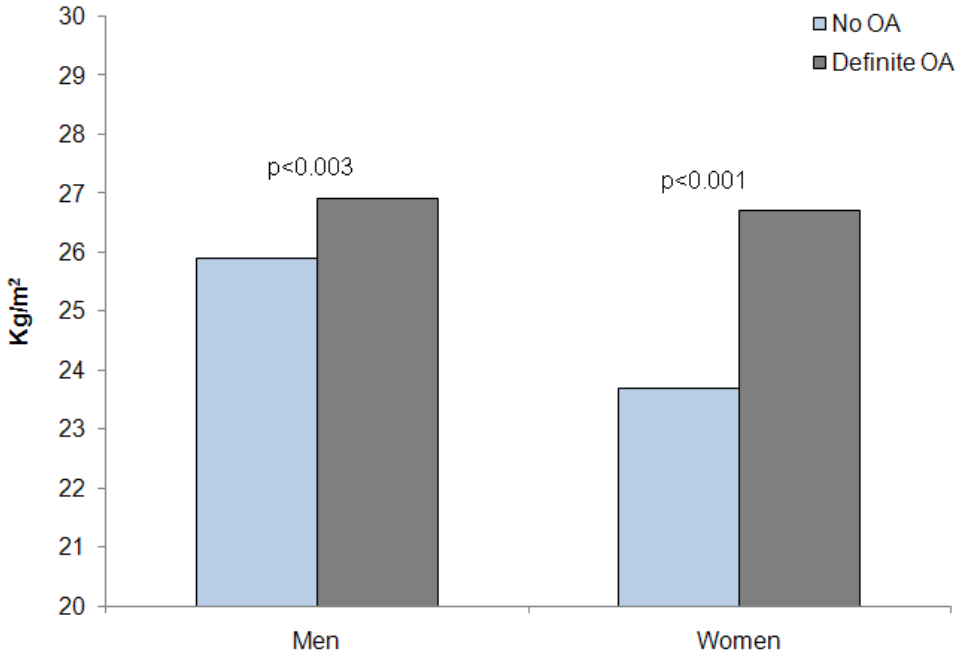


Figure 8. Age-adjusted mean of BMI (adapted from Hochberg *et al*, 1995)

Similarly, the Bristol OA study (5-years) found the main statistically significant risk factor for incident knee OA (Kellgren and Lawrence ≥1) to be obesity (OR 9.1; 95%CI 2.6, 32.2) (Cooper *et al*, 2000). Analysis of radiographic knee OA progression also showed association with the highest BMI tertile (OR 2.6; 95%CI 1.0, 6.8) (Cooper *et al*, 2000).

A three-year longitudinal study investigating predictors of knee pain found obesity to be one of the strongest independent risk factors (Jinks *et al*, 2008). A three-fold increase in incident knee pain was found for obese (BMI>30) individuals (95%CI 1.67, 5.08) in comparison to those with a normal BMI (<25). Progression of knee pain was also found to directly associate with obesity (OR 2.08; 95%CI 1.22, 3.57) (Jinks *et al*, 2008).

The majority of literature reporting the impact of BMI on knee OA or pain has found obesity to be the principle problem. Fewer studies have shown that lower BMI tertiles in the overweight category (≥25, ≤30) to be associated (Tukker *et al*, 2008). A recent cross-sectional study by Tukker *et al* (2008) reported on an 8000 strong Dutch cohort looking into musculoskeletal conditions and consequences. Moderate overweight directly correlated with self-reported knee OA (OR 1.7; 95%CI 1.4, and 2.1) and chronic pain at the lower extremities (OR 1.6; 95%CI 1.3, 1.9).

One potential reason for such a direct relationship could be that being overweight/obese leads to excessive overloading at the knee joint. This in turn could lead to mechanical injury and cartilage breakdown (Felson, 1995) potentially causing both pain and knee OA. The eventual outcome of this in some people could be requirement for total knee replacement surgery.

However, some studies have shown an association between high BMI and hand OA, which cannot so easily be explained by mechanical overloading. A ten-year longitudinal study by Grotle *et al* (2008) reported a direct relationship between obesity and hand OA (OR 2.59; 95%CI 1.08, 6.19). Felson (1995) suggested that overweight individuals could have a systemic cartilage growth factor that may cause accelerated cartilage breakdown leading to OA. Similarly, it may be that in people with a high BMI muscle is being replaced by fat during the aging process. It may be this reduced muscle mass that leads to the presentation of OA, rather than direct presence of excess fat.

1.5.4 Nutritional factors

Over the years there has been mush interest in a potential relationship between OA and nutritional intake (McAlindon and Biggee, 2005). Unhealthy diet is often associated with obesity and high BMI, which has

already been shown as a potential risk factor for knee OA/pain (Hochberg *et al*, 1995; Jinks *et al*, 2006).

Alternatively, diet may affect the knee OA/pain by a more direct method. Oxidative stress has been proposed as a potential biological process with a negative impact on knee hyaline cartilage (McAlindon and Biggee, 2005). The mechanism of action is thought to probably relate to genetic instability caused in the DNA of cartilage cells (chondrocytes) (McAlindon and Biggee, 2005). The destabilizing effect of oxidative damage may stop the chondrocytes from dividing normally, preventing their ability to repair articular cartilage (McAlindon and Biggee, 2005). This lack of cartilage renewal may in turn contribute to the incidence or progression of knee OA (McAlindon and Biggee, 2005). However, such a direct mode of action may not apply for all antioxidant micronutrients (Goggs *et al*, 2005).

It has been suggested that certain dietary components, such as vitamin C and vitamin E may protect against oxidative stress. An early study by McAlindon *et al* (1996b) reported antioxidants, such as vitamin C, may have a beneficial effect on slowing OA progression (aOR 0.3; 95%CI 0.1, 0.8). However, insignificant association was shown between antioxidant nutrients and incident knee OA (McAlindon *et al*, 1996b) with an aOR of 1.11 (95%CI 0.56, 2.18) for vitamin C and 0.71 (95%CI 0.36, 1.38) for vitamin E (McAlindon *et al*, 1996b). These findings were supported by a cross-sectional study by Wang *et al* (2007). Using a food frequency

questionnaire and multivariate analysis, high vitamin C intake was shown to associate with a reduction in bone marrow lesions (OR 0.50; 95%CI 0.29, 0.87) (Wang *et al*, 2007), though no association with cartilage defects was observed (OR 1.02; 95%CI 0.76, 1.36) (Wang *et al*, 2007). Similarly, Yudoh *et al* (2005) undertook a study whereby chondrocytes were put under oxidative stress in the presence and absence of vitamin C. Results suggested oxidative stress was greatly reduced in the presence of vitamin C and the replicating pattern of the cells was able to continue (Yudoh *et al*, 2005).

Therefore, at present it remains unclear as to whether nutrients such as antioxidants really have a beneficial effect on knee OA.

1.5.5 Smoking

Several studies have suggested a potential protective effect of smoking on incident knee OA (Wilder *et al*, 2003). In 1989 Felson *et al* used data from the Framingham Osteoarthritis study to report a modest protective effect of heavy smoking on OA (aRR 0.77; 95%CI 0.60, 0.98). Detailed findings in a later study also showed smoking to have a negative association with knee OA (OR 0.29; 95%CI 0.14, 0.62) (Samanta *et al*, 1993).

Results have been inconsistent, with some studies reporting no link between smoking and OA. Hart *et al* (1993) reported this lack of

association in the Chingford women's study (aOR 1.34; 95%CI 0.68, 2.64) (Hart *et al*, 1993). In support, the Clearwater Osteoarthritis study demonstrated that although current smoking did initially confirm a relationship between smoking and knee OA (RR 0.62; 95%CI 0.46, 0.83) this was lost after adjustment for confounders (aRR 0.97; 95%CI 0.71, 1.31) (Wilder *et al*, 2003). In contrast, a detrimental rather than protective effect was found between former smokers and incident knee pain in one 3-year longitudinal study into knee pain risk factors (OR 1.8; 95%CI 1.2, 2.7) (Miranda *et al*, 2002).

One explanation is that a component of cigarette smoke may actively prevent cartilage destruction (Miranda *et al*, 2002). A different hypothesis for such contradiction is that smoking has a protective effect on knee OA by association rather than direct influence. Felson *et al* (1989) found smokers tended to be younger, thinner and more active in leisure pursuits in comparison to non-smokers. All these characteristics may have a protective effect against knee OA, meaning the act of smoking may not directly reduce incident knee OA. In addition, many of the previous studies into smoking were undertaken in a hospital setting, and the use of hospital-based non-OA controls could have introduced a bias towards smokers who were attending hospital for smoking related disease. This would give the false impression that smoking was beneficial in preventing arthritis.

1.5.6 Genetics

Early evidence of marked heritability in OA was provided in the 1940s by Stecher (1941). He provided strong evidence of genetic predisposition to Heberden's nodes (HN).

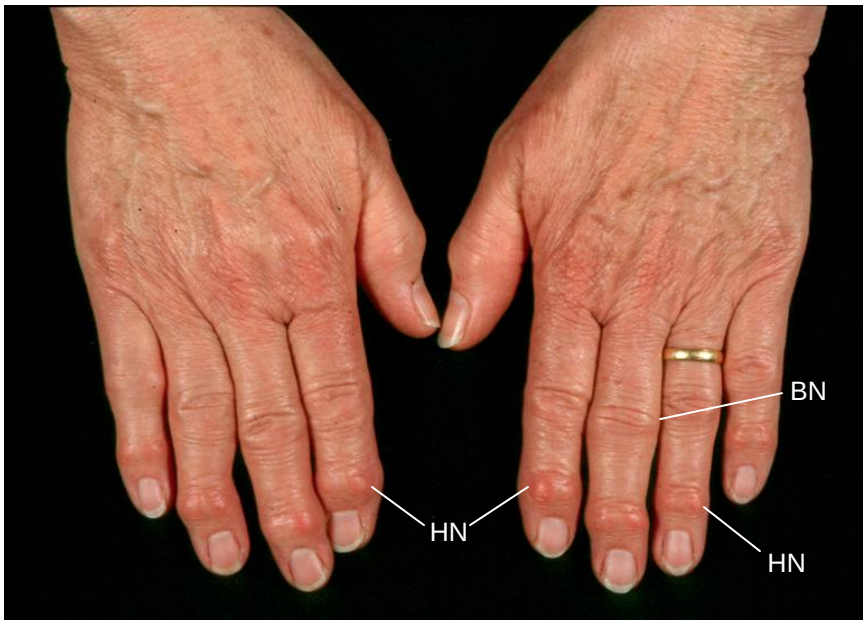


Figure 9. Example of Heberden's (HN) and Bouchard's nodes (BN)

Siblings of affected subjects were three times more likely to have Heberden's nodes than the general population (Stecher, 1941). It was suggested at this time that the risk of OA at other joint sites may also be under strong genetic predisposition.

One of the first genetic loci to be associated with knee OA was the *Taq* 1 polymorphism of the vitamin D receptor (VDR) gene (Keen *et al*, 1997) (Table 1). Approximately a three-fold increase in knee OA was found for women who had the "T" allele at the VDR locus (Keen *et al*, 1997).

Several more recent studies have investigated the role of various other genes that may be related to knee OA risk. Valdes *et al* (2008) suggested that these genes may individually be a modest risk for knee OA, but that a large number could contribute to the overall genetic etiology. This study found polymorphism rs4140564 to be associated with OA. They determined that the genes (PTGS2 and PLA2G4A) surrounding this polymorphism may also be associated with knee OA development as they are part of the prostaglandin E2 synthesis pathway involved in articular chondrocyte proliferation, and cartilage degradation through interleukin 1 beta regulation (Valdes *et al*, 2008) (Table 1).

Table 1. Examples of some genes that have shown potential associations to knee OA

Abbreviations	**Definition**
VDR	Vitamin D (1,25- dihydroxyvitamin D3) receptor – may affect articular cartilage metabolism by stimulating synthesis of proteoglycan.
PLA2G4A	Phospholipase A2, group IVA – may mediate proliferation and differentiation of articular chondrocytes, the only cells found in cartilage.
PTGS2	Prostaglandin-endoperoxide synthase 2 – may encode for COX-2 proteins often seen during early OA, in articular and fibrocartilage. It may cause a pro-inflammatory response.
DVWA	Double von Willebrand factor domain A – may interact with β-tubulin affecting its role within chondrocytes. .

(Keen *et al*, 2007, Valdes *et al*, 2008, and Meulenbelt *et al*, 2009).

A recent study by Meulenbelt *et al* (2009) suggested that the DVWA gene recently identified in a Japanese knee OA study (Miyamoto *et al*, 2008) may also contribute to global knee OA. The global effect of polymorphisms linked with DVWA was significantly associated with knee OA (OR 1.29; 95%CI 1.15, 1.45). However, this effect appeared to be lost when considering European individuals alone (p=0.063), suggesting different genes might effect knee OA development in different ethnicities (Meulenbelt *et al*, 2009).

1.5.7 Joint Laxity

Knee laxity can be a characteristic of an otherwise normal, healthy individual. It may also occur in people who have experienced trauma to the knee, where the ligaments stabilising the joint have ruptured. Both constitutional laxity and trauma–related instability could act as an insult to the knee and initiate OA.

Equally laxity can follow loss of cartilage that is attributable to OA (Figure 10) (Sharma *et al*, 1999). Joint laxity may therefore be a risk for or a consequence of OA.

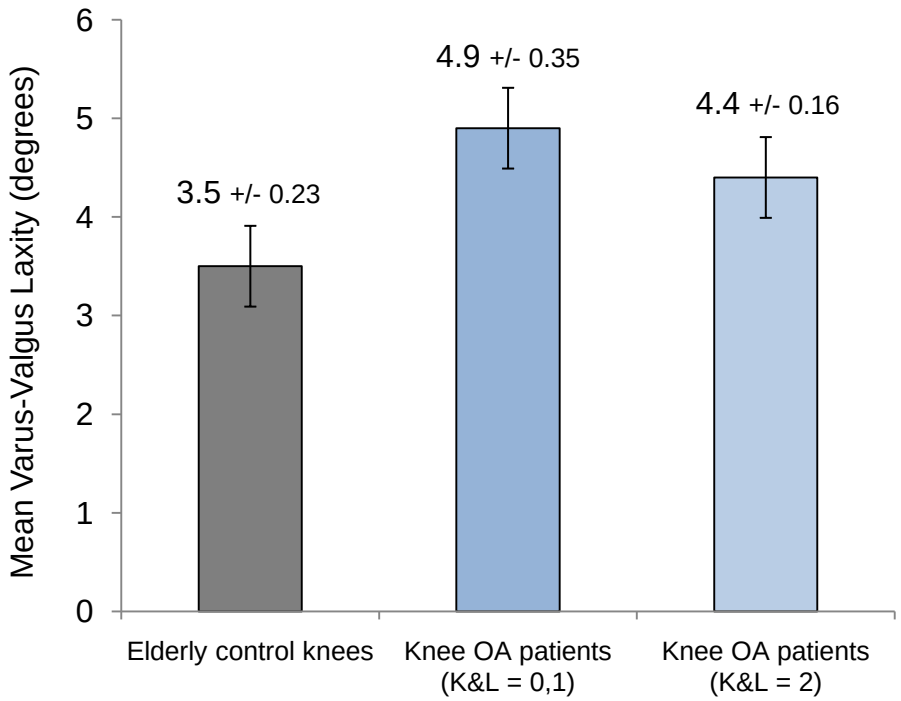


Figure 10. Joint laxity and OA patients (Adapted from Sharma *et al*, 1999)

1.5.8 Varus-Valgus knee malalignment

Different lines of investigation have shown a connection between varus-valgus malalignment and knee OA.

The first published demonstration of varus-valgus malalignment directly impacting on knee OA was in a longitudinal cohort study by Sharma *et al* (2001). Progression of OA was radiographically defined and followed over a three year period. A four-fold increase was seen for knee OA progression in individuals with confirmed varus malalignment at baseline (95%CI 2.20, 7.62) compared to those with straight alignment (Sharma *et*

al, 2001). Similarly the relationship between valgus malalignment and lateral knee OA progression was found to be significant after adjustment for confounders (aOR 4.78; 95%CI 2.08, 11.02). The risk of OA progression was also found to be linked to joint alignment in other studies (Brouwer *et al*, 2007). A six-year prospective study undertaken in Rotterdam found varus alignment significantly increased the risk of knee OA progression (OR 2.90; 95%CI 1.07, 7.88). Conversely, valgus knee alignment had no increased risk of OA progression (OR 1.39; 95%CI 0.48, 4.05).

The influence of varus-valgus malalignment has important implications on specific sites within the knees. Past research has concentrated on the tibio-femoral joint (Hunter *et al*, 2007b). A more recent study has presented the importance of patella malalignment on medial and lateral OA progression (Hunter et al, 2007b). An increased risk of medial or lateral patello-femoral JSN progression was associated with an increase in the medial or lateral displacement of the patella (p=0.03 and p=0.002 respectively) (Hunter *et al*, 2007b). Such association corroborates the earlier findings by Sharma *et al* (2001).

Until recently the main focus of varus–valgus malalignment has been with progression of knee OA. The Rotterdam study highlighted a significant association between varus alignment and development of OA (baseline K/L grade 0) (OR 1.95; 95%CI 1.02, 3.73) (Brouwer *et al*, 2007). However,

not all studies have found knee alignment to predict incident knee OA (Hunter *et al*, 2007a). After adjustment for confounders Hunter *et al* (2007a) found no association between incident knee OA and knee malalignment. The confidence intervals were found to cross the null value on all occasions (Hunter *et al*, 2007a).

A study examining the patterning of cartilage loss in neutral and malaligned knees concluded that cartilage reduction was not substantially different within compartmental sub regions (Hunter *et al*, 2007a). Indeed, one study reported varus alignment did not influence functional limitation in knee OA individuals. This group found varus individuals to perform better in functional limitation tests than those of knee normal alignment (p=0.006) (Lim *et al*, 2008).

1.5.9 Foot angulation

Outward foot angulation has been linked to knee OA. Alteration in foot angulation from the central norm could cause considerable changes in the distribution of forces through the tibial plateaux towards the lateral or medial compartment (Andrews *et al*, 1996). This in turn could lead to the onset of pain or OA at the knee. Alternatively, there is some suggestion that varus foot malalignment is directly linked to hip pain and OA (Gross *et al*, 2009). As such it is possible that in some cases pain felt in the knee may be referred from the hip joint, meaning that foot angulation is only an indirect risk factor for knee pain.

1.5.10 Knee Injury

Joint injury has long been a widely accepted risk factor for knee OA (Wilder *et al*, 2002). Wilder *et al* (2002) used Cox's regression on data collected from the Clearwater Osteoarthritis Study (14 year interval). People who sustained an acute knee injury were nine-times more likely to develop incident knee OA than individuals who had not suffered an injury (95%CI 7.8, 12.1) (Wilder *et al*, 2002). Several other investigations of this kind have been undertaken and all support the correlation between knee injury and potential onset of knee OA. A five year population study (Cooper *et al*, 2000) tracked a potential link between knee injury and incident OA cases. Adjusted odds ratios were found to be significant at 4.8 (95%CI 1.0, 24.1) for individuals with K/L score ≥1 at follow-up (Cooper *et al*, 2000). Determinants of progressive radiographic knee OA (K/L grade ≥1) did not include previous knee injury (aOR 1.2; 95%CI 0.5, 3.0) (Cooper *et al*, 2000), suggesting that knee injury may be more a potential predictor of incident knee OA than its progression.

A similar association pattern has been found for knee pain (Miranda *et al*, 2002). In one Finnish prospective cohort study individuals who had suffered a knee injury were two-times more likely to develop incident knee pain (95%CI 1.7, 3.5) (Miranda *et al*, 2002). Equally, onset of knee pain was significantly associated with baseline knee injury (OR 1.59; 95%CI 1.17, 2.17) in a three-year prospective study (Jinks *et al*, 2008). Yet,

predictors of progression from non-severe to severe knee pain were not found to include knee injury (aOR 1.06; 95%CI 0.73, 1.55) (Jinks *et al*, 2008). This suggests a local biomechanical risk for the onset of knee pain (Jinks *et al*, 2008).

1.5.11 Quadriceps muscle strength

The action of muscle groups, especially quadriceps muscles have a very complex effect on OA (Sharma, 2001). Again, associations of muscle strength to knee OA may differ between incidence and progression of the disease (Sharma, 2001). Past attention has focused on the mechanistic association of quadriceps muscle strength and knee OA, due to the decline in the strength with advancing age (O'Reilly *et al*, 1998a).

To date most studies agree that low quadriceps muscle strength is a risk factor of incident knee OA. Slemenda *et al* (1998) recorded that in the absence of pain or muscle atrophy there was an association between quadriceps muscle weakness and incident radiographic knee OA. Quadriceps muscle strength for women with incident knee OA was 18% lower than for women who had no radiographic changes (p=0.053 after adjustment for body weight) (Slemenda *et al*, 1998). However, little has been examined in relation to any potential protective effect of quadriceps strength on OA progression (Sharma et al, 2003).

It is thought that protective reflexes associated with muscle strength are used to stabilize the knee joint and protect it from stress (Sharma *et al*, 2003; Slemenda *et al,* 1998). The quadriceps muscle normally acts to reduce the impact of stress on the joint when walking and undertaking exercise (Slemenda *et al*, 1998). The absence of this ability may lead to other risk factors associated with knee OA, such as joint injury. The quadriceps muscle is also an important proprioceptive organ, and reduced muscle health could lead to reduced proprioception and increased joint trauma during walking and load-bearing.

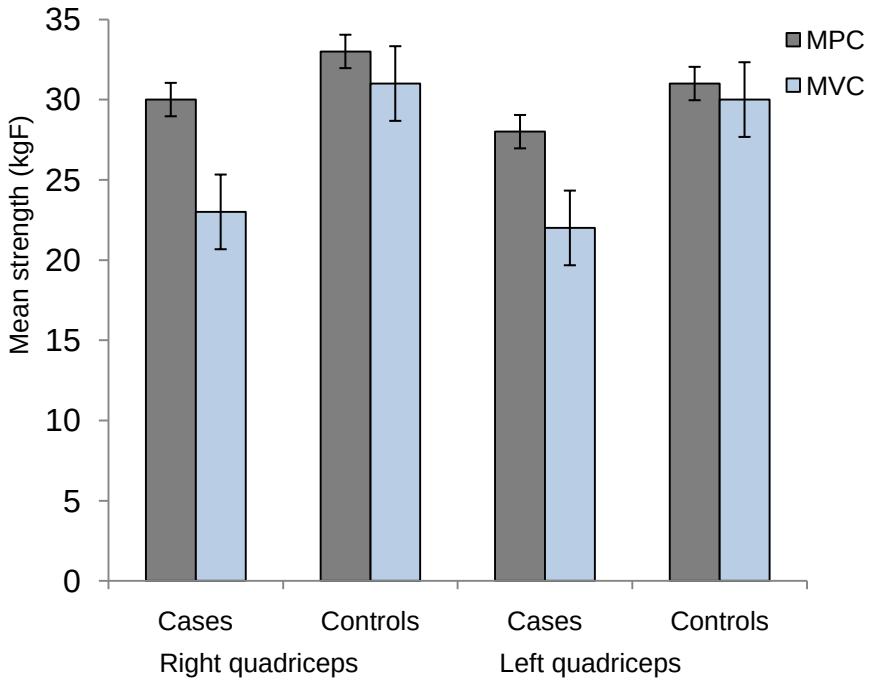


Figure 11. Mean maximum voluntary strength (MVC) and mean predicted strength (MPC) for subjects with (cases) and without (controls) knee pain (adapted O'Reilly *et al*, 1998a).

As with knee OA, lower extremity muscle weakness is a risk factor for knee pain. A nested case control study by O'Reilly *et al* (1998a) found quadriceps weakness to significantly associate with knee pain, participants

who reported no knee pain having significantly higher quadriceps muscle strength than those with knee pain ($p<0.005$) (O'Reilly *et al*, 1998a).

1.5.12 Occupational physical activity

Certain occupational activities have been shown to associate with knee OA. In several studies the risk for knee OA was significantly associated with regular squatting (OR 6.9; 95%CI 1.8, 26.4) and regular kneeling (OR 3.4; 95%CI 1.3, 9.1) (Cooper *et al*, 1994). A systematic review undertaken by Maetzel *et al* (1997) found a strong link between occupational knee bending and knee OA. A consistently positive and significant association was found between occupational exposure and knee OA in men (OR approximately 2) (Maetzel *et al*, 1997).

Such occupational related movements may damage the ligaments and capsule of the knee joint, thus indirectly leading to OA (Cooper *et al*, 1994). Alternatively it has been suggested that specific, repetitive stress on the knee joint may cause direct cartilage damage (Cooper *et al*, 1994).

By the same reasoning occupational physical activity may also be a potential risk factor for knee pain. To examine the potential relationship between occupation and knee pain O'Reilly *et al* (2000) undertook a cross-sectional study. This study clearly demonstrated that occupations with a high level of physically demanding activity directly associated with knee pain (O'Reilly *et al*, 2000). For example, carpenters (OR 4.6; 95%CI 1.9,

11.1), construction workers (OR 2.4; 95%CI 1.4, 4.1) and miners (OR 1.9; 95%CI 1.3, 2.8) were all found to have a significant increased risk of knee pain (O'Reilly *et al*, 2000).

However, the emphasis here was on job titles to reflect workplace activity (Cooper *et al*, 1995). A 2002 study by Miranda *et al* focused more directly on the individual repetitive movements that may affect the knees of workers. A three-year questionnaire survey on 7,000 workers of a forest industry company showed kneeling and squatting for prolonged periods of time was not a strong predictor of incident knee pain (OR 1.3; 95%CI 0.7, 2.3) (Miranda *et al*, 2002). Therefore, a direct association between knee pain and occupational physical activity remains unconfirmed.

1.5.13 Leisure physical activity

Exercise regimes are widely advocated for all persons to maintain physical and general health (Devos-Comby *et al*, 2006; Felson *et al*, 2007). Recreational activity helps muscular strength, thereby assisting joint stability and potentially reducing the risk of knee OA. Nevertheless debate remains as to whether recreational physical activity has a positive, negative or absent effect upon knee OA/pain (Devos-Comby *et al*, 2006).

To evaluate the potential effect of exercise upon knee OA Felson *et al* (2007) conducted a nine-year prospective study on the Framingham

population. Leisure physical activity was found to neither protect against nor increase the risk of knee OA (Felson *et al*, 2007). Risk of radiographic OA, symptomatic OA or joint space narrowing was not significantly associated with activities such as walking, jogging or working up a sweat (Table 2) (Felson *et al*, 2007).

Table 2: Incident knee OA in the Framingham population and recreational physical activity (adapted from Felson *et al*, 2007).

	Adjusted OR (95%CI)
Radiographic OA	
Walk ≥6 miles/week	1.10 (0.73, 1.66)
Sweat ≥3 times/week	1.15 (0.72, 1.82)
Symptomatic OA	
Walk ≥6 miles/week	0.78 (0.49, 1.24)
Sweat ≥3 times/week	1.23 (0.72, 2.10)
Joint space narrowing	
Walk ≥6 miles/week	0.95 (0.62, 1.45)
Sweat ≥3 times/week	1.29 (0.82, 2.02)

Adjusted for age, BMI, knee injury and sex

In contrast, a cross-sectional study on knee OA in Finland found footballers (aOR 12.3; 95%CI 1.35, 111) and weightlifters (12.9; 95%CI 1.47, 113) to be at increased risk of incidence knee OA (Kujala *et al*, 1995). The effect of recreational physical activities can also be site-specific. For example, football players are more at risk of tibio-femoral OA, whilst weightlifters are more at risk of patello-femoral OA (Kujala *et al*, 1995). Therefore intensity, load and direction of biomechanical forces achieved through joint impact are likely to be associated with incident OA (Felson *et al*, 2000).

In support of this several studies have demonstrated that participation in high physical activity (including recreational sports) can increase the risk of incident OA (McAlindon *et al*, 1999). A person who undertook ≥4 hours of heavy activity per day were 7-times (95%CI 2.5, 21) more likely to develop incident knee OA compared with someone who undertook no heavy physical activity (McAlindon *et al*, 1999). However, few associations were made between incident knee OA and moderate physical activity (p=0.5) compared to someone who undertook no moderate physical activity. Similarly, light physical activity (p=1.0) compared to no light physical activity was not found to be a risk for incident knee OA (McAlindon *et al*, 1999).

A conflicting review by Devos-Comby *et al* (2006) indicated that exercise regimes could improve the overall impact of OA, both directly and indirectly through the self perception of physical health. Further research needs to be undertaken into the area of recreational physical activity and any relationship with knee OA/pain.

1.5.14 Co-morbidities and associated pain

Severity of single regional pain, such as at the knee, can be influenced by pain at other sites (Croft *et al*, 2005). For example, Croft *et al* (2005) surveyed 8,995 individuals using component body mannequins. For those

who responded, each additional pain site increased the severity of single regional pain at the knee (Table 3).

Table 3. Severity of problems in patients with knee pain

Pain regions	Pain on WOMAC OR(95%CI)
Knee alone	**1**
Knee plus 1 additional region	1.2 (0.9, 1.7)
Knee plus 2 additional regions	**1.4 (1.0, 1.8)**
Knee plus 3 additional regions	**1.7 (1.3, 2.4)**
Knee plus 4 additional regions	**2.8 (2.0, 3.9)**
Knee plus 5 additional regions	**3.6 (2.5, 5.2)**

(adapted from Croft *et al*, 2005)

This association remained after adjustment for age, gender, BMI and laterality of knee pain, with an aOR of 1.8 (95%CI 1.4, 2.4) for pain at ≥2 additional body sites (Croft *et al*, 2005).

Similarly, Jinks *et al*, 2008 also used the pain mannequin to determine the number of painful body sites. They found that people with pain in two or more body regions were 1.47-times more likely to develop incident knee pain (95%CI 1.14, 1.89) after a three year interval. The presence of pain in a singular body region may therefore be an indication of a wider pain problem.

1.5.15 Index-ring finger ratio (2D:4D)

2D:4D is a variable trait the cause of which does appear to be linked to early life, with one hypothesis being that it is testosterone related (Robertson *et al*, 2008).

The first study to examine 2D:4D as a possible risk factor of OA was undertaken in Nottingham by Zhang *et al* (2008). This group found individuals with male patterning (Index<ring) were two-times more likely to have knee OA than those with type 1 (index>ring) or 2 (index=ring) patterning (Zhang *et al*, 2008). The mechanism accounting for this association is unknown.

A self-reported 2D4D instrument has been developed and validated in the Nottingham unit. However it has yet to be tested in population-based research.

1.5.16 Anxiety and depression

Psychological factors such as anxiety and depression have often been linked to a person's perception and reporting of pain (Creamer *et al*, 1999). The Bristol OA500 study obtained cross-sectional data in addition to other longitudinal data at an eight year review of 500 patients (Dieppe *et al*, 2000). They found that the level of anxiety or depression was much higher in the group affected by OA than was expected (Dieppe *et al*, 2000).

However, recruitment was from a hospital based rheumatology clinic and there was no control comparison for those with OA.

These findings were further extended to include a significant relationship between anxiety, depression and knee pain. A community study by Creamer *et al* (1999) used data from the Baltimore longitudinal study of ageing to report that women with knee pain but no radiographic OA have higher anxiety scores than those without knee pain ($p=0.025$). In comparison, knee pain status was not related to anxiety in men ($p>0.05$) (Creamer *et al*, 1999). They also found little association between depression and knee pain.

Other psychological factors, such as poor health perception (using the SF36 index) are also important characteristics to investigate in relation to knee pain and disability. Individuals who report low quality of life scores (including that of physical function) often significantly associate with prevalent knee pain ($p<0.001$, for all SF36 scores) (O'Reilly *et al*, 1998b). Support for this finding comes from Cecchi *et al* (2008), whose community based study produced significant association between knee pain and poor self-reported health ($p=0.008$). There is a clear association between pain and psychological distress (O'Reilly *et al*, 1998b).

1.5.17 Bone mineral density (BMD)

Numerous studies have examined BMD as a risk factor for OA. Five hundred and seventy three pre and peri-menopausal women from the Michigan Bone Health Study (Sowers *et al*, 1996) showed that high bone density was associated with radiographic knee OA (K/L ≥2) (OR 2.1; 95%CI 1.06, 4.10) (Sowers *et al*, 1996).

Data from the Baltimore longitudinal study of aging (ten-year intervals) found that BMD was an independent risk factor for incident knee OA (Hochberg *et al*, 2004). However, the significance of this association was dependent on the site of bone density testing. ORs of incident knee OA were 1.64 (95%CI 1.03, 2.61) for spinal BMD and 0.78 (95%CI 0.51, 1.20) for femoral neck BMD (Hochberg *et al*, 2004). Likewise, a sample of subjects form the six-year longitudinal Rotterdam study (Bergink *et al*, 2005) found an association between high femoral neck BMD and incident knee OA. A longitudinal study undertaken over 48 months by Hart *et al* (2002) also found spinal BMD (p=0.002) and hip BMD (p=0.02) to be significantly higher in women with incident radiographic osteophytes at the knee (Hart *et al*, 2002).

However, investigators performing longitudinal and cross-sectional studies differ in their opinion covering the effects of BMD on knee OA progression. In the Chingford population, women with progressive knee OA showed no

difference in spinal BMD compared to non-progressors (Hart *et al*, 2002). However, a positive association was suggested between low hip BMD and progression of OA, though this was statistically insignificant (Hart *et al*, 2002). Univariate analyses by Bergink *et al* (2005) found results similar to those of the Chingford study, with low femoral neck BMD potentially associating with OA progression, but the association was lost after adjustment for age, gender, BMI and mobility (p=0.55) (Bergink *et al*, 2005).

A key factor affecting bone density is vitamin D. Low vitamin D intake is thought to directly affect bone density by impairing calcium metabolism and matrix ossification (McAlindon *et al*, 1996a). In turn, any reduction in these processes may be detrimental in aiding bone response in OA progression (McAlindon *et al*, 1996a). In support of this theory, low intake of vitamin D was found to increase four-fold the risk of progression of established knee OA (95%CI 1.4, 11.6) (McAlindon *et al*, 1996a). However, there was no evidence of an association between low intake of vitamin D and incident OA (OR 1.02; 95%CI 0.47, 2.20) (McAlindon *et al*, 1996a).

Alternatively, high subchondral bone density may increase mechanical stress to the knee cartilage leading directly to damage and OA (Sowers *et al*, 1996). A cross-sectional study conducted by Lo *et al* (2008) found a direct link between meniscal damage and higher tibial BMD ($p<0.0001$ for medial compartment and $p=0.001$ for lateral). The fibro-cartilaginous

menisci assist load distribution at the knee (Lo *et al*, 2008) so could potentially be another link between bone density and risk of knee OA.

1.5.18 Balance

Balance is a complex and dynamic force that is essential to everyday activities (Hassan *et al*, 2001). Control of posture is part of this delicate process and is thought to be easily affected by joint related disorders, such as OA (Hassan *et al*, 2001). This theory was investigated by Hassan *et al* (2001) in a 140 participant case-control study. Knee OA participants were shown to have reduced balance control (higher postural sway) in comparison to controls ($p<0.001$) in both lateral and antero-posterior directions (Hassan *et al*, 2001).

Whether a reduction of postural control is a cause or a consequence of knee OA warrants further investigation. One potential explanation for balance acting as a risk for knee OA may be the linking factor of knee injury. It is possible that individuals with poor balance would be more likely to sustain a fall that could lead to knee joint damage (Hassan *et al*, 2001). Arden *et al* (2006) confirmed this connection, noting individuals with knee OA often had an increased risk of falls (OR 1.26; 95%CI 1.17, 1.36).

Postural sway has also been shown to be affected not only by knee OA, but also by knee pain. A 30-month longitudinal study by Messier *et al*

(2002) found a significant decline in the balance of adults (≥65-years) who suffered chronic knee pain ($p<0.001$). Balance and strength are both aspects of physical function (Messier *et al*, 2002). Reduced muscle strength has already been shown as a potential risk factor for knee pain.

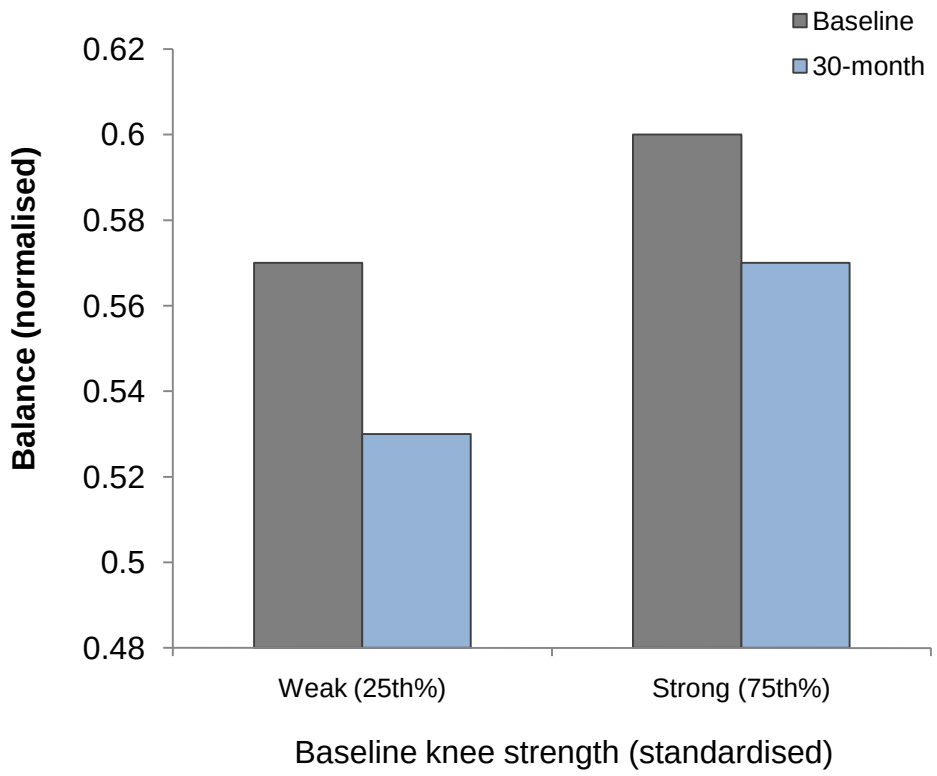


Figure 12. Changes in balance based upon baseline knee strength status (adapted from Messier *et al*, 2002).

Messier and colleagues (2002) built on this relationship supporting the idea that lower muscle strength at the knee also associates with poor balance ($p=0.023$) (Figure 12). Further research into the mechanisms of action between balance control, knee strength and knee pain would seem justified.

1.6 Summary

Epidemiological studies have largely focused on the incidence or progression of knee OA (Grotle *et al*, 2008). Although some studies have examined common knee pain (Cecchi *et al*, 2008; Thomas *et al*, 2005; O'Reilly, 1996) there have been no longitudinal studies into the long-term natural history of knee pain. Advancing our knowledge of this common condition could have implications for primary and secondary prevention.

Early Nottingham population studies were largely questionnaire driven and obtained cross-sectional data for prevalence. These studies have provided the opportunity to follow-up the incidence and outcomes of knee pain and associated risk factors some ten years after the original community studies.

1.7 Objectives

To determine in a community sample over a 10-year period:

1. The incidence of knee pain

2. The outcome of knee pain

3. The risk factors associated with the incidence and/or outcome of knee pain, and determine whether these risk factors are the same.

The secondary objectives include developing and validating:

1. a self-reported varus-valgus knee malalignment instrument

2. a self-reported foot inversion/eversion instrument

2. Method

2.1 Ethical approval

All aspects of this current study were approved by the Nottinghamshire County Teaching Primary Care Trust (PCT), Nottingham University Hospitals NHS Trust and the Nottingham1 Research Ethics committee. Examples of the relevant consent forms are appended (Appendix 1).

2.2 Study participants

Individuals were recruited from two previous community-based studies in which knee pain was the primary outcome measure. One was a cross-sectional survey to recruit people with knee pain for an intervention study (Thomas, 2001) and one was a cross-sectional survey to examine prevalence of knee pain (O'Reilly, 1996). Baseline data was collected between 1996-1999. Exclusion criteria included terminal illness, psychiatric illness, deceased, severe dementia, non-Nottingham residence (O'Reilly, 1996; Thomas, 2001), <40 and >79 years old (O'Reilly, 1996), or <45 years (Thomas, 2001). At baseline, 13,381 questionnaires were posted and 9429 people responded (2,868 knee pain positive/6,397 knee pain negative). Data included demographic, knee pain, hip and back pain and disability information. Of these respondents, 1,729 had knee radiographs undertaken and 1,386 of these also had muscle strength and other clinical assessments. Of the 1,729 participants x-rayed, 1,267 came from the study by Thomas (2001) and were originally selected because they were

knee pain positive. The remaining participants (462) were part of a case-control analysis undertaken by O'Reilly (1996), of which 244 had knee pain, and 217 had no knee pain.

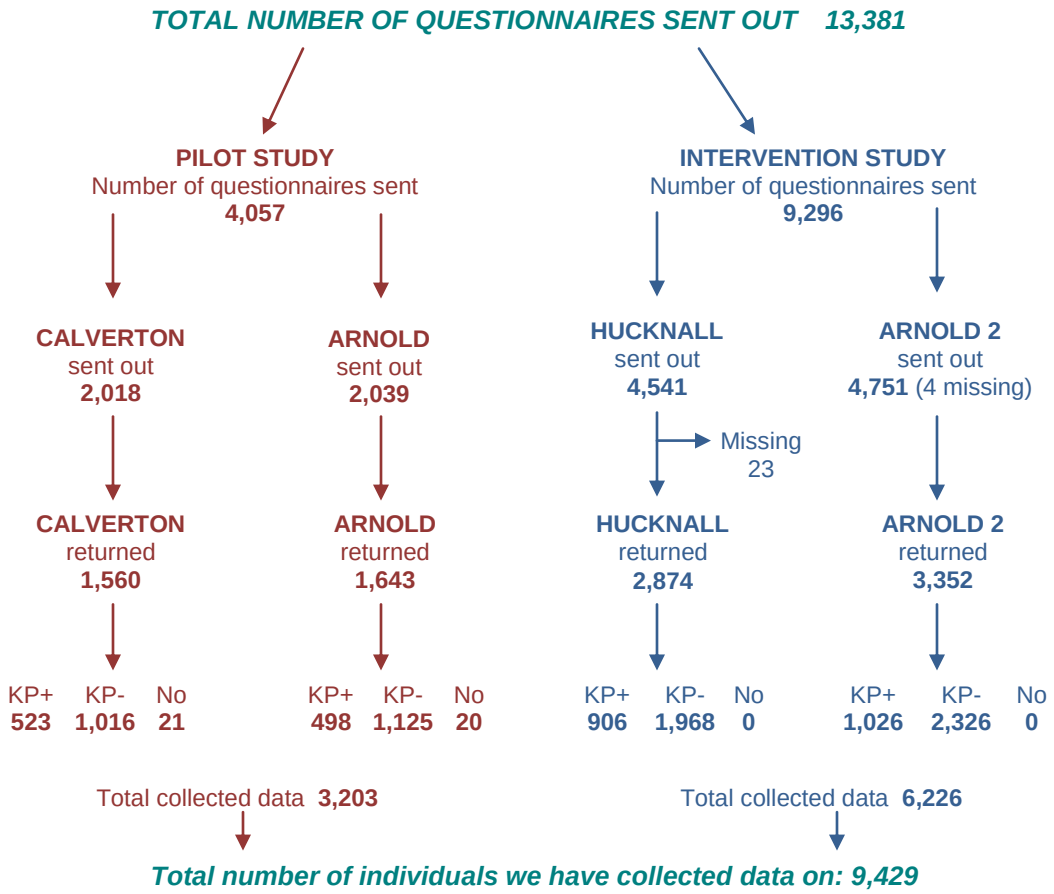


Figure 13. The number of questionnaires sent and received at baseline

The 1,729 radiographic films from the baseline studies were first examined by Neame *et al* (2002) in a case-control study. Twenty eight of the 1,729 individuals had provided no contact or questionnaire information at baseline. These individuals were not available for potential re-contact

during this study. The total number of individuals for re-contact at follow-up was 9,429.

2.3 Retrieval of the baseline data

Discs containing study information were searched for the appropriate baseline files. These were transferred to a master database in Access, allowing further evaluation of their contents. All questionnaire information from the pilot study (O'Reilly, 1996) and the primary outcome data from the intervention study (Thomas, 2001) had been double entered at baseline. A 10% random sample of the remaining data from the Thomas study (2001) had also been double entered at this time. Accuracy in all instances was above 98% (Thomas, 2001). The total number of questionnaires sent, from which GP surgeries they were sent, and how many questionnaires were returned from each surgery was recorded.

2.4 The literature search

The search began by collecting and sorting English language articles relating to knee pain and osteoarthritis. Systematic searches were engaged through the use of Medline Ovid, and Embase. The search began with the use of generic terms, like "osteoarthritis", "knee pain", and "knee osteoarthritis". Terms were then combined with more specified criteria, such as "occupational activity", and "muscle strength". Regular, updated searches were undertaken to ensure all relevant, new material

was referenced. An example of the systematic search carried out is appended (Appendix 2).

2.5 Follow-up data collection

The cohort was followed up during 2007-2008 using a retrospective cohort study design. Subjects were once again recruited via the Nottinghamshire County Teaching PCT. The cohort for this retrospective study consisted of subjects from the 4 general practices in North Nottinghamshire, including: Stenhouse Medical Centre, Arnold; Highcroft Surgery, Arnold; Torkard Hill Medical Centre, Hucknall; The Surgery (Calverton practice), Calverton.

The names of 9,429 baseline subjects for re-contact were listed alphabetically in Excel. Each individual within this ordered dataset was allocated a follow-up identification (ID) number based upon their position in the alphabetical list. The dataset, complete with follow-up ID numbers, was then transferred back into Access. Through the use of design queries and table appendages the whole dataset was split into four separate lists (Stenhouse, Highcroft, Torkard and Calverton). These were further divided into those who were originally contacted with just a questionnaire (Group A) and those who were additionally asked to attend a clinical assessment (Group B). The relevant recruitment lists were sent to each General Practice (GP) surgery. Subjects were screened by the current healthcare team at each GP surgery to ensure that they were still alive, eligible for contact, and registered with the practice.

2.5.1 Design of questionnaire

The composition of the questionnaire required consideration both of the data collected at baseline and current topics of interest. It was divided into 15 sections; demographics, employment, physical activity (occupational and leisure), knee section, foot section, hand section, finger index ratio, medical history/medication, and health perception (Appendix 3).

Demographic sections were designed to gain vital information about potential risk factors for knee pain as well as being an easy introduction for the participant.

The knee section was constructed in four chapters; knee pain, varus/valgus alignment, treatment of knee pain and views on knee pain. A validated screening question was used to determine the presence of chronic persistent knee pain: “Have you ever had knee pain in or around the knee on most days for at least a month?” (Thomas, 2001) Given the importance of this information subjects who responded “yes” were administered a series of further questions regarding pain duration, severity, site and time to event.

To examine occurrence of foot pain questions about severity, duration and location of foot pain were asked in a similar fashion to knee pain. Questions included “have you had foot pain on most days of the last month?” and “in the last 10 years, approximately how many months of

each year have you had chronic foot pain?" Foot inversion/eversion was thought to have a bearing on the outcome of weight distribution and knee pain status. Therefore a novel question with illustrations was included in the questionnaire.

A blank mannequin was used to capture information about a subject's wider pain experiences.

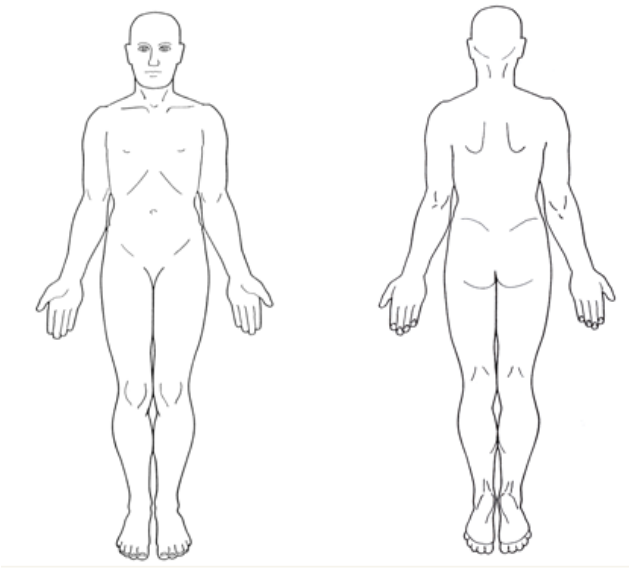


Figure 14. Example of the blank pain mannequin used in the study questionnaire

This was a minor modified version of a previously used mannequin. The modification was deemed necessary to allow for clearer distinctions between front and back. As these modifications were minor in nature it was considered unnecessary for the question to be formally re-validated.

Aspects of health perception, such as quality of life and disability were assessed using the Short Form (SF) 36.

2.5.2 Piloting the questionnaire

A pilot questionnaire was used to identify any problems with content, language, or layout. A small sample of 12 laypersons, over 40 years, and separate from the study population were given a copy of the questionnaire and invited to make comments about its ease of use. These comments were used to create the final version of the study questionnaire. Changes included provision of specific instructions on how to correctly examine knees and feet e.g. whilst walking; and simplification of the 'current medication' table by separating months and years into different columns.

2.5.3 Distribution of questionnaires

The study population was classified into two groups. Group A were individuals who responded to the baseline questionnaire, but did not undergo x-rays or clinical assessment. Group B were individuals who replied to the baseline questionnaire and in addition underwent a clinical assessment and knee radiographs. Supporting documentation is included in Appendix 4.

Potential participants were sent a letter of invitation from the general practice, along with [1] an accompanying letter from Academic Rheumatology that explained the study; [2] a participant information sheet (Group B only); [3] the follow-up questionnaire; and [4] a consent form to indicate whether or not they agreed to have their details stored for future contact. All subjects were provided with a stamped addressed envelope in

which they returned their questionnaire. Group A and group B received different letters of invitation. Groups A and B were informed that completion and return of the questionnaire would be taken as consent for us to use the information provided. Group B were asked to indicate whether they were willing to attend Academic Rheumatology for a clinical assessment and x-ray of their knees. Reading the posted information and completing the questionnaire would have taken approximately 20-30 minutes.

The new ID numbers were written on the back of all returning questionnaires allowing for de-identification of the information. New ID numbers and dates received were recorded on the GP lists. After a period of three weeks from the initial send dates lists were filtered to show persons who had not responded. A single reminder letter and questionnaire pack was then sent via the GP surgery to non-responders (3,322 reminders sent). Data from the returned questionnaires was entered onto a master file in Access. The paper copy was stored within an archiving box in the Department of Academic Rheumatology.

Group B participants who were willing to attend were contacted by telephone to arrange a mutually convenient appointment. Each complete clinical assessment and X-ray visit took approximately 1hr 45 minutes. Nearly all appointments were arranged to take place shortly after the return of the questionnaire. Group B participants were reimbursed for the travel

expenses of this visit (25p per mile if travelled by car or in a taxi that was paid for directly by Academic Rheumatology).

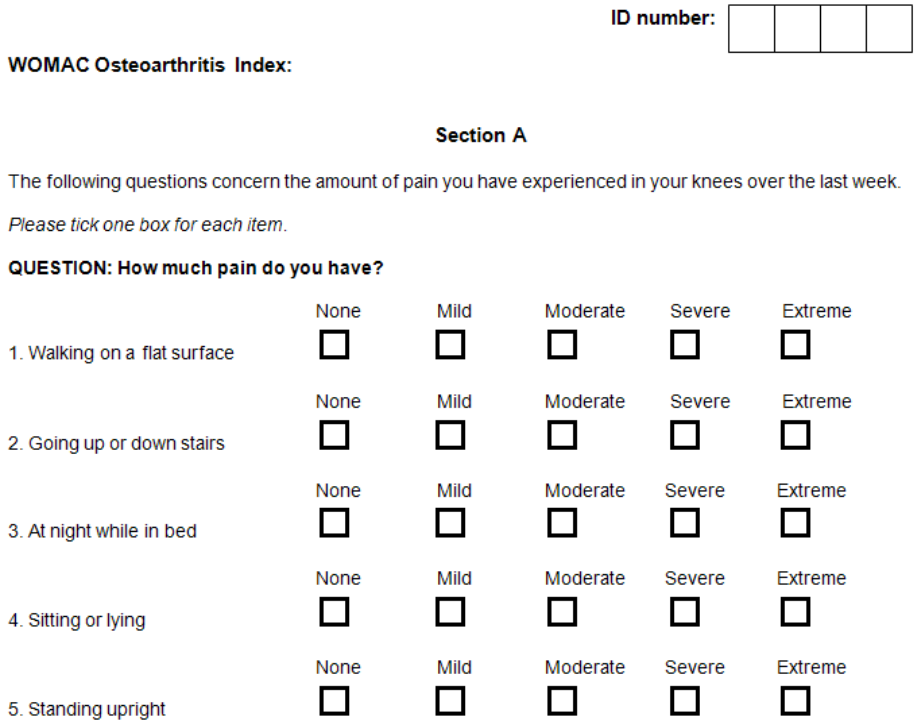
2.5.4 Clinical assessment procedures

A wide variety of additional health instruments were used at the clinical stage of the assessment. Before clinical procedures were undertaken the two researchers involved (SI, AM) underwent equipment and safety training. Procedural and update training for the DXA bone densitometer was provided by the Head of Medical Physics. Assessment order was decided during training by SI and AM and was based upon the timing of the procedures, the link between them and the requirements of two people to use one piece of equipment (e.g. DXA).

Group B participants attended a single visit at the City Hospital (Academic Rheumatology and the nearby Radiology department). Before any clinical assessments the researcher discussed the procedures with the participant and gained informed consent. If the participant agreed with each statement, they were asked to initial against each statement, then sign and date at the bottom. This was witnessed and counter-signed by the person taking consent. ICH-GCP guidelines were followed in relation to taking informed consent. Participants were given verbal feedback regarding their clinical assessment results during their visit. Letters were only sent to a participant's GP if their radiographic or bone density scores appeared to show abnormalities.

2.5.4.1 Additional questionnaire

Prior to the clinical evaluations participants completed a validated OA-specific questionnaire (the Western Ontario and McMaster Universities Osteoarthritis Index, WOMAC). This consisted of 24 items relating to pain, joint stiffness and function, all of which were rated on a numerical (Likert) scale (Angst *et al*, 2005) (See Appendix 5 for the complete WOMAC).



ID number: | | | | |

WOMAC Osteoarthritis Index:

Section A

The following questions concern the amount of pain you have experienced in your knees over the last week.

Please tick one box for each item.

QUESTION: How much pain do you have?

	None	Mild	Moderate	Severe	Extreme
1. Walking on a flat surface	☐	☐	☐	☐	☐
2. Going up or down stairs	☐	☐	☐	☐	☐
3. At night while in bed	☐	☐	☐	☐	☐
4. Sitting or lying	☐	☐	☐	☐	☐
5. Standing upright	☐	☐	☐	☐	☐

Figure 15. Example of part of the WOMAC questionnaire

Data on other potential risk factors for knee pain, including footwear through the decades and vitamin intake, were obtained during the visit. Dietician Dr Sian Roberts from the University of Southampton was consulted for advice regarding the content of the dietary questions used in this study.

2.5.4.2 *Grip strength*.

Muscle strength was measured using a JAMAR hydraulic hand dynamometer (Lafayette Instruments) (Figure 16).

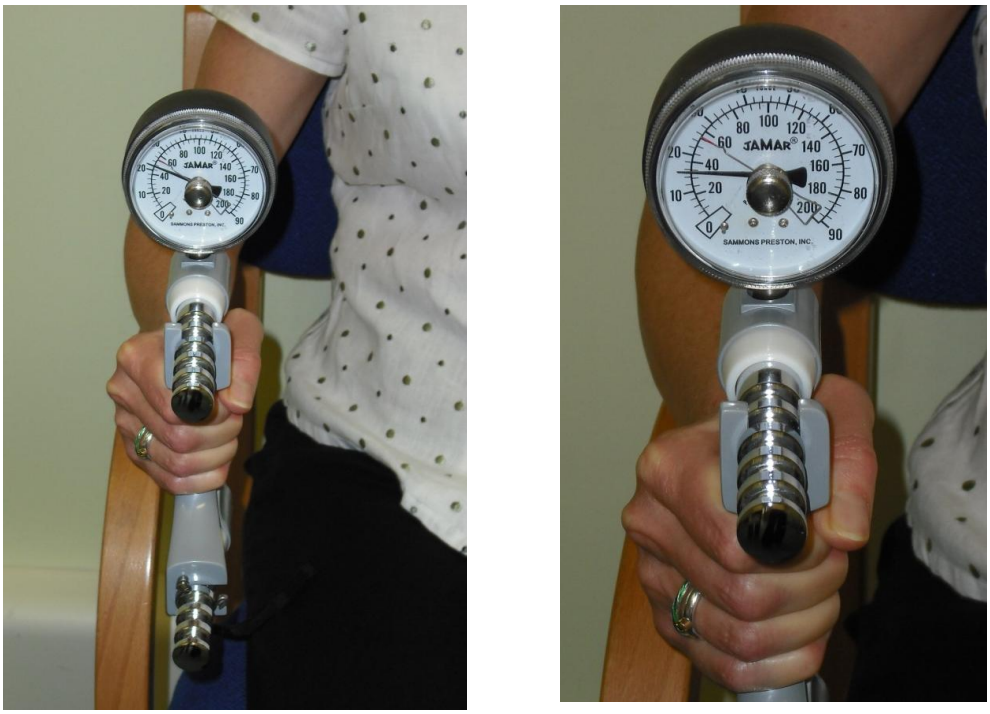


Figure 16. JAMAR hydraulic hand dynamometer

Individuals were positioned sitting upright in a stable four-legged chair with thighs horizontal, feet flat on the floor, arms on the arm-rest (upper arm vertical, lower arm horizontal), and wrists on the front edge of the rest. The grip device was then placed into the participant's hand and they squeezed the devise momentarily as hard as possible and then released their grip. This was performed three times on each hand and the mean value was obtained for each. This instrument has previously been recommended by the 'American Society of Hand Therapists' for measuring grip strength in patients, and is considered a "gold standard" (Mathiowetz, 2002)

2.5.4.3 Quadriceps muscle strength.

The 'Nicholas Manual Muscle Tester' (Lafayette Instruments) was used to assess maximum voluntary quadriceps contraction.

Figure 17. Nicholas Manual Muscle Tester

The participant sat upright on an examination couch (no arm rests) with thighs horizontal and feet flat on a foot stool (90 degrees). The couch was adjusted until the correct angle of the legs was obtained for each individual. The Muscle Tester was positioned at the bottom of the participant's tibia just above the ankle (Figure 18). The observer stood, at full lunge, directly facing the leg being examined. Observer stance was agreed during training between SI and AM to ensure continuity. However, as observer stature was shown to cause variability in results obtained (especially with knee pain negative participants) AM completed over 90% of muscle strength assessments. The participant pushed against the devise as hard as possible in an attempt to raise their leg forwards. Each

leg was measured in strength to the nearest Newton on three occasions. An Intra Class Correlation (ICC) check was carried out on the collected data to test for variability.

Figure 18. Muscle tester being positioned at the bottom of the participant's tibia

Figure 19. Nicholas Manual Muscle Tester in use

2.5.4.4 Balance.

A balance performance monitor (manufactured by SMS Healthcare) was used to measure weight-bearing postural sway (Figure 20).

Figure 20. Balance performance monitor

The distance between a participant's medial malleoli in normal stance was measured.

Figure 21. Measuring the distance of the participant's medial malleoli

Individual weight, height and stance were all entered into the DataPrint software attached to the balance console. Subjects were directed to stand in bare feet on the two footplates attached to the console. The arch of each foot was carefully placed over the central line of the plate, and the distance between the footplates was adjusted to match each subject's natural standing stance (Figure 22).

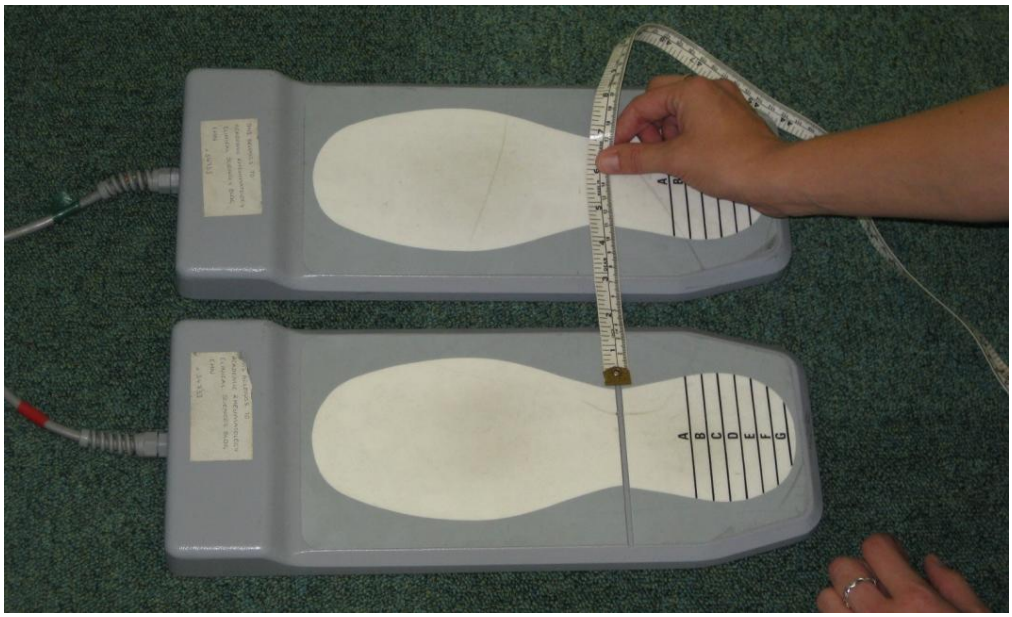


Figure 22. Measuring the correct distance for the foot plates

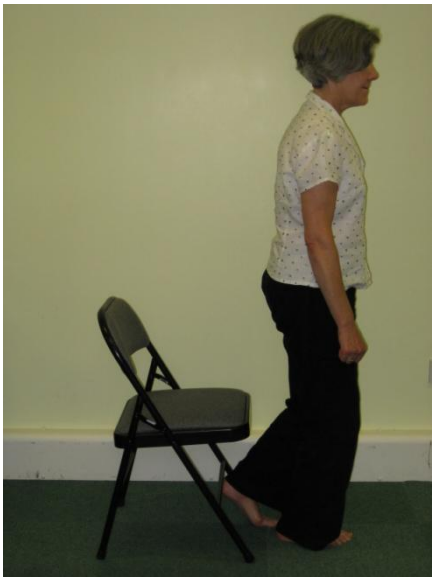
Each subject was told to focus on a point on the wall, arms by their side and to make no voluntary movements. The Information was then gathered over a 30 second period (Figure 23).

Figure 23. Gathering of participant data using the balance performance monitor

The data were presented electronically in a graphical and numerical format. The first graph depicts the sway coefficient in terms of medial-lateral movement. The second and third charts indicated anterior-posterior sway. The sway coefficient is a measure of the standard deviation of the balance coefficient (SMS Healthcare, DataPrint software v5.3 operating manual, 1998). The larger the sway coefficient, the greater the deviation from the norm, and the greater the postural instability (SMS Healthcare, DataPrint software v5.3 operating manual, 1998).

2.5.4.5 Timed Get Up and Go test.

The 'Timed Get Up and Go' was the validated objective assessment used to measure participant's mobility (Podsiadlo and Richardson, 1991). The participant sat in a chair with their back upright, feet on the floor, and any walking aid in their hand. They stood up, walked a measured distance of 3 meters, turned around, walked back to the chair and sat down (Shumway-Cook *et al*, 2000) (Figure 24).



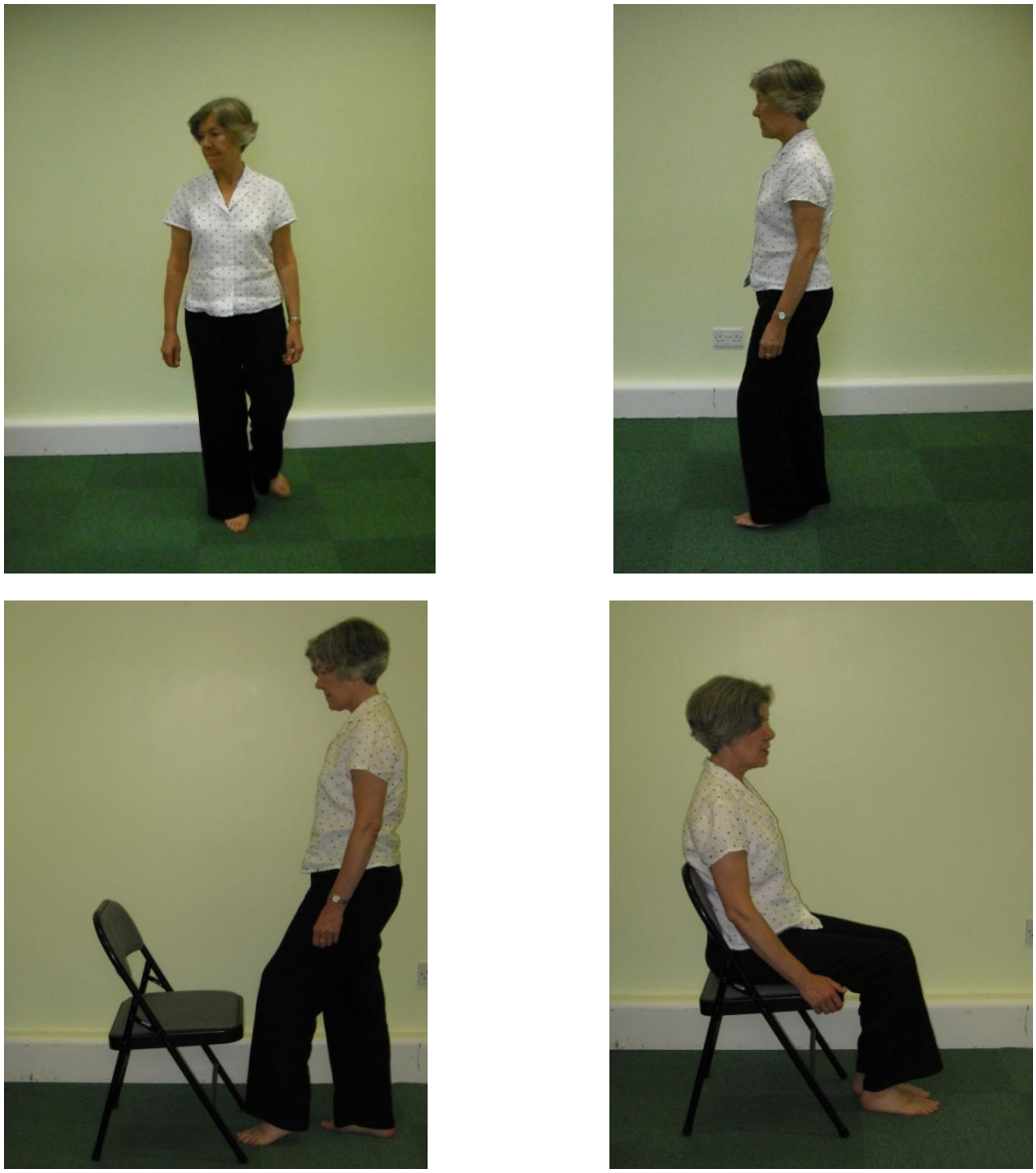


Figure 24. Sequence of photos showing a participant undertaking the 'Timed Get Up and Go' assessment

Timing, using a stop watch, began when the participant rose from the chair and ended when they completed the circuit. The entire process was timed and recorded. Longer than 20 seconds is considered to reflect mobility problems (Podsiadlo and Richardson, 1991).

2.5.4.6 Height, weight and body fat.

The participant's height was measured to the nearest 0.1cm (with shoes and socks removed) using a stadiometer. Weight (to the nearest 0.1kg) and body fat were measured (with shoes, socks and bulky clothing removed) using a body impedance monitor.

Figure 25. Participant on the body impedance monitor

2.5.4.7 Bone density

Calcaneal bone density measurements were obtained on each participant using an Apollo DXA densitometry machine. All safety and operational procedures were undertaken (specified by Health and Safety commission).

Footwear was removed and the heel of the foot on the same side of the dominant hand was placed in the depression of the machine.

Figure 26. Apollo DXA densitometry machine with participant's dominant foot

If the dominant foot had sustained a previous fracture the non-dominant foot was measured. Each participant kept their foot as still as possible during the scan, which took 15 seconds. The radiation dose exposure was equivalent to less than six hours natural background radiation (<2μSv). Project staff followed the specific operational procedures with regard to the controlled area and the manufacturer's instructions.

2.5.4.8 Radiographic assessments

Standardised weight-bearing fully extended antero-posterior radiographs (to show medial and lateral tibio-femoral compartments) and skyline radiographs (to show patello-femoral compartments) were taken at both baseline and follow-up. Skyline views were taken with knees flexed (using variable gigs) lying on a couch. All radiographs were undertaken in the same radiology unit following a standard protocol. Focus film distance was 100cm for both skyline and tibio-femoral views. The dose exposure of these was equivalent to less than two days worth of natural background radiation (50kVp/5mAs for tibio-femoral radiographs and 60kVp/5mAs for skyline radiographs). Follow-up radiographs were obtained in PACS electronic format: all measurements were performed using HIPAX Dicom software. Radiographs at baseline were scanned and entered into HIPAX. Baseline and follow-up radiographs were scored for individual features of OA by the same trained observer (SAD) whose reproducibility ranged from (κ 0.60-1.00). Both knees were assessed for all x-ray changes. The following data was obtained: osteophyte (0-5) and joint space narrowing (-1 to 5) scores in all three compartments using the Nottingham Logically Derived Line Drawing Atlas (LDLDA); an actual measurement (mm) of minimum joint space width in each compartment; varus and/or valgus deformity (°); presence or absence of chondrocalcinosis in fibrocartilage and/or hyaline cartilage; presence of subluxation (lateral/medial); presence

of attrition (present/absent); and an overall K/L grade (0-4). Films were examined blind of participant status and time order.

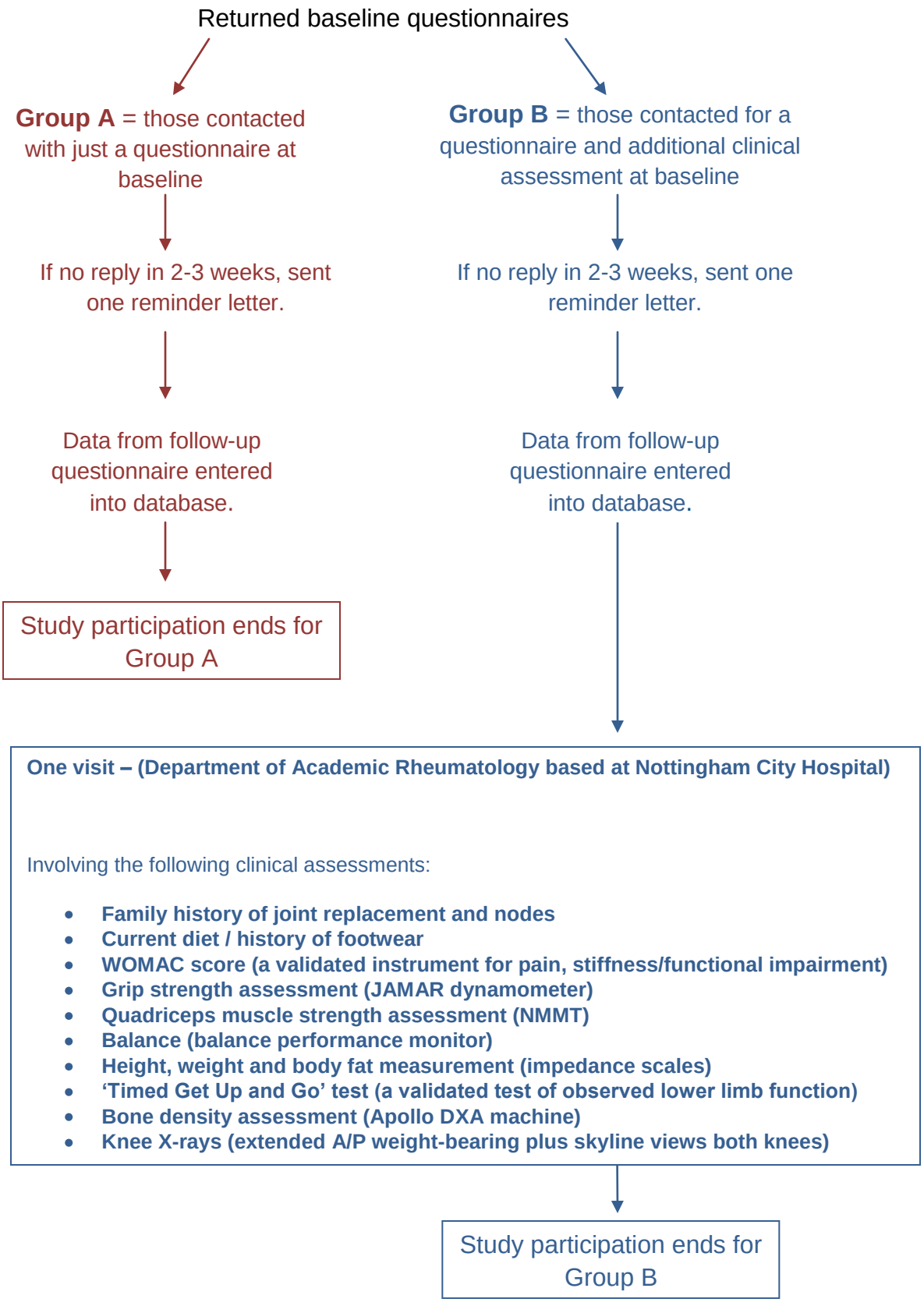


Figure 27. Flow chart summary of study design

2.6 Data management

The follow-up data were entered directly onto a pre-prepared form within the Access database. Each page of the form corresponded directly to a page within the questionnaire, with the questions laid out exactly as they were laid out in the questionnaire. This allowed for future users to easily access and enter the information.

Each participant was allocated a follow-up ID number for their records before recruitment. All data recorded and stored for each participant was then only identifiable by this new ID. Only the master list file linked this follow-up ID number, with the original baseline ID and the participant's name. The paper questionnaires and clinical assessment data were appropriately catalogued and stored within the Department of Academic Rheumatology.

2.6.1 Quality of data entry

To examine the quality of data entry a 10% random sample of questionnaires were verified against the database. The new identification numbers of all the questionnaires returned were put into an Excel spreadsheet and allocated a random number. The table was sorted in ascending order according to the randomised numbers. The first 312 (10%) in the newly ordered list were taken to be the questionnaires for verification. A direct visual comparison was undertaken between the data

recorded in the database and that written in the questionnaire. Each question was examined for errors and these were recorded in a separate chart. The mistakes for each question were totalled and a percentage error was calculated for each question. An error below 2% was considered acceptable. Only one question scored above a 2% difference; the total body pain map at 2.56%. A high level of data quality was observed and therefore double entry was not required. Errors ranged from 0% to 1.28%, and 97.6% of the questions had an error rate below 1%. This procedure was then repeated for the clinical assessment/radiographic data. Once again a high level of data entry quality was observed, with overall error rate of 0.11%. No errors were found for the validation or radiographic data. Outliers were investigated as part of the quality control; they were double checked with the hard copy of the data and corrected as required.

2.7 Statistical analysis

Using an odds ratio of 4 as an estimate of relative risk, with a significant level of 0.05 and power of 80%, at least 40 subjects were required to detect the incidence in the non-exposure group and the difference between the exposure (knee structure change) and the non-exposure (no knee structure change) groups.

This sample size was only for univariate analysis. Considering possible covariates such as age, sex, overweight, depression and inflammation, the

sample size was approximately the sample size for the univariate analysis multiplied by the number of covariates. Assuming 6 significant variables (age, sex, BMI, structural change, muscle weakness and depression) in the logistic model, we needed at least 240 subjects in each group of comparison to ensure the statistical power. Therefore the study numbers involved with this retrospective cohort were expected to give sufficient power to address the key study objectives.

Analysis of past and present data was conducted using SPSS for Windows version 8.0.

Knee pain was defined as pain around the knee for most days of at least a month. Participants without knee pain at baseline who developed knee pain during the subsequent ten years were defined as incident cases. Participants with knee pain at baseline who reported worsening of symptoms, improvement of symptoms, no change in symptoms, or who underwent TKR during the past ten years were defined as outcome cases.

2.7.1 Incident knee pain

Cumulative incidence was calculated as a percentage of the baseline knee pain negative population who became positive at follow-up. The average ***annual incidence rate*** was estimated using number of new cases with

knee pain divided by the total person-years during the follow up, where person-years were estimated using the Life table method.

For dichotomous outcomes, relative risk for different risk factors (age, gender, BMI, physical activity, joint injury, hip and back pain, co-morbidities, and psychosocial factors etc) at baseline during the observed period, or endpoint (for co-morbidities and associations) was estimated using odds ratio (OR) and 95% confidence interval (95%CI). People who did not report in the questionnaire if they had knee pain at follow-up had their data recorded as missing, as it was unknown if a knee pain event had taken place. Multiple logistic regression was undertaken to select major risk factors for incident knee pain in the absence of potential confounders. OR was adjusted for age, gender and BMI. For age, gender, and BMI OR was adjusted only with the other two potential confounders. Statistical significance was inferred when p value was less than 0.05, or when the 95% confidence intervals did not include unity (Hochberg *et al*, 1995).

For time to event outcomes, the Kaplan-Meier method was used to generate a survival curve and a log-rank test was undertaken for statistical significance between curves of different exposures. Cox regression was used to determine HR and 95%CI, adjusted for age, gender and BMI. People who clearly reported having knee pain at follow-up but failed to recall the approximate time of their first event were given a value of 6 years (the median of the time to event data).

2.7.2 Outcome of knee pain

The outcome of knee pain experienced at baseline was categorised into; no overall knee pain change, worsening knee pain, and improved knee pain. An additional outcome of total knee joint replacement was examined.

Figure 28. Radiographic example of a TKR

Only individuals who were knee pain positive at baseline were considered with respect to knee pain outcome. For all outcome categories odds ratio (95%CI) was calculated to determine relative risk for several risk factors. As with the incidence analysis, people who did not report in the questionnaire if they had knee pain at follow-up had their data recorded as missing. Multiple logistic regression was again used to determine major

risk factors for knee pain outcome in the absence of confounders. OR was adjusted for age, gender and BMI. For age, gender, BMI OR was adjusted only with the other two confounders.

A Chi square test was used to get the ptrend for TKR for men and women. To get p trend by age for men and women, the gender was examined individually. A Chi square test was undertaken using age in decades compared to TKR status.

2.7.3 Statistical analysis of the baseline clinical assessment data

All baseline clinical assessment data were examined in relation to the incidence and outcome of knee pain in the study population.

2.7.3.1 Quadriceps muscle strength

The unit of measure for quadriceps muscle strength at baseline was the MVC (maximum voluntary contraction) measured using the Tornville chair. Quadriceps muscle calculations were first undertaken using the average quadriceps strength scores. MVC was measured three times per leg/per person, these scores were averaged to provide an overall MVC score for each person's right leg and left leg. To ensure no double counting of participants the index leg used for the calculation was based upon the knee where most pain was reported. This information was obtained from the self-complete questionnaire. The average MVC scores were tertiled

using the SPSS ‘rank cases’ function. Tertile 1 represented high strength, whilst tertile 3 represented low strength. Any association between knee pain and quadriceps muscle strength was investigated using Chi squared and logistic regression. All OR were adjusted by age, gender and BMI. These calculations were then repeated using the highest MVC scores for each individual (irrespective of right or left knee).

2.7.3.2 Radiographs

Baseline OA status was determined by examining osteophytes, JSN and overall K/L OA score. Chondrocalcinosis was also scored

Osteophytes were dichotomised as present or absent within an individual. A total count of all the osteophytes in each of the three compartments of each knee was made. These scores were added together to give the number of osteophytes recorded per individual. Scores were dichotomised to show if osteophytes were absent or if they were present in any knee compartment.

X-ray examination and scoring for JSN was initially undertaken for both the right and left knees separately. The medial and lateral tibio-femoral compartments and the medial and lateral aspects of the patello-femoral compartments were first assessed as to the presence and degree of any narrowing measured as minimal joint space width. Individuals were classified into three groups: those who had JSN in the tibio-femoral

compartment only; those who had JSN in the patello-femoral compartment only; and those who had JSN in the tibio and patello-femoral compartments. These values were all compared against individuals who had no joint space narrowing at any site.

Overall OA was graded in the tibio-femoral compartments using the K/L system. A similar scoring system adapted from Kellgren and Lawrence was used to grade OA at the patello-femoral site. Individuals were classified into three groups: those who had a K/L score > or = 1 at the tibio-femoral compartment only; those who had a K/L score of > or =1 in the patello-femoral compartment only; and those who had any OA changes (K/L > or = 1) in both the tibio and patello-femoral compartments. These scores were then assessed against individuals who had a K/L score of 0 in all compartments of both knees. A K/L grade of 1 was used as the cut-off as previous studies into hand OA had potentially linked pain to early stage radiographic change. It was therefore important to capture any early OA changes in order to determine any association with knee pain.

For radiographic data we undertook person based analysis, whereby the index knee used for each participant was based upon the worst OA knee scores irrespective of right or left leg. Alongside whole person analysis, chondrocalcinosis, osteophytes, JSN and overall K/L OA score were examined for the right and left knees separately. Comparisons were made

as to the presence or absence of pain in the specific knee being examined. This information was obtained from the self-complete questionnaire.

Analysis was undertaken for incidence and outcome. Potential association between knee pain and radiographic features was investigated using Chi squared and logistic regression. All x-ray changes were based upon K/L scoring at baseline and at follow-up. All ORs were adjusted by age, gender and BMI. Chondrocalcinosis was deemed present if it appeared in either the lateral or medial tibio-femoral compartment of either knee. It was not classified further.

2.7.3.3 Regional physical assessments

Six observational clinical assessments were undertaken at baseline. Detection of knee effusion (through bulge sign presence or absence), knee temperature, knee crepitus, knee bony swelling, internal hip rotation (pain or restriction of movement), and fibromyalgia (through wince withdrawal response and identification of tender points in all 4 quadrants of the body).

These baseline assessment criteria were recorded as either present (1) or absent (0). Chi squared and logistic regressions were used to calculate any potential significant associations to knee pain. The numbers for worsening or improved knee pain were too small for a successful comparison.

2.7.3.4 WOMAC

Baseline knee stiffness was investigated using the WOMAC index. Morning stiffness and inactivity stiffness are examined as separate questions. Stiffness in the knee was reported as none, mild, moderate, severe or extreme for each question, but for analysis purposes people who reported mild, moderate, severe or extreme stiffness were grouped into a single "stiffness present" category. Chi squared and logistic regression was used to compare knee pain in knee stiffness sufferers against those who reported no knee stiffness.

2.7.3.5 SF36

SF36 questions were "scored on a scale of 0 – 100, with 100 representing the highest level of functioning possible" (www.rand.org/health/surveys). Each of the 36 questions was allocated to a specific health domain.

Table 4. The health domains of the SF36

Health Domains	**Relevant SF36 questions**
Physical Functioning	3, 4, 5, 6, 7, 8, 9, 10, 11, 12
Role limitations due to physical health	13, 14, 15, 16
Role limitations due to emotional problems	17, 18, 19
Energy/fatigue	23, 27, 29, 31
Emotional well being	24, 25, 26, 28, 30
Social Functioning	20, 32
Pain	21, 22
General Health	1, 33, 34, 35, 36

For each domain the scores from the relevant questions were averaged taking into account the number of questions answered. “For example, to measure the patient’s energy/fatigue level, add the scores from questions 23, 27, 29 and 31” (RAND scoring system). If the person answered all 4 questions the total score would be divided by 4; if only 3 were answered then the score would be divided by 3. If less than 50% of the questions in any health domain were not answered no overall domain score was given. The scale score was calculated without the missing data. All 8 health domains were scored in the same way (RAND scoring system).

The mean and standard deviation (SD) for each of the domains was calculated along with p values. These were obtained using a general linear model, specifically univariate analysis. All p values were adjusted for age, gender and BMI. The analysis was undertaken for both incidence and outcome of knee pain.

2.7.3.6 Hospital Anxiety and Depression Scale (HAD)

The HAD consisted of 14 questions; 7 related to anxiety and 7 related to depression. Each question was scored 0-3, with 0 representing a positive frame of mind, and 3 representing a negative frame of mind. The scores from the 7 anxiety related questions were added together to form a total, the same process was undertaken for those relevant to depression. The mean and SD were calculated for both anxiety and depression. P values were used to show any significant difference between the means of those

with knee pain against those without. These values were adjusted for age, gender and BMI. Analysis was undertaken for both incidence and outcome of knee pain.

2.7.4 Follow-up cross sectional analysis

All data for the cross-sectional analysis were taken from the follow-up questionnaires or clinical assessments. ORs were adjusted by age, gender and BMI at follow up.

2.7.4.1 Co-morbidities

Ten individual co-morbidities were examined. Data was dichotomised into individuals suffering a specific disease (e.g. diabetes) and those who did not. Odds ratios were calculated using Chi squared and logistic regression.

2.7.4.2 Other body pain

The number of painful body sites was calculated from the 44 different regions of the follow-up questionnaire body mannequin (excluding the four knee pain sites) (Appendix 6). For each individual the number of regions where pain was recorded was totalled. These total scores were split into 5 categories; people without body pain, pain in 1-3 regions, 4-6 regions, 7-11 regions and 12+ regions. Categorisation groups were chosen based upon examination of previous pain prevalence work by Thomas *et al* (2004).

Any potential dose response between other body pain and knee pain was examined using chi squared and logistic regression analysis. Specific OR analysis was also undertaken on foot, head and abdominal pain as individual sites potentially associated with knee pain.

The definition of chronic widespread pain (CWP) was based upon the ACR criteria for classification (Wolfe *et al*, 1990). Widespread pain is identified when all of the following are present: pain on the left side of the body, pain on the right side of the body, pain above the waist, pain below the waist (Wolfe *et al*, 1990). In addition axial skeletal pain has to be present. This definition had been accepted and used in several population studies (McFarlane *et al*, 2001). CWP was calculated from the 44 different regions of the body pain mannequin (Table 5).

Table 5. Identification of widespread body pain CWP

Body area	**Region numbers**
Axial	2 or 23 or 13
Upper left arm and shoulder	3 or 4 or 5 or 6 or 11 or 28 or 29 or 30 or 31 or 33
Upper right arm and shoulder	7 or 8 or 9 or 10 or 12 or 24 or 25 or 26 or 27 or 32
Lower left leg	14 or 14a or **15** or 16 or 17 or 39 or **40** or 41 or 42
Lower right leg	18 or 18a or **19** or 20 or 21 or 35 or **36** or 37 or 38

Values in red refer to the knee pain sites not included in final analysis.

CWP was recorded as present if a person had pain in the axial area as well as:

Lower left leg + Upper right arm and shoulder

or

Lower right leg + Upper left arm and shoulder

The knee pain sites (15, 19, 36 and 40) were not included in the final analysis, allowing for a comparison between knee pain and other chronically painful sites. Any potential association between CWP and knee pain was examined using chi squared and logistic regression analysis.

2.7.4.3 Body fat

Body fat was calculated in addition to BMI, as although there is a strong correlation between the two, there are also differences. The main difference is that body fat distinguishes between the weight of fat and that of lean body mass, while BMI does not. Therefore, a participant could have a high BMI, but the percentage of fat in their body may be low (potential high muscle mass).

The impact of body fat (measured using the impedance monitor) on knee pain was examined using Chi squared and logistic regression analysis. The World Health Organisation's (WHO) body fat range guidelines were followed in order to categorise each person based upon their age and gender.

The healthy body fat scores (code 0) were used as reference values for the analysis. These were then compared with over fat and obese fat scores for potential associations with knee pain.

Table 6. Body fat scores by age and gender

Gender	Age (years)	Category	Body fat score (%)	Code given
Female	40-59	Healthy	<= 34	0
		Over fat	> 34 and < 40	1
		Obese fat	>= 40	2
	60+	Healthy	<= 36	0
		Over fat	> 36 and <= 42	1
		Obese fat	> 42	2
Male	40-59	Healthy	< 22	0
		Over fat	>= 22 and <= 28	1
		Obese fat	> 28	2
	60+	Healthy	< 25	0
		Over fat	>= 25 and < 30	1
		Obese fat	>= 30	2

2.7.4.4 Timed Get Up and Go

Data for this analysis was split into three groups: People who had normal mobility (could complete the task in ≤10 seconds), people with mild mobility problems (completed the task in >10-≤20 seconds), people with severe mobility problems (completed the task in >20-≤30 seconds). The cut off values for these categories were based upon those used in current mobility

literature (Podsiadlo and Richardson, 1991) dose response between mobility and knee pain was examined using chi squared and logistic regression analysis.

2.7.4.5 Bone density

Z scores (bone density score of an individual in comparison to an average person of the same age) were obtained from the DXA bone densitometry machine. Scores were tertiled using SPSS. Tertile 1 represented the lowest bone density score, whilst tertile 3 represented the highest. Any potential association between bone density and knee pain was examined using chi squared and logistic regression analysis. All ORs were adjusted by age, gender and BMI. Although continuous data had been collected, categorical data was used in order to estimate the relative risk (the primary measure of OR) and determine any dose response. T scores were also collected at this time. However this data was not analysed as T scores only compare bone density of an individual to the average of a young adult at peak bone density.

2.7.4.6 Balance

Sway number is the accepted means of assessing balance. It is used to determine how steady a person is; the higher the number, the higher the deviation from zero, and the more unsteady the person (see Appendix 7).

Table 7. Categorisation of balance by sway number

Balance	Deviation from zero (sway number)
Good	0 to <2
Fair	2 to 4
Poor	5 to 6
Very poor	>6

An average of the three sway numbers was calculated for each person. Categorisation of the balance data was based upon recommendations from the balance performance monitor operating manual and reflects that used in other studies (Hassan *et al*, 2001). Any association between balance and knee pain was examined using chi squared and logistic regression analysis.

2.7.4.7 Grip strength

Overall grip strength was calculated by averaging the three clinical scores taken of each person's dominant hand. Scores were tertiled using SPSS. Tertile 1 represented the highest grip strength, whilst tertile 3 represented the lowest. Potential associations between grip strength and knee pain were calculated using Chi squared and logistic regression. All ORs were adjusted by age, gender and BMI. The process was repeated using only the right hand grip strength values.

2.7.4.8 Quadriceps muscle strength

Different methods of assessment were used for quadriceps muscle strength from baseline (Tornville chair) to follow-up (Nicholas manual muscle tester). We did anticipate that there may be a small difference in measurements due to the voluntary nature of muscle strength contribution using the Nicholas manual muscle tester. However, previous studies had shown manual muscle testing to have good validity and reliability (Cuthbert and Goodheart, 2007). A 2006 study by Martin *et al* investigated the use of hand-held dynamometers against the Biodex 'gold standard'. They showed that although hand-held dynamometers sometimes under-measured quadriceps strength in the strongest participants good correlation ($r=0.91$) and agreement ($\kappa=0.69$) was seen between the methods (Martin *et al*, 2006).

As with baseline analysis association between quadriceps muscle strength and knee pain was calculated first using the average MVC scores, and then using the highest MVC scores. For each calculation values were tertiled: tertile 1 = high muscle strength, tertile 3 = low muscle strength. Chi squared and logistic regressions were used to determine any significance of association. Adjustment was by age, gender and BMI.

3. Development and validation of novel line drawings

Two line drawings (varus-valgus knee alignment and foot angulation) were developed using similar methodology. These novel drawings were included as part of the follow-up knee pain questionnaire that was sent to 5,479 people. As previously stated 3,109 individuals completed and returned this questionnaire, 424 of who were seen for a clinical assessment (determined if they were seen clinically at baseline).

3.1 Varus-Valgus knee malalignment

The "gold standard" when determining varus-valgus alignment is weight-bearing full-limb radiographs (Sharma *et al*, 2001; Eckstein *et al*, 2008). Brouwer *et al* (2007) reported the absence of full-limb x-rays as a clear limitation of their study into knee alignment. Yet, a recent article Colebatch *et al* (2009) demonstrated that you can use standard anterior-posterior, weight-bearing, tibio-femoral views to measure knee alignment (κ 0.65-0.74). This means less radiation exposure for the participant and lower costs for the researcher.

However, for large scale epidemiological studies x-rays remain impractical and comparatively expensive. Therefore, a non-radiographic method of assessing varus-valgus knee malalignment could be useful for researchers undertaking large population studies.

3.1.1 Development of the novel varus-valgus line drawings

The novel varus-valgus knee malalignment drawings were developed by the Department of Academic Rheumatology (drawings by Prof M Doherty). The initial drawing was of a pair of legs with straight knee alignment. The other pairs of legs were then intentionally drawn with increasing 7.5 degrees of angulation in both the varus and valgus direction, making this an interval rather than an ordinal scale. Two degrees of severity in either direction were thought to be reasonable for this instrument.

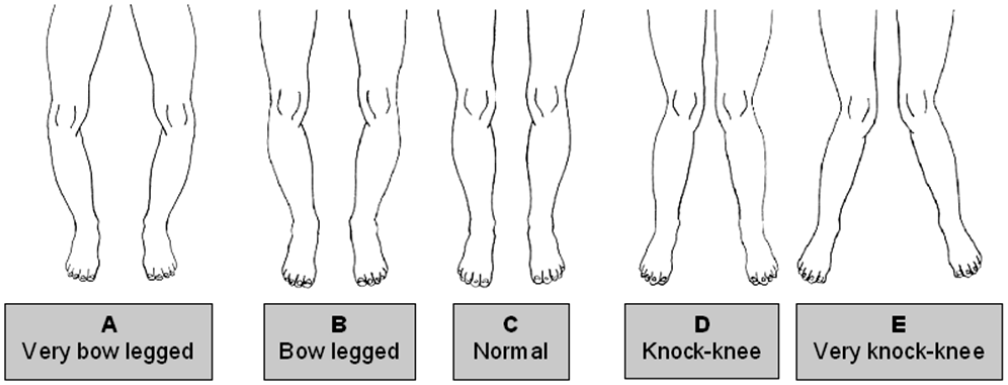


Figure 29. Example of the novel varus-valgus line drawings used in the questionnaire

3.1.2 Validation of the novel varus-valgus line drawings

Validation of the novel line drawings (participant reproducibility and participant-observer agreement) was undertaken during the clinical assessments, and was completed with the assistance of 41 study participants (approximately 10% of those seen for clinical assessment). These people were randomly selected using computer-generated random numbers in Excel.

3.1.2.1 Participant reproducibility

At the beginning of each assessment participants were required to walk bare legged around a clinic room. After one minute they were asked to stop in front of a mirror and look at the reflection of their knees straight on. Participants were shown the instrument (Figure 29) and asked to indicate which picture best represented the current angle of their knees. Each knee was classified as varus, valgus or straight. In most people the alignment of the left knee is similar to that of the right, but in a few individuals these angulations may differ. Therefore, participants were asked to classify their left and right knees separately. Results were recorded blind to their original questionnaire response.

3.1.2.2 Participant-observer agreement

The assessment made by a trained observer was taken as “gold standard”. A single trained observer (SAD) examined the study participant at the end of their assessment and categorised each knee to one of the line drawings. To prevent bias the observer was blinded to participant response. The observer classified the knee angulations from the same vantage point as the subject, using the same questionnaire line drawings.

3.1.2.3 Observer reproducibility

To ensure the validity of the “gold standard”, observer reproducibility was also measured. This was undertaken on a random sample of 10 participants on two occasions. These individuals were recruited as part of

a clinical audit, separate from the knee study, and were patients attending the NHS Rheumatology Out Patient Department. The observer classified their knee angulations as previously described, at two time points on the same day, blinded to the results of the first assessment.

3.1.3 Statistical analysis of the novel varus-valgus line drawings

All validation analyses were performed using Stats Direct or SPSS v14 (SPSS inc, Chicago, USA). Reproducibility and agreement was assessed using the weighted Kappa statistic (κ). Symmetry between left and right body sides were examined using meta-analysis of the κ data giving an overall person score (Table 8).

3.1.4 Results

Seventy three percent of participants were able to reproduce directly the results they reported in the questionnaire. Repeatability was very similar for the right and left knee, with a κ of 0.77 (95%CI 0.53, 1.02) for the right knee and 0.69 (95%CI 0.45, 0.93) for the left knee. The κ score for participant-observer agreement was very good at 0.72 (95%CI 0.40, 1.05) (Table 8).

Table 8: Reproducibility and agreement for the varus-valgus knee angulation line drawings

Knee	Reproducibility		Agreement
	Participant Intra κ(95%CI)	Observer Intra κ(95%CI)	Participant-Observer Inter κ(95%CI)
Right	**0.77 (0.53, 1.02)**	**1.00 (0.57, 1.43)**	**0.56 (0.33, 0.80)**
Left	**0.69 (0.45, 0.93)**	**0.79 (0.38, 1.19)**	**0.89 (0.64, 1.14)**
Both	**0.73 (0.56, 0.90)**	**0.89 (0.59, 1.18)**	**0.72 (0.40, 1.05)**

≤0=poor agreement, 0.01-0.20=slight agreement, 0.21-0.40=fair agreement, 0.41-0.60=moderate agreement, 0.61-0.80=substantial agreement, and 0.81-1.00=almost perfect agreement (Sim and Wright, 2005).

3.2 Inversion – Eversion foot angulation

Currently no “gold standard” exists for the assessment of foot inversion/eversion. At present many studies use digital photography to assess foot angulations (Gross *et al*, 2007). Non-weight bearing views of the feet are often taken, with images measured using digital software packages (Canvas software) (Gross *et al*, 2007).

However, as with knee malalignment, a method of assessing foot angulation that does not require participant clinical attendance could be useful for large scale epidemiological studies.

3.2.1 Development of the novel foot angulation line drawings

As with the varus-valgus line drawings the novel foot angulation drawings were developed with the same artist (MD), using the same interval scale of 7.5 degrees of angulation, with two degrees of severity in either direction.

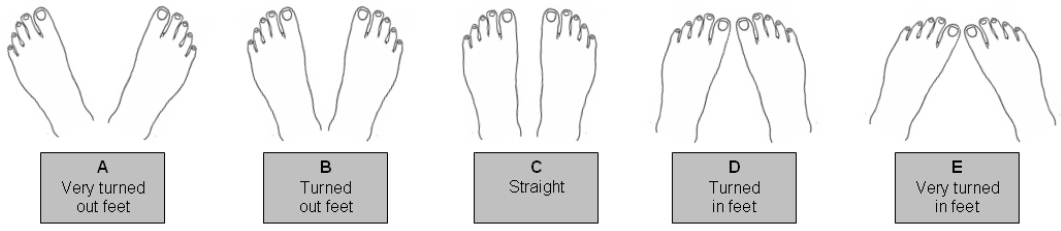


Figure 30. Novel line drawings for foot angulation

3.2.2 Validation of the novel foot angulation line drawings

For validation of the foot angulation drawings (Figure 30) the participant reproducibility, participant-observer agreement, and observer reproducibility was undertaken in identical fashion using the same participants and observer as for the varus-valgus angulation data.

3.2.3 Statistical analysis of the novel foot angulation line drawings

Reproducibility and agreement was calculated using the same statistical packages (Stats Direct or SPSS v14) and statistical analysis (κ) used for the varus-valgus data analysis.

3.2.4 Results

Reliability of the foot angulation line drawings was found to be very good, with 87% of participants being able to reproduce exactly the foot angulation grade from their questionnaires (κ 0.87; 95%CI 0.69, 1.06). Reproducibility was excellent for both right (κ 0.92; 95%CI 0.66, 1.18) and left (κ 0.83; 95%CI 0.58, 1.09) feet. Compared to participant repeatability, observer reproducibility was lower, though still excellent at 0.81 (95%CI 0.42, 1.20). The κ score for subject-observer agreement was excellent at 0.88 (95%CI 0.70, 1.06).

Table 9: Reproducibility and agreement for the foot angulation line drawings

Foot	Reproducibility		Agreement
	Participant Intra κ(95%CI)	Observer Intra κ(95%CI)	Participant-Observer Inter κ(95%CI)
Right	**0.92 (0.66, 1.18)**	**0.78 (0.18, 1.39)**	**0.92 (0.67, 1.17)**
Left	**0.83 (0.58, 1.09)**	**0.83 (0.32, 1.34)**	**0.83 (0.57, 1.09)**
Both feet	**0.87 (0.69, 1.06)**	**0.81 (0.42, 1.20)**	**0.88 (0.70, 1.06)**

≤0=poor agreement, 0.01-0.20=slight agreement, 0.21-0.40=fair agreement, 0.41-0.60=moderate agreement, 0.61-0.80=substantial agreement, and 0.81-1.00=almost perfect agreement (Sim and Wright, 2005).

3.3 Discussion of validation

This chapter details the validation of two novel, self-reporting instruments for knee malalignment and foot angulation. All grades of varus-valgus alignment and foot inversion/eversion were assessed, including a number of participants who were categorised as 'normal'. Study findings suggest that the varus-valgus and foot inversion/eversion drawings are valid for use as self reported instruments. High κ scores were found for both participant reproducibility and participant-observer agreement when assessing both of these instruments. Such excellent reliability and validity reinforces the suitability of these graded line drawings for use in self-reported questionnaires.

To our knowledge, these are the first self-reporting line drawing tools to examine knee alignment and foot angulation. The majority of previous studies of alignment have used radiographic assessment (Hunter *et al*, 2007a; Lim *et al*, 2008; Brouwer *et al*, 2007). One advantage of the line drawings over x-rays is their ability to be used in large scale epidemiological studies. It would be time-consuming and impractical to x-ray all subjects in a community study of significant size. Furthermore radiographs are disadvantaged by expense. It would cost far less to include these diagrams in a questionnaire, than it would to bring subjects to hospital for knee x-rays.

There are several caveats to this study. Firstly, the line drawings devised were limited to five severity options (including straight alignment/angulation). It was not investigated whether three or four severity intervals either side of 'normal' would have provided more accurate results. However it was thought that two grades of severity was a reasonable number for a self-reported line drawing instrument.

A second caveat is that we did not investigate whether photographic versions of the instruments would have been better self-reporting tools than the line drawings. However, one advantage of the line drawings was that they used a precise interval scale, whereas the approximation of knee and foot angles from photographs might favour an ordinal rather than interval scale. In addition, participants may not have identified with photographic images, especially between genders. To achieve a photographic severity scale, images of different peoples' legs and feet would have been required for each severity grade, making it difficult for a participant to make a direct comparison to their own knees or feet. However, the line drawings were not gender specific, nor did they have defining characteristics that would make them difficult for comparison.

Our findings suggest that these novel line drawings may have a practical use in future large scale epidemiological studies. The first application of these instruments will be in the following analysis on knee pain risk factors.

4. Recruitment

Questionnaires were returned from 9,429 individuals at baseline (Thomas, 2001; O'Reilly, 1996). A list of these original participants was sent to each of the GP surgeries. Individuals were screened for eligibility and a total of 5,479 questionnaires (58% of the original population) were sent out, with one reminder letter if not returned within two weeks. Of the 5,479 questionnaires sent, 3,109 were completed and returned, giving an overall response rate of 56.7%.

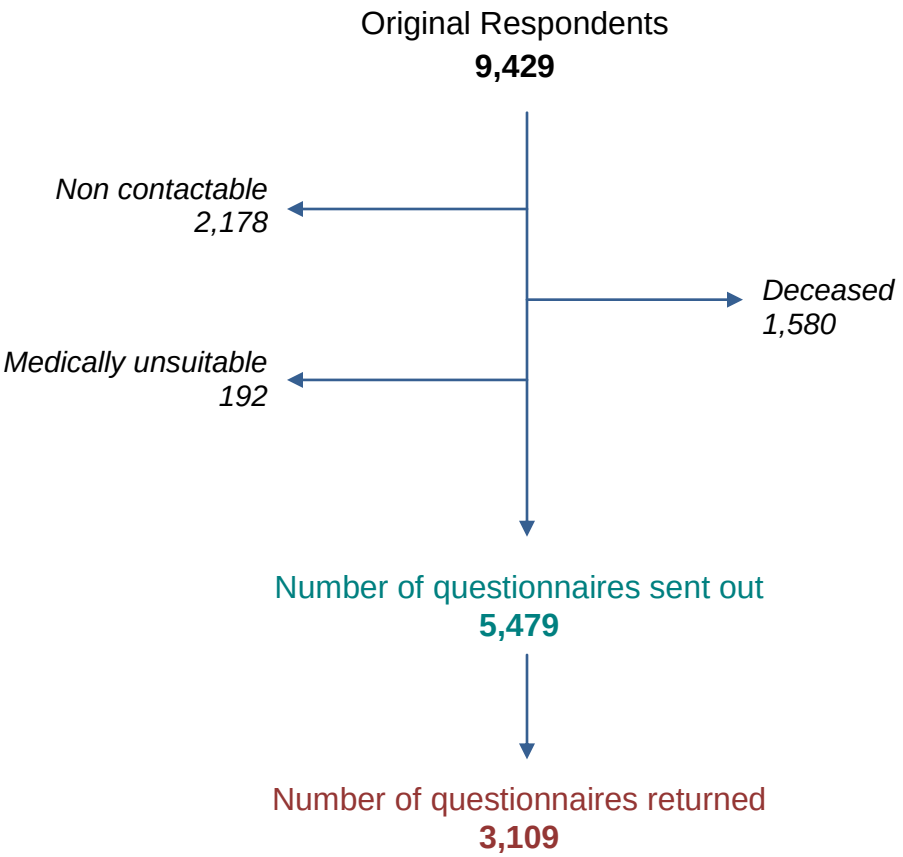


Figure 31. Summary of recruitment

Recruitment of 'Group A' individuals (those who were contacted with just a questionnaire at baseline) took place between November 2007 and February 2008. Recruitment of 'Group B' people (those contacted for a questionnaire and additional clinical assessment at baseline) took place between 15th January 2008 and 15th March 2008.

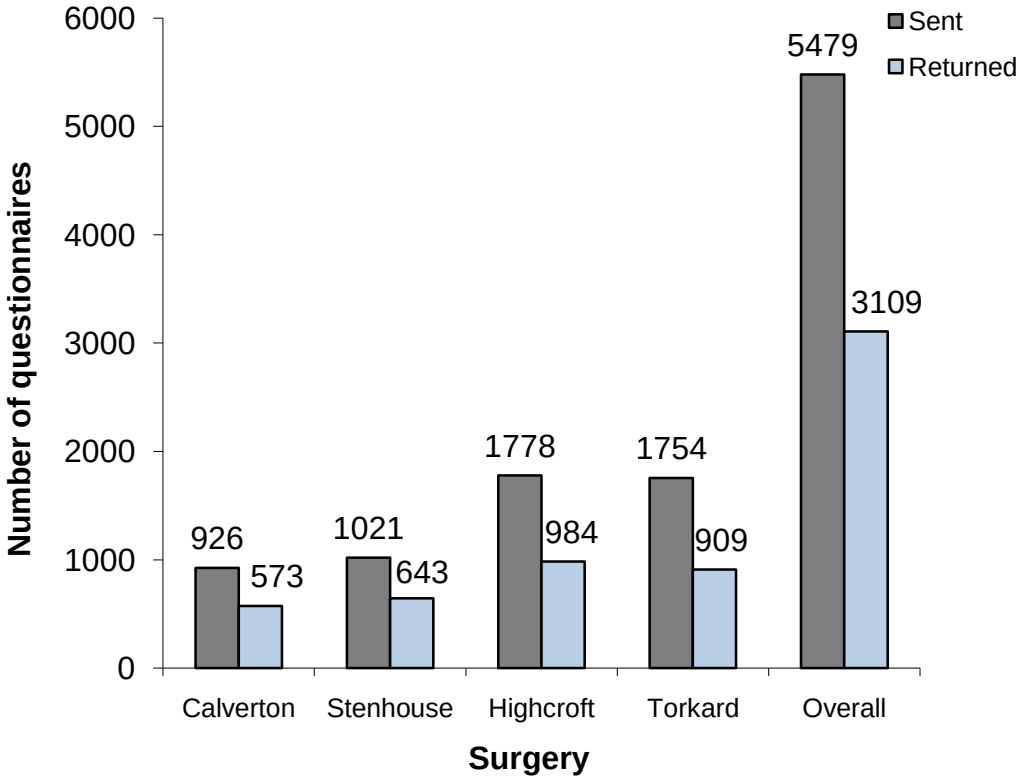
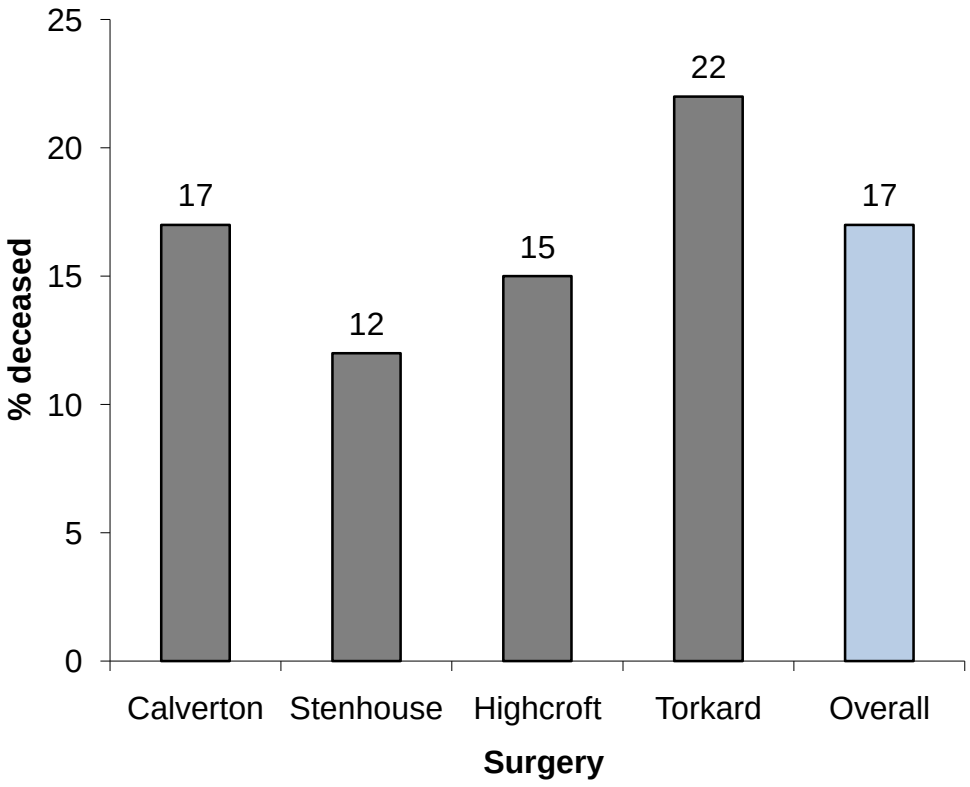


Figure 32. Response rates by General Practice

The greatest response rate came from the Stenhouse surgery (63%), with the lowest at 52% (the Torkardhill surgery) (Figure 32).

One thousand five hundred and eighty individuals deceased during the period between baseline and follow-up (17% of the 9,429 baseline cohort) (Figure 33). Further breakdown of the deceased by GP surgery showed similar percentage numbers for each. Only Torkardhill showed a higher percentage of deceased individuals (22%) than the overall value (17%). This 5% discrepancy was not considered significant.



Percentages key

Calverton	*17%*	=	*264 participants out of 1,560 baseline*
Stenhouse	*12%*	=	*202 participants out of 1,643 baseline*
Highcroft	*15%*	=	*485 participants out of 3,352 baseline*
Torkard	*22%*	=	*629 participants out of 2,874 baseline*
Overall	*17%*	=	*1,580 participants out of 9,429 baseline*

Figure 33. Breakdown of deceased by General Practice.

4.1 Breakdown of recruitment

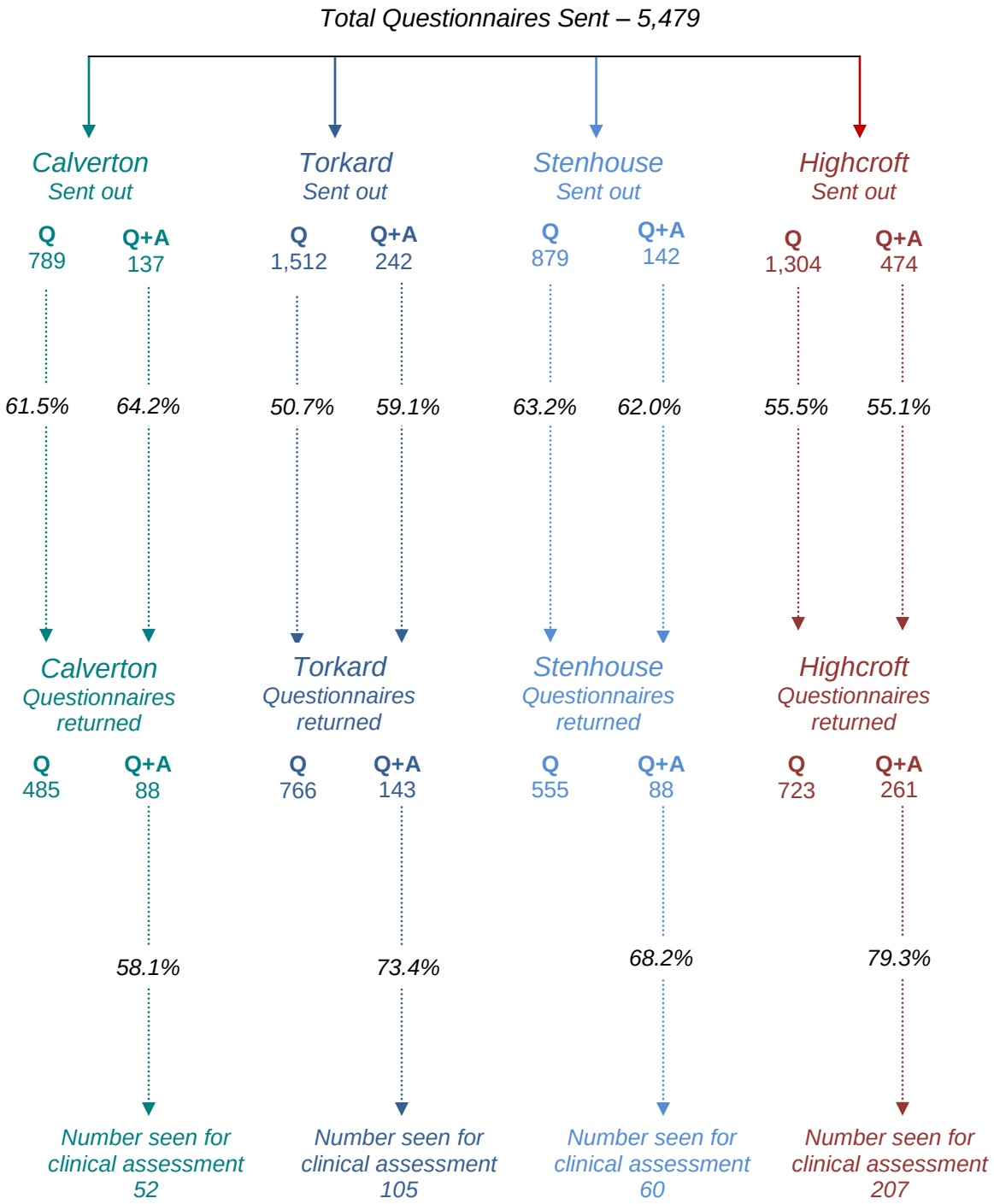


Figure 34. Recruitment by General Practice.
'Q'= those who were contacted with just a questionnaire at baseline; 'Q+A'= those contacted for a questionnaire and additional clinical assessment at baseline.

Those over 60 years of age at baseline were significantly less likely to have been recruited at follow-up, with 82% of non-responders being ≥60 years at baseline. Non-recruited subjects were marginally more likely to be smokers than recruited subjects (56% versus 51%). Conversely history of knee pain was slightly higher in the recruited (29%) versus non-recruited group (28%). Proportionally the baseline characteristics of back pain, hip pain, female gender and BMI were similar between groups (Appendix 8).

The Baseline age of this cohort ranged between 40-83 years, with a mean age of 57 years old. The male: female ratio represented the nature of the study, with a slightly higher female population 1,384:1,725 (55.5%). Women 60-69 years old gave the highest response rate (Figure 35). Men gave a better response rate than women when >70 years old.

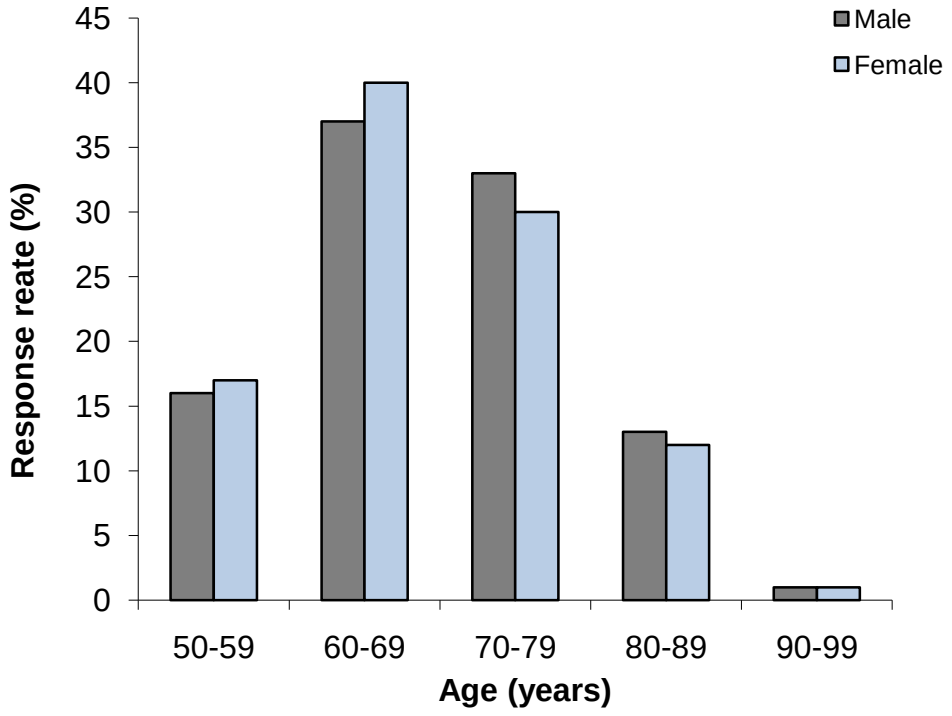


Figure 35. Response rate by age and gender (at follow-up)

No significant difference in response rate was seen between knee pain positive and negative individuals (Figure 36). Response rates were different between individuals who were sent a questionnaire only and those who were also invited for clinical assessment (Figure 36).

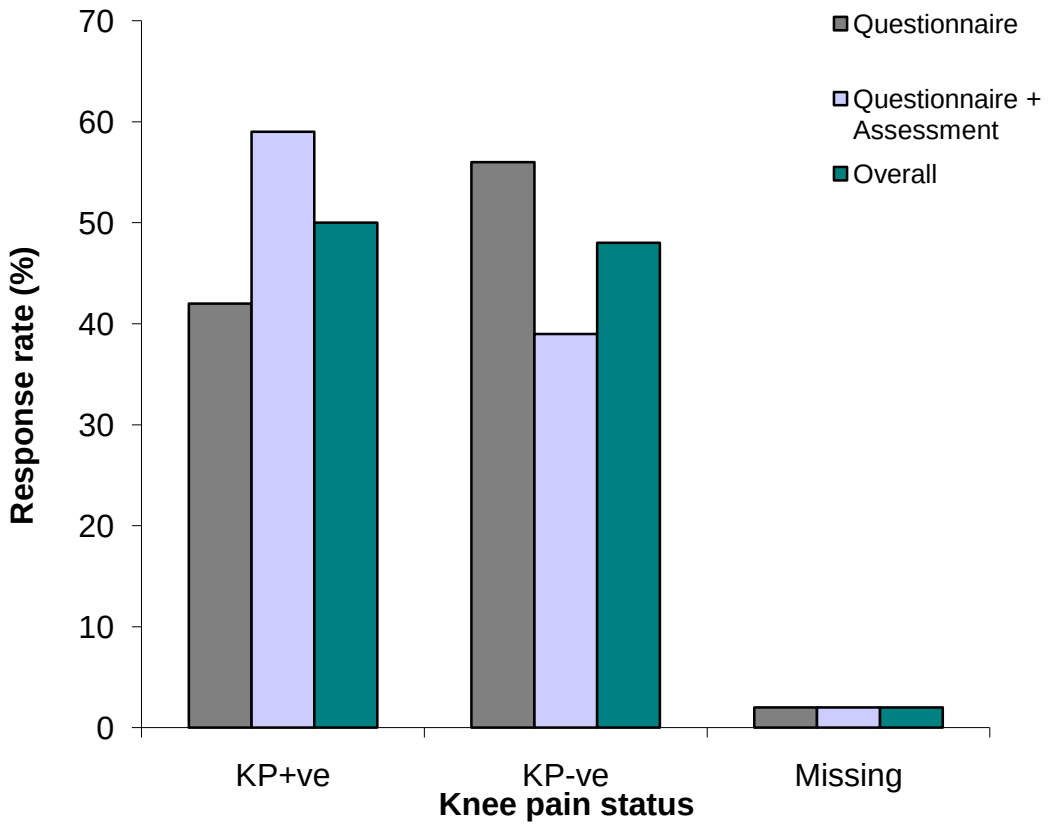


Figure 36. Response rate by knee pain status (at follow up)

There was no difference in the proportion of responders with respect to BMI (Figure 37). This was unexpected, as BMI often associates with

several co-morbidities, and poor health would have been expected to correspond with a low response rate.

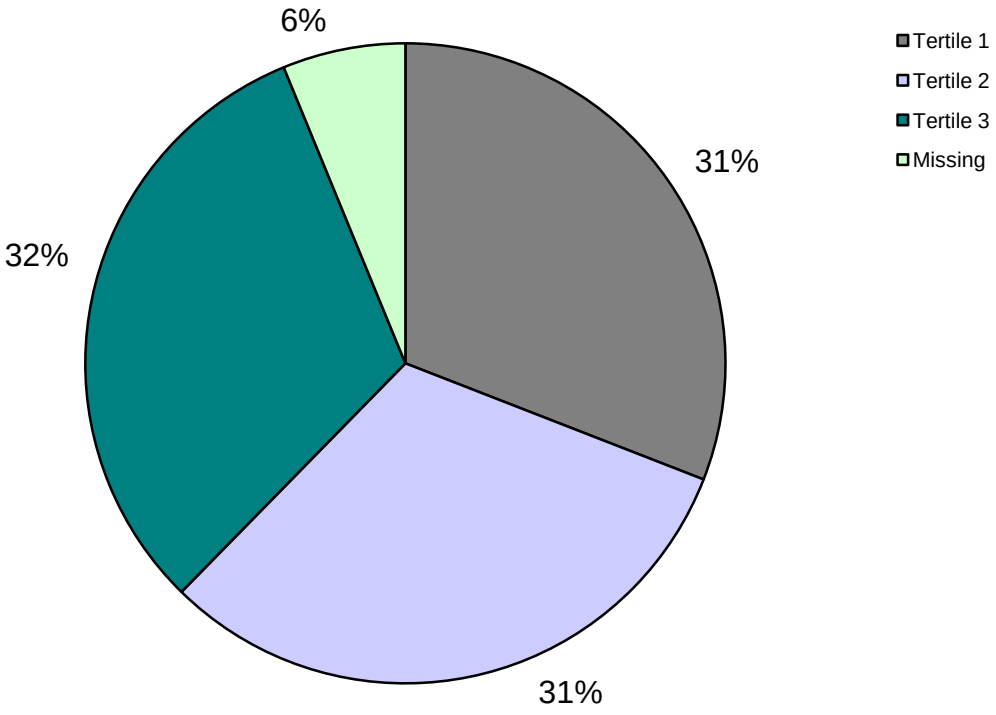


Figure 37. Proportion of responders by BMI tertiles (at follow-up)

5. Analysis of incidence of knee pain

Knee pain was defined as “pain in or around the knee on most days for at least a month”. No distinction was made between unilateral and bilateral knee pain. Of 3,109 people in this cohort, 914 had knee pain and 2195 had no knee pain at baseline. Of these 2,195 people, 2,156 provided data for the incidence analysis, with 742 of these being incident knee pain cases. The ***cumulative incidence*** in 10 years was 742/2,156 (34.4%). This was similar in men (32%) and women (35%) (p=0.076), and was not related to age (p_{trend}=0.940 and 0.149 for men and women) (Figure 38).

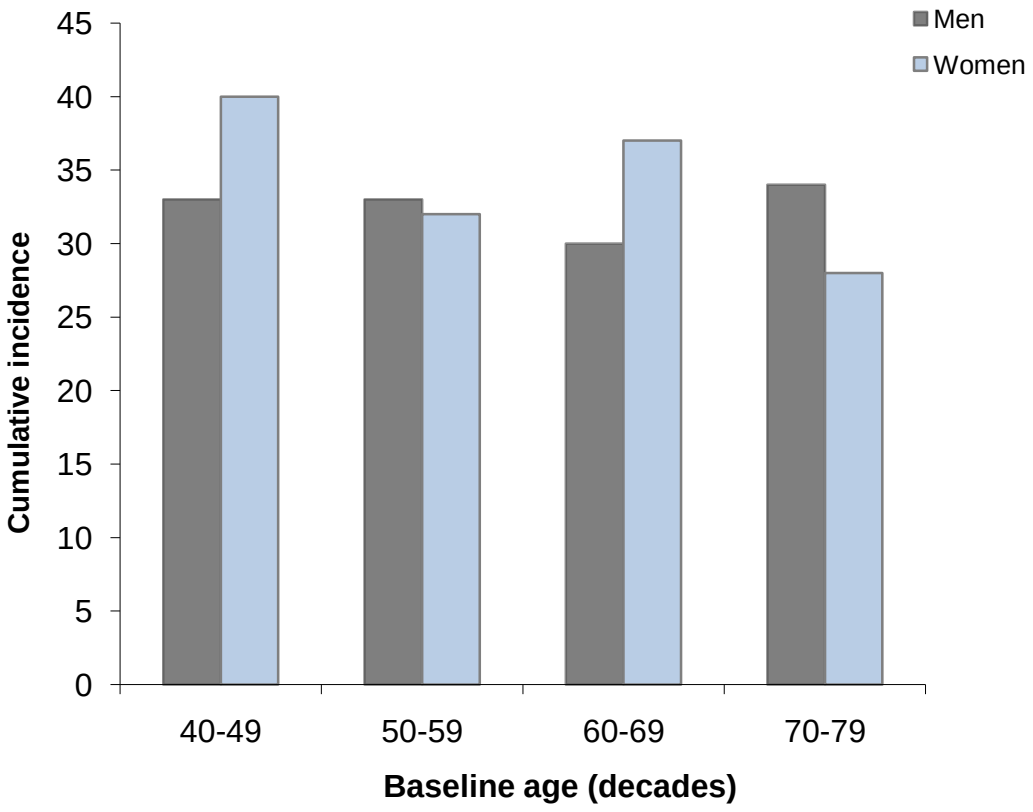


Figure 38. Cumulative incidence of knee pain by age and gender

The average ***annual incidence rate*** was estimated by dividing new knee pain cases by the total person-years during the follow up. The average annual incidence rate of knee pain was 33 per 1000 person-years, with 32 per 1000 person-years for men and 35 per 1000 person-years for women. It was not age-dependent (p_{trend}=0.962 and 0.176 for men and women respectively) (Figure 39).

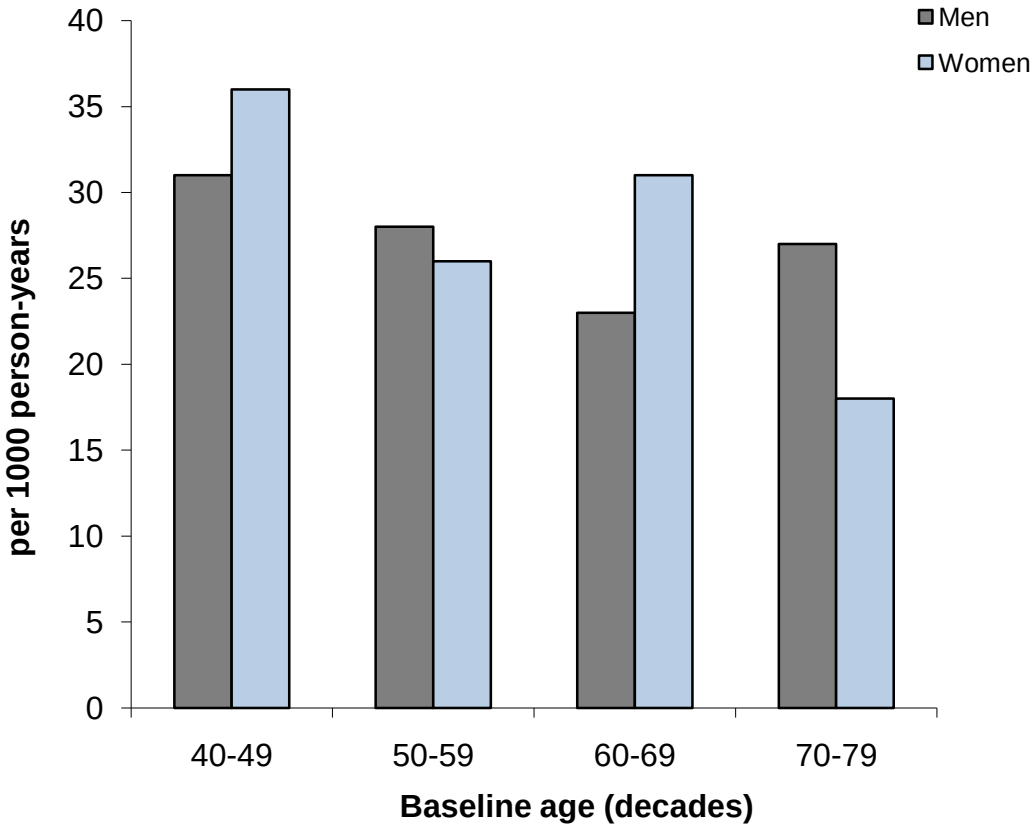


Figure 39. Annual incidence of knee pain by age and gender

Four hundred and forty out of the 742 incident cases (59.3%) consulted a doctor about their knee pain. Of these, 183 (41.6%) were referred to a rheumatologist or physiotherapist, and 62 (14.1%) were given injections into their knee.

5.1 *Constitutional factors*

Prevalence data for baseline constitutional factors is shown in Appendix 9.

5.1.1 Age

Prevalence for participants' ≥60 years old was 37%. Age at baseline was not associated with incidence of knee pain as shown in Figures 38 and 39. This was confirmed after adjustment for other risk factors (Table 10).

5.1.2 Gender

Incidence was similar between men 316/975 (32%) and women 426/1181 (35%). The crude OR for women was 1.18, with 95% confidence interval (CI) ranging from 0.98 to 1.41. However, after adjustment for age and BMI, women became at greater risk for knee pain than men (OR 1.23; 95%CI 1.02, 1.48) (Table 10).

5.1.3 BMI

People were categorised into three groups according to their baseline BMI; BMI<25, BMI 25 - 30 and BMI > 30. The incidence of knee pain during the 10-year follow up were 29.65% (284/958), 36.40% (360/989) and 48.67% (73/150) for people who were normal weight, overweight and obese respectively. A dose response OR was observed (Table 10, $p_{trend} < 0.000$). Risk and trend remained significant after the adjustment for age and gender. The aORs were 1.40 (95%CI 1.16, 1.70) for overweight and 2.28 (95%CI 1.61, 3.24) for obese (Table 10, $p_{trend} <0.000$).

5.1.4 Smoking

Of 1,082 smokers (smoking at both baseline and follow-up), 375 (34.7%) developed knee pain during follow-up. Of 1074 non-smokers (never smoking at all) 367 (34.1%) developed knee pain at review. Odds ratio to develop knee pain in 10 years was 1.02 (95%CI 0.86, 1.22) (Table 10). This lack of association was confirmed by adjusting for age, gender and BMI (aOR 1.08; 95%CI 0.89, 1.30).

Table 10. Incidence of knee pain in relation to constitutional factors

Constitutional factors		Incident rate (%)	Odds ratio (95% confidence interval) Crude	Adjusted
Age:				
	<60	488/1407 (35%)	**1**	**1**
	≥60	254/749 (34%)	0.97 (0.80, 1.17)	0.97 (0.80, 1.17)
Gender:				
	Men	316/975 (32%)	**1**	**1**
	Women	426/1181 (36%)	1.18 (0.98, 1.41)	**1.23 (1.02, 1.48)**
BMI:				
	Normal (<25)	284/958 (30%)	**1**	**1**
	Overweight (≥25, ≤30)	360/989 (36%)	**1.35 (1.12, 1.64)**	**1.40 (1.16, 1.70)**
	Obese (>30)	73/150 (49%)	**2.25 (1.59, 3.19)**	**2.28 (1.61, 3.24)**
Smoking:				
	No	367/1074 (34%)	**1**	**1**
	Yes	375/1082 (35%)	1.02 (0.86, 1.22)	1.08 (0.89, 1.30)

OR was adjusted for age, gender, BMI. Values in blue refer to risk factors significantly associated with incident knee pain.

5.2 Biomechanical factors

The prevalence data for biomechanical factors at baseline can be seen in Appendix 9.

5.2.1 Knee malalignment

Of the 58 people who reported early-life varus malalignment, 28 (48.3%) developed knee pain. The risk was approximately two-times greater (OR 1.83; 95%CI 1.08, 3.08; and aOR 2.22; 95%CI 1.29, 3.80) than those without early-life varus malalignment (33.8%). In contrast, self-reported valgus malalignment in early life (20-30 years of age) was not associated with later (after 40 years of age) development of knee pain (OR 1.54; 95%CI 0.69, 3.40; and aOR 1.60; 95%CI 0.71, 3.62) (Table 13).

5.2.2 Foot angulation

In this cohort 38 people self-reported early-life inward foot alignment, and 273 people reported early-life outward foot alignment. Outward foot alignment was found to be significantly associated with incident knee pain (OR 1.49; 95%CI 1.15, 1.93; and aOR 1.47; 95%CI 1.13, 1.93). However, no association was found between inward foot alignment and incident knee pain (OR 1.18; 95%CI 0.60, 2.29; and aOR 1.29; 95%CI 0.65, 2.55). We also examined interaction between varus knee malalignment and outward foot angulation using a logistic regression model which included each individual risk factor and the interaction term (adjusted by age, gender and

BMI). Results showed foot angulation and knee malalignment remained significant variables, but with no interaction (OR 0.53; 95%CI 0.14, 2.01).

5.2.3 Knee injury

History of significant knee injury was reported in 299 people, of which 188 (62.9%) developed incident knee pain during the 10 year follow-up period. Among 1,827 people without knee injury, 543 (29.7%) had incident knee pain. Those who suffered an early knee injury were over four-times more likely to develop knee pain (95%CI 3.10, 5.17) than those who were injury free. Corresponding adjusted odds ratios (Table 13) showed that knee injury remained highly statistically significant after correction for confounders (aOR 4.05; 95%CI 3.11, 5.27).

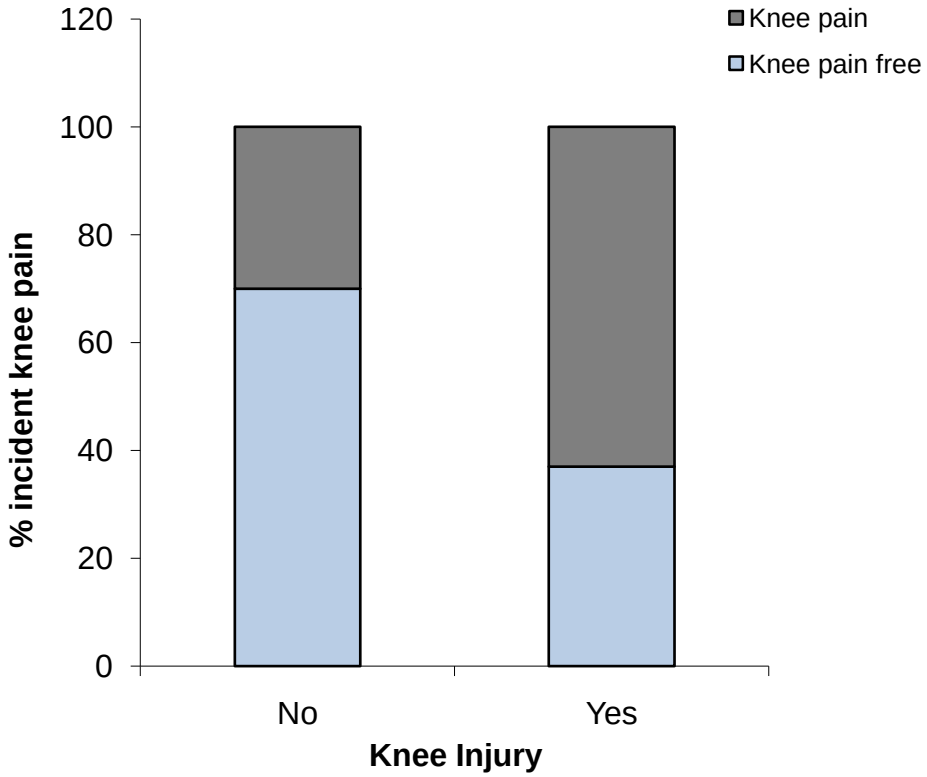


Figure 40. Incident knee pain in relation to knee injury

5.2.4 Quadriceps muscle strength

No significant association was found between baseline quadriceps muscle strength and incident knee pain (Table 13).

5.2.5 Occupational physical activity

Nine potential occupational risk factors were investigated; only one was significant to knee pain development (Table 11). Odds ratio for the effect of regularly lifting heavy loads for incident knee pain was 1.41 (95%CI 1.06, 1.88) (Table 11). The result was confirmed by adjusting for age, gender, and BMI (aOR 1.52; 95%CI 1.13, 2.05). The ORs for physical exertion and physically demanding work were 1.34 (95%CI 0.98, 1.82) and 1.33 (95%CI 0.96, 1.83) respectively (Table 11).

Table 11. Occupational activity and relative risk of incident knee pain

Occupational activity	Incident rate (%)	OR (95%CI)	aOR (95%CI)
Sit	136/422 (32%)	0.90 (0.69, 1.18)	0.85 (0.65, 1.12)
Stand	187/555 (34%)	1.03 (0.79, 1.35)	1.13 (0.86, 1.49)
Walk	193/591 (33%)	0.91 (0.70, 1.19)	0.99 (0.75, 1.31)
Lift Heavy loads	108/276 (39%)	**1.41 (1.06, 1.88)**	**1.52 (1.13, 2.05)**
Feel Tired	101/269 (38%)	1.27 (0.95, 1.69)	1.21 (0.89, 1.63)
Sweat through physical	85/219 (39%)	1.34 (0.98, 1.82)	1.34 (0.98, 1.82)
More Physical Work	78/203 (38%)	1.33 (0.96, 1.83)	1.33 (0.96, 1.83)
Walk to Work	90/253 (36%)	1.14 (0.81, 1.60)	1.16 (0.82, 1.64)
Cycle to Work	12/51 (24%)	0.57 (0.23, 1.43)	0.48 (0.18, 1.27)

OR=odds ratio, CI=confidence interval. OR was adjusted for age, gender, BMI. Values in blue refer to risk factors significantly associated with incident knee pain.

However, these potential risk factors became significant after adjustment for age, gender and BMI; (aOR 1.49; 95%CI 1.08, 2.07) for physical exertion and (aOR 1.37; 95%CI 1.00, 1.90) for physically demanding work (Table 13).

5.2.6 Leisure physical activity

The calculated ORs showed that none of the potential leisure factors had any association with incident knee pain (Table 12). This result was confirmed after adjustment for age, gender and BMI.

Table 12. Leisure activity and relative risk of incident knee pain

Leisure activity	Incident rate (%)	OR (95%CI)	aOR (95%CI)
Cause sweating	133/426 (31%)	0.90 (0.70, 1.16)	0.91 (0.70, 1.18)
Play Sports	66/196 (34%)	1.07 (0.77, 1.48)	1.23 (0.88, 1.72)
Watch TV	180/544 (33%)	1.06 (0.84, 1.35)	1.04 (0.81, 1.32)
Walking	198/648 (31%)	0.84 (0.66, 1.06)	0.90 (0.70, 1.13)
Cycling	39/99 (39%)	1.39 (0.91, 2.12)	1.52 (0.99, 2.34)
DIY	189/546 (35%)	1.20 (0.95, 1.53)	1.24 (0.97, 1.60)
Gardening	260/789 (33%)	1.07 (0.84, 1.37)	1.07 (0.83, 1.37)

OR=odds ratio, CI=confidence interval. OR was adjusted for age, gender, BMI

Table 13. Incidence of knee pain in relation to biomechanical factors

Biomechanical factors	Incident rate (%)	Odds ratio (95% confidence interval)	
		Crude	Adjusted
Knee angulation: during 20s:			
Normal	669/1977 (34%)	**1**	**1**
Varus	28/58 (48%)	**1.83 (1.08, 3.08)**	**2.22 (1.29, 3.80)**
Valgus	11/25 (44%)	1.54 (0.69, 3.40)	1.60 (0.71, 3.62)
Foot angulation during 20s:			
Normal	575/1735 (33%)	**1**	**1**
Out	116/273 (42%)	**1.49 (1.15, 1.93)**	**1.47 (1.13, 1.93)**
In	14/38 (37%)	1.18 (0.60, 2.29)	1.29 (0.65, 2.55)
Knee Injury:			
No	543/1827 (30%)	**1**	**1**
Yes	188/299 (63%)	**4.01 (3.10, 5.17)**	**4.05 (3.11, 5.27)**
Muscle Strength – using Highest score			
High strength - Tertile1	20/59 (34%)	**1**	**1**
Tertile 2	24/57 (42%)	1.46 (0.69, 3.11)	1.27 (0.51, 3.12)
Low strength - Tertile 3	21/52 (40%)	1.32 (0.61, 2.86)	0.78 (0.29, 2.11)
Muscle Strength – Average score:			
High strength - Tertile 1	20/60 (33%)	**1**	**1**
Tertile 2	24/57 (42%)	1.50 (0.71, 3.19)	1.33 (0.54, 3.28)
Low strength - Tertile 3	21/49 (43%)	1.50 (0.69, 3.27)	1.12 (0.45, 2.79)
Lift Heavy loads:			
No	232/742 (31%)	**1**	**1**
Yes	108/276 (39%)	**1.41 (1.06, 1.88)**	**1.52 (1.13, 2.05)**
Sweat through physical exertion:			
No	256/795 (32%)	**1**	**1**
Yes	85/219 (39%)	1.34 (0.98, 1.82)	**1.49 (1.08, 2.07)**
More Physical Work:			
No	251/785 (32%)	**1**	**1**
Yes	78/203 (38%)	1.33 (0.96, 1.83)	**1.37 (1.00, 1.90)**

OR was adjusted for age, gender, BMI. (did not adjust by other significant variables). Muscle assessments were conducted only for the 424 participants seen for the clinical assessment. Values in blue refer to risk factors significantly associated with incident knee pain.

5.3 Co-morbidity factors

There were 84 (32.7%) people who reported a co-morbidity alongside incident knee pain. Ten (43.9%) of these people suffered from two or more co-morbidities. No significant association was found between the listed diseases and incident knee pain (Table 14).

Table 14. Co-morbidities and relative risk of incident knee pain

Co-morbidities	Incident rate (%)	OR (95%CI)	aOR (95%CI)
Heart disease	30/108 (28%)	0.72 (0.47, 1.11)	0.77 (0.50, 1.20)
Stroke	7/20 (35%)	1.03 (0.41, 2.58)	0.88 (0.33, 2.35)
Diabetes	21/54 (39%)	1.22 (0.70, 2.12)	1.22 (0.69, 2.17)
Lung disease	19/54 (35%)	1.04 (0.59, 1.82)	1.15 (0.65, 2.04)
Cancer	21/56 (38%)	1.15 (0.66, 1.99)	1.12 (0.64, 1.95)

OR=odds ratio, CI=confidence interval. OR was adjusted for age, gender, BMI

5.3.1 Hip and back pain

People were categorised into three pain patterns; back pain, hip pain and dual pain (back and hip pain). Incident knee pain was seen during the 10-year follow up in 301 (41.0 %), 142 (45.8%) and 96 (45.5%) of people with back, hip and dual pain respectively. Both back and hip pain sites were significantly associated with incident knee pain. Those who reported back or hip pain within a year of baseline were not as significantly associated with incident knee pain as people who had ever reported such a problem. The association, however, was still a positive one (Table 17).

5.3.2 Sleep and fibromyalgia

Having <7 hours sleep/per night was not a risk factor for incident knee pain (aOR 1.29; 95%CI 0.93, 1.78). The clinical assessment for the presence of fibromyalgia at baseline also showed no connection between this disorder and incident knee pain (Table 15).

Table 15 Assessment of fibromyalgia and relative risk of incident knee pain

Physical assessment		Incident rate (%)	Odds ratio (95% confidence interval)	
			Crude	Adjusted
Fibromyalgia:				
	No	60/154 (39%)	**1**	**1**
	Yes	4/11 (36%)	0.90 (0.25, 3.19)	0.63 (0.16, 2.44)

OR was adjusted for age, gender, BMI

5.3.3 Knee stiffness

The calculated ORs showed no association between early morning stiffness (aOR 0.91; 95%CI 0.41, 2.05) or inactivity stiffness (aOR 0.66; 95%CI 0.31, 1.42) with knee pain. This result was confirmed after adjustment for age, gender and BMI.

Table 16 Assessment of stiffness and relative risk of incident knee pain

Stiffness		Incident rate (%)	Odds ratio (95% confidence interval)	
			Crude	Adjusted
Morning:				
	No	14/37 (38%)	**1**	**1**
	Yes	51/131 (39%)	1.06 (0.50, 2.25)	0.91 (0.41, 2.05)
Inactivity				
	No	18/42 (43%)	**1**	**1**
	Yes	47/126 (37%)	0.80 (0.40, 1.64)	0.66 (0.31, 1.42)

OR was adjusted for age, gender, BMI. WOMAC on 424 clinical assessment participants

We undertook a regression analysis to examine whether self-reported RA interacted with morning stiffness, given an assumption they were independent risk factors for knee pain. The results showed there was no interaction between RA and stiffness, even when RA and stiffness were precluded from the model (aOR 1.89; 95%CI 0.88, 4.07).

Table 17. Incidence of knee pain and co-morbidity factors

Co-morbidity factors	Incident rate (%)	Odds ratio (95% confidence interval)	
		Crude	Adjusted
Co-morbidities:			
No	658/1899 (35%)	**1**	**1**
1	74/233 (32%)	0.88 (0.66, 1.18)	0.91 (0.67, 1.22)
≥2	10/24 (42%)	1.35 (0.60, 3.05)	1.19 (0.79, 1.80)
Rheumatoid arthritis (RA):			
No	711/2093 (34%)	**1**	**1**
Yes	31/63 (49%)	**1.88 (1.14, 3.11)**	**1.92 (1.15, 3.22)**
Back Pain:			
No	429/1403 (31%)	**1**	**1**
Yes	301/734 (41%)	**1.58 (1.31, 1.90)**	**1.59 (1.32, 1.93)**
Back Pain last Year:			
No	593/1828 (32%)	**1**	**1**
Yes	142/310 (46%)	**1.57 (1.26, 2.00)**	**1.57 (1.25, 1.97)**
Hip Pain:			
No	628/1882 (33%)	**1**	**1**
Yes	91/200 (46%)	**1.76 (1.38, 2.25)**	**1.78 (1.38, 2.29)**
Hip pain last year:			
No	629/1922 (33%)	**1**	**1**
Yes	96/201 (48%)	**1.67 (1.24, 2.24)**	**1.64 (1.21, 2.23)**
Back plus Hip Pain:			
No	629/1922 (33%)	**1**	**1**
Yes	96/201 (48%)	**1.88 (1.40, 2.52)**	**1.84 (1.36, 2.49)**
Sleep:			
>7 hours	327/1066 (31%)	**1**	**1**
<7 hours	75/207 (36%)	1.25 (0.92, 1.71)	1.29 (0.93, 1.78)

OR was adjusted for age, gender, BMI. Values in blue refer to risk factors significantly associated with incident knee pain.

5.4 Heberden's and Bouchard's nodes

Heberden's and Bouchard's nodes were examined at follow-up. Of the 693 people with HN/BN, 292 (42.1%) reported knee pain; whereas 1,429 people without HN/BN, only 438 (30.7%) had knee pain in the past 10-years. This association between nodes and incident knee pain remained significant after adjustment (Table 18).

Table 18. Nodes and relative risk of incident knee pain

Radiographic factors		Incident rate (%)	Odds ratio (95% confidence interval) Crude	Adjusted
Nodes:				
	No	438/ 1429 (31%)	**1**	**1**
	Yes	292/693 (42%)	**1.65 (1.37, 1.99)**	**1.66 (1.36, 2.03)**

OR was adjusted for age, gender, BMI. Values in blue refer to risk factors significantly associated with incident knee pain.

5.5 Radiographic features

Tibio-femoral and patello-femoral scores were examined both separately and together. Fifty four percent (7/13) of people with isolated tibio-femoral OA at baseline (K/L ≥1) went on to report incident knee pain. These individuals were 4-times more likely to get incident knee pain than people with no tibio-femoral OA at baseline (aOR 3.69; 95%CI 1.05, 13.00). No significant association was made between isolated patello-femoral OA and incident knee pain (aOR 2.66; 95%CI 0.96, 7.39). Conversely, OA (K/L ≥1) in both tibio-femoral and patello-femoral sites was a significant risk factor for incident knee pain (aOR 10.22; 95%CI 3.74, 27.90).

Separate analysis for osteophytes and joint space narrowing showed both to be independently associated with incident knee pain. Adjusted OR was 3.70 (95%CI 1.85, 7.40) for osteophytes (Table 19). Isolated tibio-femoral (aOR 4.57; 95%CI 1.37, 15.23) and isolated patello-femoral (aOR 4.25; 95%CI 1.70, 10.59) JSN were equally important risk factors for incident knee pain.

The percentage of people with baseline tibio-femoral and patello-femoral OA (Kellgren and Lawrence ≥1) who progressed to incident knee pain was 70% (14/20) for the right knee and 53% (10/19) for the left knee. All radiographic features in the right knee directly associated with incident right knee pain (Table 20). However, ORs for tibio-femoral JSN, tibio-femoral OA, and chondrocalcinosis at the left knee showed no significant association with incident left knee pain

Changes in radiographic OA from baseline to follow-up at the tibio-femoral site showed significant association with incident knee pain. Adjusted OR was 2.59 (95%CI 1.25, 5.37) for the right knee and 2.80 (95%CI 1.28, 6.10) for the left knee. No association between patello-femoral OA change and incident knee pain was found for either the right or left knee (Table 21).

Table 19. Assessment of “whole person” x-ray features (combined right and left findings) and risk of incident knee pain

Radiographic factors		Incident rate (%)	Odds ratio (95% confidence interval) Crude	Adjusted
Osteophytes:				
	No	34/119 (29%)	**1**	**1**
	Yes	39/66 (59%)	**3.71 (1.96, 7.00)**	**3.70 (1.85, 7.40)**
Isolated tibio-femoral JSN:				
	No	61/169 (36%)	**1**	**1**
	Yes	12/16 (75%)	**5.21 (1.61, 16.87)**	**4.57 (1.37, 15.23)**
Isolated patello-femoral JSN:				
	No	54/158 (34%)	**1**	**1**
	Yes	19/27 (70%)	**4.49 (1.84, 10.92)**	**4.25 (1.70, 10.59)**
Isolated tibio-femoral OA:				
	K/L 0	31/118 ((27%)	**1**	**1**
	K/L ≥1	7/13 (54%)	**3.88 (1.15, 13.14)**	**3.69 (1.05, 13.00)**
Isolated patello-femoral OA:				
	0	31/118 (26%)	**1**	**1**
	≥1	9/20 (45%)	2.27 (0.86, 6.00)	2.66 (0.96, 7.39)
Tibio-femoral plus patello-femoral OA:				
	K/L 0	31/118 (26%)	**1**	**1**
	K/L ≥1	6/34 (18%)	**9.02 (3.69, 22.01)**	**10.22 (3.74, 27.90)**
Chondrocalcinosis:				
	No	70/180 (39%)	**1**	**1**
	Yes	3/5 (60%)	2.31 (0.38, 14.20)	2.05 (0.32, 13.14)

OR: adjusted by age, gender and BMI. X-rays were conducted only for the participants seen at the clinical assessment

Table 20. Assessment of x-ray features in the right and left knees and relative risk of ipsilateral incident knee pain

Radiographic factors	Right knee			Left knee		
	Incidence	OR (95%CI)	aOR (95%CI)	Incidence	OR (95%CI)	aOR (95%CI)
Osteophytes:						
No	29/129 (22%)	**1**	**1**	23/137 (18%)	**1**	**1**
Yes	30/56 (54%)	**4.38 (2.18, 8.81)**	**4.55 (2.05, 10.07)**	24/48 (50%)	**6.13 (2.81, 13.37)**	**5.49 (2.33, 12.92)**
Isolated tibio-femoral JSN:						
No	50/174 (29%)	**1**	**1**	45/174 (26%)	**1**	**1**
Yes	9/11 (82%)	**9.72 (2.03, 46.65)**	**8.30 (1.63, 42.25)**	2/11 (18%)	1.18 (0.21, 6.66)	1.11 (0.19, 6.51)
Isolated patello-femoral JSN:						
No	44/163 (27%)	**1**	**1**	37/164 (23%)	**1**	**1**
Yes	15/22 (68%)	**5.91 (2.15, 16.23)**	**4.82 (1.65, 14.13)**	10/21 (48%)	**4.69 (1.59, 13.79)**	**4.01 (1.31, 12.32)**
Isolated tibio-femoral OA:						
K/L 0	24/122 (20%)	**1**	**1**	20/124 (16%)	**1**	**1**
K/L ≥1	4/9 (44%)	**4.89 (1.02, 23.35)**	**5.40 (1.03, 28.24)**	3/7 (43%)	4.40 (0.83, 23.43)	3.61 (0.63, 20.62)
Isolated patello-femoral OA:						
0	23/120 (19%)	**1**	**1**	21/128 (16%)	**1**	**1**
≥1	8/18 (44%)	**3.03 (1.07, 8.54)**	**4.29 (1.30, 12.17)**	4/10 (40%)	**4.43 (1.02, 19.16)**	**5.60 (1.15, 27.17)**
Tibio-femoral plus patello-femoral OA:						
K/L 0	24/121 (20%)	**1**	**1**	20/122 (16%)	**1**	**1**
K/L ≥1	14/20 (70%)	**16.72 (4.44, 63.01)**	**19.63 (4.17,**	10/19 (53%)	**10.88 (3.09, 38.24)**	**10.80 (2.69, 43.45)**
Chondrocalcinosis:						
No	57/181 (31%)	**1**	**1**	45/180 (25%)	**1**	**1**
Yes	2/4 (50%)	1.90 (0.26, 13.81)	1.41 (0.17, 11.39)	2/5 (40%)	2.40 (0.33, 17.57)	1.72 (0.22, 13.57)

OR: adjusted by age, gender and BMI. X-rays were conducted only for the participants seen at the clinical assessment.

Table 21. Change in radiographic knee OA status during the 10-year follow-up period and relative risk of incident knee pain

	Right knee			Left knee		
	Incidence (%)	OR (95%CI)	aOR (95%CI)	Incidence	OR (95%CI)	aOR (95%CI)
Change in K/L OA grade in tibio-femoral compartment (≥1):						
No	28/109 (26%)	**1**	**1**	23/110 (21%)	**1**	**1**
Yes	29/58 (50%)	**2.89 (1.48, 5.66)**	**2.59 (1.25, 5.37)**	23/46 (50%)	**3.78 (1.81, 7.92)**	**2.80 (1.28, 6.10)**
Change in OA grade in patello-femoral compartment (≥1):						
No	31/77 (40%)	**1**	**1**	39/110 (36%)	**1**	**1**
Yes	26/59 (44%)	**1.96 (1.01, 3.79)**	1.45 (0.72, 2.95)	21/46 (46%)	1.53 (0.76, 3.08)	1.37 (0.64, 2.91)

OR: adjusted by age, gender and BMI. X-rays were conducted only for the participants seen at the clinical assessment. Values in blue refer to risk factors significantly associated with incident knee pain.

5.6 2D:4D finger index (ring: index finger ratio)

Finger length patterns were visually classified as, Type 1 (2D>4D), Type 2 (2D=4D) and Type 3 (2D<4D) using a self-reported questionnaire.

Incidence of knee pain was similar among the three different types. Neither type 1 (index>ring) or type 3 (index<ring) were associated with incident knee pain. The ORs compared with type 2 finger pattern were 1.02 (95%CI 0.76, 1.38) and 1.00 (95%CI 0.80, 1.24) respectively (Figure 41). The ORs adjusted for age, gender and BMI were 1.00 (95%CI 0.80, 1.25) for type 1 and 1.00 (95%CI 0.74, 1.37) for type 3.

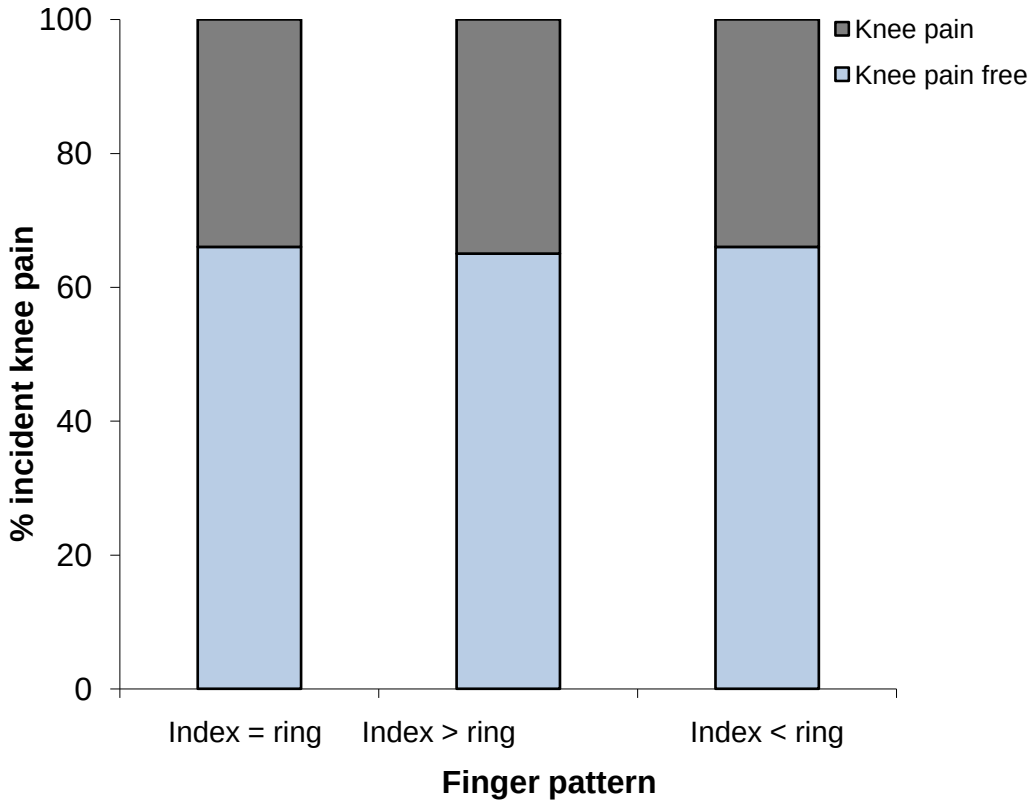


Figure 41. Incident knee pain in relation to 2D:4D

5.7 Psychological factors

Examination of baseline quality of life showed a non-normal distribution of data, so OR could not be calculated. Mean values for total SF36 showed no difference between people with incident knee pain and those without (adjusted p= 0.74) (Table 22). Depression showed no link to incident knee (adjusted p value was >0.05). In contrast, high anxiety levels did show a potential significant association with incident knee pain (p<0.05).

Table 22. Quality of life, Had scores, and incident knee pain

Quality of life index	Incident knee pain (Mean ±SD)		p values	
	Yes	No	Crude	Adjusted
SF36 total	**77.8** ±18.5	**79.4** ±15.7	0.55	0.74
Physical function	**80.0** ±21.1	**82.8** ±19.9	0.37	0.95
Role physical health	**76.4** ±39.1	**83.6** ±32.2	0.18	0.51
Role emotional problems	**85.2** ±32.4	**85.7** ±30.6	0.92	0.70
Energy/Fatigue	**63.4** ±22.6	**62.1** ±22.7	0.72	0.90
Emotional wellbeing	**78.9** ±15.5	**77.6** ±17.2	0.60	0.94
Social functioning	**92.2** ±17.0	**91.0** ±16.2	0.63	0.72
Pain	**76.8** ±23.7	**80.9** ±20.7	0.22	0.59
General health	**71.5** ±19.7	**69.8** ±18.0	0.56	0.54
HAD anxiety	**14.1** ±5.3	**12.4** ±6.5	0.07	**0.04**
HAD depression	**10.1** ±6.1	**11.0** ±5.5	0.32	0.13

The higher the mean score for the SF36, the healthier the person. The higher the mean scores for the HAD index, the more anxious or depressed the person. Values in blue refer to risk factors significantly associated with incident knee pain.

5.8 Physical examination features

The physical assessment of knees at baseline showed no association between regional knee OA findings and incident knee pain (Table 23).

A crude OR of 1.46 (95%CI 0.56, 3.82) was observed for people with bony swelling of the knee at baseline. For individuals who had baseline crepitus the crude OR was also insignificant (OR 1.47; 95%CI 0.74, 3.00). After adjusting for confounding factors regional knee OA findings remained un-associated with incident knee pain (Table 23).

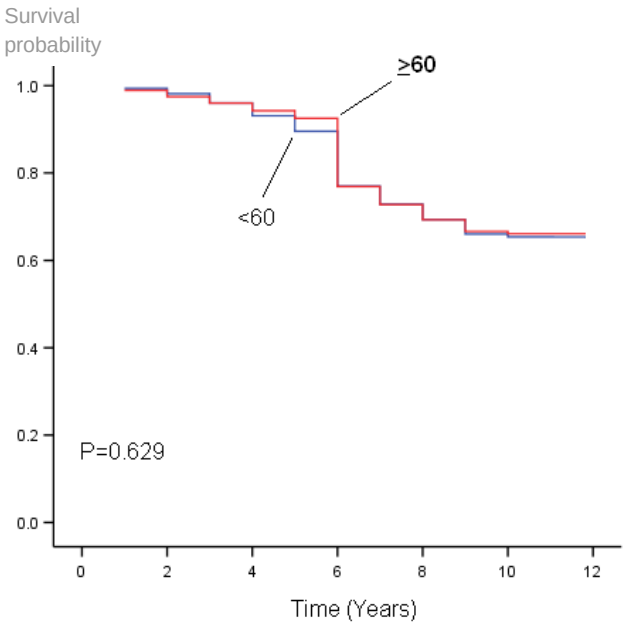
Table 23. Assessment of knee pain and relative risk of incident knee pain

Physical assessment	Incident rate (%)	Odds ratio (95% confidence interval)	
		Crude	Adjusted
Effusion			
No	56/139 (40%)	**1**	**1**
Yes	9/26 (35%)	0.79 (0.33, 1.89)	0.80 (0.32, 1.96)
Bony swelling			
No	56/147 (38%)	**1**	**1**
Yes	9/19 (47%)	1.46 (0.56, 3.82)	1.35 (0.49, 3.71)
Crepitus			
No	26/76 (34%)	**1**	**1**
Yes	39/90 (43%)	1.47 (0.78, 2.76)	1.49 (0.74, 3.00)
Restricted hip rotation			
No	46/123 (37%)	**1**	**1**
Yes	19/44 (43%)	1.33 (0.66, 2.68)	1.32 (0.63, 2.78)

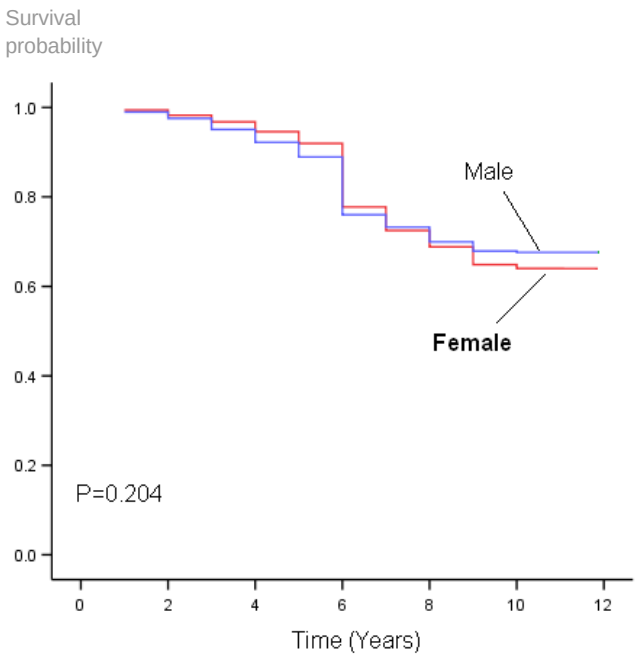
OR=Odds ratio, CI=confidence interval. OR was adjusted for age, gender, BMI

5.9 Survival analysis

Survival outcome was defined as time (years) from baseline to the onset of knee pain in the people at risk (i.e. pain free at baseline).



Age



Gender

Figure 42. Survival (knee pain free) probability in 10 years for age and gender.

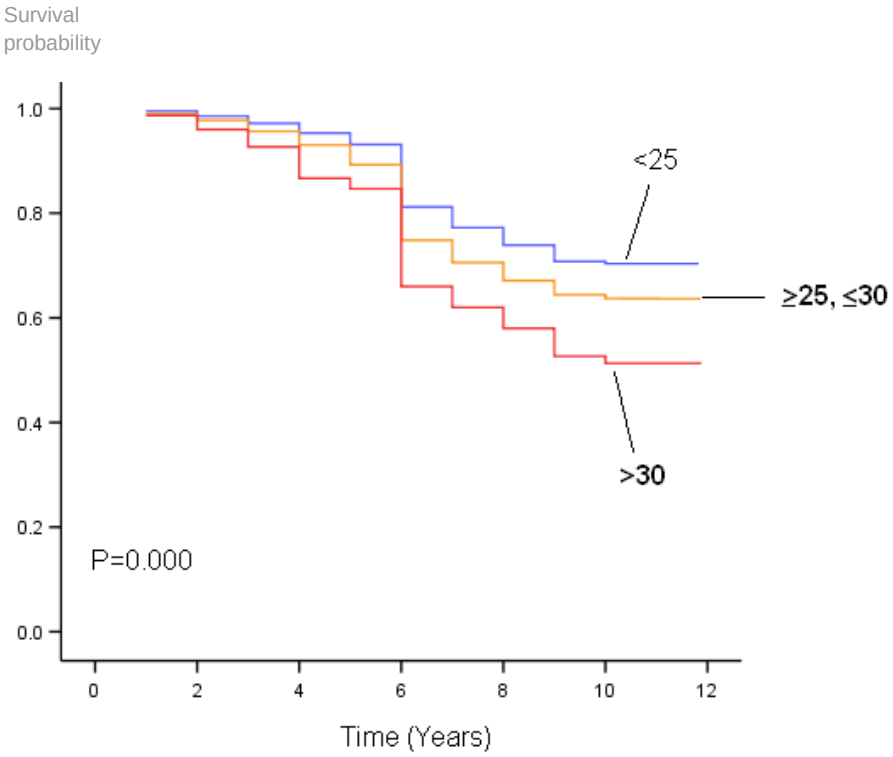


Figure 43. Survival (knee pain free) probability in 10 years for BMI. Missing values were given the median time to event value of 6 years, explaining the steep jump in data at this time point.

There were 167 individuals who were reported at incidence cases at follow-up, but failed to recall the approximate time of their first event. These individuals were given the median time to event of six years. This handling of missing values accounts for the steep jump at year six with regards to the survival data (Figure 42 and 43).

The 10-year survival (i.e. knee pain free) probability was 74%. The probability was not dependent on age (p=0.629) and was similar between men and women (p=0.204) (Figure 42). However, people who were overweight or obese became knee pain positive much sooner after

baseline than those who were normal weight (BMI<25) (p<0.000) (Figure 43).

Other risk factors associated with the probability were examined using the COX-regression model. Heberden's nodes, varus alignment, outward foot angulation, back and hip pain, knee injury, and lifting heavy loads were significantly associated with the shorter time to knee pain onset after adjustment for other risk factors (Appendix 10). Radiographic features, such as osteophytes and joint space narrowing were also associated with a shorter time to the onset of knee pain. However, the effect of high occupational physical exertion on survival outcome changed from non-significant to significant after adjustment for age, gender and BMI (aHR 1.35; 95%CI 1.04, 1.74).

5.10 Summary of findings for incidence of knee pain

Approximately three out of ten people developed incident knee pain during the follow-up period. Constitutional, biomechanical, co-morbidity, radiographic and psychological factors were found to be risks for incident knee pain. Specific factors associated with the incidence of knee pain are shown in Table 24.

Table 24. Risk factors for the incidence of knee pain

Risk factors
Female gender
BMI (overweight and obese)
Varus knee malalignment
Outward foot angulation
Knee injury
Regular lifting of heavy loads
Regular physical labour
Back pain
Hip pain
Rheumatoid Arthritis
Nodes on hands
Osteophytes in knee joint
Tibio-femoral and Patello-femoral JSN
Tibio-femoral and Patello-femoral OA
Anxiety

6. Outcome analysis of knee pain

Outcome was determined by questionnaire data and divided into poor outcome (persistent or worsening knee pain, including those who went on to have a total knee replacement) and good outcome (improved knee pain). Worsening of knee pain and TKR were examined separately and as part of the overall poor outcome of knee pain. Baseline risk factors and some factors at follow-up were examined in relation to outcome.

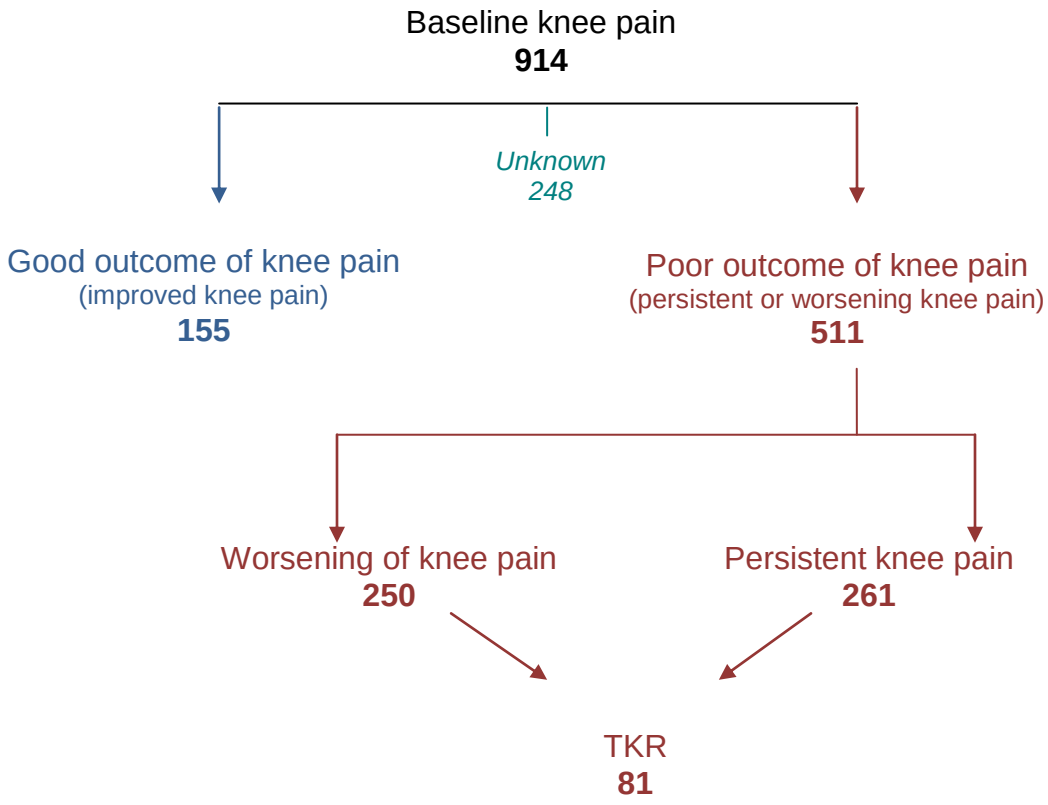


Figure 44. Summary of knee pain outcome

6a Poor outcome of knee pain

Poor outcome of knee pain was determined from a self-reported question. People with knee pain at baseline were asked to answer whether his/her knee pain had worsened or remained the same since it began. Of the 914 people who had baseline knee pain 511 (55.9%) either reported persistent or worsening knee pain.

6.1 Constitutional factors

6.1.1 Age

Age at baseline was examined in relation to poor knee pain status. Of 375 people who were <60 years old, 249 (66.4%) reported continuing or worsening knee pain, similarly among 230 people ≥60 years old, 167 (72.6%) had poor outcome of knee pain. The crude OR was 1.34 (95%CI 0.94, 1.92), and adjusted OR was 1.33 (95%CI 0.92, 1.92) (Table 25). Age was therefore not associated with poor outcome of knee pain.

6.1.2 Gender

Out of 325 women, 223 (68.6%) associated with poor knee pain at follow up. There was no association between gender and overall knee pain outcome (OR 0.99; 95%CI 0.70, 1.39; and aOR 0.98; 95%CI 0.69, 1.40) (Table 25).

6.1.3 BMI

Poor knee pain status was similar between people who were normal weight 113/169 (66.9%), overweight 211/314 (67.2%) and obese 68/93 (73.1%) (Figure 45). Crude odds ratio of 1.02 and 95% confidence interval (CI) from 0.68 to 1.51 was calculated for overweight (BMI ≥25, ≤30) people. For obese individuals (BMI >30) OR was also insignificant (1.35; 95%CI 0.77, 2.36). This absence of association remained after adjustment for possible confounders (Table 25).

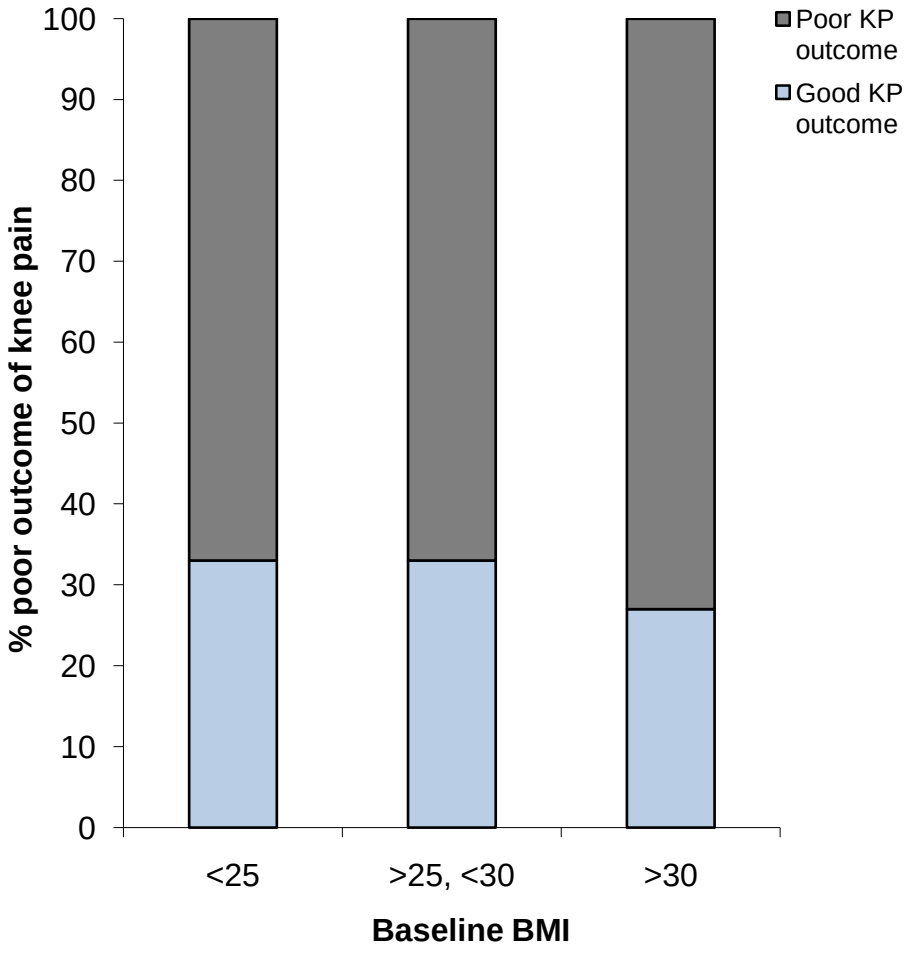


Figure 45. BMI and overall poor outcome of knee pain

6.1.4 Smoking

Out of 327 baseline smokers, 232 (70.9%) reported a poor outcome in their knee pain status at follow-up. However, there was no significant association to the poor outcome of knee pain (OR 1.25; 95%CI 0.88, 1.80; and aOR 1.28; 95%CI 0.89, 1.84).

Table 25. Poor outcome of knee pain in relation to constitutional factors

Constitutional factors	Poor knee pain outcome		Odds ratio (95% confidence interval)	
	Yes	No	Crude	Adjusted
Age:				
<60	249	126	**1**	**1**
≥60	167	63	1.34 (0.94, 1.92)	1.33 (0.92, 1.92)
Gender:				
Men	193	87	**1**	**1**
Women	223	102	0.99 (0.70, 1.39)	0.98 (0.69, 1.40)
BMI:				
Normal (<25)	113	56	**1**	**1**
Overweight (≥25, ≤30)	211	103	1.02 (0.68, 1.51)	1.03 (0.69, 1.54)
Obese (>30)	68	25	1.35 (0.77, 2.36)	1.45 (0.82, 2.55)
Smoking:				
No	184	94	**1**	**1**
Yes	232	95	1.25 (0.88, 1.76)	1.28 (0.89, 1.84)

OR was adjusted for age, gender, BMI. For age, gender, BMI OR was adjusted only with the other two confounders.

6.2 Biomechanical factors

Those who undertook more physically intensive jobs were more likely to have a poor outcome of knee pain (aOR 1.88; 95%CI 1.02, 3.50).

Table 26. Poor outcome of knee pain in relation to biomechanical factors

Biomechanical factors	Poor knee pain outcome		Odds ratio (95% confidence interval)	
	Yes	No	Crude	Adjusted
Knee angulation during 20s:				
Normal	371	167	**1**	**1**
Varus	16	5	1.44 (0.52, 4.00)	1.36 (0.48, 3.86)
Valgus	5	5	0.45 (0.13, 1.58)	0.44 (0.12, 1.53)
Foot angulation during 20s:				
Normal	307	145	**1**	**1**
Out	61	25	1.15 (0.70, 1.91)	1.10 (0.65, 1.85)
In	9	4	1.06 (0.32, 3.51)	0.83 (0.24, 2.92)
Knee Injury:				
No	273	113	**1**	**1**
Yes	138	73	0.78 (0.55, 1.12)	0.79 (0.55, 1.15)
Muscle Strength – Highest:				
High strength - Tertile 1	37	16	**1**	**1**
Tertile 2	38	17	0.97 (0.43, 2.19)	1.26 (0.48, 3.26)
Low strength - Tertile 3	47	10	2.03 (0.83, 5.00)	2.71 (0.78, 9.42)
Muscle Strength – Average:				
High strength - Tertile 1	37	16	**1**	**1**
Tertile 2	38	16	1.03 (0.45, 2.35)	1.34 (0.51, 3.49)
Low strength - Tertile 3	47	11	1.85 (0.77, 4.46)	2.03 (0.60, 6.90)
Lift Heavy loads:				
No	115	54	**1**	**1**
Yes	96	34	1.33 (0.80, 2.20)	1.42 (0.82, 2.46)
Sweat through physical exertion:				
No	127	63	**1**	**1**
Yes	82	25	1.63 (0.95, 2.79)	1.75 (0.99, 3.11)
More Physical Work:				
No	140	69	**1**	**1**
Yes	65	18	1.78 (0.98, 3.23)	**1.88 (1.02, 3.50)**

OR was adjusted for age, gender, BMI. Muscle assessments were conducted only for the 424 participants seen for the clinical assessment. Values in blue refer to risk factors significantly associated with poor outcome of knee pain.

No associations were found for the other potential biomechanical risk factors, including knee or foot angulation in their 20's, baseline quadriceps muscle strength, or other aspects of occupation (Table 26).

6.3 Co-morbidity factors

Back pain within the last year (aOR 1.47; 95%CI 1.02, 2.10) associated with a greater likelihood of a poor outcome of knee pain. No other potential co-morbidity risk factors showed any association (Table 28).

6.3.1 Sleep

Having <7 hours sleep/per night was a risk factor for poor outcome of knee pain (aOR 2.23, 95%CI 1.30, 3.84) (Table 28).

6.3.2 Knee stiffness

The calculated ORs showed a significant association between morning stiffness (aOR 7.37; 95%CI 1.20, 45.25) and poor outcome of knee pain. However, no other associations were made (Table 27).

Table 27. Assessment of stiffness and poor outcome of knee pain

Stiffness		Poor knee pain outcome		Odds ratio (95% confidence interval)	
		Yes	No-	Crude	Adjusted
Morning					
	No	3	4	**1**	**1**
	Yes	119	39	4.07 (0.87, 19.0)	**7.37 (1.20, 45.25)**
Inactivity					
	No	5	1	**1**	**1**
	Yes	117	42	0.56 (0.06, 4.91)	0.75 (0.08, 7.52)

OR was adjusted for age, gender, BMI. WOMAC assessments were conducted only for the 424 participants seen for the clinical assessment. Values in blue refer to risk factors significantly associated with poor outcome of knee pain.

Table 28. Association between poor outcome of knee pain and co-morbidities

Co-morbidity factors	Poor knee pain outcome		Odds ratio (95% confidence interval)	
	Yes	No	Crude	Adjusted
Co-morbidities:				
No	354	161	**1**	**1**
1	57	27	0.96 (0.59, 1.57)	0.85 (0.51, 1.42)
≥2	5	1	2.27 (0.26, 19.62)	1.97 (0.22, 17.30)
RA:				
No	366	156	**1**	**1**
Yes	50	33	0.65 (0.40, 1.04)	0.58 (0.35, 1.96)
Back Pain:				
No	158	77	**1**	**1**
Yes	255	112	1.11 (0.78, 1.58)	1.13 (0.79, 1.62)
Back Pain last year:				
No	213	114	**1**	**1**
Yes	199	72	**1.48 (1.04, 2.11)**	**1.47 (1.02, 2.10)**
Hip Pain:				
No	252	122	**1**	**1**
Yes	158	65	1.18 (0.82, 1.69)	1.11 (0.76, 1.61)
Hip pain last year:				
No	279	137	**1**	**1**
Yes	127	45	1.39 (0.93, 2.06)	1.29 (0.86, 1.93)
Back plus Hip Pain:				
No	291	138	**1**	**1**
Yes	117	49	1.13 (0.77, 1.67)	1.08 (0.72, 1.61)
Sleep:				
>7 hours	166	94	**1**	**1**
<7 hours	92	23	**2.27 (1.34, 3.82)**	**2.23 (1.30, 3.84)**

OR was adjusted for age, gender, BMI. Values in blue refer to risk factors significantly associated with poor outcome of knee pain.

6.4 Radiographic features

Radiographic OA was classified by several different criteria; osteophytes, isolated tibio-femoral JSN, isolated patello-femoral JSN, JSN both in the tibio-femoral and patello-femoral compartments, isolated tibio-femoral OA, isolated patello-femoral OA, and K/L OA both in tibio-femoral and patello-femoral compartments. Of the 70 people who were assessed as having some degree of tibio-femoral and patello-femoral OA at baseline (K/L $\geq$1), 48 (68.6%) went on to report poor knee pain status at follow-up.

Baseline radiographic OA at the tibio-femoral and patello-femoral sites did not correspond with an increased risk of poor outcome of knee pain (aOR 0.79; 95%CI 0.35, 1.77). Also, individuals with confirmed osteophytes (OR 1.33; 95%CI 0.66, 2.67), JSN, or chondrocalcinosis were not at any greater risk of having persistent or worsening knee pain (Table 29).

No significant associations were found between radiographic right knee OA at baseline, and poor outcome of right knee pain (Table 30). These findings also applied to site specific features examined for left knee pain. Similarly neither change in radiographic OA at the tibio-femoral compartment or at the patello-femoral compartment had any association with poor right or left knee pain outcome (Table 31).

Table 29. Association between "whole person" radiographic features (combined right and left knee findings) and poor outcome of knee pain

Radiographic factors		Poor knee pain outcome		Odds ratio (95% confidence interval)	
		Yes	No	Crude	Adjusted
Osteophytes:					
	No	55	21	**1**	**1**
	Yes	73	21	1.33 (0.66, 2.67)	1.44 (0.70, 3.08)
Isolated tibio-femoral JSN:					
	No	104	32	**1**	**1**
	Yes	26	13	0.62 (0.28, 1.34)	0.63 (0.27, 1.50)
Isolated patello-femoral JSN:					
	No	96	34	**1**	**1**
	Yes	32	8	1.42 (0.60, 3.37)	1.56 (0.60, 4.02)
Isolated tibio-femoral OA:					
	K/L 0	55	20	**1**	**1**
	K/L ≥1	11	0	8.50 (0.48, 150.80)	N/A
Isolated patello-femoral OA:					
	0	55	20	**1**	**1**
	≥1	16	3	1.94 (0.51, 7.37)	1.84 (0.44, 7.81)
Tibio-femoral plus patello-femoral OA:					
	K/L 0	55	20	**1**	**1**
	K/L ≥1	48	22	0.79 (0.39, 1.63)	0.79 (0.35, 1.77)
Chondrocalcinosis:					
	No	122	44	**1**	**1**
	Yes	8	1	2.89 (0.35, 23.73)	1.87 (0.22, 17.08)

OR: adjusted by age, gender and BMI. X rays were conducted only for the 424 participants seen for the clinical assessment.

Table 30. Assessment of x-ray features in right and left knees and relative risk of ipsilateral poor outcome of knee pain

Radiographic factors	Right knee			Left knee		
	Poor KP	OR (95%CI)	aOR (95%CI)	Poor KP	OR (95%CI)	aOR (95%CI)
Osteophytes:						
No	58/76 (76%)	**1**	**1**	57/76 (75%)	**1**	**1**
Yes	51/69 (74%)	0.88 (0.41, 1.87)	0.79 (0.35, 1.79)	53/71 (75%)	0.98 (0.47, 2.07)	1.13 (0.48, 2.62)
Isolated tibio-femoral JSN:						
No	91/122 (75%)	**1**	**1**	97/126 (77%)	**1**	**1**
Yes	18/26 (69%)	0.77 (0.30, 1.94)	0.68 (0.24, 1.96)	15/24 (63%)	0.50 (0.20, 1.26)	0.61 (0.22, 1.69)
Isolated patello-femoral JSN:						
No	86/116 (74%)	**1**	**1**	89/119 (75%)	**1**	**1**
Yes	23/29 (79%)	1.34 (0.50, 3.60)	1.21 (0.41, 3.54)	21/28 (75%)	1.01 (0.39, 2.62)	1.22 (0.42, 3.56)
Isolated tibio-femoral OA:						
K/L 0	91/122 (75%)	**1**	**1**	97/126 (77%)	**1**	**1**
K/L ≥1	18/26 (69%)	0.77 (0.30, 1.94)	0.68 (0.24, 1.96)	15/24 (63%)	0.50 (0.20, 1.26)	1.22 (0.42, 3.56)
Isolated patello-femoral OA:						
0	51/69 (74%)	**1**	**1**	52/68 (76%)	**1**	**1**
≥1	8/10 (80%)	1.41 (0.27, 7.28)	1.11 (0.20, 6.32)	9/11 (82%)	1.39 (0.27, 7.08)	1.35 (0.22, 8.21)
Tibio-femoral plus patello-femoral OA:						
K/L 0	54/73 (74%)	**1**	**1**	57/78 (73%)	**1**	**1**
K/L ≥1	35/49 (71%)	0.88 (0.39, 1.98)	0.73 (0.30, 1.78)	28/42 (67%)	0.74 (0.33, 1.66)	0.70 (0.29, 1.69)
Chondrocalcinosis:						
No	N/A	N/A	N/A	107/144 (74%)	**1**	**1**
Yes	N/A	N/A	N/A	5/6 (83%)	1.73 (0.20, 15.29)	0.73 (0.07, 7.74)

OR: adjusted by age, gender and BMI. X rays were conducted only for the 424 participants seen for the clinical assessment.

Table 31. Association between change in radiographic knee OA status during the 10-year follow-up period and poor outcome of knee pain

	Right knee			Left knee		
	Poor KP	OR (95%CI)	aOR (95%CI)	Poor KP	OR (95%CI)	aOR (95%CI)
Change in K/L OA grade in tibio-femoral compartment ≥1:						
No	55/67 (82%)	**1**	**1**	60/76 (79%)	**1**	**1**
Yes	46/59 (78%)	0.77 (0.32, 1.86)	0.73 (0.29, 1.83)	46/55 (84%)	1.36 (0.55, 3.36)	1.43 (0.56, 3.64)
Change in OA grade in patello-femoral compartment ≥1:						
No	43/57 (75%)	**1**	**1**	50/63 (79%)	**1**	**1**
Yes	58/69 (84%)	1.72 (0.71, 4.15)	1.43 (0.57, 3.59)	54/66 (82%)	1.17 (0.49, 2.80)	1.19 (0.48, 2.93)

OR: adjusted by age, gender and BMI. X rays were conducted only for the 424 participants seen for the clinical assessment. Values in blue refer to risk factors significantly associated with poor outcome of knee pain.

6.5 Psychological factors

No association was found between poor outcome of knee pain and baseline perception of a low quality of life; adjusted p values were non-significant ($p \geq 0.05$).

Table 32. Association between quality of life, HAD scores, and poor outcome of knee pain

Quality of life index	Poor outcome of knee pain (Mean ±SD)		p values	
	Yes	No	Crude	Adjusted
SF36 total	**59.6** ±20.4	**61.9** ±19.2	0.51	0.37
Physical function	**60.2** ±27.9	**61.0** ±26.5	0.88	0.63
Role physical health	**50.6** ±41.3	**42.8** ±41.5	0.28	0.37
Role emotional problems	**66.1** ±42.4	**78.8** ±36.7	0.08	0.05
Energy/Fatigue	**45.4** ±20.9	**51.5** ±17.3	0.08	0.08
Emotional wellbeing	**69.7** ±17.1	**72.4** ±17.4	0.37	0.22
Social functioning	**76.1** ±26.6	**76.6** ±25.7	0.92	0.93
Pain	**54.5** ±24.2	**57.4** ±23.4	0.49	0.49
General health	**56.1** ±21.1	**56.5** ±19.7	0.90	0.70
HAD anxiety	**14.4** ±5.4	**15.1** ±5.2	0.51	0.87
HAD depression	**12.1** ±4.6	**11.7** ±4.7	0.61	0.79

The higher the mean score for the SF36, the healthier the person. The higher the mean scores for the HAD index, the more anxious or depressed the person.

6b Worsening of knee pain

Deterioration in knee pain, and factors that may associate with this, were examined specifically. Of the 914 people who had baseline knee pain 250 (27.4%) reported worsening at follow up.

6.6 Constitutional factors

6.6.1 Age

Age was not significantly associated with worsening knee pain (OR 1.36; 95%CI 0.91, 2.01). This was confirmed after adjusting for confounders (aOR 1.34; 95%CI 0.89, 2.00) (Table 33).

6.6.2 Gender

Worsening of knee pain was seen in 127 (56.3%) women and 123 (58.6%) men. Female gender was not significantly associated with knee pain worsening (aOR of 0.89; 95%CI 0.60, 1.31) (Table 33).

6.6.3 BMI

BMI was not associated with worsening of knee pain during the 10 year follow-up interval (Table 33). The aORs were 1.08 (95%CI 0.69, 1.69) for overweight and 1.50 (95%CI 0.80, 2.80) for obese individuals (Table 33).

6.6.4 Smoking

Worsening of knee pain was reported in 61.2% (150/245) of smokers. Smokers were 1.48-times more likely to suffer with worsening of knee pain (95%CI 1.01, 2.17) in comparison to non-smokers. However, this became insignificant after adjustment for confounders (Table 33).

Table 33. Association between worsening of knee pain and constitutional factors

Constitutional factors	Worsening knee pain		Odds ratio (95% confidence interval)	
	Yes	No	Crude	Adjusted
Age:				
<60	149	126	**1**	**1**
≥60	101	63	1.36 (0.91, 2.01)	1.34 (0.89, 2.00)
Gender:				
Men	123	87	**1**	**1**
Women	127	102	0.88 (0.60, 1.29)	0.89 (0.60, 1.31)
BMI:				
Normal (<25)	65	56	**1**	**1**
Overweight (≥25, ≤30)	128	103	1.07 (0.69, 1.67)	1.08 (0.69, 1.69)
Obese (>30)	41	25	1.41 (0.77, 2.61)	1.50 (0.80, 2.80)
Smoking:				
No	100	94	**1**	**1**
Yes	150	95	**1.48 (1.01, 2.17)**	1.46 (0.97, 2.17)

OR was adjusted for age, gender, BMI. For age, gender, BMI OR was adjusted only with the other two confounders. Values in blue refer to risk factors significantly associated with worsening knee pain.

6.7 Biomechanical factors

6.7.1 Knee malalignment

Neither varus nor valgus malalignment were associated with knee pain worsening. ORs adjusted for age, gender and BMI were 1.41 (95%CI 0.46, 4.26) for varus malalignment and 0.29 (95%CI 0.06, 1.51) when malalignment was valgus (Table 36).

6.7.2 Foot angulation

Outward foot angulation was not associated with worsening of knee pain (aOR 1.00; 95%CI 0.55, 1.79). Likewise, inward foot angulation was not associated with knee pain (aOR 0.57; 95%CI 0.12, 2.62) (Table 36).

6.7.3 Knee injury

Knee injury was not associated with worsening of knee pain. This was confirmed after adjustment for age, gender and BMI (aOR 0.76; 95%CI 0.50, 1.15) (Table 36).

6.7.4 Quadriceps muscle strength

Quadriceps muscle strength was categorised into three tertiles; high muscle strength (tertile 1), medium muscle strength (tertile 2) and low muscle strength (tertile 3). It was hypothesised that low quadriceps muscle strength would correlate with worsening of knee pain. However, this was not found to be the case, even after adjustment for age, gender and BMI (Table 36).

6.7.5 Occupational physical activity

None of the potential occupational risk factors were found to be associated significantly with worsening of knee pain (Table 34).

Table 34. Occupational activity and relative risk of worsening knee pain

Occupational activity	Worse knee pain		OR (95%CI)
	Yes	No	
Sit	39/65	26/65	1.14 (0.63, 2.06)
Stand	75/133	58/133	0.87 (0.49, 1.54)
Walk	76/136	60/136	0.84 (0.47, 1.49)
Lift Heavy loads	55/89	34/89	1.32 (0.76, 2.31)
Feel Tired	40/78	38/78	0.67 (0.38, 1.18)
Sweat through physical exertion	49/74	25/74	1.76 (0.98, 3.18)
More Physical Work	37/55	18/55	1.77 (0.93, 3.39)
Walk to Work	36/59	23/59	1.37 (0.68, 2.74)

OR=Odds ratio, CI=confidence interval. OR was adjusted for age, gender, BMI

6.7.6 Leisure physical activity

Neither a negative nor positive association was seen for any of the leisure activities upon worsening of knee pain (Table 35). The 95% confidence intervals crossed null on all occasions.

Table 35. Leisure activity and relative risk of worsening knee pain

Leisure activity	Worse knee pain		OR (95%CI)	aOR (95%CI)
	Yes	No		
Cause sweating	43/72	29/72	1.16 (0.67, 2.03)	1.28 (0.70, 2.33)
Play Sports	89/145	56/145	1.56 (0.94, 2.58)	1.46 (0.87, 2.46)
Watch TV	64/121	57/121	0.76 (0.47, 1.24)	0.81 (0.49, 1.33)
Walking	86/149	63/149	1.11 (0.68, 1.81)	1.24 (0.75, 2.06)
Cycling	14/24	10/24	1.09 (0.46, 2.55)	1.02 (0.42, 2.48)
DIY	81/133	52/133	1.42 (0.88, 2.14)	1.49 (0.89, 2.50)
Gardening	103/172	69/172	1.46 (0.88, 2.42)	1.43 (0.85, 2.41)

OR=Odds ratio, CI=confidence interval. OR was adjusted for age, gender, BMI

Table 36. Association between biomechanical factors and worsening of knee pain

Biomechanical factors	Worse knee pain		Odds ratio (95% confidence interval)	
	Yes	No	Crude	Adjusted
Knee angulation: during				
Normal	227	167	**1**	**1**
Varus	11	5	1.62 (0.55, 4.75)	1.41 (0.46, 4.26)
Valgus	2	5	0.29 (0.06, 1.53)	0.29 (0.06, 1.51)
Foot angulation during 20s:				
Normal	188	145	**1**	**1**
Out	34	25	1.05 (0.60, 1.84)	1.00 (0.55, 1.79)
In	5	4	0.96 (0.25, 3.65)	0.57 (0.12, 2.62)
Knee Injury:				
No	167	113	**1**	**1**
Yes	81	73	0.75 (0.51, 1.12)	0.76 (0.50, 1.15)
Muscle Strength – Highest score:				
High strength - Tertile 1	26	16	**1**	**1**
Tertile 2	29	17	1.05 (0.44, 2.49)	1.91 (0.63, 5.80)
Low strength - Tertile 3	29	10	1.79 (0.69, 4.62)	3.50 (0.76, 16.22)
Muscle Strength – Average score:				
High strength - Tertile 1	26	16	**1**	**1**
Tertile 2	30	16	1.15 (0.48, 2.75)	2.12 (0.70, 6.45)
Low strength - Tertile 3	28	11	1.57 (0.62, 4.00)	2.14 (0.47, 9.77)
Lift Heavy loads:				
No	66	54	**1**	**1**
Yes	55	34	1.32 (0.76, 2.31)	1.30 (0.72, 2.36)
Sweat through physical exertion:				
No	70	63	**1**	**1**
Yes	49	25	1.76 (0.98, 3.18)	1.78 (0.95, 3.33)
More Physical Work:				
No	80	69	**1**	**1**
Yes	37	18	1.77 (0.93, 3.39)	1.85 (0.94, 3.62)

OR was adjusted for age, gender, BMI. Muscle assessments were conducted only for the 424 participants seen for the clinical assessment

6.8 Co-morbidly factors

Individuals with baseline co-morbidities (≥1 reported) were not found to be at any more risk of worsening knee pain than those with no additional disease (Table 37).

Table 37. Co-morbidities and relative risk of worsening knee pain

Co-morbidities	Worse knee pain		OR (95%CI)	aOR (95%CI)
	Yes	No		
Heart disease	18/31	13/31	1.05 (0.50, 2.20)	0.80 (0.36, 1.76)
Diabetes	5/8	3/8	1.27 (0.30, 5.36)	0.90 (0.19, 4.15)
Lung disease	9/16	7/16	0.97 (0.36, 2.66)	0.84 (0.30, 2.37)
Cancer	7/13	6/13	0.88 (0.29, 2.66)	0.88 (0.29, 2.68)

OR=Odds ratio, CI=confidence interval. OR was adjusted for age, gender, BMI

6.8.1 Hip and back pain

Back (aOR 1.33; 95%CI 0.89, 1.99) and hip pain (aOR 1.13; 95%CI 0.75, 1.70) were not significantly associated with worsening of knee pain. However, those who reported back pain within one year of baseline were found to be at greater risk of worsening symptoms (OR 1.69; 95%CI 1.15, 2.49). This association remained after adjustment for age, gender and BMI (Table 38).

6.8.2 Sleep and fibromyalgia

Individuals with <7 hours of sleep a night at baseline had a two-fold risk of worsening knee pain (OR 1.86; 95%CI 1.03, 3.35). However this association was lost after adjustment for age, gender and BMI (Table 38).

Table 38. Worsening knee pain and co-morbidity factors

Co-morbidity factors		Worse knee pain		Odds ratio (95% confidence interval)	
		Yes	No	Crude	Adjusted
Co-morbidities:					
	No	214	161	**1**	**1**
	1	34	27	0.95 (0.55, 1.63)	0.77 (0.43, 1.36)
	≥2	2	1	1.51 (0.14, 16.74)	1.17 (0.10, 13.44)
RA:					
	No	223	156	**1**	**1**
	Yes	27	33	0.57 (0.33, 1.99)	0.53 (0.29, 0.95)
Back Pain:					
	No	84	77	**1**	**1**
	Yes	163	112	1.33 (0.90, 1.97)	1.33 (0.89, 1.99)
Back Pain within last year:					
	No	120	114	**1**	**1**
	Yes	128	72	**1.69 (1.15, 2.49)**	**1.62 (1.09, 2.41)**
Hip Pain:					
	No	151	122	**1**	**1**
	Yes	97	65	1.21 (0.81, 1.79)	1.13 (0.75, 1.70)
Hip pain within last year:					
	No	166	137	**1**	**1**
	Yes	77	45	1.41 (0.92, 2.18)	1.30 (0.83, 2.04)
Back plus Hip Pain:					
	No	174	138	**1**	**1**
	Yes	72	49	1.17 (0.76, 1.79)	1.13 (0.72, 1.76)
Sleep:					
	>7 hours	106	94	**1**	**1**
	<7 hours	44	21	**1.86 (1.03, 3.35)**	1.70 (0.91, 3.18)

OR was adjusted for age, gender, BMI. Values in blue refer to risk factors significantly associated with worsening knee pain.

6.8.3 Knee stiffness

No association was made between worsening knee pain and morning or inactivity stiffness (Table 39).

Table 39. Assessment of stiffness and worsening knee pain

Stiffness		Worsening knee pain		Odds ratio (95% confidence interval)	
		Yes	No	Crude	Adjusted
Morning					
	No	3	4	**1**	**1**
	Yes	81	39	2.77 (0.59, 12.98)	5.24 (0.84, 32.68)
Inactivity					
	No	5	1	**1**	**1**
	Yes	79	42	0.38 (0.04, 3.33)	0.54 (0.06, 5.35)

OR was adjusted for age, gender, BMI. WOMAC assessments were conducted only for the 424 participants seen for the clinical assessment.

6.9 Heberden's and Bouchard's nodes

Baseline nodes were seen in 191 people of whom 113 (59.2%) reported worsening of knee pain. However, the association between nodes and worsening of knee pain was not significant (Table 40).

Table 40. Nodes and relative risk of worsening knee pain

Radiographic factors		Worse knee pain		Odds ratio (95% confidence interval)	
		Yes	No	Crude	Adjusted
Nodes:					
	No	132	110	**1**	**1**
	Yes	113	78	1.21 (0.82, 1.77)	1.27 (0.84, 1.94)

OR=Odds ratio, CI=confidence interval. OR was adjusted for age, gender, BMI

6.10 Radiographic features

Neither Osteophytes (aOR 1.01; 95%CI 0.45, 2.28), JSN (aOR 1.66; 95%CI 0.61, 4.51), K/L OA (aOR 0.54; 95%CI 0.23, 1.29), or chondrocalcinosis (aOR 2.46; 95%CI 0.26, 23.55) were found to associate significantly with worsening of knee pain (Table 41).

With respect to ipsilateral change, the odds ratios for the worsening of right and left knee pain showed no statistically significant association with any of the radiographic features examined (Table 42). No association was made between any change in K/L OA grade and worsening of knee pain (Table 43).

Table 41. Association between "whole person" radiographic features (combined right and left knee findings) and worsening of knee pain

Radiographic factors		Worse knee pain		Odds ratio (95% confidence interval)	
		Yes	No	Crude	Adjusted
Osteophytes:					
	No	42	21	**1**	**1**
	Yes	46	21	1.10 (0.53, 2.29)	1.01 (0.45, 2.28)
Isolated tibio-femoral JSN:					
	No	72	32	**1**	**1**
	Yes	17	13	0.58 (0.25, 1.34)	0.51 (0.20, 1.32)
Isolated patello-femoral JSN:					
	No	65	34	**1**	**1**
	Yes	23	8	1.50 (0.61, 3.72)	1.66 (0.61, 4.51)
Isolated tibio-femoral OA:					
	K/L 0	42	20	**1**	**1**
	K/L ≥1	5	0	5.31 (0.28, 100.64)	N/A
Isolated patello-femoral OA:					
	0	42	20	**1**	**1**
	≥1	11	3	1.75 (0.44, 6.96)	1.69 (0.36, 7.87)
Tibio-femoral plus patello-femoral OA:					
	K/L 0	42	20	**1**	**1**
	K/L ≥1	31	22	0.67 (0.31, 1.44)	0.54 (0.23, 1.29)
Chondrocalcinosis:					
	No	82	44	**1**	**1**
	Yes	7	1	3.76 (0.45, 31.51)	2.46 (0.26, 23.55)

OR: adjusted by age, gender and BMI. X rays were conducted only for the 424 participants seen for the clinical assessment.

Table 42. Assessment of x-ray features in right and left knees and relative risk of ipsilateral worsening knee pain

Radiographic factors	Right knee			Left knee		
	Worse KP	OR (95%CI)	aOR (95%CI)	Worse KP	OR (95%CI)	aOR (95%CI)
Osteophytes:						
No	44/62 (71%)	**1**	**1**	42/61 (69%)	**1**	**1**
Yes	35/53 (66%)	0.80 (0.36, 1.75)	0.63 (0.26, 1.52)	34/52 (65%)	0.85 (0.39, 1.88)	0.90 (0.37, 2.19)
Isolated tibio-femoral JSN:						
No	68/99 (69%)	**1**	**1**	69/98 (70%)	**1**	**1**
Yes	11/19 (58%)	0.63 (0.23, 1.71)	0.48 (0.15, 1.57)	8/17 (47%)	0.37 (0.13, 1.06)	0.33 (0.10, 1.12)
Isolated patello-femoral JSN:						
No	61/91 (67%)	**1**	**1**	61/91 (67%)	**1**	**1**
Yes	18/24 (75%)	1.48 (0.53, 4.10)	1.35 (0.43, 4.20)	15/22 (68%)	1.05 (0.39, 2.86)	1.32 (0.43, 4.02)
Tibio-femoral plus patello-femoral OA:						
K/L 0	41/60 (68%)	**1**	**1**	41/62 (66%)	**1**	**1**
K/L ≥1	24/38 (63%)	0.79 (0.34, 1.87)	0.55 (0.21, 1.45)	19/33 (58%)	0.70 (0.29, 1.66)	0.62 (0.24, 1.60)
Chondrocalcinosis:						
No	73/111 (66%)	**1**	**1**	73/110 (66%)	**1**	**1**
Yes	6/7 (86%)	3.12 (0.36, 26.89)	2.02 (0.20, 20.46)	4/5 (80%)	2.03 (0.22, 18.79)	0.73 (0.06, 8.65)

OR: adjusted by age, gender and BMI. X rays were conducted only for the 424 participants seen for the clinical assessment.

Table 43. Association between change in radiographic knee OA status during the 10-year follow-up period and worsening of knee pain

	Right knee			Left knee		
	worse knee pain	OR (95%CI)	aOR (95%CI)	worse knee pain	OR (95%CI)	aOR (95%CI)
Change in K/L OA grade in tibio-femoral compartment ≥1:						
No	36/48 (75%)	**1**	**1**	42/58 (72%)	**1**	**1**
Yes	38/51 (75%)	0.97 (0.39, 2.41)	0.96 (0.36, 2.52)	31/40 (78%)	1.31 (0.51, 3.36)	1.28 (0.47, 3.45)
Change in OA grade in patello-femoral compartment ≥1:						
No	29/43 (67%)	**1**	**1**	32/45 (71%)	**1**	**1**
Yes	45/56 (80%)	1.98 (0.79, 4.94)	1.71 (0.65, 4.46)	40/52 (77%)	1.35 (0.54, 3.37)	1.47 (0.56, 3.82)

OR: adjusted by age, gender and BMI. X rays were conducted only for the 424 participants seen for the clinical assessment.

6.11 2D:4D finger index

Neither type 1 (index>ring) nor type 3 (index<ring) patterning associated significantly with worsening of knee pain (Table 44).

Table 44. 2D:4D and relative risk of worsening knee pain

Finger pattern	Worse knee pain		OR (95%CI)
	Yes	No	
Index = ring	44	38	1
Index > ring	46	32	1.24 (0.66, 2.32)
Index < ring	134	107	1.08 (0.65, 1.79)

OR=Odds ratio, CI=confidence interval. OR was adjusted for age, gender, BMI

6.12 Psychological factors

A positive association was seen between people who reported worsening knee pain and those suffering emotional problems (p=0.02). No association could be made between worsening knee pain and anxiety or depression (p>0.05).

Table 45. Quality of life, HAD scores, and worsening knee pain

Quality of life index	Worse knee pain (Mean ±SD)		p values	
	Yes	No	Crude	Adjusted
SF36 total	**59.0** ±20.3	**61.9** ±19.2	0.44	0.34
Physical function	**60.4** ±26.8	**61.0** ±26.5	0.91	0.73
Role physical health	**50.9** ±41.5	**42.8** ±41.5	0.29	0.32
Role emotional problems	**62.1** ±43.7	**78.8** ±36.7	0.03	**0.02**
Energy/Fatigue	**46.0** ±20.2	**51.5** ±17.3	0.12	0.08
Emotional wellbeing	**68.9** ±16.5	**72.4** ±17.4	0.27	0.10
Social functioning	**75.9** ±26.8	**76.6** ±25.7	0.88	0.98
Pain	**55.9** ±24.8	**57.4** ±23.4	0.73	0.81
General health	**54.7** ±21.6	**56.5** ±19.7	0.65	0.54
HAD anxiety	**14.3** ±5.4	**15.1** ±5.2	0.46	0.63
HAD depression	**11.9** ±4.6	**11.7** ±4.7	0.75	0.65

The higher the mean score for the SF36, the healthier the person. The higher the mean scores for the HAD index, the more anxious or depressed the person. Values in blue refer to risk factors significantly associated with worsening knee pain.

6c Total knee replacement (TKR)

TKR was determined from a self-reported question. Of the 2,195 people with no knee pain at baseline, none reported TKR at follow-up. Of the 914 baseline knee pain positive people, 81 (8.9%) went on to report TKR. Overall risk of TKR was similar between men (9.0%) and women (8.7%) (p=0.476), but was dependent on age (p_{trend}=0.051 for men and p_{trend}=0.001 for women) (Figure 46).

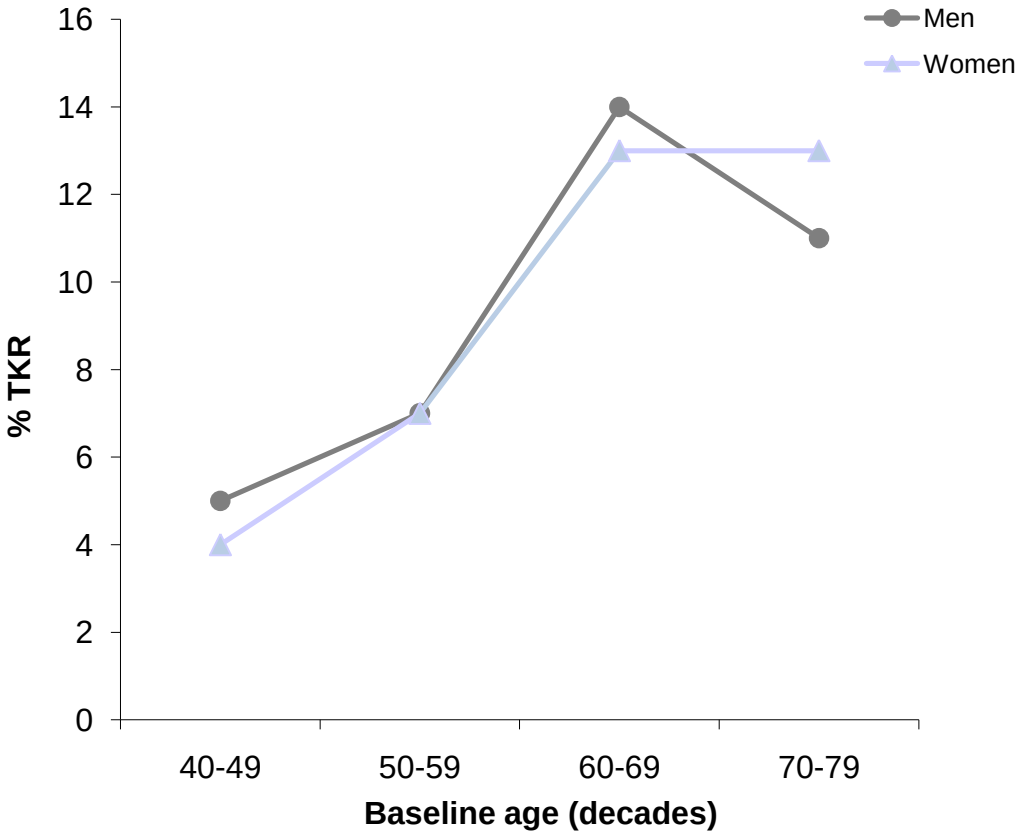


Figure 46. Total knee replacement by age and gender

6.13 Constitutional factors

6.13.1 Age

After adjustment for gender and BMI those >60 years old were two-times more likely to have a TKR (aOR 1.59; 95%CI 1.11, 2.29) than those <60 years old (Table 46).

6.13.2 Gender

Eleven percent (36/327) of men and 9.4% (45.477) of women had a TKR during the 10-year follow-up. Female gender was not found to be a significant risk factor for the outcome of TKR (Table 46).

6.13.3 BMI

Compared to people with a healthy BMI, those categorised as obese (BMI >30) had twice the risk of undergoing TKR (95%CI 1.18, 4.89). No increased risk was found for individuals categorised as overweight (OR 1.55; 95%CI 0.86, 2.79) (Table 46).

6.13.4 Smoking

Nine percent (40/424) of baseline smokers progressed to a TKR. No association was found between smoking and TKR (aOR 0.74; 95%CI 0.45, 1.23).

Table 46. Total knee replacement in relation to constitutional factors

Constitutional factors	TKR		Odds ratio (95% confidence interval)	
	Yes	No	Crude	Adjusted
Age:				
<60	33	451	**1**	**1**
≥60	48	272	**2.41 (1.51, 3.85)**	**1.59 (1.11, 2.29)**
Gender:				
Men	36	291	**1**	**1**
Women	45	432	0.84 (0.53, 1.34)	0.90 (0.55, 1.46)
BMI:				
Normal (<25)	17	235	**1**	**1**
Overweight (≥25, ≤30)	40	358	1.55 (0.86, 2.79)	1.54 (0.85, 2.81)
Obese (>30)	17	98	**2.40 (1.18, 4.89)**	**2.54 (1.23, 5.25)**
Smoking:				
No	41	339	**1**	**1**
Yes	40	384	0.86 (0.54, 1.36)	0.74 (0.45, 1.23)

OR was adjusted for age, gender, BMI. For age, gender, BMI OR was adjusted only with the other two confounders. Values in blue refer to risk factors significantly associated with TKR.

6.14 Biomechanical factors

6.14.1 Knee malalignment

Of the 23 people with early-life varus alignment, five (21.7%) reported TKR. In contrast, only one out of the 19 people with early-life valgus alignment had a TKR. After adjustment for age, gender and BMI the risk of having a TKR was approximately three-times greater (aOR 3.16; 95%CI 1.06, 9.40) for those with early-life varus knee alignment. Those with early-life valgus alignment showed no increased risk of TKR (aOR 0.48; 95%CI 0.06, 3.72).

6.14.2 Foot angulation

The risk of TKR was not directly associated with foot angulation (Table 48). The percentage of TKRs was 11.1% (69/619), 4.9% (5/102) and 23.1% (3/13) for people who had: no angulation, outward angulation and inward angulation respectively.

6.14.3 Knee injury

Injury at baseline was associated TKR outcome (OR 1.80; 95%CI 1.08, 3.00). This was confirmed by the adjustment for age, gender and BMI (aOR 1.89; 95%CI 1.10, 3.25) (Table 48).

6.14.4 Quadriceps muscle strength

Low quadriceps muscle strength at baseline was not significantly associated with TKR (aOR 1.22; 95%CI 0.31, 4.81). Similarly no association with TKR was found when the average muscle strength scores were used (Table 48).

6.14.5 Occupational physical activity

No associations were made between any occupational activities and the outcome of TKR (Table 47).

Table 47. Occupational activity and relative risk of total knee replacement

Occupational activity	Knee joint replacement		OR (95%CI)
	Yes	No	
Sit:	25	924	0.82 (0.51, 1.32)
Stand:	44	1574	0.81 (0.53, 1.25)
Walk:	48	1701	0.83 (0.54, 1.29)
Lift heavy loads:	19	556	1.13 (0.67, 1.90)
Lift with knees bent:	26	723	1.23 (0.77, 1.97)
Kneel:	16	417	1.31 (0.75, 2.28)
Sweat through physical exertion:	14	523	0.86 (0.48, 1.53)
Minutes walked to and from work:	25	470	**1.69 (1.06, 2.68)**
Minutes cycled to and from work:	4	88	1.46 (0.52, 4.06)

OR=Odds ratio, CI=confidence interval. OR was adjusted for age, gender, BMI. Values in blue refer to risk factors significantly associated with TKR.

Table 48. Association between biomechanical factors and requirement for total knee replacement

Biomechanical factors	TKR		Odds ratio (95% confidence interval)	
	Yes	No	Crude	Adjusted
Knee angulation: during 20s:				
Normal	70	639	**1**	**1**
Varus	5	18	2.54 (0.91, 7.04)	**3.16 (1.06, 9.40)**
Valgus	1	18	0.51 (0.07, 3.86)	0.48 (0.06, 3.72)
Foot angulation during 20s:				
Normal	69	550	**1**	**1**
Out	5	97	0.41 (0.16, 1.05)	0.35 (0.12, 1.01)
In	3	10	2.39 (0.64, 8.90)	1.71 (0.34, 8.55)
Knee Injury:				
No	52	559	**1**	**1**
Yes	25	149	**1.80 (1.08, 3.00)**	**1.89 (1.10, 3.25)**
Muscle Strength – Highest score:				
High strength - Tertile1	8	54	**1**	**1**
Tertile 2	11	57	1.30 (0.49, 3.48)	1.34 (0.43, 4.19)
Low strength - Tertile 3	10	63	1.07 (0.40, 2.91)	1.22 (0.31, 4.81)
Muscle Strength – Average score:				
High strength - Tertile 1	7	55	**1**	**1**
Tertile 2	12	55	1.71 (0.63, 4.68)	1.74 (0.54, 5.58)
Low strength - Tertile 3	10	64	1.23 (0.44, 3.44)	2.75 (0.59, 12.79)
Lift Heavy loads:				
No	24	222	**1**	**1**
Yes	18	136	1.22 (0.64, 2.34)	1.23 (0.61, 2.50)
Sweat through physical exertion:				
No	28	245	**1**	**1**
Yes	14	112	1.09 (0.55, 2.16)	0.98 (0.46, 2.10)
More Physical Work:				
No	29	260	**1**	**1**
Yes	12	89	1.21 (0.59, 2.47)	1.22 (0.56, 2.66)

OR was adjusted for age, gender, BMI. Muscle assessments were conducted only for the 424 participants seen for the clinical assessment. Values in blue refer to risk factors significantly associated with TKR.

6.15 Co-morbidity factors

Of the five co-morbidities examined none associated with an increased risk of TKR (Table 49). Univariate analysis indicated that rheumatoid arthritis (RA) was a risk factor for TKR (OR 2.10; 95%CI 1.15, 3.81), but this was insignificant after adjustment for age, gender and BMI (Table 51).

Table 49. Co-morbidities and relative risk of total knee replacement

Co-morbidities	TKR		OR (95%CI)	aOR (95%CI)
	Yes	No		
Heart disease	6/57	51/57	1.05 (0.44, 2.54)	0.46 (0.16, 1.33)
Stroke	0/5	5/5	0.90 (0.88, 0.92)	N/A
Diabetes	2/20	18/20	0.99 (0.23, 4.35)	0.77 (0.17, 3.49)
Lung disease	2/23	21/23	0.85 (0.20, 3.68)	0.72 (0.16, 3.22)
Cancer	0/23	23/23	0.90 (0.88, 0.92)	N/A

OR=odds ratio, CI=confidence interval. OR was adjusted for age, gender, BMI

6.15.1 Hip and back pain

Neither back nor hip pain was associated significantly with TKR outcome (Table 51).

6.15.2 Sleep and fibromyalgia

Reduced hours of sleep (<7 hours) was not a risk factor for TKR (aOR 0.48, 95%CI 0.20, 1.17). Additionally no association was made between baseline fibromyalgia and TKR (Table 50).

Table 50. Fibromyalgia and relative risk of total knee replacement

Physical assessment	TKR		Odds ratio (95% confidence interval)	
	Yes	No	Crude	Adjusted
Fibromyalgia:				
No	28	158	**1**	**1**
Yes	1	12	0.47 (0.06, 3.76)	1.00 (0.12, 8.65)

OR=Odds ratio, CI=confidence interval. OR was adjusted for age, gender, BMI

Table 51. Total knee replacement and co-morbidity factors

Co-morbidity factors		TKR		Odds ratio (95% confidence interval)	
		Yes	No	Crude	Adjusted
Co-morbidities:					
	No	72	614	**1**	**1**
	1	8	100	0.68 (0.32, 1.46)	0.38 (0.16, 0.91)
	≥2	1	9	0.95 (0.12, 7.59)	0.44 (0.05, 3.64)
RA:					
	No	65	647	**1**	**1**
	Yes	16	76	**2.10 (1.15, 3.81)**	1.71 (0.90, 3.25)
Back Pain:					
	No	33	294	**1**	**1**
	Yes	48	427	1.00 (0.63, 1.60)	0.89 (0.54, 1.46)
Back Pain within last year:					
	No	43	401	**1**	**1**
	Yes	35	315	1.04 (0.65, 1.66)	0.99 (0.60, 1.64)
Hip Pain:					
	No	51	460	**1**	**1**
	Yes	28	256	0.99 (0.61, 1.60)	0.96 (0.57, 1.61)
Hip pain within last year:					
	No	52	507	**1**	**1**
	Yes	24	199	1.18 (0.71, 1.96)	1.06 (0.62, 1.83)
Back plus Hip Pain:					
	No	57	530	**1**	**1**
	Yes	22	185	1.11 (0.66, 1.86)	1.01 (0.58, 1.77)
Sleep:					
	>7 hours	41	318	**1**	**1**
	<7 hours	10	134	0.58 (0.28, 1.19)	0.48 (0.20, 1.17)

OR=Odds ratio, CI=confidence interval. OR was adjusted for age, gender, BMI. Values in blue refer to risk factors significantly associated with TKR.

6.15.3 Knee stiffness

No association was made between worsening knee pain and morning stiffness (Table 52).

Table 52. Assessment of stiffness and total knee replacement

Stiffness		TKR		Odds ratio (95% confidence interval)	
		Yes	No	Crude	Adjusted
Morning					
	No	1	7	**1**	**1**
	Yes	28	168	1.17 (0.14, 9.85)	1.08 (0.11, 10.20)

OR was adjusted for age, gender, BMI. WOMAC assessments were conducted only for the 424 participants seen for the clinical assessment.

6.16 Heberden's and Bouchard's nodes

Nodes were reported by 357 people in this cohort, of which 31 (8.7%) received a TKR. No significant association was made between the presence of nodes and TKR (Table 53).

Table 53. Nodes and relative risk of total knee replacement

Radiographic factors		TKR		Odds ratio (95% confidence interval)	
		Yes	No	Crude	Adjusted
Nodes:					
	No	45	383	**1**	**1**
	Yes	31	326	0.81 (0.50, 1.31)	1.00 (0.59, 1.70)

OR=Odds ratio, CI=confidence interval. OR was adjusted for age, gender, BMI

6.17 Radiographic factors

Individuals with radiographic OA in the patello-femoral compartment were not at greater risk of TKR (aOR 3.37; 95%CI 0.59, 19.39). Similarly, no association was made between isolated patello JSN and TKR (aOR 1.30; 95%CI 0.48, 3.52). In contrast, people whose narrowing was isolated to the tibio-femoral compartment were 10-times more likely to have a TKR (aOR 10.12, 95%CI 4.13, 24.80). Correspondingly, those with x-ray changes at both tibio-femoral plus patello-femoral compartments were 12-times more likely to have a TKR (aOR 11.62; 95%CI 3.54, 38.15). Osteophytes (aOR 5.92; 95%CI 1.88, 18.67) and combined JSN (aOR 8.60; 95%CI 3.09, 23.94) were also associated with TKR outcome (Table 54). There was also no significant link between TKR and chondrocalcinosis (aOR 2.86; 95%CI 0.64, 12.74).

Table 54. Association between "whole person" radiographic features (combined right and left knee findings) and TKR

Radiographic factors		TKR		Odds ratio (95% confidence interval)	
		Yes	No	Crude	Adjusted
Osteophytes:					
	No	4	103	**1**	**1**
	Yes	24	81	**7.63 (2.55, 22.87)**	**5.92 (1.88, 18.67)**
Isolated tibio-femoral JSN:					
	No	12	161	**1**	**1**
	Yes	19	24	**10.62 (4.58, 24.61)**	**10.12 (4.13, 24.80)**
Isolated patello-femoral JSN:					
	No	20	148	**1**	**1**
	Yes	8	36	1.64 (0.67, 4.03)	1.30 (0.48, 3.52)
Tibio-femoral plus patello-femoral JSN:					
	No	6	132	**1**	**1**
	Yes	22	52	**9.31 (3.57, 24.26)**	**8.60 (3.09, 23.94)**
Isolated tibio-femoral OA:					
	K/L 0	0	103	**1**	**1**
	K/L ≥1	4	12	**74.52 (3.78, 1467.36)**	N/A
Isolated patello-femoral OA:					
	0	4	103	**1**	**1**
	≥1	3	20	3.86 (0.80, 18.60)	3.37 (0.59, 19.39)
Tibio-femoral and patello-femoral OA:					
	K/L 0	4	103	**1**	**1**
	K/L ≥1	24	50	**12.36 (4.08, 37.55)**	**11.62 (3.54, 38.15)**
Chondrocalcinosis:					
	No	28	176	**1**	**1**
	Yes	3	9	2.10 (0.53, 8.21)	2.86 (0.64, 12.74)

OR: adjusted by age, gender and BMI. X rays were conducted only for the 424 participants seen for the clinical assessment.

Table 55. Assessment of x-ray features in right and left knees and relative risk of ipsilateral total knee replacement

Radiographic factors	Right knee			Left knee		
	TKR	OR (95%CI)	aOR (95%CI)	TKR	OR (95%CI)	aOR (95%CI)
Osteophytes:						
No	3/106 (3%)	**1**	**1**	5/102 (5%)	**1**	**1**
Yes	14/71 (20%)	**8.43 (2.34, 30.58)**	**7.10 (1.80, 28.05)**	17/75 (23%)	**5.89 (1.99, 16.23)**	**4.17 (1.31, 13.28)**
Isolated tibio-femoral JSN:						
No	11/157 (7%)	**1**	**1**	13/154 (8%)	**1**	**1**
Yes	9/23 (39%)	**8.53 (3.02, 24.08)**	**8.53 (2.62, 27.76)**	10/25 (40%)	**7.23 (2.71, 19.29)**	**6.08 (2.06, 17.94)**
Isolated patello-femoral JSN:						
No	14/145 (10%)	**1**	**1**	16/150 (11%)	**1**	**1**
Yes	3/32 (9%)	1.00 (0.26, 3.59)	0.55 (0.13, 2.38)	6/27 (22%)	2.39 (0.84, 6.80)	1.60 (0.49, 5.28)
Tibio-femoral and patello-femoral OA:						
K/L 0	2/103 (2%)	**1**	**1**	7/105 (7%)	**1**	**1**
K/L ≥1	12/47 (26%)	**17.31 (3.69, 81.21)**	**14.91 (2.84, 78.42)**	12/42 (29%)	**5.60 (2.02, 15.50)**	**5.81 (1.87, 18.03)**

OR: adjusted by age, gender and BMI. X rays were conducted only for the 424 participants seen for the clinical assessment.

Table 56. Association between change in radiographic knee OA status during the 10-year follow-up period and total knee replacement

	Right knee			Left knee		
	TKR	OR (95%CI)	aOR (95%CI)	TKR	OR (95%CI)	aOR (95%CI)
Change in K/L OA grade at tibio-femoral site ≥1:						
No	1/89 (1%)	**1**	**1**	3/99 (3%)	**1**	**1**
Yes	1/70 (1%)	1.28 (0.08, 20.76)	1.05 (0.06, 18.46)	4/62 (7%)	2.21 (0.48, 10.21)	1.51 (0.30, 7.64)
Change in OA grade at patello-femoral site ≥1:						
No	0/84 (0%)	**1**	**1**	3/84 (4%)	**1**	**1**
Yes	2/75 (3%)	1.03 (0.99, 1.07)	N/A	4/76 (5%)	1.50 (0.33, 6.93)	1.64 (0.34, 7.93)

OR: adjusted by age, gender and BMI. X rays were conducted only for the 424 participants seen for the clinical assessment. Values in blue refer to risk factors significantly associated with TKR.

6.18 Psychological factors

Both poor physical function (p=0.03) and pain (p=0.03) showed direct association with TKR.

Table 57. Association between baseline quality of life and total knee replacement

Quality of life index	TKR (Mean ±SD)		p values	
	Yes	No	Crude	Adjusted
SF36 total	**59.1** ±21.4	**63.1** ±18.9	0.30	0.30
Physical function	**52.2** ±25.7	**65.3** ±24.8	**0.01**	**0.03**
Role physical health	**46.6** ±43.2	**53.2** ±40.7	0.42	0.85
Role emotional problems	**78.6** ±38.7	**70.3** ±40.8	0.32	0.45
Energy/Fatigue	**51.2** ±22.7	**48.2** ±20.6	0.47	0.85
Emotional wellbeing	**71.7** ±19.9	**70.7** ±17.2	0.77	0.86
Social functioning	**75.7** ±26.5	**79.5** ±23.6	0.41	0.33
Pain	**49.4** ±21.6	**58.2** ±22.0	**0.04**	**0.03**
General health	**52.4** ±20.6	**59.6** ±20.1	0.07	0.10
HAD anxiety	**14.6** ±5.3	**14.9** ±4.9	0.69	0.62
HAD depression	**11.6** ±5.0	**12.3** ±4.4	0.74	0.33

The higher the mean score for the SF36, the healthier the person. The higher the mean scores for the HAD index, the more anxious or depressed the person. Values in blue refer to risk factors significantly associated with TKR.

6.19 Physical examination features

Baseline knee effusion was found to increase the risk of TKR 2-fold (95%CI 1.13, 7.40). This remained significant after adjusting for age, gender and BMI (aOR 2.87; 95%CI 1.01, 8.20). Both crepitus (aOR 2.69; 95%CI 1.01, 7.16) and knee swelling (aOR 3.71; 1.38, 10.00) were also found to increase the risk of TKR.

Univariate analysis for increased knee temperature found an association with TKR (OR 3.26; 95%CI 1.26, 8.42), but this was insignificant after adjusting for age, gender and BMI (aOR 2.59; 95%CI 0.91, 7.33). No association was found between reduced hip rotation and TKR outcome (aOR 0.42; 95%CI 0.13, 1.33).

Table 58. Baseline assessment of knee and requirement for total knee replacement

Physical assessment		TKR Yes	TKR No	OR (95%CI)	aOR (95%CI)
Effusion					
	No	21	152	**1**	**1**
	Yes	8	20	**2.90 (1.13, 7.40)**	**2.87 (1.01, 8.20)**
Swelling					
	No	153	19	**1**	**1**
	Yes	19	10	**4.24(1.72,10.45)**	**3.71 (1.38, 10.0)**
Crepitus					
	No	6	77	**1**	**1**
	Yes	23	95	**3.11 (1.21, 8.01)**	**2.69 (1.01, 7.16)**
Hip rotation					
	No	24	130	**1**	**1**
	Yes	5	42	0.65 (0.23, 1.80)	0.42 (0.13, 1.33)

OR=Odds ratio, CI=confidence interval. OR was adjusted for age, gender, BMI. Values in blue refer to risk factors significantly associated with TKR.

6.20 Summary of poor outcome of knee pain

A little over ½ of the people with knee pain at baseline had a poor outcome at follow-up, with ¼ experiencing worsening of knee pain symptoms. Risk factors for poor outcome are shown in Table 59, and include manual labour, back pain and emotional problems.

Table 59. Risk factors for the poor outcome of knee pain

Risk factors
High physical labour
Back pain within last year
Reduced sleep
Morning stiffness
Emotional problems

Approximately one in 11 required a TKR during the follow-up period. Specific factors associated with TKR are shown in Table 60; these differ to those found for poor outcome of knee pain.

Table 60. Risk factors for total knee replacement

Risk factors
Older age
Obesity
Varus knee malalignment
Knee injury
Osteophytes in the knee joint
Tibio-femoral and Patello-femoral joint space narrowing
Tibio-femoral and Patello-femoral OA
Perceived reduction in physical function
Perceived pain
Knee effusion
Knee bony swelling
Crepitus

6d Good outcome of knee pain (Improvement)

Of the 914 people who had knee pain at baseline, 155 reported improvement in their pain during follow up.

6.21 Constitutional factors

None of the potential constitutional risk factors were found to be associated significantly with improvement in knee pain (Table 61).

Table 61. Improved knee pain and constitutional factors

Constitutional factors	Improved knee pain		Odds ratio (95% confidence interval)	
	Yes	No	Crude	Adjusted
Age:				
<60	83	249	**1**	**1**
≥60	41	167	0.74 (0.48, 1.12)	0.73 (0.47, 1.13)
Gender:				
Men	58	193	**1**	**1**
Women	66	223	0.99 (0.66, 1.47)	0.96 (0.64, 1.46)
BMI:				
Normal (<25)	42	113	**1**	**1**
Overweight (≥25, ≤30)	62	211	0.79 (0.50, 1.24)	0.76 (0.48, 1.21)
Obese (>30)	16	68	0.63 (0.33, 1.21)	0.60 (0.31, 1.15)
Smoking:				
No	61	184	**1**	**1**
Yes	63	232	0.82 (0.55, 1.22)	0.80 (0.52, 1.23)

OR was adjusted for age, gender, BMI. For age, gender, BMI OR was adjusted only with the other two confounders.

6.22 Biomechanical factors

Potential biomechanical factors were not found to associate with improved knee pain. However, occupation physical exertion (aOR 0.46; 95%CI 0.23, 0.92) had a negative association with improvement in knee pain.

Table 62. Association between biomechanical factors and improved knee pain

Biomechanical factors	Improved		Odds ratio (95% confidence interval)	
	Yes	No	Crude	Adjusted
Knee angulation: during 20s:				
Normal	113	371	**1**	**1**
Varus	3	16	0.62 (0.18, 2.15)	0.63 (0.18, 2.23)
Valgus	4	5	2.63 (0.69, 9.95)	2.66 (0.70, 10.13)
Foot angulation during 20s:				
Normal	95	307	**1**	**1**
Out	18	61	0.95 (0.54, 1.69)	1.02 (0.57, 1.84)
In	1	9	0.36 (0.05, 2.87)	0.48 (0.06, 4.00)
Knee Injury:				
No	76	273	**1**	**1**
Yes	45	138	1.17 (0.77, 1.79)	1.20 (0.78, 1.85)
Muscle Strength –Highest:				
High strength – Tertile 1	11	37	**1**	**1**
Tertile 2	13	38	1.15 (0.46, 2.89)	0.77 (0.26, 2.29)
Low strength - Tertile 3	5	47	0.36 (0.11, 1.12)	0.24 (0.05, 1.18)
Muscle Strength – Average:				
High strength - Tertile 1	12	37	**1**	**1**
Tertile 2	12	38	0.97 (0.39, 2.44)	0.62 (0.21, 1.82)
Low strength - Tertile 3	5	47	0.33 (0.11, 1.01)	0.23 (0.05, 1.12)
Lift Heavy loads:				
No	35	115	**1**	**1**
Yes	24	96	0.82 (0.46, 1.48)	0.78 (0.41, 1.47)
Sweat through physical exertion:				
No	45	127	**1**	**1**
Yes	14	82	**0.48 (0.25, 0.93)**	**0.46 (0.23, 0.92)**
More Physical Work:				
No	45	140	**1**	**1**
Yes	13	65	0.62 (0.31, 1.23)	0.61 (0.30, 1.23)

OR was adjusted for age, gender, BMI. Muscle assessments were conducted only for the 424 participants seen for the clinical assessment. Values in red refer to risk factors negatively associated with improved knee pain.

6.23 Co-morbidity factors

None of the potential co-morbidity risk factors were found to be associated significantly with improved knee pain (Table 63). However, <7 hours sleep (aOR 0.39; 95%CI 0.20, 0.77) and morning stiffness (aOR 0.08; 95%CI 0.01, 0.53) had a negative association with improved knee pain (Table 63).

Table 63. Improvement in knee pain in relation to co-morbidity factors

Co-morbidity factors		Improved		Odds ratio (95% confidence interval)	
		Yes	No	Crude	Adjusted
Co-morbidities:					
	No	109	354	**1**	**1**
	1	14	57	0.80 (0.43, 1.49)	0.91 (0.48, 1.72)
	≥2	1	5	0.65 (0.08, 5.62)	0.74 (0.08, 6.61)
RA:					
	No	107	366	**1**	**1**
	Yes	17	50	1.16 (0.64, 2.10)	1.32 (0.70, 2.46)
Back Pain:					
	No	48	158	**1**	**1**
	Yes	76	255	0.98 (0.65, 1.48)	0.95 (0.63, 1.45)
Back Pain within last year:					
	No	76	213	**1**	**1**
	Yes	47	199	0.66 (0.44, 0.99)	0.67 (0.44, 1.02)
Hip Pain:					
	No	81	252	**1**	**1**
	Yes	41	158	0.81 (0.53, 1.24)	0.88 (0.57, 1.36)
Hip pain within last year:					
	No	89	279	**1**	**1**
	Yes	30	127	0.74 (0.47, 1.18)	0.82 (0.51, 1.32)
Back plus Hip Pain:					
	No	89	291	**1**	**1**
	Yes	33	117	0.92 (0.59, 1.45)	0.99 (0.63, 1.58)
Sleep:					
	>7 hours	63	166	**1**	**1**
	<7 hours	14	92	**0.40 (0.21, 0.76)**	**0.39 (0.20, 0.77)**
Morning stiffness					
	No	4	3	**1**	**1**
	Yes	25	119	**0.16 (0.03, 0.75)**	**0.08 (0.01, 0.53)**

OR was adjusted for age, gender, BMI. WOMAC conducted only for the 424 participants seen for the clinical assessment. Values in red refer to risk factors negatively associated with improved knee pain.

6.24 Psychological factors

No association was found between improvement in knee pain and baseline perception of a low quality of life ($p \geq 0.05$).

Table 64. Association between baseline quality of life and improved knee pain

Quality of life index	Improved knee pain (Mean ±SD)		p values	
	Yes	No	Crude	Adjusted
SF36 total	**62.4** ±20.7	**59.8** ±20.4	0.50	0.40
Physical function	**59.8** ±26.9	**60.2** ±27.9	0.40	0.80
Role physical health	**42.5** ±41.1	**50.6** ±41.3	0.34	0.51
Role emotional problems	**81.6** ±34.0	**66.1** ±42.4	0.07	0.05
Energy/Fatigue	**51.0** ±19.0	**45.4** ±20.9	0.18	0.21
Emotional wellbeing	**72.0** ±19.8	**69.7** ±17.1	0.52	0.37
Social functioning	**78.8** ±28.0	**76.1** ±26.6	0.62	0.79
Pain	**59.3** ±25.6	**54.5** ±24.2	0.34	0.38
General health	**57.1** ±20.0	**56.1** ±21.1	0.81	0.72
HAD anxiety	**15.1** ±5.4	14.4 ±5.4	0.55	0.48
HAD depression	**11.5** ±5.1	**12.1** ±4.6	0.64	0.62

The higher the mean score for the SF36, the healthier the person. The higher the mean scores for the HAD index, the more anxious or depressed the person.

6.25 Radiographic factors

Radiographic OA in the patello-femoral or tibio-femoral compartment was not associated with improved knee pain (Table 65). Similarly, no association was made between osteophytes (aOR 0.87; 95%CI 0.36, 2.14) or JSN (aOR 1.37; 95%CI 0.57, 3.31) and improvement of knee pain. With respect to ipsilateral change, the odds ratios for the improvement of right and left knee pain showed no statistically significant association with any of the radiographic features examined (Table 66). In addition, no association was made between change K/L OA and good knee pain outcome.

Table 65. Association between “whole person” radiographic features (right and left knee findings) and improved knee pain

Radiographic factors		Improved knee pain		Odds ratio (95% confidence interval)	
		Yes	No	Crude	Adjusted
Osteophytes:					
	No	12	55	**1**	**1**
	Yes	16	73	1.01 (0.44, 2.30)	0.87 (0.36, 2.14)
Isolated tibio-femoral JSN:					
	No	20	104	**1**	**1**
	Yes	10	26	2.00 (0.84, 4.79)	1.93 (0.74, 5.06)
Isolated patello-femoral JSN:					
	No	23	96	**1**	**1**
	Yes	5	32	0.65 (0.23, 1.86)	0.56 (0.18, 1.74)
Tibio-femoral plus patello-femoral JSN:					
	No	15	80	**1**	**1**
	Yes	13	48	1.44 (0.63, 3.29)	1.37 (0.57, 3.31)
Isolated tibio-femoral OA:					
	K/L 0	11	55	**1**	**1**
	K/L ≥1	0	11	0.21 (0.01, 3.82)	N/A
Isolated patello-femoral OA:					
	0	11	55	**1**	**1**
	≥1	3	16	0.94 (0.23, 3.77)	0.99 (0.21, 4.71)
Tibio-femoral and patello-femoral OA:					
	K/L 0	11	55	**1**	**1**
	K/L ≥1	16	48	1.67 (0.71, 3.94)	1.57 (0.60, 4.08)
Chondrocalcinosis:					
	No	29	122	**1**	**1**
	Yes	1	8	0.53 (0.06, 4.37)	0.79 (0.09, 7.19)

OR was adjusted for age, gender, BMI. X rays were conducted only for the 424 participants seen for the clinical assessment

Table 66. Assessment of x-ray features in right and left knees and relative risk of ipsilateral improved knee pain

Radiographic factors	Right knee			Left knee		
	Improved KP	OR (95%CI)	aOR (95%CI)	Improved KP	OR (95%CI)	aOR (95%CI)
Osteophytes:						
No	9/67 (13%)	**1**	**1**	11/68 (16%)	**1**	**1**
Yes	13/64 (20%)	1.64 (0.65, 4.16)	1.67 (0.62, 4.56)	15/68 (22%)	1.47 (0.62, 3.48)	1.20 (0.46, 3.14)
Isolated tibio-femoral JSN:						
No	18/109 (17%)	**1**	**1**	18/115 (16%)	**1**	**1**
Yes	6/24 (25%)	1.69 (0.59, 4.83)	1.66 (0.50, 5.54)	8/23 (35%)	2.87 (0.06, 7.77)	2.50 (0.83, 7.46)
Isolated patello-femoral JSN:						
No	18/104 (17%)	**1**	**1**	21/110 (19%)	**1**	**1**
Yes	4/27 (15%)	0.83 (0.26, 2.70)	0.84 (0.24, 3.01)	5/26 (19%)	1.01 (0.34, 3.00)	0.71 (0.21, 2.46)
Isolated patello-femoral OA:						
K/L 0	8/58 (14%)	**1**	**1**	9/58 (16%)	**1**	**1**
K/L ≥1	0/5 (0%)	0.54 (0.03, 10.69)	N/A	0/7 (0%)	0.34 (0.02, 6.61)	N/A
Isolated patello-femoral OA:						
0	9/60 (15%)	**1**	**1**	9/61 (15%)	**1**	**1**
≥1	2/10 (20%)	1.42 (0.26, 7.79)	1.91 (0.29, 12.51)	2/11 (18%)	1.28 (0.24, 6.94)	1.45 (0.21, 10.28)
Tibio-femoral and patello-femoral OA:						
K/L 0	8/62 (13%)	**1**	**1**	13/70 (19%)	**1**	**1**
K/L ≥1	11/46 (24%)	2.12 (0.78, 5.80)	2.46 (0.82, 7.38)	11/39 (28%)	1.72 (0.69, 4.33)	1.81 (0.67, 4.88)

OR was adjusted for age, gender, BMI. X rays were conducted only for the 424 participants seen for the clinical assessment

Table 67. Association between change in radiographic knee OA status during the 10-year follow-up period and improved knee pain

	Right knee			Left knee		
	Improved KP	OR (95%CI)	aOR (95%CI)	Improved KP	OR (95%CI)	aOR (95%CI)
Change in K/L OA grade at tibio-femoral site ≥1:						
No	6/61 (10%)	**1**	**1**	9/69 (13%)	**1**	**1**
Yes	7/53 (13%)	1.40 (0.44, 4.44)	1.49 (0.44, 5.01)	5/51 (10%)	0.73 (0.23, 2.31)	0.64 (0.19, 2.17)
Change in OA grade at patello-femoral site ≥1:						
No	10/53 (19%)	**1**	**1**	10/60 (17%)	**1**	**1**
Yes	3/61 (5%)	0.22 (0.06, 0.86)	0.27 (0.07, 1.08)	4/58 (7%)	0.37 (0.12, 1.26)	0.37 (0.10, 1.30)

OR was adjusted for age, gender, BMI. X rays were conducted only for the 424 participants seen for the clinical assessment

6.26 Summary of good outcome of knee pain

Approximately 1/6 of people reported improvement in their knee pain during the follow-up period. No factors were found to associate with good knee pain outcome. Specific factors negatively associated with improved knee pain are shown in Table 68.

Table 68. Risk factors negatively associated with improved knee pain

Risk factors
Occupational physical exertion
<7 hours sleep
Morning stiffness

7. Follow-up cross-sectional analysis

Of 3,109 people in this cohort, 1408 (45.3%) reported knee pain at follow-up and 1653 (53.2%) reported having no knee pain at follow-up, independent of their baseline status. The presence of knee pain at follow-up was similar among women (56.3%) and men (43.8%) (p=0.274), and among the different age groups (p=0.208 for women and p=0.686 for men).

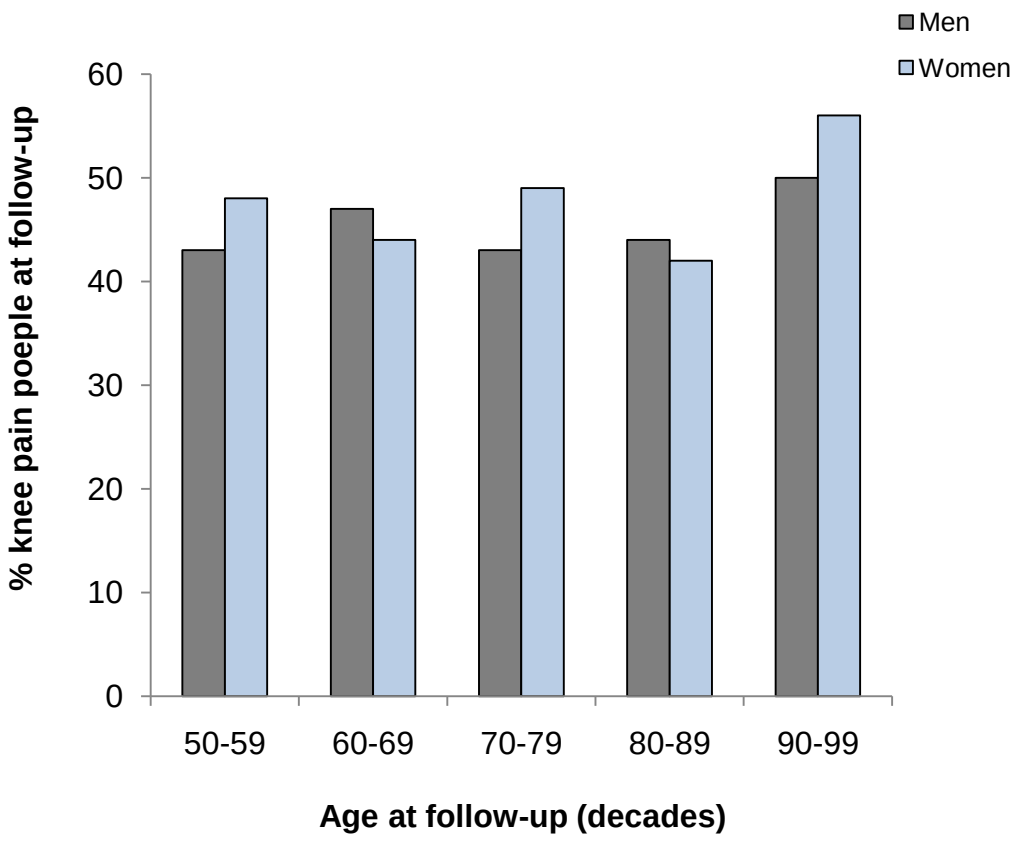


Figure 47. % of people at follow-up who had knee pain by age and gender

7.1 Co-morbidities

Ten individual co morbidities were examined at follow-up. Of these, six musculoskeletal disorders were found to significantly associate with knee pain.

The strongest association was with RA. A person with RA was almost four-times more likely to have knee pain. Hallux-valgus (OR 1.24; 95%CI 1.03, 1.49), gout (OR 1.61; 95%CI 1.20, 2.14), hip OA (OR 1.86; 95%CI 1.38, 2.50) and osteoporosis (OR 1.66; 95%CI 1.24, 2.22) were also significantly associated with knee pain. The results were confirmed by the further analysis adjusting for age, gender and BMI (Table 69).

People with angina were twice as likely to suffer knee pain. High blood pressure associated with knee pain on univariate analysis (OR 1.21; 95%CI 1.05, 1.40), but this was insignificant after adjusting for age, gender and BMI.

Table 69. Association between co-morbidities and knee pain in follow-up cross-sectional study

Co-morbidity factors		Knee pain		Odds ratio (95%CI)	
		Yes	No	Crude	Adjusted
Hallux valgus – left foot:					
	No	231	327	**1**	**1**
	Yes	1139	1300	**1.24 (1.03, 1.49)**	**1.34 (1.10, 1.64)**
Hallux valgus – right foot:					
	No	242	327	**1**	**1**
	Yes	1128	1303	1.17 (0.97, 1.41)	**1.23 (1.01, 1.49)**
Hip OA:					
	No	1291	1576	**1**	**1**
	Yes	117	77	**1.86 (1.38, 2.50)**	**1.88 (1.37, 2.58)**
Hand nodes:					
	No	802	1122	**1**	**1**
	Yes	578	505	**1.60 (1.38, 1.86)**	**1.67 (1.41, 1.97)**
High blood pressure:					
	No	783	996	**1**	**1**
	Yes	625	657	**1.21 (1.05, 1.40)**	1.02 (0.87, 1.19)
Angina:					
	No	1235	1524	**1**	**1**
	Yes	173	129	**1.66 (1.30, 2.10)**	**1.60 (1.24, 2.07)**
Heart attack:					
	No	1300	1552	**1**	**1**
	Yes	108	101	1.28 (0.96, 1.69)	1.24 (0.91, 1.68)
RA:					
	No	1251	1597	**1**	**1**
	Yes	157	56	**3.58 (2.62, 4.90)**	**3.73 (2.66, 5.23)**
Gout:					
	No	1294	1567	**1**	**1**
	Yes	114	86	**1.61 (1.20, 2.14)**	**1.49 (1.09, 2.03)**
Diabetes:					
	No	1262	1509	**1**	**1**
	Yes	146	144	1.21 (0.95, 1.54)	0.90 (0.69, 1.17)
Osteoporosis:					
	No	1293	1569	**1**	**1**
	Yes	115	84	**1.66 (1.24, 2.22)**	**1.84 (1.34, 2.54)**
Cancer:					
	No	1277	1509	**1**	**1**
	Yes	131	144	1.08 (0.84, 1.38)	1.16 (0.89, 1.51)

OR was adjusted for age, gender, BMI. Values in blue refer to prevalent factors with association to knee pain.

7.2 Other body pain

A dose response was seen for the increasing number of painful body sites (p_{trend} <0.001). People who reported pain in 1-3 body regions (other than the knee) were 2-times more likely to also suffer with knee pain (aOR 1.77; 95%CI 1.48, 2.12), than someone who had no pain at other body sites. Similarly, those who reported pain at more than 12 body regions (other than the knee) were 6 times more likely to also report knee pain (aOR 6.34; 95%CI 3.97, 10.22).

A significant association was found between knee pain and CWP (aOR 3.25; 95%CI 2.49, 4.24), indicating a significant association between single regional pain, such as the knee, and pain at other body sites. Foot pain, headache and abdominal pain were investigated separately for any potential associations to knee pain. The ORs were 2.75 (95%CI 2.34, 3.23), 1.76 (95%CI 1.08, 2.88) and 1.48 (95%CI 1.04, 2.11) respectively (Table 70). These associations remained after adjustment for age, gender and BMI.

Table 70. Association between other body pain and knee pain in follow-up cross-sectional study

	Knee pain		Odds ratio (95%CI)	
	Yes	No	Crude	Adjusted
Number of body sites with pain (excluding the knee):				
No pain	420	856	1	1
Pain in 1-3 body regions	454	524	**1.77 (1.49, 2.10)**	**1.77 (1.48, 2.12)**
Pain in 4-6 body regions	285	174	**3.34 (2.67, 4.17)**	**3.39 (2.68, 4.29)**
Pain in 7-11 body regions	163	72	**4.61 (3.42, 6.23)**	**4.51 (3.29, 6.20)**
Pain in 12+ body regions	86	27	**6.49 (4.15, 10.16)**	**6.34 (3.94, 10.22)**
ptrend			<0.001	<0.001
Widespread body pain (excluding the knee):**				
No	1171	1563	1	1
Yes	237	90	**3.52 (2.73, 4.53)**	**3.25 (2.49, 4.24)**
Foot pain:				
No	771	1245	1	1
Yes	586	344	**2.75 (2.34, 3.23)**	**2.52 (2.13, 2.98)**
Headache:				
No	1368	1626	1	1
Yes	40	27	**1.76 (1.08, 2.88)**	**1.99 (1.19, 3.34)**
Abdominal pain:				
No	1336	1595	1	1
Yes	72	58	**1.48 (1.04, 2.11)**	**1.56 (1.07, 2.25)**

**widespread pain was identified when all of the following were present: pain on the left side of the body, pain on the right side of the body, pain above the waist, pain below the waist. In addition axial skeletal pain had to be present. OR was adjusted for age, gender, BMI. Values in blue refer to prevalent factors with association to knee pain.

7.3 Body fat

Seventy percent of participants who had 'over fat' levels of body fat were overweight according to their BMI. However, 22% of those who had 'over fat' body percentages had a BMI in the 'healthy' range. People who were

classified as 'over fat' had no association with knee pain status (aOR 0.69; 95%CI 0.38, 1.23). In contrast, those with obese levels of fat were approximately three-times more likely to suffer knee pain (aOR 2.84; 95%CI 1.62, 4.98) when adjusted for age and gender. This result correlates directly with BMI, as 88% of obese participants were found to have obese body fat percentages. Significance was lost when adjusted for age, gender and BMI (Table 71).

Table 71. Association between body fat and knee pain in follow-up cross-sectional study

Body Fat	Knee pain		Odds ratio (95%CI)		
	Yes	No-	Crude	Adjusted *	Adjusted **
Healthy	63	48	**1**	**1**	**1**
Over fat	82	70	0.89 (0.55, 1.46)	0.94 (0.57, 1.55)	0.69 (0.38, 1.23)
Obese fat	120	37	**2.47 (1.46, 4.18)**	**2.84 (1.62, 4.98)**	1.61 (0.72, 3.58)

*adjusted by age and gender; **adjusted by age, gender and BMI. Healthy, over fat and obese fat are all categorized according to the WHO standardization chat, which is dependent on age and gender. Values in blue refer to prevalent factors with association to knee pain.

7.4 Timed Get Up and Go

A dose response was observed between individuals classified as having mild (>10 - <20 seconds) or severe (>20 seconds) mobility problems (p_{trend} <0.001) compared to those with normal mobility. ORs were 4.05 (95%CI 2.46, 6.65) and 5.52 (95%CI 1.59, 19.19) for mild and severe disability

respectively (Table 72). These associations remained after adjustment for age, gender and BMI (Table 72).

Table 72. Association between mobility and knee pain in follow-up cross-sectional study

	Knee pain		Odds ratio (95%CI)	
	Yes	No-	Crude	Adjusted
Timed Get Up and Go:				
Normal mobility (≤10 seconds)	138	127	**1**	**1**
Mild mobility problems (>10-≤20 seconds)	110	25	**4.05 (2.46, 6.65)**	**4.39 (2.45, 7.87)**
Severe mobility problems (>20-≤30 seconds)	18	3	**5.52 (1.59, 19.19)**	**5.24 (1.34, 20.56)**

OR was adjusted for age, gender, BMI. Values in blue refer to prevalent factors with association to knee pain.

7.5 Bone mineral density

BMD at follow-up was not associated with knee pain for either medium (OR 1.60; 95%CI 0.95, 2.71) or high density (OR 1.50; 95%CI 0.89, 2.54). This was not altered by adjustment for age, gender and BMI (Table 73).

7.6 Balance

Balance was categorized into; good, fair, poor or very poor. Balance was not significantly associated with knee pain on univariate analysis or after adjustment for age, gender and BMI (Table 73).

7.7 Quadriceps muscle strength

Only low muscle strength was significantly associated with knee pain (OR 2.87; 95%CI 1.72, 4.78). This significance was maintained after adjustment for age, gender and BMI.

7.8 Grip strength

Of 424 people seen for clinical assessment, 400 (94.3%) were right hand dominant, and 24 (5.7%) were left hand dominant. Among those who were knee pain positive at follow-up right handedness was similar between men (77/83 92.8%) and women (95.1% 174/183) (p=0.449). Low grip strength in the dominant hand was associated with knee pain (aOR 3.35; 95%CI 1.28, 8.76). There was no association with knee pain when only the right hand grip strength scores were used (aOR 2.11; 95%CI 0.94, 4.75).

Table 73. Association between clinical assessments and knee pain in follow-up cross sectional study

	Knee pain		Odds ratio (95%CI)	
	Yes	No	Crude	Adjusted
Bone density (Z score):				
Low bone density – Tertile 1	65	52	**1**	**1**
Medium bone density – Tertile 2	80	40	1.60 (0.95, 2.71)	1.48 (0.84, 2.61)
High bone density – Tertile 3	77	41	1.50 (0.89, 2.54)	1.02 (0.56, 1.86)
Balance:				
Good (deviation from 0 is <2)	16	13	**1**	**1**
Fair (deviation from 0 is 2-4)	225	125	1.46 (0.68, 3.14)	1.10 (0.46, 2.63)
Poor (deviation from 0 is 5-6)	14	6	1.90 (0.57, 6.32)	0.96 (0.20, 4.78)
Very poor (deviation from 0 is >6)	9	5	1.46 (0.39, 5.45)	0.45 (0.09, 2.42)
Quadriceps muscle strength- using highest score recorded:				
High muscle strength - Tertile 1	74	66	**1**	**1**
Tertile 2	84	55	1.36 (0.85, 2.19)	1.04 (0.60, 1.83)
Low muscle strength - Tertile 3	106	33	**2.87 (1.72, 4.78)**	**2.61 (1.36, 5.01)**
Grip Strength – using right hand:				
High grip strength - Tertile 1	80	61	**1**	**1**
Tertile 2	83	55	1.15 (0.71, 1.85)	1.49 (0.73, 3.03)
Low grip strength - Tertile 3	102	37	**2.10 (1.27, 3.47)**	2.11 (0.94, 4.75)
Grip Strength – using dominant hand:				
High grip strength - Tertile 1	78	61	**1**	**1**
Tertile 2	86	57	1.18 (0.74, 1.90)	1.40 (0.66, 2.97)
Low grip strength - Tertile 3	100	35	**2.23 (1.34, 3.72)**	**3.35 (1.28, 8.76)**

OR was adjusted for age, gender, BMI. Values in blue refer to prevalent factors with association to knee pain.

8. Discussion

This is the first 10 year study to document the natural history of knee pain in the community. As such, it has expanded previous observations regarding knee pain (Jinks *et al*, 2008), and has added to one longitudinal study of knee OA (Grotle *et al*, 2008). Risk factors for incidence and outcome have been identified.

8.1 Main study findings

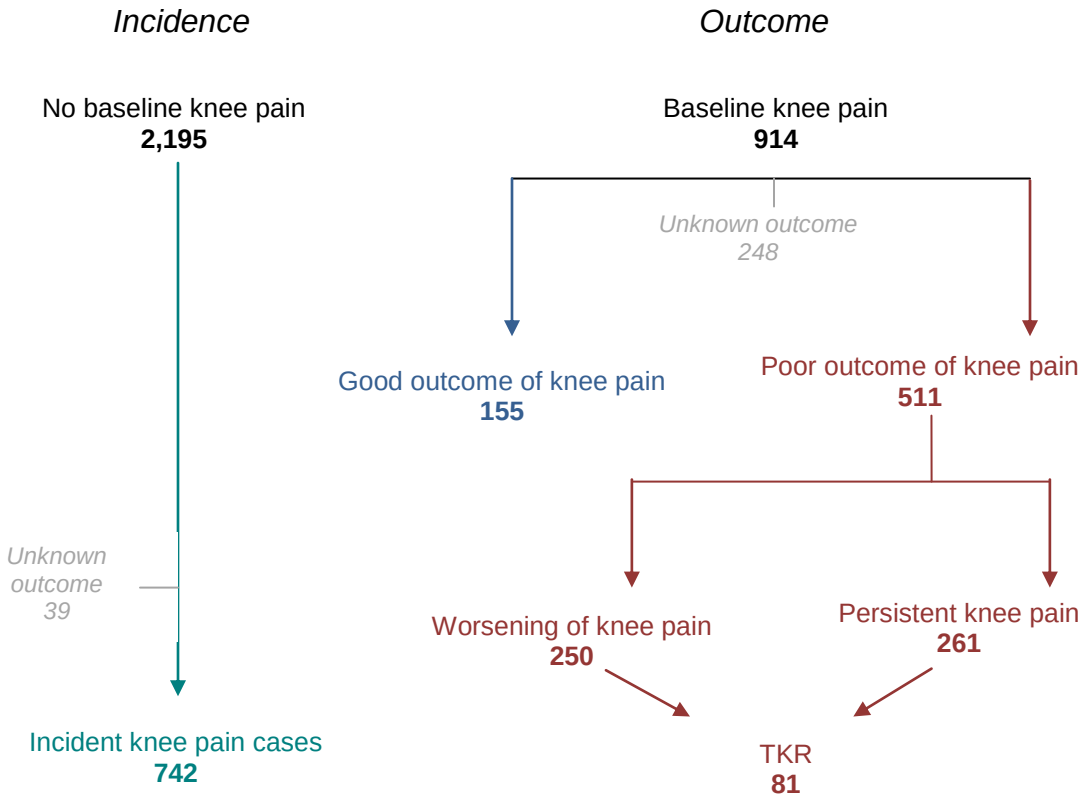


Figure 48. Summary of the natural history of knee pain in this Nottingham community

This study confirms that knee pain is a common disorder. A high rate of incident knee pain over 10 years was found among the Nottingham community (34.4%). In agreement with the majority of published studies of knee OA, the annual incidence rate of knee pain was approximately 3.3% (Cooper *et al,* 1994; Hart *et al*, 1999). Twenty seven percent of people with knee pain at baseline experienced worsening of knee pain over the 10 year period, resulting in a significant number of individuals undergoing TKR (8.9%).

A number of risk factors were found for incident and poor outcome of knee pain. However, no factors appeared to associate positively with a good outcome of knee pain, though several negative associations were made including occupational physical exertion, reduced sleep and morning stiffness. Risk factors were found to be different for incidence and poor outcome of knee pain. Constitutional (female gender, BMI), genetic, and radiographic factors risk factors were found to be particularly relevant to incident knee pain. More psychological factors (emotional problems, perceived physical function) were found to be a greater risk for the progression of pain in participants.

8.1.1 Biomechanical risk factors

Biomechanical forces at the knee appear to play an important role in the overall natural history of knee pain. Varus malalignment, knee injury, and

obesity were found to associate with greater risk for both incident knee pain and TKR, whereas physical occupational activity was associated with poor outcome of knee pain and incident knee pain. Outward foot angulation however was only found to be a risk factor for incident knee pain. The physiological changes in joint stress/load distribution that occur with any of these forces are particularly relevant to structural breakdown and pain initiation (Felson, 1995; Sharma *et al*, 1999; Eckstein *et al*, 2008). The strong influence of biomechanical factors on knee pain is supported by the consensus of the NIH conference into Osteoarthritic insights (Felson *et al*, 2000) as well as more recent studies by Jinks *et al* (2008).

Varus alignment has obvious face validity as a risk factor causing alteration in stress distribution through the joint which may lead to tissue damage and pain. This is the first time that a self-reported early life varus/valgus instrument has been used; it demonstrated excellent validity and reliability. Previous studies have mainly examined varus alignment in the context of progression of established OA rather than incidence of knee pain (Sharma *et al*, 2001; Brouwer *et al*, 2007).

Outward foot angulation is also strongly associated with incident knee pain, as supported by the validated instrument into self-reported foot alignment. Alteration in foot angulation from the norm could cause changes in the distribution of forces through the tibial plateaux, which increases in either

the lateral or medial compartment (Andrews *et al*, 1996), predisposing to the onset of knee pain and OA (Andrews *et al*, 1996).

The dose response observed with overweight and obese individuals strongly supports high body mass index as a risk factor for incident knee pain. This trend is reflected in previous observations from longitudinal studies (Jinks *et al*, 2008; Cooper *et al*, 2000). The link between the onset of knee pain and structural body weight could be explained by either a biomechanical or a more systemic constitutional effect. Increase in overloading and mechanical stress at the knee joint has already been described as a potential cause of cartilage breakdown and knee OA (Felson, 1995). However, fat cells may have more of a direct effect upon knee pain by replacing muscle tissue (leading to reduced structural integrity in the joint) (Visser *et al*, 2002). It is also possible that these fat cells contain a systemic factor involved in cartilage breakdown, which again may lead to OA and pain (Felson, 1995).

The positive association between obesity and TKR also adds to previous findings concerning knee pain and OA risk factors. These data support the possible community benefits of primary and secondary preventative measures regarding maintenance of ideal body weight (Jinks *et al*, 2008). However, the absence of BMI as a risk factor for worsening of knee pain contrasts with past study findings (Cooper *et al*, 2000; Jinks *et al*, 2008).

One explanation could be differences in the subjective outcome measure used to define worsening of knee pain between studies.

Trauma appears to play a significant role in predisposing to subsequent knee pain. As with varus alignment, this association has obvious face validity. A study by Jinks *et al* (2008) found knee injury to be the strongest risk factor for incident knee pain. Our findings corroborate this conclusion, with knee injury being the second strongest risk factor for incident knee pain. Most previous studies have examined knee injury in the context of incident knee OA (Miranda *et al*, 2002, Wilder *et al*, 2002, Cooper *et al*, 2000). We expanded these observations and found that knee injury was also linked to increased risk of requirement for TKR. In contrast, we did not find prior injury to be a strong predictor of poor knee pain outcome, which corresponds with findings by Jinks *et al* (2008).

Physical demands of occupation may have an influence on the health of the knee joint. We found physically demanding labour to have a similar increased risk of incident knee pain as outward foot angulation. This degree of risk agrees with previous studies (O'Reilly *et al*, 2000; Miranda *et al*, 2002). This suggests that chronic mechanical stress or repetitive microtrauma resulting from certain occupational activities may cause joint injury and the development of pain.

Conversely, leisure activities were found to have no effect on either incidence or outcome of knee pain. Our findings corroborate those of a similar nine year study of knee OA undertaken by Felson *et al* (2007). However, Kujala and colleagues (1995) reported that high stress sport, such as football and weightlifting, may lead to the onset of knee pain. One reason for this discrepancy may be that Kujala *et al* (1995) focused on specific elite sports rather than more commonly undertaken physical activities, making it difficult to directly compare findings. Additionally, the influence of direct trauma on incident pain must be taken into consideration when analysing their data.

Slemenda and colleagues (1998) suggested that low quadriceps muscle strength plays a significant role in incident knee OA/pain. Surprisingly our study found no such association. It is possible that the short examination interval (31 months) and higher retention of participants in the study by Slemenda *et al* (1998) accounts for this difference. Alternatively, this inconsistency may be because the incidence data from our cohort was underpowered or it may relate to the type of measurement tool used in our study to obtain maximum voluntary contraction (see study caveats). Nevertheless, low quadriceps muscle strength, and grip strength (linked to overall muscular strength) were found to relate to prevalent knee pain. This is consistent with past prevalence studies of knee pain and OA (O'Reilly *et al*, 1998a), and improvements in knee pain and function following quadriceps strengthening exercises (Thomas *et al*, 2002)

8.1.2 Co-morbidity risk factors

Multiple health problems are directly related to knee pain (Wood *et al*, 2008; Jinks *et al*, 2008). Our study results lend themselves to the conclusion that although health associations are linked to prevalence, they are not always associated with onset or outcome. However, not surprisingly, rheumatoid arthritis was found to confer a high risk for incident knee pain, reflecting the fact that the knee is a common target site for this pathologically damaging polyarticular inflammatory disease (Hirose *et al*, 2009).

Regional body pain, specifically at the hip and back, was found to be a significant risk factor for the onset of knee pain. This corresponds with results from longitudinal (Jinks *et al*, 2008) and prevalence studies (Croft *et al*, 2005; Cecchi *et al*, 2008). It is surmised from this study that back pain may indicate a wider pain problem of which knee pain could be a part. Hip pain can be described as causing referred knee pain, but has also been shown to increase the risk of OA at the opposite knee. However, this study found no link between baseline fibromyalgia and incident knee pain.

Mixed results have been found regarding outcome of knee pain. A study by Jinks *et al* (2008) found no evidence of a relationship between pain in the hip or back and poor outcome of knee pain. Conversely, results of this current study do show a link between recent back pain (in the last year) and worsening of pain at the knee joint. This corresponds with a disability

study by Leveille *et al*, (2001), where widespread musculoskeletal pain appeared to predict progression. It is possible that knee pain may be a consequence of referred pain from the hip or spine, but the prevalent association found between headaches, abdominal pain, and knee pain more support knee pain being just one region of involvement in a more widespread multiple regional pain disorder (Bliddal and Danneskiold-Samsoe, 2007; Rohrbeck *et al*, 2007).

8.1.3 Radiographic risk factors

Interestingly, osteophytes and joint space narrowing were not found to be risk factors for worsening knee pain. However, other studies do show a direct association between prevalent/incident knee pain and radiographic OA (Duncan *et al*, 2006; Blagojevic *et al*, 2008). Nevertheless, our findings confirm the importance of OA in relation to incident knee pain, particularly with respect to OA of the patello-femoral compartment. Our results show that isolated patello-femoral JSN has a higher OR for incident knee pain than isolated tibio-femoral JSN, though change in patello-femoral JSN was not a strong independent predictor of TKR. From a health economics and surgical perspective there is generally greater interest in the tibio-femoral compartment than the patello-femoral compartment, as TKR usually is only undertaken when OA is confirmed at the tibio-femoral site not the patello-femoral compartment (NICE osteoarthritis guidelines, 2008).

Stecher's study (1941) suggested a link between genetic predisposition to Heberden's nodes and OA at other body sites. This connection was supported by our study results, where nodal presence almost doubled the risk of incident knee pain. However, Heberden's nodes did not associate with worsening knee pain, suggesting that genetic predisposition to nodes is linked to onset and prevalence of knee pain rather than to its progression.

Zhang *et al* (2008) determined that individuals with 2D:4D ratios are at greater risk of knee OA. In contrast, this study did not find the 2D:4D ratio to be a risk factor for incident or progressive knee pain. This lack of association may be due to the self-reported nature and poor reproducibility of the 2D:4D line drawings used in our study (unpublished data) and to the fact that Zhang *et al* (2008) used radiographic measurements to determine the 2D:4D ratio.

8.1.4 Psychological risk factors

Our data provides long-term observations concerning anxiety, depression and knee pain. Jinks *et al* (2008) found an association between depression and an increased risk of onset of knee pain. However, our results suggest that it is anxiety, not depression, which is a risk factor for incident knee pain. This finding agrees with observations from the

Baltimore longitudinal study of aging (Creamer *et al*, 1999; Creamer *et al*, 2000).

Anxiety and depression were not found to be risk factors for worsening of knee pain. These findings are consistent with a recent long-term, epidemiological study by Jinks *et al* (2008). Conversely, heightened emotional problems were found to increase risk for worsening of knee pain. This may lend some support to the importance of psychological factors in knee pain experience (O'Reilly *et al*, 1998b; Cecchi *et al*, 2008; Dieppe *et al*, 2000). In addition, the impact of self-reported reduction in physical function and increase in pain were risk factors for TKR. This is not surprising as they are the main indicators for knee joint replacement (NICE osteoarthritis guidelines, 2008).

8.1.5 Constitutional risk factors

Age was not found to be a risk factor for incident knee pain or poor outcome of knee pain. This could imply that degenerative factors are not as significant to the natural history of pain as other risk factors. However, these findings contradict data from previous studies (Felson *et al*, 1987; Hart *et al*, 1999), where age was found to be highly significant to both onset and outcome of pain and structural OA. However, the study by Hart *et al* (1999) found only osteophytes, not joint space narrowing, to correspond with incident knee pain.

Female gender and associated hormonal factors were found to increase the risk of incident knee pain. This supports previous observations concerning gender and incident knee OA (Felson *et al*, 1995; Jinks *et al*, 2008; Hart *et al*, 1999). Similarly, no studies (including ours) directly connected female gender to progression of pain (Felson *et al*, 1995; Jinks *et al*, 2008).

Finally, this study found that smoking has no positive or negative risk to knee pain outcome or onset. Studies by Hart *et al* (1993) and Wilder *et al* (2003) corroborate these findings. However, other studies disagree, and both protective and detrimental risks of smoking have been reported in relation to knee OA (Felson *et al*, 1989; Samanta *et al*, 1993). Such heterogeneity of results underlines the continued misconceptions and unknown effects of smoking upon knee pain and OA.

8.2 Prevalent associations

Prevalent associations were investigated separately. Some of our results agreed with those found at baseline (O'Reilly, 1996; Thomas, 2001), such as associations between prevalent knee pain and disability/co-morbidities.

Disability at baseline was measured using the self-reported SF36 and WOMAC and assessment scales (O'Reilly, 1996; Thomas, 2001), at follow-up mobility was clinically assessed using the 'Timed Get Up and Go'

assessment. Our study found a dose response between those with mild-severe mobility problems and knee pain. There are two direct explanations for these findings. Firstly, if pain is present at the knee individuals may not be willing to use the limb normally (due to potential increase in pain) leading to deterioration in quadriceps muscle tone and a subsequent reduction in mobility (Messier *et al*, 2002). Alternatively, a conscious reduction in mobility will lead to deterioration in muscle tone at the knee joint, which in turn may lead to the presence of pain at the knee. Subsequent observational studies are required to determine the exact nature of the association.

High blood pressure, angina and heart attack are all vascular related diseases. Singh *et al* (2002) have suggested a direct link between vascular disease, including hypertension, and OA occurs in 40% of OA cases (Singh *et al*, 2002). However, in our study high blood pressure and myocardial infarction lost association with knee pain after adjustment for age, gender and BMI. It is therefore possible that although vascular disease may associate with structural OA, it has less influence on knee pain per se. In addition, changes in body mass composition, exercise ability, and medication must all be considered when analyzing cardiovascular data (Singh *et al*, 2002).

We also found that gout emerged as a potentially preventable association with prevalent knee pain. This could be because the knee is a target site

for gout, or it could reflect the association between OA and local crystal deposition, including urate crystals (Roddy *et al*, 2007).

The presence of other knee pain risk factors, such as osteoporosis, may link to more chronic, persistent problems. Furthermore, a dose-response effect was found regarding chronic widespread pain and prevalent knee pain ($p<0.001$), indicating that single regional pain may be an indicator of a more widespread problem with pain. In support of this the association found between headaches, abdominal pain, and knee pain may be indicative of systemic factors rather than local biomechanical or structural factors.

Not all of our cross-sectional results matched those recorded at baseline (O'Reilly, 1996; Thomas, 2001). O'Reilly (1996) found low quadriceps muscle strength to be significantly associated with prevalent knee pain ($p<0.005$). However, this study found no associations between low quadriceps muscle strength and prevalent knee pain.

Novel prevalent factors not measured at baseline included high body fat. This was found to significantly associate with prevalent knee pain. The strongest association was seen in individuals with obese fat levels, a pattern reflecting that seen between high BMI and incident pain. However, body fat does not just correlate with BMI. With age and infirmity, fat may replace muscle tissue and thus pathologically influence strength,

proprioception and balance. As previously discussed, reduction in muscle strength can lead to instability at the knee joint (Sharma *et al*, 2003). Thus excess body fat may not just cause pain through mechanical overloading, but also through effects resulting from replacement of muscle tissue with fat cells (Visser *et al*, 2002). Subsequently there may be a direct link between body fat levels, reduced muscle mass, and age; a factor that requires further investigation in a prospective longitudinal study

In addition, bone mineral density was not associated with prevalent knee pain. This result conflicts with one cross-sectional investigation by Sowers *et al* (1996). Such inconsistency may have arisen due to the younger age group studied by Sowers *et al* (1996) (24-45 years) or to the different measurement methods. It suggests hormonal factors associated with female gender may not be as significant to community knee pain as biomechanical forces.

Finally, this study did not find any association between prevalent knee pain and poor balance. However, Hassan *et al* (2001) used identical equipment and did find a positive association between balance and knee OA. Differences between results may be due to the use of different study populations.

8.3 Study caveats

This study has several caveats. As always the sample size available for study should be carefully considered before forming any conclusions. Another concern relates to the high attrition due to deceased individuals (16.8%) and those non-contactable (23.1%). Both of these values were much higher than initially anticipated at the start of recruitment. However, only three exclusion criteria were included (including death and non-contactibility), allowing for maximum recruitment.

One of the main caveats was that participants were questioned and assessed at only two time points over the 10-year period. Previous studies have examined their participants at regular intervals; the Framingham study re-assessed participants every two years (Felson *et al*, 1997) and the Chingford study (Hart *et al*, 1999) examined their cohort annually, allowing for a timeline of incidence and outcome to be better established between baseline and endpoint.

A further caveat was that the presence of knee pain was defined through answers provided in a self-reported questionnaire (Grotle *et al*, 2008). This could have led to problems with recall bias and subjectivity. However, the question used did contain very specific criteria (“pain in or around a knee on most days for at least a month”) to ensure the best possible capture of people with significant knee pain. It can also be argued that by using a self-reported questionnaire a greater number of the Nottingham community

was accessible in the short time available (Thomas, 2001). Furthermore, self-reporting ensured the absence of interview bias from the study results (O'Reilly, 1996).

Like many observational studies our cohort study was prone to a number of bias including confounding bias, selection bias, survival bias (left censorship), and information bias (Hawthorne effect – patient behaviour change is a bias for all observational studies). In terms of age and gender this cohort study was found to be representative of the general population. However, 99% of the study population were Caucasian, meaning that the cohort study cannot be generalizable in terms of race.

A further limitation is the lack of information relating to pain localisation or physical examination findings. It is possible that pain experienced in one knee may influence pain reporting in the other (Doherty and Jones, 1998). However, left and right knee pain was assessed separately and together to try to account for any interaction.

There were also possible methodological errors for some of the clinical measurements. Balance reproducibility had been previously assessed by Hassan *et al* (2001) and was found to be very good (ICC 0.87; 95%CI 0.68, 0.95). Grip strength (Mathiowetz, 2002) and 'Timed Get Up and Go' (Podsiadlo and Richardson, 1991; Ng and Hui-Chan, 2005) were two other

methods that had already been shown by previous studies to have good reliability. However, potential problems were associated with the 'Nicholas manual muscle tester'. The ability to measure voluntary muscle contraction is largely dependent on subjective factors (Thomas, 2001). People with a significant level of pain in the knee were unlikely to contribute the voluntary effort required to show true muscle strength in that leg (Thomas, 2001). Generalisability to all knee pain individuals cannot therefore be assumed, and results should be viewed with caution (Roddy *et al*, 2007b). Because of this problem previous studies have used electrical stimulation to obtain maximum quadriceps activation in the presence of knee pain (O'Reilly *et al*, 1998a; Thomas, 2001). However, the use of twitch superimposition would have likely reduced recruitment numbers for the clinical assessment, and would not have been as true a representation of participant movements. Therefore the use of the Tornville chair was not deemed suitable for this study.

Finally, our procedure to assess bone density may be criticised. Individuals were categorised as 'normal, osteopeanic or osteoporotic' based on their overall score and age group ('Z' scores). However, standardisation could only be applied to participants under age 80. In addition, the gold standard sites for measuring bone density are the hip, spine and distil radius rather than the calcaneum which mainly measures medullary bone. However, the calcaneum is less affected by OA, and the

measurements are very simple and quick with minimal x-ray exposure to both the researcher and participants.

8.4 Questions remaining

Further observational studies in other cohorts are required to confirm the associations made between knee pain and risk factors. If associations are confirmed the next stage would be to assess any interactions between the risk factors, such as footwear and varus alignment, or balance and muscle strength. Finally to undertake intervention studies to examine possible modifiable factors, such as the examination of the effect of lateral wedged insoles as a method for correcting knee malalignment and knee pain, or weight loss and reduction of BMI as a method for preventing knee pain onset. These studies could be of great importance for primary and secondary prevention strategies.

Most studies up to now have focused on pain/OA at the knee and hand joints. However, due to the close association between foot angulation and knee load distribution there may be some link between risk factors for knee, foot, hip, and even back pain, that warrants further investigation.

Similarly, although study outcome was investigated to the level of TKR, it would be useful to extend this information further to investigate potential risk factors for mortality outcome in participants who had suffered with

knee pain. A sub-study is already underway to determine any links between cause of death and knee pain.

8.5 Conclusion

In conclusion, for people over the age of 40 years old, 1 in 3 will develop significant knee pain in the next 10 years. Of people with knee pain, 1 in 4 will worsen over a 10 year period and 1 in 11 will require surgery. Psychological risk factors and possible referred pain correlated with incident knee pain and poor outcome of knee pain, whilst radiographic OA and constitutional risk factors associated with only incident knee pain and TKR. More local biomechanical factors were found to play a highly significant role in the overall natural history of knee pain. The further development of risk predictive models to prevent and manage community knee pain merits future research.

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Appendices

Appendix 1: Consent forms

Visit to Academic Rheumatology at Nottingham City Hospital

Please tick the most appropriate box

Yes, I would like to participate in the clinical assessment stage of the follow-up study called 'Knee pain progression and risk factors', and understand that once I have returned this questionnaire, I will be contacted by telephone to arrange a mutually convenient appointment. ☐

No, I prefer not to participate in the clinical assessment stage of the study called 'Knee pain progression and risk factors' ☐

If you have answered "yes" to the above question, please give your name, address and telephone number below:

Name:
……

Address:
……..

……

Postcode: ……

Tel: ……

Consent to keep information for possible future studies

"I agree that my personal details, including name, address, date of birth and telephone number, will be stored on a secure computer within Academic Rheumatology and that I may be contacted again in the future regarding participation in future knee pain and osteoarthritis research studies. I understand I will be given information about any future studies and I may or may not wish to participate in these studies. If I decline to participate in any future study, I understand this will not affect in any way the care that I receive at the Nottingham University Hospitals NHS Trust or my GP's surgery."

If you are happy to agree with the above statement then please sign and date below. Otherwise it will be taken that you do not consent to your information being stored.

Signature:
……..

Date:
……

If you have not given your details on the previous page please complete them below:

Name:
……..

Address:
……..

……

Postcode: ……

CONSENT FORM – CLINICAL ASSESSMENT

(Principal Investigator: Professor Michael Doherty)

please initial boxes

I confirm that I have read and understood the information sheet dated 14/08/07 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care being affected.	
I understand that participation in this part of the study will involve the following clinical assessments and further questioning concerning diet, family history, footwear and knee pain severity.	
I understand that participation in this study will involve having x-rays of both knees and my heel bone density measured.	
I understand that the electronic images of my x-rays will be stored within Academic Rheumatology for research purposes.	
I understand that relevant sections of my study notes may be looked at by responsible individuals from the University of Nottingham, the Nottingham University Hospitals NHS trust, the Nottinghamshire County Teaching PCT, or from regulatory authorities. I give permission for these individuals to have access to my study records.	
I agree to participate in the above study	

_____	_____	_____
Name of patient	Signature of patient	Date

_____	_____	_____
Name of researcher	Signature of researcher	Date

Appendix 2: Example of systematic literature search

Database: EMBASE <1980 to 2007 Week 28> Search Strategy:

1 exp cohort studies/ (42724)

2 cohort stud$.mp. (28930)

3 exp prospective studies/ (66442)

4 relative risk$.mp. (29741)

5 incidence.mp. or exp incidence/ (307215)

6 prospective stud$.mp. (112102)

7 1 or 2 or 3 or 4 or 5 or 6 (463094)

8 knee osteoarthritis.mp. or exp knee osteoarthritis/ (4823)

9 knee osteoarthrosis.mp. (46)

10 gonarthritis.mp. (116)

11 knee pain.mp. or exp knee pain/ (3079)

12 osteoarthritis.mp. or exp osteoarthritis/ (28821)

13 osteoarthrosis.mp. (1756)

14 osteophyte.mp. or exp osteophyte/ (1862)

15 joint space narrowing.mp. (601)

16 degenerative joint disease$.mp. (999)

17 12 or 13 or 14 or 15 or 16 (31897)

18 knee.mp. or exp knee/ (56618)

19 17 and 18 (9242)

20 8 or 9 or 10 or 11 or 19 (11416)

21 7 and 20 (1175)

22 body weight/ or obese.mp. or obesity/ or weight loss/ (144402)

23 21 and 22 (82)

24 (metabolic syndrome or obesity or hypercholesterolemia or hypertension).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (330349)

25 21 and 24 (93)

26 (joint alignment or malalignment or mechanical).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (97991)

27 21 and 26 (60)

28 (muscle strength or muscle or weakness).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (536157)

29 (quadriceps or forearm).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (26276)

30 21 and 28 and 29 (38)

31 (occupational or physical or activity or job or manual or labour or employment).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1708882)

32 21 and 31 (338)

33 (non occupational or physical or activity or leisure or past time or sport).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1584391)

34 21 and 33 (343)

35 (Joint instability or injury or unsteadiness or damage).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (570676)

36 21 and 35 (229)

37 genetics.mp. (96628)

38 21 and 37 (4)

39 (nutritional factors or vitamin C or vitamin D or nutrition or food).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (265313)

40 21 and 39 (25)

41 (age or elderly or pentioner).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (868196)

42 21 and 41 (389)

43 (bone density or homones or hormonal).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (98733)

44 21 and 43 (40)

45 (gender or female or sex).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2356435)

46 21 and 45 (816)

Appendix 3: Questionnaire

Nottingham University Hospitals NHS
NHS Trust

The University of Nottingham

KNEE PAIN PROGRESSION AND RISK FACTORS

This questionnaire has been prepared by The Department of Academic Rheumatology, University of Nottingham based at the Nottingham City Hospital in coordination with your doctor's surgery and the Primary Care Trust.

We want to find out more about knee pain in the community, particularly in relation to the risk factors linked with its development or progression. It is therefore of great importance that you help us by filling in this questionnaire. **Even if you do not have knee pain, please fill it in**, as we are still very interested in your responses. We think you will find the questionnaire interesting and it should only take about 20-30 minutes to complete.

You may remember that **you kindly completed a previous questionnaire into knee pain** for The Department of Academic Rheumatology, City Hospital between 1996 and 2001. We are aware a few questions in this questionnaire may therefore seem familiar – this is intentional and necessary for our research. Please fill in **all** of them to the best of your ability. Most of the question answers require a tick in a box or a comparative examination of a diagram. For all questions clear instructions are given.

Please return in the self-addressed, pre-paid envelope (no stamp required) as soon as possible to The Department of Academic Rheumatology, City Hospital, Nottingham.

Your answers are strictly confidential.

Please do not pass this questionnaire onto anyone else.

If you have any questions about this work please ring:

Sarah Ingham tel: 0115 82 31756 or email: msxsi@nottingham.ac.uk

Thank you for your assistance with this important area of research.

arc Committee against arthritis

BUPA*foundation*

Funded by the Arthritis Research Campaign and the BUPA Foundation

Version 2 14/08/07

SECTION 1: ABOUT YOURSELF

1. What is your full name?

   .....

2. What is your date of birth?

   ☐☐ day ☐☐ month ☐☐ year

3. What sex are you?

   ☐ Male ☐ Female

4. What is your marital status?

   ☐ Married ☐ Single ☐ Divorced ☐ Widowed ☐ Separated

5. What is your height?

   ☐ Feet ☐☐ Inches **or** ☐☐☐ cm

6. What is your weight?

   ☐☐ Stones ☐☐ lbs **or** ☐☐ Kgs

7. Have you **ever** smoked regularly? (at least **once a day for at least 3 months**)

   ☐ Yes – age started ☐☐ Years old ☐ No **(if no please go to section 2)**

8. Have you stopped smoking?

   ☐ Yes–age stopped ☐☐ Years old ☐ No

9. Approximately **how many** did you or do you smoke?

   ☐☐☐ Cigarettes per day (**including cigarillos and rollups**)

   ☐☐☐ Cigars per day

   ☐☐☐ Ounces of pipe tobacco per week

SECTION 2: ABOUT YOUR EMPLOYMENT

10. Please give details of your current or last job **(even if you are now retired)**

What was the job title? (Include Housewife / Husbandband)

.....

.....

11. Approximately when did you **start** this job?

☐☐ Month ☐☐ Year

12. Approximately when did you **finish** this job?

☐☐ Month ☐☐ Year

☐ I am still employed in this job

13. Please give details of the **longest** job you have held.

What was the job title? (Include housewife / husbandband)

.....

.....

If this is the same job as above, please tick here ☐ *and* **Move to section 3, page 3.**

14. Approximately when did you **start** this job?

☐☐ Month ☐☐ Year

15. Approximately when did you **finish** this job?

☐☐ Month ☐☐ Year

SECTION 3: ABOUT OCCUPATIONAL PHYSICAL ACTIVITY

Consider the majority of your daily activities related to your job **over the last 10 years**.....

16. **For most days**, did you sit....
☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Always

17. **For most days**, did you stand....
☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Always

18. **For most days**, did you walk....
☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Always

19. **For most days**, did you lift heavy loads?
☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Always

20. **For most days**, did you lift heavy loads with your knees bent?
☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Always

21. **For most days**, did you kneel?
☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Always

22. **For most days**, did you sweat through physical exertion?
☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Always

23. How many minutes did you walk per day **to and from** work?
☐☐☐ Minutes ☐ I don't walk to or from work

24. How many minutes did you cycle per day **to and from** work?
☐☐☐ Minutes ☐ I don't cycle to or from work

SECTION 4: LEISURE TIME PHYSICAL ACTIVITY

Consider the majority of activities related to your leisure time **over the last 10 years**.....

25. Have you played any sports (e.g. golf, tennis, cricket etc), or participated in any physical activities (e.g. ballroom dancing, aerobics, hiking, walking, gardening etc)?

☐ Yes ☐ No **(if no please go to question 26)**

If yes, what sports/physical activities did you participate in?

	Name of sport/activity	Hours per Week participated	Months per Year participated	Number of years participated
1				
2				
3				
4				
5				

26. Do you think in comparison with others your own age, physical activity during your leisure time has been...

☐ Much more ☐ More ☐ The same ☐ Less ☐ Much less

27. During your leisure time, have your **activities** caused you to sweat.....

☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often

28. During your leisure time did you walk....

☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often

29. During your leisure time did you cycle...

☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often

30. During your leisure time did you do DIY activities....

☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often

31. During your leisure time did you work in the garden....

☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often

SECTION 5: TIREDNESS AND SLEEP

32. In the last 10 years, did you often get up after sleep feeling un-refreshed?

☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Very Often

33. In the last 10 years, did you feel tired on most days?

☐ Never ☐ Seldom ☐ Sometimes ☐ Often ☐ Always

SECTION 6: ABOUT KNEE PAIN

34. Have you **ever** had pain in or around a knee on most days for **at least a month?**

☐ Yes ☐ No **(if no please go to question 39)**

If yes, at what age did you first notice this type of knee pain? ☐☐ Years old

35. Have you had knee pain on most days of the **last month**?

☐ Yes ☐ No **(if no please go to question 36)**

If yes, in your opinion how severe is the pain in your knee(s)?

☐ Mild ☐ Moderate ☐ Severe ☐ Worst ever pain

36. In the last 10 years, approximately how many **months of each year** have you had **chronic** knee pain (pain felt on most days of each month)

*(Please write the **approximate number of months under each year**, if no pain please put 0)*

1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐

37. Since it has started, do you think the severity of your knee pain has overall……

☐ Greatly Improved ☐ Slightly improved ☐ Worsened ☐ Remained the same

38. Which knee(s) do you / did you experience the pain in?

☐ Left ☐ Right ☐ Both

If both, which overall is the worst knee?

☐ Left ☐ Right

39. Have you **ever** suffered significant injury to either of your knees?

☐ Yes *(please specify)*…….. ☐ No

If yes, did this knee injury require medical/hospital treatment?

☐ Yes ☐ No

40. **In the last 10 years,** have you been given a diagnosis of osteoarthritis in your knee by a doctor?

☐ Yes ☐ No **(if no please go to question 41)**

If yes, at what age did this occur? ☐☐ Years old

If yes, in which knee(s) was this diagnosed?.....

41. Have you **ever** had an operation on either of your knees?

☐ Yes ☐ No **(if no please go to question 42)**

If yes, what type of operation did you undergo? *(If you did not undergo one of the specific operations then please leave the related boxes blank)*

Type of Operation	Knee operated on (right, left, both)	Age at time of operation (years)
Arthroscopy/ Telescope/keyhole		
Ligament Repair		
Meniscus or Cartilage removal		
Joint replacement		
Other (please specify)		

42. Have you broken either of your legs **in the last 10 years**?

☐ Yes ☐ No **(if no please go to section 7, page 8)**

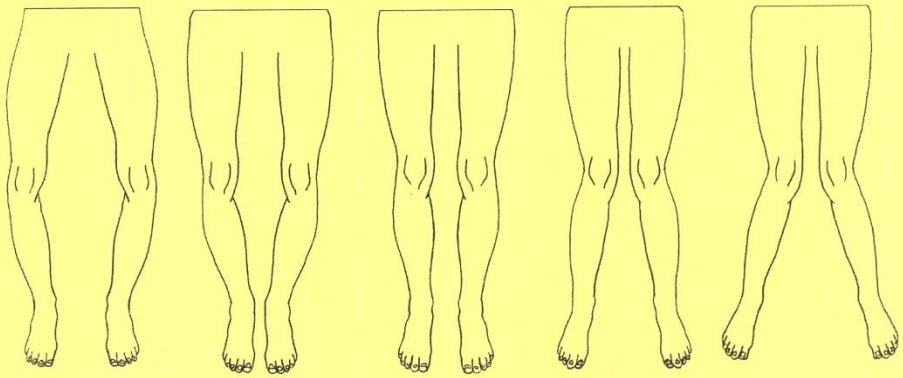
If yes, at what age did this break occur? ☐☐

If yes, on which bone was the break? .....

SECTION 7: ABOUT THE ANGLE OF YOUR LEGS

We are interested in the angle at your knees (that is straight legs, bow-legged or knock-knees) as this may have relevance to the development of osteoarthritis. Please look at your knees **whilst standing** (preferably in front of a mirror) and tick the appropriate box to indicate the angle of your knees.

Most people will have similar angulations in their left and right knees, but in a few people these angulations may differ. We therefore would like you to score your knees separately.



A	B	C	D	E
Very bow legged	Bow legged	Normal	Knock-knee	Very knock-knee

43. Which picture best shows the **current** angle of **each** of your legs?

Right knee ▶ ☐A ☐B ☐C ☐D ☐E

Left knee ▶ ☐A ☐B ☐C ☐D ☐E

44. Which picture do **you think** best shows the angle of **each** of your legs **in your 20s?**

Right knee ▶ ☐A ☐B ☐C ☐D ☐E

Left knee ▶ ☐A ☐B ☐C ☐D ☐E

SECTION 8: ABOUT TREATMENT OF KNEE PAIN

These questions are to be answered by people who have experienced knee pain **in the last 10 years**. If you have **not** had knee pain **please go to section 10 page 12.**

45. Have you **ever** consulted a doctor (GP or hospital) about your knee pain?

☐ Yes ☐ No

46. What form of treatment(s)/procedure(s) have you had since you developed knee pain? *(tick more than one box if required)*

	Self-prescribed	Doctor prescribed
Exercise (general activity)	☐	☐
Aerobic exercise (e.g. dance)	☐	☐
Strengthening exercise (e.g. swimming)	☐	☐
Weight loss exercise (e.g. gym)	☐	☐
Footwear with a thick, soft sole & no heel	☐	☐
Cream to rub on your knee	☐	☐
Painkiller tablets	☐	☐
Dietary changes	☐	☐
None	☐	☐

47. Have you ever had steroid injections into your knee?

☐ Yes ☐ No

48. Have you ever had hyaluronic acid injections into your knee?

☐ Yes ☐ No

49. Were you ever referred to a physiotherapist?

☐ Yes ☐ No

50. Were you ever referred to a rheumatologist?

☐ Yes ☐ No

51. Were you ever directed towards any literature about knee pain or knee osteoarthritis?

☐ Yes *(please specify)*..... ☐ No

SECTION 9: YOUR VIEWS ABOUT YOUR KNEE PAIN

These questions are to be answered by people who have **current knee pain.** If you **do not** have current knee pain then **please go to section 10, page 12**

52. Listed below are a number of symptoms that you may or may not have experienced **because of your knee problem**. **Please indicate by** putting a tick in the box for yes or no, **to tell us whether** you have experienced **any of these symptoms** because of your knee problem.

	Yes	No
Pain/ache	☐	☐
Fatigue	☐	☐
Stiff joints	☐	☐
Sleep difficulties	☐	☐
Loss of strength	☐	☐

53. We are interested in your **own personal views** on how you see your current knee problem. Please indicate how much you agree or disagree with the following statements about your knee problem by putting **a cross in one box on each line**.

	Strongly disagree	**Disagree**	**Neither agree or disagree**	**Agree**	**Strongly agree**
My knee problem will last for a long time					
My knee problem has major consequences on my life					
There is a lot which I can do to control my knee symptoms					
What I do can determine whether my knee problem gets better or worse					
Treatment can control my knee problem					
I don't understand my knee problem					
My knee symptoms come and go in cycles					
My knee problem affects me emotionally (e.g. it makes me feel frustrated, anxious, angry, afraid, upset or depressed)					

54. We are **now** interested in what you consider **may have been the cause** of your knee problem. As people are very different, there is no correct answer for this question. We are **most** interested in **your own views** about the factors that cause your knee problem rather than what others (including doctors or family) may have suggested.

Below is a list of possible causes for your knee problem. Please indicate how much you agree or disagree that they were causes for your knee problem by **putting a cross in one box on each line**.

	Strongly disagree	**Disagree**	**Neither agree or disagree**	**Agree**	**Strongly agree**
Hereditary – it runs in my family					
Ageing					
An accident or injury					
Chance or bad luck					
My own behaviour					
Work					

55. Please list in rank-order the three most important factors that you believe caused **your** knee pain. ***The most important causes for me:-***

1. .....

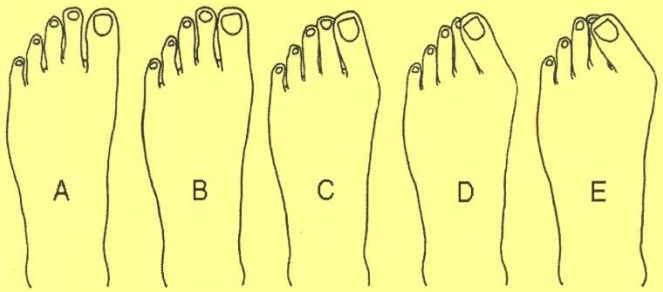
2. .....

3. .....

SECTION 10: ABOUT YOUR FEET

We are interested in whether your **big toes** are straight or angled sideways **NOT your whole foot**. **First,** please look at your **left big toe** whilst standing without shoes and socks on. Ignore the positioning and the gaps between your other toes and try to **focus only on your big left toe.** Select from the first set of pictures below labelled from A to E which one best shows the angle of your **left big toe** and tick the appropriate boxes.

LEFT FOOT



56. Which picture best shows the angle of your big toe **currently?**

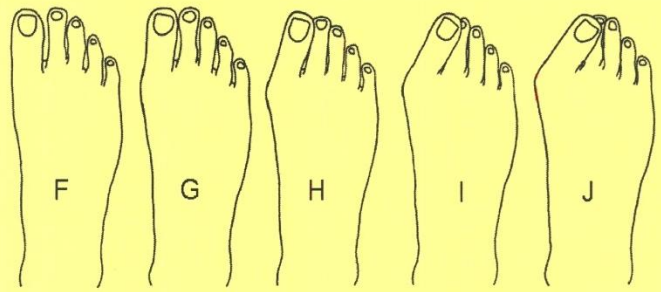
☐A ☐B ☐C ☐D ☐E

57. Which picture do **you think** best shows the angle of your big toe **in your 20s?**

☐A ☐B ☐C ☐D ☐E

Now, do the same for your **right big toe** joint using the set of pictures below labelled F to J.

RIGHT FOOT



58. Which picture best shows the angle of your big toe **currently?**

☐F ☐G ☐H ☐I ☐J

59. Which picture do **you think** best shows the angle of your big toe **in your 20s?**

☐F ☐G ☐H ☐I ☐J

We are now interested in the angle at your feet when you are **walking** (that is straight, turned in or turned out feet) as this may have relevance to the development of OA. Please look at your feet **whilst walking** and tick the appropriate box to indicate the angle of your feet.

Most people will have similar angulations in their left and right feet, but in a few people these angulations may differ. We therefore would like you to score your feet separately.

A	B	C	D	E
Very turned out feet	Turned out feet	Straight	Turned in feet	Very turned in feet

60. Which picture best shows the **current** angle of **each** of your feet?

Right foot ▶ ☐A ☐B ☐C ☐D ☐E

Left foot ▶ ☐A ☐B ☐C ☐D ☐E

61. Which picture do **you think** best shows the angle of **each** of your feet **in your 20s?**

Right foot ▶ ☐A ☐B ☐C ☐D ☐E

Left foot ▶ ☐A ☐B ☐C ☐D ☐E

SECTION 11: ABOUT YOUR FOOT PAIN

We would now like you to consider **any pain** that you may have within your feet (from toes to ankle joint).

62. Have you **ever** had pain in your foot/feet on most days for **at least** a month?

☐ Yes ☐ No **(if no please go to section 12, page 15)**

If yes, at what age did you first notice this type of foot pain?

☐☐ Years old

63. Have you had foot pain on most days of the **last month**?

☐ Yes ☐ No **(if no please go to question 64)**

If yes, in your opinion how severe is the pain in your foot/feet?

☐ Mild ☐ Moderate ☐ Severe ☐ Worst I have ever experienced

64. In the last 10 years, approximately how many **months of each year** have you had **chronic** foot pain (pain felt on most days of each month)

*(Please write the **approximate number of months** under each year)*

1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐

65. Since it has started, do you think the severity of your foot pain has overall.....

☐ Greatly Improved ☐ Slightly improved ☐ Worsened ☐ Remained the same

66. Which foot/feet do you / did you experience the pain in?

☐ Right ☐ Left ☐ Both

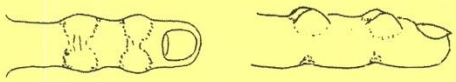
SECTION 12: ABOUT YOUR HANDS

We are interested in knowing whether you have any finger nodes. These sometimes relate to arthritis at the hand and other joints. A finger **node** is a firm, bobbly swelling on the back of the finger joint.

For example:

A finger **without** nodes:

A finger **with** nodes:



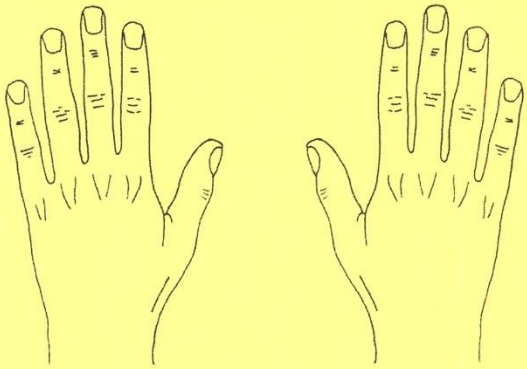
Please look at your hands and then answer the following questions

67. Do you think you have any **nodes/swellings** on your hands?

☐ Yes ☐ No **(please move to question 68)**

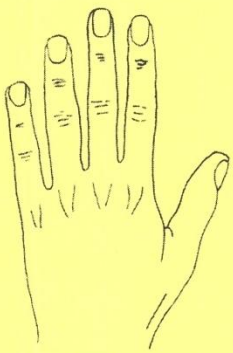
If yes, for each hand please circle the finger joint(s) where you have these nodes. (You may circle several joints)

LEFT **RIGHT**



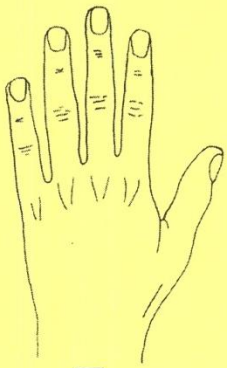
68. We are now interested in which of your **index** and **ring** fingers is longer. **First,** please look at your **left hand** with your fingers straight inline with your forearm. **Ignore your middle finger** and try to **focus only on your left index and ring fingers.** Select from the pictures below the one that best shows the length of your **left index finger** in comparison to your **left ring finger** and tick the appropriate box.

Index finger longer than ring finger



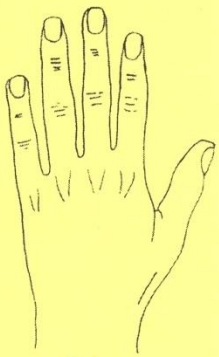
☐

Both fingers equal length



☐

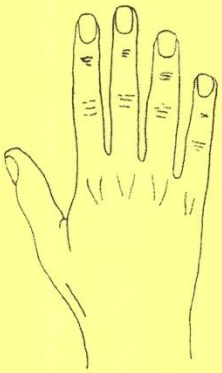
Ring finger longer than index finger



☐

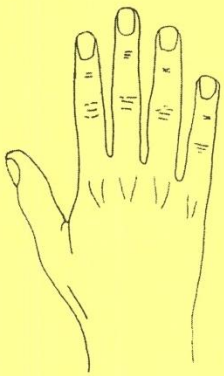
69. Now, do the same for your **right index and ring fingers** using the set of pictures below.

Index finger longer than ring finger



☐

Both fingers equal length



☐

Ring finger longer than index finger

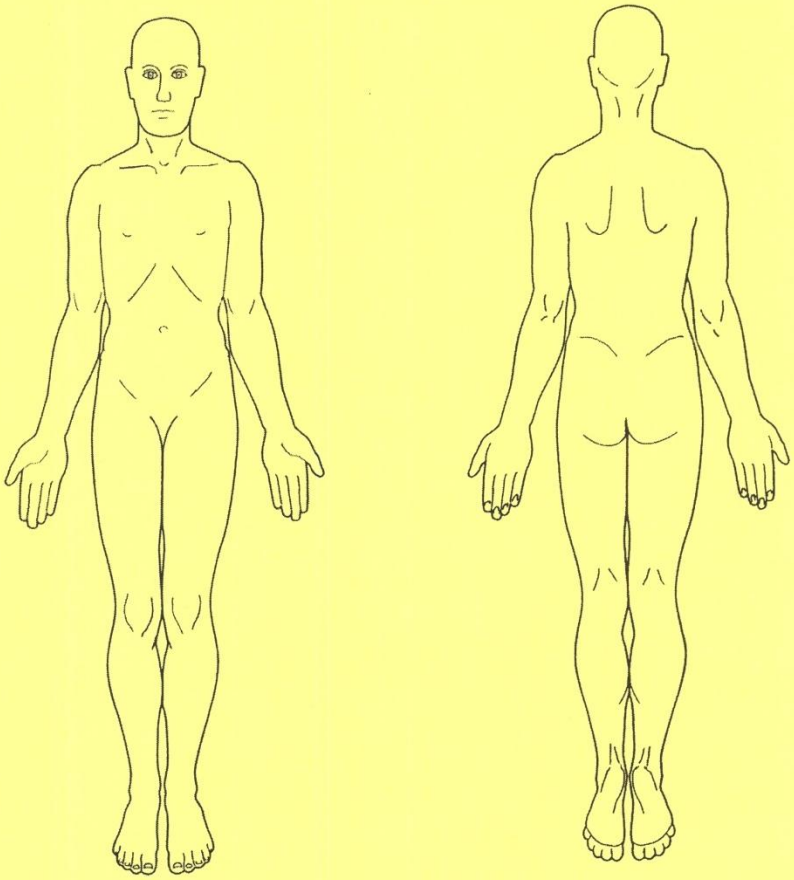
☐

SECTION 13: ABOUT TOTAL BODY PAIN

70. This question is about **recent pain** you may have had in **any part of your body**. Please shade in the diagram below, to indicate where **any pain** that has lasted for **one day or longer in the last 4 weeks**.

By pain we also mean aching, discomfort and/or stiffness. Please **do not include** pain due to feverish illness such as 'flu or headache.

If you **have not** had any body pain that has lasted for one day or longer in the last 4 weeks, please tick this box ☐ and **move to section 14 on page 18.**



SECTION 14: ABOUT YOUR MEDICAL HISTORY AND MEDICATION

71. Have you **ever** been diagnosed by your doctor as having any of the following?

☐ Diabetes ☐ High blood pressure ☐ Angina

☐ Heart attack ☐ Rheumatoid arthritis ☐ Gout

☐ Hip osteoarthritis ☐ Osteoporosis

☐ Cancer, *please specify where* .....

☐ Other .....

☐ No

72. Please list **all** your **current medication** including those **prescribed by your doctor** and those **bought yourself** over the counter (*please **include any hormonal medication** such as oestrogen supplements, **vitamin supplements and alternative medicines**) Please indicate the approximate number of months or years you have taken each of these.*

Name of medicine ..... ☐☐ Months ☐☐ Years taken

Name of medicine ..... ☐☐ Months ☐☐ Years taken

Name of medicine ..... ☐☐ Months ☐☐ Years taken

Name of medicine ..... ☐☐ Months ☐☐ Years taken

Name of medicine ..... ☐☐ Months ☐☐ Years taken

Name of medicine ..... ☐☐ Months ☐☐ Years taken

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Name of medicine ..... ☐☐ Months ☐☐ Years taken

Name of medicine ..... ☐☐ Months ☐☐ Years taken

Name of medicine ..... ☐☐ Months ☐☐ Years taken

Name of medicine ..... ☐☐ Months ☐☐ Years taken

SECTION 15: YOUR THOUGHTS ABOUT YOUR CURRENT HEALTH

73. In general, would you say your health is:.....*(tick one box)*

Excellent	Very Good	Good	Fair	Poor
☐	☐	☐	☐	☐

74. Compared to **one year ago**, how would you rate your general health now?

Much better now than one year ago	Somewhat better than one year ago	About the same as one year ago	Somewhat worse than one year ago	Much worse now than one year ago
☐	☐	☐	☐	☐

75. The following questions are about activities you might do during a typical day. **Does your health limit you in these activities? If so, how much?** *(tick one box for each question)*

	Yes, limited a lot	**Yes, limited a little**	**No, not limited at all**
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sport	☐	☐	☐
Moderate activities, such as moving a table, pushing a vaccum cleaner, bowling	☐	☐	☐
Lifting or carrying groceries	☐	☐	☐
Climbing **several** flights of stairs	☐	☐	☐
Climbing **one** flight of stairs	☐	☐	☐
Bending, kneeling or stooping	☐	☐	☐
Walking **more than** a mile	☐	☐	☐
Walking **half** a mile	☐	☐	☐
Walking **100 yards**	☐	☐	☐
Bathing and dressing yourself	☐	☐	☐

76. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?** *(please tick one box on each line)*

	All of the time ▼	Most of the time ▼	Some of the time ▼	A little of the time ▼	None of the time ▼
Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
Accomplished less than you would like	☐	☐	☐	☐	☐
Were limited in the **kind** of work or other activities	☐	☐	☐	☐	☐
Had **difficulty** performing the work or other activities (took extra effort)	☐	☐	☐	☐	☐

77. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of emotional problems?** (such as feeling depressed or anxious)? *(please tick one box on each line)*

	All of the time ▼	Most of the time ▼	Some of the time ▼	A little of the time ▼	None of the time ▼
Cut down on the **amount of time** you spent on work or other activities	☐	☐	☐	☐	☐
Accomplished less than you would like	☐	☐	☐	☐	☐
Did work or other activities **Less carefully than usual**	☐	☐	☐	☐	☐

78. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups? *(please tick one)*

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

79. How much physical pain have you had during the **past 4 weeks**? *(please tick one)*

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐

80. During the **past 4 weeks**, how much did pain interfere with your normal work, including work both outside the home and housework? *(please tick one)*

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

81. These questions are about how you feel and how things have been with you **during the past month.** (For each question please indicate the one that comes closest to the way you have been feeling). *(Please tick one box on each line)*

	All of 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 ▼
Did you feel full of life?	☐	☐	☐	☐	☐	☐
Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
Did you have lots of energy?	☐	☐	☐	☐	☐	☐
Have you felt downhearted and low?	☐	☐	☐	☐	☐	☐
Did you feel worn out?	☐	☐	☐	☐	☐	☐
Have you been a happy person?	☐	☐	☐	☐	☐	☐
Did you feel tired?	☐	☐	☐	☐	☐	☐
Has your **health limited your social activities** (like visiting relatives and friends)?	☐	☐	☐	☐	☐	☐

82. Please choose the answer that best describes how **true** or **false** each of the following statements is for you. *(Please tick one box on each line)*

	Definitely true ▼	Mostly true ▼	Not sure ▼	Mostly false ▼	Definitely false ▼
I seem to get ill more easily than other people	☐	☐	☐	☐	☐
I am as healthy as anybody I know	☐	☐	☐	☐	☐
I expect my health to get worse	☐	☐	☐	☐	☐
My health is excellent	☐	☐	☐	☐	☐

Appendix 4: Supporting documentation

(Examples of letter from Academic Rheumatology and Participant information sheet)

Academic Rheumatology
Clinical Sciences Building
City Hospital
Nottingham
NG5 1PB, UK

Tel: +44 (0) 115 8231756
Fax: +44 (0) 115 8231757
msxsi@nottingham.ac.uk

Dear patient

Re: Knee pain progression and risk factors

You may remember that you kindly participated in a knee pain study between 1996 and 1999 for The Department of Academic Rheumatology, City Hospital. This involved having x-rays of your knees. The results of that study provided important information regarding the high frequency of knee pain and its impact on people's life, and suggested a number of factors that may associate with having knee pain.

We are now conducting a follow-up study, approximately 10 years later, to determine the rate of development of knee pain in people who were initially pain-free, and to determine the long-term outcome of people who have had knee pain. This will be the longest follow-up study of knee pain ever undertaken in Europe and should provide important information on this common and often disabling condition.

We are inviting you to participate in this follow-up survey. This will involve completion of the enclosed questionnaire which will take approximately 20-30 minutes of your time. We need information both from people with knee pain and from people without knee pain. Therefore, whether or not you have knee pain, your reply will prove very valuable to the study.

In addition to the questionnaire, we are also inviting you to have repeat x-rays of your knees, together with some simple tests to determine your muscle strength, balance and bone density. This would involve you coming to the Academic Rheumatology Department, based at Nottingham City Hospital, on a single occasion. This assessment does **not** involve you taking any special medication, and is **not** a drugs trial. Again, we are interested in obtaining these x-rays and tests in people both with and without knee pain.

I enclose an information sheet which explains this study in more detail. Please read through this at your convenience and discuss it with your friends and family if you wish. If you have any questions about the questionnaire or the x-ray and clinical assessment, please do not hesitate to contact Sarah Ingham, the PhD student coordinating this study. She is available by telephone (0115 8231756) and will be happy to answer any queries you may have. The completion of the questionnaire and participation in the x-ray and clinical assessment are completely voluntary. If you decide not to participate in the study this will in no way affect any future treatment you receive at the hospital or your local GP surgery.

If you have read through the information sheet and decide that you would like to participate, then please complete and return the enclosed questionnaire to Sarah Ingham in the stamped addressed envelope provided. Please indicate on the back of the questionnaire if you would also be willing to undergo the x-ray and clinical assessment. If we do not receive this reply in 2-3 weeks, you will be sent one reminder letter. If after this second letter we have still not received your questionnaire we will assume that you do not wish to participate in this study and you will receive no further information. If you indicate that you are willing to undergo the x-ray and clinical assessment you will be contacted as soon as possible by a member of the study team who will arrange a mutually convenient time for you to come to Academic Rheumatology.

The Department of Academic Rheumatology undertakes many studies into pain and arthritis to better improve our knowledge and understanding of these common disabling conditions. Such studies require the voluntary co-operation of people such as yourself. If you are happy to complete the questionnaire you will find on the last page a consent form which asks if you would be willing for Academic Rheumatology to securely store your contact details for possible future contact concerning new studies. If you are happy for us to do this then please fill in this form and sign it. If you would prefer us not to store your contact details then please **do not** complete this part of the questionnaire.

Thank you for taking the time to read this information. We look forward to hearing from you.

Yours sincerely

Professor Michael Doherty
Professor of Rheumatology

Nottingham University Hospitals NHS

BUPA*foundation*

The University of Nottingham

Knee pain progression and risk factors

PARTICIPANT INFORMATION SHEET

Principal Investigator: Professor Michael Doherty

Study contact: Sarah Ingham, PhD student and Project Coordinator, Academic Rheumatology, Clinical Sciences Building, City Hospital, Hucknall Road, Nottingham, NG5 1PB, Tel: 0115 8231756

You are being invited to take part in a study that involves having an x-ray and clinical assessment for research purposes. Before you decide whether to take part in this study, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like further information. Take time to decide whether or not you wish to take part.

Background to the study

Knee pain is a common condition and a leading cause of disability. Its frequency gets more common as we get older. One important cause of knee pain is osteoarthritis (OA), which is by far the commonest form of arthritis world-wide. The changes of knee OA can be identified on an x-ray. Although our Unit has examined the frequency and impact of knee pain and knee OA in Nottinghamshire, we still do not know what happens long-term to people with knee pain and knee OA. In particular, we have little understanding of the lifestyle factors that may determine whether people do well or badly. We hope that improved understanding of this common condition will lead to improvements in clinical care.

You may remember that you kindly volunteered to take part in a knee pain questionnaire study between 1996 and 1999 undertaken by our Department of Academic Rheumatology, based at the City Hospital. The results of that study provided important information regarding the high frequency of knee pain and its impact on people's life, and suggested a number of factors that may associate with having knee pain. We are now asking as many as possible of the original 9,427 people who completed this questionnaire to repeat a second questionnaire. This will allow us to determine the rate of development of knee pain in people who were initially pain-free, and to determine the long-term outcome of people who have had knee pain. In addition we will be able to examine a number of possible "risk" factors that may contribute to the development or progression of knee pain. To fully understand such risk factors we need to examine people both with and without knee pain. A sample of people who completed the questionnaire between 1996 and 1999, some with knee pain and some without, also had x-rays taken of their knees to look for changes of OA. We now wish to obtain current knee x-rays in these same people to see what changes have occurred over the past 10 years and to determine how important are any changes in joint structure in terms of causing joint pain and related disability.

Why have I been chosen?

You have been identified as someone who participated in the knee pain study between 1996 and 1999 and who also had an x-ray taken of your knees. In addition to receiving current information from you in the enclosed postal questionnaire, we would like to invite you to attend the Academic Rheumatology Department for repeat knee x-rays, to see if any changes have occurred since the original study, as well as a clinical assessment. The clinical assessment includes some additional questions but also some tests to determine your muscle strength, your balance while standing, and your bone density. This is because some people with knee pain or knee OA may have reduced muscle strength, impaired balance and higher than average bone density.

Do I have to take part?

Participation in this study is entirely voluntary and it is up to you to decide whether or not you wish to take part. You should only take part in this study if you want to. If you decide not to participate in the questionnaire or in the clinical assessment this will in no way affect any future treatment you receive at the hospital or your local GP surgery.

You are free to withdraw from this study at any time, without giving a reason. This will in no way affect any future treatment you receive at the hospital or your local GP surgery.

What will happen to me if I take part?

If you do wish to participate in the questionnaire part of the study then please complete the enclosed questionnaire and return it in the envelope provided. If you also wish to take part in the second part of the study, involving the repeat x-rays and clinical assessment, we ask you to indicate your agreement to this in the consent section at the back of the questionnaire.

If you have indicated that you are willing to take part in the second stage of this study, we will contact you shortly after we receive your returned questionnaire, to arrange a mutually convenient appointment to attend Academic Rheumatology at the City Hospital. When you arrive at Academic Rheumatology a member of the research team will again explain the assessments that you will undergo (see below), and answer any questions you may have, to make sure you fully understand what is involved. You will then be asked to sign a consent form for the study.

This is **not** a drug-trial, and you will **not** be asked to take any special medication.

During your single visit to Academic Rheumatology you will undergo the following clinical assessments:

- **Family history**: You will be asked some detailed questions about any joint pain or injury within your family.
- **Current diet**: You will be asked to complete questions about your current diet.
- **Footwear history**: You will complete several short questions about the types of shoes or boots you have worn as an adult.
- **"WOMAC" questionnaire**: You will complete a short questionnaire designed to measure the severity of on pain, stiffness, and disability related to knee pain and knee OA.
- **Assessment of grip strength**: This is a simple method of assessing how generally strong you are. It involves you sitting in a chair with your arm on the arm rest. We will ask you to squeeze hard for just a few seconds on a small hand-held device (JAMAR dynamometer) that gives a reading of the strength of your grip. We will ask you to squeeze hard 3 times for each hand to provide an average score.
- **Assessment of quadriceps (thigh) muscle strength**: This is to assess how strong your main thigh muscles are. You will be asked to sit upright in a chair with your thighs horizontal and feet on the floor. You are then asked to push your leg forwards against a small padded device (the Nicholas Manual Muscle Tester) that is held against the front of your lower shin, just above the ankle, by the researcher. You will be asked to push hard 3 times on each leg to obtain an average score.
- **Assessment of balance**: You will be asked to step onto a "balance monitor" (a small flat machine placed on the floor that looks like bathroom scales) and stand as still as you can for 30 seconds. During this period the force plates in the machine measure how much you are swaying. You are able to stay in your normal footwear but you will be asked not to use any walking aid for the 30 seconds of the test.
- **Measurement of height, weight and body fat**: We will use standard equipment you would find at your doctors (stadiometer and electrical balance) to measure these items.

- **'Timed get up and go' test**: This is a quick combined test of your ability to walk, stand and sit down. You start the test sitting in a chair; and then we ask you to stand up and walk a distance of 3 metres, turn around, walk back to the chair and sit down. We time how long it takes you to do this. You do this test in your normal footwear and you can use any walking aid that you normally require.

- **Assessment of bone density**: Your bone density (DXA scan) will be measured using a small machine in the Academic Rheumatology Unit. While sitting, you will be asked to place your heel in a depression in the machine, allowing a special x-ray to measure the bone density in your heel bone (calcaneum).

- **Knee X-ray**: You will undergo an x-ray of both knees in two positions – one standing with your knees straight, and one seated on a couch with your knees bent. These x-rays will be used to assess the presence and severity of any changes of OA (narrowing of the joint space through loss of cartilage, and overgrowth of bone at the joint margins).

- **Hand, knee and foot examination**: You may be one of a small number of people who have their hands, knees and feet briefly examined. This is to test the reliability of the information that has been obtained in the previously returned questionnaire with respect to the newly devised picture questions concerning finger length, knee alignment and foot angulation. This is a standard requirement for newly designed, self-reported picture questions.

The entire clinical assessment will take approximately 1 hour 45 minutes of your time.

What will happen to my information?

The study is designed in such a way that your personal information, such as name and address, will be kept separate from your study information. All data collected will be stored on a secure, password protected computer within Academic Rheumatology using a unique identification number for reference. The paper copies of your study forms will also be securely filed and stored within the department. Only study personnel will have access to these records.

What are the side-effects of participating in this study?

Both your knees will be x-rayed during this visit. Having x-rays of your knees exposes you to a very small amount of radiation, approximately equivalent to less than 2 days worth of natural background radiation. Having an x-ray of a joint involves the least amount of radiation of having any x-ray. This study has been approved by radiation advisors within the Medical Physics Department of the City Hospital. There is also a very small amount of radiation involved in having a DXA scan of your heel; however, this is the equivalent to less than 6 hours background radiation.

All of the clinical assessments are simple, brief tests that should not cause any pain or distress, although some people who already suffer from knee pain may feel some discomfort when asked to get up and down from the chair, or to stand still without any walking aid.

Neither the x-ray nor the clinical assessments will form part of your usual investigation or treatment, and are purely being performed for research purposes.

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

You will receive no direct benefit from participating in this study. However, the information we obtain might help improve the treatment of people with knee pain in the future.

What if something goes wrong?

It is very unlikely that something should go wrong if you take part in this study. If you have concerns about your participation in the study, please address them to a member of the study team as soon as possible, in order for your concerns to be resolved promptly.

Will my taking part in the study be kept confidential?

Your details will be kept strictly confidential and you will be identified by a unique identification number. Your personal and medical details will be linked to this number. This link will be held in a secure file within Academic Rheumatology and will only be accessed by study personnel.

What will happen to my information once the study has finished?

All data collected will remain confidential and only be linked by your unique ID number. It will be stored within Academic Rheumatology, Clinical Sciences Building. Only study personnel will have access to this information.

Has this study been approved by an Ethics Committee?

An independent NHS Research Ethics Committee has approved this study. In their opinion, this study does not propose any undue discomfort or risk to those taking part. Academic Rheumatology follows ICH-GCP (good clinical practice) guidelines.

Will I be paid for participating in this study?

Participation in this study is entirely voluntary. You will receive no payment for your participation. All reasonable expenses incurred through participation, for example travel costs to and from the City Hospital, will be reimbursed.

Who is organising and funding the research?

This study has been organised by members of staff in Academic Rheumatology, who are a department of the University of Nottingham and who are based at the City Hospital. Funding for this study is being provided by two national charities - the Arthritis Research Campaign and the BUPA Foundation.

What will happen to the results of the research study?

The information collected during this study will be compared with the information we obtained in the previous study undertaken almost 10 years ago. This will allow us to determine the risk factors for the development and progression of knee pain and knee OA. The results from this large-scale study, the longest ever longitudinal study of knee pain, will be published in scientific and medical journals. This study will also form part of a PhD qualification for Sarah Ingham.

Study team members

Ms Sarah Ingham, PhD student and Project Coordinator within Academic Rheumatology
Professor Michael Doherty, Professor of Rheumatology
Dr Weiya Zhang, Associate Professor of Musculoskeletal Epidemiology
Mrs Sally Doherty, Senior Research Metrologist
Mrs Eleanor Mitchell, Research Manager

Who do I contact if I have any questions?

If you have any questions about the study please do not hesitate to contact Sarah Ingham on 0115 82 31756.

Thank you for taking the time to read this information sheet

Appendix 5: WOMAC

ID number: | | | | |

WOMAC Osteoarthritis Index:

Section A

The following questions concern the amount of pain you have experienced in your knees over the last week.

Please tick one box for each item.

QUESTION: How much pain do you have?

	None	Mild	Moderate	Severe	Extreme
1. Walking on a flat surface	☐	☐	☐	☐	☐
2. Going up or down stairs	☐	☐	☐	☐	☐
3. At night while in bed	☐	☐	☐	☐	☐
4. Sitting or lying	☐	☐	☐	☐	☐
5. Standing upright	☐	☐	☐	☐	☐

Section B

The following questions concern the amount of stiffness (not pain) you have experienced in your knees over the last week. Stiffness is a sensation of restriction or slowness in the ease in which you move your joints.

Please tick one box for each item.

1. How severe is your stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

2. How severe is you stiffness after sitting, lying or resting later in the day?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Section C

The following concern your physical function. By this we mean your ability to move around and look after yourself. For each of the following activities, please indicate the degree of difficulty you have experienced over the last week due to problems with your knees. *Please tick one box for each item.*

QUESTION: What degree of difficulty do you have with:

	None	Mild	Moderate	Severe	Extreme
1. Descending stairs	☐	☐	☐	☐	☐
2. Ascending stairs	☐	☐	☐	☐	☐
3. Rising from sitting	☐	☐	☐	☐	☐
4. Standing	☐	☐	☐	☐	☐
5. Bending to floor	☐	☐	☐	☐	☐
6. Walking on the flat	☐	☐	☐	☐	☐
7. Getting in/out of car	☐	☐	☐	☐	☐
8. Going shopping	☐	☐	☐	☐	☐
9. Putting on shoes/socks	☐	☐	☐	☐	☐
10. Rising from bed	☐	☐	☐	☐	☐
11. Taking off socks/stockings	☐	☐	☐	☐	☐

	None	Mild	Moderate	Severe	Extreme
12. Lying in bed	☐	☐	☐	☐	☐
13. Getting in/out of bath	☐	☐	☐	☐	☐
14. Sitting	☐	☐	☐	☐	☐
15. Getting on/off toilet	☐	☐	☐	☐	☐
16. Heavy domestic duties	☐	☐	☐	☐	☐
17. Light domestic duties	☐	☐	☐	☐	☐

Thank you for completing this questionnaire

Appendix 6: Body pain mannequin

(Showing 44 different pain regions).

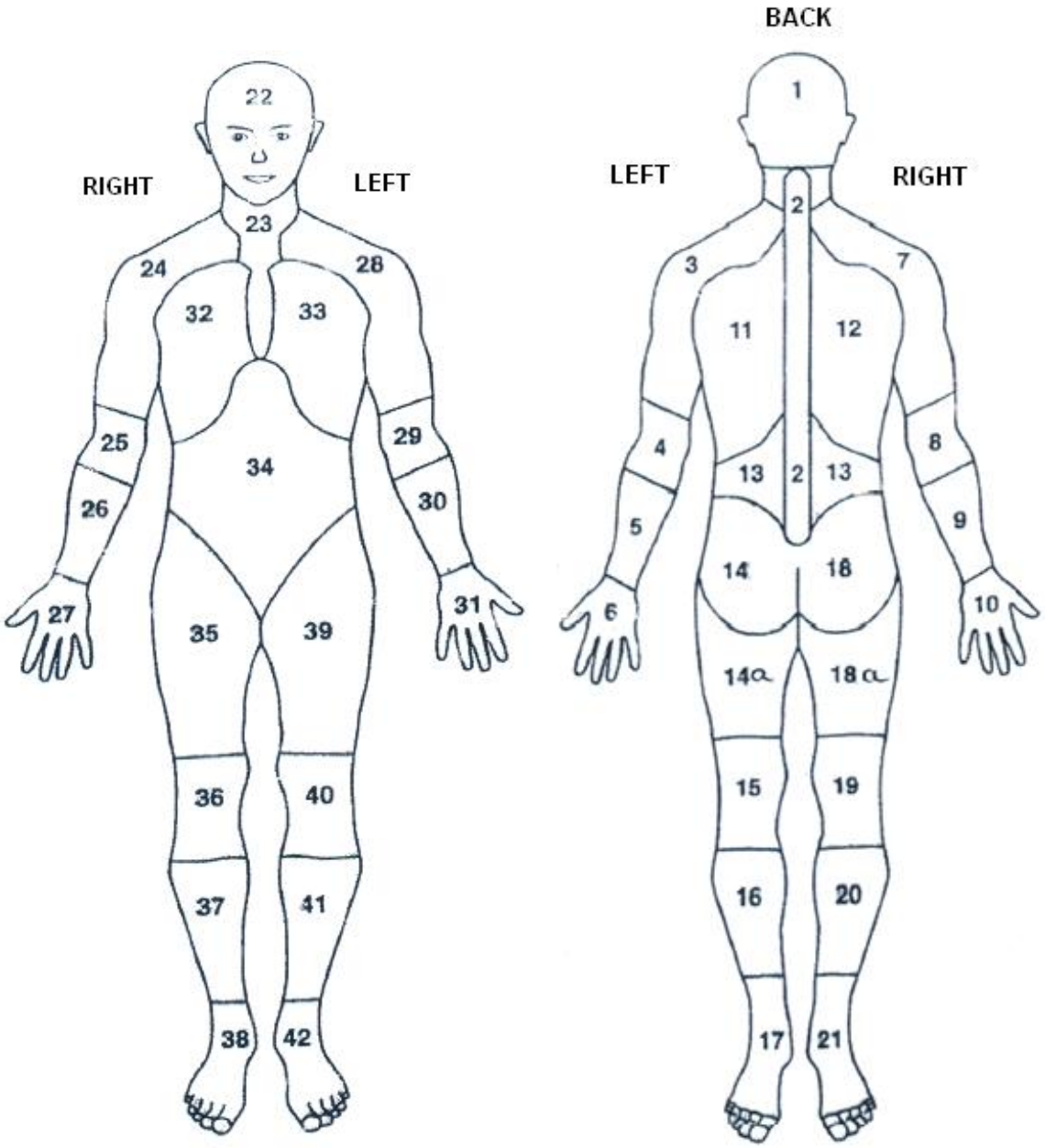
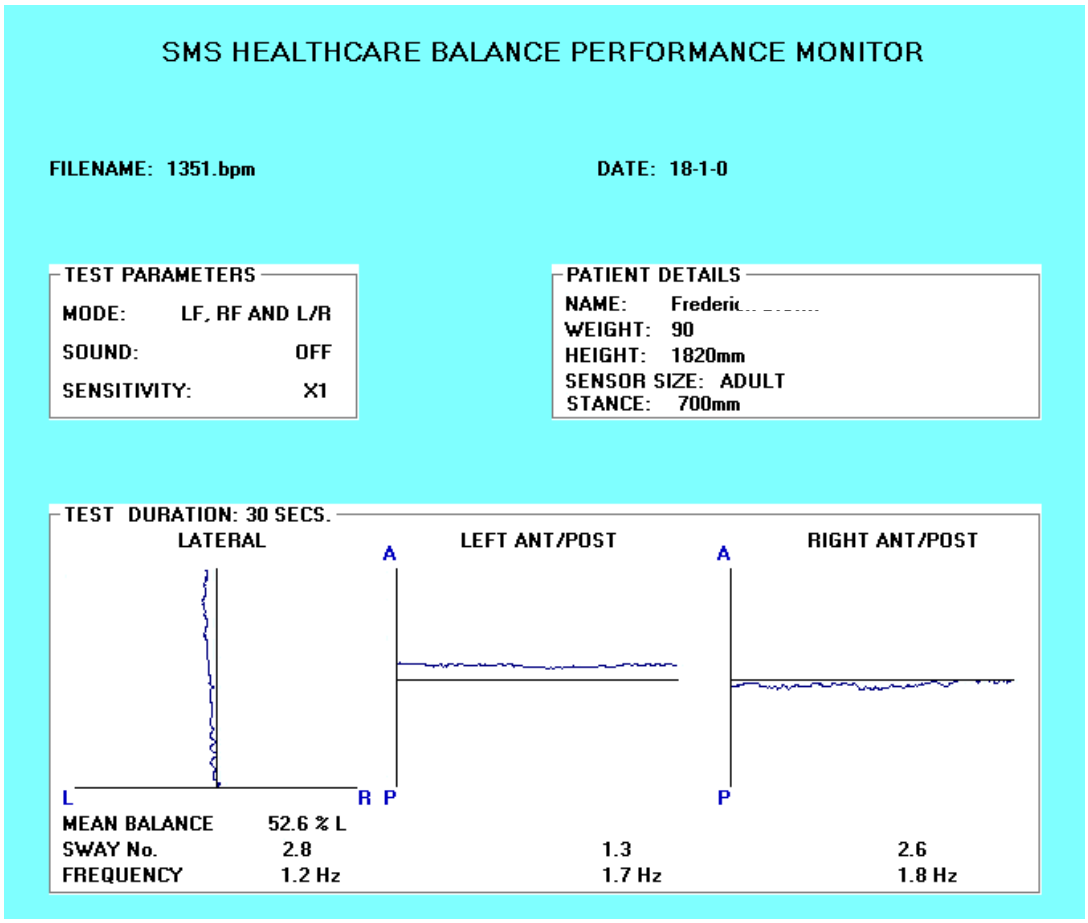


Fig. Body pain mannequin showing the 44 different regions.

Appendix 7: Example of Sway output

(Balance performance monitor).



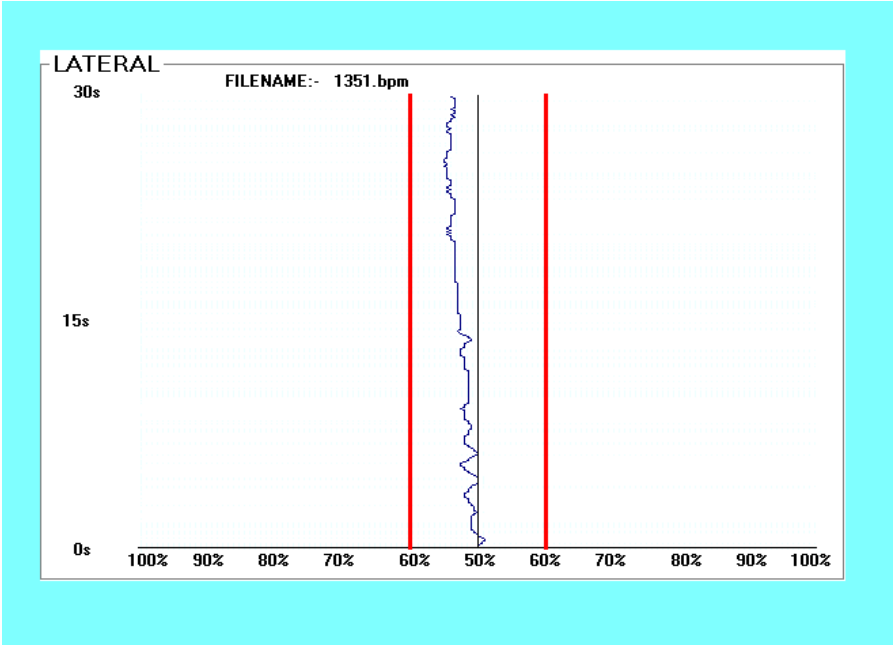


Fig. Example of sway output using the balance performance monitor.

Appendix 8: Baseline characteristics

(Responders versus non-responders).

Baseline characteristics of responders versus non-responders

Characteristics at baseline	Responders n=3109	Non-Responders n=2370
Age:		
<60	1968 (63%)	427 (18%)
≥60	1141 (37%)	1943 (82%)
Gender:		
Men	1384 (44%)	1066 (45%)
Women	1725 (56%)	1304 (55%)
BMI:		
Normal (<25)	1262 (41%)	949 (40%)
Overweight (≥25, ≤30)	1465 (47%)	1101 (46%)
Obese (>30)	280 (9%)	320 (14%)
Smoking:		
No	1517 (49%)	1050 (44%)
Yes	1592 (51%)	1320 (56%)
Knee pain		
No	2195 (71%)	1696 (72%)
Yes	914 (29%)	674 (28%)
Back pain		
No	1800 (58%)	1386 (58%)
Yes	1284 (41%)	948 (40%)
Missing	25 (1%)	36 (2%)
Hip pain		
No	2443 (79%)	1892 (80%)
Yes	636 (20%)	435 (18%)
Missing	30 (1%)	43 (2%)

Appendix 9: Prevalence of risk factors at baseline

Prevalence of risk factors at baseline

Characteristics at baseline		Prevalence n=3109
Age:		
	<60	1968 (63%)
	≥60	1141 (37%)
Gender:		
	Men	1384 (44%)
	Women	1725 (56%)
BMI:		
	Normal (<25)	1262 (41%)
	Overweight (≥25, ≤30)	1465 (47%)
	Obese (>30)	280 (9%)
Smoking:		
	No	1517 (49%)
	Yes	1592 (51%)
Knee pain:		
	No	2195 (71%)
	Yes	914 (29%)
Back pain:		
	No	1800 (58%)
	Yes	1284 (41%)
	Missing	25 (1%)
Hip pain:		
	No	2443 (79%)
	Yes	636 (20%)
	Missing	30 (1%)
Knee malalignment:		
	Normal	2841 (91%)
	Varus	94 (3%)
	Valgus	53 (2%)
	Missing	121 (4%)
Foot angulation:		
	Normal	2473 (80%)
	Out	414 (13%)
	In	60 (2%)
	Missing	162 (5%)
Knee injury:		
	No	1319 (42%)
	Yes	385 (12%)
	Missing	1405 (46%)
Nodes:		
	No	1946 (63%)
	Yes	1101 (35%)
	Missing	62 (2%)

Appendix 10: Survival analysis of knee pain

Constitutional factors

Time to onset of knee pain and Constitutional factors

Constitutional factors	Incident rate (%)	Hazard ratio (95% confidence interval)	
		Crude	Adjusted
Age:			
<60	488/1407 (35%)	**1**	**1**
≥60	254/749 (34%)	0.97 (0.83, 1.12)	0.96 (0.83, 1.12)
Gender:			
Men	316/975 (32%)	**1**	**1**
Women	426/1181 (36%)	1.10 (0.95, 1.27)	1.13 (0.97, 1.31)
BMI:			
Normal (<25)	284/958 (30%)	**1**	**1**
Overweight (≥25, ≤30)	360/989 (36%)	**1.29 (1.11, 1.51)**	**1.31 (1.12, 1.54)**
Obese (>30)	73/150 (49%)	**1.87 (1.44, 2.41)**	**1.88 (1.45, 2.43)**
Smoking:			
No	367/1074 (34%)	**1**	**1**
Yes	375/1082 (35%)	1.02 (0.88, 1.18)	1.05 (0.91, 1.23)

HR was adjusted for age, gender, BMI

Biomechanical Factors

Time to onset of knee pain and Biomechanical factors

Biomechanical factors	Incident rate (%)	Hazard ratio (95% confidence interval) Crude	Adjusted
Knee angulation: during 20s:			
Normal	669/1977 (34%)	**1**	**1**
Varus	28/58 (48%)	**1.56 (1.07, 2.27)**	**1.76 (1.20, 2.58)**
Valgus	11/25 (44%)	1.36 (0.75, 2.47)	1.39 (0.76, 2.52)
Foot angulation during 20s:			
Normal	575/1735 (33%)	**1**	**1**
Out	116/273 (42%)	**1.34 (1.10, 1.64)**	**1.31 (1.07, 1.61)**
In	14/38 (37%)	1.13 (0.66, 1.92)	1.20 (0.71, 2.04)
Knee Injury:			
No	543/1827 (30%)	**1**	**1**
Yes	188/299 (63%)	**2.58 (2.19, 3.05)**	**2.54 (2.14, 3.01)**
Muscle Strength – using Highest score:			
High strength – Tertile1	20/59 (34%)	**1**	**1**
Tertile 2	24/57 (42%)	1.31 (0.72, 2.37)	1.24 (0.62, 2.48)
Low strength - Tertile 3	21/52 (40%)	1.21 (0.66, 2.24)	0.85 (0.41, 1.78)
Muscle Strength – Average:			
High strength - Tertile 1	20/60 (33%)	**1**	**1**
Tertile 2	24/57 (42%)	1.38 (0.76, 2.49)	1.26 (0.64, 2.51)
Low strength - Tertile 3	21/49 (43%)	1.33 (0.72, 2.46)	1.07 (0.53, 2.13)
Lift Heavy loads:			
No	232/742 (31%)	**1**	**1**
Yes	108/276 (39%)	**1.34 (1.06, 1.68)**	**1.40 (1.11, 1.78)**
Sweat through physical exertion:			
No	256/795 (32%)	**1**	**1**
Yes	85/219 (39%)	1.25 (0.98, 1.60)	**1.35 (1.04, 1.74)**
More Physical Work:			
No	251/785 (32%)	**1**	**1**
Yes	78/203 (38%)	1.24 (0.96, 1.60)	1.26 (0.97, 1.63)

HR was adjusted for age, gender, BMI. (did not adjust by other significant variables). Muscle assessments were conducted only for the 424 participants seen for the clinical assessment

Co-morbidity factors

Time to onset of knee pain and co-morbidity factors

Co-morbidity factors	Incident rate (%)	Hazard ratio (95% confidence interval) Crude	Adjusted
Co-morbidities:			
No	658/1899 (35%)	**1**	**1**
1	74/233 (32%)	0.90 (0.71, 1.14)	0.92 (0.72, 1.18)
≥2	10/24 (42%)	1.20 (0.64, 2.25)	1.21 (0.65, 2.28)
RA:			
No	711/2093 (34%)	**1**	**1**
Yes	31/63 (49%)	**1.57 (1.10, 2.25)**	**1.61 (1.12, 2.32)**
Back Pain:			
No	429/1403 (31%)	**1**	**1**
Yes	301/734 (41%)	**1.41 (1.21, 1.63)**	**1.41 (1.21, 1.64)**
Back Pain last Year:			
No	544/1689 (32%)	**1**	**1**
Yes	172/402 (43%)	**1.42 (1.20, 1.68)**	**1.41 (1.18, 1.68)**
Hip Pain:			
No	593/1828 (32%)	**1**	**1**
Yes	142/310 (46%)	**1.57 (1.30, 1.88)**	**1.57 (1.31, 1.90)**
Hip pain last year:			
No	628/1882 (33%)	**1**	**1**
Yes	91/200 (46%)	**1.49** (1.20, 1.86)	**1.49** (1.18, 1.87)
Back plus Hip Pain:			
No	629/1922 (33%)	**1**	**1**
Yes	96/201 (48%)	**1.66** (1.34, 2.06)	**1.63** (1.31, 2.03)
Sleep:			
>7 hours	327/1066 (31%)	**1**	**1**
<7 hours	75/207 (36%)	**1.22** (0.95, 1.57)	**1.24** (0.95, 1.60)
Morning stiffness			
No	14/37 (38%)	**1**	**1**
Yes	51/131 (39%)	**1.03** (0.57, 1.86)	**0.91** (0.49, 1.69)
Inactivity stiffness			
No	18/42 (43%)	**1**	**1**
Yes	47/126 (37%)	**0.84** (0.49, 1.45)	**0.72** (0.41, 1.27)

HR was adjusted for age, gender, BMI. WOMAC assessments were conducted only for the 424 participants seen for the clinical assessment.

Assessment of “whole person” x-ray features (combined right and left findings) and time to onset of knee pain

Radiographic factors		Incident rate (%)	Hazard ratio (95% confidence interval) Crude	Adjusted
Osteophytes:				
	No	34/119 (29%)	**1**	**1**
	Yes	39/66 (59%)	**2.56 (1.61, 4.06)**	**2.48 (1.52, 4.06)**
Isolated tibio-femoral JSN:				
	No	61/169 (36%)	**1**	**1**
	Yes	12/16 (75%)	**2.57 (1.38, 4.79)**	**2.23 (1.18, 4.23)**
Isolated patello-femoral JSN:				
	No	54/158 (34%)	**1**	**1**
	Yes	19/27 (70%)	**2.75 (1.62, 4.64)**	**2.63 (1.54, 4.51)**
Isolated tibio-femoral OA:				
	K/L 0	31/118 (26%)	**1**	**1**
	K/L ≥1	7/13 (54%)	**2.33 (1.02, 5.29)**	**2.18 (0.91, 5.26)**
Isolated patello-femoral OA:				
	0	31/118 (26%)	**1**	**1**
	≥1	9/20 (45%)	1.93 (0.92, 4.05)	2.08 (0.98, 4.44)
Tibio-femoral plus patello-femoral OA:				
	K/L 0	31/118 (26%)	**1**	**1**
	K/L ≥1	6/34 (18%)	**4.04 (2.39, 6.83)**	**4.37 (2.38, 8.01)**
Chondrocalcinosis:				
	No	70/180 (39%)	**1**	**1**
	Yes	3/5 (60%)	2.02 (0.64, 6.41)	1.74 (0.54, 5.65)

HR: adjusted by age, gender and BMI. X-rays were conducted only for the 406 participants seen at the clinical assessment

Assessment of x-ray features in the right and left knees and relative risk of ipsilateral onset of knee pain

Radiographic factors	Right knee			Left knee		
	Incidence (%)	HR (95%CI)	aHR (95%CI)	Incidence	HR (95%CI)	aHR (95%CI)
Osteophytes:						
No	29/129 (22%)	**1**	**1**	23/137 (17%)	**1**	**1**
Yes	30/56 (54%)	**3.01 (1.80, 5.02)**	**2.87 (1.65, 5.00)**	24/48 (50%)	**3.75 (2.11, 6.66)**	**3.31 (1.78, 6.17)**
Isolated tibio-femoral JSN:						
No	50/174 (29%)	**1**	**1**	45/174 (26%)	**1**	**1**
Yes	9/11 (82%)	**4.11 (2.42, 6.98)**	**3.38 (1.91, 6.00)**	2/11 (18%)	1.14 (0.28, 4.71)	1.09 (0.26, 4.51)
Isolated patello-femoral JSN:						
No	44/163 (27%)	**1**	**1**	37/164 (23%)	**1**	**1**
Yes	15/22 (68%)	**3.45 (1.69, 7.07)**	**2.52 (1.19, 5.32)**	10/21 (48%)	**2.98 (1.48, 5.99)**	**2.66 (1.30, 5.41)**
Isolated tibio-femoral OA:						
K/L 0	24/122 (20%)	**1**	**1**	20/124 (16%)	**1**	**1**
K/L ≥1	4/9 (44%)	**3.23 (1.12, 9.34)**	2.94 (0.96, 9.02)	3/7 (43%)	2.68 (0.80, 9.02)	2.23 (0.63, 7.92)
Isolated patello-femoral OA:						
0	23/120 (19%)	**1**	**1**	21/128 (16%)	**1**	**1**
≥1	8/18 (44%)	**2.55 (1.14, 5.71)**	**2.91 (1.25, 6.78)**	4/10 (40%)	**3.15 (1.08, 9.18)**	**3.55 (1.11, 11.31)**
Tibio-femoral plus patello-femoral OA:						
K/L 0	24/121 (20%)	**1**	**1**	20/122 (16%)	**1**	**1**
K/L ≥1	14/20 (70%)	**5.75 (2.95, 11.21)**	**5.58 (2.62, 11.92)**	10/19 (53%)	**5.42 (2.52, 11.64)**	**4.75 (2.00, 11.27)**
Chondrocalcinosis:						
No	57/181 (32%)	**1**	**1**	45/180 (25%)	**1**	**1**
Yes	2/4 (50%)	1.59 (0.39, 6.52)	1.28 (0.30, 5.46)	2/5 (40%)	1.96 (0.48, 8.07)	1.60 (0.37, 6.91)

HR: adjusted by age, gender and BMI. X-rays were conducted only for the 406 participants seen at the clinical assessment