THE ASSOCIATION OF PHYSICAL ACTIVITY, OBESITY AND INJURY ON THE RISK OF KNEE OSTEOARTHRITIS

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Abstract

Title:

The association of physical activity, obesity and injury on the risk of knee osteoarthritis (OA)

Purpose:

1) To examine the effect of interactions between physical activity, obesity and injury on the incidence and progression of radiographic and symptomatic knee OA;
2) To establish age and gender specific normative data for knee pain, symptoms, function and knee related quality of life (QOL) as the clinical outcome measures in assessing people with knee OA and to examine their associations with OA risk factors including obesity, injury and physical activity.

Methods:

1) Using existing cohort data from Osteoarthritis Initiative (OAI) and Multicenter Osteoarthritis Study (MOST) for interaction analyses

Participants without radiographic knee OA at baseline were followed for the incidence of radiographic and symptomatic knee OA. In OAI, the focus was on the tibiofemoral joints (TF) only, so TF-OA was defined as a knee with a Kellgren and

Lawrence (KL) grade 2 or greater. In MOST, knee OA was defined as a knee with TF-OA (KL ≥2) and/or patellofemoral-OA (osteophyte ≥2; or joint space narrowing ≥1 plus any cyst, osteophyte, or sclerosis using Osteoarthritis Research Society International atlas). The co-occurrence of radiographic knee OA and the frequent knee symptoms (pain, ache, or stiffness on most days of a month over the past 12 months) at the last follow-up was considered as the incidence of symptomatic knee OA.

Progression of radiographic knee OA was determined as either one grade increase in KL score or one grade worsening in joint space narrowing at the last follow-up, in participants with radiographic knee OA at baseline. For the progression of symptomatic knee OA, participants with frequent knee symptoms at baseline were included. An increase of greater than 9.29 points in the total Western Ontario and McMaster Universities Osteoarthritis Index score from baseline to last follow-up was considered as a cut-off point (minimal clinical important worsening) for considering a person with symptom progression. Body mass index (obese/non-obese), injury (yes/no), physical activity (active/inactive), age and gender data were also collected at baseline in both databases. The measures of interactions on both additive and multiplicative

scales were computed using the generalized estimation equation.

2) Establishing age and gender specific reference values data for Knee Injury and Osteoarthritis Outcome Score (KOOS) and Oxford Knee Score (OKS)

Volunteer participants were recruited via a postal survey. From a list of 25,695 postcodes specified by Nottinghamshire local authorities and in the City of Nottingham, 2,500 postcodes were randomly selected. This was based on the proportion of the population in each local authority and in the City of Nottingham. 2,500 postcodes were then equally and randomly assigned into three age groups of 18-44, 45-69 and ≥70 years old. From each postcode assigned to the specific age group, one name and address was randomly selected. Participants were required to complete the questionnaire booklet once only. The questionnaire booklet consisted of the OKS and the KOOS questionnaires. It also collected information regarding participants' age, gender, height, weight, history of injury and knee joint replacement and physical activity.

Results:

Interaction analysis

In both cohorts, active and inactive people had a similar risk of incident radiographic or symptomatic knee OA (p >0.05). This effect was not modified by obesity and/or injury in either cohort ($p_{\text{interactions}}$ >0.05). No significant interactions were also found between physical activity, obesity and injury on the risk of radiographic or symptomatic knee OA progression ($p_{\text{interaction}}$ >0.05). Obese people in both cohorts were significantly at a higher risk of incident radiographic and symptomatic knee OA when compared to non-obese people (p <0.01); injury also increased the incident risk of knee OA (p <0.01). There were some evidence of positive interactions between obesity and injury on the risk of incident knee OA. This reached statistical significance on additive and multiplicative scales in OAI ($aOR_{\text{-Symptomatic-multiplicative interaction}}$: 2.83, 95%CI: 1.01 to 7.93; $aOR_{\text{-Symptomatic-additive interaction}}$: 3.13, 95%CI: 0.05 to 6.21) and on additive scale in MOST ($aOR_{\text{-Radiological-additive interaction}}$: 1.51, 95%CI: 0.10 to 2.93). There was no evidence of any statistically significant interaction between obesity and injury on the progressive risk of knee OA.

Reference values data

The overall response rate was 16.5% (n =414, 45% male, 55% female), with the highest in the middle age group with 24%, 18% in the old age and 8% in young age group. A significant dose response relationship was seen between increasing age and worsening scores of KOOS-Pain; KOOS-Activities of daily living (ADL); KOOS-QOL; and OKS (p <0.05). The median (M) and inter quartile range (IQ) in old, middle and young age groups were as follows: KOOS-Pain (M, IQ: 91.6, 58.3-100; 94.4, 77.7-100; 100, 80.5-100), KOOS-ADL (M, IQ: 91.1, 59.3-100; 98.5, 77.2-100; 100, 89.7-100), KOOS-QOL (M, IQ: 81.2, 43.7-100; 87.5, 62.5-100; 87.5, 68.7-100), and OKS (M,IQ: 42.3, 29-48; 46, 38-48; 47, 42-48). The oldest age group had the worst scores in KOOS-Pain, KOOS-ADL; KOOS-QOL; and OKS compared to the young or middle age groups (p <0.05). However, the differences between young and middle age groups were not statistically significant in any KOOS or OKS scores (p >0.05). Data were also stratified by gender. There was no gender difference in any KOOS or OKS scores (p >0.05). Obesity and injury were also found as the strongest predictors for the worsening score in all KOOS and OKS subscale scores (p <0.05), whereas physical activity was significantly associated with a lower risk of knee related complaints (p <0.05).

Conclusion:

Physical activity did not increase the risk of incident or progressive knee OA at any level of obesity and/or injury in middle aged and older people with or at high risk of knee OA. In addition, meeting the minimum physical activity guidelines was significantly associated with lower self-reported knee complaints evaluated by KOOS and OKS. Therefore, moderate levels of physical activity appears to be safe to recommend to the general population and people with or at high risk of knee OA regardless of obesity and injury status. There was also some modest evidence of positive interaction between obesity and injury on the risk of incident knee OA. Hence, weight gain prevention strategies may protect injured people against further increase in the risk of knee OA.

This study also provided normative data for KOOS and OKS. The self-reported knee complaints were found to vary with age (not gender) being highest in the oldest age group. This suggests that treatment outcomes in people with knee injury and knee OA should be compared against age-matched reference values from the general population.

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Abbreviations

ACL	Anterior cruciate ligament
ACR	American College of Rheumatology
ADL	Activities of daily living
aOR	Adjusted odds ratio
BMI	Body mass index
CPAQ	Clinical Use Physical Activity Questionnaire
EULAR	European League Against Rheumatism
GDF5	Growth differentiation factor 5
GEE	Generalized estimation equation
GOAL	Genetic of Osteoarthritis and Life Style
IQ	Inter quartile
JSN	Joint space narrowing
KL	Kellgren and Lawrence
KOOS	Knee Injury and Osteoarthritis Outcome Score
MOST	Multicenter Osteoarthritis Study
MRC-HCS	Medical Research Council Hertfordshire Cohort Study
MRI	Magnetic resonance imaging
NHANES	National Health and Nutrition Examination Survey
OA	Osteoarthritis
OAI	Osteoarthritis Initiative
OARSI	Osteoarthritis Research Society International
OKS	Oxford Knee Score
OKS-FCS	Functional Component Score of OKS

OKS-PCS	Pain Component Score of OKS
OR	Odds ratio
PASE	Physical Activity Scale for Elderly
PF	Patellofemoral
QOL	Quality of life
RERI	Relative excess risk due to interaction
ROAD	Research on Osteoarthritis/Osteoporosis Against Disability
RR	Relative risk
SD	Standard deviation
Sport/Rec	Sport and recreation function
TF	Tibiofemoral
TKR	Total knee replacement
VAS	Visual analogue scale
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Arthritis Index

1 Introduction

This chapter outlines the rationale of the studies undertaken in this PhD thesis. It begins with a summary of the background information about osteoarthritis (OA), and follows with an overview of the natural history, pathology and clinical features of OA. It then explains the common methods used for evaluating and defining the disease. Prevalence of OA and its risk factors are also described, with the main focus on the risk of knee OA and it association with obesity, injury and physical activity. Finally, the research question of this PhD is presented through a list of specific aims and objectives.

1.1 Osteoarthritis (OA)

OA is the most prevalent form of chronic joint disease affecting millions of people worldwide (Cooper and Arden 2011; March, Smith, Hoy et al. 2014). Evidence of osteoarthritic changes is also observed in fossil animals and skeletal remains of preindustrial humans, indicating the extensive history of OA (Rogers, Watt and Dieppe 1981; Jurmain and Kilgore 1995).

OA is the third main musculoskeletal disorder contributing in "Years Lived with Disabilities' after low back pain and neck pain in both the UK and the rest of the world (Murray, Vos, Lozano et al. 2012; March et al. 2014). It can occur in any synovial joint, but the hip and knee are the most affected sites in terms of pain and disability in the lower limb. Pain in weight bearing joints such as the knee can also affect the walking ability of individuals (Zhang and Jordan 2010). Therefore, more advanced OA is more likely to be associated with more pain, reduction in mobility, increase in disability and lower quality of life (QOL).

OA accounts for 15% of all musculoskeletal consultations in people aged over 45, and as much as 25% in people aged 75 years and over in the UK (Jordan, Clarke, Symmons et al. 2007). The new consultation for the incidence of knee pain is

approximately 10% each year in the UK adults aged over 50 (Jordan et al. 2007; Yu, Peat, Bedson et al. 2015). 93% of knee and hip joint replacements in the UK are also due to OA (Conaghan, Kloppenburg, Schett et al. 2014). OA thus poses a large economic burden on the UK, similar to other western countries (March and Bachmeier 1997; Hiligsmann, Cooper, Arden et al. 2013).

In 2010, the direct cost of OA treatment was estimated over £1 billion, of which £850 million was spent on total knee and hip replacements. This was 66% higher compared to 10 years previously (Chen, Gupte, Akhtar et al. 2012). The indirect cost attributed to OA was also high, estimated at £3.2 billion due to productivity loss and £2.58 million spent on social and community services (Chen et al. 2012). Therefore, pain and disability due to OA not only affects the QOL of millions in both the UK and worldwide, but is also a major contributor to the social and economic burden of disease (Litwic, Edwards, Dennison et al. 2013).

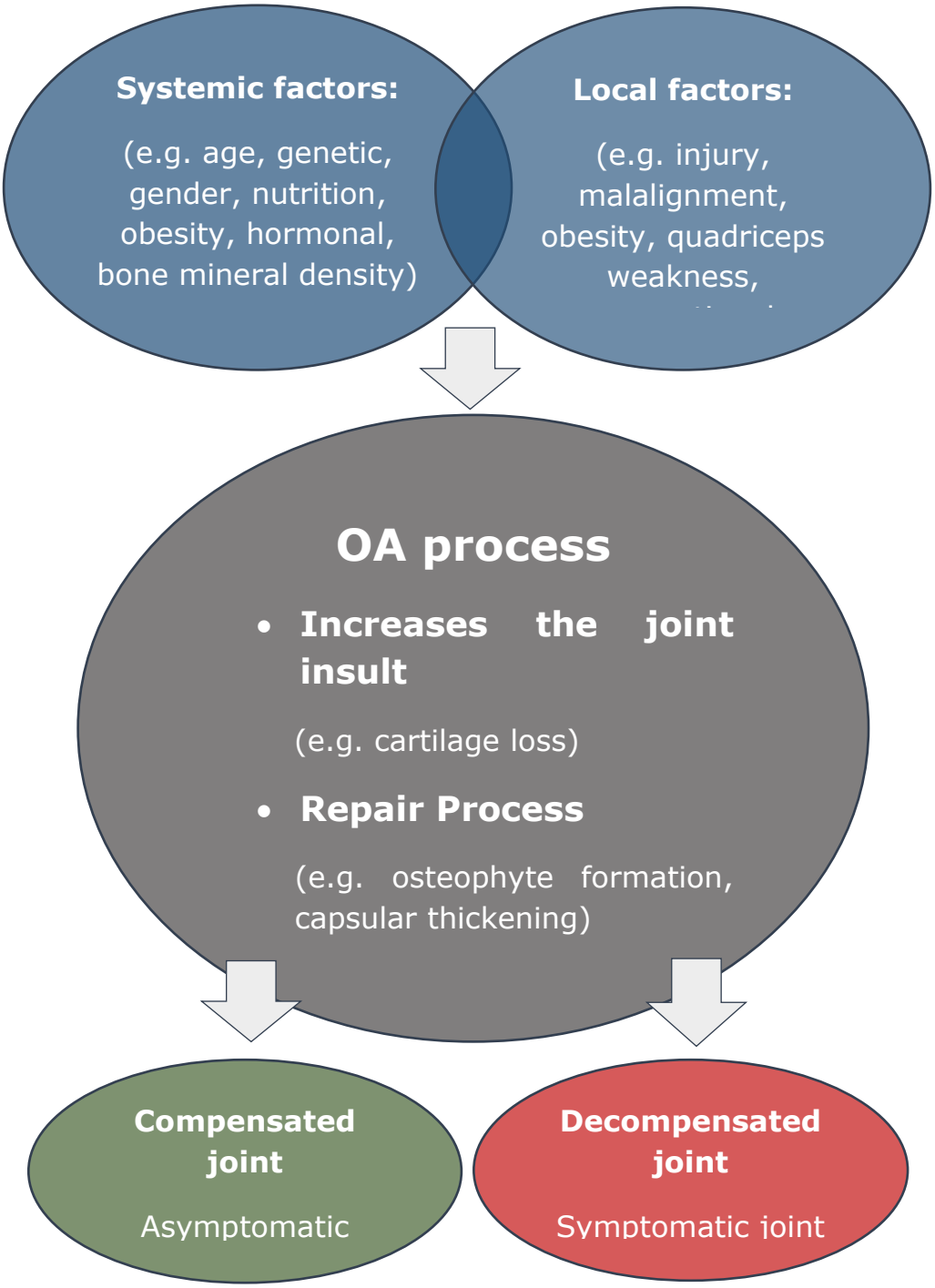
1.2 The natural history and pathology of OA

Until 250 years ago, all rheumatic complaints were considered as "gout" (Dequeker and Luyten 2008). Many efforts were made to differentiate the various form of arthritis from each other. The current title of "OA" was first proposed by A E Garrod in 1890, he explained OA as a separate disorder with features distinguishable from other forms of arthritis (Dequeker and Luyten 2008).

Today, the natural history of OA is regarded as an active and dynamic metabolic process, in which tissues homeostasis of the joint are altered by various mechanical and biological insults (Iannone and Lapadula 2003; Martel-Pelletier 2004). The joint pathology in OA is diverse and includes a combination of new tissue production and tissue attrition (Jones and Doherty 1995). This is characterised by the localised damage and loss of focal hyaline cartilage, increased bone remodelling, new bone formation at the margin of the joint, thickening of synovial membrane, muscle weaknesses, ligamentous laxity, subchondral cyst development, and in some cases low grade inflammation (Arden and Nevitt 2006). Therefore, OA is more a failure of a joint as an organ than a discrete disease entity (Brandt, Dieppe and Radin 2008; Brandt, Dieppe and Radin 2009).

The structural alterations in osteoarthritic joints are a product of attempted repair to an initial insult or damage (Arden and Nevitt 2006). For instance, it is proposed that marginal osteophyte formation and capsular thickening may compensate or minimize the joint instability due the cartilage damage. Hence, OA can be asymptomatic in many individuals (Brandt et al. 2009). Structural alterations in asymptomatic joints are considered as a successful adaptive response to an initial insult (Doherty 2001). This also supports that OA as an inherent repair process of synovial joints (Figure 1-1). However, failure in this process due to an overwhelming insult or compromised repair capacity results in joint symptoms developing (NICE 2008).

Figure 1-1: OA as a complex process of insult and repair triggered by various factors (genetic, constitutional and environmental) and their interactions.



During the symptomatic stage of OA, pain is the most predominant clinical presentation. In the early stages, pain in the hips and knees is generally intermittent and intense. Over time, it becomes chronic and turns into a persistent background ache with episodes of intermittent intense pain (Hawker, Stewart, French et al. 2008). Consequently, pain can have a negative effect on OA patients' function and sleep. Sleep disturbance is associated with greater pain, fatigue and anxiety in OA patients. Loss of range of motion, crepitus and stiffness are the other OA symptoms (Yang, Saris, Dhert et al. 2004). Ultimately, severe pain and movement restriction can lead to significant functional impairment, disability and reduction in QOL of OA patients.

Therefore, OA should be described as a clinical endpoint of several disorders of a joint (Sokolove and Lepus 2013). However, it should not be thought of as a passive and always progressive process which inevitably results in developing symptoms (Dieppe 2011). Instead, OA, particularly knee OA, is a slow process that may take several years to disease evolution. Even once the disease is established, the condition can be stable for several years (Arden and Nevitt 2006). Hence, OA can be defined based on the pathological alteration of joint, the clinical presentation, or a combination of both.

1.3 Diagnosis and classification of OA

OA has historically been classified into idiopathic and secondary categories. Idiopathic or primary OA is defined when an unrecognized reason causes the disease, while OA is classified as secondary when a recognized reason, such as injury, contributes to its development (Altman, Asch, Bloch et al. 1986). However, this classification is unable to reflect the severity of disease. Therefore, various OA biomarkers have been developed to provide clinicians and scientists with more objective details about the disease.

Biomarkers are used as a tool to diagnose OA, evaluate the severity of disease and identify the underlying pathology of the disease process (Mobasheri 2012). One category of biomarkers comprises biochemical and genetic markers. These can be found in the serum, blood, synovial fluid and urine samples. Monitoring the OA biochemical markers may reflect the early changes occurring in various stages of the incidence and progression of disease. However, the vast majority of OA biochemical markers have not been adequately investigated and the role of many of them in diagnosis, incidence and progression of OA require further investigation.

The other category of OA biomarker- that is used more frequently in epidemiological studies of OA risk factors

evaluates the severity of OA based on A: structural changes appearing in magnetic resonance imaging scan (MRI), radiograph or ultrasound scan, and/or B: clinical presentation of the disease such as pain, stiffness, function or QOL of OA patients (Mobasheri 2012).

1.3.1 *Radiographic diagnosis of OA*

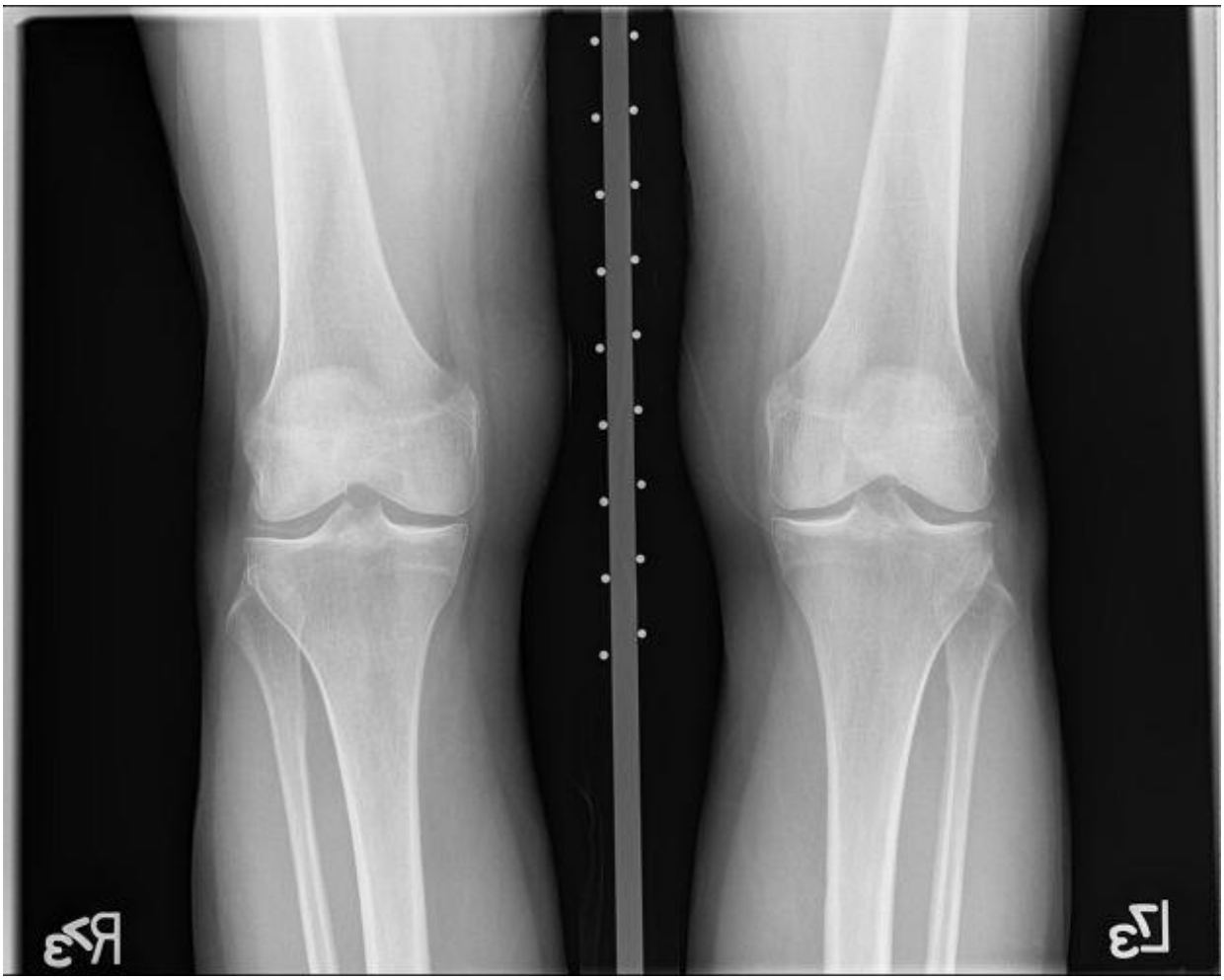
X-ray technology was first invented and introduced in 1895. Later, "hypertrophic" changes were identified as the distinct features of subjects with radiographic OA, whereas atrophic changes were regarded as features of rheumatoid disorders (Dequeker and Luyten 2008). In the 1950s, Kellgren and Lawrence (KL) introduced the first radiographic grading scale for the measurement of severity of OA (Kellgren and Lawrence 1957). This grading scale was approved by the World Health Organization (WHO), following which the first atlas of OA was published in 1961. Hence, for the first time, a scoring system enabled clinicians and researchers across the world to assess the severity of OA (Altman and Gold 2007) (Table 1-1).

Table 1-1: KL radiographic grading scale for the assessment of OA

OA grade	Criteria for the radiographic assessment of OA
0 None	No osteoarthritis
1 Doubtful	Doubtful narrowing of joint space and possible osteophytic lipping
2 Mild	Definite osteophytes and possible narrowing of joint space
3 Moderate	Multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends
4 Severe	Large osteophyte, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends

Obtained from Schiphof et al. (2011, Ann Rheum Disorder: 70:1422-1427)

Figure 1-2: Mild signs of OA (KL2) in medial tibiofemoral compartment in both knees (data from OAI study)

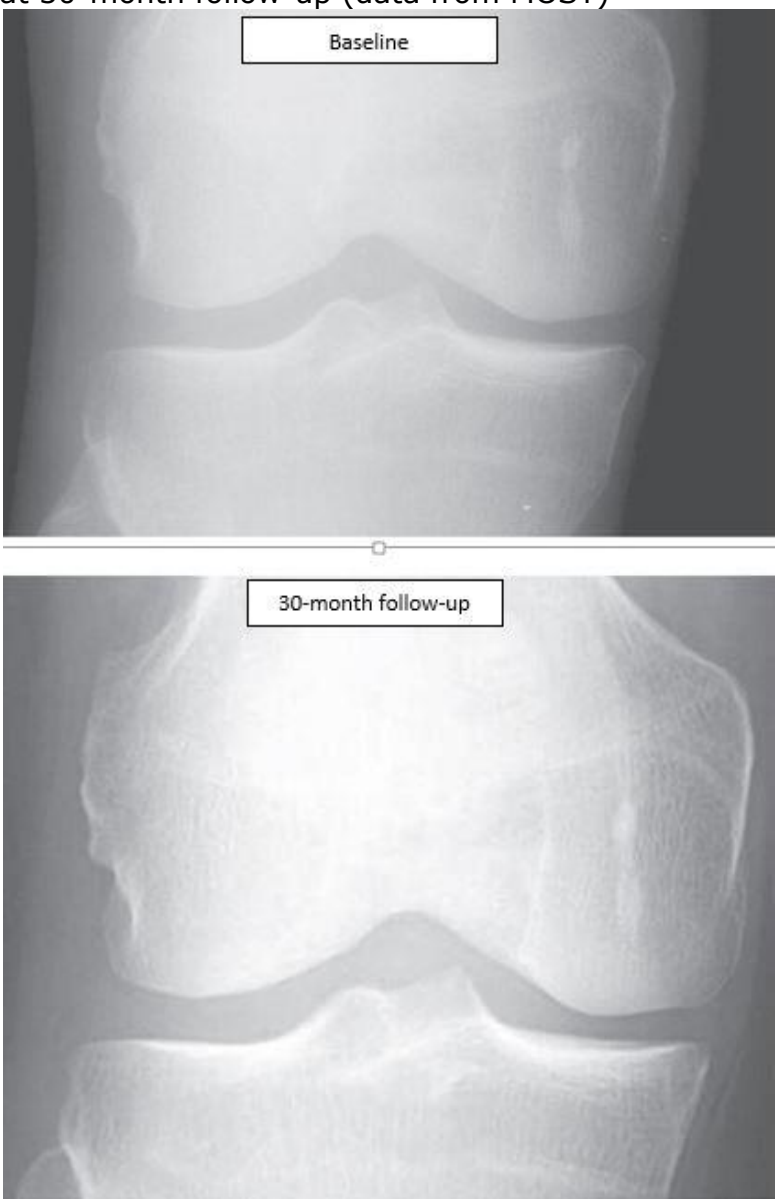


There have been some criticisms of KL classification over the years. One is the inconsistency in descriptions of KL scores. For instance, the WHO originally described the KL2 as "definite osteophyte and possible joint space narrowing (JSN)" (Figure 1-2), whereas several other definitions such as "definite osteophyte with unimpaired JSN" have been found in the literature. Another is the lack of clarity of KL scoring system in defining the new incidence or progression of OA. Conventionally, KL2 has been accepted as the threshold for new incidence of OA. However, the favoring of osteophyte formation over JSN as a diagnosis criterion OA is a limitation.

An osteophyte is a three dimensional structure (Felson, Niu, Guermazi et al. 2011) and might become invisible in a radiograph with slight rotation of joint position (Felson et al. 2011) (Figure 1-3). In addition, cartilage loss is one of the key changes that occur in OA. Hence, the sole consideration of osteophytes as a radiographic feature of OA ignores the significance of cartilage loss and meniscal degeneration, usually indicated radiographically by JSN (Roemer, Eckstein, Hayashi et al. 2014). Some authors have defined progression of OA as a minimum of one grade increase in KL score. However, KL classification seems to be insensitive to identifying many instances of progression, especially in

subjects with KL3. KL3 includes any radiographs with JSN ranging from mild to severe. Therefore, subjects developing a half grade JSN, but not one full grade, will be missed based on this definition (Felson et al. 2011).

Figure 1-3: Visibility of osteophyte at baseline, but it is not visible at 30-month follow-up (data from MOST)



Obtained from Felson et al. 2011 Ann Rheum Dis. 2011 Nov; 70(11): 1884–1886.

Following the criticisms regarding the KL classification, in 1996, Osteoarthritis Research Society International (OARSI) introduced a new atlas of OA using a semi-quantitative scaling system to separately grade radiographic features of OA, such as JSN, osteophytes and subchondral bone sclerosis (Altman, Hochberg, Murphy et al. 1995). In this classification, the severity of JSN and osteophytes are graded based on a 4-point scales (0-3) (Altman and Gold 2007). Specifically, JSN and osteophyte formation can be scored for medial tibiofemoral (TF), lateral TF and patellofemoral (PF) compartments. This compartmental grading scale has also been found to be more sensitive to the longitudinal changes in x-rays compared to KL classification.

Further effort has also been made to enhance the photographic atlases. Line drawing atlas is another validated method developed for the radiographic assessment of JSN and osteophyte formation in TF and PF joints (Nagaosa, Mateus, Hassan et al. 2000; Wilkinson, Carr and Doherty 2005). In this method, the severity of JSN is graded from -3 to 3, -4 to 4, or -5 to 5 (Nagaosa et al. 2000; Wilkinson et al. 2005). Grade 0 represents no JSN, while grade 1, 2, 3, 4 and 5 represent 20%, 40%, 60%, 80% and 100% narrowing (Wilkinson et al. 2005). Accordingly, negative grades reflect joint space

widening. This is similar for the osteophyte growth, but with positive grades. These grades were calculated based on normal joint space width and maximum size of osteophyte in a hospital based knee OA (Nagaosa et al. 2000). Importantly, this method evaluates the severity of JSN and osteophyte formation using the skyline view as the optimal view for assessing the PF joint. Hence, using skyline view and mathematically calculated grades from the maximum size of osteophyte and normal joint space has led to better face and content validity compared to other methods like OARSI or KL classification, in which, respectively either lateral x-ray view was used for the evaluation of PF joint or PF was not assessed at all (Nagaosa et al. 2000; Wilkinson et al. 2005).

1.3.2 *Other imaging methods for diagnosis of OA*

Over the past decade, the development of advanced imaging techniques such as MRI has dramatically enhanced the understanding of OA (Favero, Ramonda, Goldring et al. 2015). Conventional MRI can detect the morphological changes related to early OA, including cartilage damage, meniscal tear, ligament injury, bone marrow lesions, and synovitis (Guermazi, Roemer, Burstein et al. 2011). Compositional MRI has also enabled researchers to progress one step further by detecting the biochemical changes occurring in cartilage and

all joint tissues in the early stages of OA (Guermazi et al. 2011). However, these methods are relatively expensive and time consuming (Roemer et al. 2014). Additionally, some compositional MRI techniques require intravenous injections (Glyn-Jones, Palmer, Agricola et al. 2015). Therefore, these limitations have made the application of MRI scan difficult for wide use in clinical practice and research.

Other novel imaging techniques such as ultrasonography have also been developed over the past years for evaluation of the joint pathologies of OA especially synovitis (Joshua, Lassere, Bruyn et al. 2007; Keen, Wakefield and Conaghan 2009). However, utilizing the ultrasound in research has its own limitations such as inability to demonstrate intrinsic bone abnormalities (i.e. bone marrow lesson) or its operator-dependency (Keen and Conaghan 2009; Favero et al. 2015). Overall, radiography and KL classification is still the most common imaging method used in OA research in spite of all these advancements (Braun and Gold 2012).

1.3.3 *Clinical Diagnosis of OA*

Despite the advancements in imaging techniques, the clinical features of symptomatic OA do not strongly correlate with the imaging evidence of the condition (Duncan, Peat, Thomas et al. 2007; Javaid, Kiran, Guermazi et al. 2012). There are still many symptomatic cases where radiographs do not show any significant structural changes, and many asymptomatic people have high prevalence of abnormalities in their radiograph or MRI scans (Williams and Spector 2006; Bedson and Croft 2008; Guermazi, Niu, Hayashi et al. 2012). Therefore, imaging approaches alone may not precisely reflect the clinical burden of OA. Instead, considering the clinical features of symptomatic OA in diagnosing the condition can be an alternative approach to this issue. In 1981, the American College of Rheumatology (ACR) established a subcommittee to develop classification criteria for the clinical diagnosis of patients with symptomatic OA (Altman et al. 1986). ACR criteria are mainly based on symptoms, clinical signs, and/or radiographs/laboratory findings. Pain on most days of the previous month is the main inclusion criterion of this classification. The other criteria, of which three are required to establish the diagnosis of clinical knee OA, are age >50, stiffness <30 minutes, crepitus during active movement, bony tenderness, bony enlargement, and no palpable warmth

(Altman et al. 1986). Similarly, The European League Against Rheumatism (EULAR) recommendation, considered the most useful signs and symptoms for the clinical diagnosis of knee OA, is based on presentation of three clinical signs (crepitus, bony enlargement and restricted movement) and three clinical symptoms (persistent pain, reduced function and limited morning stiffness) (Zhang, Doherty, Peat et al. 2010).

However, both ACR and EULAR classifications seem to be more appropriate for more severe cases than for subjects with early stage disease. In addition, the simple definition of the symptom used in these classifications does not precisely reflect the intensity, duration or frequency of pain. Therefore, other instruments such as Knee Injury and Osteoarthritis Outcome Score (KOOS), Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Oxford Knee Score (OKS) have been developed and validated for the evaluation of the symptoms in patients with knee OA. There are however limitations in the application of these tools. First, there is either limited or no normative data for these instruments to compare the scores in OA versus non-OA patients. Furthermore, there is no established cut-off point for defining the incidence of symptomatic OA using these measures. Hence, these methods are mainly used in clinical trials to

measure the outcomes of interventions rather than to define the incidence of symptomatic OA.

Despite the strengths and weaknesses of all the classifications and measures discussed above, the application of the "frequent knee symptoms" (knee pain, ache and stiffness on most days in the past month) in combination with the radiographic evidence of OA (KL classification) has remained as the hallmark of defining symptomatic knee in most OA research. The "frequent knee symptoms" definition has also been validated and highly correlated with the WOMAC activity-related pain score, activity limitation and evidence of radiographic OA (Felson and Nevitt 2004).

1.4 Epidemiology of OA

Several epidemiological studies have been conducted to identify the prevalence of OA and its predictors over the past decades. According to the WHO, approximately 10% of men and 18% of women over the age of 60 suffer from symptomatic OA worldwide. Prevalence of OA is higher in the US and European countries reportedly (Woolf and Pfleger 2003). 40 million individuals in Europe suffer from clinical OA (Conaghan et al. 2014), as do 27 million in the US (Lawrence, Felson, Helmick et al. 2008). The OA figure for the UK is also reported at 8.75 million people (Arthritis Research UK 2013).

From a meta-analysis study of seventy-two papers, overall prevalence rates for hand, knee and hip OA in adults are estimated at 43%, 24% and 11% respectively (Pereira, Peleteiro, Araujo et al. 2011). However, the estimate rates vary greatly among OA studies depending on the case definition of OA and the study population.

In most population-based studies, symptomatically diagnosed OA is less prevalent than radiographically diagnosed OA (Johnson and Hunter 2014). From UK data, the prevalence of radiographic hand, knee and hip OA are 41%, 25% and 11% respectively. However, the estimates are lower for the prevalence of symptomatic knee (18%), hip (0.7-4.4%) and

hand OA (2.5%) (Arden and Nevitt 2006; NICE 2008). This is because symptomatic OA has been typically defined by the presence of symptoms in combination with the radiographic evidence of OA (Johnson and Hunter 2014).

Prevalence of OA also varies in studies with different study populations. The prevalence of radiographic and symptomatic knee OA was 19% and 7% respectively in adults aged 45 and over in the Framingham OA study (Lawrence, Felson, Helmick et al. 2008), and 28% and 17% respectively in the Johnston County OA project (Lawrence et al. 2008). Among older adults in the Framingham OA study, the prevalence of radiographic and symptomatic knee OA rose respectively to 44% and 11% in people aged 80 and over. In the Johnston County OA project this increased to 50% for radiographic knee OA and 33% for symptomatic knee OA in people aged 75 years or older (Suri, Morgenroth and Hunter 2012). Thus, this shows that the prevalence of symptomatic and radiographic knee OA is higher in the older population.

OA is also a concern in Asian countries as their longevity increases. It is reported that the prevalence of symptomatic knee OA is significantly higher in adults living in the rural communities of China, Japan and India compared to urban regions. In these countries, rural populations are involved with

significantly higher levels of heavy occupational activity such as prolonged kneeling, climbing, standing and lifting heavy weight (Fransen, Bridgett, March et al. 2011). Higher prevalence of OA is also reported in the affluent population of Pakistan when compared to the poor population, which has been attributed to rising obesity in wealthier families (Gibson, Hameed, Kadir et al. 1996). Therefore, cultural lifestyle in different regions seems to have an impact on the prevalence of OA.

Prevalence of OA also varies amongst populations with different races and ethnicities. The Johnston County OA project (Jordan, Helmick, Renner et al. 2007) and the National Health and Nutrition Examination Survey III (NHANES) study (Dillon, Rasch, Gu et al. 2006) both showed a higher prevalence of radiographic and symptomatic knee OA in black Americans. Furthermore a study comparing the prevalence of OA between the Chinese population and the Framingham OA population showed that the prevalence of symptomatic and radiographic knee OA was higher in Chinese people compared to white Americans (Zhang, Xu, Nevitt et al. 2001). In contrast, the prevalence of hip (Nevitt, Xu, Zhang et al. 2002) and hand OA (Zhang, Xu, Nevitt et al. 2003) in the Chinese were considerably lower than white Americans. Hence,

prevalence of OA varies among different populations due to the variations in age and ethnicity structures as well as differences in life styles.

1.5 Risk factors for OA

The biological or physiological aetiology of OA is largely unknown. However, multiple risk factors for the development and progression of the disease have been identified. OA risk factors can be divided into the two main categories of systemic and local factors (Suri et al. 2012). Local factors are predominantly biomechanical and comprise abnormal or excessive mechanical stress to joints. It includes joint injury, occupation, sport, constitutional malalignment, and excessive load due to obesity. In contrast, systemic factors increase the propensity of joints to injury by direct damage to the joint or reduction in the joint tissue's ability to respond adequately to stresses (Litwic et al. 2013). Examples of systemic factors are age, gender, ethnicity/race, metabolic factors (obesity), nutrition, bone mineral density (BMD) and genetic factors.

There are also other risk factors that are recently identified. For instance, Zhang and colleagues have found an association between the index to ring finger (2D:4D) length ratio (pattern 3 where ring length>index length) and an increased risk of radiographic knee OA. However, the role of such risk factors

on the risk of OA requires more investigation (Zhang, Robertson, Doherty et al. 2008).

Of the systemic risk factors, the heritable component of OA is well documented (Loughlin 2015). From studies of twins in the UK, the heritability of OA is estimated to be 39%, 60% and 65% of the risk of knee, hip and hand OA respectively (Spector, Cicuttini, Baker et al. 1996; MacGregor, Antoniades, Matson et al. 2000; Spector and MacGregor 2004). It has also been found that the risk of knee OA is two to three times higher in siblings of people with knee OA compared to the general population (Neame, Muir, Doherty et al. 2004; Spector and MacGregor 2004). This highlights the large heritable component of OA.

Several genetic studies have also attempted to identify OA susceptibility genes. The growth differentiation factor 5 (GDF5) is one of the OA susceptibility genes which has been repeatedly found across European and East Asian cohort studies (Suri et al. 2012; Tsezou 2014). A large scale meta-analysis of OA genetic studies has also conferred a strong link between GDF5 and the risk of knee OA (Evangelou, Chapman, Meulenbelt et al. 2009). However, OA heredity is polygenic in nature (Valdes and Spector 2008; Panoutsopoulou, Southam, Elliott et al. 2011) and many genes contributing to the

susceptibility of the disease have not yet been discovered (Tsezou 2014).

Other systemic risk factors include age, gender, race/ethnicity and BMD. Of those, age is one of the strongest factors for the risk of OA (Dagenais, Garbedian and Wai 2009). The majority of the population has evidence of radiographic OA by the age of 65, increasing to 80% in people aged 75 years and over (Arden and Nevitt 2006). Previous meta-analysis investigating the association of age and the risk of knee OA was unable to create a pooled odds ratio (OR) for the relationship between OA and age due to the heterogeneity in the age classification across studies. However, a consistent trend is seen across studies indicating a sharp increase in the risk of OA between the age of 50 and 80 but a level-off or decline in those over age 80.

Age affects the cell's ability to maintain the articular tissues' homeostasis in response to excessive or abnormal mechanical stresses (Anderson and Loeser 2010). Thus, age increases the joint susceptibility to OA. However, the nature of OA is multifactorial rather than a simple consequence of joint tissue aging (Anderson and Loeser 2010). Therefore, OA develops only when other local and systemic factors become involved (Anderson and Loeser 2010).

Many large-scale population based studies of OA risk factors have also shown a higher risk of OA in women than men (Oliveria, Felson, Reed et al. 1995; Allen and Golightly 2015; Plotnikoff, Karunamuni, Lytvyak et al. 2015). A meta-analysis of sex differences in 34 population-based studies has shown that the incidence of knee, hip and hand OA were higher in women than men, in particular after the age of 55 years (Srikanth, Fryer, Zhai et al. 2005). In addition, results from another systematic review and meta-analysis of 11 cohorts reported a greater risk of knee OA in women than men with a pooled OR of 1.63 (95% confidence interval(CI): 1.37 - 2.07) (Silverwood, Blagojevic-Bucknall, Jinks et al. 2015). However, the gender differences in OA mainly appear at the sixth decade around the age of menopause (Felson and Hodgson 2014). This indicates the contribution of age in the sex differences (Plotnikoff et al. 2015). It has also raised questions regarding the role of oestrogen in development of OA (Felson and Hodgson 2014). Findings from observational studies and control trials have been inconsistent (Wluka, Cicuttini and Spector 2000; Neogi and Zhang 2013). Some studies support the protective effect of hormone replacement therapy against knee, hip and hand OA, while some others including systematic reviews showed either limited or no clear association (Spector, Nandra, Hart et al. 1997; Nevitt, Felson,

Williams et al. 2001; Cirillo, Wallace, Wu et al. 2006; de Klerk, Schiphof, Groeneveld et al. 2009; de Klerk, Schiphof, Groeneveld et al. 2009).

In general, factors such as age, gender, ethnicity or race are immutable. However, identifying the modifiable risk factors contributing to the incidence and progression of disease may help to prevent or slow down the development or progression of the disease. Obesity, injury and physical activity are three main modifiable factors and their relationships with knee OA will be discussed in more detail in the next section.

1.6 Obesity and knee OA

Obesity and overweight are the terms used to explain the accumulation of excessive body fat (WHO 1998). Obesity and overweight can be described by various classifications based on the weight and body fat measures. Dual energy x-ray absorptiometry is one of the most precise methods for the measurement of body composition including lean and fat mass (Laskey 1996; Rothney, Brychta, Schaefer et al. 2009). However, it is prohibitively expensive and time consuming for population studies (Klein, Allison, Heymsfield et al. 2007). Therefore, other techniques such as measurement of waist circumference, waist hip ratio and body mass index (BMI) have been developed as cheap alternatives (Lean, Han and

Morrison 1995; Seidell, Pérusse, Després et al. 2001; Klein et al. 2007).

Of these, BMI is the common method of describing the body size (Dalton, Cameron, Zimmet et al. 2003). It is calculated based on adult body weight (kg) divided by height squared (m^2). WHO has determined the cut-off point criteria for obesity and overweight in adults based on the association of BMI with mortality. This is defined as underweight (BMI < 18.5 kg/m^2), normal (BMI 18.5-24.99 kg/m^2), overweight (BMI 25.0- 29.99 kg/m^2) and obese (grade I: BMI 30-34.99 kg/m^2, grade II BMI 35-39.99 kg/m^2, grade III BMI ≥ 40 kg/m^2) (WHO 1998). This classification has also been used extensively in population studies of OA risk factors.

The relationship between obesity and the risk of knee OA was initially determined based on the US data from the NHANES I and Framingham Heart Cohort study (Anderson and Felson 1988; Felson, Anderson, Naimark et al. 1988). NHNS I first highlighted that the risk of radiographic knee OA was four to five times higher in people with BMI ≥30 compared to those with normal BMI (Anderson and Felson 1988). Later, findings from the Framingham study also showed a substantial increase in the risk of knee OA in obese people, with a stronger association in women (relative risk (RR): 2.07,

95%CI: 1.67 to 2.55) than men (RR: 1.51, 95%CI: 1.14 - 1.98) (Felson et al. 1988).

The Framingham Study continued for another 8 years (Felson, Zhang, Hannan et al. 1997). Weight-bearing anteroposterior radiographs of the knees in 979 participants without knee OA at baseline were obtained again in 1994. After adjusting for multiple confounders, the results showed a 60% rise in the risk of knee OA with every 5-unit increase in BMI (adjusted OR (aOR): 1.6 per 5 unit BMI, 95% CI: 1.2 - 2.2), or a 40% rise in risk of knee OA for every 10 pounds increase in weight (aOR: 1.4 per 10-lb increase, 95% CI: 1.1 - 1.8). In this study, high BMI was a risk factor for both PF-OA (aOR: 3.7), and TF-OA (aOR: 1.9) (McAlindon, Zhang, Hannan et al. 1996). Therefore, findings of the Framingham Study highlight a strong link between obesity and the increased risk of knee OA in the elderly population (mean age: >73 years).

A similar association between obesity and the risk of knee OA has also been observed in middle aged populations (Spector, Hart and Doyle 1994). Data from the Chingford Study, a cohort of 1003 women, showed that 5kg increase in baseline weight was also associated with 35% increase in the risk of knee OA (Hart, Doyle and Spector 1999). Likewise, a longitudinal study of Finnish farmers including middle-age men

and women followed over a 10-year period showing a 40% rise in the risk of disabling knee OA per 3.8-unit increase in BMI (RR: 1.4, 95%CI: 1.2 - 1.5) (Manninen, Riihimaki, Heliovaara et al. 1996). Similar association between obesity and the risk of total knee replacement (TKR) in middle-age women has been reported (RR: 2.47, 95%CI: 2.11 - 2.89) (Liu, Balkwill, Banks et al. 2007). Other large population based studies of 1675 Norwegian and 27,960 Swedish people followed for 10-11 years also reveal similar findings in the middle-age individuals (Grotle, Hagen, Natvig et al. 2008; Lohmander, Gerhardsson de Verdier, Rollof et al. 2009). In the Norwegian study, obese individuals (BMI >30) were at almost 3 times greater risk of symptomatic knee OA (aOR: 2.81; 95%CI: 1.32 - 5.96) (Grotle et al. 2008); in the Swedish cohort study, obesity was associated with an 8 fold increase in the risk of severe knee OA required TKR (RR: 8.1, 95%CI: 5.3 - 12.4) (Lohmander et al. 2009). Hence, middle-age obesity is strongly linked with greater risk of knee OA in later life.

Evidence is also consistent regarding the correlation between early life adiposity and the risk of knee OA in later life. “The Genetic of Osteoarthritis and Life Style” study (GOAL) which was a large database of 1042 knee OA cases and 1121

controls showed a dose-response relationship between lifetime BMI and the risk of severe knee OA, with the highest risk among those who were overweight in their 20s (Holliday, McWilliams, Maciewicz et al. 2011). Data from Johns Hopkins Precursors Study also indicated that high BMI at the ages of 20-29 were significantly associated with a greater risk of symptomatic knee OA in a 36-year follow-up (RR: 1.7 per 2.7-unit increase in BMI, 95%CI: 1.3-2.1) (Gelber, Hochberg, Mead et al. 1999).

Today, the relation between high BMI and the increased risk of knee OA has been broadly reported by numerous population-based studies of OA risk factors in the UK, Netherlands, Sweden, Japan, and many other countries (Hochberg, Lethbridge-Cejku, Scott et al. 1995; Cicuttini, Baker and Spector 1996; Cooper, Snow, McAlindon et al. 2000; Manek, Hart, Spector et al. 2003; Holmberg, Thelin and Thelin 2005; Jarvholm, Lewold, Malchau et al. 2005; Reijman, Pols, Bergink et al. 2007; Sudo, Miyamoto, Horikawa et al. 2008; Nishimura, Hasegawa, Kato et al. 2011). This finding has also been conveyed by a meta-analysis, in which the pooled OR for the risk of knee OA in obese (BMI ≥30) compared with a normal BMI was 2.63 (95%CI: 2.28 - 3.05); for overweight compared with normal BMI was 2.18 (95%CI: 1.86 - 2.55);

and for obese and overweight combined when compared with normal BMI was 2.96 (95%CI: 2.56 - 3.43) (Blagojevic, Jinks, Jeffery et al. 2010). Another meta-analysis of observational studies has also confirmed the dose response relationship between increase in weight and higher risk of knee OA. This meta-analysis reported that a 5-unit increase in BMI was associated with a 35% rise in the risk of knee OA (RR: 1.35, 95%CI: 1.21 - 1.51) (Jiang, Tian, Wang et al. 2012). Hence, obesity has a significant role in increasing the risk of knee OA.

1.7 Physical activity and knee OA

Physical activity is defined as "any bodily movement produced by skeletal muscles that result in energy expenditure" (Caspersen, Powell and Christenson 1985). It can be classified in various ways. In the general population, a simple way to categorize physical activity is by splitting it into occupational and non-occupational physical activity groups (British Heart Foundation 2012). Occupational physical activity comprises any activity according to the job demands of individuals (i.e. working with computers, driving and mining). Non-occupational physical activity consists of any type of day-to-day physical activity outside of the work environment. This ranges from sedentary activity, such as sitting, watching TV and reading the newspaper, to casual physical activity in/out

of leisure such as gardening, playing basketball, volleyball or other sports with various intensities.

Evidence is consistent with respect to the role of occupational physical activity on the risk of knee OA. A Japanese occupational OA study showed a higher prevalence of knee OA amongst agricultural, fishery, and forestry workers (Muraki, Akune, Oka et al. 2009). OA studies of white populations have also shown a high risk of knee OA in individuals whose job requires frequent squatting, kneeling, heavy weight lifting or frequent knee bending activities (Felson, Hannan, Naimark et al. 1991; Cooper, McAlindon, Coggon et al. 1994; Coggon, Croft, Kellingray et al. 2000). This finding has also been confirmed by systematic reviews of the studies that looked at the association between occupational activity and risk of knee OA (Maetzel, Makela, Hawker et al. 1997; Vignon, Valat, Rossignol et al. 2006).

However, the evidence is less clear with regard to the role of non-occupational physical activity on the risk of knee OA. Heavy physical activity for more than four hours/day in the elderly population of the Framingham study was shown to increase the risk of knee OA (McAlindon, Wilson, Aliabadi et al. 1999). Meanwhile, other studies have reported no association between habitual physical activity during middle age and knee

OA in later life (Hannan, Felson, Anderson et al. 1993). Some evidence also shows the protective effect of moderate exercise on the risk of knee OA (White, Wright and Hudson 1993; Manninen, Riihimaki, Heliovaara et al. 2001). Regarding the role of more intense exercise on knee OA risk, the results of some studies support that elite or amateur long distance runners are not at higher risk of knee OA (Lane, Bloch, Jones et al. 1986; Konradsen, Hansen and Sondergaard 1990). However, others have reported an increased risk of knee OA in long distance runners (Spector, Harris, Hart et al. 1996), cross country skiers (Michaelsson, Byberg, Ahlbom et al. 2011) footballers and weight lifters (Kujala, Kettunen, Paananen et al. 1995). This controversy in the literature could be explained by a number of reasons such as type, intensity and duration of activity, study design (i.e. prospective cohort study, case-control etc.), recording of the life time physical activity or physical activity at one time point, and using various definitions of knee OA (i.e. self-diagnosis, total joint replacement etc.).

1.8 Injury and knee OA

Participation in recreational activity or competitive sports could place individuals at higher risk of overuse and traumatic injuries (Yang, Bowling, Lewis et al. 2005). In studies of OA

risk factors, various definitions of injury are seen. Some studies used a simple and non-specific definition of injury, in which impaired weight bearing was considered as evidence of injury (Muthuri, McWilliams, Doherty et al. 2011). Such non-specific definition included both severe and less severe injuries. In other studies, injury definition was more specific as defined by the type of injury such as anterior cruciate ligaments rupture (ACL), meniscal tear, articular cartilage damage or fracture.

In one of the earliest studies of OA risk factors (Felson et al. 1997), non-specific knee injury was not found to be a risk factor for knee OA (aOR: 0.7, 95% CI: 0.1 - 3.2). Similarly, a 4-year prospective study of women from the Chingford cohort (Hart et al. 1999) did not show a significant association between injury and the risk of knee OA. The reason why these studies failed to show any significant associations was mainly due to the inclusion criteria and inadequate follow-up. For instance, participants with knee OA at baseline were excluded from studies. Thus, injured participants who had possibly developed knee OA before baseline were not accounted in the risk assessment, and the follow-up for the remaining injured participants possibly was not long enough to develop knee OA.

However, studies with long-term follow-up and large sample size have shown a strong relationship between injury and the increased risk of knee OA. A cohort study of 8000 Finnish people found the risk of knee OA was five-fold higher at 22 years follow-up in participants with baseline knee injuries (aOR: 5.1 95%CI: 1.4 - 19.0) (Toivanen, Heliovaara, Impivaara et al. 2010). A prospective study of 1321 former medical students followed for 36 years also showed that the baseline joint injury was associated with a three-fold increase in the risk of symptomatic knee OA (RR: 2.95, 95% CI: 1.35 – 6.45). This association was even stronger when injuries during follow-up were added into the analysis (RR: 5.17, 95% CI: 3.07 to 8.71) (Gelber, Hochberg, Mead et al. 2000).

Similarly, a strong association was found in a prospective cohort study of 1436 adults aged 40 years old and over, in which participants with acute knee injuries were at a 7-times higher risk of knee OA compared to uninjured counterparts. (Wilder, Hall, Barrett Jr et al. 2002). NHANES I data also indicated a significant increase in the risk of radiographic knee OA in participants with acute knee injuries (Davis, Ettinger, Neuhaus et al. 1989). In this study, acute injury was defined as a history of fracture, severe knee twisting that was

associated with swelling for ≥2 weeks, or any other knee injuries associated with pain for most days of a month.

Previous injuries have been reported also as the potential reason for the increased risk of knee OA in former football players and ex-weight lifters (Kujala et al. 1995). A high prevalence of radiographic knee OA was reported in male football players who sustained ACL injury 14 years earlier (von Porat, Roos and Roos 2004). A long term follow-up study of female footballers with ACL injury also showed similar findings, where radiographic changes, pain and functional limitation were highly prevalent at 12 years post-injury (Lohmander, Ostenberg, Englund et al. 2004).

Specifically, ACL injury is a strong risk factor for developing knee OA. A review of OA risk factors in patients with ACL rupture has shown a substantial increase in the prevalence of knee OA at 20 year follow-up in both surgically (14%-37%) or non-surgically treated participants (60%-100%) (Louboutin, Debarge, Richou et al. 2009). This was confirmed by a meta-analysis study, in which the risk of knee OA was significantly higher in ACL injured participants treated non-operatively (RR: 4.98, 95%CI: 2.45 - 10.15) and operatively (RR: 3.62, 95%CI: 2.40 - 5.47) (Ajuied, Wong, Smith et al. 2014). A systematic review of 20 studies also found the presence of OA

biomarkers in ACL deficient or reconstructed participants (Harkey, Luc, Golightly et al. 2015).

The worst clinical outcomes are seen when ACL injury is associated with chondral or meniscal injury (Shelbourne and Gray 2000). A systematic review of 31 studies with a minimum follow-up of 10 years has revealed the prevalence of knee OA in subjects with isolated ACL rupture was 0%-13% as compared to 21%-48% in subjects with combined ACL and meniscal injuries (Oiestad, Engebretsen, Storheim et al. 2009).

Meniscal tear regardless of treatment types and extent of damage is also another significant contributor to the risk of knee OA. Numerous studies have reported the relationship between meniscal injury and the increased risk of radiographic and symptomatic knee OA (Englund and Lohmander 2004; McDermott and Amis 2006; Englund, Niu, Guermazi et al. 2007; Salata, Gibbs and Sekiya 2010). In surgically treated subjects, the risk of symptomatic knee OA has been reported as 7 times higher for degenerative meniscal tear and 3 times higher for traumatic tear during a 16 year follow-up (Englund, Roos and Lohmander 2003). Similarly, in non-surgically treated subjects, minor and severe degenerative meniscal tears have been found to substantially increase the risk of

knee OA in middle aged and older people (Englund, Guermazi, Roemer et al. 2009). A systematic review of partial meniscectomy studies also indicated a substantial increase in the risk of knee OA 8-16 years after arthroscopy (Petty and Lubowitz 2011). Total meniscectomy is associated with even worse long-term clinical and radiographic outcomes than partial or limited meniscectomy (Englund, Roos, Roos et al. 2001; Papalia, Del Buono, Osti et al. 2011). Hence, meniscal injury has a key role in increasing the risk of knee OA.

Overall, the current evidence conveys a strong association between knee injury and the increased risk of knee OA. This has been confirmed by a meta-analysis of 20,997 participants from 24 observational studies included 7 cohort studies, 5 cross-sectional studies and 12 case controlled studies. The overall pooled OR for the association between injury and the risk of knee OA was 4.20 (95%CI 3.11 - 5.66), with the OR of 5.95 (95%CI: 4.57 - 7.75) for specified injury and OR of 3.12 (95%CI: 2.17 - 4.50) for non-specified injury (Muthuri et al. 2011).

1.9 Study rationale

Given the strong relationship between obesity and knee OA, and the increasing prevalence of obesity globally over the last two decades (Yoshiike, Seino, Tajima et al. 2002; Flegal, Carroll, Ogden et al. 2010), the individual, social, medical and economic burden of knee OA is likely to increase. Clearly, obesity prevention strategies are crucial to at least delay or slow down the incidence/progression of knee OA (as well as other morbidities associated with obesity). If obesity prevalence were reduced by 1%, it would result in a £50 million reduction in healthcare costs (Scarborough, Bhatnagar, Wickramasinghe et al. 2011).

For overweight and obese people, weight loss is one of the main recommended strategies to prevent OA or slow down the disease progression. It is reported that a 5kg weight loss could decrease the risk of knee OA by 50% approximately (Felson, Zhang, Anthony et al. 1992). Given physical activity can aid weight loss, promoting the physical activity is vital to the public health strategy in the UK. However, physical activity may have an adverse effect on the risk of knee OA due to substantial acute or chronic injury to the joints. Moreover, many people question whether physical activity will increase

the risk of knee OA in those who are obese/overweight or suffer a knee injury.

Therefore, understanding the interaction between various modifiable risk factors, in particular obesity, injury and physical activity, will allow the exploration of the underlining mechanism leading to the incidence and progression of disease. It will also enable the identification of the high risk groups and consequently aid the development of appropriate prevention strategies. To the best of our knowledge, there is limited or no investigations that have looked at the various interactions between physical activity, obesity and injury on the risk of knee OA.

Assessing the outcomes of knee treatment is also crucial in both clinical practice and research to understand how well patients have recovered in response to a particular treatment (Dawson and Carr 2001). Typically, validated questionnaires are used to evaluate the functionality of the knee after various treatments such as surgery or rehabilitation (Dawson, Fitzpatrick, Murray et al. 1998; Roos and Lohmander 2003). Therefore, understanding the effect of various OA factors in particular modifiable ones such as physical activity, obesity, and injury on the treatment outcomes is valuable information for optimizing the effect of treatments. In addition, having

normative data for the treatment outcomes (knee pain, function and QOL) would be useful in examining the optimal recovery expected to be achieved in patients with knee problems. However, no such data have been examined in the UK population to date.

1.10 Thesis aims

The principal aim of this study is to examine the association of physical activity, obesity and injury on the risk of knee OA. More specifically:

1. To examine the effect of interactions between physical activity, obesity and injury on knee OA;
2. To establish normative data for knee pain, symptoms, function and knee related QOL as the clinical outcome measures in assessing people with knee OA and to examine their associations with OA risk factors including obesity, injury and physical activity.

1.10.1 *Objectives (Aim 1)*

Using the Osteoarthritis Initiative (OAI) and Multicenter Osteoarthritis Study (MOST) datasets:

1. To identify the effects of two-way and three-way interactions between physical activity, obesity and knee injury

on the incidence of radiographic and separately symptomatic knee OA;

2. To identify the effects of two-way and three-way interactions between physical activity, obesity and knee injury on the progression of radiographic and separately symptomatic knee OA;

3. To compare and contrast the interaction analysis results of incident and separately progressive radiographic and symptomatic knee OA in the OAI and MOST dataset.

1.10.2 *Objectives (Aim 2)*

Collecting primary data in the Nottinghamshire area ("Nottingham Knee Study") regarding self-reported knee complaints using KOOS and OKS questionnaires:

1. To establish age and gender specific normative knee data for the KOOS subscales of knee pain, symptoms, function in daily living, function in sport and recreation and knee related QOL;
2. To establish age and gender specific normative knee data for OKS and its subscales of knee pain and function;

3. To examine the association of obesity, injury and physical activity with self-reported knee complaints assessed by KOOS and OKS.
4. To examine the association of obesity, injury and physical activity with the risk of clinical knee OA in the Nottinghamshire area and compare self-reported knee complaints measured by KOOS and OKS in individuals with and without clinical knee OA.

2 Methodology

This chapter is divided into two main sections, namely: "Interaction analysis study" and "Nottingham Knee Study". Each section describes the methods employed in this project to achieve the aims of this thesis.

2.1 Interaction analysis study

This section describes the existing cohorts data used in this project for the analyses of interactions between physical activity, obesity and injury on the risk of knee OA. This part begins by describing the choices of databases, their study populations and recruitment procedures. It continues by explaining the clinical and imaging variables that were measured in the original cohorts and were used for the purpose of this study. Finally, the statistical methods employed for the analyses of interactions are described in detail. The ethical approval obtained for conducting the project is also presented for each part of the study.

2.1.1 *Data sources*

TwinsUK, GOAL, Chingford 1000 Women Study, Medical Research Council Hertfordshire Cohort Study (MRC-HCS), OAI, MOST, Research on Osteoarthritis/Osteoporosis Against Disability (ROAD), and Rotterdam are examples of databases used for OA studies worldwide. This study used data from cohorts that collected data on physical activity, obesity, injury and OA. TwinsUK and GOAL databases could not be used for this project because physical activity and injury were not collected. Chingford and HCS had other weaknesses: limited number of participants at follow-up, only female gender (Chingford) or no knee musculoskeletal follow-up in HCS. Rotterdam and ROAD databases were not available to use. Thus, the remaining databases that could be used for this project were OAI and MOST. These databases have a high number of participants with data on physical activity, injury, obesity and OA. More importantly, these databases were specifically designed to investigate the incidence and progression of knee OA. Therefore, this study used existing American cohort data of OAI and MOST to examine the interactions between physical activity, obesity and injury on the risk of knee OA.

2.1.2 *OAI database*

OAI is a longitudinal study of incidence and progression of knee OA risk factors in men and women aged between 45-79 years. Between 2004 and 2006, 4796 participants with a diverse ethnic background were recruited from the four communities of Columbus, Ohio; Baltimore, Maryland; Pittsburgh, Pennsylvania and Providence, Rhode Island in the US. Ethnic minorities made 19% of the cohort (Nevitt, Felson and Lester 2006).

At baseline (2004-06), OAI recruited individuals with or at high risk of developing symptomatic knee OA, plus a small subset of participants without any knee OA risk factors. The risk factors allowing for eligibility into the high risk group were frequent knee symptoms, overweight, history of knee surgery, family history of TKR, Heberden's nodes, frequent knee bending activity, age 70-79 and history of knee injury causing difficulties in walking ability for at least one week. This eligibility criterion was age-specific, in which younger participants required to have more risk factors for eligibility compared to older participants (Table 2-1). Exclusion criteria were bilateral TKR, candidate for bilateral TKR, any type of inflammatory joint disorders, contraindication to MRI scan,

positive pregnancy test and bilateral severe JSN (OARSI grade 3).

Table 2-1: Age-specific eligibility criteria in OAI

Age(years)	Inclusion criteria
45-49	Having frequent knee symptoms, or frequent use of medication for knee symptoms, **Plus** having one or more other OA risk factors*
50-69	Having frequent knee symptoms, or frequent use of medication for knee symptoms, or being overweight, or having two or more other OA risk factors*
70-79	Having frequent knee symptoms, or frequent use of medication for knee symptoms, or having one or more other OA risk factors*
* overweight, history of knee surgery, family history of total knee replacement, heberden's nodes, frequent knee bending activity, and knee injury causing difficulties in walking ability for at least one week.	

The OAI study collected clinical, radiographic images and biospecimen data at baseline assessment. Radiological assessments included x-rays and MRI scans of knee joints. Clinical evaluation data obtained via questionnaire and examination. The questionnaire contained the following measures: demographics; employment status; knee symptoms; function and QOL; general health; health behaviour and OA risk factors; and medication for knee symptoms. Clinical examination measures included height and

weight; abdominal circumference; blood and urine samples; blood pressure; performance measure of physical activity; and hand and knee examinations. All baseline measurements were repeated at 12, 24, 36 and 48-month.

This thesis used the physical activity, injury, height, weight, age, gender and OA data at baseline and 48-month follow-up.

2.1.2.1 OA data

The OAI study collected posteroanterior radiographs of TF compartment taken in full weight bearing with knees in 20-30 degrees flexion and 10 degrees internal rotation of feet at baseline and follow-up time points 12, 24, 36 and 48-month. Each participant's x-ray was also scored according to KL grading system at baseline and each visit in the OAI database.

This thesis used OAI radiograph data at two time points only: baseline and 48-month follow-up. Participants without radiographic knee OA at baseline were followed for the both incidence of radiographic and symptomatic knee OA. Radiographic knee OA was defined as a knee with TF-OA (KL ≥2). The co-occurrence of radiographic knee OA and the frequent knee symptoms at the 48-month follow-up was also considered as the incidence of symptomatic knee OA in participants without radiographic knee OA at baseline.

Frequent knee symptoms were defined in the OAI dataset as knee pain, aching, or stiffness on most days for at least one month during past 12 months.

The OAI study also graded each participant's knee radiographs (TF compartment) for osteophyte and JSN according to the OARSI atlas. In this thesis, progression of radiographic knee OA was determined as either one grade increase in KL score or one grade worsening in TF-JSN at 48-month follow-up, in participants with radiographic knee OA at baseline. For the progression of symptomatic knee OA, participants with frequent knee symptoms at baseline were included. An increase of greater than 9.29 points in the total WOMAC score from baseline to 48-month follow-up was considered as a cut-off point (minimal clinical important worsening) for considering a person with symptom progression.

Participants with a history of rheumatoid arthritis or missing OA data in either knee at baseline or follow-up were entirely excluded from the study. For the radiographic progression study, knees with KL score of 4, JSN grade of 3 or a knee with prosthesis at the baseline were also excluded.

2.1.2.2 Obesity Data

The OAI study measured the height and weight in all participants at the baseline assessment and follow-up time points 12, 24, 36 and 48-month. The baseline BMI data (body weight in kilograms divided by height in meters squared ($kg.m^{-2}$)) was used in this thesis to determine the obesity status. Participants were defined as non-obese if BMI <30 $kg.m^{-2}$ and obese if BMI ≥30 $kg.m^{-2}$ (WHO 1998). All participants with missing data at baseline were excluded from the analyses.

2.1.2.3 Physical activity data

The Physical Activity Scale for Elderly questionnaire (PASE) is a well-validated instrument for the measurement of physical activity in epidemiological studies of older adults (Washburn, Smith, Jette et al. 1993). The OAI study used the PASE questionnaire to evaluate the physical activity levels of participants over the past 7 days at baseline and follow-up time points 12, 24, 36, 48-month.

The PASE covered three domains of physical activity, which were leisure activities, household activities and occupational activities. The total PASE score was derived from a sum of these three domains of activity. This thesis used the total PASE score at baseline to determine the participants' activity

level. Previous research has shown that individuals with the activity level equal to the PASE score ≥200 had higher cartilage and meniscal abnormalities than those with the PASE score <200 (Stehling, Liebl, Krug et al. 2010). Thus, in this project, participants were defined as active if PASE score ≥200 and inactive if PASE score <200. If the PASE score was not recorded for a participant, that participant's data was completely excluded from analyses.

2.1.2.4 Injury data

At the baseline assessment for the OAI cohort, the following question "have you ever injured your knee badly enough to limit your ability to walk for at least two days?" was asked for each knee separately to determine participants with the history of injury. The same injury data was also collected at follow-up time point 12, 24, 36, 48-month in OAI. This thesis used the baseline injury data for the analyses. If there were a missing injury data for a participant in one or both knee(s) that participant was excluded from analysis.

2.1.2.5 Other data

Age (in years) and gender were determined from the baseline questionnaire for each participant. Participants were categorized into three age groups of 45-55, 55-65 and 65-79.

Participants with missing age and gender data were excluded from the analyses.

2.1.2.6 Outcome measures

1. The incidence of radiographic and separately symptomatic TF-OA at 48-month follow-up.
2. The progression of radiographic and separately symptomatic TF-OA at 48-month follow-up.

2.1.3 *MOST database*

MOST is an observational study of incidence and progression of knee OA risk factors. In 2003, MOST recruited 3026 residents aged between 50 and 79 at the baseline assessment from communities of Birmingham, labama and Iowa City, Iowa in the US (Sharma, Song, Dunlop et al. 2010). MOST selected participants who either had pre-existing knee OA or were at high risk of knee OA. The high risk group was defined as a participant having knee symptoms, history of knee injury or surgery, or being overweight (Segal, Nevitt, Gross et al. 2013). Participants with a history of rheumatoid or any other inflammatory arthritis, bilateral joint replacement, cancer or similar life threatening conditions were excluded from study at baseline.

Baseline assessment included musculoskeletal and imaging assessments of the knee. Information such as demographics, general health, health behaviour and OA risk factors, medication, knee pain and symptoms, knee-related function and QOL, MRI, x-ray as well as other joints symptoms, knee and hand examination, and blood and urine sample were obtained during baseline. Then, they were all repeated at 15, 30 and 60-months follow-ups.

This study used the following data from the MOST dataset: physical activity, injury, height, weight, age, gender and OA at baseline and 60-month follow-up.

2.1.3.1 OA data

The MOST study collected posteroanterior radiographs of TF joints taken in full weight bearing with knees in 20-30 degrees flexion and 10 degrees internal rotation of feet at baseline and follow-up time points 15, and 30 and 60-month. Semi-flexion lateral x-ray views of knees in full weight bearing were also obtained for examining PF-OA at baseline, 15, 30 and 60-month.

This study used MOST radiograph data at two time points only: baseline and 60-month follow-up. Participants without radiographic knee OA at baseline were followed for the both

incidence of radiographic and symptomatic knee OA. Radiographic knee OA was defined as a knee with TF-OA and/or PF-OA. TF-OA was defined same as OAI (KL ≥2). PF-OA was defined as any osteophyte ≥2; or JSN ≥1 plus any cyst, osteophyte, or sclerosis ≥1 (OARSI atlas) at the 60-month follow-up. The symptomatic knee OA was also defined as a knee with the co-occurrence of frequent knee symptoms and radiographic whole knee OA (TF and/or PF knee OA) at 60-month follow-up. Frequent knee symptom was defined same as OAI.

The MOST study also graded each participant's knee radiographs (TF and PF compartments) for osteophyte and JSN according to the OARSI atlas. In this thesis, progression of radiographic knee OA was determined as either one grade increase in KL score in TF joint or one grade worsening in TF/PF-JSN at 60-month follow-up in participants with radiographic knee OA at baseline. The progression of symptomatic knee OA was defined same as OAI.

Participants with a history of rheumatoid arthritis or missing OA data in either knee at baseline or follow-up were entirely excluded from the study. For the radiographic progression study, knees with KL score of 4, JSN grade of 3 or a knee with prosthesis at the baseline were also excluded.

2.1.3.2 Obesity data

Obesity data was defined the same as OAI.

2.1.3.3 Physical activity data

Physical activity data was defined the same as OAI.

2.1.3.4 Injury data

Injury data was defined the same as OAI.

2.1.3.5 Other data

Age and gender data was defined the same as OAI.

2.1.3.6 Outcome measures

1. The incidence of radiographic and separately symptomatic whole knee OA (TF-OA and/or PF-OA) at 60-month follow-up.
2. The progression of radiographic and separately symptomatic whole knee OA (TF-OA and/or PF-OA) at 60-month follow-up.

Table 2-2: The similarity and contrasting aspect of MOST and OAI

		MOST	**OAI**
		Baseline and 60-month	**Baseline and 48-month**
Age	In year	✓	✓
Gender	Male/Female	✓	✓
Body size	BMI	✓	✓
Physical activity	PASE	✓	✓
Injury	Unable to walk for at least two days	✓	✓
x-ray: PA view	KL and JSN (OARSI atlas)	✓	✓
X-ray: lateral view	(OARSI atlas)	✓	✗
Sample population	People with or at high risk of knee OA	✓	✓
Readers who grades x-rays		Same readers as OAI	Same readers as MOST

2.1.4 *Data analysis*

This study used data about obesity, physical activity, injury, age, gender and OA. Descriptive statistics such as mean, range, minimum-maximum and standard deviation (SD) for continuous variables, and the frequency tables (count and percentage) for categorical variables will be presented.

In this study, the outcomes for the incidence and progression of knee OA were binary: participants had incidence of knee OA or not, or participants had progression of knee OA or not. Therefore, a logistic regression model was used to calculate the crude and adjusted ORs and their 95% CIs for the association between knee OA and the predictor variables, namely: obesity and knee OA; physical activity and knee OA; injury and knee OA; age and knee OA; and gender and knee OA at the last follow-up.

Statistical analyses were performed at knee level in this study. Therefore, using the standard logistic regression would have underestimated the standard errors due to the inter-knees correlation in each subject; and consequently, resulted in underestimation of corresponding ORs and incorrect *p* values. Hence, the logistic regression model was performed using the generalized estimating equation (GEE) with exchangeable correlation matrix to adjust for the correlation between knees

within subject (Niu, Zhang, LaValley et al. 2003; Haugen, Slatkowsky-Christensen, Bøyesen et al. 2013).

This study also examined the two-way and three-way interactions between, physical activity, obesity and injury on the risk of incidence and progression of radiographic and symptomatic knee OA. Generally, the interaction can be assessed based on additive or multiplicative scales.

The multiplicative measure of interaction has been more frequently reported in epidemiological literature when the outcome was binary. This is because it could be easily obtained from a logistic regression model using the standard statistical software packages. However, assessing the measure of interaction on an additive scale needed extra analysis, which is not readily available in standard statistical software packages. Thus, this could be another reason for more frequent reporting of multiplicative over the additive interaction, rather than a careful thought given on the choice of interaction.

However, there is a general consensus that the measure of interaction on an additive scale is more appropriate for evaluating the interaction in the biological and public health research (Knol and VanderWeele 2012). Therefore, this study

assessed the measure of interaction on both additive and multiplicative scales.

In this study, the relative excess risk due to interaction (RERI) on the multiplicative scale was obtained by entering the interaction term into the logistic regression model (Figure 2-1). For instance, to investigate the two-way interaction between physical activity and injury on the risk of knee OA, the model included obesity, injury, physical activity, age and gender as independent variables, knee OA as the outcome measure, plus the two-way interaction term of "physical activity*injury". Similar models were used to investigate the other two-way and three-way interactions.

Figure 2-1: The interaction model for the multiplicative scale

Logistic regression model:

In (OR) = $\beta_0+\beta_1$ (exposure A^+B^-) + β_2 (exposure A^-B^+) + β_3 (exposure A^+B^+) + ……..

- β_0 = In (reference group) = regression coefficient of back ground risk when both exposure A and B are absent (intercept)
- β_1 = In (OR_{A+B-}) = regression coefficient of main effect of exposure A on the outcome when exposure B is absent
- β_2 = In (OR_{B+A-}) = regression coefficient of main effect of exposure B on the outcome when exposure A is absent
- β_3 = In **(**(OR_{A+B+}) / (OR_{A+B-} * OR_{B+A-})**)**

RERI $_{\textbf{multiplicative}}$ **=** $e^{\beta 3}$ = (OR_{A+B+}) / (OR_{A+B-} * OR_{B+A-})

Thus, if:

- RERI > 1: positive interaction
- RERI < 1: negative interaction
- RERI = 1: no interaction

RERI $_{\textbf{multiplicative-three way interaction}}$ = (OR_{A+B+C+}) / (OR_{A+B-C-} * OR_{B+A-C-} * OR_{C+A-B-} * OR_{A+B+C-} * OR_{A+C+B-} * OR_{A-B+C+})

For the additive scale, the RERI was also estimated by using OR values. This was calculated based on the Rothman's method, a linear OR model of regression (Rothman 1986; Richardson and Kaufman 2009). In this method, all odds values (regression coefficients) used in the linear regression model were turned into OR by dividing them into the background odds of disease (Figure 2-2; Figure 2-3). Thus, the regression coefficient of interaction in the linear regression model was computed based on the OR differences rather than the odds differences. The formula in Figure 2-2 and Figure 2-3 describes how the measure of interaction on the additive scale was derived from the linear regression model using ORs (Knol, van der Tweel, Grobbee et al. 2007).

Figure 2-2: The two-way interaction model for the additive scale

Linear regression model:

$Y = \alpha_0 + \alpha_1$ (exposure A^+B^-) + α_2 (exposure A^-B^+) + α_3 (exposure A^+B^+) + ...

- P = odds
- α_0 = (P_{A-B-}) = Regression coefficient of back ground effect when exposure A and B are both absent (intercept)
- α_1 = $(P_{A+B-} - P_{A-B-})$ = Regression coefficient of main effect of exposure A on the outcome when exposure B is absent
- α_2 = $(P_{B+A-} - P_{A-B-})$ = Regression coefficient of main effect of exposure B on the outcome when exposure A is absent
- α_3 = amount of interaction on the additive scale base on the odds difference: $(P_{A+B+} - P_{A-B-}) - ((P_{A+B-} - P_{A-B-}) + (P_{B+A-} - P_{A-B-}))$ = $\mathbf{P_{A+B+} - P_{A+B-} - P_{B+A-} + P_{A-B-}}$

Rothman model: (using ORs in the linear regression model)

- $\alpha_3 = P_{A+B+} - P_{A+B-} - P_{B+A-} + P_{A-B-} \rightarrow$ **$RERI_{OR}$** = $(P_{A+B+}/P_{A-B-}) - (P_{A+B-}/P_{A-B-}) - (P_{B+A-}/P_{A-B-}) + (P_{A-B-}/P_{A-B-}) \rightarrow$

$RERI_{additive\ (OR)}$ = $(OR_{A+B+}) - (OR_{A+B-}) - (OR_{B+A-}) + 1$

Thus, if:

- RERI > 0: positive interaction
- RERI < 0: negative interaction
- RERI = 0: no interaction

Delta method was used to estimate the 95% CIs and the corresponding *p* value for RERI on additive scale (Hosmer and Lemeshow 1992). These were obtained via the nlcom comment in Stata.

Figure 2-3: The three-way interaction model for the additive scale

Rothman model: (using ORs in the linear regression model)

RERI $_{\textbf{three-way interaction (OR)}}$ = (OR_{A+B+C+}) - (OR_{A+B-C-}) – (OR_{B+A-C-}) – (OR_{C+A-B-}) – $(RERI_{A+B+C-})$ - $(RERI_{A+C+B-})$ - $(RERI_{A-B+C+})$ + 2

Thus, if:

- RERI > 0: positive interaction
- RERI < 0: negative interaction
- RERI = 0: no interaction

In the three way interaction model, the two way interactions between A and B; A and C; B and C were computed as follows:

- $RERI_{A+B+C-} = (OR_{A+B+C-}) – (OR_{A+B-C-}) – (OR_{A-B+C-}) + 1$
- $RERI_{A+C+B-} = (OR_{A+C+B-}) – (OR_{A+C-B-}) – (OR_{A-C+B-}) + 1$
- $RERI_{A-B+C+} = (OR_{A-B+C+}) – (OR_{A-B+C-}) – (OR_{A-B-C+}) + 1$

Findings of interactions analyses were presented according to the STROBE recommendations (Knol and VanderWeele 2012), where the separate effects of exposures and their joint effects were reported in addition to the measure of interaction on additive and multiplicative scales. For all interaction analyses, the lowest risk groups were considered as the single reference category. For instance, for the interaction between obesity and injury on the risk of knee OA, participants were divided into the four categories of "obese and injured", "obese and uninjured", "non-obese and injured", and "non-obese and uninjured" groups. The group of "non-obese and uninjured"

individuals were considered as the reference category, so the risk of knee OA in the other three groups were compared with the single reference category. These analyses were repeated for the two-way interactions between physical activity and obesity (reference category: inactive-non-obese), and separately for the two-way interaction between physical activity and injury (reference category: inactive-uninjured). For the three-way interaction analyses, data were stratified by physical activity, obesity and injury, in which "non-obese-uninjured-inactive" group was considered as the single reference category. The interaction on multiplicative scale was present if the combined effect of both exposures on the outcome was larger (or smaller) than the multiple of the individual effects of each exposure. For the additive scale, the interaction was present if the combined effect of both exposures on the outcome was larger (or smaller) than the sum of the individual effects of each exposure (Knol et al. 2007).

In this study, all the analyses were performed using Stata version 13 for Windows. In addition, all ORs were adjusted for the confounding effect of age, gender, obesity, injury and physical activity.

2.1.5 *Regulatory approvals*

This work was approved by The University of Nottingham Research Ethics Committee (Ethics Reference No: Q06062013 SCS Sports Med; date 19/08/2013) (Appendix 1). In addition, permissions were obtained from OAI and MOST for using their datasets.

2.2 Nottingham Knee Study

This section describes the method used to examine normative data for the knee pain, symptoms, function and knee related QOL, and the associations of these clinical outcome measures with obesity, injury and physical activity.

This part begins with outlining the study design, and follows with describing the study area, recruitment procedures and eligibility criteria. It then explains how and what data were collected for this study. Thereafter, data management, sample size calculation and data analyses are described in detail. Finally, the statement of the ethical approval for this study is presented.

2.2.1 *Study design*

- A community-based questionnaire survey

2.2.2 *Participants and recruitment*

This study recruited volunteer participants from the community to take part in a questionnaire survey. The study area comprised the seven local authorities in Nottinghamshire County and the City of Nottingham, which collectively had a population of just over one million people (Office for National Statistics 2011). Approximately one third of the population lived in the City of Nottingham (28%), whereas each local

authority in Nottinghamshire County had approximately 10% of the total population.

From a list of 25,695 postcodes in this study area, obtained from the Census data (2011), 2,500 postcodes were randomly selected. This was based on the proportion of the population in each local authority and the City of Nottingham. The postcodes were then equally and randomly assigned into three age groups of 18-44, 45-69 and ≥70 years old (using a random generator in Stata). Finally, from each postcode assigned to the specific age group, one name and address were randomly selected. People's names/addresses were purchased from the Marketing File Ltd., the UK's largest online supplier of direct marketing lists. Marketing File Ltd.'s data was gathered from 80 multiple sources including private companies (i.e. insurance, retail and finance sectors, etc.), open sources (i.e. Open Register and Land Registry, etc.), and market research (i.e. YouGov, etc.).

The recruitment in this study involved mailing a postal survey. The survey package included an invitation letter, a Participant Information Sheet, a questionnaire booklet (described below) and a pre-paid return envelope (Appendix 2). Participants were required to complete the questionnaire booklet once only, which took approximately 20 minutes. To be included in

the study, participants needed to be adults who were able to understand and complete the questionnaire booklet (in English) independently or with minimal assistance from friends or family.

2.2.3 *Data collection*

The questionnaire booklet consisted of two sections: "background information" and "questionnaire". The contents of these sections are summarized in the Figure 2-4.

Figure 2-4: The questionnaire booklet contents

Questionnaire booklet content

Background information section

- Self-reported anthropometrics and demographics
  - Age, sex, postcode, height and weight
- Self-reported history of knee injury/surgery/knee joint replacement
- Knee OA: NICE criteria

Questionnaire section

- Knee pain, symptoms, functions and knee related QOL
  - KOOS
  - OKS
- Quality of life
  - EQ-5D-5L
- Physical activity
  - Clinical Use Physical Activity Questionnaire

The “Background information” section collected primary data regarding participants’ age, gender, postcode and self-reported measures of height and weight. Height and weight data were used to calculate each participant’s BMI, which was body weight in kilograms divided by height in meters squared ($kg.m^{-2}$). Participants were defined as non-obese if BMI <30 $kg.m^{-2}$ and obese if BMI ≥30 $kg.m^{-2}$ (WHO 1998).

The background information section also collected data to examine the participants with severe knee injury, clinical knee OA, and knee joint replacement. The following questions "have you ever had surgery/arthroscopy for ligament and meniscal repair in one or both knee(s)?” and “have you ever had a knee joint replacement in one or both knee(s)?” were also used to determine individuals with a history of severe knee injury and knee joint replacement, respectively (Appendix 2, questionnaire booklet: page 2).

Participants with clinical knee OA were determined using the UK NICE criteria 2014, which was a person who was 45 years old and older, had activity related joint pain, and had either no morning stiffness or morning stiffness that lasts no longer than 30 minutes (NICE 2014). Therefore, the background information section included questions asking about these

criteria to determine whether or not a participant had clinical knee OA (Appendix 2, questionnaire booklet: page 2).

To establish normative data, the "Questionnaire section" examined participants' perceptions about their knee pain, symptoms, functions and knee related QOL using KOOS and OKS questionnaires which are described in detail below. Participants were requested to complete the questionnaire for their knees even if they were both normal. If one or both knees caused a problem, they were requested to answer the questions for their worst knee.

This section also collected information regarding the participants' general health and their physical activity level using EQ-5D-5L and Clinical Use Physical Activity Questionnaire (CPAQ) respectively, which are described in detail below.

2.2.3.1 KOOS

KOOS is a well validated instrument broadly used in clinical practice and research to evaluate both long and short term changes in pain, symptoms, function and knee related QOL of subjects with knee injury and knee OA (Roos and Lohmander 2003) (Appendix 2, questionnaire booklet: page 3-10). KOOS consists of 42 questions categorized in the 5 subscales of pain

(9 questions), other symptoms (7 questions), activities of daily living (ADL: 17 questions), sport and recreation function (Sport/Rec: 5 questions) and knee-related QOL (4 questions).

All questions were set based on a 5 point Likert scale, where 0 was no problem and 4 was the extreme problem. Each subscale score was calculated by dividing the mean value of all items within the subscale by 4 and then multiplying by 100 to transform it into the percentage (KOOS 2012). 100% was the worst and 0% the best score. The percentage was eventually subtracted from 100. Therefore, each final subscale score was presented based on a 100 point scale, where with 0 representing extreme problem and 100 corresponding to no problem.

The subscale score was not calculated if more than 50% of the subscale questions were unanswered. Therefore, a minimum of 5 answers for the pain subscale, 4 for the symptom subscale, 9 for the ADL subscale, 3 for Sport/Rec subscale, and 2 for QOL subscale were required for calculating the overall score of each subscale. If two answers were marked for a question, the more severe response was considered acceptable (KOOS 2012).

2.2.3.2 OKS

OKS is another short, practical and validated knee specific questionnaire widely used in the UK to assess patients' perception about knee pain and function after knee replacement surgery and arthroscopy (Dawson et al. 1998). OKS consists of 12 questions (Appendix 2, questionnaire booklet: page 10-12). Each question had five answers scoring from 0 to 4 (Murray, Fitzpatrick, Rogers et al. 2007). "0" represented the worst and "4" indicated the best condition. The overall score was the summed score of all 12 items. The overall score was ranged from 0 to 48, where "0" was the worst and "48" was the best score (Murray et al. 2007). If one or two items were unanswered, they were substituted with the mean value of the other 10 responses. The total scores were not calculated if more than 2 items are unanswered (Murray et al. 2007).

The OKS score was also separately reported for the subscales of pain and function. The Pain Component Score of OKS (OKS-PCS) only included items 2, 3, 7, 11 and 12 and the Functional Component Score (OKS-FCS) included items 1, 4, 5, 6, 8, 9 and 10 (Appendix 2, questionnaire booklet: page 10-12) (Harris, Dawson, Jones et al. 2013). The summed score for

OKS-PCS and OKS-FCS were transferred to the 100 point scale, where 0 was the worst and 100 was best score.

2.2.3.3 Quality of life measures

EQ-5D-5L is a generic health questionnaire designed by the EuroQol Group to evaluate people's health status (Herdman, Gudex, Lloyd et al. 2011; Krabbe, Devlin, Stolk et al. 2014). It consists of a descriptive system evaluating 5 different dimensions of health (health profile) specifically mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Herdman et al. 2011; Krabbe et al. 2014). The severity of each dimension was defined by the five levels of "no problems", "slight problems", "moderate problems", "severe problems", and "extreme problems" (Appendix 2, questionnaire booklet: page 13-14). Only one answer was acceptable for each dimension of health. If more than one box were ticked for each dimension of health that was considered as the missing data (Oemar and Janssen 2013).

EQ-5D-5L also comprises a visual analogue scale (VAS), in which responders report their "overall health" status. This was based on a 100 point vertical scale. 100 was the "best imaginable health state" and 0 was the "worst imaginable health" (Herdman et al. 2011).

2.2.3.4 Physical activity measure

CPAQ is newly developed at the University of Nottingham by the Sports and Exercise Medicine group (Evans, Edwards and Batt 2014). CPAQ is a rapid, simple and accurate screening tool for the use in clinical settings to identify whose physical activity level fails to meet the UK Government guidelines (Power, Evans and Tsintzas 2013). CPAQ collected the amount (in minutes) of moderate or vigorous physical activity undertaken by participants every day of the week in the past seven days (Appendix 2, questionnaire booklet: page 15). This included both home/leisure time and work/college related activities.

In the present study, participants were divided into active and inactive groups. The term "active" referred to a person who met the minimum UK Government guidelines. This was a minimum of 150 minutes moderate physical activity per week, 75 minutes vigorous physical activity per week, or a combination of both. Moderate activity was defined as "any activity that gets you mildly sweaty and out of breath" such as brisk walking, and vigorous activity was defined as "any activity the involves hard physical effort and make you breathe much harder than normal" such as fast bicycling (Appendix 2, questionnaire booklet page 15). If the reported

activity time was less than 10 minutes that was not counted since each bout of exercise had to be at least 10 minutes long as defined in the guideline.

2.2.4 *Outcome measures*

1. The KOOS scores (KOOS-Pain, KOOS-Symptom, KOOS-ADL, KOOS-Sport/Rec, and KOOS-QOL) specified by the age groups and gender.
2. The OKS scores (total-OKS, OKS-PCS and OKS-FCS) specified by the age groups and gender.

2.2.5 *Data management*

Prior to sending the questionnaire booklets to participants, each booklet was assigned with a unique follow-up ID number linked with a participant's name. Names with the allocated ID numbers were saved in a separate password protected file. Therefore, the recorded data on the questionnaire booklets or on the excel spreadsheet database were de-identified, and could not linked to named individuals.

All returned questionnaire booklets were kept strictly confidential and stored in a secure and locked office at Academic Orthopaedics, Trauma and Sports Medicine, University of Nottingham. A 'cooling-off' period of one week

was provided in case any participants subsequently wished to withdraw from the study. During this period, if a participant wished to withdraw from the study, the questionnaire booklet was either destroyed or returned back to the participant. After this time, data were entered into a password protected excel spreadsheet.

Two individual people from the research team examined the accuracy of data entry by checking 10% of spreadsheet data against the questionnaire booklets. An error less than 2% was considered acceptable.

2.2.6 *Sample size*

A sample size calculation indicated that 192 participants were required for this study, with 64 participants in each age group of "18-44", "45-69" and "≥70" years old.

The sample size was based on power calculations using a power of 80% and significance level of 5% (α) for an unpaired study (Campbell, Julious and Altman 1995). The effect size was based on the widely accepted minimum clinically important difference ($\mu_1 - \mu_2$) of 10 points on the 100 point scale of KOOS and SD (σ) of 20 (Figure 2-5) (Roos and Lohmander 2003; Paradowski, Bergman, Sunden-Lundius et al. 2006).

To attain the target sample in this study (192 participants), 2500 questionnaires were distributed based on the return rate of 8%. This was almost 25-30% lower than the return rates observed in recent postal surveys of knee OA in the UK (Moreton, Wheeler, Walsh et al. 2012; Cooper, Scammell, Batt et al. 2016). This strategy aimed to maximize the number of responders in this project.

Figure 2-5: Sample size calculation

Sample size (n) = Numerator x $[\sigma / (\mu_1 - \mu_2)]^2$

$\alpha = 0.0.5$ β (false positive rate) $= 0.2$

Power = $1 - \beta = 1 - 0.2 = 0.8$

$\sigma = 20$ $\mu_1 - \mu_2 = 10$

N (per each arm) = 16 X $(20/10)^2$ = 64

2.2.7 *Data analysis*

Participants' characteristics were presented using descriptive statistics such as mean, range, minimum-maximum and SD for continuous variables, and the frequency tables (count and percentage) for categorical variables.

Normative values for all subscales of KOOS and OKS were presented by age groups and gender. Mean, SD, median and interquartile range (IQ) were presented for normative values. Similar descriptive values for KOOS and OKS were also presented for participants with and without clinical knee OA.

All analyses in this study were based on the non-parametric method since the data were not normally distributed. Even square and cube transformations did not normalize the data adequately. Therefore the Kruskal-Wallis test was used to identify any differences between three age groups for each normative outcome (KOOS and OKS) (Sedgwick 2014). When the Kruskal-Wallis test results were statistically significant, Dunn's test were applied for the pairwise comparisons of outcome differences between the age groups. Mann–Whitney U test was used to determine any differences in outcomes by gender and, separately by knee OA status (Hart 2001).

The multivariable logistic regression model was also used to examine the effect of obesity, injury, physical activity, age and gender on the clinical outcome measures assessed by KOOS and OKS. Obesity, injury, physical activity, age and gender were included in the model as predictor variables. Then, the model was run separately for each of the following outcomes: KOOS-Pain, KOOS-ADL, KOOS-Symptoms, KOOS-Sport/Rec, KOOS-QOL, total-OKS, OKS-PCS, and OKS-FCS. Each outcome was categorized into "low score" (lowest quartile score) and "high score" (highest three quartiles score). The term "low score" was referred to as "high knee complaints". This cut-off point was based on the 25% lower quartile score of each outcome (KOOS-Pain: ≤72.2, KOOS-Symptoms: ≤75.0, KOOS-ADL: ≤75.0, KOOS-Sport/Rec: ≤75.0, KOOS-QOL: ≤56.2, total-OKS: ≤36.00, OKS-PCS: ≤75.0, and OKS-FCS: ≤75.0). The 25% lower quartile score for each outcome in this study was almost similar to the KOOS and OKS scores of patients with adequate knee symptom requiring treatment (Englund et al. 2003; Harris et al. 2013).

The logistic regression model was also used to calculate the crude and adjusted ORs and 95% CIs for the association between clinical knee OA and the predictor variables, namely: obesity and knee OA; physical activity and knee OA; injury

and knee OA; age and knee OA; and gender and knee OA. All statistical analysis was performed using Stata version 13 for windows.

2.2.8 *Ethical approval*

This study was approved by The University of Nottingham Research Ethics Committee (Ethics Reference No: F14082014 SoM ROD PhD date; 25/11/2014) (Appendix 3). In addition, permissions were obtained from the Isis Innovation Company and EuroQol group for using OKS and EQ-5D-5L questionnaires. No license was needed for the KOOS or CPAQ questionnaires.

This project was a postal survey involving no sensitive topic and not having any significant burden on participants. Therefore, returning a completed questionnaire booklet was regarded as adequate evidence of implicit consent.

3 Results: Interaction Analysis Study

This first results chapter reports the results of the analyses of the two-way and three-way interactions between physical activity, obesity and injury on the risk of incident radiographic and separately symptomatic knee OA. It then continues onto the interaction analyses results for the progression of radiographic and symptomatic knee OA (Section 3.3 and 3.4). The results for the Nottingham Knee Study are presented in chapter 4.

3.1 Incidence of radiographic knee OA

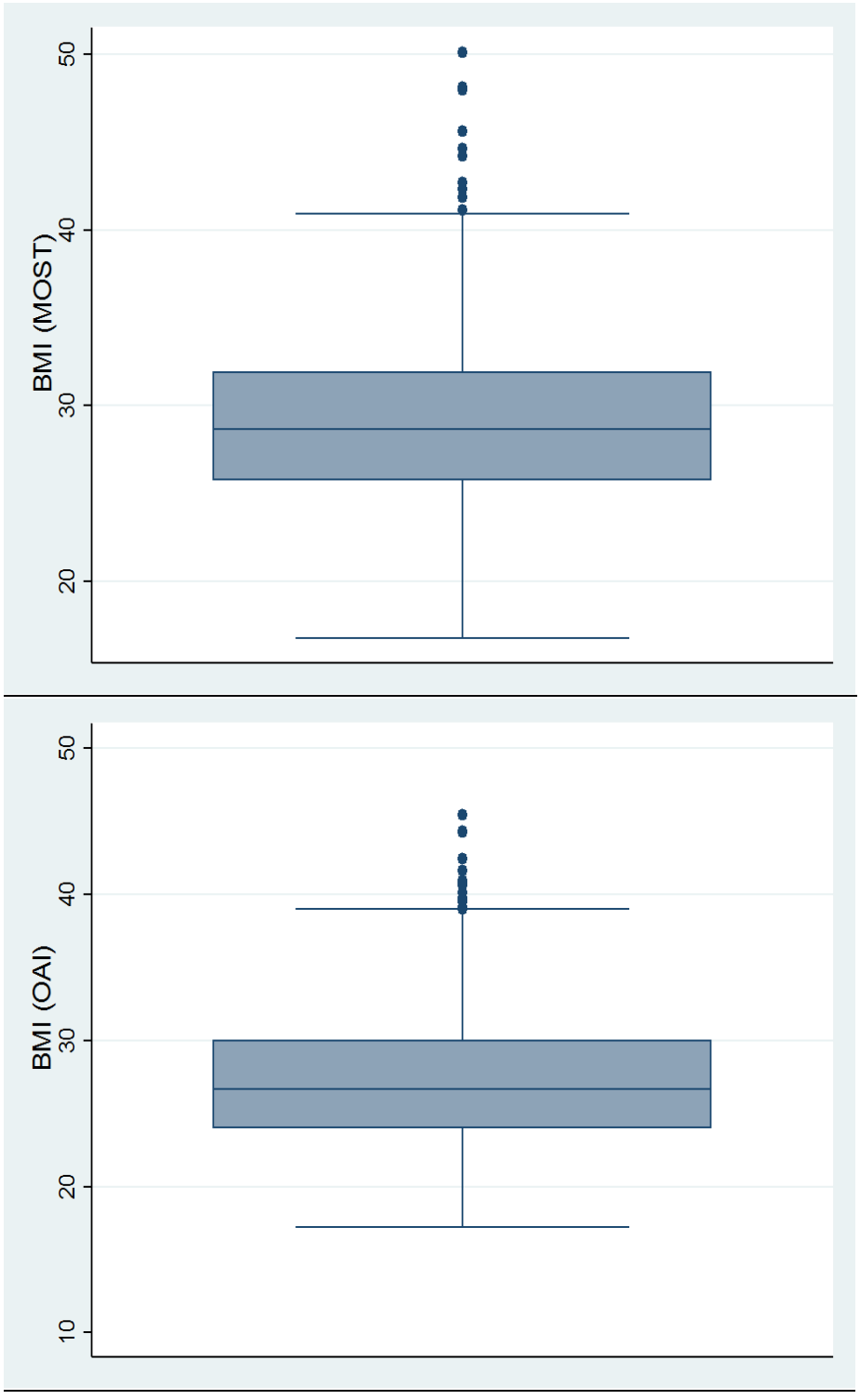
3026 and 4796 participants in MOST and OAI cohorts respectively had x-ray data at baseline. Of those, 1007 participants from MOST and 1558 participants from OAI met the inclusion criteria for the incident radiographic knee OA study (that is, they did not have radiographic knee OA in either knee at baseline). In MOST, 4 participants and in OAI 28 participants were excluded due to missing injury (either knee), physical activity or BMI data at the baseline assessment. Therefore, 2006 knees (1003 participants) in MOST and 3060 knees (1530 participants) in OAI were included in the data analysis.

Participants' characteristics are presented in Table 3-1. In MOST, the mean age of participants at the baseline was 60.2 years, which was comparable to the mean age of 59.2 years in OAI (Table 3-1). In OAI, the participants' ages ranged from 45 to 70 years old, which was slightly broader than in MOST with the range of 50 to 79 years old (Table 3-1). The mean BMI of 29.0 $kg.m^{-2}$ at baseline in MOST was slightly higher than OAI (27.1 $kg.m^{-2}$) (Table 3-1 and Figure 3-1). The mean PASE score in MOST at the baseline was 185.7, which was higher than OAI (170.4) (Table 3-1 and Figure 3-2).

Table 3-1: Participants' characteristics data at baseline

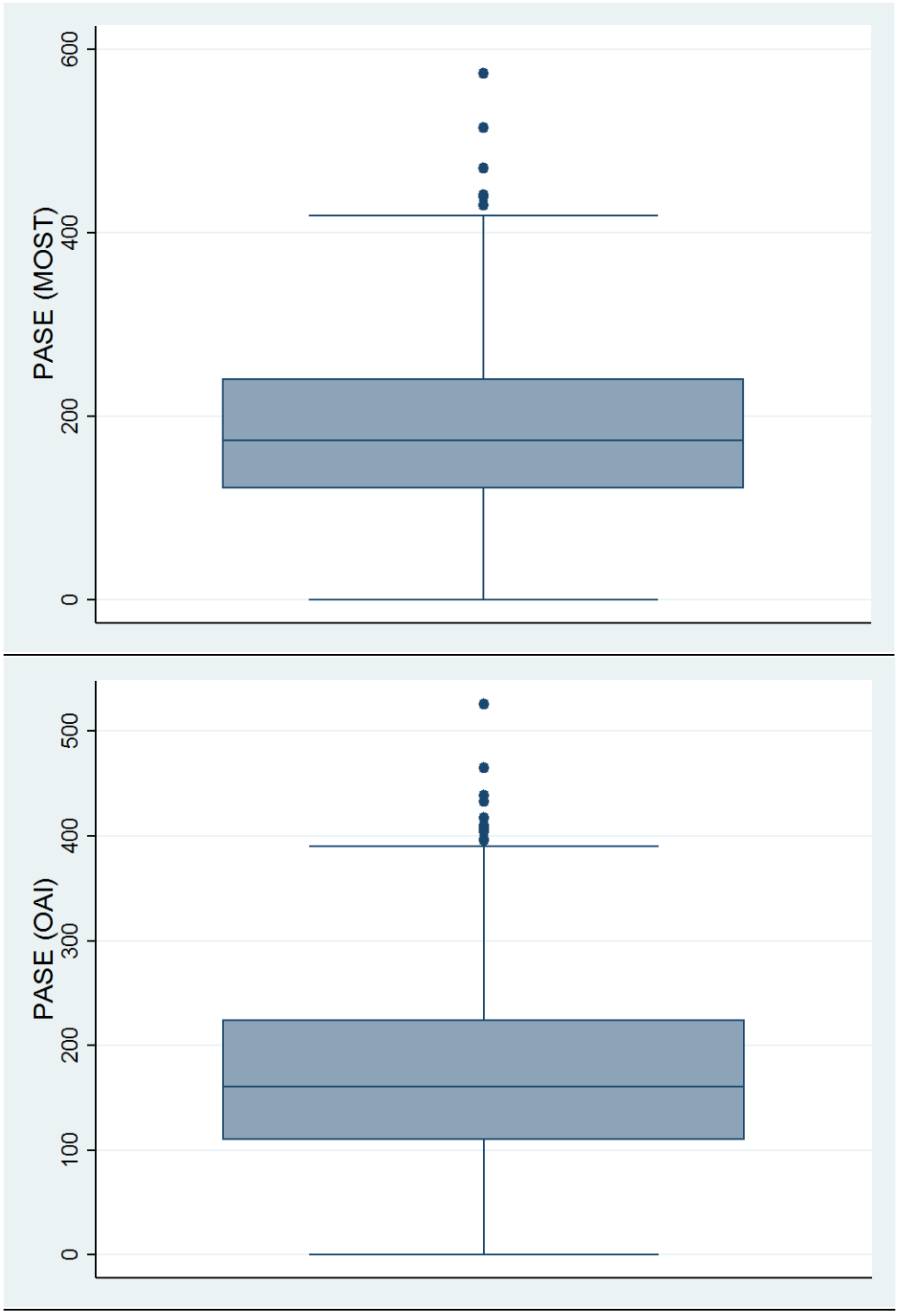
Cohort		AGE	BMI (Baseline)	PASE (Baseline)
MOST	Mean ± SD	60.22 ± 7.56	29.00 ± 4.64	185.73 ± 87.63
	Min-Max	50-79	16.72-50.13	0-573.20
	Range	29	33.41	573
OAI	Mean ± SD	59.22 ± 9.07	27.19 ± 4.44	170.41 ± 82.56
	Min-Max	45-79	17.2-45.4	0-526
	Range	34	28.2	526

Figure 3-1: Distribution of BMI data at baseline



*BMI: Body mass index

Figure 3-2: Distribution of PASE data at baseline



* PASE: Physical activity scale for elderly

3.1.1 *Gender and risk of incident radiographic knee OA*

The majority of participants (59%) were female in both MOST and OAI radiographic incident study. In both cohorts, female gender was found as a predictor for incident radiographic knee OA, albeit a weaker association in MOST (aOR: 1.34, 95% 1.00-1.80) than OAI (aOR: 1.74, 95%CI: 1.22-2.48) (Table 3-2).

Table 3-2: Gender and risk of incident radiographic knee OA

Cohort	Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	Male	708 (86.3.1%)	112 (13.7%)	820	-	-
	Female	994 (84.8%)	192 (15.2%)	1186	1.22 (0.92 – 1.63) $p = 0.17$	1.34 (1.00 – 1.80) $p = 0.049$
OAI	Male	1203 (95.2%)	61 (4.8%)	1264	-	-
	Female	1662(92.5%)	134 (7.5%)	1796	1.59 (1.12 – 2.25) $p = 0.009$	1.74 (1.22 – 2.48) $p = 0.002$

***Odds ratio (OR) adjusted for Injury, obesity, age and physical activity**

3.1.2 *Age and risk of incident radiographic knee OA*

In MOST, no significant associations were found between age and incident radiographic knee OA (Table 3-3). In OAI, both the middle age group (aOR: 1.59) and old age group (aOR: 1.39) were at greater risk of radiographic knee OA compared to the young age group. However, it was only statistically significant in the middle age group (aOR: 1.59, 95%CI: 1.07-2.35) (Table 3-3).

Table 3-3: Age and risk of incident radiographic knee OA

Cohort	Age Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	45-55	495 (83.1%)	101 (16.9%)	596	-	-
	55-65	699 (86.5%)	109 (13.5%)	808	0.76 (0.55 - 1.07) $p = 0.12$	0.79 (0.56 - 1.11) $p = 0.17$
	65-79	508 (84.4%)	94 (15.6%)	602	0.91 (0.64 - 1.29) $p = 0.58$	1.03 (0.71 - 1.49) $p = 0.88$
OAI	45-55	1099 (94.7%)	61 (5.3%)	1160	-	-
	55-65	902 (92.0%)	78 (8.0%)	980	1.56 (1.06 - 2.29) $p = 0.02$	1.59 (1.07 – 2.35) $p = 0.02$
	65-79	864 (93.9%)	56 (6.1%)	920	1.17 (0.77 - 1.77) $p = 0.47$	1.39 (0.90 – 2.17) $p = 0.14$

*** Odds ratio (OR) adjusted for Injury, obesity, gender and physical activity**

3.1.3 *The association between obesity and the risk of incident radiographic knee OA*

At baseline, more participants were obese in MOST (37.3%) than OAI (25.6%) (Table 3-4). The prevalence of knee OA was almost double in the obese than non-obese group in both cohorts at the last follow-up (MOST: 60-month; OAI: 48-month) (Table 3-4). In addition, obesity was significantly associated with the increased risk of incident radiographic knee OA in both MOST (aOR: 2.16, 95%CI: 1.63-2.86) and OAI (aOR: 2.11, 95%CI: 1.50-2.96) (Table 3-4).

Table 3-4: Obesity and risk of incident radiographic knee OA

Cohort	Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	Non-obese	1112 (88.5%)	144 (11.5%)	1256	-	
	Obese	590 (78.7%)	160 (21.3%)	750	2.09 (1.59-2.77) $p < 0.001$	2.16 (1.63-2.86) $p < 0.001$
OAI	Non-obese	2156 (94.8%)	118 (5.2%)	2274	-	
	Obese	709 (90.2%)	77 (9.8%)	786	1.98 (1.42-2.77) $p < 0.001$	2.11 (1.50-2.96) $p < 0.001$

***Odds ratio (OR) adjusted for Injury, age, gender and physical activity**

3.1.4 *The association between injury and the risk of incident radiographic knee OA*

Approximately 21% of participants in each cohort had injury at baseline (Table 3-5). Injury was also significantly associated with the increased risk of incident radiographic knee OA in both cohorts ($aOR_{\text{-MOST}}$: 1.54, 95%CI: 1.16-2.05; $aOR_{\text{-OAI}}$: 1.56, 95%CI: 1.12-2.17).

Table 3-5: Injury and risk of incident radiographic knee OA

Cohort	Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	Uninjured	1366 (85.6%)	229 (14.4%)	1595	-	-
	Injured	336 (81.8%)	75 (18.2%)	411	1.48 (1.12-1.95) p = 0.005	1.54 (1.16-2.05) p = 0.003
OAI	Uninjured	2247 (94.1%)	141 (5.9%)	2388	-	-
	Injured	618 (92.0%)	54 (8.0%)	672	1.50 (1.06-2.01) p = 0.021	1.56 (1.12-2.17) p = 0.008

***OR adjusted for obesity, age, gender and physical activity**

3.1.5 *The association between physical activity and risk of incident radiographic knee OA*

40% of MOST participants were active compared to 33% in OAI (Table 3-6). No significant association was found between physical activity and incident radiographic knee OA in either MOST (OR: 0.98, 95%CI: 0.74-1.31) or OAI (OR: 1.08 95%CI: 0.77-1.52*)*. The risk of radiographic knee OA due to physical activity was close to one in both cohorts. That is, activity neither increased nor protected against the risk of incident radiographic knee OA. Adjusting for confounders did not make any significant change to the results in either cohort (Table 3-6).

Table 3-6: Physical activity and risk of incident radiographic knee OA

Cohort	Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	Inactive	1012 (84.8%)	182 (15.2%)	1194	-	-
	Active	690 (85.0%)	122 (15.0%)	812	0.98 (0.74-1.31) $p = 0.91$	0.98 (0.73-1.33) $p = 0.91$
OAI	Inactive	1917 (93.8%)	127 (6.2%)	2044	-	-
	Active	948 (93.3%)	68 (6.7%)	1016	1.08 (0.77-1.52) $p = 0.65$	1.20 (0.83-1.72) $p = 0.33$

***OR adjusted for Injury, obesity, age and gender**

3.1.6 *The interaction between obesity and injury on the risk of incident radiographic knee OA*

In order to investigate the two-way interaction between obesity and injury on the risk of incident radiographic knee OA, the data were stratified by obesity and injury.

In MOST, obesity in the absence of injury increased the risk of radiographic knee OA by 1.93 times (95%CI: 1.41-2.65) (Table 3-7). Conversely, injury in the absence of obesity also mildly raised the risk of radiographic knee OA, although by less and not statistically significant, at 1.23 times (95%CI: 0.81-1.86). When obesity and injury were presented together, the estimated risk of radiographic knee OA was further raised to 3.67 times (95%CI: 2.42-5.58) (Table 3-7).

Therefore, the combined effect of obesity and injury on the risk of radiographic knee OA was larger than the the multiple or the sum of individual effects of obesity and injury. This highlighted a positive interaction between obesity and injury on the risk of radiographic knee OA, which was statistically significant on the additive scale (RERI aOR 1.51, 95%CI: 0.10 to 2.92). The positive interaction on the multiplicative scale did not reach statistical significance (RERI aOR: 1.55, 95%CI: 0.87 to 2.74).

Similar results were found in the OAI study. There were positive interactions between obesity and injury on the risk of incident radiographic knee OA on both scales (Table 3-8). However, the magnitude of interaction on both scales was smaller in OAI ($RERI_{-additive}$ aOR: 1.13 and $RERI_{-multiplicative}$ aOR: 1.25) than MOST ($RERI_{-additive}$ aOR: 1.51 and $RERI_{-multiplicative}$ aOR: 1.55). These positive interactions in OAI did not reach statistical significance on either additive (p = 0.21) or multiplicative scales (p = 0.52).

Table 3-7: The interaction between obesity and injury on the risk of incident radiographic knee OA in MOST

	Non-obese		Obese		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	114/883	1 (reference)	115/483	1.93 (1.41 - 2.65); $p < 0.001$	1.95 (1.42 - 2.68); $p < 0.001$
Injured	30/229	1.23 (0.81- 1.86); $p = 0.33$	45/107	3.67 (2.42 - 5.58); $p < 0.001$	3.50 (2.05 - 5.96); $p < 0.001$
Adjusted ORs[2] (95% CI)		1.21 (0.80 - 1.85); $p = 0.37$		1.92 (1.30- 2.84); $p = 0.001$	

Measure of interaction on multiplicative scale: RERI aOR: 1.55, 95%CI: 0.87-2.74, $p = 0.14$.
Measure of interaction on additive scale: RERI aOR: 1.51, 95%CI: 0.10 to 2.92, $p = 0.036$.
*ORs adjusted for age, gender and physical activity

1. ORs for the effect modification of injury on the role of obesity in development of radiographic knee OA

2. ORs for the effect modification of obesity on the role of injury in development of radiographic knee OA

Table 3-8: The interaction between obesity and injury on the risk of incident radiographic knee OA in OAI

	Non-obese		Obese		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	86/1687	1 (reference)	55/560	1.98 (1.34 - 2.92); $p = 0.001$	2.00 (1.34 - 2.96); $p = 0.001$
Injured	32/469	1.43 (0.94- 2.18); $p = 0.09$	22/149	3.55 (2.11 - 5.97); $p < 0.001$	2.51 (1.40 - 4.52); $p = 0.002$
Adjusted ORs[2] (95% CI)		1.42 (0.93 - 2.16); $p = 0.12$		1.98 (1.16- 3.38); $p = 0.013$	

Measure of interaction on multiplicative scale: RERI aOR: 1.25, 95%CI: 0.64 to 2.45, $p = 0.52$.
Measure of interaction on additive scale: RERI aOR: 1.13, 95%CI: -0.63 to 2.89, $p = 0.21$.
*ORs adjusted for age, gender and physical activity

1. ORs for the effect modification of injury on the role of obesity in development of radiographic knee OA

2. ORs for the effect modification of obesity on the role of injury in development of radiographic knee OA

3.1.7 *The interaction between physical activity and obesity on the risk of incident radiographic knee OA*

Data were also stratified by obesity and physical activity to investigate the two-way interaction between physical activity and obesity on the risk of incident radiographic knee OA (Table 3-9 and 3-10).

In MOST, the Obese and Inactive group were 1.87 times (95%CI: 1.30-2.69) more likely to develop radiographic knee OA, which was not largely different to the 2.18 (95%CI: 1.46-3.26) times higher risk of radiographic knee OA in the Obese and Active group (Table 3-9).

Likewise, in OAI, obesity in inactive people increased the risk of radiographic knee OA by 1.34 (95%CI: 1.55-3.55), which was similar to the 131% (95%CI: 1.32-4.04) higher risk of radiographic knee OA in the subgroup of Obese and Active individuals (Table 3-10). That is, physical activity did not have a large interactive effect with obesity on the risk of incident radiographic knee OA in either cohort. This was supported by the statistical test, in which no significant interactions were found on either additive or multiplicative scales (Table 3-9; Table 3-10).

The effect of physical activity on the risk of incident radiographic knee OA across the stratum of obesity (obese and non-obese) was also studied (Table 3-9 and 3-10). In both MOST and OAI, the effect of physical activity on the risk of radiographic knee OA across the strata of obesity (Table 3-9; Table 3-10) was similar to the main effect of physical activity on the risk of radiographic knee OA ($aOR_{\text{-MOST}}$: 0.98, $aOR_{\text{-OAI}}$: 1.20, Table 3-6). This indicated that the main effect of activity on the risk of radiographic knee OA was not modified by the presence or absence of obesity. These data were also supported by the statistical test, where no significant interactions were found (RERI $p_{\text{additive/multiplicative}} > 0.2$) (Table 3-9; Table 3-10).

Table 3-9: The interaction between physical activity and obesity on the risk of incident radiographic knee OA in MOST

	Inactive		Active		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Non-obese	96/678	1 (reference)	48/434	0.82 (0.53 - 1.25); $p = 0.35$	0.85 (0.55 - 1.30); $p = 0.45$
Obese	86/334	1.87 (1.30 - 2.69); $p < 0.001$	74/256	2.18 (1.46 - 3.26); $p < 0.001$	1.13 (0.74 - 1.74); $p = 0.57$
Adjusted ORs[2] (95% CI)		1.91 (1.31 - 2.77); $p < 0.001$		2.70 (1.74 - 4.19); $p < 0.001$	

Measure of interaction on multiplicative scale: RERI aOR: 1.43, 95%CI: 0.81 to 2.55, $p = 0.22$
Measure of interaction on additive scale: RERI aOR: 0.50, 95%CI: -0.38 to 1.37, $p = 0.27$
*ORs adjusted for age, gender and injury

1. ORs for the effect modification of obesity on the role of physical activity in development of radiographic knee OA

2. ORs for the effect modification of physical activity on the role of obesity in development of radiographic knee OA

Table 3-10: The interaction between physical activity and obesity on the risk of incident radiographic knee OA in OAI

	Inactive		Active		
	(N) OA/no- OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Non-obese	74/1450	1 (reference)	44/706	1.35 (0.86 - 2.11); $p = 0.19$	1.41 (0.90 - 2.23); $p = 0.14$
Obese	53/467	2.34 (1.55 - 3.55); $p < 0.001$	24/242	2.31 (1.32 - 4.04); $p = 0.003$	0.94 (0.51 - 1.74); $p = 0.84$
Adjusted ORs[2] (95% CI)		2.34 (1.54 - 3.55); $p < 0.001$		1.71 (0.96 - 3.05); $p < 0.07$	

Measure of interaction on multiplicative scale: RERI aOR: 0.73, 95%CI: 0.36 to 1.50, $p = 0.39$
Measure of interaction on additive scale: RERI aOR: -0.38, 95%CI: -1.82 to 1.07, $p = 0.61$
*ORs adjusted for age, gender and injury

1. ORs for the effect modification of obesity on the role of physical activity in development of radiographic knee OA

2. ORs for the effect modification of physical activity on the role of obesity in development of radiographic knee OA

3.1.8 *The interaction between physical activity and injury on the risk of incident radiographic knee OA*

Finally, the two-way interaction between physical activity and injury on the risk of incident radiographic knee OA was investigated.

In MOST, activity in the absence of injury showed a protective effect on the risk of radiographic knee OA although it was not statistically significant (aOR: 0.87, 95%CI: 0.62-1.22). Conversely, injury in the absence of activity increased the risk of radiographic knee OA by 1.2 time (aOR: 1.24, 95%CI: 0.84-1.84). This increase rose to 1.7 time higher risk when the effect of injury was combined with activity (aOR: 1.73, 95%CI, 1.13-2.66). These highlighted a positive cross over interaction between physical activity and injury on the risk of incident radiographic knee OA. This positive interaction did not reach a statistical significance on either additive (RERI aOR: 0.62, 95%CI: -0.16 to 1.41) or multiplicative (RERI aOR: 1.61, 95%CI: 0.91 to 2.85) scales (Table 3-11).

Moving from MOST to OAI, here, activity in the absence of injury and injury in the absence of activity, both increased the risk of radiographic knee OA (Table 3-12). However, the joint effect of activity and injury on the risk of radiographic knee OA was smaller than the multiple or the sum of the individual

effects of physical activity and injury (Table 3-12). These results highlight that there was a suppressing and negative interaction between injury and activity on the risk of incident radiographic knee OA. However, this negative interaction was negligibly small and not statistically significant on either additive (RERI aOR: -0.38, 95%CI: -1.47 to 0.72) or multiplicative (RERI aOR: 0.74, 95%CI: 0.37 to 1.44) scales.

Table 3-11: The interaction between physical activity and injury on the risk of incident radiographic knee OA in MOST

	Inactive		Active		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	146/828	1 (reference)	83/538	0.87 (0.62 - 1.22); p = 0.42	0.84 (0.60 - 1.18); p = 0.32
Injured	36/184	1.24 (0.84 - 1.84); p = 0.28	39/152	1.73 (1.13 - 2.66); p = 0.01	1.66 (0.93 - 2.97); p = 0.08
Adjusted ORs[2] (95% CI)		1.28 (0.87 - 1.89); p = 0.21		1.92 (1.25 – 2.96); p = 0.003	

Measure of interaction on multiplicative scale: RERI aOR: 1.61, 95%CI: 0.91 to 2.85, p = 0.11.
Measure of interaction on additive scale: RERI aOR: 0.62, 95%CI: -0.16 to 1.41, p = 0.12.
*ORs adjusted for age, gender and obesity

1. ORs for the effect modification of injury on the role of physical activity in development of radiographic knee OA

2. ORs for the effect modification of physical activity on the role of injury in development of radiographic knee OA

Table 3-12: The interaction between physical activity and injury on the risk of incident radiographic knee OA in OAI

	Inactive		Active		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	94/1557	1 (reference)	47/690	1.31 (0.87 - 1.99); p = 0.19	1.25 (0.82 - 1.92); p = 0.30
Injured	33/360	1.75 (1.16 -2.65); p = 0.008	21/258	1.69 (0.99 - 2.90); p = 0.055	1.10 (0.60 - 2.00); p = 0.76
Adjusted ORs[2] (95% CI)		1.78 (1.17 -2.69); p = 0.007		1.29 (0.75 – 2.22); p = 0.36	

Measure of interaction on multiplicative scale: RERI aOR: 0.74, 95%CI: 0.37 to 1.44, p = 0.37.
Measure of interaction on additive scale: RERI aOR: -0.38, 95%CI: -1.47 to 0.72, p = 0.50.
*ORs adjusted for age, gender and obesity

1. ORs for the effect modification of injury on the role of physical activity in development of radiographic knee OA

2. ORs for the effect modification of physical activity on the role of injury in development of radiographic knee OA

3.1.9 *The interaction between obesity, injury and physical activity on the risk of incident radiographic knee OA*

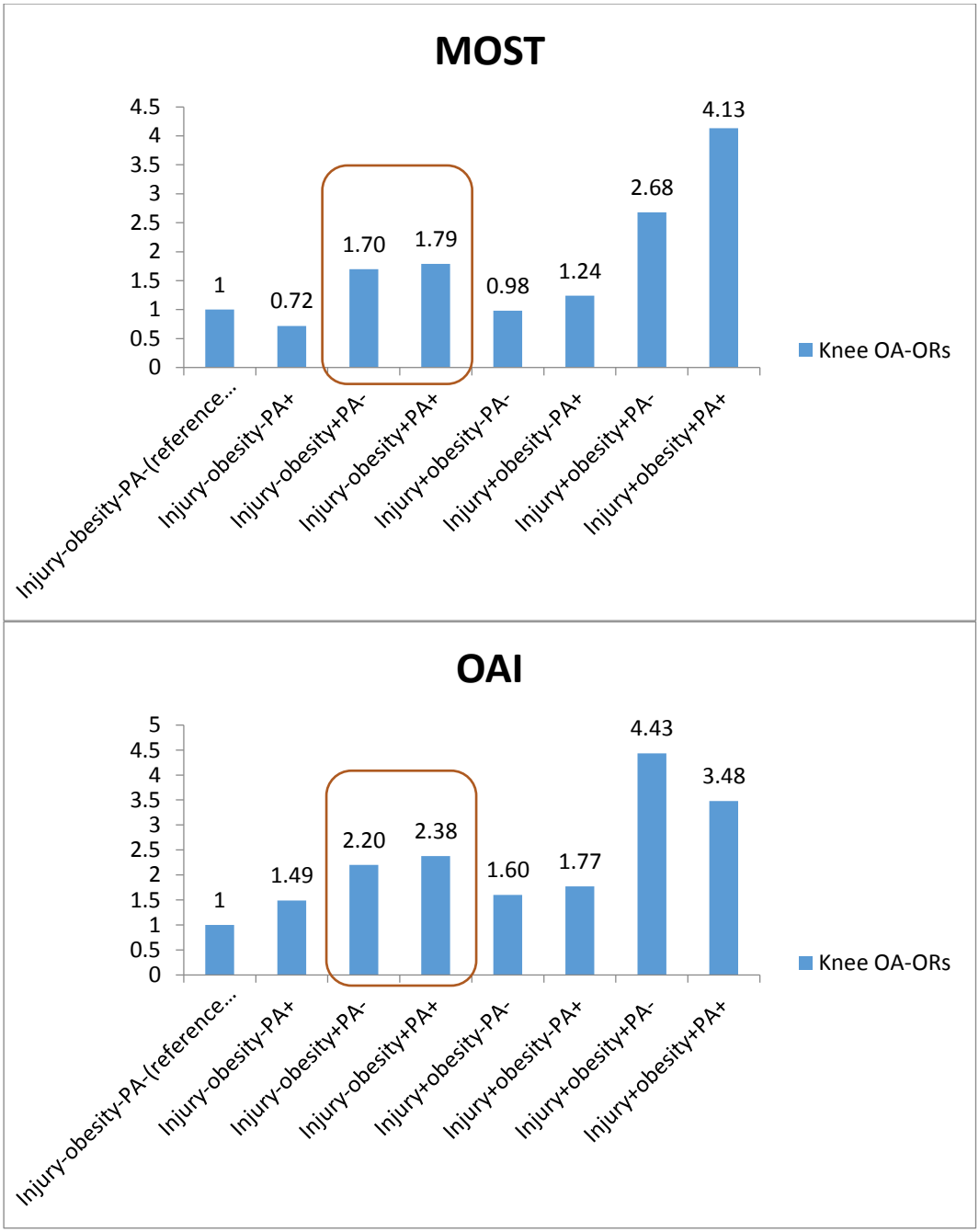
In these last results for incident radiographic knee OA, the three-way interaction between all three variables of obesity, injury and physical activity were examined.

For the MOST dataset (Figure 3-3 and Table 3-13), in the subgroup of Obese and Uninjured people, the active (aOR: 1.79, 95CI: 1.14-2.80) and inactive (aOR: 1.70, 95CI: 1.14-2.54) group both had a similar risk of incident radiographic knee OA as compared to the background risk group (non-obese, uninjured and inactive people).

Similarly, in OAI, active (aOR: 2.38) and inactive (aOR: 2.20) people in the subgroup of Obese and Uninjured individuals had similar risk of incident radiographic knee OA (Figure 3-3 and Table 3-14). That is, physical activity did not have much interactive effect with obesity on the risk of incident radiographic knee OA when injury was absent. This was also confirmed by the statistical tests, in which no significant interactions were found between physical activity and obesity on either additive ($RERI_{\text{-MOST}}$ aOR: 0.36, 95%CI: -0.49 to 1.22; $RERI_{\text{-OAI}}$ aOR: -0.31, 95%CI: -1.99 to 1.36) or

multiplicative scales ($RERI_{-MOST}$ aOR: 1.46, 95%CI: 0.75 to 2.81; $RERI_{-OAI}$ aOR: 0.72, 95%CI: 0.31 to 1.64).

Figure 3-3: The risk of incident radiographic knee OA in different subgroups of obesity-injury-physical activity



*ORs adjusted for age and gender and obesity
PA+: active group; PA-: inactive group; Injury+: injured group; Injury-: uninjured group, Obesity+: obese group; Obesity-: non-obese group

Table 3-13: The interaction between physical activity, obesity and injury on the risk of incident radiographic knee OA in MOST

	Non-obese		Obese	
	Uninjured	Injured	Uninjured	Injured
	aOR* (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Inactive	1	0.98 (0.56 - 1.73); $p = 0.94$	1.70 (1.14 - 2.54); $p = 0.009$	2.68 (1.52 - 4.72); $p = 0.001$
Active	0.72 (0.44 - 1.17); $p = 0.19$	1.24 (0.67 - 2.28); $p = 0.50$	1.79 (1.14 - 2.80); $p = 0.01$	4.13 (2.99 - 7.41); $p < 0.001$

Measure of interaction on multiplicative scale (obesity+, injury+, physical activity+): RERI aOR: 0.83, 95%CI: 0.26-2.67, $p = 0.76$.
Measure of interaction on multiplicative scale (obesity-, injury+, physical activity+): RERI aOR: 1.75, 95%CI: 0.75 to 4.08, $p = 0.19$.
Measure of interaction on multiplicative scale (obesity+, injury-, physical activity+): RERI aOR: 1.46, 95%CI: 0.75 to 2.81, $p = 0.25$.
Measure of interaction on multiplicative scale (obesity+, injury+, physical activity-): RERI aOR: 1.60, 95%CI: 0.72 to 3.56, $p = 0.24$.

Measure of interaction on additive scale (obesity+, injury+, physical activity+): RERI aOR: 0.82, 95%CI: -1.86 to 3.52, $p = 0.58$.
Measure of interaction on additive scale (obesity-, injury+, physical activity+): RERI aOR: 0.53, 95%CI: -0.32 to 1.40, $p = 0.22$.
Measure of interaction on additive scale (obesity+, injury-, physical activity+): RERI aOR: 0.36, 95%CI: -0.49 to 1.22, $p = 0.40$.
Measure of interaction on additive scale (obesity+, injury+, physical activity-): RERI aOR: 0.99, 95%CI: -0.48 to 2.47, $p = 0.18$.

***ORs adjusted for age and gender**

Table 3-14: The interaction between physical activity, obesity and injury on the risk of incident radiographic knee OA in OAI

	Non-obese		Obese	
	Uninjured	Injured	Uninjured	Injured
	aOR* (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Inactive	1	1.60 (0.93 - 2.75); $p = 0.09$	2.20 (1.37 - 3.55); $p = 0.001$	4.43 (2.36 – 8.34); $p < 0.001$
Active	1.49 (0.89 - 2.48); $p = 0.13$	1.77 (0.92 - 3.41); $p = 0.09$	2.38 (1.26 - 4.49); $p = 0.008$	3.48 (1.44 - 8.40); $p = 0.006$

Measure of interaction on multiplicative scale (obesity-, injury+, physical activity+): RERI aOR: 0.97, 95%CI: 0.23-4.01, $p = 0.97$.
Measure of interaction on multiplicative scale (obesity-, injury+, physical activity+): RERI aOR: 0.74, 95%CI: 0.31 to 1.73, $p = 0.49$.
Measure of interaction on multiplicative scale (obesity+, injury-, physical activity+): RERI aOR: 0.72, 95%CI: 0.31 to 1.64, $p = 0.44$.
Measure of interaction on multiplicative scale (obesity+, injury+, physical activity-): RERI aOR: 1.25, 95%CI: 0.54 to 2.89, $p = 0.59$.

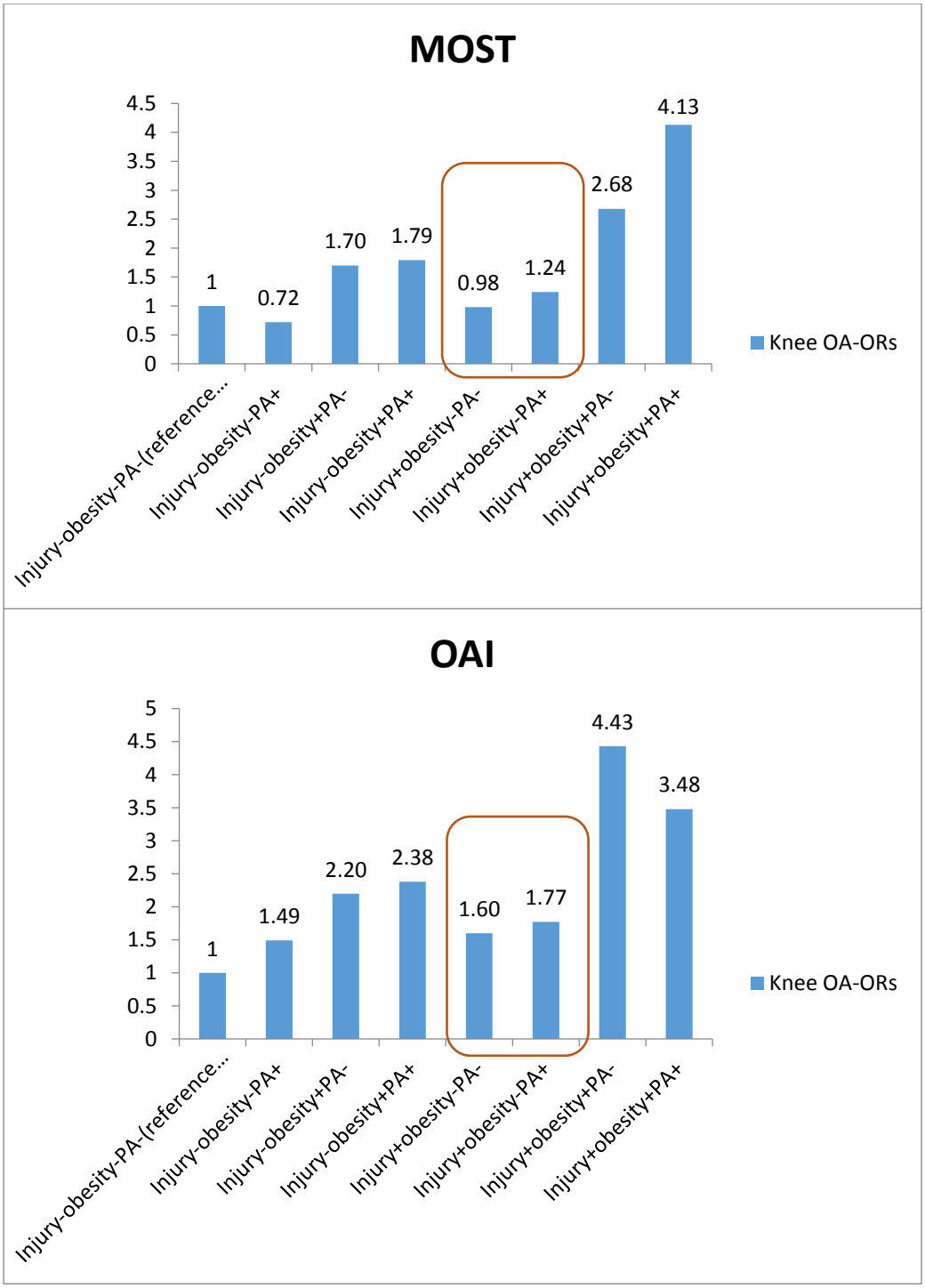
Measure of interaction on additive scale (obesity+, injury+, physical activity+): RERI aOR: -0.80, 95%CI: -4.91 to 3.30, $P = 0.70$
Measure of interaction on additive scale (obesity-, injury+, physical activity+): RERI aOR: -0.32, 95%CI: -1.70 to 1.06, $p = 0.65$.
Measure of interaction on additive scale (obesity+, injury-, physical activity+): RERI aOR: -0.31, 95%CI: -1.99 to 1.36, $p = 0.71$.
Measure of interaction on additive scale (obesity+, injury+, physical activity-): RERI aOR: 1.62, 95%CI: -1.01 to 4.27, $p = 0.22$.

***ORs adjusted for age and gender**

Secondly, for the subgroup of non-obese people with injury in the MOST dataset, those who were active had an aOR of 1.24- a slightly greater risk of radiographic knee OA than inactive people with aOR of 0.98 (Figure 3-4 and Table 3-13).

This highlighted a small cross over effect (positive interaction) of physical activity on the risk of radiographic knee OA in the presence versus absence of injury in non-obese people. However, the magnitude of interaction was relatively small and did not have a significant effect on the risk of radiographic knee OA ($RERI_{-additive}$ aOR: 0.53, 95%CI: -0.32 to 1.40; $RERI_{-multiplicative}$ aOR: 1.75, 95%CI: 0.75 to 4.08). Similarly, in OAI, activity did not have a significant interactive effect with injury on the risk of incident radiographic knee OA when obesity was absent ($RERI_{-additive}$ aOR: -0.32, 95%CI: -1.70 to 1.06; $RERI_{-multiplicative}$ aOR: 0.74, 95%CI: 0.31 to 1.73 (Figure 3-4 and Table 3-14).

Figure 3-4: The incident risk of radiographic knee OA in different subgroups of obesity-injury-physical activity



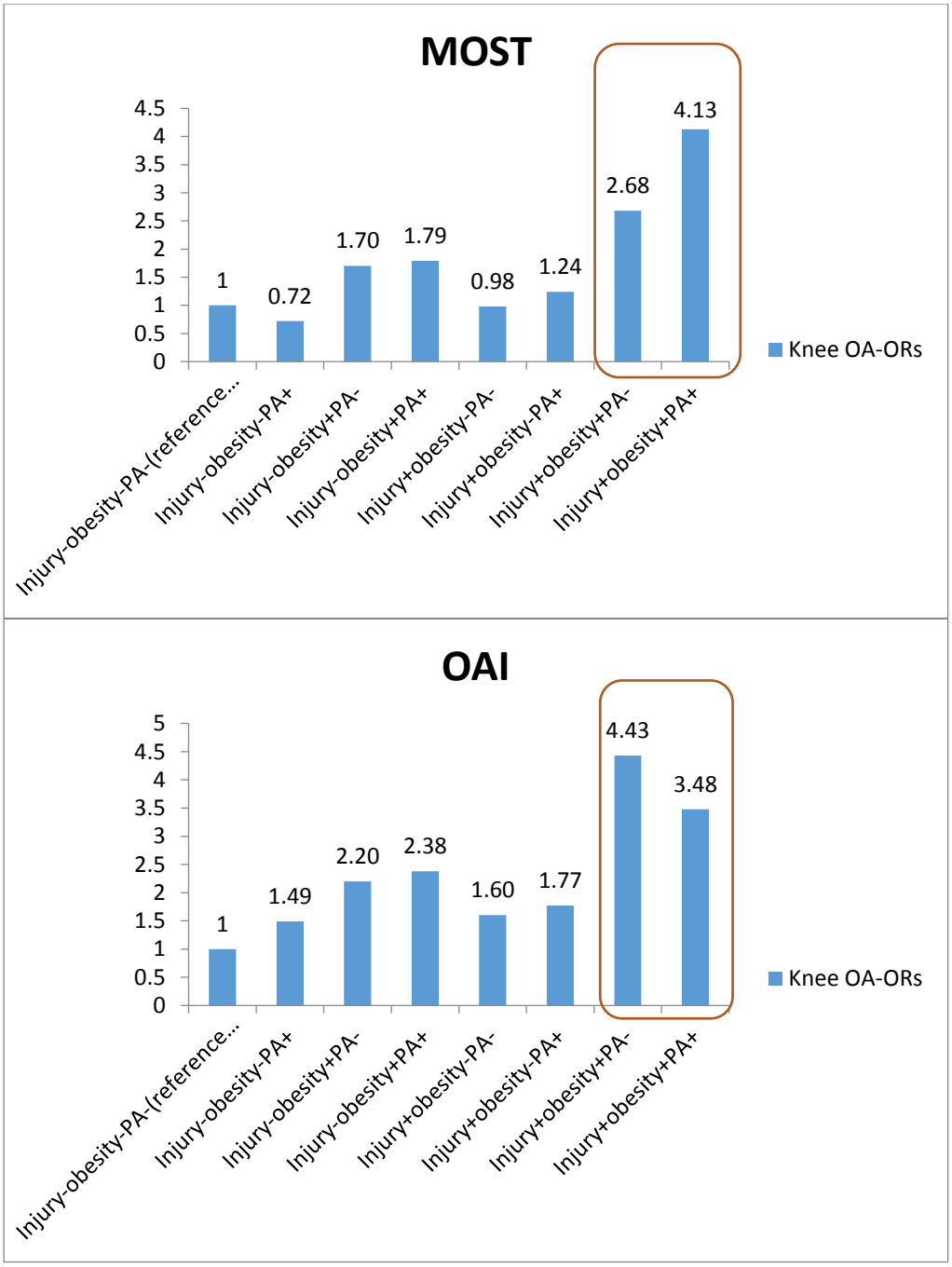
*ORs adjusted for age and gender and obesity

PA+: active group; PA-: inactive group; Injury+: injured group; Injury-: uninjured group, Obesity+: obese group; Obesity-: non-obese group

Thirdly, for the Injured and Obese group in MOST, those who were active had an aOR of 4.13- a greater risk of radiographic knee OA than inactive people with aOR of 2.68 (Figure 3-5 and Table 3-13). This showed a positive three-way interaction between obesity, injury and activity on the additive scale, but a small negative interaction on the multiplicative scale. However, none of these interactions were statistically significant ($RERI_{-additive}$ aOR: 0.82, 95%CI: -1.86 to 3.52; $RERI_{-multiplicative}$ aOR: 0.83, 95%CI: 0.26 to 2.67). More importantly, the confidence limits on both scales were wide. Therefore, it would be impossible to conclude any potential positive or negative interactions.

In OAI (Figure 3-5 and Table 3-14), when injury and obesity were presented together, active people (aOR: 3.48) had lower risk of radiographic knee OA than inactive participants (aOR: 4.43). That is, there was a small negative three-way interaction between obesity, injury and physical activity. However, this was not statistically significant on either additive (RERI aOR: -0.80, 95%CI: -4.91 to 3.30) or multiplicative (RERI aOR: 0.97, 95%CI: 0.23 to 4.01) scales.

Figure 3-5: The incident risk of radiographic knee OA in different subgroups of obesity-injury-physical activity



*ORs adjusted for age and gender and obesity
PA+: active group; PA-: inactive group; Injury+: injured group; Injury-: uninjured group, Obesity+: obese group; Obesity-: non-obese group

Finally, the Obese and Injured subgroup was at the highest risk of radiographic knee OA in both cohorts regardless of being active or inactive (Figure 3-5). This was partly due to the single effect of obesity, injury and also due to their interactions. Mild evidence of positive interactions between obesity and injury on risk of incident radiographic knee OA were also found in both cohorts. However, the magnitudes of interactions were not large enough to reach statistical significant on either additive ($RERI_{-MOST}$ aOR: 0.99, 95%CI: -0.48 to 2.47; $RERI_{-OAI}$ aOR: 1.62, 95%CI: -1.01 to 4.27) or multiplicative scales in either cohort ($RERI_{-MOST}$ aOR: 1.60, 95%CI: 0.72 to 3.56; $RERI_{-OAI}$ aOR: 1.25, 95%CI: 0.54 to 2.89).

3.2 Incidence of symptomatic knee OA

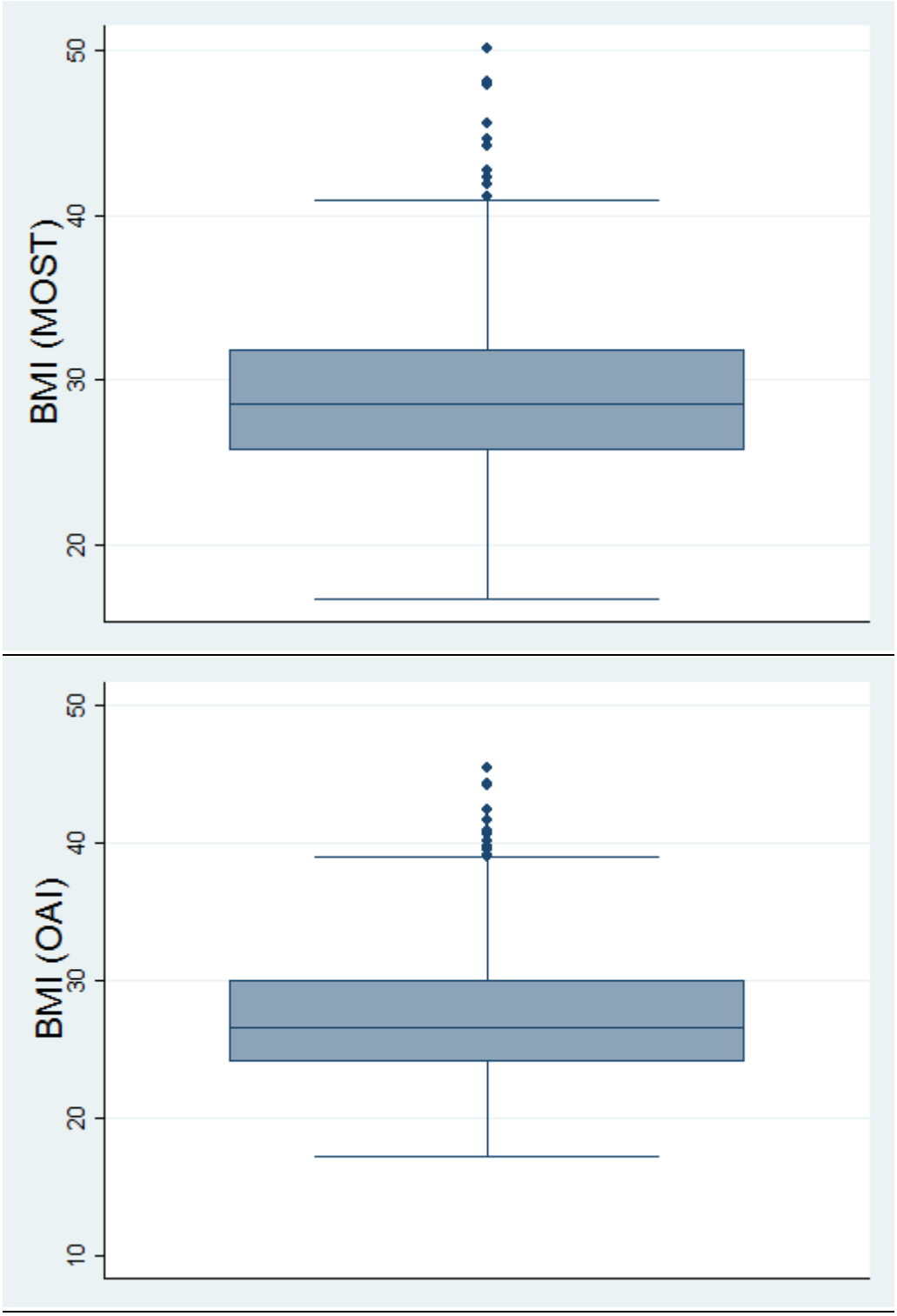
1004 participants from MOST and 1558 participants from OAI met the inclusion criteria for the incident symptomatic knee OA study (that is, they did not have symptomatic knee OA in either knee at baseline). In MOST, 4 participants and in OAI 28 participants were excluded due to missing injury (either knee), physical activity or BMI data at the baseline assessment. Therefore, 2000 knees (1000 participants) in MOST and 3060 knees (1530 participants) in OAI were included in the data analysis.

Participants' characteristics are presented in Table 3-15 (Figure 3-6; Figure 3-7). Similar to the incident radiographic knee OA study, the mean age of participants in MOST and OAI were similar, but the mean BMI and PASE score were slightly higher in MOST than OAI. (Table 3-15; Table 3-1).

Table 3-15: Participants' characteristics data at baseline

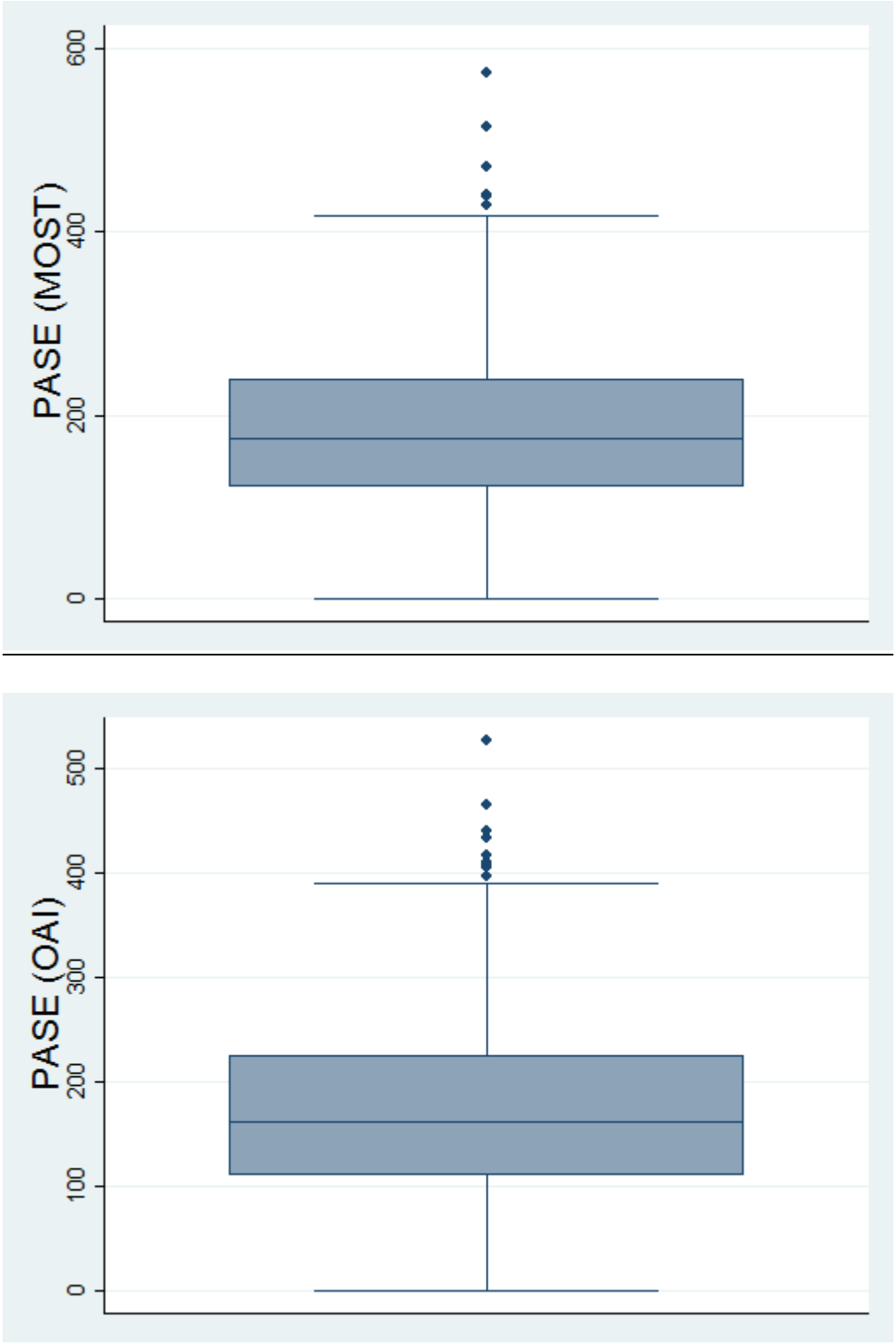
Cohort		AGE	BMI (Baseline)	PASE (Baseline)
MOST	Mean ± SD	60.24 ± 7.56	28.98 ± 4.63	185.53 ± 87.48
	Min-Max	50-79	16.72-50.13	0-573.20
	Range	29	33.41	573
OAI	Mean ± SD	59.22 ± 9.07	27.19 ± 4.44	170.41 ± 82.56
	Min-Max	45-79	17.2-45.4	0-526
	Range	34	28.20	526

Figure 3-6: Distribution of BMI data at baseline



*BMI: Body mass index

Figure 3-7: Distribution of PASE data at baseline



*PASE: Physical Activity Scale for Elderly

3.2.1 *Gender and risk of incident symptomatic knee OA*

The majority of participants (59%) were female in both cohorts. In MOST, the risk of symptomatic knee OA was significantly higher in females than males (aOR: 1.70, 95%CI: 1.10-2.71). In contrast, whilst there was a slightly higher risk for females in OAI it was not statistically significant (aOR: 1.26, 95%CI: 0.72-2.19). (Table 3-16).

Table 3-16: Gender and risk of incident symptomatic knee OA

Cohort	Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	Male	779 (95.5%)	37 (4.5%)	816	-	-
	Female	1102 (93.1%)	82 (6.9%)	1184	1.57 (1.00 – 2.47) $p = 0.052$	1.70 (1.10 – 2.71) $p = 0.025$
OAI	Male	1236 (97.8%)	28 (2.2%)	1264	-	-
	Female	1751 (97.5%)	45 (2.5%)	1796	1.14 (0.66 – 1.96) $p = 0.65$	1.26 (0.72 – 2.19) $p = 0.42$

***Odds ratio (OR) adjusted for Injury, obesity, age and physical activity**

3.2.2 *Age and risk of incident symptomatic Knee OA*

In MOST, the risk of incident symptomatic knee OA was almost 40% lower in both middle age and old age groups compared to the young age groups (Table 3-17). In OAI, both the middle age (aOR: 1.55) and old age (aOR: 1.22) groups were at higher risk than the young age group. However, these associations were not statistically significant in either MOST or OAI (Table 3-17).

Table 3-17: Age and risk of incident symptomatic knee OA

Cohort	Age Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	45-55	546 (91.9%)	48 (8.1%)	594	-	-
	55-65	763 (94.9%)	41 (5.1%)	804	0.61 (0.37 - 1.00) $p = 0.052$	0.61 (0.37 - 1.01) $p = 0.053$
	65-79	572 (95.0%)	30 (5.0%)	602	0.60 (0.35 - 1.02) $p = 0.061$	0.63 (0.36 - 1.11) $p = 0.11$
OAI	45-55	1136 (97.9%)	24 (2.1%)	1160	-	-
	55-65	950 (96.9%)	30 (3.1%)	980	1.50 (0.81 – 2.77) $p = 0.20$	1.55 (0.83 - 2.92) $p = 0.17$
	65-79	901 (97.9%)	19 (2.1%)	920	1.00 (0.50 - 1.99) $p = 0.996$	1.22 (0.59- 2.54) $p = 0.60$

***OR adjusted for Injury, obesity, gender and physical activity**

3.2.3 *The association between obesity and the risk of incident symptomatic knee OA*

At baseline, 37% of MOST participants were obese, which was higher than OAI (26%) (Table 3-18). At the last follow-up (MOST: 60-month, OAI: 48-month), the prevalence of knee OA was almost double in the obese than non-obese group in both cohorts (Table 3-18). The risk of incident symptomatic knee OA was significantly higher in obese than non-obese individuals in MOST (aOR: 1.92, 95%CI: 1.25-2.95). This association was even stronger in OAI (aOR: 2.40, 95%CI: 1.39-4.12) in spite of having a shorter follow-up period of 48-months compared to 60-months in MOST (Table 3-18).

Table 3-18: Obesity and risk of incident symptomatic knee OA

Cohort	Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	Non-obese	1199 (95.5%)	57 (4.5%)	1256	-	
	Obese	682 (91.7%)	62 (8.3%)	744	1.91 (1.25-2.93) $p = 0.003$	1.92 (1.25-2.95) $p = 0.003$
OAI	Non-obese	2233 (98.2%)	41 (1.8%)	2274	-	
	Obese	754 (95.9%)	32 (4.1%)	786	2.31 (1.35-3.96) $p = 0.002$	2.40 (1.39-4.12) $p = 0.002$

***OR adjusted for Injury, age, gender and physical activity**

3.2.4 *The association between injury and the risk of incident symptomatic Knee OA*

Approximately 21% of participants in each cohort had injury at baseline (Table 3-19). In MOST, the risk of incident symptomatic knee OA was significantly higher in injured than uninjured individuals (aOR: 1.88, 95%CI: 1.26-2.83). In OAI, the risk of incident symptomatic knee OA was also higher in injured compared to uninjured people, but it did not reach a statistical significance (aOR: 1.63, 95%CI: 0.98-2.70).

Table 3-19: Injury and risk of incident symptomatic knee OA

Cohort	Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR * (95% CI)
		Without OA (%)	OA (%)			
MOST	Uninjured	1505 (94.7%)	85 (5.3%)	1590	-	-
	Injured	376 (91.7%)	34 (8.3%)	410	1.78 (1.20-2.64) $p = 0.004$	1.88 (1.26-2.83) $p = 0.002$
OAI	Uninjured	2337 (97.9%)	51 (2.1%)	2388	-	-
	Injured	650 (96.7%)	22 (3.3%)	672	1.58 (0.96-2.60) $p = 0.07$	1.63 (0.98-2.70) $p = 0.06$

***OR adjusted for obesity, age, gender and physical activity**

3.2.5 *The association between physical activity and the risk of incident symptomatic Knee OA*

40% of MOST participants were active compared to 33% in OAI. At the last follow-up (MOST: 60-month; OAI: 48-month), the prevalence of symptomatic knee OA was similar amongst active and inactive people in both cohorts (Table 3-20). No significant association was found between physical activity and symptomatic knee OA in either MOST (p = 0.42) or OAI (p = 0.64). The risk of symptomatic knee OA due to physical activity was close to one in both MOST (OR: 0.89, 95%CI: 0.57-1.38) and OAI (OR: 1.12 95%CI: 0.64-1.95). That is, the activity neither increased nor protected against the risk of symptomatic knee OA. Adjusting for confounders did not make any significant change to the results (Table 3-20).

Table 3-20: Physical activity and risk of incident symptomatic knee OA

Cohort	Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	Inactive	1116 (93.8%)	74 (6.2%)	1190	-	-
	Active	765 (94.4%)	45 (5.6%)	810	0.89 (0.57-1.38) p = 0.59	0.83 (0.52-1.31) p = 0.42
OAI	Inactive	1997 (97.7%)	47 (2.3%)	2044	-	-
	Active	990 (97.4%)	26 (2.6%)	1016	1.12 (0.64-1.95) p = 0.70	1.15 (0.64-2.06) p = 0.64

***OR adjusted for Injury, obesity, age and gender**

3.2.6 *The interaction between obesity and injury on the risk of incident symptomatic knee OA*

In order to investigate the effect of two-way interaction between obesity and injury on the incident symptomatic knee OA, the data were stratified by obesity and injury.

In MOST, obesity in the absence of injury increased the risk of symptomatic knee OA by 1.69 times (95%CI: 1.03-2.78). Conversely, injury in the absence of obesity also mildly raised the risk of symptomatic knee OA by 1.49 times (95%CI: 0.82-2.75). When obesity and injury were presented together, the estimated risk of symptomatic knee OA was further raised to four folds approximately (aOR: 3.85, 95%CI: 2.14-6.92). Therefore, the combined effect of obesity and injury on the risk of symptomatic knee OA was larger than the multiple or the sum of individual effects of obesity and injury. This highlighted a positive interaction between obesity and injury on the risk of symptomatic knee OA on both additive (RERI aOR 1.65, 95%CI: -0.38 to 3.68) and multiplicative scales (RERI aOR: 1.51, 95%CI: 0.67 - 3.42) (Table 3-21).

Similarly, there was a positive interaction between obesity and injury on the risk of symptomatic knee OA in OAI on both scales (Table 3-22). The magnitude of the excess risk due to interaction between obesity and injury was larger on both

additive ($RERI_{-additive}$ aOR: 3.13) and multiplicative scale ($RERI_{-multiplicative}$ aOR: 2.83) in OAI compared to the $RERI_{-additive}$ of 1.65 and $RERI_{-multiplicative}$ of 1.51 in MOST. This reached a statistical significance on both additive (p = 0.046) and multiplicative scales (p = 0.048) in OAI, but not in MOST (p > 0.1).

Table 3-21: The interaction between obesity and injury on the risk of incident symptomatic knee OA in MOST

	Non-obese		Obese		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	43/954	1 (reference)	42/551	1.69 (1.03 - 2.78); $p = 0.04$	1.79 (1.08 - 2.96); $p = 0.02$
Injured	14/245	1.49 (0.82- 2.75); $p = 0.19$	20/131	3.85 (2.14 - 6.92); $p < 0.001$	2.60 (1.27 - 5.32); $p = 0.01$
Adjusted ORs[2] (95% CI)		1.53 (0.83 - 2.82); $p = 0.17$		2.24 (1.28- 3.91); $p = 0.005$	

Measure of interaction on multiplicative: scale: RERI aOR: 1.51, 95%CI: 0.67 to 3.42, $p = 0.32$.
Measure of interaction on additive scale: RERI aOR: 1.65, 95%CI: -0.38 to 3.68, $p = 0.11$.
*ORs adjusted for age, gender and physical activity `

1. ORs for the effect modification of injury on the role of obesity in development of symptomatic knee OA
2. ORs for the effect modification of obesity on the role of injury in development of symptomatic knee OA

Table 3-22: The interaction between obesity and injury on the risk of incident symptomatic knee OA in OAI

	Non-obese		Obese		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	32/1741	1 (reference)	19/596	1.71 (0.90 - 3.27); $p = 0.10$	1.70 (0.90 - 3.22); $p = 0.10$
Injured	9/492	1.00 (0.48- 2.10); $p = 0.998$	13/158	4.84 (2.38 - 9.83); $p < 0.001$	5.25 (2.15 - 12.81); $p < 0.001$
Adjusted ORs[2] (95% CI)		0.99 (0.47 - 2.07); $p = 0.97$		3.04 (1.46- 6.33); $p = 0.003$	

Measure of interaction on multiplicative scale: RERI aOR: 2.83, 95%CI: 1.01 to 7.93, $p = 0.048$.
Measure of interaction on additive scale: RERI aOR: 3.13, 95%CI: 0.05 to 6.21, $p = 0.046$.
*ORs adjusted for age, gender and physical activity

1. ORs for the effect modification of injury on the role of obesity in development of symptomatic knee OA
2. ORs for the effect modification of obesity on the role of injury in development of symptomatic knee OA

3.2.7 *The interaction between physical activity and obesity on the risk of incident symptomatic knee OA*

Data were also stratified by obesity and physical activity to investigate the effect of two-way interaction between physical activity and obesity on incident symptomatic knee OA (Table 3-23; Table 3-24).

In MOST, obesity in inactive people increased the risk of symptomatic knee OA by 62% (95%CI: 0.94-2.80), which was similar to the 64% (95%CI: 0.9-3.00) risk of symptomatic knee OA in the subgroup of Obese and Active individuals (Table 3-23).

Likewise, in OAI, the Obese and Inactive group were 2.5 times (95%CI: 1.28-4.89) at higher risk of knee OA, which was comparable to 2.68 (95%CI: 1.14-6.31) times the risk of symptomatic knee OA in the Obese and Active group. That is, physical activity did not have much interactive effect with obesity on the risk of symptomatic knee OA in either cohort. This was supported by the statistical test, in which no significant interactions were found on either additive or multiplicative scales (Table 3-23; Table 3-24).

The effect of physical activity on the risk of incident symptomatic knee OA across the stratum of obesity (obese and non-obese) was also studied (Table 3-23 and Table 3-24).

In both MOST and OAI, the effect of physical activity across the strata of obesity was similar to the main effect of physical activity (aOA_{-MOST}: 0.83, aOR_{-OAI}: 1.15) on incident symptomatic knee OA. This indicated that the effect of activity on the risk of symptomatic knee OA was not modified by the effect of obesity. These data were also supported by the statistical test, where no significant interactions were found (RERI $p_{additive/multiplicative} > 0.3$) (Table 3-23; Table 3-24).

Table 3-23: The interaction between physical activity and obesity on the risk of incident symptomatic knee OA in MOST

	Inactive		Active		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Non-obese	40/734	1 (reference)	17/465	0.65 (0.33 - 1.28); p = 0.21	0.66 (0.33 - 1.33); p = 0.24
Obese	34/382	1.62 (0.94 - 2.80); p = 0.08	28/300	1.64 (0.90 - 3.00); p = 0.11	1.00 (0.54 - 1.87); p = 1.00
Adjusted ORs[2] (95% CI)		1.67 (0.95 - 2.93); p = 0.07		2.55 (1.29 - 5.03); p = 0.007	

Measure of interaction on multiplicative scale: RERI aOR: 1.56, 95%CI: 0.64 to 3.79, p = 0.33.
Measure of interaction on additive scale: RERI aOR: 0.37, 95%CI: -0.70 to 1.44, p = 0.50.
*ORs adjusted for age, gender and injury

1. ORs for the effect modification of obesity on the role of physical activity in development of symptomatic knee OA

2. ORs for the effect modification of physical activity on the role of obesity in development of symptomatic knee OA

Table 3-24: The interaction between physical activity and obesity on the risk of incident symptomatic knee OA in OAI

	Inactive		Active		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Non-obese	26/1498	1 (reference)	15/735	1.21 (0.57 - 2.59); p = 0.63	1.26 (0.57 - 2.75); p = 0.57
Obese	21/499	2.50 (1.28 - 4.89); p = 0.008	11/255	2.68 (1.14 - 6.31); p = 0.02	1.05 (0.43 - 2.56); p = 0.92
Adjusted ORs[2] (95% CI)		2.55 (1.32 – 4.93); p = 0.005		2.11 (0.85 - 5.22); p = 0.11	

Measure of interaction on multiplicative scale: RERI aOR: 0.89, 95%CI: 0.29 to 2.74, p = 0.84.
Measure of interaction on additive scale: RERI aOR: -0.02, 95%CI: -2.41 to 2.37, p = 0.99.
*ORs adjusted for age, gender and injury

1. ORs for the effect modification of obesity on the role of physical activity in development of symptomatic knee OA

2. ORs for the effect modification of physical activity on the role of obesity in development of symptomatic knee OA

3.2.8 *The interaction between physical activity and injury on the risk of incident symptomatic knee OA*

Finally, the two-way interaction between physical activity and injury on the risk of symptomatic knee OA was investigated.

In MOST, activity in the absence of injury showed a protective effect on the risk of symptomatic knee OA although it was not statistically significant (aOR: 0.66, 95%CI: 0.38-1.14) (Table 3-25). Conversely, injury in the absence of activity increased the risk of symptomatic knee OA by 40% (aOR: 1.40, 95%CI: 0.80-2.45). This increase rose to 85% when the effect of injury was combined with activity (aOR: 1.85, 95%CI, 1.01-3.36). These results highlighted a positive cross-over interaction between physical activity and injury on the risk of incident symptomatic knee OA. This positive interaction did not reach a statistical significance on either additive (RERI aOR: 0.79, 95%CI: -0.38 to 1.96) or multiplicative (RERI aOR: 2.00, 95%CI: 0.87 to 4.57) scales (Table 3-25).

Moving from MOST to OAI, here, activity in the absence of injury and injury in the absence of activity, both increased the risk of symptomatic knee OA (Table 3-26). However, the join effect of activity and injury on the risk of symptomatic knee OA was smaller than the multiple or the sum of individual effects of physical activity and injury. These results highlight

that there is a suppressing and a negative interaction between injury and obesity on the risk of incident symptomatic knee OA. This negative interaction was small and not statistically significant on either additive (RERI aOR: -0.70, 95%CI: -2.44 to 1.04) or multiplicative (RERI aOR: 0.61, 95%CI: 0.21 to 1.73) scales. The confidence limits were also wide, which would preclude any conclusions about any potential interactions between physical activity and injury on the risk of incident symptomatic knee OA.

Table 3-25: The interaction between physical activity and injury on the risk of incident symptomatic knee OA in MOST

	Inactive		Active		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	58/913	1 (reference)	27/592	0.66 (0.38 - 1.14); p = 0.14	0.64 (0.37 - 1.12); p = 0.12
Injured	16/203	1.40 (0.80 - 2.45); p = 0.25	18/173	1.85 (1.01 - 3.36); p = 0.045	1.41 (0.65 - 3.04); p = 0.38
Adjusted ORs[2] (95% CI)		1.46 (0.84 - 2.55); p = 0.18		2.53 (1.35 – 4.74); p = 0.004	

Measure of interaction on multiplicative scale: RERI aOR: 2.00, 95%CI: 0.87 to 4.57, p = 0.10.
Measure of interaction on additive scale: RERI aOR: 0.79, 95%CI: -0.38 to 1.96, p = 0.19.
*ORs adjusted for age, gender and obesity

1. ORs for the effect modification of injury on the role of physical activity in development of symptomatic knee OA

2. ORs for the effect modification of physical activity on the role of injury in development of symptomatic knee OA

Table 3-26: The interaction between physical activity and injury on the risk of incident symptomatic knee OA in OAI

	Inactive		Active		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	32/1619	1 (reference)	19/718	1.35 (0.69 - 2.64); p = 0.38	1.29 (0.66 - 2.52); p = 0.45
Injured	15/387	1.95 (1.04 - 3.66); p = 0.04	7/272	1.60 (0.67 - 3.81); p = 0.29	0.81 (0.31 - 2.11); p = 0.67
Adjusted ORs[2] (95% CI)		2.08 (1.10 – 3.96); p = 0.025		1.13 (0.48 - 2.63); p = 0.79	

Measure of interaction on multiplicative scale: RERI aOR: 0.61, 95%CI: 0.21 to 1.73, p = 0.35.
Measure of interaction on additive scale: RERI aOR: -0.70, 95%CI: -2.44 to 1.04, p = 0.43.
*ORs adjusted for age, gender and obesity

1. ORs for the effect modification of injury on the role of physical activity in development of symptomatic knee OA

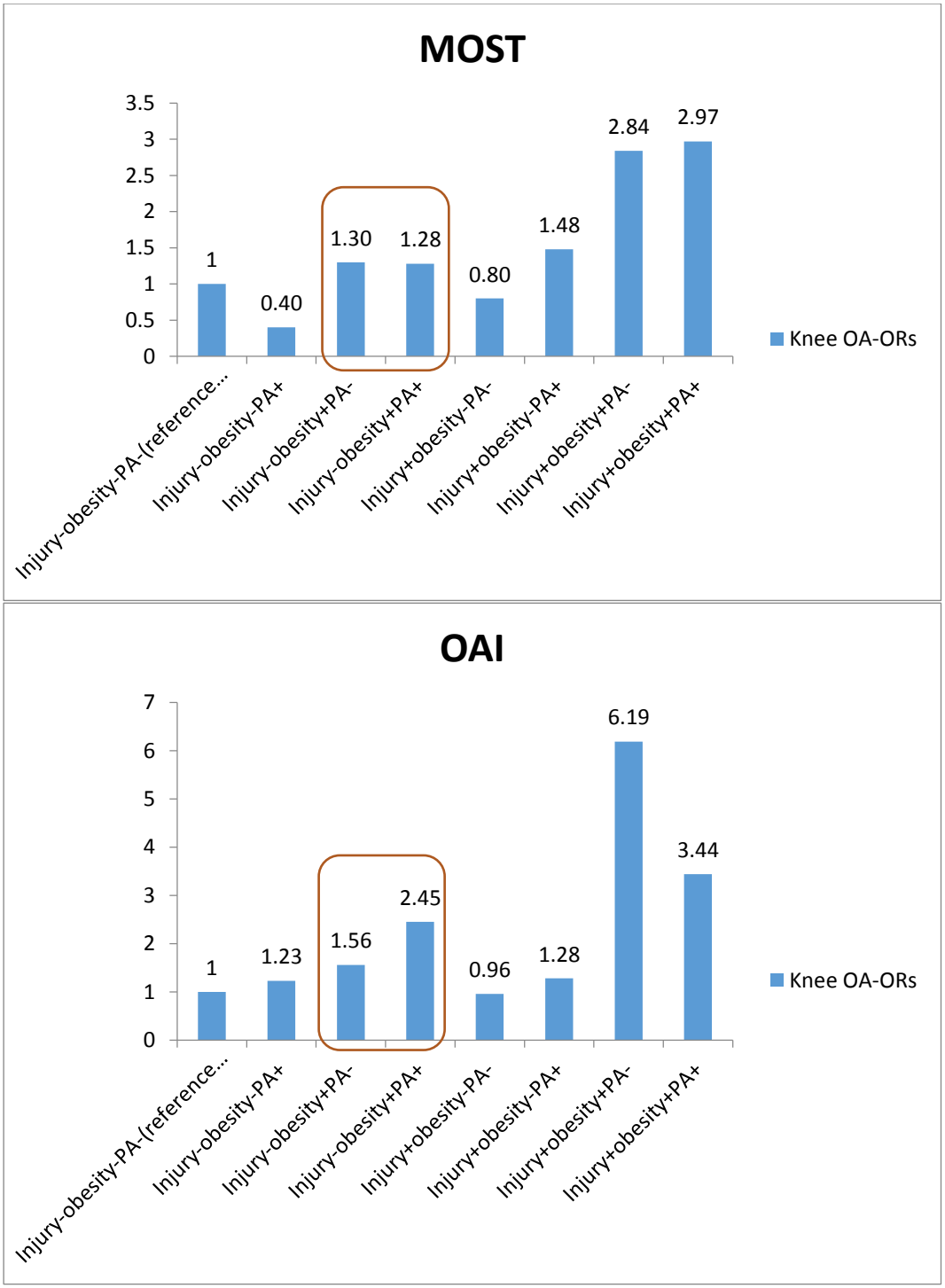
2. ORs for the effect modification of physical activity on the role of injury in development of symptomatic knee OA

3.2.9 *The interaction between obesity, injury and physical activity on the risk of incident symptomatic knee OA*

In these last results for incident symptomatic knee OA, the three-way interaction between all three variables of obesity, injury and physical activity were examined.

For the subgroup of obese people with no injury, in both cohorts, (Figure 3-8, Table 3-27 and Table 3-28), there was some evidence of positive interaction between physical activity and obesity on the risk of incident symptomatic knee OA. However, the magnitude of interaction was not large enough to have any significant effect more than the individual effect of obesity and activity on the risk of incident symptomatic knee OA. This was confirmed by the statistical tests, in which no significant interactions were found between obesity and activity on the risk of incident symptomatic knee OA on either additive ($RERI_{\text{-MOST}}$ aOR: 0.57, 95%CI: -0.40 to 1.55; $RERI_{\text{-OAI}}$ aOR: 0.67, 95%CI: -1.69 to 3.03) or multiplicative ($RERI_{\text{-MOST}}$ aOR: 2.45, 95%CI: 0.81 to 7.42; $RERI_{\text{-OAI}}$ aOR: 1.28, 95%CI: 0.34 to 4.80) scales.

Figure 3-8: The incident risk of symptomatic knee OA in different subgroups of obesity-injury-physical activity



*ORs adjusted for age and gender and obesity
PA+: active group; PA-: inactive group; Injury+: injured group; Injury-: uninjured group, Obesity+: obese group; Obesity-: non-obese group

Table 3-27: The interaction between physical activity, obesity and injury on the risk of incident symptomatic knee OA in MOST

	Non-obese		Obese	
	Uninjured	Injured	Uninjured	Injured
	aOR* (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Inactive	1	0.80 (0.33 - 1.99); $p = 0.64$	1.30 (0.71 - 2.40); $p = 0.39$	2.84 (1.32 - 6.07); $p = 0.007$
Active	0.40 (0.17 - 0.95); $p = 0.04$	1.48 (0.65 - 3.38); $p = 0.36$	1.28 (0.65 - 2.52); $p = 0.48$	2.97 (1.32 - 6.71); $p < 0.009$

Measure of interaction on multiplicative scale (obesity+, injury+, physical activity+): RERI aOR: 0.23, 95%CI: 0.04 to 1.32, $p = 0.10$.
Measure of interaction on multiplicative scale (obesity-, injury+, physical activity+): RERI aOR: 4.61, 95%CI: 1.22 to 17.41, $p = 0.02$.
Measure of interaction on multiplicative scale (obesity+, injury-, physical activity+): RERI aOR: 2.45, 95%CI: 0.81 to 7.42, $p = 0.11$.
Measure of interaction on multiplicative scale (obesity+, injury+, physical activity-): RERI aOR: 2.71, 95%CI: 0.83 to 8.88, $p = 0.10$.

Measure of interaction on additive scale (obesity+, injury+, physical activity+): RERI aOR: -1.11, 95%CI: -4.18 to 1.96, $p = 0.48$.
Measure of interaction on additive scale (obesity-, injury+, physical activity+): RERI aOR: 1.27, 95%CI: -0.005 to 2.56, $p = 0.051$.
Measure of interaction on additive scale (obesity+, injury-, physical activity+): RERI aOR: 0.57, 95%CI: -0.40 to 1.55, $p = 0.25$.
Measure of interaction on additive scale (obesity+, injury+, physical activity-): RERI aOR: 1.72, 95%CI: -0.32 to 3.78, $p = 0.1$.

***ORs adjusted for age and gender**

Table 3-28: The interaction between physical activity, obesity and injury on the risk of incident symptomatic knee OA in OAI

	Non-obese		Obese	
	Uninjured	Injured	Uninjured	Injured
	aOR* (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Inactive	1	0.96 (0.35 - 2.60); $p = 0.93$	1.56 (0.68 - 3.55); $p = 0.29$	6.19 (2.67 - 14.34); $p < 0.001$
Active	1.23 (0.53 - 2.86); $p = 0.63$	1.28 (0.42 - 3.89); $p = 0.66$	2.45 (0.94 - 6.36); $p = 0.07$	3.44 (0.97 - 12.21); $p = 0.06$

Measure of interaction on multiplicative scale (obesity-, injury+, physical activity+): RERI aOR: 0.32, 95%CI: 0.04 to 2.82, *P* = 0.31.
Measure of interaction on multiplicative scale (obesity-, injury+, physical activity+): RERI aOR: 1.09, 95%CI: 0.25 to 4.82, *p* = 0.91.
Measure of interaction on multiplicative scale (obesity+, injury-, physical activity+): RERI aOR: 1.28, 95%CI: 0.34 to 4.80, *p* = 0.71.
Measure of interaction on multiplicative scale (obesity+, injury+, physical activity-): RERI aOR: 4.16, 95%CI: 1.09 to 15.86, *p* = 0.04.

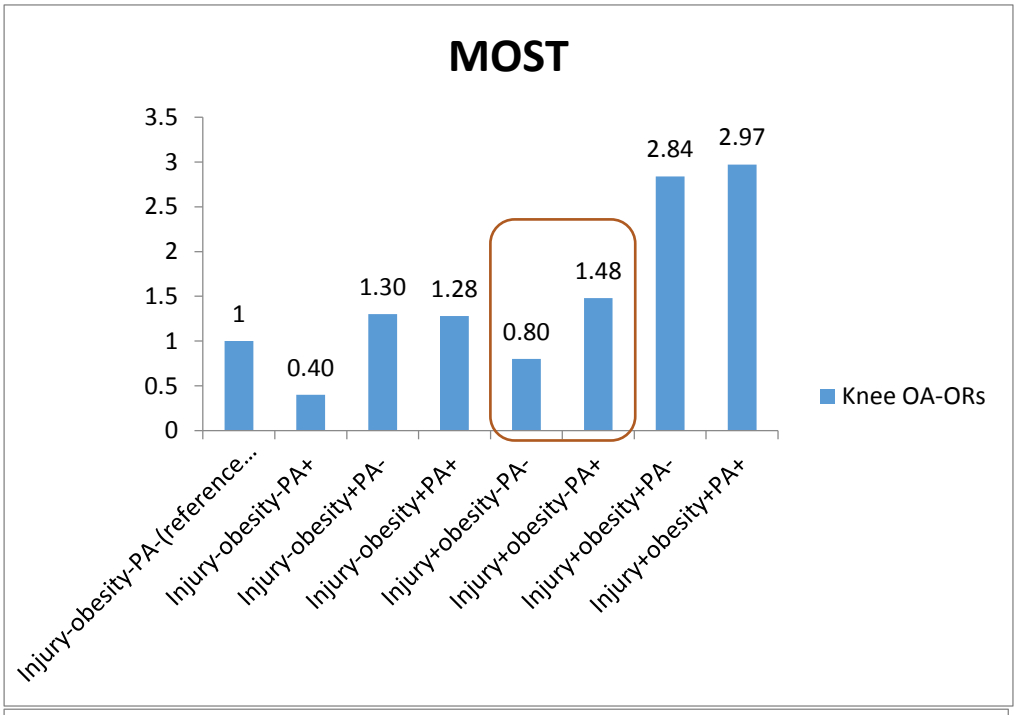
Measure of interaction on additive scale (obesity+, injury+, physical activity+): RERI aOR: -3.74, 95%CI: -10.03 to 2.54, *P* = 0.24
Measure of interaction on additive scale (obesity-, injury+, physical activity+): RERI aOR: 0.09, 95%CI: -1.59 to 1.78, *p* = 0.91.
Measure of interaction on additive scale (obesity+, injury-, physical activity+): RERI aOR: 0.67, 95%CI: -1.69 to 3.03, *p* = 0.58.
Measure of interaction on additive scale (obesity+, injury+, physical activity-): RERI aOR: 4.68, 95%CI: -0.05 to 9.41, *p* = 0.052.

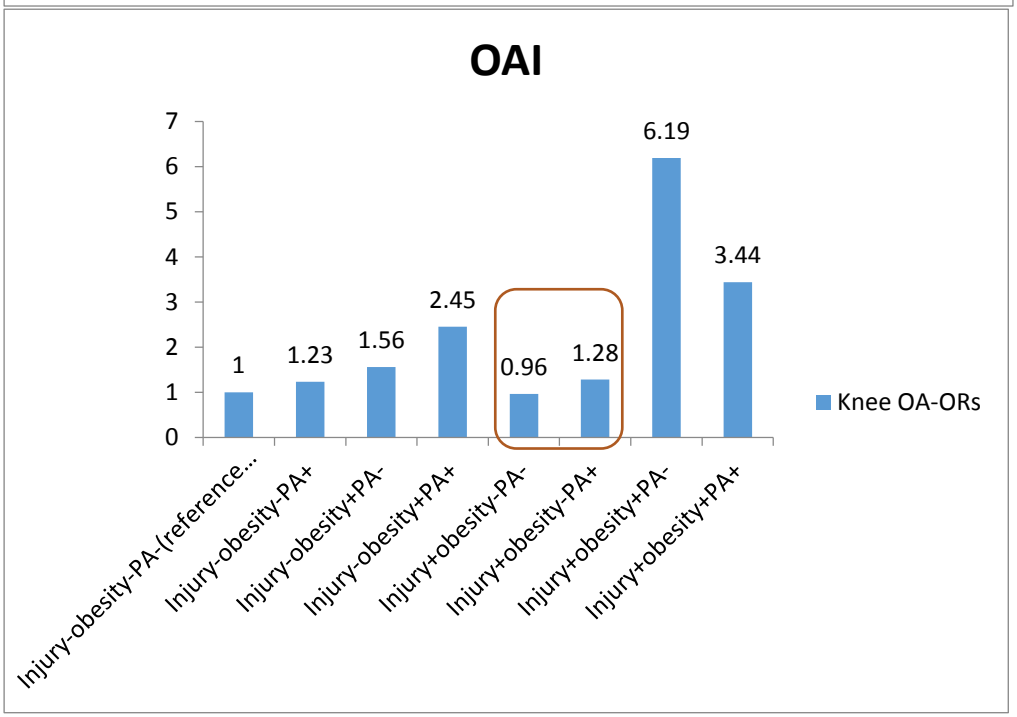
***ORs adjusted for age and gender**

Secondly, for the subgroup of non-obese people with injury in MOST, those who were active had an aOR of 1.48 (95%CI: 0.65 to 3.38)- a greater risk of symptomatic knee OA than inactive people with aOR of 0.80 (95%CI: 0.33 to 1.99) (Figure 3-9 and Table 3-27).

This highlighted a cross-over effect (positive interaction) of physical activity on the risk of symptomatic knee OA in the presence versus the absence of injury in non-obese people. This positive interaction between physical activity and injury was statistically significant on the multiplicative scale (RERI aOR: 4.61, 95%CI: 1.22 to 17.41, p = 0.02). On the additive scale, it was marginally insignificant (RERI aOR: 1.27, 95%CI: -0.005 to 2.56, p = 0.051). However, in OAI, there was no evidence of any significant interactions between physical activity and injury on the risk of symptomatic knee OA ($RERI_{-additive}$ aOR: 0.09, 95%CI: -1.59 to 1.78; $RERI_{-multiplicative}$ aOR: 1.09, 95%CI: 0.25 to 4.82) (Table 3-28).

Figure 3-9: The incident risk of symptomatic knee OA in different subgroups of obesity-injury-physical activity

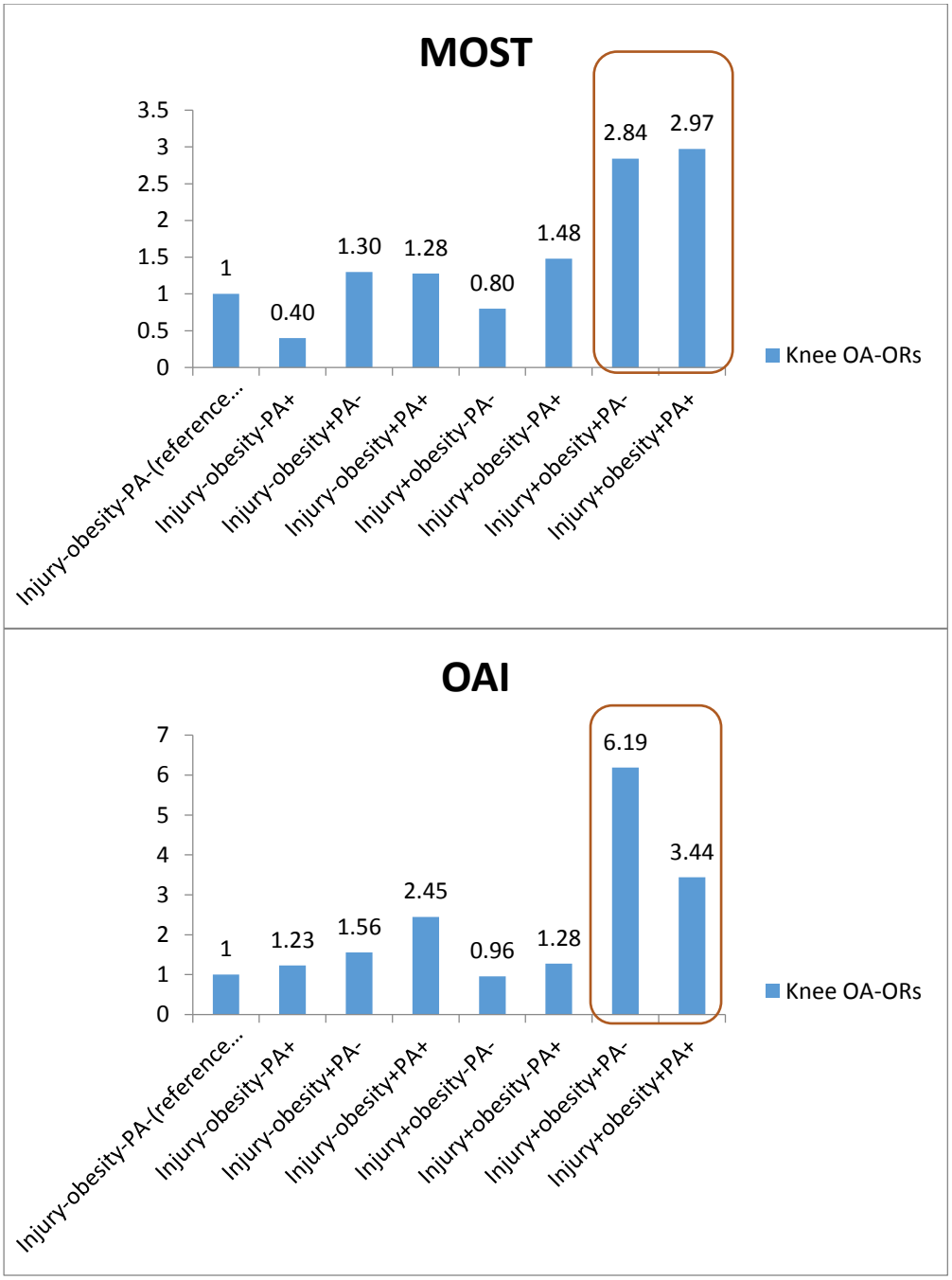




*ORs adjusted for age and gender and obesity
PA+: active group; PA-: inactive group; Injury+: injured group; Injury-: uninjured group, Obesity+: obese group; Obesity-: non-obese group

Thirdly, for the Injured and Obese subgroup in both datasets, there was some evidence of a negative three-way interaction between obesity, injury and physical activity on the risk of incident symptomatic knee OA (Table 3-27 and Table 3-28). This was further highlighted in the OAI database (Figure 3-10), where active people in the subgroup of Obese and Injured people were at lower risk of symptomatic knee OA than inactive people with similar injury and obesity status. However, none of these interactions were statically significant in either cohort ($RERI_{\text{-MOST-additive}}$ aOR: -1.11, 95%CI: -4.18 to 1.96; $RERI_{\text{-MOST-multiplicative}}$ aOR: 0.23, 95%CI: 0.04 to 1.32; $RERI_{\text{-OAI-additive}}$ aOR: -3.74, 95%CI: -10.03 to 2.54; $RERI_{\text{-OAI-multiplicative}}$ aOR: 0.32, 95%CI: 0.04 to 2.82). In addition, the confidence limits on both scales were wide, which would preclude any conclusions about any potential interactions.

Figure 3-10: The incident risk of symptomatic knee OA in different subgroups of obesity-injury-physical activity



*ORs adjusted for age and gender and obesity
PA+: active group; PA-: inactive group; Injury+: injured group; Injury-: uninjured group, Obesity+: obese group; Obesity-: non-obese group

Finally, the Obese and Injured subgroup was at the highest risk of symptomatic knee OA in both cohorts regardless of being active or inactive (Figure 3-10). This was partly due to the single effect of obesity, injury and also due to their interactions. In both cohorts, there was moderate evidence of positive interaction between obesity and injury on risk of incident symptomatic knee OA on both the additive and multiplicative scales. However, it was statistically significant on the multiplicative scale in OAI only (RERI aOR: OR: 4.16, 95%CI: 1.09 to 15.86). On additive scales in OAI, this positive interaction was marginally insignificant (RERI aOR: 4.68, 95%CI: -0.05 to 9.41, p = 0.052).

3.3 Progression of radiographic knee OA

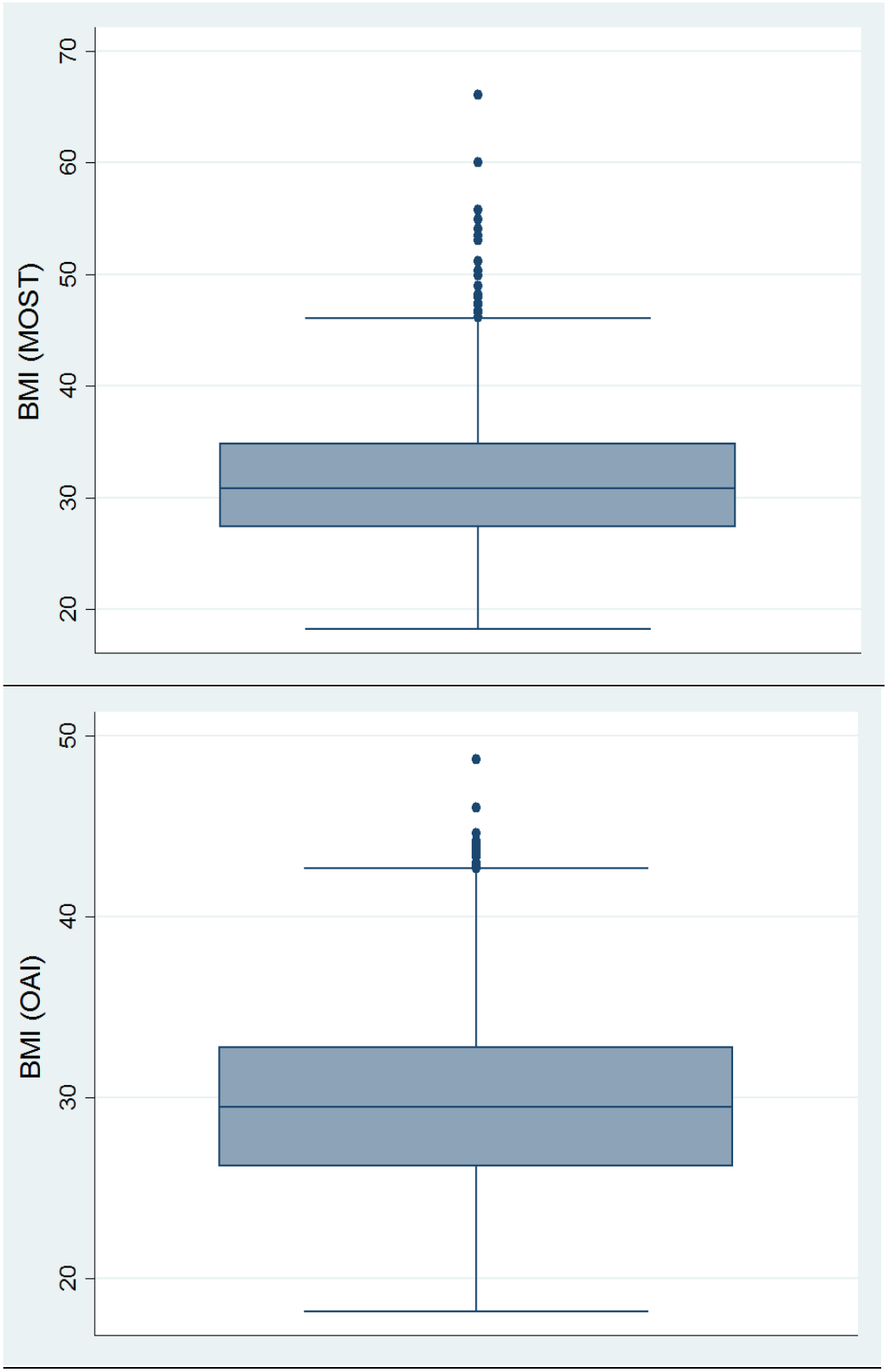
3026 and 4796 participants in MOST and OAI respectively had x-ray data at baseline. Of those, 1214 knees from MOST and 2835 knees from OAI met the inclusion criteria for the radiographic knee OA progression study (knees with radiographic knee OA at baseline). In MOST, 5 knees and in OAI 45 knees were excluded due to missing injury, physical activity or BMI data at the baseline assessment. Therefore, 1209 knees in MOST and 2790 knees in OAI were included in the data analysis.

Participants' characteristics are presented in Table 3-29. In MOST, the mean age of participants at the baseline was 63.4 years, which was comparable to the mean age of 62.3 years in OAI (Table 3-29). In OAI, the participants' ages ranged from 45 to 70 years old, which was slightly broader than in MOST with the range of 50 to 79 years old (Table 3-29). The mean BMI of 31.7 $kg.m^{-2}$ at baseline in MOST was slightly higher than OAI (29.7 $kg.m^{-2}$) (Table 3-29; Figure 3-11). The mean PASE score in MOST at the baseline was 173.8, which was higher than in OAI (156.5) (Table 3-29 and Figure 3-12).

Table 3-29: Participants' characteristics data at baseline

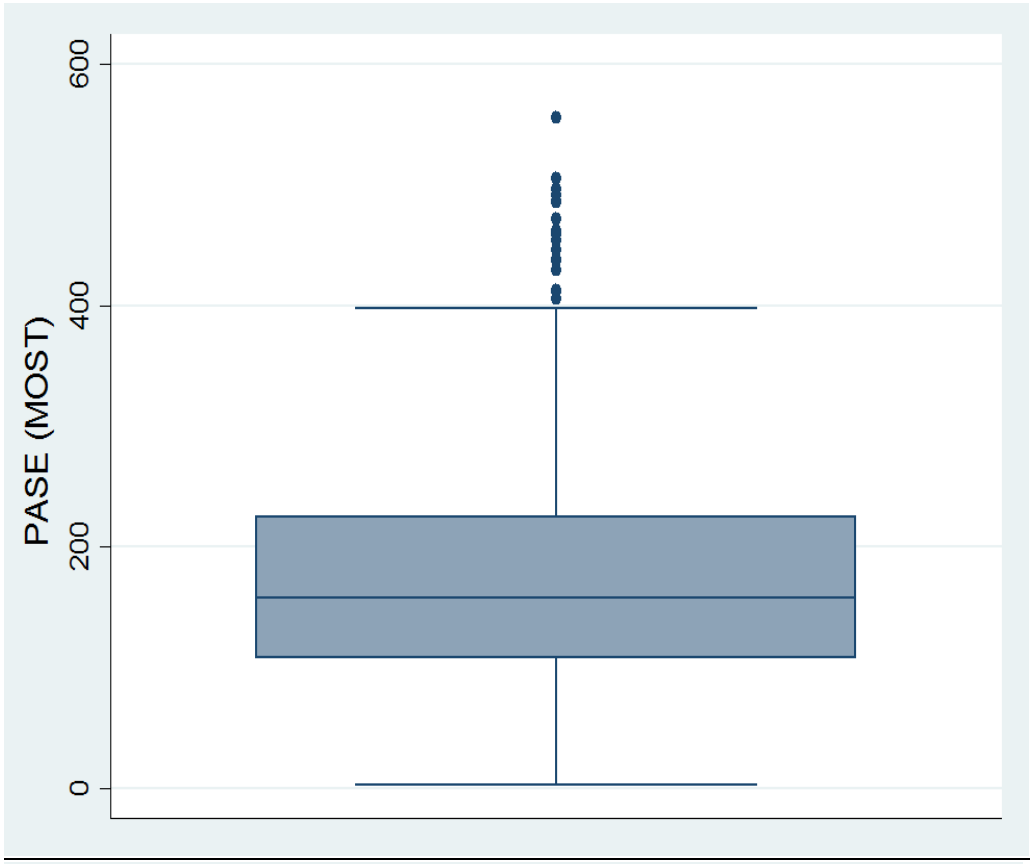
Cohort		AGE	BMI (Baseline)	PASE (Baseline)
MOST	Mean ± SD	63.48 ± 7.81	31.70 ± 6.09	173.81 ± 90.04
	Min-Max	50-79	18.25-66.12	2.2-555.4
	Range	29	47.87	553.2
OAI	Mean ± SD	62.35 ± 8.89	29.78 ± 4.84	156.54 ± 81.39
	Min-Max	45-79	18.2-48.7	2-531
	Range	34	30.5	529

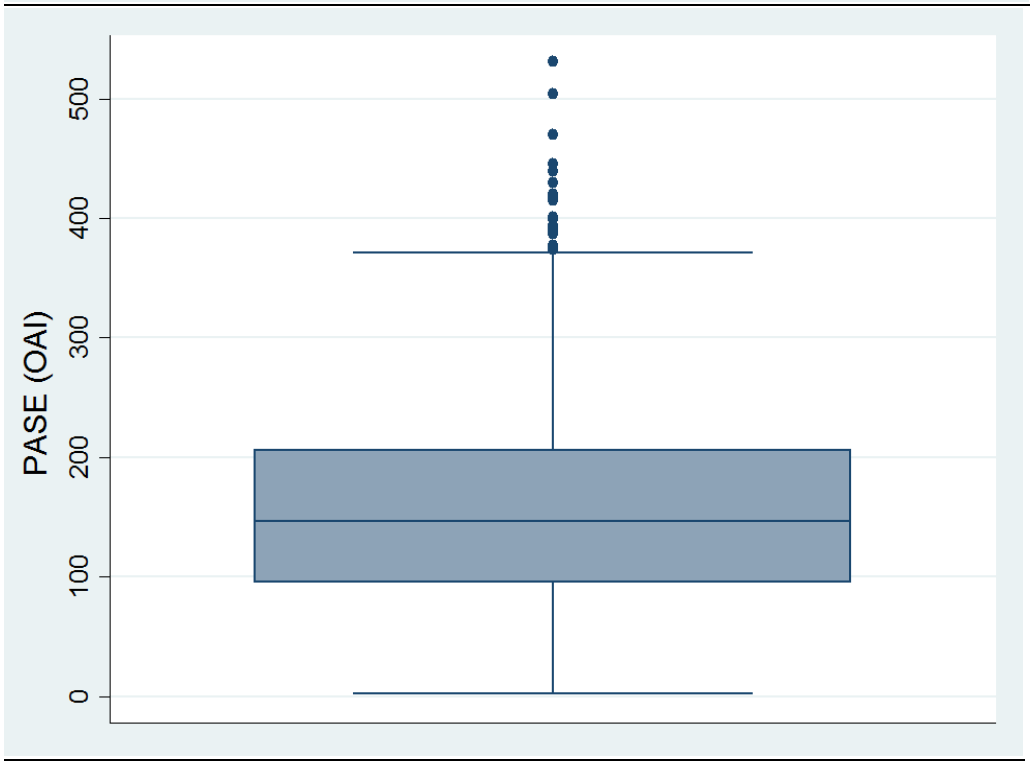
Figure 3-11: Distribution of BMI data at baseline



*BMI: Body mass index

Figure 3-12: Distribution of PASE data at baseline





*PASE: Physical Activity Scale for Elderly

3.3.1 *Gender and risk of radiographic knee OA progression*

The majority of participants were female in MOST (62%) and OAI (60%) radiographic progression study. In both cohorts, the risk of radiographic knee OA progression was slightly higher in females than in males (aOR_{-MOST}: 1.22, 95%CI: 0.94-1.59, aOR_{-OAI}: 1.19, 95%CI: 0.97-1.47). The differences were not statistically significant in either MOST or OAI (Table 3-30).

Table 3-30: Gender and risk of radiographic knee OA progression

Cohort	Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	**Male**	187 (41.3%)	266 (58.7%)	453	-	
	Female	270 (35.7%)	486 (64.3%)	756	1.26 (0.97 - 1.62) $p = 0.07$	1.22 (0.94 – 1.59) $p = 0.12$
OAI	**Male**	905 (81.5%)	206 (18.5%)	1111	-	-
	Female	1317 (78.4%)	362 (21.6%)	1679	1.20 (0.98 – 1.47) $p = 0.06$	1.19 (0.97 – 1.47) $p = 0.09$

***OR adjusted for Injury, obesity, age and physical activity**

3.3.2 *Age and risk of radiographic knee OA progression*

In MOST, the middle age and old age groups respectively were at 17% and 25% lower risk of radiographic knee OA progression compared to the young age group (Table 3-31). However, neither of them reached statistical significance even after adjusting for confounders (aOR_{55-65}: 0.83, 95%CI: 0.57-1.20; aOR_{65-79}: 0.75, 95%CI: 0.52-1.09) (Table 3-31).

In OAI, the middle age group was 33% at higher risk of knee OA progression compared to the young age group, which was statistically significant (aOR: 1.33, 95%CI: 1.02-1.75). However, the estimate risk did not continue to increase from the middle age to the old age group although the old age group was still at greater risk of knee OA progression as compared to the young age group (aOR: 1.22, 95% CI: 0.92-1.61) (Table 3-31).

Table 3-31: Age and risk of radiographic knee OA progression

Cohort	Age Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	45-55	72 (34.3%)	138 (65.7%)	210	-	-
	55-65	167 (37.3%)	281 (62.7%)	448	0.87 (0.61 - 1.25) $p = 0.48$	0.83 (0.57 - 1.20) $p = 0.33$
	65-79	218 (39.6%)	333 (60.4%)	551	0.80 (0.57 - 1.14) $p = 0.23$	0.75 (0.52 - 1.09) $p = 0.14$
OAI	45-55	537 (82.0%)	118 (18.0%)	655	-	-
	55-65	726 (77.5%)	211 (22.5%)	937	1.32 (1.01 - 1.73) $p = 0.03$	1.33 (1.02 – 1.75) $p = 0.03$
	65-79	959 (80.1%)	239 (19.9%)	1198	1.13 (0.87 - 1.47) $p = 0.33$	1.22 (0.92- 1.61) $p = 0.15$

***OR adjusted for Injury, obesity, gender and physical activity**

3.3.3 *The association between obesity and the risk of radiographic knee OA progression*

At baseline, 55% and 46% of MOST and OAI participants were obese. In MOST, obese and non-obese people had a similar risk of radiographic knee OA progression (aOR: 1.05, 95%CI: 0.81-1.35) (Table 3-32). In contrast, the risk of radiographic knee OA progression in OAI was significantly higher in obese than non-obese people (aOR: 1.37, 95%CI: 1.12-1.67) (Table 3-32).

Table 3-32: Obesity and risk of radiographic knee OA progression

Cohort	Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	Non-obese	209 (39.0%)	327 (61.0%)	536	-	
	Obese	248 (36.9%)	425 (63.1%)	673	1.08 (0.84 -1.38) $p = 0.53$	1.05 (0.81 -1.35) $p = 0.69$
OAI	Non-obese	1225 (82.1%)	268 (17.9%)	1493	-	
	Obese	997 (76.9%)	300 (23.1%)	1297	1.37 (1.13-1.67) $p = 0.001$	1.37 (1.12 -1.67) $p = 0.002$

***OR adjusted for Injury, age, gender and physical activity**

3.3.4 *The association between injury and the risk of radiographic knee OA progression*

At baseline, 28% and 33% of participants in MOST and OAI had previously been injured (Table 3-33). No significant association were found between injury and radiographic knee OA progression in either MOST or OAI ($aOR_{\text{-MOST}}$: 0.81, 95%CI: 0.63-1.06; aOR: 1.18, 95%CI: 0.97-1.44) (Table 3-33).

Table 3-33: Injury and risk of radiographic knee OA progression

Cohort	Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	Uninjured	317 (36.6%)	550 (63.4%)	867	-	-
	Injured	140 (40.9%)	202 (59.1%)	342	0.80 (0.62 -1.04) p = 0.10	0.81 (0.63 - 1.06) p = 0.13
OAI	Uninjured	1492 (80.3%)	365 (19.7%)	1857	-	-
	Injured	730 (78.2%)	203 (21.8%)	933	1.14 (0.94-1.39) p = 0.16	1.18 (0.97-1.44) p = 0.08

***OR adjusted for obesity, age, gender and physical activity**

3.3.5 *The association between physical activity and the risk of radiographic knee OA progression*

34% of MOST participants were active compared to 27% in OAI (Table 3-34). At the last follow-up (MOST: 60-month; OAI: 48-month), the prevalence of radiographic knee OA progression was similar amongst active and inactive people in both cohorts (Table 3-34). No significant association was found between physical activity and radiographic knee OA progression in either MOST (p = 0.63) or OAI (p = 0.95). The risk of knee OA progression due to physical activity was close to one in both MOST (aOR: 0.93, 95%CI: 0.70-1.23) and OAI (aOR: 0.99, 95%CI: 0.78-1.26). This suggested that activity neither increased nor protected against the risk of knee OA progression (Table 3-34).

Table 3-34: Physical activity and risk of radiographic knee OA progression

Cohort	Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	Inactive	298 (37.3%)	502 (62.7%)	800	-	-
	Active	159 (38.9%)	250 (61.1%)	409	0.92 (0.71 -1.20) p = 0.57	0.93 (0.70 -1.23) p = 0.63
OAI	Inactive	1617 (79.4%)	420 (20.6%)	2037	-	-
	Active	605 (80.4%)	148 (19.6%)	753	0.93 (0.74 -1.17) p = 0.56	0.99 (0.78-1.26) p = 0.95

***OR adjusted for Injury, obesity, age and gender**

3.3.6 *The interaction between obesity and injury on the risk of radiographic knee OA progression*

In order to investigate the two-way interaction between obesity and injury on the risk of radiographic knee OA progression, the data were stratified by obesity and injury.

In both cohorts, the combined effect of obesity and injury on the risk of radiographic knee OA progression was similar to the multiple or the sum of individual effects of obesity and injury (Table 3-35; Table 3-36). This was supported by the statistical tests where no significant interactions were found between obesity and injury on the risk of knee OA progression on either additive ($RERI_{\text{-MOST-additive}}$ aOR: -0.32, 95%CI: -0.86 to 0.20; $RERI_{\text{-OAI-additive}}$ aOR: 0.18, 95%CI: -0.31 to 0.69) or multiplicative scales ($RERI_{\text{-MOST-multiplicative}}$ aOR: 0.71, 95%CI: 0.42 to 1.19; $RERI_{\text{-OAI-multiplicative}}$ aOR: 1.09, 95%CI: 0.74 – 1.61).

Table 3-35: The interaction between obesity and injury on the risk of radiographic knee OA progression in MOST

	Non-obese		Obese		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	234/149	1 (reference)	316/168	1.16 (0.86 - 1.55); p = 0.31	1.15 (0.85 - 1.55); p = 0.33
Injured	93/60	0.98 (0.66- 1.44); p = 0.93	109/80	0.81 (0.56 - 1.18); p = 0.28	0.80 (0.50 - 1.27); p = 0.35
Adjusted ORs[2] (95% CI)		0.95 (0.64 - 1.41); p = 0.82		0.70 (0.49 - 1.00); p = 0.05	

Measure of interaction on multiplicative: scale: RERI aOR: 0.71, 95%CI: 0. 42 to 1.19, p = 0.20.
Measure of interaction on additive scale: RERI aOR: -0.32, 95%CI: -0.86 to 0.20, p = 0.22.
*ORs adjusted for age, gender and physical activity

1. ORs for the effect modification of injury on the role of obesity in progression of radiographic knee OA
2. ORs for the effect modification of obesity on the role of injury in progression of radiographic knee OA

Table 3-36: The interaction between obesity and injury on the risk of radiographic knee OA progression in OAI

	Non-obese		Obese		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	176/822	1 (reference)	189/670	1.32 (1.04 - 1.69); p = 0.02	1.34 (1.05 - 1.72); p = 0.01
Injured	92/403	1.13 (0.85- 1.50); p = 0.392	111/327	1.64 (1.24 - 2.19); p = 0.001	1.45 (1.05 - 2.01); p = 0.02
Adjusted ORs[2] (95% CI)		1.12 (0.84 - 1.49); p = 0.41		1.24 (0.94 - 1.63); p = 0.11	

Measure of interaction on multiplicative scale: RERI aOR: 1.09, 95%CI: 0.74 to 1.61, p = 0.64.
Measure of interaction on additive scale: RERI aOR: 0.18, 95%CI: -0.31 to 0.69, p = 0.46.
*ORs adjusted for age, gender and physical activity

1. ORs for the effect modification of injury on the role of obesity in progression of radiographic knee OA
2. ORs for the effect modification of obesity on the role of injury in progression of radiographic knee OA

3.3.7 *The interaction between physical activity and obesity on the risk of radiographic knee OA progression*

Data were also stratified by obesity and physical activity to investigate the two-way interaction between physical activity and obesity on the risk of radiographic knee OA progression (Table 3-37; Table 3-38).

In MOST, the risk of knee OA progression in the subgroup of Obese and Inactive people was close (aOR: 1.17, 95%CI: 0.85-1.60) to the risk of knee OA progression in the Obese and Active subgroup (aOR: 0.95, 95%CI: 0.64-1.41). Likewise, the risk of radiographic knee OA progression in the subgroup Obese and Inactive individuals in OAI (aOR: 1.28, 95%CI: 1.02-1.62) was similar to the risk of knee OA progression in the Obese and Active subgroup (aOR: 1.44, 95%CI: 1.03-2.00) (Table 3-38). That is, physical activity did not have an interactive effect with obesity on the risk of radiographic knee OA progression in either cohorts. This was supported by the statistical test, in which no significant interactions were found on either additive ($RERI_{-MOST}$ aOR: -0.32, 95%CI: -0.91 to 0.26; $RERI_{-OAI}$ aOR: 0.28, 95%CI: -0.23 to 0.79) or multiplicative scales ($RERI_{-MOST}$ aOR: 0.73, 95%CI: 0.43 to 1.23; $RERI_{-OAI}$ aOR: 1.28, 95%CI: 0.81 to 2.00) (Table 3-37; Table 3-38).

The effect of physical activity on the risk of radiographic knee OA progression across the stratum of obesity (obese and non-obese) was also studied (Table 3-37; Table 3-38). In both cohorts, the effect of physical activity on the risk of knee OA progression across the strata of obesity was similar to the main effect of physical activity on the risk of knee OA progression ($aOA_{\text{-MOST}}$: 0.93 95%CI: 0.70-1.23, $aOR_{\text{-OAI}}$: 0.99, 95%CI: 0.78-1.26 Table 3-34). This indicated that the main effect of activity on the risk of knee OA progression was not modified by the presence or absence of obesity. These data were also supported by the statistical test, where no significant interactions were found (RERI $p_{\text{additive/multiplicative}} > 0.2$) (Table 3-37; Table 3-38).

Table 3-37: The interaction between physical activity and obesity on the risk of radiographic knee OA progression in MOST

	Inactive		Active		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Non-obese	208/138	1 (reference)	119/71	1.10 (0.74 - 1.65); p = 0.61	1.13 (0.73 - 1.73); p = 0.57
Obese	294/160	1.17 (0.85 - 1.60); p = 0.31	131/88	0.95 (0.64 - 1.41); p = 0.81	0.80 (0.55 - 1.16); p = 0.25
Adjusted ORs[2] (95% CI)		1.17 (0.86 - 1.61); p = 0.30		0.86 (0.56 - 1.32); p = 0.49	

Measure of interaction on multiplicative scale: RERI aOR: 0.73, 95%CI: 0.43 to 1.23, p = 0.24.
Measure of interaction on additive scale: RERI aOR: -0.32, 95%CI: -0.91 to 0.26, p = 0.27.
*ORs adjusted for age, gender and injury

1. ORs for the effect modification of obesity on the role physical activity in progression of radiographic knee OA

2. ORs for the effect modification of physical activity on the role of obesity in progression of radiographic knee OA

Table 3-38: The interaction between physical activity and obesity on the risk of knee OA progression in OAI

	Inactive		Active		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Non-obese	201/880	1 (reference)	67/345	0.87 (0.62 - 1.22); p = 0.43	0.85 (0.60 - 1.20); p = 0.36
Obese	219/737	1.28 (1.02 - 1.62) p = 0.03	81/260	1.44 (1.03 - 2.00); p = 0.03	1.15 (0.82 - 1.61); p = 0.39
Adjusted ORs[2] (95% CI)		1.27 (1.01 - 1.60); p = 0.03		1.68 (1.12 - 2.50); p = 0.01	

Measure of interaction on multiplicative scale: RERI aOR: 1.28, 95%CI: 0.81 to 2.00, p = 0.28.
Measure of interaction on additive scale: RERI aOR: 0.28, 95%CI: -0.23 to 0.79, p = 0.28.
*ORs adjusted for age, gender and injury

1. ORs for the effect modification of obesity on the role of physical activity in progression of radiographic knee OA

2. ORs for the effect modification of physical activity on the role of obesity in progression of radiographic knee OA

3.3.8 *The interaction between physical activity and injury on the risk of radiographic knee OA progression*

Finally, the two-way interaction between physical activity and injury on the risk of radiographic knee OA progression was examined. In both cohorts, the effect of physical activity on the risk of knee OA progression across the strata of injury (Table 3-39; Table 3-40) was similar to the main effect of physical activity on the risk of radiographic knee OA progression (aOA_{-MOST}: 0.93 95%CI: 0.70-1.23, aOR_{-OAI}: 0.99, 95%CI: 0.78-1.26, Table 3-34). In addition, the join effect of activity and injury on the risk of knee OA progression was similar to the multiple or the sum of individual effects of physical activity and injury in both cohorts (Table 3-39; Table 3-40). These results highlights the absence of any large interaction between activity and injury on the risk of radiographic knee OA progression in either cohort. This was supported by the statistical tests where no significant interactions were found between physical activity and injury on the risk of knee OA progression on either additive ($RERI_{-MOST-additive}$ aOR: 0.17, 95%CI: -0.26 to 0.61; $RERI_{-OAI-additive}$ aOR: -0.23, 95%CI: -0.72 to 0.26) or multiplicative scales ($RERI_{-MOST-multiplicative}$ aOR: 1.22, 95%CI: 0.71 – 2.09; $RERI_{-OAI-multiplicative}$ aOR: 0.81, 95%CI: 0.52 to 1.25).

Table 3-39: The interaction between physical activity and injury on the risk of radiographic knee OA progression in MOST

	Inactive		Active		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	381/212	1 (reference)	169/105	0.87 (0.63 - 1.21); p = 0.43	0.91 (0.65 - 1.27); p = 0.59
Injured	121/86	0.76 (0.54 - 1.05); p = 0.09	81/54	0.81 (0.53 - 1.24); p = 0.35	0.91 (0.54 - 1.52); p = 0.72
Adjusted ORs[2] (95% CI)		0.76 (0.55 - 1.05); p = 0.10		0.93 (0.59 - 1.44); p = 0.74	

Measure of interaction on multiplicative scale: RERI aOR: 1.22, 95%CI: 0.71 to 2.09, p = 0.46.
Measure of interaction on additive scale: RERI aOR: 0.17, 95%CI: -0.26 to 0.61, p = 0.42.
*ORs adjusted for age, gender and obesity

1. ORs for the effect modification of injury on the role of physical activity in progression of radiographic knee OA

2. ORs for the effect modification of physical activity on the role of injury in progression of radiographic knee OA

Table 3-40: The interaction between physical activity and injury on the risk of radiographic knee OA progression in OAI

	Inactive		Active		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	277/1140	1 (reference)	88/352	1.07 (0.80 - 1.44); p = 0.61	1.10 (0.81 - 1.50); p = 0.50
Injured	143/477	1.25 (0.99 - 1.58); p = 0.053	60/253	1.10 (0.78 - 1.54); p = 0.56	0.82 (0.56 - 1.18); p = 0.29
Adjusted ORs[2] (95% CI)		1.26 (1.00 - 1.60); p = 0.045		1.03 (0.71 - 1.50); p = 0.85	

Measure of interaction on multiplicative scale: RERI aOR: 0.81, 95%CI: 0.52 to 1.25, p = 0.35.
Measure of interaction on additive scale: RERI aOR: -0.23, 95%CI: -0.72 to 0.26, p = 0.36.
*ORs adjusted for age, gender and obesity

1. ORs for the effect modification of injury on the role of physical activity in progression of radiographic knee OA

2. ORs for the effect modification of physical activity on the role of injury in progression of radiographic knee OA

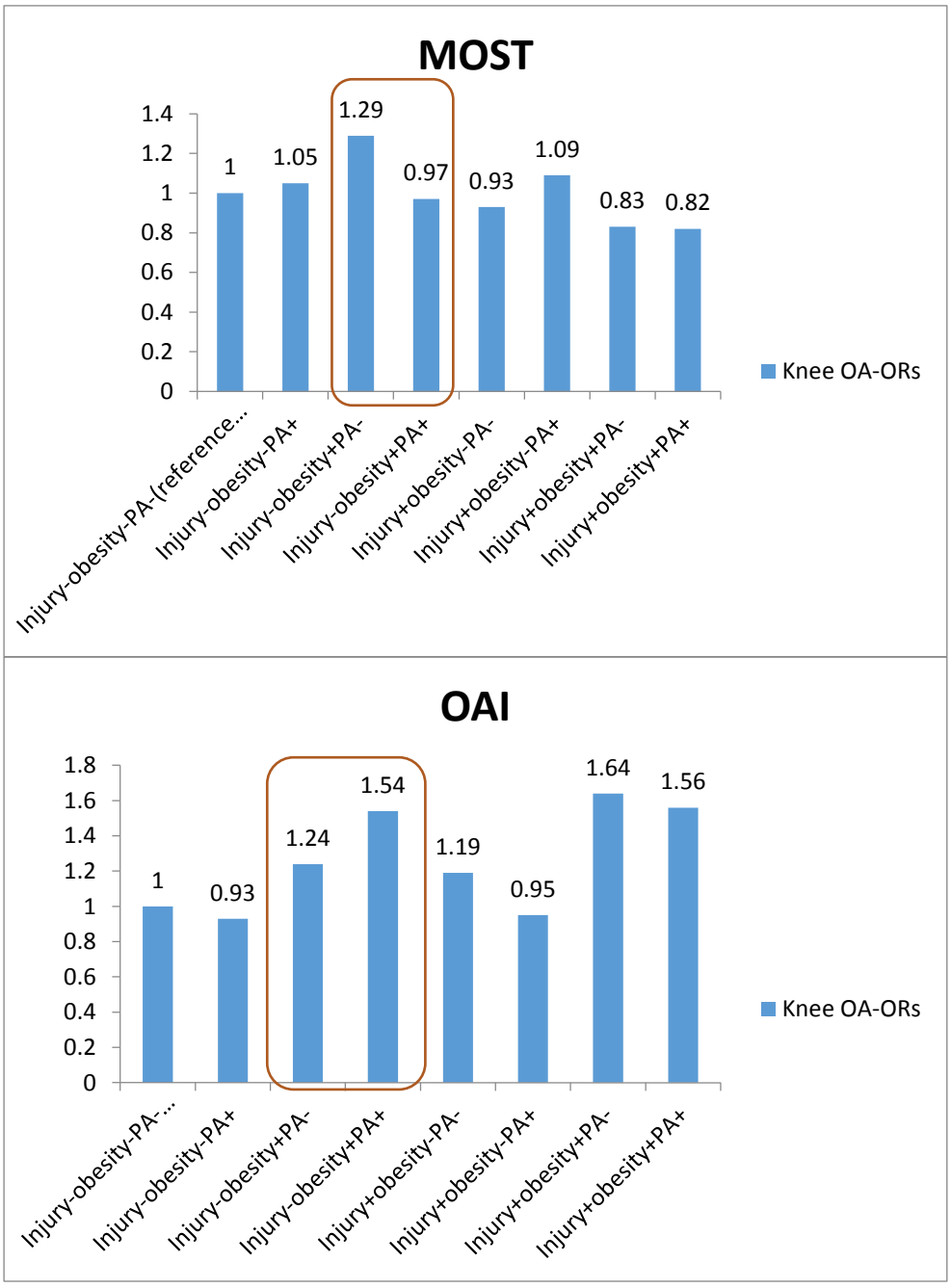
3.3.9 *The interaction between obesity, injury and physical activity on the risk of radiographic knee OA progression*

In the last results for radiographic knee OA progression, the three-way interaction between all three variables of obesity, injury and physical activity was examined.

For the subgroup of obese people with no injury in MOST (Figure 3-13), the risk of radiographic knee OA progression was lower in active (aOR: 0.97, 95%CI: 0.62-1.53) than inactive (aOR: 1.29, 95%CI: 0.90-1.85) individuals. This indicated a negative interaction between activity and obesity on the risk of radiographic knee OA progression ($RERI_{-additive}$ aOR: -0.37, 95%CI: -1.08 to 0.33; $RERI_{-multiplicative}$ aOR: 0.71, 95%CI: 0.38 to 1.33) (Table 3-41). In contrast, for the subgroup of obese people with no injury in OAI (Figure 3-13), the risk of radiographic knee OA progression was slightly higher in active (aOR: 1.54, 95%CI: 1.02-2.32) than inactive (aOR: 1.24, 95%CI: 0.94-1.63) individuals suggesting a positive interaction between activity and obesity on the risk radiographic knee OA progression ($RERI_{-additive}$ aOR: 0.36, 95%CI: -0.31 to 1.05; $RERI_{-multiplicative}$ aOR: 1.33, 95%CI: 0.75 to 2.34). However, in both studies, the magnitudes of

interactions were small and non-significant (Table 3-41 and Table 3-42).

Figure 3-13: The progressive risk of radiographic knee OA in different subgroups of obesity-injury-physical activity



*ORs adjusted for age and gender and obesity
PA+: active group; PA-: inactive group; Injury+: injured group; Injury-: uninjured group, Obesity+: obese group; Obesity-: non-obese group

Table 3-41: The interaction between physical activity, obesity and injury on the risk of radiographic knee OA progression in MOST

	Non-obese		Obese	
	Uninjured	Injured	Uninjured	Injured
	aOR* (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Inactive	1	0.93 (0.57 - 1.52); p = 0.78	1.29 (0.90 - 1.85); p = 0.15	0.83 (0.52 - 1.32); p = 0.45
Active	1.05 (0.66 - 1.69); p = 0.81	1.09 (0.60 - 1.99); p = 0.76	0.97 (0.62 - 1.53); p = 0.92	0.82 (0.46 - 1.47); p = 0.51

Measure of interaction on multiplicative scale (obesity+, injury+, physical activity+): RERI aOR: 1.17, 95%CI: 0.40 to 3.44, p = 0.76.
Measure of interaction on multiplicative scale (obesity-, injury+, physical activity+): RERI aOR: 1.10, 95%CI: 0.50 to 2.45, p = 0.79.
Measure of interaction on multiplicative scale (obesity+, injury-, physical activity+): RERI aOR: 0.71, 95%CI: 0.38 to 1.33, p = 0.29.
Measure of interaction on multiplicative scale (obesity+, injury+, physical activity-): RERI aOR: 0.69, 95%CI: 0.35 to 1.33, p = 0.27.

Measure of interaction on additive scale (obesity+, injury+, physical activity+): RERI aOR: 0.19, 95%CI: -0.87 to 1.27, p = 0.71.
Measure of interaction on additive scale (obesity-, injury+, physical activity+): RERI aOR: 0.10, 95%CI: -0.71 to 0.92, p = 0.80.
Measure of interaction on additive scale (obesity+, injury-, physical activity+): RERI aOR: -0.37, 95%CI: -1.08 to 0.33, p = 0.30.
Measure of interaction on additive scale (obesity+, injury+, physical activity-): RERI aOR: -0.39, 95%CI: -1.07 to 0.28, p = 0.25.

***ORs adjusted for age and gender**

Table 3-42: The interaction between physical activity, obesity and injury on the risk of radiographic knee OA progression in OAI

	Non-obese		Obese	
	Uninjured	Injured	Uninjured	Injured
	aOR* (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Inactive	1	1.19 (0.85 - 1.65); p = 0.30	1.24 (0.94 - 1.63); p = 0.12	1.64 (1.17 - 2.29); p =0.003
Active	0.93 (0.61 - 1.40); p = 0.73	0.95 (0.59 - 1.54); p = 0.86	1.54 (1.02 - 2.32); p = 0.03	1.56 (0.98 - 2.49); p = 0.057

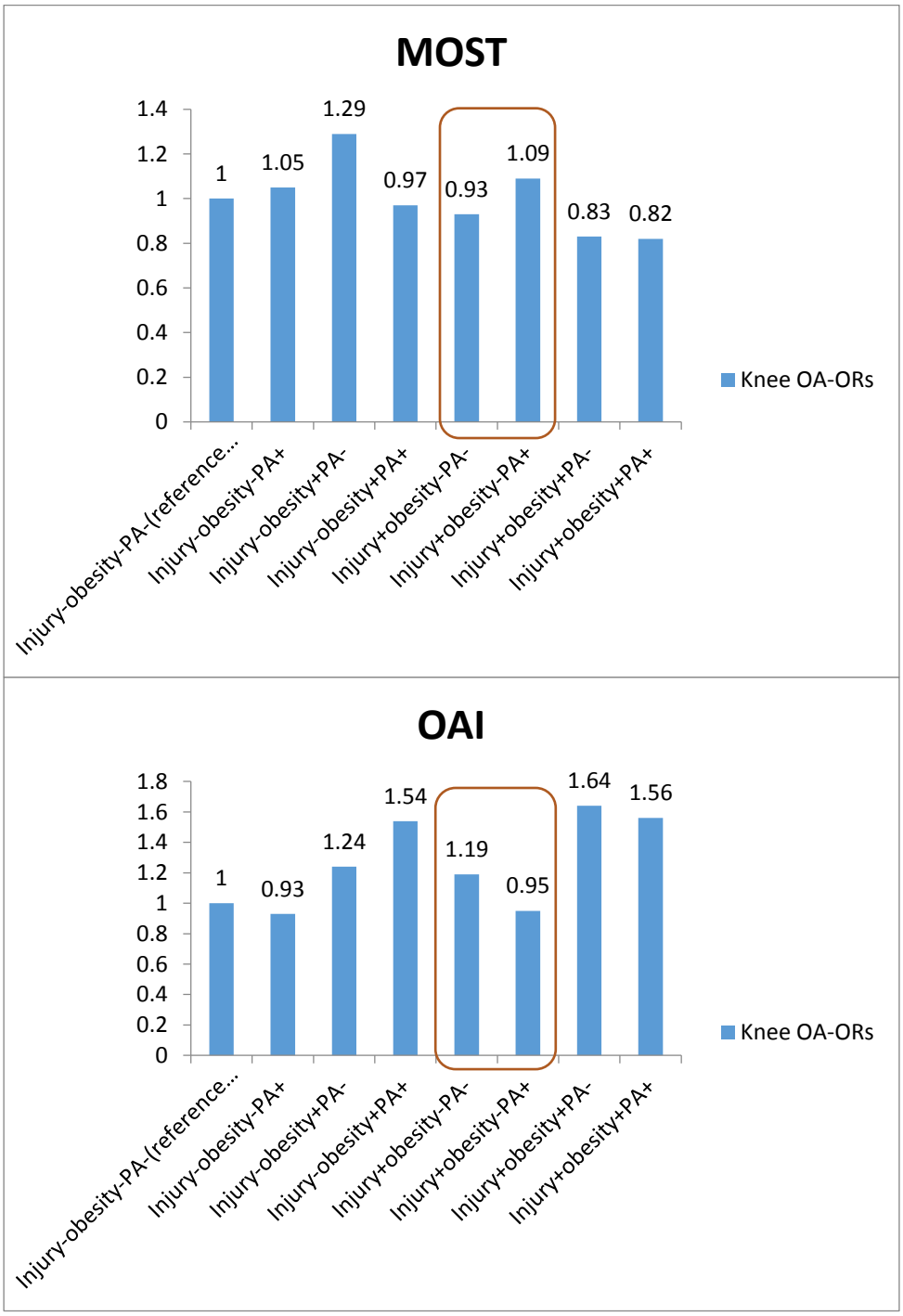
Measure of interaction on multiplicative scale (obesity-, injury+, physical activity+): RERI aOR: 0.88, 95%CI: 0.37 to 2.12, *P* = 0.79.
Measure of interaction on multiplicative scale (obesity-, injury+, physical activity+): RERI aOR: 0.86, 95%CI: 0.46 to 1.62, *p* = 0.64.
Measure of interaction on multiplicative scale (obesity+, injury-, physical activity+): RERI aOR: 1.33, 95%CI: 0.75 to 2.34, *p* = 0.32.
Measure of interaction on multiplicative scale (obesity+, injury+, physical activity-): RERI aOR: 1.11, 95%CI: 0.70 to 1.76, *p* = 0.64.

Measure of interaction on additive scale (obesity+, injury+, physical activity+): RERI aOR: -0.21, 95%CI: -1.33 to 0.91, *P* = 0.71
Measure of interaction on additive scale (obesity-, injury+, physical activity+): RERI aOR: -0.16, 95%CI: -0.80 to 0.47, *p* = 0.61.
Measure of interaction on additive scale (obesity+, injury-, physical activity+): RERI aOR: 0.36, 95%CI: -0.31 to 1.05, *p* = 0.29.
Measure of interaction on additive scale (obesity+, injury+, physical activity-): RERI aOR: 0.21, 95%CI: -0.38 to 0.81, *p* = 0.48.

***ORs adjusted for age and gender**

Secondly, for the subgroup of non-obese people with injury in MOST (Figure 3-14), the risk of radiographic knee OA progression was close to one in both active (aOR: 1.09, 95%CI: 0.60-1.99) and inactive individuals (aOR: 0.93, 95%CI: 0.57-1.52) (Table 3-41). This was similar in OAI with aOR of 0.95 (95%CI: 0.59-1.54) in active people and aOR of 1.19 (95%CI: 0.85-1.65) in inactive people (Figure 3-14). That is, physical activity did not have an interactive effect with injury on the risk of radiographic knee OA progression in either cohort when obesity was absent. This was also confirmed by the statistical tests, in which no significant interactions were found between injury and physical activity on either additive ($RERI_{-MOST}$ aOR: 0.10, 95%CI: -0.71 to 0.92; $RERI_{-OAI}$ aOR: -0.16, 95%CI: -0.80 to 0.47) or multiplicative scales ($RERI_{-MOST}$ aOR: 1.10, 95%CI: 0.50 to 2.45; $RERI_{-OAI}$ aOR: 0.86, 95%CI: 0.46 to 1.62) in either cohort (Table 3-41 and Table 3-42).

Figure 3-14: The progressive risk of radiographic knee OA in different subgroups of obesity-injury-physical activity

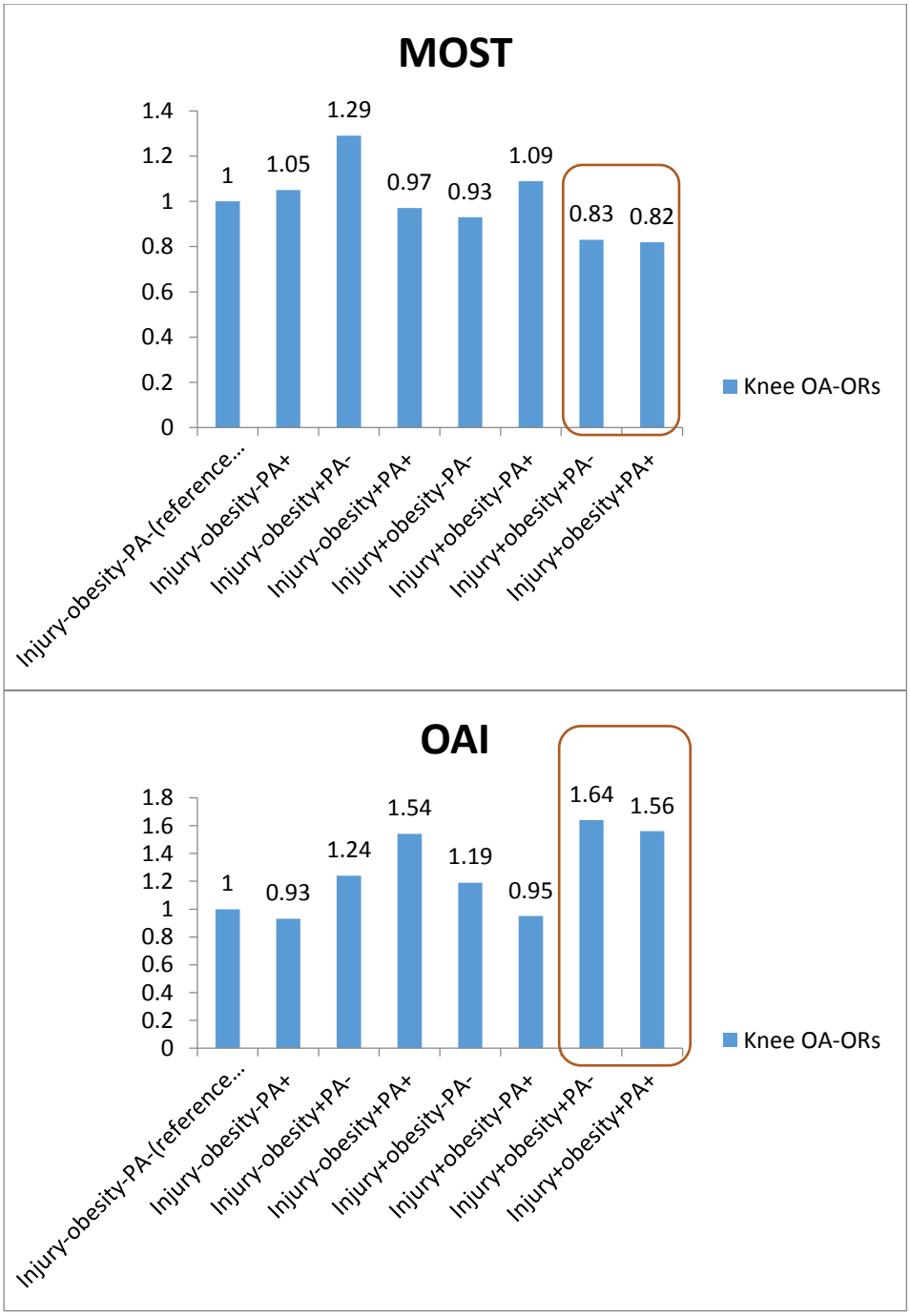


*ORs adjusted for age and gender and obesity
PA+: active group; PA-: inactive group; Injury+: injured group; Injury-: uninjured group, Obesity+: obese group; Obesity-: non-obese group

Thirdly, in the subgroup of Obese and Injured people in both cohorts (Figure 3-15), the risk of radiographic knee OA progression was close in active and inactive individuals (MOST: $aOR_{\text{-active}}$: 0.82, 95%CI: 0.46-1.47 and $aOR_{\text{-inacitve}}$: 0.83, 95%CI: 0.52-1.32; OAI: $aOR_{\text{-active}}$: 1.56, 95%CI: 0.98-2.49 and $aOR_{\text{-inactive}}$: 1.64, 95%CI: 1.17-2.29). This indicated the effect of activity on the risk of radiographic knee OA progression was not largely modified by the presence of obesity and injury together. This was also supported by the statistical tests, in which no significant three-way interaction were found on either additive ($RERI_{\text{-MOST}}$ aOR: 0.19, 95%CI: -0.87 to 1.27; $RERI_{\text{-OAI}}$ aOR: -0.21, 95%CI: -1.33 to 0.91) or multiplicative scales in either cohort ($RERI_{\text{-MOST}}$ aOR: 1.17, 95%CI: 0.40 to 3.44; $RERI_{\text{-OAI}}$ aOR: 0.88, 95%CI: 0.37 to 2.12) (Table 3-41 and Table3-42).

Finally, regardless of activity level in the subgroup of obese and injured people, no evidence of any statistically significant interactions was found between obesity and injury in either MOST ($RERI_{\text{-additive}}$ aOR: -0.39, 95%CI: -1.07 to 0.28; $RERI_{\text{-multiplicative}}$ aOR: 0.69, 95%CI: 0.35 to 1.33) or OAI ($RERI_{\text{-additive}}$ aOR: 0.21, 95%CI: -0.38 to 0.81; $RERI_{\text{-multiplicative}}$ aOR: 1.11, 95%CI: 0.70 to 1.76) Table 3-41 and Table 3-42).

Figure 3-15: The progressive risk of radiographic knee OA in different subgroups of obesity-injury-physical activity



*ORs adjusted for age and gender and obesity
PA+: active group; PA-: inactive group; Injury+: injured group; Injury-: uninjured group, Obesity+: obese group; Obesity-: non-obese group

3.4 Progression of symptomatic knee OA

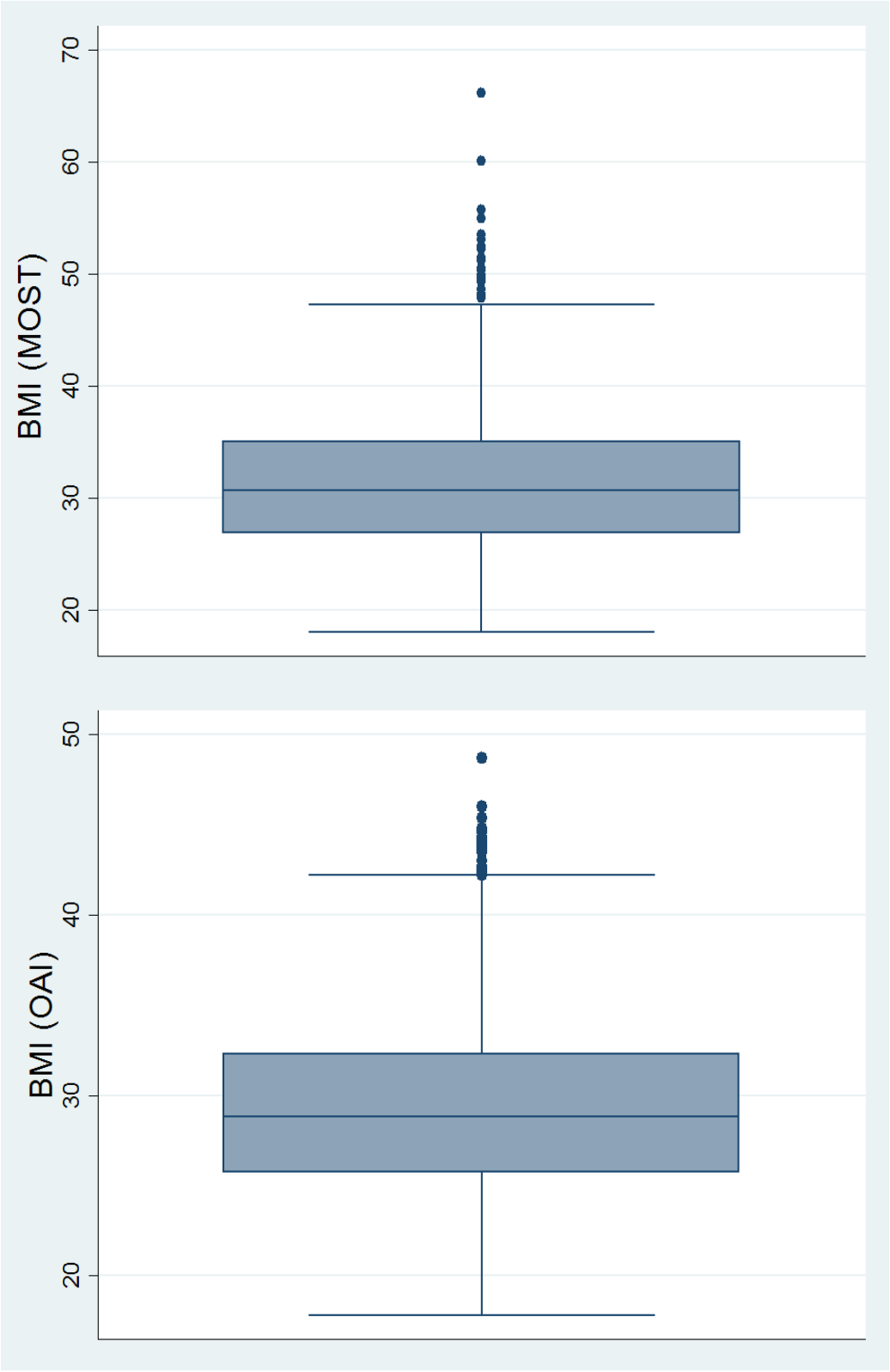
1679 knees from MOST and 2833 knees from OAI met the inclusion criteria for the symptomatic knee OA progression study (knees with frequent knee symptoms at baseline). In MOST, 12 knees were excluded due to missing injury, physical activity or BMI data at the baseline assessment. Therefore, 1667 knees in MOST and 2833 knees in OAI were included in the data analysis.

Participants' characteristics are presented in Table 3-43. Similar to the incident radiographic knee OA progression study, the mean age of participants in MOST and OAI were similar, but the mean BMI and PASE score were slightly higher in MOST than OAI (Table 3.43; Figure 3-16; Figure 3-17).

Table 3-43: Participants' characteristics data at baseline

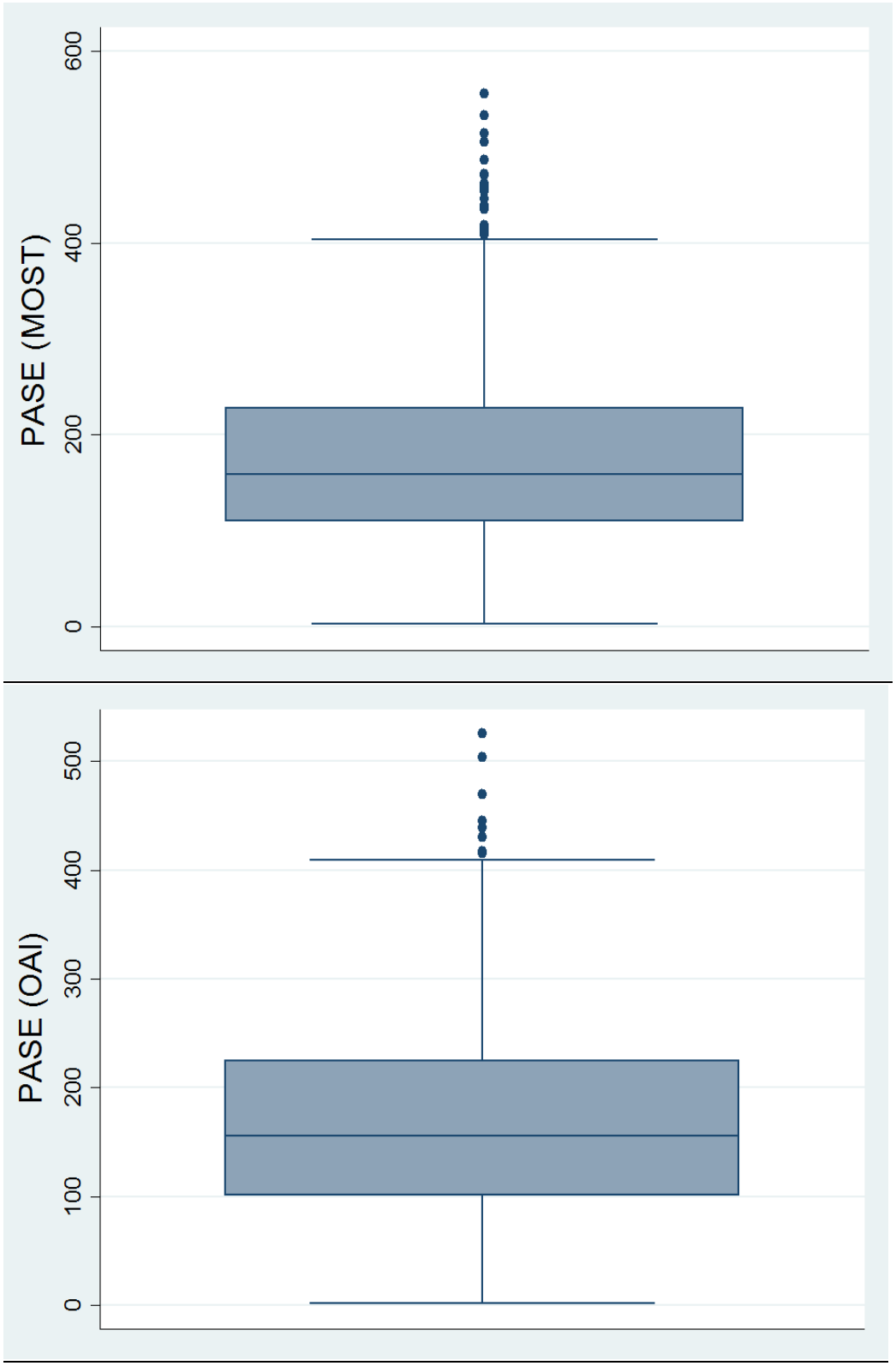
Cohort		AGE	BMI (Baseline)	PASE (Baseline)
MOST	Mean ± SD	61.70 ± 7.72	31.52 ± 6.54	175.02 ± 89.60
	Min-Max	50-79	18.04-66.12	2.2-555.4
	Range	29	48.08	553.2
OAI	Mean ± SD	60.15 ± 8.96	29.22 ± 4.88	167.71 ± 86.16
	Min-Max	45-79	17.8-48.7	2-526
	Range	34	30.9	524

Figure 3-4: Distribution of BMI data at baseline



*BMI: body mass index

Figure 3-5: Distribution of PASE data at baseline



*PASE: Physical Activity Scale for Elderly

3.4.1 *Gender and risk of symptomatic knee OA progression*

The majority of participants were female in the MOST (66%) and OAI (58%) symptomatic knee OA progression study. In MOST, males and females had a similar risk of knee OA progression at 60-months follow-up (OR: 0.96, 95%CI: 0.69-1.33). After adjusting for confounders, females were 10% at higher risk of knee OA progression compared to males (aOR: 1.10, 95%CI: 0.78-1.56). However, this association was not statistically significant. Likewise, no gender difference was found in OAI (OR: 0.90, 95%CI: 0.71-1.14). This remained unchanged after adjusting for confounders (aOR: 0.88, 95%CI: 0.69-1.12) (Table 3-44).

Table 3-44: Gender and risk of symptomatic knee OA progression

Cohort	Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	Male	473 (83.9%)	91 (16.1%)	564	-	
	Female	931 (84.4%)	172 (15.6%)	1103	0.96 (0.69 - 1.33) $p = 0.83$	1.10 (0.78 – 1.56) $p = 0.56$
OAI	Male	1006 (84.7%)	182 (15.3%)	1188	-	-
	Female	1412 (85.8%)	233 (14.2%)	1645	0.90 (0.71 – 1.14) $p = 0.39$	0.88 (0.69 – 1.12) $p = 0.30$

***OR adjusted for Injury, obesity, age and physical activity**

3.4.2 *Age and risk of symptomatic knee OA progression*

In MOST, the risk of symptomatic knee OA progression was 28% and 27% lower respectively in the middle age and old age groups as compared to the young age group (Table 3-45). However, these associations were not statistically significant ($aOR_{\text{-middle age}}$: 0.72, 95%CI: 0.49 - 1.07; $aOR_{\text{-old}}$: 0.73, 95%CI: 0.48 - 1.10). In OAI, no age differences were found between young, middle age and old age group ($aOR_{\text{-middle age}}$: 1.09, $aOR_{\text{-old}}$: 1.05) (Table 3-45).

Table 3-45: Age and risk of symptomatic knee OA progression

Cohort	Age Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	45-55	315 (79.7%)	80 (20.3%)	395	-	-
	55-65	542 (84.6%)	99 (15.4%)	641	0.69 (0.46 - 1.01) $p = 0.06$	0.72 (0.49 - 1.07) $p = 0.10$
	65-79	547 (86.7%)	84 (13.3%)	631	0.64 (0.43 - 0.95) $p = 0.03$	0.73 (0.48 - 1.10) $p = 0.13$
OAI	45-55	792 (85.6%)	133 (14.4%)	925	-	-
	55-65	809 (84.9%)	144 (15.1%)	953	1.09 (0.81 - 1.46) $p = 0.55$	1.09 (0.81 – 1.47) $p = 0.54$
	65-79	817 (85.5%)	138 (14.5%)	955	1.02 (0.76 - 1.37) $p = 0.86$	1.05 (0.77- 1.43) $p = 0.73$

***OR adjusted for Injury, obesity, gender and physical activity**

3.4.3 *The association between obesity and the risk of symptomatic knee OA progression*

At baseline, 54% of MOST participants were obese compared to 41% in OAI (Table 3-46). In MOST, obese and non-obese people had similar risk of symptomatic knee OA progression (aOR: 0.98, 95%CI: 0.71-1.34). However, in OAI, obese people were significantly at greater risk of symptomatic knee OA progression than non-obese individuals (aOR: 1.33, 95%CI: 1.04-1.69).

Table 3-46: Obesity and risk of symptomatic knee OA progression

Group	Cohort	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	Non-obese	648 (84.4%)	120 (15.6%)	768	-	
	Obese	756 (84.1%)	143 (15.9%)	899	0.99 (0.72 -1.35) $p = 0.95$	0.98 (0.71 -1.34) $p = 0.90$
OAI	Non-obese	1444 (86.7%)	221 (13.3%)	1665	-	
	Obese	974 (83.4%)	194 (16.6%)	1168	1.31 (1.03-1.67) $p = 0.02$	1.33 (1.04 -1.69) $p = 0.02$

***OR adjusted for Injury, age, gender and physical activity**

3.4.4 *The association between injury and the risk of symptomatic knee OA progression*

At baseline, 32% and 35% of participants in MOST and OAI had previously been injured (Table 3-47). No significant association was found between injury and knee OA progression in either MOST (p = 0.74) or OAI (p = 0.70). The risk of symptomatic knee OA progression due to injury was close to one in both MOST (aOR: 0.96 95%CI: 0.77-1.20) and OAI (aOR: 0.95, 95%CI: 0.76-1.19). This suggests that injury neither increased nor protected against the risk of symptomatic knee OA progression (Table 3-47).

Table 3-47: Injury and risk of symptomatic knee OA progression

Cohort	Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	Uninjured	957 (84.3%)	178 (15.7%)	1135	-	-
	Injured	447 (84.0%)	85 (16.0%)	532	0.97 (0.78 -1.20) p = 0.81	0.96 (0.77 - 1.20) p = 0.74
OAI	Uninjured	1569 (85.6%)	263 (14.4%)	1832	-	-
	Injured	849 (84.8%)	152 (15.2%)	1001	0.98 (0.79-1.21) p = 0.87	0.95 (0.76-1.19) p = 0.70

***OR adjusted for obesity, age, gender and physical activity**

3.4.5 *The association between physical activity and the risk of symptomatic knee OA progression*

At baseline, 35% and 33% of participants in MOST and OAI were active. In MOST, the risk of symptomatic knee OA progression was 52% higher in active than inactive individuals (aOR: 1.52, 95%CI: 1.08-2.14) (Table 3-48). However, in OAI, the risk of symptomatic knee OA progression was similar among active and inactive individuals (aOR: 1.02, 95%CI: 0.78-1.33) (Table 3-48).

Table 3-48: Physical activity and risk of symptomatic knee OA progression

Cohort	Group	OA Condition		Total	Crude OR (95% CI)	Adjusted OR* (95% CI)
		Without OA (%)	OA (%)			
MOST	Inactive	939 (86.5%)	146 (13.5%)	1085	-	-
	Active	465 (79.9%)	117 (20.1%)	582	1.55 (1.13 -2.13) p = 0.006	1.52 (1.08 -2.14) p = 0.01
OAI	Inactive	1616 (85.3%)	278 (14.7%)	1894	-	-
	Active	802 (85.4%)	137 (14.6%)	939	1.01 (0.78 -1.30) p = 0.90	1.02 (0.78-1.33) p = 0.86

***OR adjusted for Injury, obesity, age and gender**

3.4.6 *The interaction between obesity and injury on the risk of symptomatic knee OA progression*

The study also investigated the two-way interaction between obesity and injury on the risk of symptomatic knee OA progression.

In MOST, the subgroup of Obese and Injured individuals had a similar risk of symptomatic knee OA progression (aOR: 0.95, 95%CI: 0.64-1.40) compared to the risk in the subgroups of Obese and Uninjured (aOR: 0.94, 95%CI: 0.67-1.34) and Non-obese and Injured people (aOR: 0.91, 95%CI: 0.65-1.26) (Table 3-49). This highlighted the absence of any major interactions between obesity and injury on the risk of symptomatic knee progression in MOST. It was also supported by the statistical test, where no significant interactions were found between obesity and injury on the risk of symptomatic knee OA progression on either additive (RERI aOR: 0.09, 95%CI: -0.31 to 0.50) or multiplicative scales (RERI aOR: 1.10, 95%CI: 0.70 to 1.72).

Moving from MOST to OAI, here, injury in the absence of obesity showed a protective effect on the risk of symptomatic knee OA progression although it was not statistically significant (aOR: 0.77, 95%CI: 0.56-1.05). Conversely, obesity in the absence of injury increased the risk of

symptomatic knee OA progression by about 13% (aOR: 1.13, 95%CI: 0.84-1.51). When injury and obesity were present together, the estimate risk of symptomatic knee OA progression rose even more, up to 35% (aOR: 1.35, 95%CI, 0.99-1.85). This highlighted a mild positive cross over interaction between obesity and injury on the risk of symptomatic knee OA progression in OAI. This interaction was marginally insignificant on both additive (RERI aOR: 0.44, 95%CI: -0.002 to 0.89) and multiplicative (RERI aOR: 1.54, 95%CI: 0.99 to 2.38) scales (Table 3-50).

Table 3-49: The interaction between obesity and injury on the risk of symptomatic knee OA progression in MOST

	Non-obese		Obese		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	84/448	1 (reference)	94/509	0.94 (0.67 - 1.34); p = 0.76	0.97 (0.67 - 1.40); p = 0.88
Injured	36/200	0.91 (0.65- 1.26); p = 0.57	49/247	0.95 (0.64 - 1.40); p = 0.81	1.12 (0.68 - 1.86); p = 0.63
Adjusted ORs[2] (95% CI)		0.92 (0.66 - 1.28); p = 0.65		0.99 (0.73 - 1.35); p = 0.97	

Measure of interaction on multiplicative scale: RERI aOR: 1.10, 95%CI: 0.70 to 1.72, p = 0.65.
Measure of interaction on additive scale: RERI aOR: 0.09, 95%CI: -0.31 to 0.50, p = 0.64.
*ORs adjusted for age, gender and physical activity

1. ORs for the effect modification of injury on the role of obesity in progression of symptomatic knee OA
2. ORs for the effect modification of obesity on the role of injury in progression of symptomatic knee OA

Table 3-50: The interaction between obesity and injury on the risk of symptomatic knee OA progression in OAI

	Non-obese		Obese		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	153/957	1 (reference)	110/612	1.13 (0.84 - 1.51); p = 0.40	1.14 (0.85 - 1.54); p = 0.37
Injured	68/487	0.77 (0.56- 1.05); p = 0.10	84/362	1.35 (0.99 – 1.85); p = 0.058	1.76 (1.20 - 2.59); p = 0.004
Adjusted ORs[2] (95% CI)		0.76 (0.56 - 1.03); p = 0.08		1.22 (0.88 - 1.68); p = 0.22	

Measure of interaction on multiplicative scale: RERI aOR: 1.54, 95%CI: 0.99 to 2.38, p = 0.051.
Measure of interaction on additive scale: RERI aOR: 0.44, 95%CI: -0.002 to 0.89, p = 0.051.
*ORs adjusted for age, gender and physical activity

1. ORs for the effect modification of injury on the role of obesity in progression of symptomatic knee OA
2. ORs for the effect modification of obesity on the role of injury in progression of symptomatic knee OA

3.4.7 *The interaction between physical activity and obesity on the risk of symptomatic knee OA progression*

Data were also stratified by obesity and physical activity to investigate the two-way interaction between physical activity and obesity on the risk of symptomatic knee OA progression.

In both cohorts, the effect of activity or obesity on the risk of disease progression was not largely modified by the presence or absence one or the other (Table 3-51; Table 3-52). In addition, the combined effect of obesity and activity on the risk of disease progression in both cohorts was similar to the multiple or the sum of the individual effects of obesity and injury (Table 3-51; Table 3-52). This highlighted the absence of any large interaction between activity and obesity on the risk of symptomatic knee OA progression in both cohorts. This was also supported by the statistical test, in which no significant interactions were found on either additive ($RERI_{-MOST}$ aOR: 0.18, 95%CI: -0.59 to 0.97; $RERI_{-OAI}$ aOR: -0.15, 95%CI: -0.79 to 0.47) or multiplicative scales ($RERI_{-MOST}$ aOR: 1.17, 95%CI: 0.62 to 2.20; $RERI_{-OAI}$ aOR: 0.87, 95%CI: 0.52 to 1.45) (Table 3-51; Table 3-52).

Table 3-51: The interaction between physical activity and obesity on the risk of symptomatic knee OA progression in MOST

	Inactive		Active		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Non-obese	68/429	1 (reference)	52/219	1.39 (0.86 - 2.27); p = 0.17	1.48 (0.89 - 2.46); p = 0.12
Obese	78/510	0.91 (0.60 - 1.38); p = 0.68	65/246	1.50 (0.94 - 2.40); p= 0.08	1.57 (0.98 - 2.49); p = 0.057
Adjusted ORs[2] (95% CI)		0.91 (0.60 - 1.38); p = 0.67		1.09 (0.67 - 1.79); p = 0.70	

Measure of interaction on multiplicative scale: RERI aOR: 1.17, 95%CI: 0.62 to 2.20, p = 0.62.
Measure of interaction on additive scale: RERI aOR: 0.18, 95%CI: -0.59 to 0.97, p = 0.63.
*ORs adjusted for age, gender and injury

1. ORs for the effect modification of obesity on the role of obesity in progression of symptomatic knee OA

2. ORs for the effect modification of physical activity on the role of obesity in progression of symptomatic knee OA

Table 3-52: The interaction between physical activity and obesity on the risk of symptomatic knee OA progression in OAI

	Inactive		Active		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Non-obese	141/943	1 (reference)	80/501	1.08 (0.76 - 1.53); p = 0.64	1.13 (0.79 - 1.62); p = 0.48
Obese	137/673	1.39 (1.03 - 1.86) p = 0.02	57/301	1.31 (0.89 - 1.95); p = 0.16	0.88 (0.59 - 1.31); p = 0.54
Adjusted ORs[2] (95% CI)		1.37 (1.02 - 1.84); p = 0.03		1.25 (0.82 - 1.90); p = 0.29	

Measure of interaction on multiplicative scale: RERI aOR: 0.87, 95%CI: 0.52 to 1.45, p = 0.60.
Measure of interaction on additive scale: RERI aOR: -0.15, 95%CI: -0.79 to 0.47, p = 0.62.
*ORs adjusted for age, gender and injury

1. ORs for the effect modification of obesity on the role of physical activity in progression of symptomatic knee OA

2. ORs for the effect modification of physical activity on the role of obesity in progression of symptomatic knee OA

3.4.8 *The interaction between physical activity and injury on the risk of symptomatic knee OA progression*

Finally, the two-way interaction between physical activity and injury on the risk of symptomatic knee OA progression was examined.

In both cohorts, the effect of physical activity on symptomatic knee OA progression across the strata of injury (able 3-53; Table 3-54) was similar to the main effect of physical activity on the risk of disease progression ($aOA_{\text{-MOST}}$: 1.52, $aOR_{\text{-OAI}}$: 1.02, Table 3-48). In addition, in both cohorts, the combined effect of injury and activity on the risk of disease progression was similar to the multiple or the sum of the individual effects of obesity and injury (Table 3-53; Table 3-54). This highlighted the absence of any large interaction between activity and injury on the risk of symptomatic knee OA progression in both cohorts. This was also supported by the statistical test, in which no significant interactions were found on either additive ($RERI_{\text{-MOST}}$ aOR: -0.06, 95%CI: -0.64 to 0.51; $RERI_{OAI}$ aOR: -0.27, 95%CI: -0.75 to 0.20) or multiplicative scales ($RERI_{\text{-MOST}}$ aOR: 0.96, 95%CI: 0.62 to 1.50; $RERI_{OAI}$ aOR: 0.76, 95%CI: 0.48 to 1.20) (able 3-53; Table 3-54).

Table 3-53: The interaction between physical activity and injury on the risk of symptomatic knee OA progression in MOST

	Inactive		Active		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	103/666	1 (reference)	75/291	1.54 (1.06 - 2.24); p = 0.02	1.76 (1.18 - 2.62); p = 0.005
Injured	43/273	0.97 (0.73 - 1.31); p = 0.88	42/174	1.45 (0.95 - 2.21); p = 0.07	1.34 (0.78 - 2.29); p = 0.27
Adjusted ORs[2] (95% CI)		1.00 (0.73 - 1.35); p = 0.99		0.94 (0.69 - 1.27); p = 0.69	

Measure of interaction on multiplicative scale: RERI aOR: 0.96, 95%CI: 0.62 to 1.50, p = 0.87.
Measure of interaction on additive scale: RERI aOR: -0.06, 95%CI: -0.64 to 0.51, p = 0.82.
*ORs adjusted for age, gender and obesity

1. ORs for the effect modification of injury on the role of physical activity in progression of symptomatic knee OA

2. ORs for the effect modification of physical activity on the role of injury in progression of symptomatic knee OA

Table 3-54: The interaction between physical activity and injury on the risk of symptomatic knee OA progression in OAI

	Inactive		Active		
	(N) OA/no-OA	Adjusted ORs (95% CI)	(N) OA/no-OA	Adjusted ORs* (95% CI)	Adjusted ORs[1] (95% CI)
Uninjured	181/1097	1 (reference)	82/472	1.13 (0.83 - 1.56); p = 0.41	1.09 (0.78 - 1.52); p = 0.60
Injured	97/519	1.05 (0.80 - 1.37); p = 0.71	55/330	0.91 (0.63 - 1.32); p = 0.63	0.85 (0.56 - 1.29); p = 0.45
Adjusted ORs[2] (95% CI)		1.04 (0.79 - 1.36); p = 0.74		0.81 (0.56 - 1.19); p = 0.30	

Measure of interaction on multiplicative scale: RERI aOR: 0.76, 95%CI: 0.48 to 1.20, p = 0.24.
Measure of interaction on additive scale: RERI aOR: -0.27, 95%CI: -0.75 to 0.20, p = 0.26.
*ORs adjusted for age, gender and obesity

1. ORs for the effect modification of injury on the role of physical activity in progression of symptomatic knee OA

2. ORs for the effect modification of physical activity on the role of injury in progression of symptomatic knee OA

3.4.9 *The interaction between obesity, injury and physical activity on the risk of symptomatic knee OA progression*

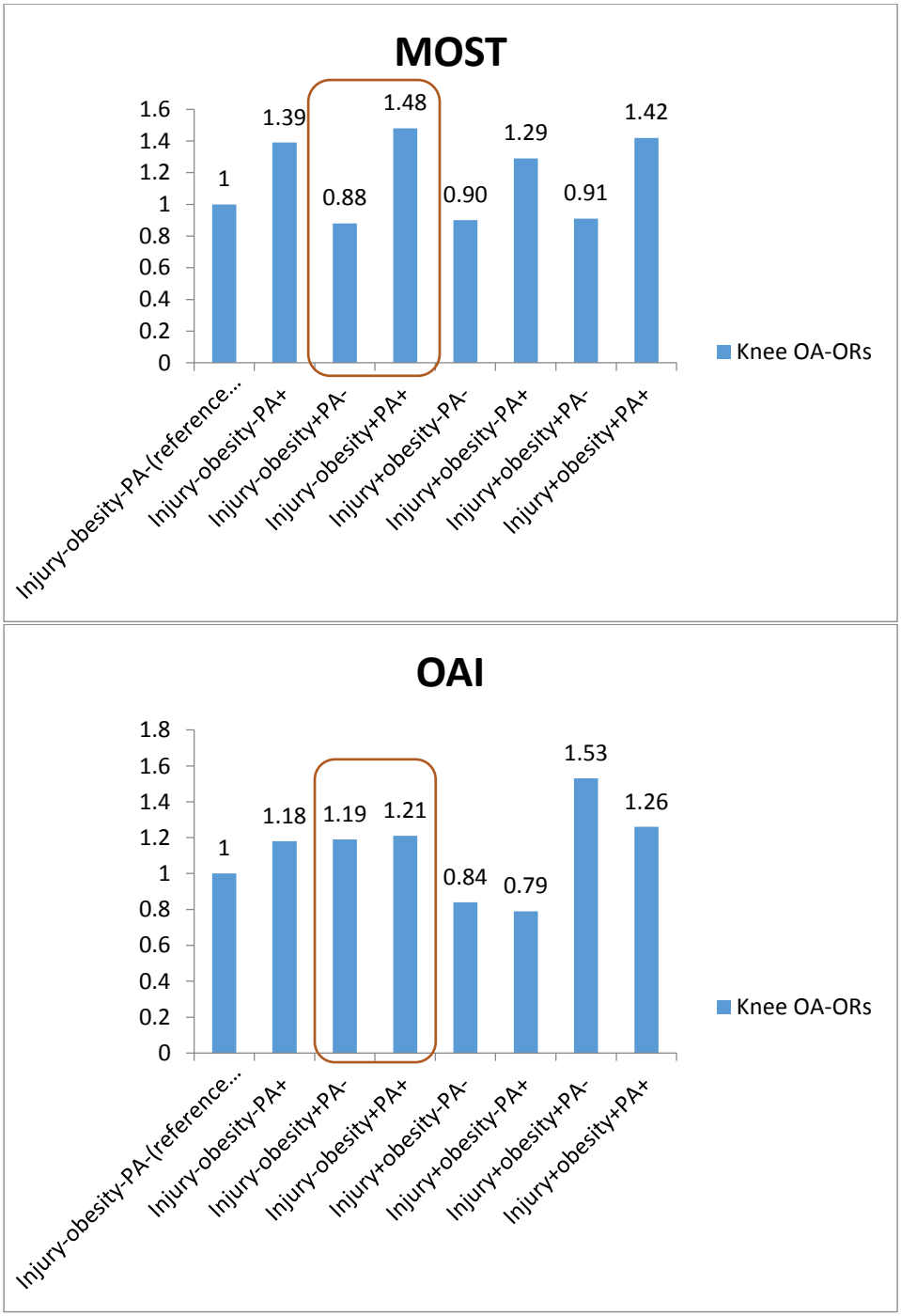
In these last results for symptomatic knee OA progression, the three-way interaction between all three variables of obesity, injury and physical activity were examined.

For the subgroup of obese people with no injury in MOST (Figure 3-18), the risk of symptomatic knee OA progression was higher in active (aOR: 1.48, 95%CI: 0.88-2.46) than inactive (aOR: 0.88, 95%CI: 0.56-1.37) individuals. However, the pattern and magnitude of increase from inactive to active people was similar among uninjured people with and without obesity (uninjured-non-obese: $aOR_{\text{-inactive}}$: 1 → $aOR_{\text{-active}}$: 1.39; uninjured-obese: $aOR_{\text{-inactive}}$: 0.88 → $aOR_{\text{-active}}$: 1.48) (Table 3-55). This highlighted that activity had a similar effect on the risk of symptomatic knee progression in subgroup of uninjured people with and without obesity. This was also supported by the statistical tests, in which no significant interaction were found between physical activity and obesity on either additive (RERI aOR: 0.20, 95%CI: -0.66 to 1.07) or multiplicative scales (RERI aOR: 1.20, 95%CI: 0.59 to 2.43) (Table 3-55).

In the subgroup of obese people with no injury in OAI (Figure 3-18), the risk of symptomatic knee OA progression was

similar in both active (aOR: 1.21, 95%CI: 0.74-1.98) and inactive individuals (aOR: 1.19, 95%CI: 0.84-1.69). This also indicated that activity did not have an interactive effect with obesity on the risk of symptomatic knee OA progression when injury was absent. This was confirmed by the statistical tests, in which no significant interactions were found between obesity and physical activity on either additive (RERI aOR: -0.17, 95%CI: -0.92 to 0.58) or multiplicative (RERI aOR: 0.85, 95%CI: 0.45 to 1.59) scales (Table 3-56).

Figure 3-6: The progressive risk of symptomatic knee OA in different subgroups of obesity-injury-physical activity



*ORs adjusted for age and gender and obesity
PA+: active group; PA-: inactive group; Injury+: injured group; Injury-: uninjured group, Obesity+: obese group; Obesity-: non-obese group

Table 3-55: The interaction between physical activity, obesity and injury on the risk of symptomatic knee OA progression in MOST

	Non-obese		Obese	
	Uninjured	Injured	Uninjured	Injured
	aOR* (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Inactive	1	0.90 (0.58 - 1.40); *p* = 0.66	0.88 (0.56 - 1.37); *p* = 0.57	0.91 (0.55 -1.51); *p* =0.73
Active	1.39 (0.81 - 2.38); *p* = 0.21	1.29 (0.71 - 2.33); *p* = 0.39	1.48 (0.88 - 2.46); *p* = 0.13	1.42 (0.80 - 2.50); *p* = 0.22

Measure of interaction on multiplicative scale (obesity+, injury+, physical activity+): RERI aOR: 0.90, 95%CI: 0.37 to 2.22, *p* = 0.83.
Measure of interaction on multiplicative scale (obesity-, injury+, physical activity+): RERI aOR: 1.01, 95%CI: 0.52 to 1.98, *p* = 0.95.
Measure of interaction on multiplicative scale (obesity+, injury-, physical activity+): RERI aOR: 1.20, 95%CI: 0.59 to 2.43, *p* = 0.60.
Measure of interaction on multiplicative scale (obesity+, injury+, physical activity-): RERI aOR: 1.14, 95%CI: 0.63 to 2.07, *p* = 0.64

Measure of interaction on additive scale (obesity+, injury+, physical activity+): RERI aOR: -0.07, 95%CI: -1.15 to 0.99, *p* = 0.88.
Measure of interaction on additive scale (obesity-, injury+, physical activity+): RERI aOR: -0.01, 95%CI: -0.80 to 0.77, *p* = 0.97.
Measure of interaction on additive scale (obesity+, injury-, physical activity+): RERI aOR: 0.20, 95%CI: -0.66 to 1.07, *p* = 0.64.
Measure of interaction on additive scale (obesity+, injury+, physical activity-): RERI aOR: 0.12, 95%CI: -0.40 to 0.66, *p* = 0.63.

***ORs adjusted for age and gender**

Table 3-56: The interaction between physical activity, obesity and injury on the risk of symptomatic knee OA progression in OAI

	Non-obese		Obese	
	Uninjured	Injured	Uninjured	Injured
	aOR* (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Inactive	1	0.84 (0.57 - 1.25); p = 0.40	1.19 (0.84 - 1.69); p = 0.30	1.53 (1.04 - 2.25); p = 0.02
Active	1.18 (0.79 - 1.76); p = 0.39	0.79 (0.47 - 1.31); p = 0.36	1.21 (0.74 - 1.98); p = 0.43	1.26 (0.76 - 2.11); p = 0.36

Measure of interaction on multiplicative scale (obesity-, injury+, physical activity+): RERI aOR: 1.03, 95%CI: 0.41 to 2.61, p = 0.94.
Measure of interaction on multiplicative scale (obesity-, injury+, physical activity+): RERI aOR: 0.78, 95%CI: 0.41 to 1.47, p = 0.45.
Measure of interaction on multiplicative scale (obesity+, injury-, physical activity+): RERI aOR: 0.85, 95%CI: 0.45 to 1.59, p = 0.62.
Measure of interaction on multiplicative scale (obesity+, injury+, physical activity-): RERI aOR: 1.51, 95%CI: 0.88 to 2.58, p = 0.13.

Measure of interaction on additive scale (obesity+, injury+, physical activity+): RERI aOR: -0.03, 95%CI: -1.09 to 1.01, p= 0.94.
Measure of interaction on additive scale (obesity-, injury+, physical activity+): RERI aOR: -0.24, 95%CI: -0.84 to 0.36, p = 0.43.
Measure of interaction on additive scale (obesity+, injury-, physical activity+): RERI aOR: -0.17, 95%CI: -0.92 to 0.58, p = 0.65.
Measure of interaction on additive scale (obesity+, injury+, physical activity-): RERI aOR: 0.48, 95%CI: -0.11 to 1.09, p = 0.11.

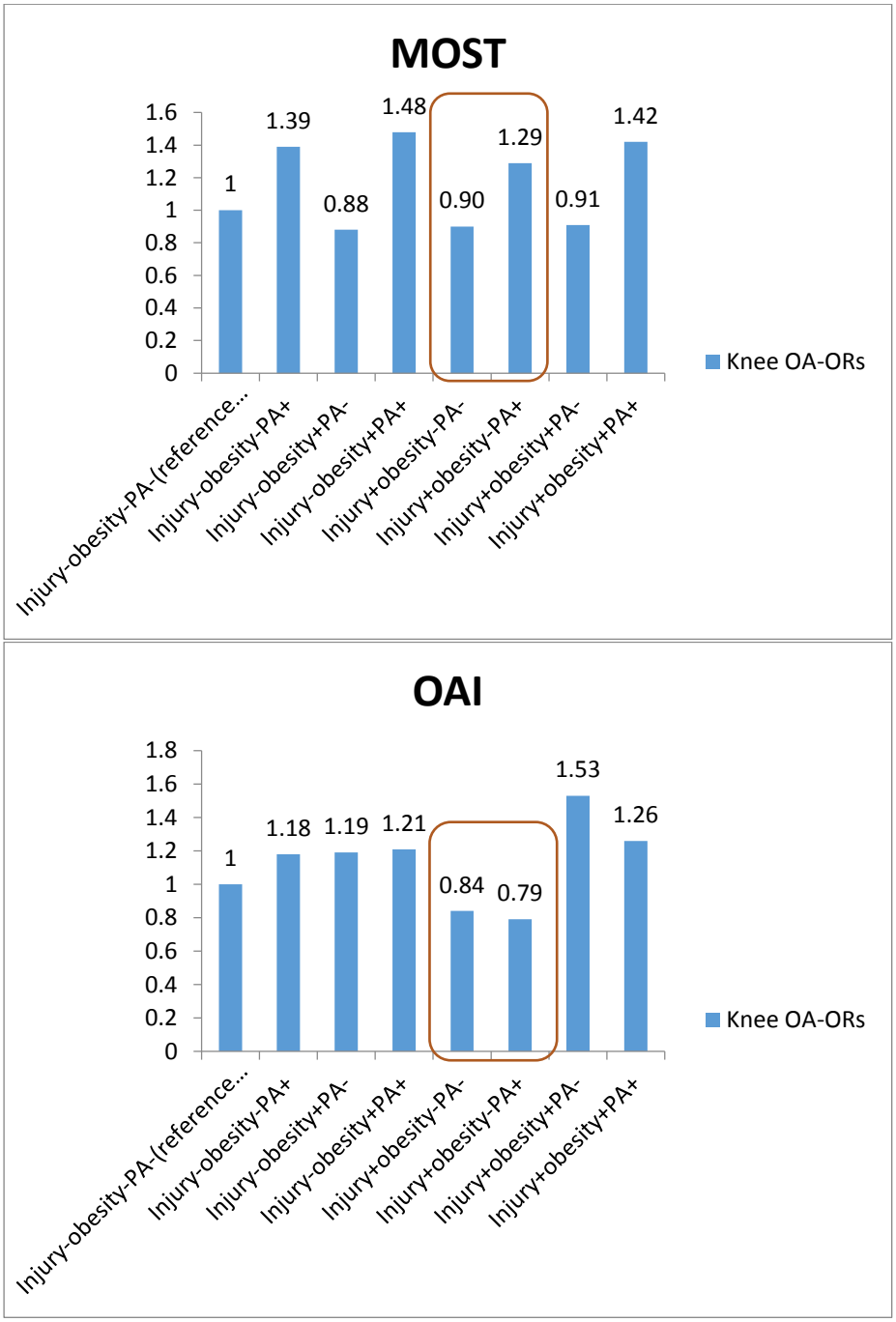
***ORs adjusted for age and gender**

Secondly, for the subgroup of Non-obese and Injured people in MOST (Figure 3-19), the risk of symptomatic knee OA progression was higher in active (aOR: 1.29, 95%CI: 0.71-2.33) than inactive (aOR: 0.90, 95%CI: 0.58-1.40) individuals. However, the pattern and magnitude of increase from inactive to active was similar among non-obese people with and without injury (non-obese-uninjured: $aOR_{\text{-inactive}}$: 1 → $aOR_{\text{-active}}$: 1.39; non-obese-injured: $aOR_{\text{-inactive}}$: 0.90 → $aOR_{\text{-active}}$: 1.29) (Table 3-55). This highlighted that activity had a similar effect on the risk of symptomatic knee progression in the subgroup of non-obese people with and without injury. This was also supported by the statistical tests, in which no significant interaction was found between physical activity and injury on either additive (RERI aOR: -0.01, 95%CI: -0.80 to 0.77) or multiplicative (RERI aOR: 1.01, 95%CI: 0.52 to 1.98) scales (Table 3-55).

Moving from MOST to OAI, in the subgroup of obese people with no injury in OAI (Figure 3-19), the risk of symptomatic knee OA progression was similar in both active (aOR: 0.79, 95%CI: 0.47-1.31) and inactive individuals (aOR: 0.84, 95%CI: 0.57-1.25). This indicated that activity did not have an interactive effect with injury on the risk of symptomatic knee OA progression when obesity was absent. This was also

confirmed by the statistical tests, in which no significant interactions were found between obesity and physical activity on either additive (RERI aOR: -0.24, 95%CI: -0.84 to 0.36) or multiplicative scales (RERI aOR: 0.78, 95%CI: 0.41 to 1.47) (Table 3-56).

Figure 3-19: The progressive risk of symptomatic knee OA in different subgroups of obesity-injury-physical activity



*ORs adjusted for age and gender and obesity
PA+: active group; PA-: inactive group; Injury+: injured group; Injury-: uninjured group, Obesity+: obese group; Obesity-: non-obese group

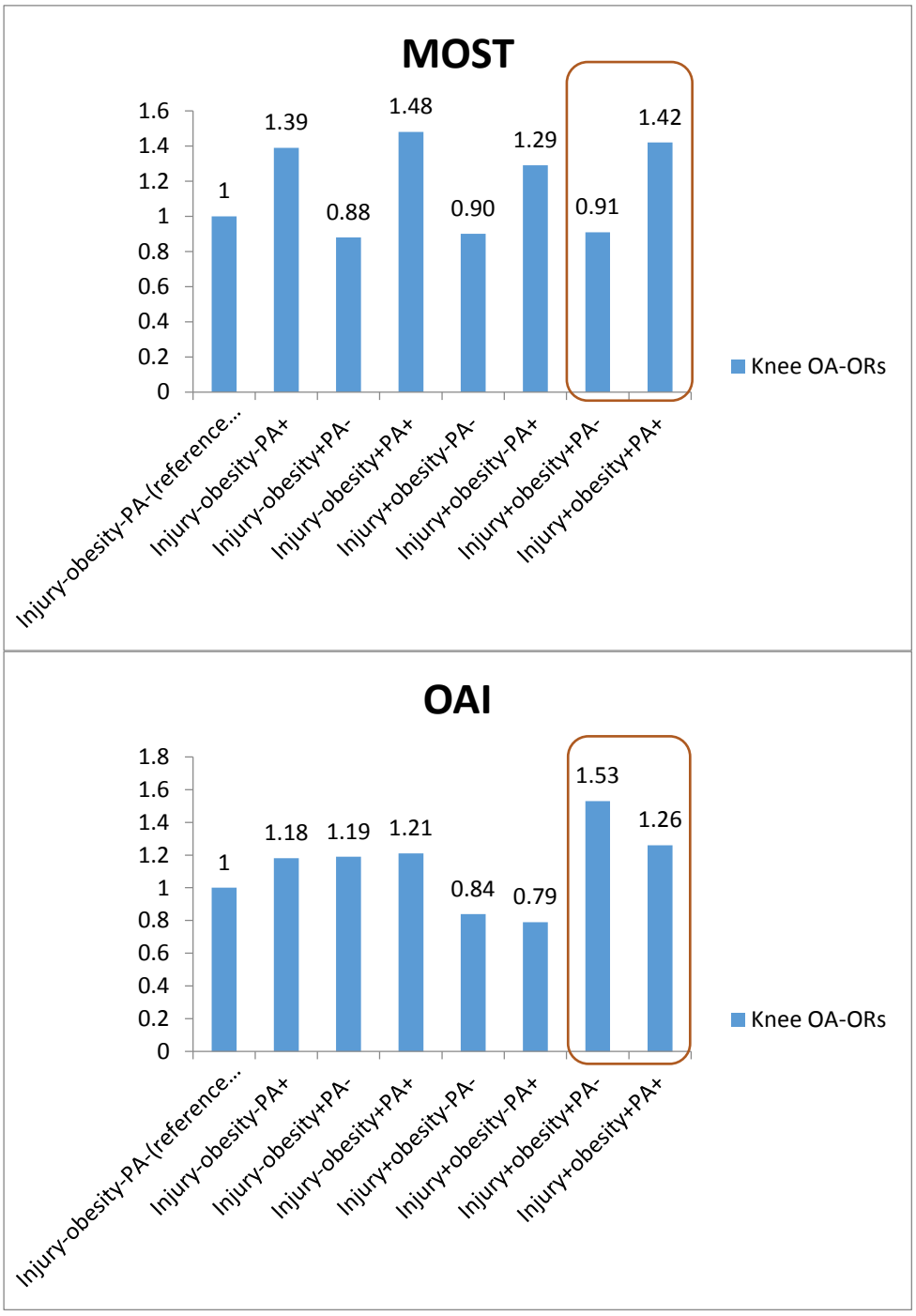
Thirdly, for the subgroup of obese people with injury in MOST (Figure 3-20), the risk of symptomatic knee OA progression was higher in active (aOR: 1.42, 95%CI: 0.80-2.50) than inactive (aOR: 0.91, 95%CI: 0.55-1.51) individuals. However, the pattern and magnitude of increase was similar among obese people with and without injury (obese-uninjured: $aOR_{-inactive}$: 0.88 → $aOR_{-active}$: 1.48; obese-injured: $aOR_{-inactive}$: 0.91 → $aOR_{-active}$: 1.42) (Table 3-55). This indicated that the effect of activity on the risk of symptomatic knee OA progression was not largely modified by the presence of obesity and injury together. This was also supported by the statistical tests, in which no significant three-way interaction was found on either additive (RERI aOR: -0.07, 95%CI: -1.15 to 0.99) or multiplicative (RERI aOR: 0.90, 95%CI: 0.37 to 2.22) scales (Table 3-55).

For the subgroup of obese people with injury in OAI (Figure 20), the risk of symptomatic knee OA progression was close in active (aOR: 1.26, 95%CI: 0.76-2.11) and inactive individuals (aOR: 1.53, 95%CI: 1.04-2.25). This indicated that the effect of activity on the risk of radiographic knee OA progression was not largely modified by the presence of obesity and injury together in OAI. This was also supported by the statistical tests, in which no significant three-way interaction were found

on either additive (RERI aOR: -0.03, 95%CI: -1.09 to 1.01) or multiplicative scales (RERI aOR: 1.03, 95%CI: 0.41 to 2.61) (Table 3-56).

Finally, regardless of activity level, no evidence of any statistically significant interactions was found between obesity and injury on the risk of symptomatic knee OA progression in MOST ($RERI_{-additive}$ aOR: 0.12, 95%CI: -0.40 to 0.66; $RERI_{-multiplicative}$ aOR: 1.14, 95%CI: 0.63 to 2.07). However, in OAI, there was a suggestion of possible positive interaction between obesity and injury on risk of symptomatic knee OA progression on both additive and multiplicative scales ($RERI_{-additive}$ aOR: 0.48, 95%CI: -0. 11 to 1.09; $RERI_{-multiplicative}$ aOR: 1.51, 95%CI: 0.88 to 2.58). However, the magnitudes of interactions on both additive and multiplicative scales were small and not statistically significant (Table 3-55 and Table 3-56).

Figure 3-20: The progressive risk of symptomatic knee OA in different subgroups of obesity-injury-physical activity



*ORs adjusted for age and gender and obesity
PA+: active group; PA-: inactive group; Injury+: injured group; Injury-: uninjured group, Obesity+: obese group; Obesity-: non-obese group

4 Results: Nottingham Knee Study

This chapter reports the results of the primary data collection undertaken to establish normative data for knee pain, symptoms, function and knee related QOL, and their associations with risk factors for OA including obesity, injury and physical activity.

Of 2500 postal questionnaires sent to people in the community, 414 participants responded (16.5%). The highest response rate was amongst the middle age group with 23.5% (n = 196); followed by the old age group with 18.1% (n = 151); and then the young age group with 8.0% (n = 67) (Table 4-1).

The mean age of participants was 64.6 years old (SD: 14.3 years), ranged from 19 to 91 years (Table 4-2). More than half of the responders were female (n = 227, 54.8%). In the young age group, the proportion for females participation was twice that of males (M/F: 31.3% / 68.7%), while this proportion was more similar in the middle age (M/F: 49% / 51%) and old groups (M/F: 46.4% / 53.6%) (Table 4-1).

Table 4-1: Participants' characteristics data

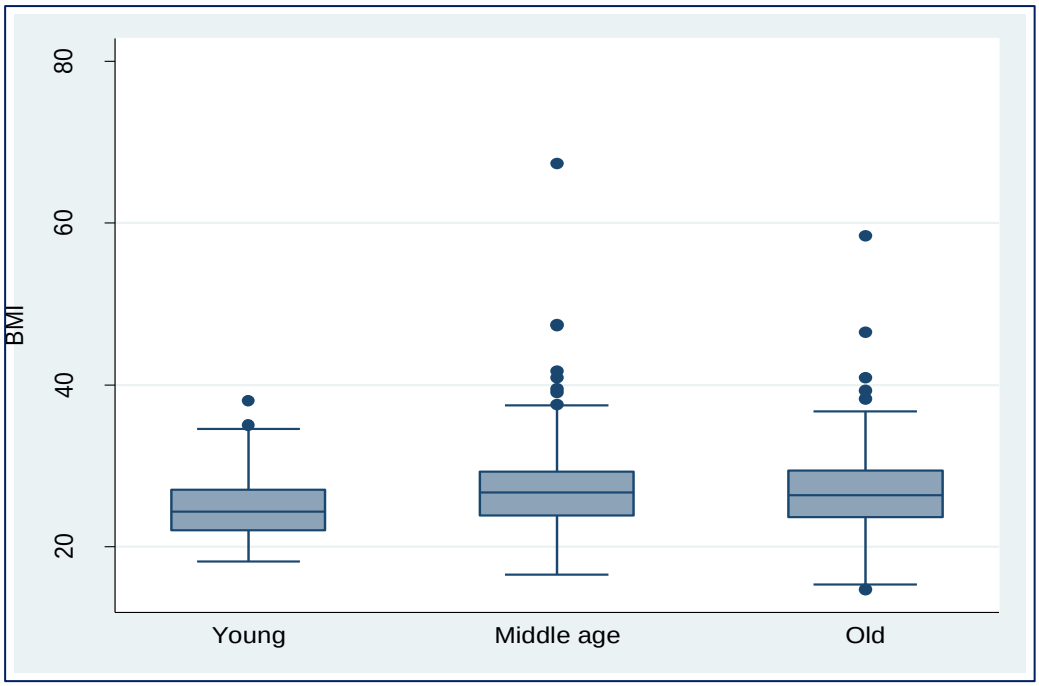
Participants' characteristics	Total N (%)	Young N (%)	Middle age N (%)	Old N (%)
Age category	n = 414 (100%)	n = 67 (16.2%)	n = 196 (47.3%)	n =151 (36.5%)
Gender category	187 (45.2%)	21 (31.3%)	96 (49.0%)	70 (46.4%)
Female	227 (54.8%)	46 (68.7%)	100 (51.0%)	81 (53.6%)

BMI was calculated for 394 participants (response rate of 95.1%), who reported both height and weight (Mean BMI= 26.8, SD = 5.4) (Table 4-2). The mean BMI of participants were similar in the middle age (Mean = 27.3, SD = 5.7) and the old age groups (Mean = 26.9, SD = 5.4). This was slightly lower amongst the young age group (Mean = 25.0, SD = 4.1) (Table 4-2; Figure 4-1).

Table 4-2: Participants' characteristics data (Age and BMI)

Participants' characteristics	Total	Young	Middle age	Old
Age	n = 390	n = 66	n = 187	n = 137
Mean ± SD	64.65 ± 14.3	39.81 ± 5.30	63.20 ± 5.59	78.59 ± 5.55
Minimum-Maximum	19 – 91	19 – 44	45 – 69	70 – 91
BMI	n = 394	n = 66	n = 182	n = 146
Mean ± SD	26.81 ± 5.49	25.07 ± 4.19	27.33 ± 5.7	26.96 ± 5.49
Minimum-Maximum	14.6 - 67.3	18.1 - 37.9	16.5 - 67.3	14.6 - 58.3

Figure 4-1: Age specific distribution of BMI data



Participants' physical activity level, obesity status, history of injury and knee joint replacement were also evaluated (Table 4-3). A small percent of participants had a history of injury (n = 50, 12.1%) or joint replacement (n = 24, 5.8%).

Table 4-3: Participants' characteristics data (obesity, injury, physical activity and knee joint replacement)

Participants' characteristics	Obesity Status	Injury	Physical activity	Knee Joint replacement
	Obese/non-obese	Injured/uninjured	Active/inactive	Yes/ No
N (%)	72 (17.4%)	50 (12.1%)	202 (48.8%)	24 (5.8%)
	322 (77.8%)	357 (86.2%)	169 (40.8%)	387 (93.5%)
Missing	20 (4.8%)	7 (1.7%)	43 (10.4%)	3 (0.7%)

Participants' health status was also assessed using the EQ-5D-5L questionnaire. There was a decrease in the percentage of participants reporting "no problems" in each EQ-5D-5L health dimension as age increased (except for the anxiety and depression dimension where young group reported very similar status to the old age group) (Table 4-4). Conversely, the proportion of participants having "any problem" increased with the age (Table 4-4; Figure 4-2).

The EQ-5D-5L VAS score also showed a negative association between age and QOL, in which the old age group had a lower score (worst health) compared to the middle age group ($p = 0.01$) and the young age group ($p < 0.001$) (Table 4-5). However, the young and middle age groups had a similar VAS score ($p = 0.1$) (Table 4-5).

Table 4-4: Age specific EQ-5D-5L health profile data

Mobility (problems in walking about)	**Age 18-44** N (%)	**Age 45-69** N (%)	**Age >70** N (%)	**Total** N (%)
no problems	54 (80.6)	146 (74.4)	69 (47.9)	269 (66.1)
slight problems	8 (11.9)	27 (13.7)	22 (15.2)	57 (14.0)
moderate problems	4 (5.9)	17 (8.6)	34 (23.6)	55 (13.5)
Unable or severe problems	1 (1.4)	6 (3.0)	19 (13.1)	26 (6.3)
SELF-CARE (Problems washing or dressing myself)				
no problems	61 (91.4)	175 (82.2)	104 (71.2)	340 (83.1)
slight problems	2 (2.9)	14 (7.1)	20 (13.7)	36 (8.8)
moderate problems	4 (5.9)	5 (2.5)	17 (11.6)	26 (6.3)
unable or severe problems	0 (0)	2 (1.0)	5 (3.4)	7 (1.7)
USUAL ACTIVITIES (problems doing my usual activities)				
no problems	54 (80.6)	148 (75.5)	72 (49.6)	274 (67.1)
slight problems	5 (7.4)	27 (13.7)	30 (20.6)	62 (15.2)
moderate problems	8 (11.9)	15 (7.6)	28 (19.3)	51 (12.5)
unable or severe problems	0 (0)	6 (3.1)	15 (10.3)	21 (5.1)
PAIN / DISCOMFORT				
no pain and discomfort	43 (64.1)	107 (54.5)	62 (43.0)	212 (52.1)
slight pain and discomfort	13 (19.4)	61 (31.1)	36 (25.0)	110 (27.0)
moderate pain and discomfort	5 (7.4)	23 (11.7)	31 (21.5)	59 (14.5)
severe/extreme pain and discomfort	6 (8.9)	5 (2.5)	15 (1.3)	26 (6.3)

Anxiety and Depression				
no anxious or depressed	46 (68.6)	140 (73.6)	90 (63.8)	276 (69.3)
slightly anxious or depressed	10 (14.9)	39 (20.5)	31 (21.9)	80 (20.1)
moderately anxious or depressed	9 (13.4)	6 (3.1)	17 (12.0)	32 (8.0)
severely/extremely anxious or depressed	2 (2.9)	5 (2.6)	3 (2.0)	10 (2.5)

Figure 4-2: Age specific EQ-5D-5L health profile data-categorised by "no" and "any problems"

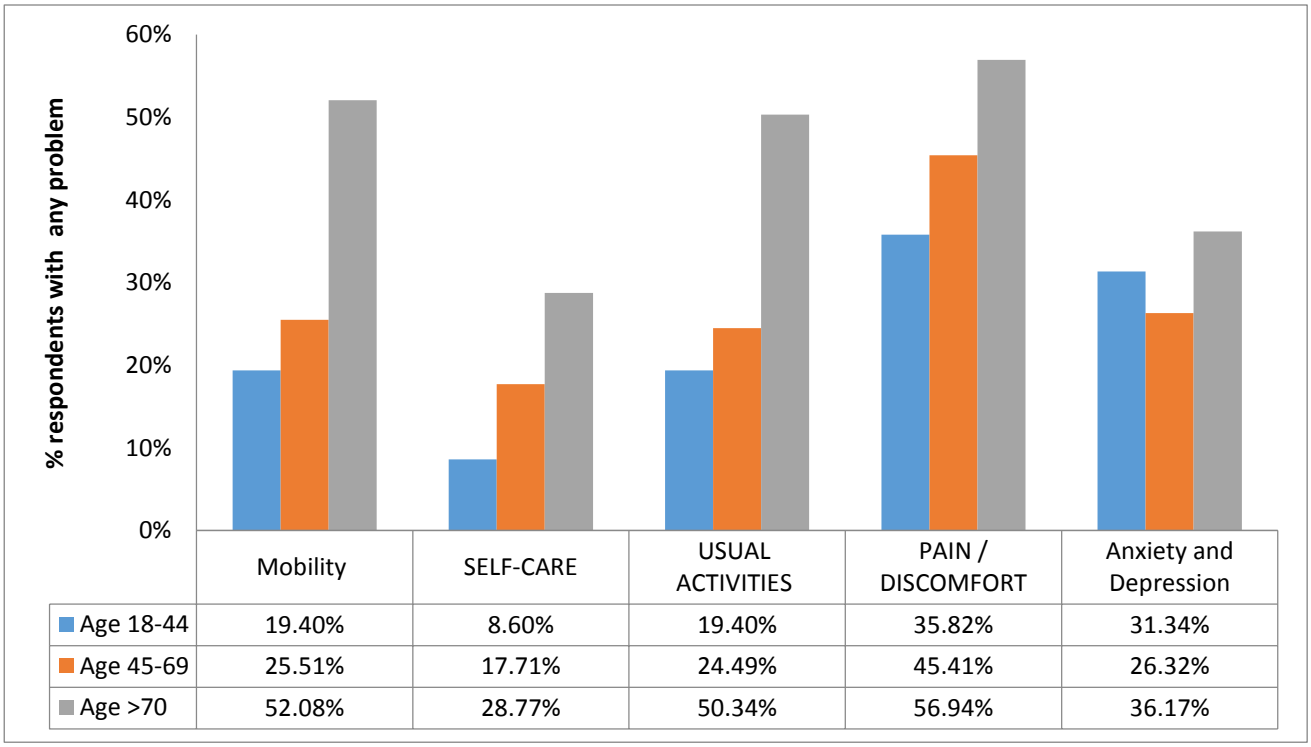


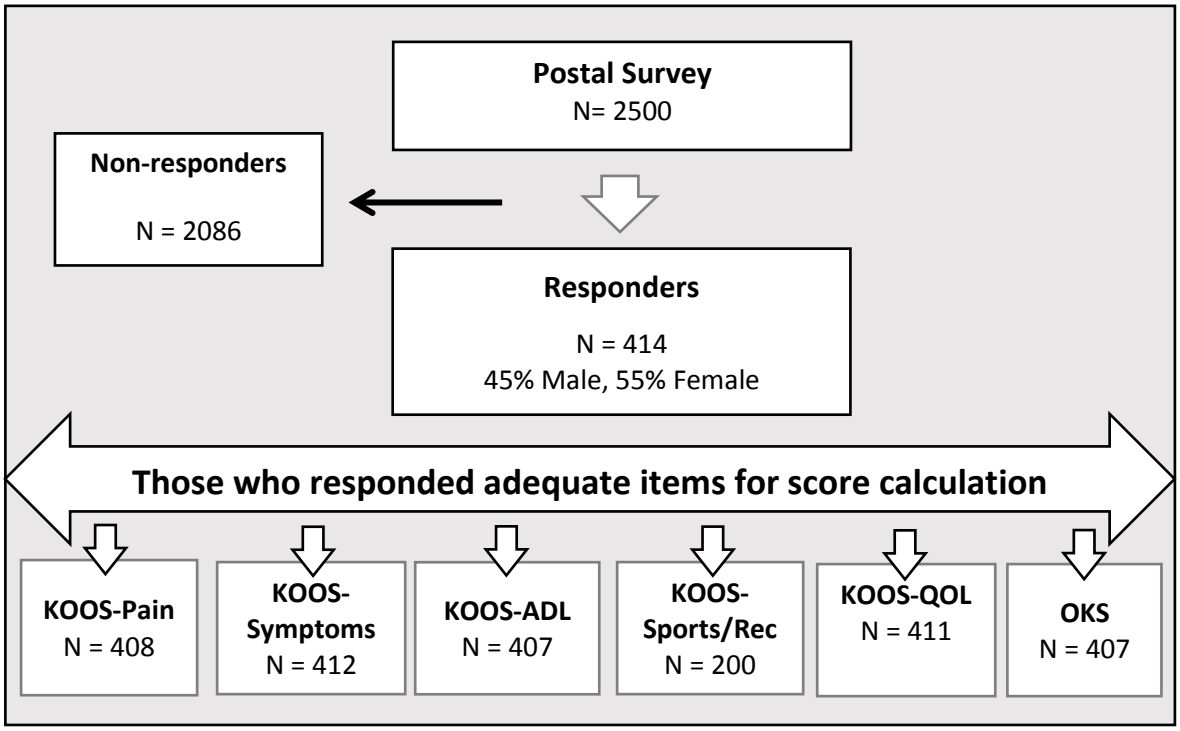
Table 4-5: Age specific EQ-5D-5L overall health data

VAS score	Total	Age 18-44	Age 45-69	Age >70
Mean	78.08	80.26	80.74	73.38
Median (25^{th}-75^{th})	80 (70-95)	80 (75-90)	84 (70-95)	80 (65-89)

4.1 KOOS: Normative data

Of 414 responders, there were 408 valid KOOS scores for the pain subscale, 412 for the symptoms, 407 for the ADL function, 200 for sports and recreation function, and 411 for the QOL subscale (Figure 4-3).

Figure 4-3: Number of responders to each subscale of KOOS and OKS



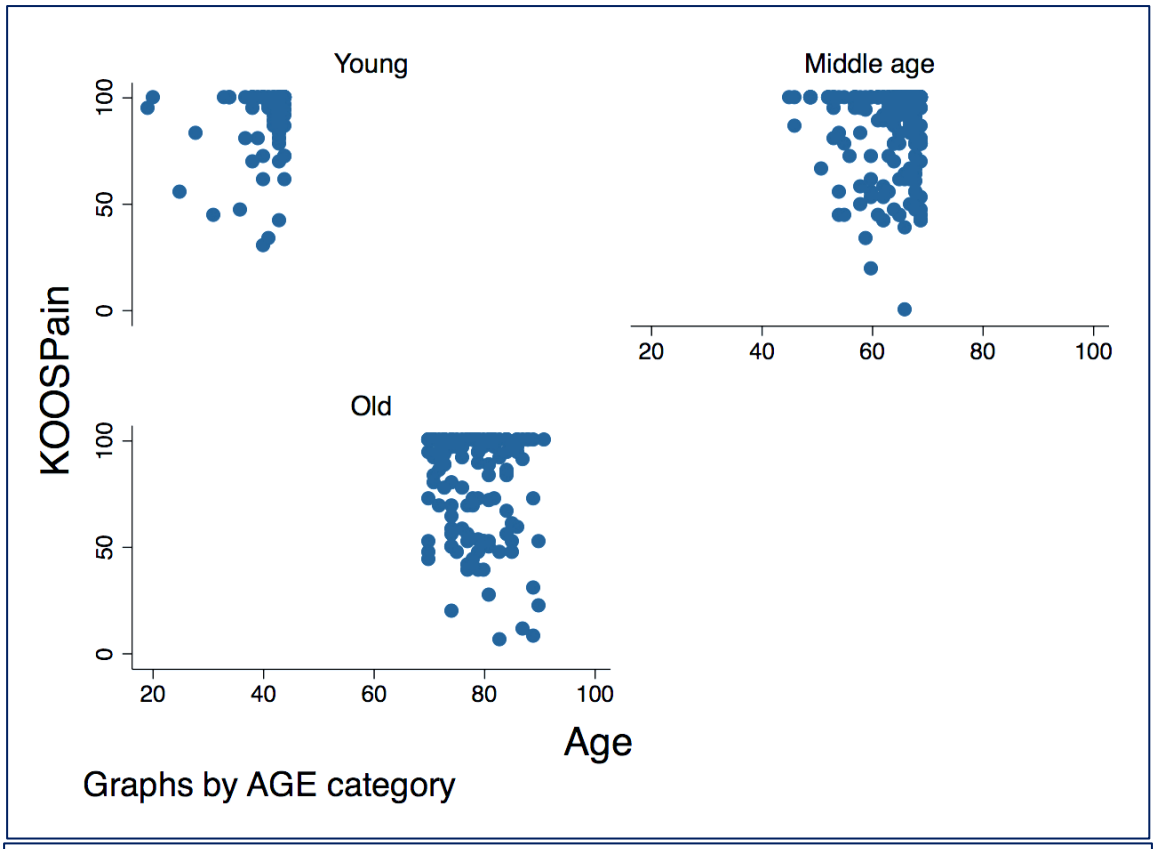
Age specific normative data for the KOOS is presented in Table 4-6. A significant dose response relationship was visible between increasing age and worsening scores for KOOS-Pain (p_{trend} = 0.007); KOOS-ADL (p_{trend} = 0.002); and KOOS-QOL subscale scores (p_{trend} = 0.020) (Table 4-6).

Table 4-6: Normative data for KOOS specified by age (lower score equates to worse outcome): mean ± standard deviation, median (interquartile range), minimum-maximum

KOOS	Total	Age Group			
		18-44	45-69	+70	*p* value for trend
KOOS-Pain	N = 408 83.4 ± 22.0 94.4 (72.2 - 100) 0 - 100	N = 67 87.2 ± 19.9 100 (80.5 - 100) 19.4 - 100	N = 193 85.1 ± 20.4 94.4 (77.7 - 100) 0 - 100	N = 148 79.5 ± 24.4 91.67 (58.3 - 100) 6.2 -100	0.007
KOOS-Symptoms	N = 412 83.8 ± 19.6 92.8 (75.0 - 100) 0 - 100	N = 67 84.5 ± 19.4 91.6 (78.5 - 96.4) 17.8 - 100	N = 194 84.9 ± 18.3 92.8 (75.0 - 100) 0 - 100	N = 151 82.2 ± 21.4 92.8 (67.8 - 100) 16.6 - 100	0.79
KOOS-ADL	N = 407 84.8 ± 21.9 97.0 (75.0 - 100) 1.6 - 100	N = 66 90.5 ± 17.3 100 (89.7 - 100) 25 - 100	N = 196 86.8 ± 20.1 98.5 (77.2 - 100) 1.6 - 100	N = 145 79.7 ± 25.0 91.1 (59.3 - 100) 3.3 - 100	0.002
KOOS-Sports/Rec	N = 200 82.1 ± 24.5 93.3 (75.0 - 100) 0 - 100	N = 52 82.0 ± 23.7 90.0 (75.0 - 100) 0 - 100	N = 107 81.6 ± 24.9 91.6 (75.0 - 100) 10 - 100	N = 41 83.3 ± 25.0 100 (75.0 - 100) 5 - 100	0.45
KOOS-QOL	N = 411 75.9 ± 27.7 87.5 (56.2 - 100) 0 - 100	N = 67 81.1 ± 23.2 87.5 (68.7 - 100) 12.5 - 100	N = 196 78.1 ± 25.8 87.5 (62.5 - 100) 0 - 100	N = 148 70.6 ± 31.2 81.2 9 (43.7 - 100) 0 -100	0.02

Pairwise comparisons of scores in the three age groups showed that the old age group had the worst KOOS-pain, KOOS-ADL, and KOOS-QOL scores compared to the young and middle age groups (*p*-value old versus young = 0.007, 0.002, 0.03 respectively; *p*-value old versus middle age = 0.01, 0.007, 0.01 respectively) (Figure 4-4; Figure 4-5; Figure 4-6). However, no significant differences were found between young and middle age groups (*p-values* > 0.05). In addition, for the KOOS-Symptoms and KOOS-Sports/Rec function, all age groups had similar scores (Figure 4-7; Figure 4-8).

Figure 4-4: Age specific distribution of KOOS-pain data (scatter plot and box plot)



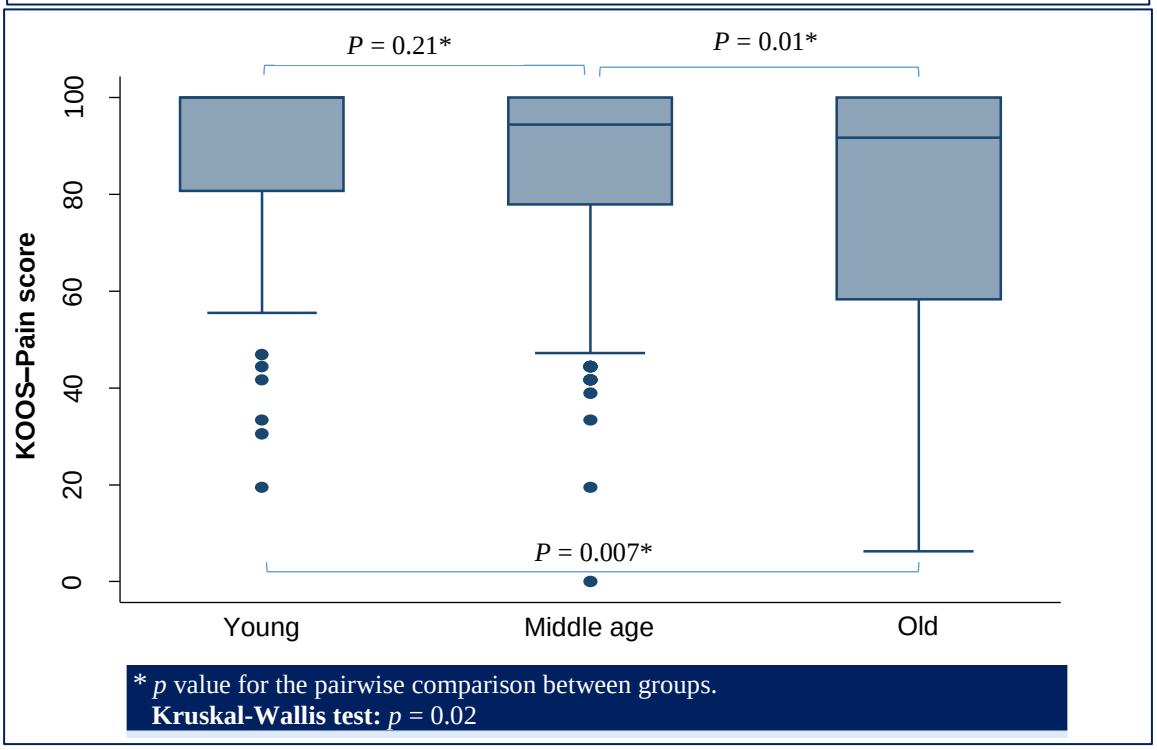
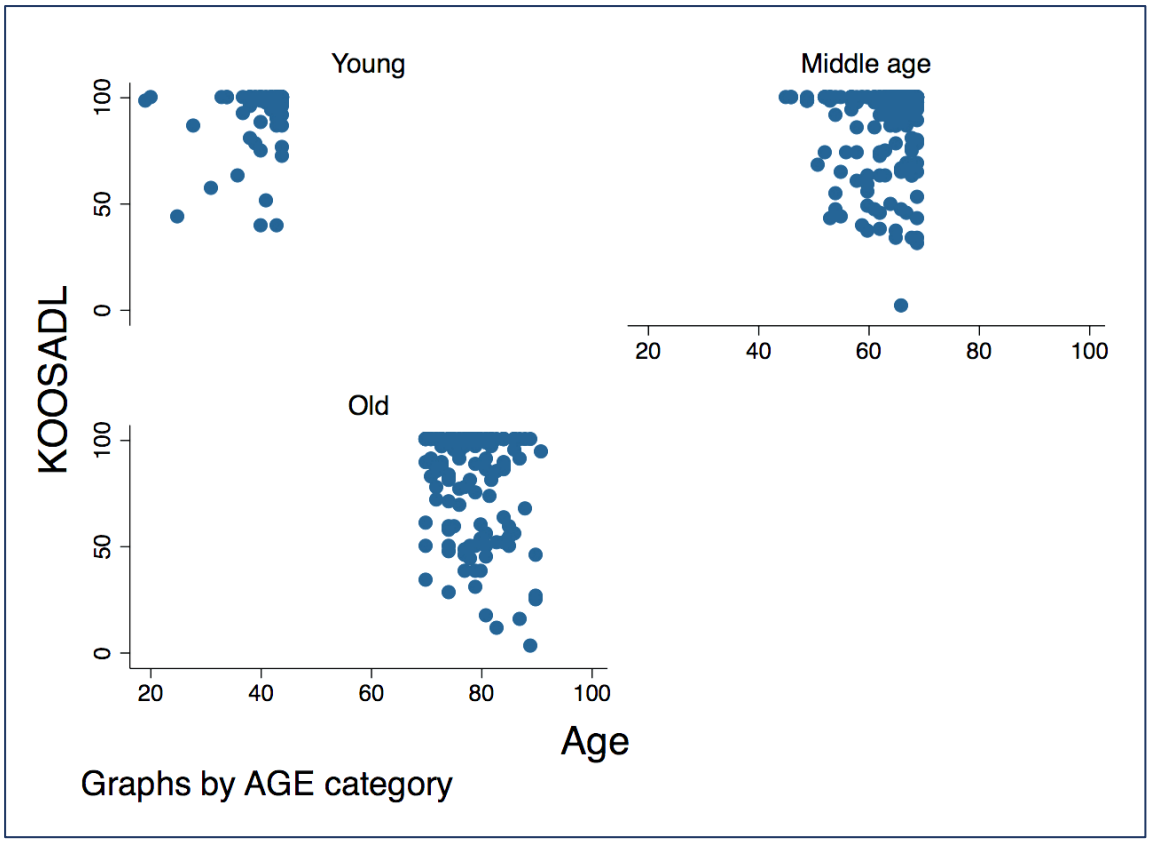


Figure 4-5: Age specific distribution of KOOS-ADL data (scatter plot and box plot)



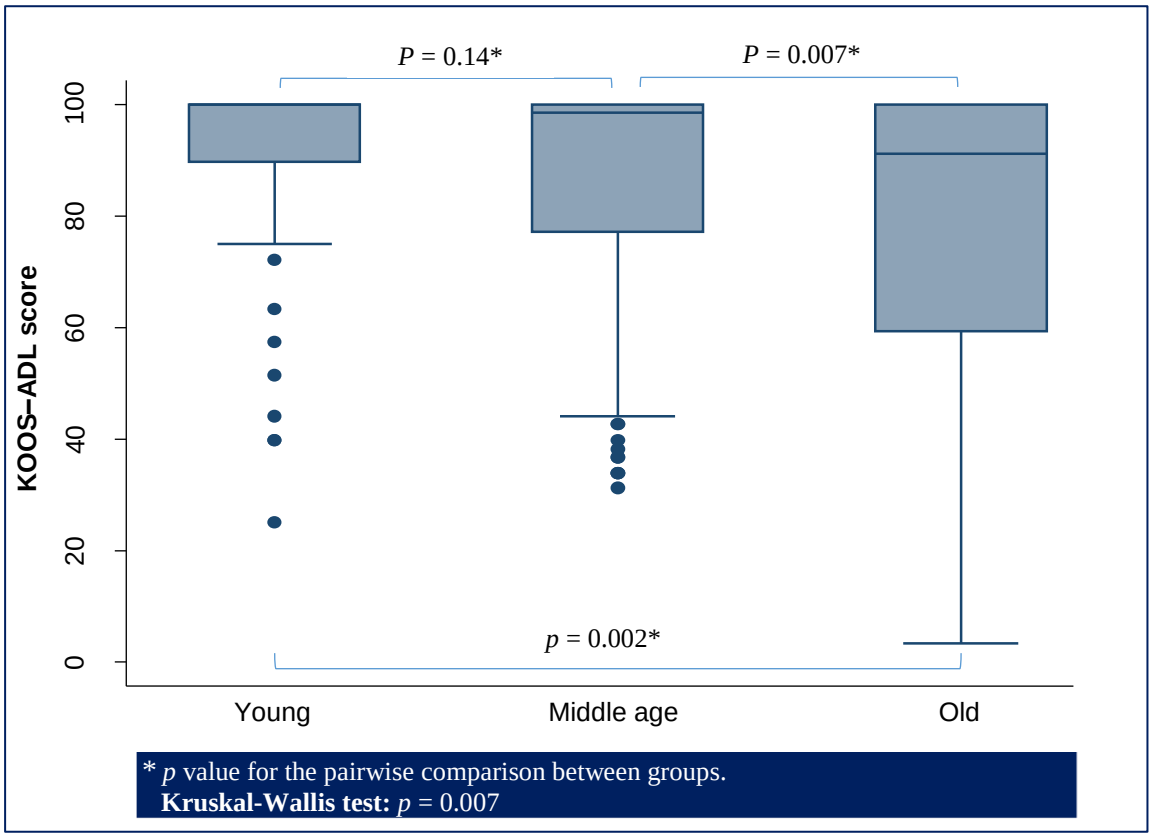
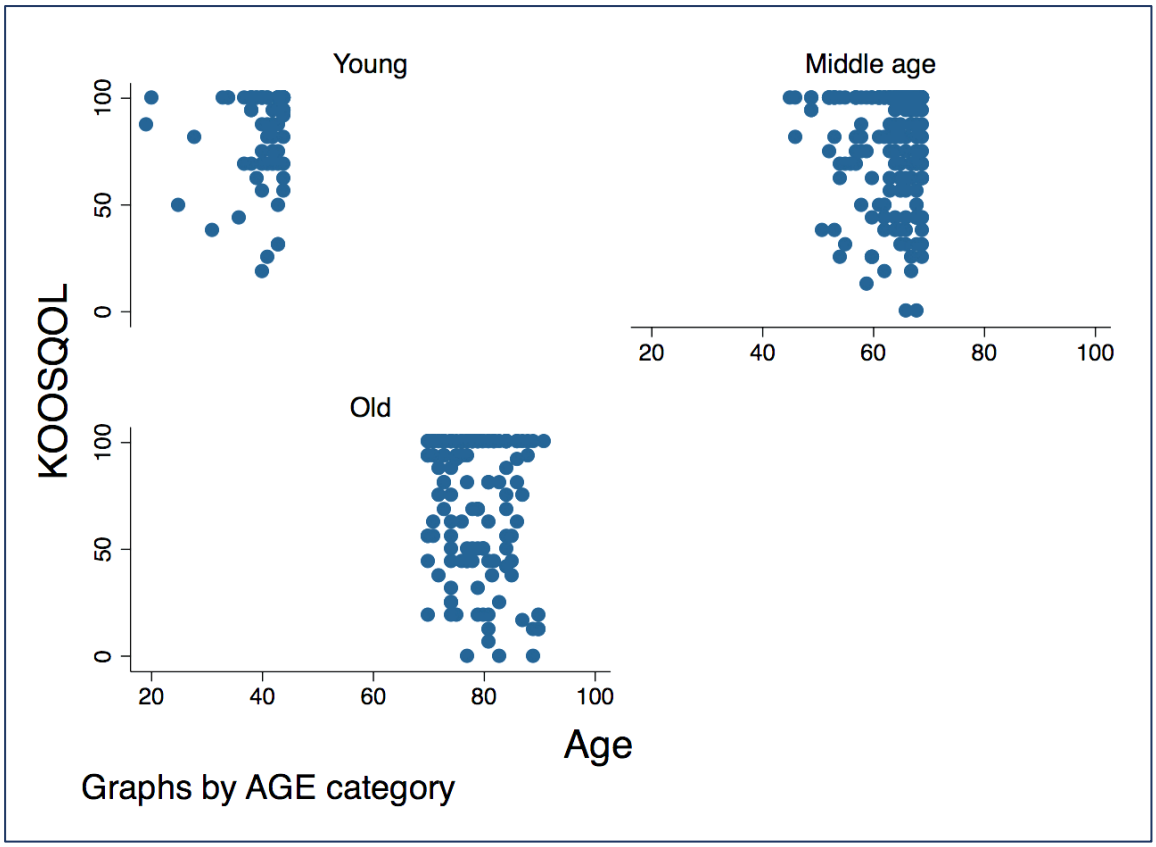


Figure 4-6: Age specific distribution of KOOS-QOL data (scatter plot and box plot)



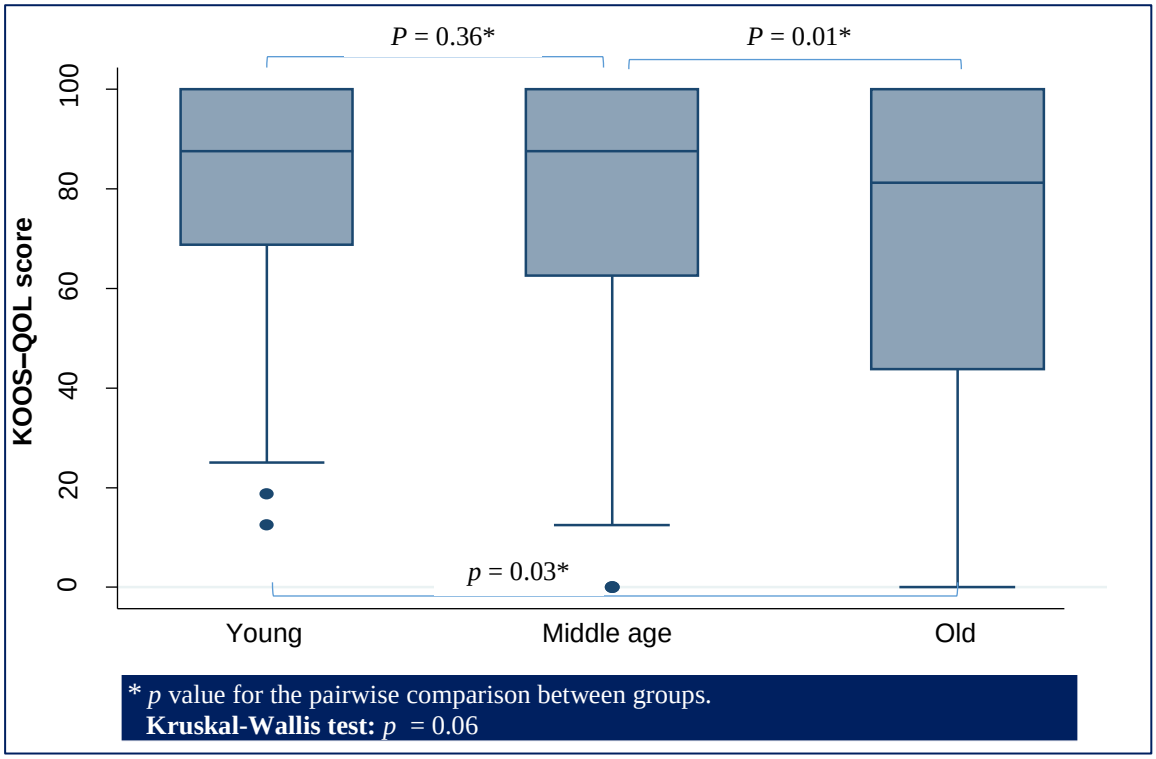
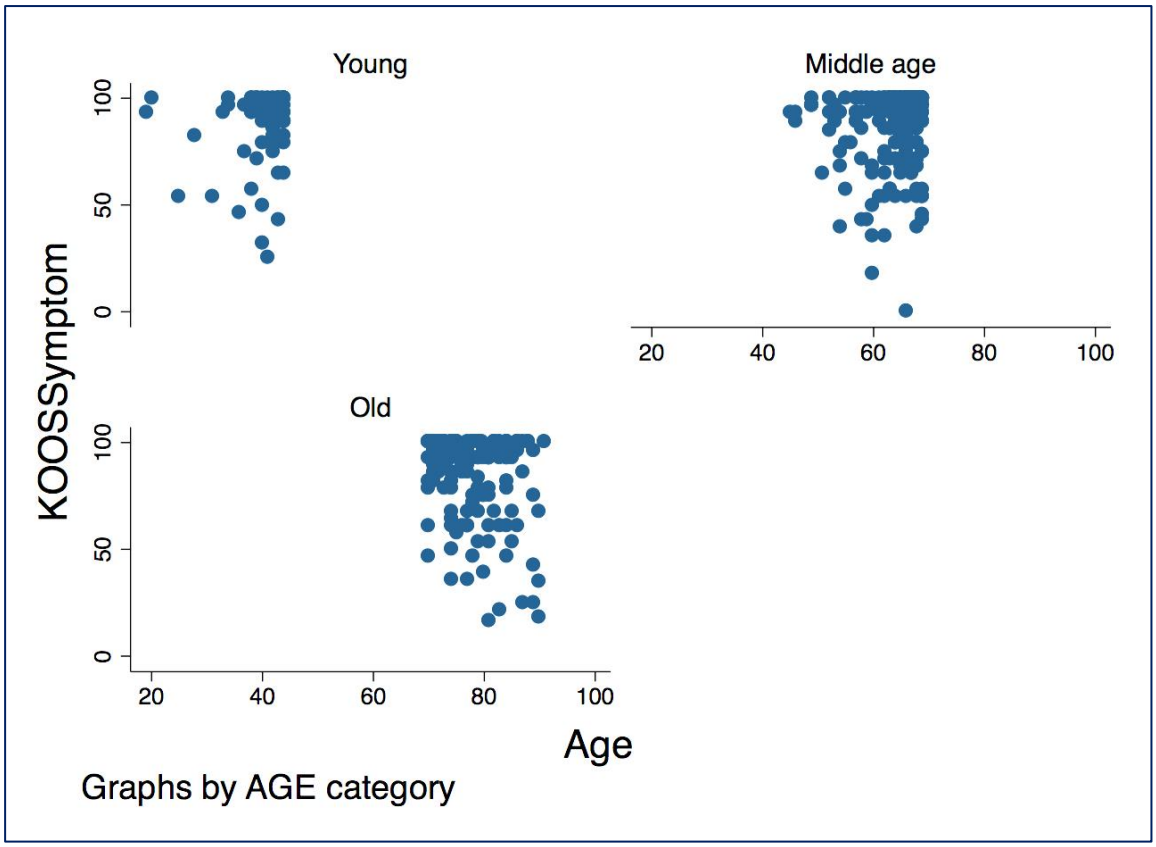


Figure 4-7: Age specific distribution of KOOS-symptom data (scatter plot and box plot)



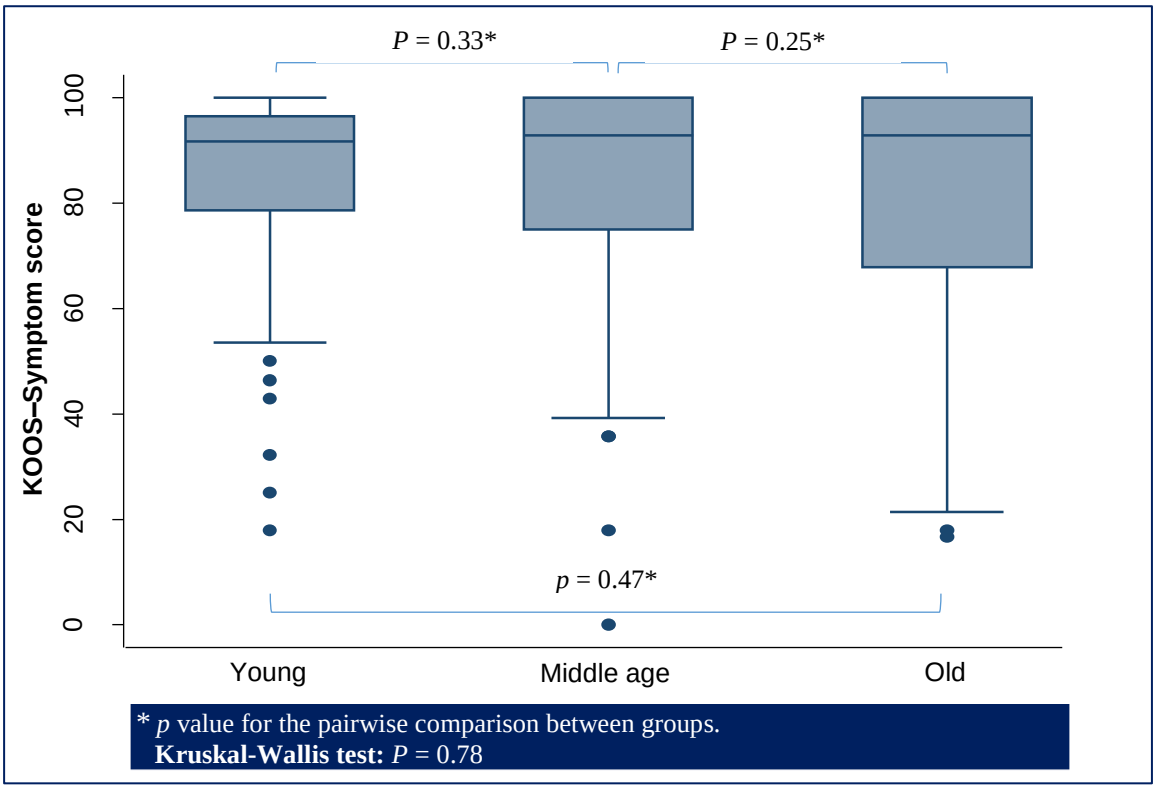
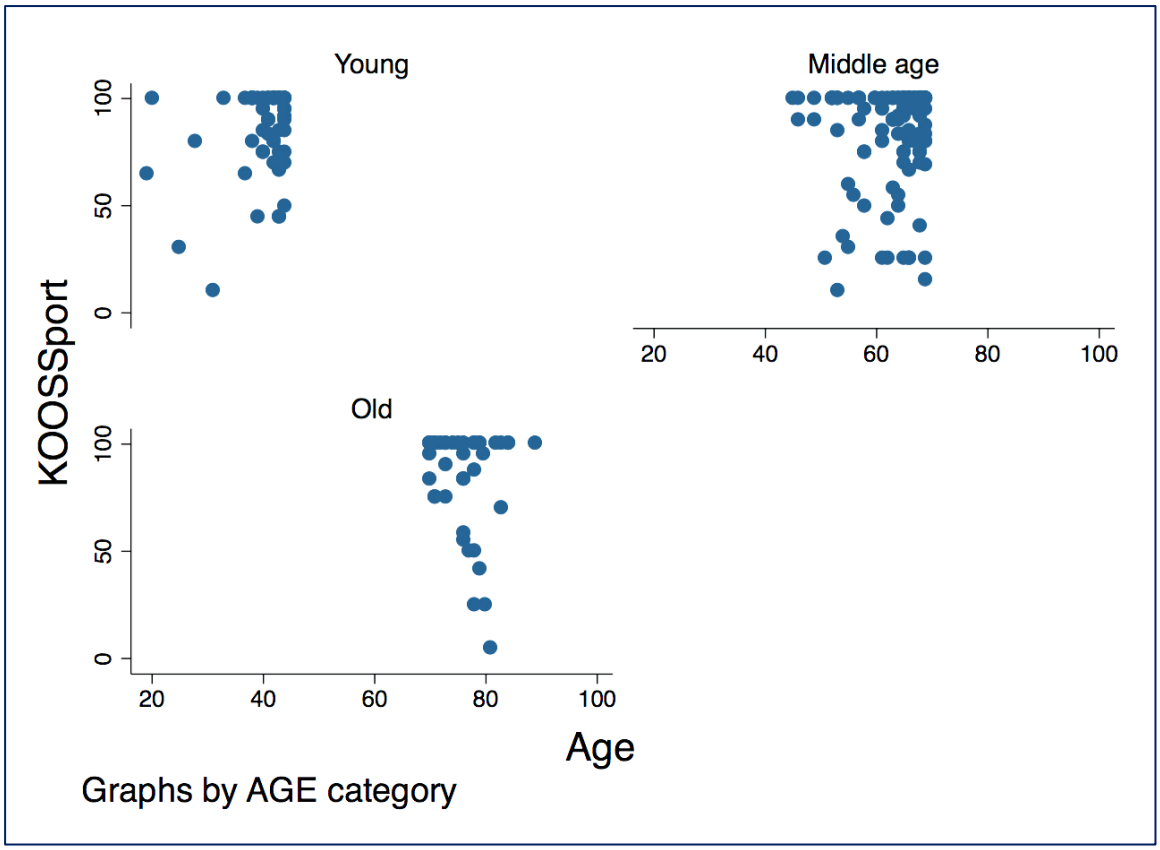
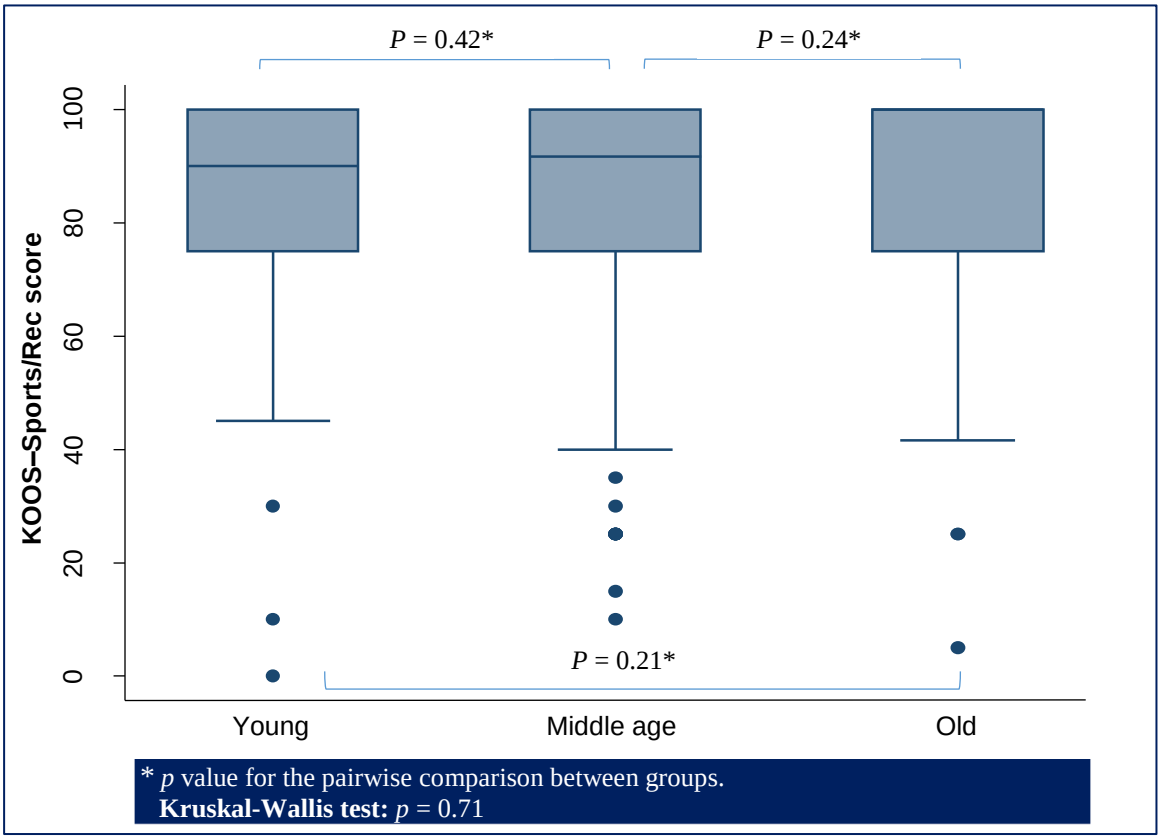


Figure 4-8: Age specific distribution of KOOS-Sports/Rec data (scatter plot and box plot)





Normative data for the KOOS specified by age and gender are also presented in Table 4-7. In all KOOS subscales, the proportion of young female participants was approximately double that of young males, while in the old and middle age groups, they were almost equal. No gender difference was found in any KOOS subscale scores in the old and middle age groups (p-values > 0.05) (Table 4-7). However, the young male group had significantly lower scores (worst) for KOOS-Pain, KOOS-Symptoms, KOOS-ADL, and KOOS-QOL scores than the young female group (p-value = 0.02, 0.02, 0.02, 0.01 respectively).

Table 4-7: Normative data for KOOS specified by age and gender (lower score equates to worse outcome): mean ± standard deviation, median (interquartile range), minimum-maximum

KOOS	Gender	Total	Age Group		
			18-44	45-69	+70
KOOS-Pain	Male	N = 185	N = 21	N = 95	N = 69
		82.6 ± 21.5	76.4 ± 27.4	85.8 ± 18.2	80.0 ± 23.4
		94.4 (69.4 - 100)	88.8 (61.1 - 100)	94.4 (77.7 - 100)	91.6 (58.3 - 100)
		19.4 - 100	19.4 -100	41.6 -100	19.4 - 100
	Female	N = 223	N = 46	N = 98	N = 79
		84.1 ± 22.4	92.1 ± 13.0	84.5 ± 22.4	79.01 ± 25.4
		96.8 (72.2 - 100)	100 (86.1 - 100)	98.6 (77.7 - 100)	90.6 (59.3 - 100)
		0 - 100	69.4 - 100	0 - 100	6.2 - 100
	***p* value**	**0.23**	**0.02**	**0.63**	**0.90**
KOOS-Symptoms	Male	N = 187	N = 21	N = 96	N = 70
		82.8 ± 19.8	73.9 ± 26.6	85.2 ± 16.5	82.2 ± 21.9
		89.2 (75 - 100)	85.7 (53.5 - 92.8)	89.2 (76.7 - 100)	91.0 (75 - 100)
		16.6 - 100	17.8 - 100	35.71 - 100	16.6 - 100
	Female	N = 225	N = 46	N = 98	N = 81
		84.7 ± 19.5	89.3 ± 12.6	84.6 ± 19.9	82.2 ± 21.7
		92.8 (78.5 - 100)	92.8 (89.2 - 100)	92.8 (75 - 100)	92.8 (67.8 - 100)
		0 - 100	46.4 - 100	0 - 100	17.8 - 100
	***p* value**	**0.37**	**0.02**	**0.82**	**0.85**
	Female	N = 223	N = 45	N = 100	N = 78
		85.3 ± 22.6	94.6 ± 11.0	85.9 ± 22.1	79.2 ± 26.2
		98.5 (77.9 - 100)	100 (94.1 - 100)	98.5 (78.8 - 100)	92.6 (57.8 - 100)
		1.6 - 100	44.1 - 100	1.6 - 100	3.3 - 100
	***p* value**	**0.41**	**0.02**	**0.77**	**1.00**

Table 4-7: Normative data for KOOS specified by age and gender: mean ± standard deviation, median (interquartile range), minimum-maximum

KOOS	Gender	Total	Age Group		
			18-44	45-69	+70
KOOS-ADL	Male	N = 184	N = 21	N = 96	N = 67
		84.3 ± 21.1	81.5 ± 24.2	87.7 ± 17.9	80.2 ± 23.8
		95.5 (73.56 - 100)	95.5 (75 - 100)	97.0 (75.7- 100)	89.7 (60.2 - 100)
		17.1 - 100	25 - 100	36.7 - 100	17.1 - 100
	Female	N = 223	N = 45	N = 100	N = 78
		85.3 ± 22.6	94.6 ± 11.0	85.9 ± 22.1	79.2 ± 26.2
		98.5 (77.9 - 100)	100 (94.1 - 100)	98.5 (78.8 - 100)	92.6 (57.8 - 100)
		1.6 - 100	44.1 - 100	1.6 - 100	3.3 - 100
	***p* value**	**0.41**	**0.02**	**0.77**	**1.00**
KOOS-Sports/Rec	Male	N = 82	N = 16	N = 46	N = 20
		80.8 ± 26.9	75.3 ± 31.3	83.1 ± 24.1	79.8 ± 29.7
		95.0 (75 - 100)	80.0 (72.5 - 100)	95.0 (75 - 100)	100 (72.5 - 100)
		0 - 100	0 - 100	10 - 100	5 - 100
	Female	N = 118	N = 36	N = 61	N = 21
		83.0 ± 22.8	85.0 ± 19.1	80.5 ± 25.6	86.7 ± 19.5
		91.6 (75 - 100)	90.8 (75 - 100)	90.0 (75 - 100)	95.0 (83.3 - 100)
		15 -100	30 - 100	15 - 100	41.6 - 100
	***p* value**	**0.89**	**0.30**	**0.53**	**0.84**

Table 4-7: Normative data for KOOS specified by age and gender: mean ± standard deviation, median (interquartile range), minimum-maximum

KOOS	Gender	Total	Age Group		
			18-44	45-69	+70
KOOS-QOL	Male	N = 186	N = 21	N = 96	N = 69
		73.8 ± 28.8	70.5 ± 28.9	77.8 ± 25.7	69.2 ± 32.2
		81.2 (50 - 100)	81.2 (62.5 - 93.7)	84.3 (62.5 - 100)	81.2 (43.7 - 100)
		6.2 - 100	12.5 - 100	18.7 - 100	6.2 - 100
	Female	N = 225	N = 46	N = 100	N = 79
		77.6 ± 26.7	85.9 ± 18.5	78.3 ± 26.0	71.8 ± 30.4
		87.5 (62.5 - 100)	93.7 (75 - 100)	87.5 (62.5 - 100)	81.2 (50 - 100)
		0 - 100	31.2 - 100	0 - 100	0 - 100
	***p* value**	**0.25**	**0.01**	**0.91**	**0.80**

4.2 OKS: Normative data

Of 414 responders, there were 407 valid scores for total-OKS, OKS-PCS and OKS-FCS. Age specific normative data for the OKS are presented in Table 4-8.

A significant dose response relationship was found between the increase in age and worsening of scores of total-OKS, OKS-PCS, and OKS-FCS (*p*-value for trend < 0.001, = 0.004, < 0.001 respectively) (Table 4-8). The total-OKS, OKS-PCS, and OKS-FCS scores were significantly lower (worse) in the old age group than corresponding scores in the young and middle age groups (*p*-value old versus young < 0.001, =0.008, < 0.001 respectively; *p*-value old versus middle age

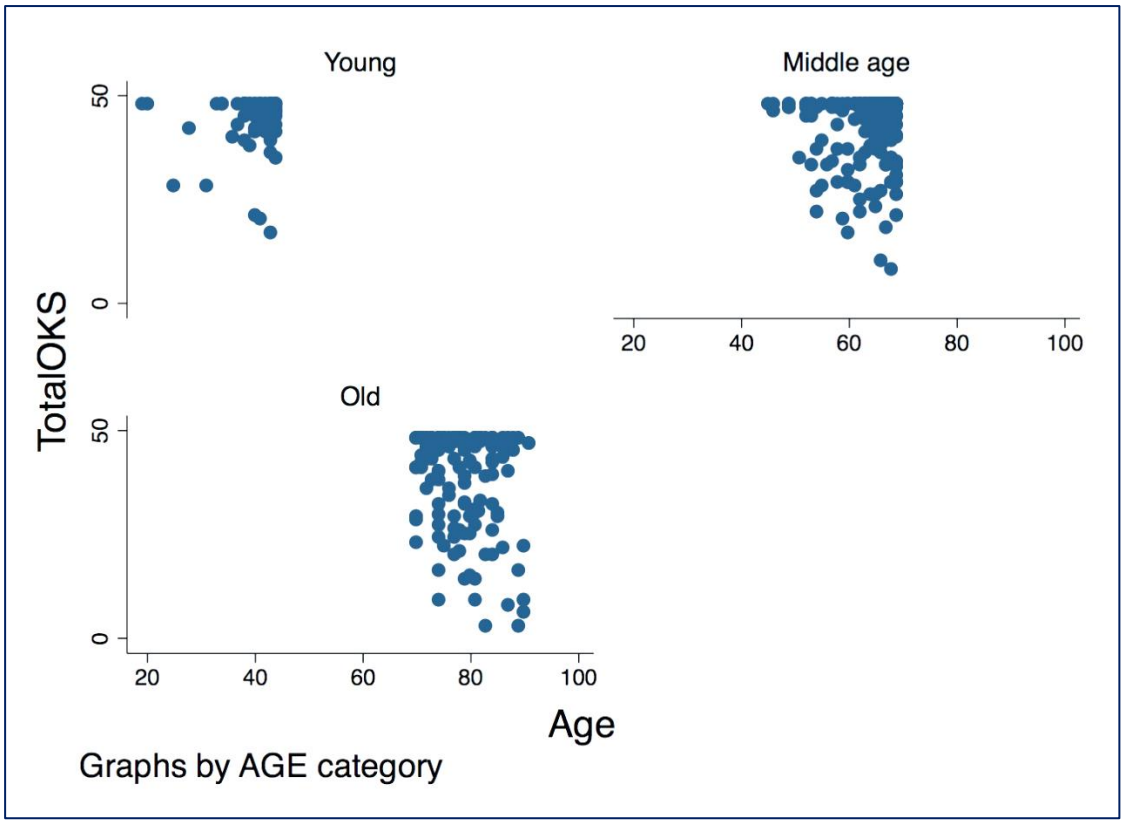
< 0.001, =0.001, < 0.001 respectively) (Figure 4-9; Figure 4-10; Figure 4-11).

The pairwise comparisons between young and middle age groups showed a significant decrease (i.e. worse scores) in OKS-FCS score in the middle age compared to young age group (*p*-value < 0.03). However, young and middle age groups had similar scores for OKS-PCS and total-OKS (*p*-value > 0.2) (Table 4-8; Figure 4-9; Figure 4-10). Thus, the young age group had a better knee function score compared to the middle age group in spite of having a similar knee pain score.

Table 4-8: Normative data for OKS specified by age (lower score equates to worse outcome): mean ± standard deviation, median (interquartile range), minimum-maximum

OKS	Total	Age Group			
		18-44	45-69	+70	*p* value for trend
Total-OKS	N = 407 40.5 ± 10.1 46.0 (36.0 - 48.0) 3 - 48	N = 67 43.1 ± 8.1 47.0 (42 - 47) 10 - 48	N = 196 42.0 ± 8.4 46.0 (38 - 48) 8 - 48	N = 144 37.2 ± 12.2 42.3 (29 - 48) 3 - 48	<0.001
OKS-PCS	N = 407 84.1 ± 22.0 96.3 (74.9 - 99.9) 3.5 - 99.9	N = 67 88.1 ± 19.2 96.3 (85.6 - 99.9) 7.1 - 99.9	N = 196 87.0 ± 18.6 96.3 (74.9 - 99.9) 17.8 - 99.9	N = 144 78.4 ± 26.0 89.2 (60.6 - 99.9) 3.5 - 99.9	0.004
OKS-FCS	N = 407 84.8 ± 21.3 95.0 (75 - 100) 0 - 100	N = 67 92.5 ± 14.4 100 (95 - 100) 40 - 100	N = 196 88.3 ± 16.9 95.0 (80 - 100) 15 - 100	N = 144 76.4 ± 26.2 87.5 (60 - 100) 0 - 100	<0.001

Figure 4-9: Age specific distribution of Total-OKS data (scatter and box plot)



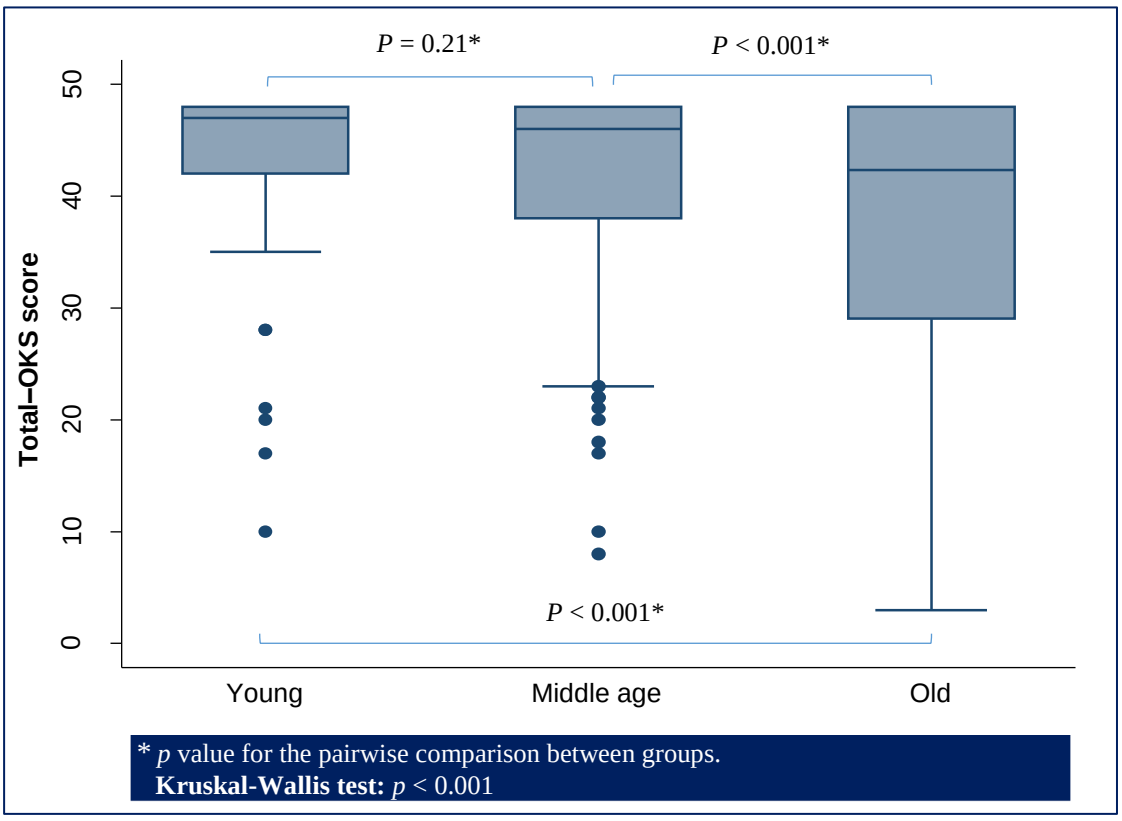


Figure 4-10: Age specific distribution of OKS-pain data

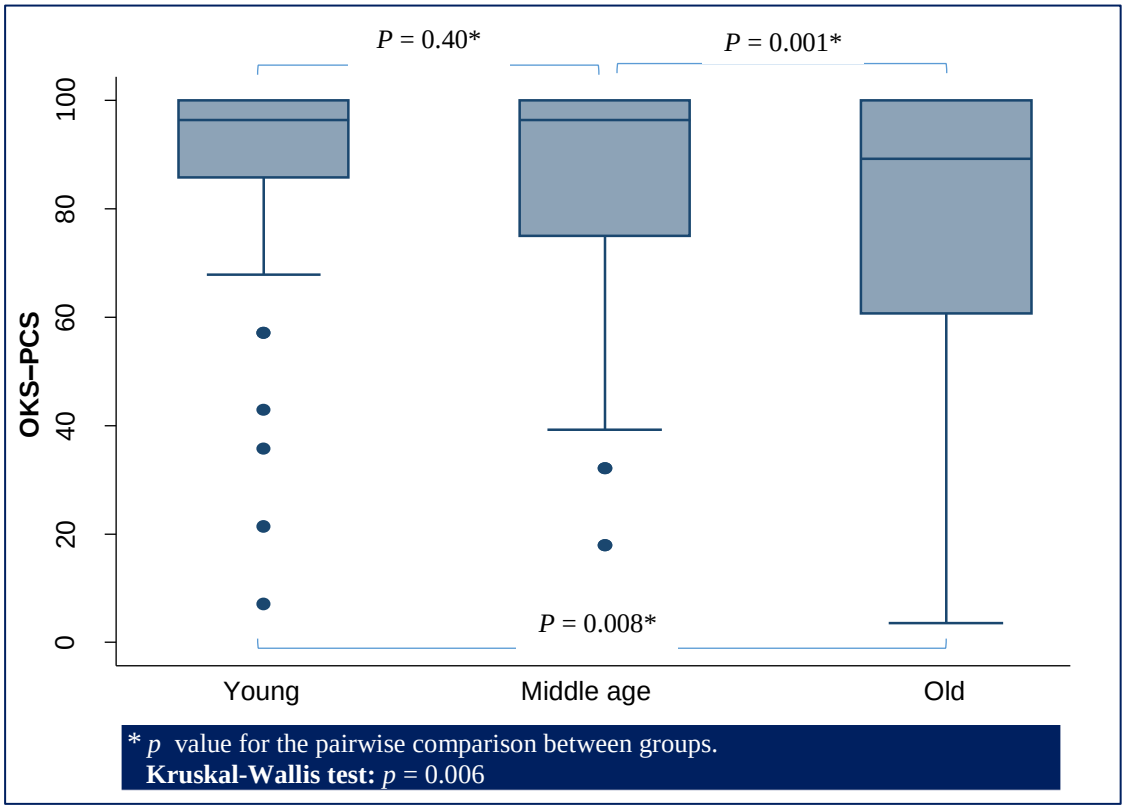
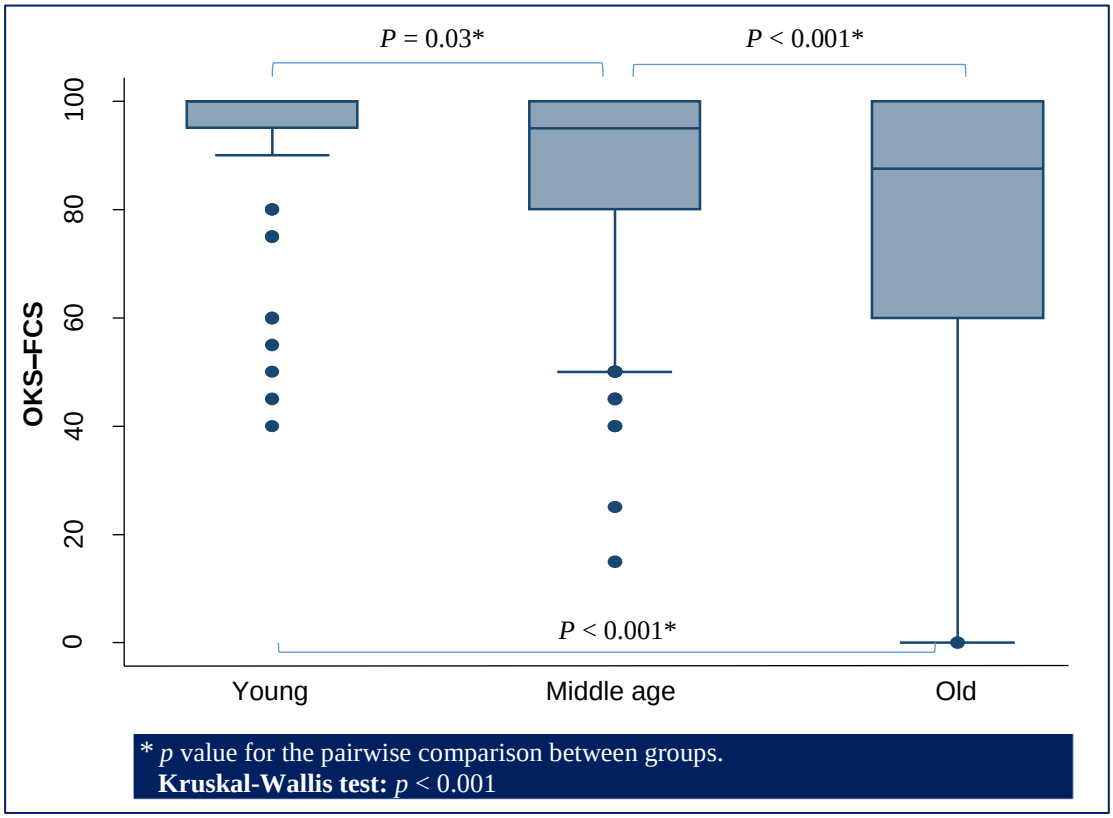


Figure 4-11: Age specific distribution of OKS-function data



Normative data for the OKS specified by age and gender is also presented in Table 4-9. Similar to the KOOS study, no gender differences were found in any OKS scores in the old or middle age groups (*p*-values > 0.05) (Table 4-9). However, young male participants had significantly lower scores for total-OKS, OKS-PCS and OKS-FCS compared to females (*p*-value = 0.01, 0.007, 0.02 respectively) (Table 4-9).

Table 4-9: Normative data for OKS specified by age and gender (lower score equates to worse outcome): mean ± standard deviation, median (interquartile range), minimum-maximum

OKS	Gender	Total	Age Group		
			18-44	45-69	+70
Total-OKS	Male	N = 183	N = 21	N = 96	N = 66
		39.9 ± 10.1	38.5 ± 11.9	42.2 ± 7.5	37.2 ± 12.1
		45.0 (34 - 48)	44.0 (35 - 47)	46.0 (37 - 48)	41.5 (27 - 48)
		9 - 48	10 - 48	18 - 48	9 - 48
	Female	N = 224	N = 46	N = 100	N = 78
		40.9 ± 10.1	45.3 ± 4.3	41.8 ± 9.2	37.2 ± 12.3
		46.0 (38 - 48)	47.5 (44 - 48)	47.0 (38.5 - 48)	43.0 (29.5 - 47)
		3 - 48	28 - 48	8 - 48	3 - 48
	***p* value**	**0.30**	**0.01**	**0.73**	**0.77**
OKS-PCS	Male	N = 183	N = 21	N = 96	N = 66
		82.5 ± 22.7	77.3 ± 28.1	87.3 ± 16.8	77.2 ± 26.6
		92.8 (67.8 - 99.9)	89.2 (67.8 - 96.3)	96.3 (74.9 - 99.9)	89.2 (57.1 - 99.9)
		7.1 - 99.9	7.1 - 99.9	32.1 - 99.9	10.7 - 99.9
	Female	N = 224	N = 46	N = 100	N = 78
		85.4 ± 21.4	93.0 ± 10.6	86.6 ± 20.3	79.4 ± 25.6
		96.3 (78.5 - 99.9)	99.9 (89.2 - 99.9)	98.1 (78.5 - 99.9)	91.0 (62.8 - 99.9)
		3.5 - 99.9	57.1 - 99.9	17.8 - 99.9	3.5 - 99.9
	***p* value**	**0.14**	**0.007**	**0.67**	**0.76**
OKS-FCS	Male	N = 183	N = 21	N = 96	N = 66
		84.3 ± 20.5	84.5 ± 21.1	88.6 ± 15.4	77.9 ± 25.0
		95.0 (75 - 100)	95.0 (75 - 100)	95.0 (80 - 100)	90.0 (60 - 100)
		15 - 100	40 - 100	45 - 100	15 - 100

	Female	N = 224	N = 46	N = 100	N = 78
		85.2 ± 21.9	96.1 ± 7.9	88.0 ± 18.2	75.1 ± 27.2
		95.0 (75 - 100)	100.0 (95 - 100)	95.0 (80 - 100)	85.0 (60 - 100)
		0 - 100	60 - 100	15 - 100	0 - 100
	***p* value**	**0.45**	**0.02**	**0.75**	**0.43**

4.3 Self-reported knee complaints and knee OA

This study also compared the KOOS and OKS scores in participants with and without clinical knee OA (NICE criteria). Individuals with clinical knee OA had a lower score (worse) in all KOOS and OKS subscales (*p-values* < 0.01) (Table 4-10).

The effects of obesity, injury, physical activity, age and gender on the KOOS and OKS scores were also studied (Table 4-11; Table 4-12). Obesity and injury were found to be the strongest predictors for development of a "low score" (high knee related complaints) in all KOOS subscales of pain, symptoms, ADL, Sports/Rec, and QOL as well as total-OKS, OKS-PCS, and OKS-FCS (Table 4-11; Table 4-12). Similarly, obesity (aOR: 3.82, 95%CI: 1.73-8.43) and injury (aOR: 3.23, 95%CI: 1.10-9.46) were associated with an increased risk of clinical knee OA, which were statistically significant (Table 4-13).

In contrast, no significant association was found between physical activity and risk of clinical knee OA (aOR: 1.50, 95CI: 0.79- 2.84) (Table 4-13). In addition, physical activity was significantly associated with a lower risk of knee related complaints in all KOOS (except KOOS-Sport/Rec), total-OKS and OKS-FCS subscales (Table 4-11; Table 4-12).

Table 4-10: KOOS and OKS scores in participants with and without clinical knee OA

		N	Mean ± SD	Median (IQ)	Minimum-Maximum	*p value*
KOOS-Pain	No-OA	153	97.43 ± 6.00	100 (97.2 - 100)	58.3 - 100	0.001
	OA	70	73.98 ± 16.74	77.7 (60.7 - 88.8)	38.8 - 100	
KOOS-Symptoms	No-OA	154	95.52 ± 6.66	96.43 (92.8 - 100)	60.7 - 100	0.001
	OA	72	76.80 ± 15.55	78.5 (67.2 - 89.2)	39.2 - 100	
KOOS-ADL	No-OA	153	97.99 ± 5.28	100 (100 - 100)	67.6 - 100	0.001
	OA	72	79.19 ± 17.43	83.8 (63.9 - 94.1)	33.8 - 100	
KOOS-Sport	No-OA	75	95.48 ± 9.12	100 (95 - 100)	50 - 100	0.001
	OA	37	69.93 ± 22.34	75(58.3 - 90)	25 - 100	
KOOS-QOL	No-OA	153	95.32 ± 9.79	100 (93.7 - 100)	43.7 - 100	0.001
	OA	72	63.51 ± 20.45	68.75 (50 - 81.2)	0 - 100	
Total-OKS	No-OA	152	46.58 ± 2.79	48 (46 - 48)	32.4 - 48	0.001
	OA	72	38.09 ± 7.90	39.5 (33 - 45)	8 - 48	
OKS-PCS	No-OA	152	97.50 ± 5.87	99.9 (99.9 - 99.9)	67.8 - 99.9	0.001
	OA	72	78.68 ± 16.75	82.1 (64.2 - 92.8)	17.8 - 99.9	
OKS-FCS	No-OA	152	96.38 ± 7.91	100 (95 - 100)	42 - 100	0.001
	OA	72	80.27 ± 17.93	82.5 (70 - 95)	15 - 100	

Table 4-11: Factors predicting of KOOS score

Outcomes	Predictors	aOR (95% CI)	*p value*
KOOS-Pain	Obesity	3.94 (2.14 - 7.26)	<0.001
	Injury	4.52 (2.19 - 9.35)	<0.001
	Physical activity	0.51 (0.29 - 0.88)	0.01
	Gender	0.96 (0.56 - 1.63)	0.88
	Age (Middle age/Young)	1.04 (0.49 - 2.21)	0.91
	Age (Old/Young)	1.41 (0.64 - 3.11)	0.38
KOOS-Symptoms	Obesity	3.36 (1.84 - 6.13)	<0.001
	Injury	3.86 (1.88 - 7.91)	<0.001
	Physical activity	0.49 (1.28 - 0.85)	0.01
	Gender	1.05 (0.62 - 1.77)	0.85
	Age (Middle age/Young)	1.33 (0.63 - 2.83)	0.44
	Age (Old/Young)	1.09 (0.49 - 2.44)	0.81
KOOS-ADL	Obesity	4.45 (2.41 - 8.24)	<0.001
	Injury	4.37 (2.08 - 9.17)	<0.001
	Physical activity	0.49 (0.28 - 0.87)	0.01
	Gender	0.92 (0.53 - 1.60)	0.79
	Age (Middle age/Young)	1.88 (0.79 - 4.43)	0.14
	Age (Old/Young)	2.23 (0.91 - 5.44)	0.07
KOOS-Sports/Rec	Obesity	3.20 (1.11 - 9.22)	0.03
	Injury	3.82 (1.36 - 10.72)	0.01
	Physical activity	0.65 (0.30 - 1.42)	0.28
	Gender	1.15 (0.55 - 2.41)	0.69

	Age (Middle age/Young)	0.77 (0.35 - 1.72)	0.53
	Age (Old/Young)	1.11 (0.42 - 2.93)	0.82
KOOS-QOL	Obesity	5.27 (2.79 - 9.97)	<0.001
	Injury	8.60 (3.96 – 18.66)	<0.001
	Physical activity	0.54 (0.30 - 0.97)	0.042
	Gender	0.98 (0.55 - 1.72)	0.94
	Age (Middle age/Young)	1.29 (0.55 - 3.01)	0.54
	Age (Old/Young)	2.30 (0.96 - 5.49)	0.06

Table 4-12: Factors predicting of OKS score

	Predictors	aOR (95% CI)	*p value*
Total-OKS	Obesity	6.02 (3.23 - 11.24)	<0.001
(n =348)	Injury	3.42 (1.61 - 7.25)	0.001
	Physical activity	0.51 (0.29 - 0.91)	0.02
	Gender	0.84 (0.48 - 1.47)	0.55
	Age (Middle age/Young)	1.63 (0.68 - 3.88)	0.26
	Age (Old/Young)	2.56 (1.04 - 6.26)	0.03
OKS-PCS	Obesity	4.48 (2.43 - 8.27)	<0.001
(n =348)	Injury	4.72 (2.27 - 9.79)	<0.001
	Physical activity	0.64 (0.37 - 1.12)	0.11
	Gender	0.89 (0.52 - 1.52)	0.68
	Age (Middle age/Young)	1.52 (0.68 - 3.40)	0.30
	Age (Old/Young)	2.15 (0.93 - 4.97)	0.07
OKS-FCS	Obesity	5.25 (2.77 - 9.97)	<0.001
(n =348)	Injury	3.58 (1.63 - 7.85)	0.001
	Physical activity	0.39 (0.22 - 0.71)	0.002
	Gender	1.11 (0.63 - 1.95)	0.71
	Age (Middle age/Young)	1.42 (0.57 - 3.55)	0.44
	Age (Old/Young)	3.77 (1.50 - 9.45)	0.005

Table 4-13: Clinical knee OA and predictor factors

	OA/no-OA	Crude OR (95%CI)	aOR (95%CI)
non-obese	53/139	-	-
Obese	19/15	3.32 (1.57 - 7.01)	3.82 (1.73 - 8.43)
		p = 0.002	*p* = 0.001
Uninjured	62/147	-	-
Injured	10/7	3.38 (1.23 - 9.30)	3.23 (1.10 - 9.46)
		p = 0.01	*p* = 0.03
Inactive	27/74	-	-
Active	45/80	1.54 (0.86 - 2.73)	1.50 (0.79 - 2.84)
		p = 0.13	*p* = 0.21
Male	34/72	-	-
Female	38/82	0.98 (0.56 - 1.71)	1.02 (0.56 - 1.87)
		p = 0.94	*p* = 0.93
Middle age	52/88	-	-
Old	20/66	0.51 (0.27 - 0.94)	0.60 (0.31 - 1.15)
		p = 0.003	*p* = 0.13

5 DISCUSSION

5.1 Summary of main findings

This study showed that obesity and injury increased the risk of incident knee OA. Moderate evidence of positive interactions was also found between obesity and injury on the risk of radiographic and symptomatic knee OA. This highlights that obesity has a greater effect on developing knee OA in injured than uninjured individuals. In addition, active and inactive people had a similar risk of knee OA. This effect was not modified by obesity and/or injury, indicating that high levels of community-based physical activity does not increase the risk of incident knee OA at any level of obesity and/or injury.

Findings for the progression of knee OA were very similar to incidence results. The effects of physical activity on the progressive risk of knee OA also was not modified by obesity and/or injury status. Obesity was a significant risk factor for the progression of knee OA and there was also weak evidence of a positive interaction between obesity and injury on the risk of symptomatic knee OA progression.

This study also reports normative data for KOOS and OKS, by age and gender. Obesity and injury were the strongest predictors for the high self-reported knee complaints assessed

by OKS and KOOS. Further these data demonstrated that obesity and injury were significantly associated with the increased risk of clinical knee OA in people aged 45 years and older (NICE criteria). No significant association was found between physical activity and risk of clinical knee OA. However, meeting the UK minimum physical activity guideline was strongly associated with the lower self-reported knee complaints in all KOOS and OKS subscales, suggesting the moderate levels of physical activity appears to be safe to be recommended to the general population.

5.2 Interpretation of results

5.2.1 *Physical activity and the incidence of knee OA*

Data from cohort studies of the general population indicate that habitual levels of physical activity are not associated with the incidence of radiographic or symptomatic knee OA (Neogi and Zhang 2013). The current study also did not find any significant association between community-based physical activity and the risk of incident radiographic or symptomatic knee OA in either OAI or MOST. The ORs for the associations between physical activity and knee OA was close to one and the confidence limits were narrow. This suggested that physical activity neither increased nor protected against the risk of radiographic or symptomatic knee OA in middle aged

and older adults with or at high risk of knee OA. Similarly, in the middle aged people in the Framingham Study, moderate recreational activities including walking, jogging or frequent working up to a sweat were not associated with the incidence of radiographic or symptomatic knee OA (Felson, Niu, Clancy et al. 2007).

Framingham and the current study both used the same case definition for diagnosing incident radiographic and symptomatic knee OA. However, radiograph views were different. In the Framingham study, radiographs were taken in full weight bearing with knees in full extension, while this study used the semi-flexed posteroanterior radiograph view of the knee in full weight bearing. Although both studies showed similar findings, the semi-flexed posteroanterior radiograph view is reported as the optimal view for the radiographic assessment of knee OA (Buckland-Wright, Wolfe, Ward et al. 1999).

Our study findings were also similar to those studies that used self-reported doctor diagnosis as the case definition of knee OA. A large longitudinal study of American adults from the Cooper Clinic, with a 12.8 year average follow-up, showed that participation in recreational activities imposing moderate joint stresses did not increase the risk of self-reported doctor

diagnosed knee OA (Hootman, Macera, Helmick et al. 2003). Another large population-based cohort study of Swedish adults also found that leisure time physical activity was not associated with the risk of severe knee OA in middle aged people over an 11 year follow-up (Ageberg, Engström, Gerhardsson de Verdier et al. 2012).

However, some studies conflict with the current study reporting a positive relationship between physical activity and the risk of knee OA (Johnsen, Hellevik, Baste et al. 2016). A prospective cohort study of the Australian population showed that increasing the levels of leisure time physical activity was positively associated with an increased risk of severe knee OA over a 10 year period (Wang, Simpson, Wluka et al. 2011). Cheng et al. also found that jogging and walking more than 20 miles per week elevated the risk of symptomatic knee OA at around the 12^{th} year of follow-up in young men (age 20-49) (Cheng, Macera, Davis et al. 2000). However, there were some important limitations to these studies. Firstly, the effect of physical activity on the risk of knee OA in the Australian cohort was small and even the upper confidence limit did not reach the acceptable level of two fold risk. Secondly, injury was not adjusted in the study by Cheng et al. even though injury is a common condition in young active individuals and it

is a strong risk factor for developing knee OA. Therefore, the lack of injury data was a potential source of bias for a tendency towards the overestimation of the effect of low/moderate recreational activity on the risk of knee OA in the young population of the Cheng et al. study.

A study of older adults in the Framingham Study has also found that walking more than four hours per day increased the risk of radiographic and symptomatic knee OA (mean age: 80.7) (McAlindon et al. 1999). However, the participants of this study were relatively older than our study population. In addition, sarcopenia is a common condition in older adults resulting in muscle weakness. Muscular weakness is an important risk factor for symptomatic knee OA (Segal, Glass, Felson et al. 2010; Segal, Glass, Torner et al. 2010; Glass, Torner, Frey Law et al. 2013). Quadriceps weakness in people with knee OA can results in less dynamic joint stability during activity (Rice, McNair and Lewis 2011). Hence, minor injuries due to inadequate physiological support during activity might be a reason for the greater risk of knee OA in the elderly population of the Framingham Study.

5.2.2 *Does physical activity increase the risk of knee OA at different level of obesity and/or injury?*

Data from cohort studies of runners have shown that recreational running does not increase the risk of radiographic and clinical knee OA at 2, 5 and 9 years follow-up as compared to nonrunners (Lane, Bloch, Hubert et al. 1990; Lane, Michel, Bjorkengren et al. 1993; Lane, Oehlert, Bloch et al. 1998). However, a greater risk of knee OA has been reported among footballers (Roos, Lindberg, Gardsell et al. 1994; Kujala et al. 1995), weight lifters (Kujala et al. 1995), cross country skiers (Michaelsson et al. 2011), and hockey players (Sandmark and Vingard 1999). A large international systematic review group has also highlighted that participation in sports would place individuals at a higher risk of OA (Vignon, Valat, Rossignol et al. 2006). This has been further supported by a recent systematic review in which competitor soccer players, wrestlers and weight lifters had substantially greater risk of developing knee OA (Driban, Hootman, Sitler et al. 2015).

Injury has been proposed as one of the main reasons for the higher risk of knee OA in such intense activities (Lefèvre-Colau, Nguyen, Haddad et al. ; Lane 1996; Lequesne, Dang and Lane 1997; Thelin, Holmberg and Thelin 2006). In addition, high BMI and frequent squatting may be another

reason for the higher risk of knee OA in some sports such as weight lifting (Kujala, Kaprio and Sarna 1994; Kujala et al. 1995). Hence, the effect of physical activity on the risk of knee OA may be modified by factors such as obesity and injury.

That said, this study did not find any significant interaction between physical activity and obesity on the risk of incident radiographic or symptomatic knee OA in either OAI or MOST. This indicated that the neutralized effect of physical activity on the risk of incident knee OA was not modified by presence or absence of obesity.

Investigations in relation to the interactive effect of obesity and physical activity on the risk of knee OA are fairly limited (Urquhart, Soufan, Teichtahl et al. 2008). Only a few studies have been published with this respect. One was a 12 year longitudinal study conducted by Hootman and colleagues. Similar to our findings, BMI did not modify the effect of recreational activities on the risk of self-reported doctor diagnosed knee OA (Hootman et al. 2003). The other was a cohort study of middle aged and older adults of the Framingham Study (Felson et al. 2007). At 9 years follow-up, moderate recreational activity was not associated with the increased risk of radiographic or symptomatic knee OA in

different weight groups. Results from a very large prospective cohort of 77,216 Norwegians also did not find any evidence of positive interaction between obesity and various levels of recreational activity on the risk of self-reported doctor diagnosed knee OA (Mork, Holtermann and Nilsen 2012). Although the self-reporting of OA has an acceptable level of reliability in epidemiological studies (Peeters, Alshurafa, Schaap et al. 2015), our study was superior to previous ones in terms of having a larger sample size and using the optimal x-ray view for the assessment of radiographic knee OA in addition to the symptomatic definition.

In contrast, some studies have reported that physical activity has a greater effect on the risk of knee OA in people within higher weight groups. A large cohort of the UK population showed that manual occupational activity was associated with a greater increase in risk of symptomatic knee OA in people with high BMI than individuals with low BMI (Martin, Kuh, Harris et al. 2013). In addition, heavy physical activity in older adults in the Framingham Study was associated with a higher risk of knee OA especially in people with high BMI (McAlindon et al. 1999). There could be several reasons for different findings between these studies and ours. One could be the differences between intensity and the type of activities used

across studies. Our study did not distinguish the occupational and non-occupational activity in the analyses, whereas large prospective studies of OA with long follow-ups have shown that manual occupations and activities requiring frequent squatting and knee bending increase the risk of knee OA (Felson et al. 1991; Toivanen, Heliovaara, Impivaara et al. 2010). Therefore, our study is unable to rule out the likelihood of interaction between obesity and occupational activity on the risk of knee OA. However, our findings were more definite compared to the Framingham Study of older adults. In the Framingham Study, the difference between weight groups did not reach a level of statistical signficance, and their sample size was small for the subgroup analysis. In addition, muscle weakness and consequent injury to the joint during activity was proposed for the higher risk of knee OA in the elderly adults of the Framingham Study.

That said, injury is also one of the main contributors to the development of the risk of knee OA. However, no investigation has tested if physical activity has a similar or a different effect on the risk of knee OA in injured versus uninjured people. Therefore, for the first time, we studied the effect of interaction between physical activity and injury on the risk of knee OA using OAI and MOST data. No statistically significant

interactions were found between physical activity and injury on the risk of incident radiographic or symptomatic knee OA in either cohort. This highlighted that the high levels of community-based physical activity had a similar effect on the risk of knee OA in injured versus uninjured individuals.

However, the findings obtained in MOST differed in some respects from those obtained in OAI. In MOST, activity had a small and insignificant protective effect on the risk of knee OA in the absence of injury. In the presence of injury, activity increased the risk of knee OA. Such a crossover effect of activity at different levels of injury on the risk of knee OA was an indication of positive interaction. In addition, the lower confidence limits on both additive and multiplicative scales were close to unity suggesting a tendency towards a positive statistically significant interaction in MOST. Thus, this may imply that community based physical activity may increase the risk of knee OA in the presence but not the absence of injury. However, no indication of any cross-over interaction was seen in the OAI study and the confidence limits were wide.

Some possible explanations for these conflicting results between MOST and OAI could be attributed to the differences in the sample population, period of the follow-up and case definition of knee OA. In OAI, there were age-specific inclusion

criteria to select a participant at high risk of knee OA. The youngest age group needed to have frequent knee symptoms plus one of the other OA risk factors such as frequent knee bending activity, injury or obesity, while the oldest age group only needed to have one risk factor to be eligible for the study. However, MOST had less specific inclusion criteria. The high risk group was defined as a participant having a knee symptom, with a history of knee injury or surgery, or being overweight regardless of the age (Segal et al. 2013). This resulted in a very high percentage of obese and overweight people in MOST (81%) compared to OAI (66.2%) and during follow-up a higher percentage of participants developed knee OA in MOST than OAI. Therefore, the wide confidence limits for the interaction between physical activity and injury in OAI could be due to the lower numbers of participants who developed knee OA. In addition, the focus of the OAI study was on TF OA at 48-month follow-up, while MOST considered both the TF and PF compartments for the assessment of knee OA at 60-month follow-up. Hence, a shorter follow-up period and different definition of knee OA in OAI could be the other reasons for the lower prevalence of knee OA and different results in OAI findings compared to MOST.

Given how complex OA is and the multitude of risk factors, it is important to understand how physical activity interacts with obesity and injury when they are presented together. That said, this study for the first time examined the three-way interaction between obesity, injury and physical activity on risk of incident radiographic and symptomatic knee OA. Results showed no evidence of any statistically significant three-way interaction between obesity, injury and physical activity. This indicated that the effect of physical activity on the risk of knee OA was not significantly modified by the presence of obesity and injury together.

However, the clinical interpretations of the three-way interaction findings were slightly different from its statistical interpretations in both OAI and MOST. In the subgroup of obese and injured people in OAI, the risk of radiographic knee OA was lower in active (aOR: 4.43, 95%CI: 2.36-8.34) compared to inactive people (aOR: 3.48, 95%CI: 1.44-8.40). The magnitude of difference was even larger for the risk of incident symptomatic knee OA. This may imply a beneficial effect of activity against the risk of symptomatic knee OA in obese and injured people. Similarly, for the symptomatic knee OA in MOST, activity had a large negative interaction with obesity and injury. This further supports the argument that

moderate physical activity may have a protective rather than detrimental effect on the risk of incident knee OA in obese and injured people. However, this effect was only seen when obesity and injury were present together. Therefore, moderate community-based physical activity appears to be safe even for obese individuals with injury.

5.2.3 *Does injury increase the risk of knee OA in obese more than non-obese people?*

The effects of obesity and injury on the risk of knee OA have been widely investigated. Numerous population-based studies of OA risk factors have constantly reported the strong relationship of obesity and injury with the increased risk of incident knee OA (Blagojevic et al. 2010; Muthuri et al. 2011). Our study findings were also in agreement with previous literature. In both OAI and MOST, obesity and injury were significantly associated with an increased risk of incident radiographic and symptomatic knee OA.

Obesity has also been found as a strong predictor for the high risk of knee OA, pain and functional limitation in later life in injured people (Englund and Lohmander 2004). However, there has been no study to examine whether obesity has a greater effect on the risk of incident knee OA in injured versus uninjured individuals. Therefore, we examined the effect of

interaction between obesity and injury on the risk of incident radiographic and symptomatic knee OA using OAI and MOST cohorts.

In both cohorts and regardless of activity level, the subgroup of 'obese and injured' individuals had the highest risk of incident radiographic knee OA. The higher risk was mainly due to the single effect of obesity and injury. In addition, there was some evidence of positive interactions between obesity and injury on the risk of radiographic knee OA in both cohorts.

A similar interaction was also seen for incident symptomatic knee OA. In OAI, the magnitude of interaction was even larger for the risk of incident symptomatic compared to radiographic knee OA. These interaction findings were statistically significant on both additive and multiplicative scales for the risk of incident symptomatic knee OA in OAI, and on additive scale for the risk of incident radiographic knee OA in MOST. Where the magnitude of interactions did not reach a statistically significant level, their lower confidence limits were close to unity suggesting a tendency towards statistical significance. Therefore, our findings suggest that obesity has a greater effect on the risk of incident radiographic and symptomatic knee OA in injured than uninjured individuals.

To the best of our knowledge, this was the first study to investigate the interaction between obesity and injury on the risk of knee OA. Hence, the findings need to be confirmed by other studies.

5.2.4 *The association of physical activity, obesity and injury on the risk of knee OA progression*

Quicker progression of knee OA results in more disability, joint replacements and ultimately a greater economic burden. Risk factors for the progression of knee OA seem to differ from those for the incidence of disease (Felson 2009). Therefore, identifying the risk factors contributing to disease progression is crucial. This study thus examined the association between obesity, injury and physical activity on the progressive risk of radiographic and symptomatic knee OA.

In OAI, both active and inactive people had a similar risk of progression of radiographic and symptomatic knee OA. This effect was not modified by obesity or injury since no significant interactions were found between any of them. Likewise, no significant interactions were found between physical activity, obesity and injury on the risk of progression of radiographic or symptomatic knee OA in MOST. This highlights that the effect of physical activity on the risk of knee OA progression is not modified by either obesity and/or

injury. These results were in line with the findings from our incidence study in OAI and MOST.

Prior studies have also reported similar findings for the relationship between physical activity and the progression of knee OA. A 12 year follow-up study of prognostic factors for joint space loss in the general population did not find any significant association between general activity and disease progression (Schouten, van den Ouweland and Valkenburg 1992). In another study conducted by Cooper et al, moderate leisure activity was not associated with a progression in KL score at 5 years follow-up in participants with knee OA at baseline (KL≥2) (Cooper et al. 2000).

Although evidence is yet limited, current systematic reviews of risk factors for the progression of knee OA did not find any significant association between moderate levels of physical activity and the risk of knee OA progression (Belo, Berger, Reijman et al. 2007; Bastick, Belo, Runhaar et al. 2015). Similar results have also been found for the relationship between injury and disease progression (Belo et al. 2007; Bastick et al. 2015). In both studies by Cooper et al. and Schouten et al., injury did not significantly increase the risk of radiographic knee OA progression (Schouten et al. 1992; Cooper et al. 2000). Likewise, our study did not find any

significant association between injury and progression of radiographic and symptomatic knee OA in either cohort.

However, the effect of obesity on the risk of knee OA progression was different in MOST compared to OAI. In MOST, both obese and non-obese individuals had a similar risk of radiographic and symptomatic knee OA progression. In addition, no significant interactions were found between obesity and injury on the risk of disease progression. In contrast, obesity significantly increased the risk of both symptomatic and radiographic knee OA progression in OAI. There was also a weak positive interaction on both additive and multiplicative scales between obesity and injury for progression of symptomatic knee OA. Hence, OAI findings highlighted that obesity had a slightly greater effect on the worsening of symptoms, but not radiographs, in injured than uninjured individuals.

Such inconsistency has been seen in previous population based studies that investigated the relationship between BMI and the progression of knee OA (Wolfe and Lane 2002; Reijman et al. 2007; Chapple, Nicholson, Baxter et al. 2011; Muraki, Akune, Oka et al. 2012). Among women with unilateral knee OA, high BMI was found as a strong predictor for the incidence of knee OA, but not for the radiographic

progression of knee OA (Spector et al. 1994). This was similar to the results in MOST, in which obesity was a significant risk factor for the incidence, but not progression of disease. Likewise, no significant associations were identified between high BMI and disease progression in the earlier studies conducted by Cooper et al., Dieppe et al, Nishimura et al., and Niu et al. (Dieppe, Cushnaghan, Young et al. 1993; Cooper et al. 2000; Niu, Zhang, Torner et al. 2009; Nishimura et al. 2011).

In contrast, Lendingham et al. reported a significant relationship between high BMI and progression of JSN in patients with symptomatic knee OA (Ledingham, Regan, Jones et al. 1995). Felson et al. also found a positive association between obesity and progression of radiographic knee OA (Felson, Goggins, Niu et al. 2004). High BMI has also been found as a significant predictor for the worsening of pain and function in subjects with symptomatic knee OA (Sharma, Cahue, Song et al. 2003; Holla, Steultjens, Roorda et al. 2010; Collins, Katz, Dervan et al. 2014; Holla, van der Leeden, Heymans et al. 2014). These findings were in line with the findings of the OAI study.

Several reasons have been proposed for this controversy between studies. Index event bias (collider bias) could be one

explanation for the paradoxical effect of obesity found in the study of knee OA progression in MOST as well as previous investigations. Index event bias is a type of selection bias occurring because of conditioning on the outcome (Zhang, Niu, Felson et al. 2010; Choi, Nguyen, Niu et al. 2014). For instance, this occurs by selecting participants with pre-existing knee OA from a cohort of people with and without knee OA, for a prognostic risk factors study. In this example, if obesity was assumed as the only risk factor for the progression of knee OA, unknown risk factors would be the only explanation for developing knee OA in non-obese individuals (unknown risk group). In MOST and OAI, the prevalence of knee OA progression was fairly high in the unknown risk group. This led to a decline in the ORs for the effect of obesity on the risk of knee OA progression. However, the decline in the risk due to the index event bias in the OAI study was not much of a concern since no obesity paradox was identified.

Similar decline in risk has been also found in previous investigations when ORs for the incidence and progression of knee OA were compared (Cooper et al. 2000; Niu et al. 2009). Therefore, comparing obese and non-obese people requires a very strict adjustment for all potential confounders to avoid underestimating the overall effect of obesity on the risk of

knee OA progression (Zhang et al. 2010). Nevertheless, adjusting for all confounders would be impossible as many of them are yet unrecognized.

Another explanation could be the longer interval between baseline assessment and follow-up in MOST (60 months) compared to OAI (48 months). If the progression of knee OA to the end stage of disease (ceiling effect) is faster in obese than non-obese individuals, then longer follow-up would result in more knee OA progression in non-obese individuals, and this eventually would lower the effect of obesity on the risk of knee OA progression towards unity (Zhang et al. 2010). Index event bias and longer interval follow-up could also be the reasons for the paradoxical effect of injury found in the present and past studies.

Various definitions used for the progression of radiographic knee OA is another reason for various findings among studies. For instance, in the Rotterdam Study, the association between high BMI and the risk of knee OA progression varied depending on the definition of progression (Reijman et al. 2007). The aOR was 1.4 when the progression was defined as JSN≥1 mm, it increased to 3.2 when it was defined as JSN ≥1.5 mm, and declined to 2.1 when it was defined as one grade increase in KL score. Various radiograph views used for

the evaluation of disease progression is also another methodological issue that may explain this discrepancy in the literature. This study used the semi-flexed posteroanterior radiograph view of the knee in full weight bearing as the optimal view for the assessment of JSN and KL score for TF joint. However, the full extended anteroposterior view was used in many former studies to evaluate JSN or KL score in participants' radiographs. A review of 12 observational studies has reported the full extended anteroposterior tends to report lower estimation in JSN compared to those that used the semi-flexed posteroanterior view (Emrani, Katz, Kessler et al. 2008).

Lack of consensus in defining symptom progression is another source of bias for various findings. A systematic review of prognostic factors for the progression of clinical knee OA highlighted that pooling of OR was impossible due the wide heterogeneity in definition of symptom progression (9 different definitions across a very limited number of studies) and several different definitions for selecting participants with clinical knee OA (Bastick, Runhaar, Belo et al. 2015). For instance, some studies defined changes in walking speed as the outcome measure for the progression, while some others used the WOMAC pain or function score. Hence, various

definitions used in studies could potentially be the reason for the different findings in previous literature.

5.2.5 *The association of obesity, injury and physical activity with the risk of self-reported knee complaints*

Data collected from the general population for the Nottingham Knee Study showed that 22% of the population had clinical knee OA (NICE definition). Similar prevalence of painful knee has also been reported in previous UK population studies (O'Reilly, Muir and Doherty 1996; O'Reilly, Muir and Doherty 1998; Peat, McCarney and Croft 2001). In agreement with literature, data from the Nottingham Knee Study also showed that obesity and injury significantly increased the risk of clinical knee OA. In addition, no significant association was found between physical activity and the increased risk of clinical knee OA. Therefore, these findings were in line with OAI and MOST results.

Similarly, obesity and injury were found to be the strongest predictors for the high knee related complaints measured by OKS and KOOS. Meanwhile, meeting the UK minimum physical activity guideline was significantly associated with a lower risk of knee related complaints. Therefore, these findings indicate the significant role of obesity and injury on developing the risk of knee OA and self-reported knee complaints, whereas

moderate level of physical activity seems to be safe in the general population.

5.2.6 *Age and gender specific normative data*

The current study also provided age and gender specific reference values for knee pain, symptoms, functions and knee related QOL assessed by KOOS and OKS in a representative group of people from Nottinghamshire, UK.

5.2.6.1 Age related knee complaints

This study found a dose response relationship between increasing age and worsening knee function (KOOS-ADL; OKS-FCS) and knee related QOL (KOOS-QOL). Previous published normative studies also reported similar relationships (Paradowski et al. 2006; Bellamy, Wilson and Hendrikz 2011). Knee pain also increased with age, which was in line with previous literature (Paradowski et al. 2006; Bellamy et al. 2011).

For the KOOS-Pain, KOOS-ADL and KOOS-QOL, the difference between young and middle age groups were none or relatively small. This began to become significant from the middle age to the old age group. A similar trend was also seen for the OKS-PCS. However, OKS-FCS revealed that the young age group had better knee function than middle age group despite

having a similar pain score. This highlighted that OKS, compared to KOOS, had better ability to distinguish the functional differences between the young and middle age groups when both had a similar pain score. Better performance of OKS compared to KOOS physical function subscale has also been previously reported (Harris, Dawson, Jones et al. 2013).

5.2.6.2 Gender related knee complaints

In this study, no gender differences were found for knee complaints in the old age group. Previously published normative data for KOOS in a population-based sample of Southern Sweden also showed similar results for the old age category (Paradowski et al. 2006). However, findings for the young and middle age groups were different between the present and past studies. In the Swedish study, no gender difference were found for any knee complaints in the young age group, while the middle age female group had higher knee complaints than male counterparts of the same age group. Conversely, knee complaints in our study varied in the young age but not the middle age group.

The inconsistencies between studies could be explained by differences in age classification and menopausal age at the sixth decade, when females are at greater risk of knee OA and

musculoskeletal pain (Fillingim 2000; Felson and Hodgson 2014). In our study, all individuals aged between 45-70 years old were included in the middle age group, while this was limited to individuals of 55-65 years old in the Swedish study. Hence, the gender difference in the Swedish study could be attributed to the menopausal age. However, this effect could be biased in our study due to the inclusion of younger individuals in the middle age group.

In the young age category, males had higher knee complaints than females in all subscales of KOOS and OKS in our study. Firstly, this difference may be partly due to injury, as young males were injured 7 times more frequently than young females. Injury has also been found to be a reason for the high number of knee complaints in the young active population in the US Normative study (Cameron, Thompson, Peck et al. 2013). Secondly, the number of young male participants in our study was half of the number of young female participants. This indicated the responder bias in which more young males with knee problems participated in our study when compared to young females. Hence, this could explain a slight underestimation of normative values for the young age group in our study as compared to KOOS reference values of the young age group in Swedish and US studies

(Paradowski et al. 2006; Cameron et al. 2013). However, the high tendency to respond to a survey in young people with knee problems than those without problems is the limitation of all medical survey studies (Baker, Reading, Cooper et al. 2003).

5.3 Clinical relevance of findings

The OAI and MOST studies showed that active and inactive people had a similar risk of knee OA. This effect was not also modified by obesity or injury. Therefore, promoting the moderate levels of community-based physical activity appears to be safe and does not increase the risk of knee OA in high risk individuals with different status of obesity and injury.

This is also an important clinical finding since physical activity is vital for public health in particular in high risk people, where the moderate levels of physical activity aids to improve or maintain their physical health and mental well-being. In addition, low stressful and non-injurious activity contributes to joint health by improving the muscle strength, blood flow and the synovial fluid mobility as the essential sources of nutrition for the joint tissues (Hootman et al. 2003; Felson 2004).

Our data also found the combined effect of obesity and injury on the risk of knee OA is greater than the sum or the multiple

of the individual effects of obesity and injury (positive interaction). This advises the importance of injury prevention in obese individuals when encouraging them to be active. Hence, less injurious and low impact physical activities should be emphasised for obese people and those who are at high risk of knee OA to avoid or at least minimize the likelihood of direct or indirect joint damage during activity. Similarly, weight gain prevention and weight loss strategies such as diet and exercise can protect the subgroup of injured people against further increase in the risk of knee OA. Strengthening and proprioceptive exercises can be also considered as an injury preventive strategy by providing more dynamic stability to the joint during activity.

The present study also provided reference values for the KOOS and OKS according to the gender and age status. To the best of our knowledge, this was the first study reporting the normative data for OKS. Compared to the KOOS, OKS showed similar findings in which old people had more knee pain and difficulties in function. However, OKS had a slightly better performance in distinguishing functional differences, especially in young and middle aged people. In addition, OKS can be completed in a shorter time than KOOS. Therefore, the reference values for KOOS, and in particular for OKS, can be

used in clinical practice to compare the effect of treatment with their age-matched normative data from the general population. Further research is also warranted to examine normative values in young populations without injury.

5.4 Study Caveats

This project used two of the largest cohort studies of people with or at high risk of knee OA to look at the effect of interactions between physical activity, obesity and injury on the knee OA. Having a large sample size and a prospective study design with a small dropout rate at follow-up were the main strengths of this study. Obtaining the optimal x-ray view for TF joint in both databases, and also including the PF-OA in analysis (MOST only) were the other strengths of this study. However, there were some important limitations to the OAI and MOST studies.

Physical activity level of individuals participating in this study was assessed using the PASE questionnaire. The PASE covers three domains of physical activity, which are leisure activities, household activities and occupational activities. A combination of activities involving walking, light or heavy house work, a job with mainly standing or walking and lawn work or yard care would account for a high PASE score (Felson, Niu, Yang et al. 2013). This advises the high levels of physical activity in

the current study could be only referred to as community-based physical activity rather than sports participations. Therefore, more intense exercise may have a different effect on the risk of incidence and progression of knee OA when combined with obesity and/or injury.

PASE did not also distinguish the types of the activity such as weight bearing or non-weight bearing exercise (Lin, Alizai, Joseph et al. 2013). Weight bearing type activities such as running may have a different effect on the knee joint compared to swimming as a non-weight bearing physical activity. Additionally, PASE evaluated the physical activity levels of participants over the past 7 days at baseline which may not be a representation of participants' life time physical activity.

The definition of injury in the present study was also simple and not specific enough to determine the type of injuries. As was previously discussed, the effect of physical activity on the risk of knee OA was not significantly modified by injury. More severe type of injuries such as cruciate ligament rupture may have a greater effect on the risk of knee OA in active compared to inactive people. However, severe knee injuries are less likely to happen with a high level of community-based physical activity which is mainly a combination of activities

involving walking, light or heavy house work, a job with mainly standing or walking and lawn work or yard care. The high level of sports participations is also unlikely in inactive, obese or older adults.

Findings of OAI and MOST should be interpreted with caution since both studies are the cohort of individuals with or at high risk of knee OA. Therefore, the clinical interpretation of our findings is more generalizable to people with or at high risk of knee OA. One may also argue that using high risk group would overestimate the actual risks and the measure of associations in the general population. However, the purpose of our study was not to examine the prevalence or the risk of disease in the general population. Instead, it aimed to explore the mechanistic of possible interactions between modifiable risk factors (obesity, injury and activity) on the risk of incidence and progression of disease. This needed a sample with adequate cases of disease to enable us to analyse interactions. In addition, high risk individuals are usually the interested target groups for disease prevention (Felson and Nevitt 2004; Felson and Hodgson 2014).

As discussed previously, index event bias and the definitions used for defining the progression of radiographic and symptomatic knee OA can be the other limitations of this

study. However, the lack of consensus in defining knee OA progression and the index event bias are the methodological issues of all other studies evaluating the disease progression.

Injury is a major risk factor for knee OA (Muthuri et al. 2011). Early and optimal recovery in young people following injury is also crucial to mitigate or delay the risk of early onset of knee OA. Therefore, using KOOS or OKS to evaluate the optimal recovery in injured young people requires having normative values in uninjured young individuals.

There were also some limitations to the Nottingham Knee Study. The response rate (16.5%) was lower compared to Swedish (68%) and US (93%) studies. However, the response rate was similar to the recent knee OA studies conducted in the UK, in particular the response rate of middle age and older adults (Cooper et al. 2016). The sampling strategy in this study was based on the postcode approach, which was different to previous UK studies recruiting participants via GP practices. In the UK, 98% of the population is registered with GPs (Bowling, Bond, Jenkinson et al. 1999). Hence, the GP approach had a better population coverage compared to the registered population in our data source (77%). The sampling strategy via postcode in our study was also a concern for the lower response rate as compared to the GP approach.

However, the power calculation in the present study was based on approximately 90% non-responders rate as compared to 75% in the GPs sampling method. Thus, this led to a similar response rate to the GPs sampling method and avoided the study becoming under-powered.

The Nottingham Knee Study had lower response rate among young age group. The low response rate among young individuals is also a common limitation in all medical surveys. This requires sending more questionnaires to young individuals. Therefore, sending questionnaires equally to different age groups was another limitation of the Nottingham Knee Study. This led to a selection bias in favour of young people with knee problems and consequently underestimation of normative values. The middle age category was also very broad, including participants aged 45 to 70, in which reference values may vary by the age decade. Therefore, this was the other caveat of the Nottingham Knee Study.

5.5 Future studies

Our study represents a noteworthy contribution to the current literature regarding the effect of interactions between obesity, injury and physical activity on the incidence and progression of knee OA. We found no significant interactions between physical activity and obesity or between physical activity and

injury on the risk of knee OA. These findings suggest that promoting the moderate level of community-based physical activity is safe and does not increase the risk of knee OA in individuals with different status of obesity and injury. Conducting the meta-analysis of results from both studies in thesis could also increase the power of our findings.

The longer term follow-up of our results is also warranted to confirm the absence of interactions between physical activity and obesity or between physical activity and injury on the risk of knee OA in people with or at high risk of knee OA. Importantly, the effect of these interactions on knee OA requires to be investigated in other cohorts that represents the general population.

Our study used a non-specific definition of injury that included any cases with mild injuries. Therefore, the effect of moderate levels of community-based physical activity on knee OA in individuals suffering from severe injuries such as cruciate ligaments rupture or significant meniscal damage remains unclear and needs to be addressed in future studies. The effect of physical activity on knee OA may also be modified with other factors including genetic, muscle strength deficit and malalignment of knee. Hence, addressing above uncertainties in future studies can further elucidate and help

to better understanding of the effect of physical activity on the risk of knee OA.

Our study also provided normative data for KOOS and OKS. The self-reported knee complaints assessed by KOOS and OKS were found to vary with age (but not gender) being highest in the oldest age group. Confirmation of these findings in other population is required. In addition, future studies can establish normative data for the short version of KOOS. The short version can have a better clinical application as it can be completed in a shorter period. Establishing normative values for each decade of age than three age categories can be also an advantage to the present study since it can better demonstrate the trend of changes in self-reported knee complaint. Finally, early and optimal recovery in young people following injury is crucial to mitigate or delay the risk of early onset of knee OA. Therefore, using KOOS or OKS to evaluate the optimal recovery in injured young people requires having normative values in uninjured young individuals.

5.6 Conclusions

This study examined the effect of interactions between physical activity, obesity and injury on the incidence and progression of radiographic and symptomatic knee OA. The high levels of community-based physical activity did not increase the risk of incident or progressive radiographic or symptomatic knee OA at any level of obesity and/or injury in the middle aged and older people with or at high risk of knee OA. Thus, advising high risk groups to be active is good for their health and does not increase the risk of incidence or progression of disease.

Modest evidence for a positive interaction was also found between obesity and injury on the incident disease, suggesting weight loss and weight gain prevention strategies may protect injured people against further increase in the risk of knee OA.

The Nottingham knee study also showed self-reported knee complaints were substantially higher among obese and injured individuals, while meeting the minimum physical activity guideline was associated with the lower self-reported knee complaints. Therefore, moderate levels of physical activity appears to be safe to be recommended to the general population.

In addition, self-reported knee complaints assessed by KOOS and OKS were found to vary with age (not gender) being highest in the oldest age group. This suggests that treatment outcomes in people with knee injury and knee OA should be compared against age-matched reference values from the general population.

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Appendix 1: Ethical approval for using OAI and MOST databases

Direct line/e-mail
+44 (0) 115 8232561
Louise.Sabir@nottingham.ac.uk

Faculty of Medicine and Health Sciences

Research Ethics Committee
Division of Respiratory Medicine
D Floor, South Block
Queen's Medical Centre
Nottingham University Hospitals
Nottingham
NG7 2UH

19th August 2013

Hessam Soutakbar
PhD Student
c/o Dr Kimberley Edwards
Course Director MSc in Sport & Exercise Medicine
Center for Sports Medicine
School of Clinical Sciences
C Floor, West Block
QMC Campus
Nottingham University Hospitals
NG7 2UH

Dear Hessam

Ethics Reference No: Q06062013 SCS Sports Med
Study Title: The Association between Obesity, Physical Activity and Injury on the Risk of Knee Osteoarthritis in the General Population (an analysis using cohort study data).
Chief Investigator/Supervisors: Dr Kimberley Edwards, Course Director, MSc in Sport and Exercise Medicine, Dr Lisa Hodgson, University Teacher, Center for Sports Medicine, School of Clinical Sciences.
Lead Investigators: Hessam Soutakbar, PhD Student, Center for Sports Medicine, School of Clinical Sciences.
Duration of Study: 1/8/2013-31/10/2015 **No of Subjects:** 966 data sets from MRC Hertfordshire cohort database, "Osteoarthritis Initiative" and "Multicentre Osteoarthritis" (MOST) and one from UK: Chingford 1000 Women Study.

Thank your letter dated 15th August 2013 notifying the Committee of Amendment no 1: 14 August 2013 as follows:

- Addition of the use of the three following databases: two from US: "Osteoarthritis Initiative" and "Multicentre Osteoarthritis" (MOST) and one from UK: Chingford 1000 Women Study.

and the following documents were received:

1. Study Protocol for Chingford Study, version 1.0, 14.08.2013.
2. Study Protocol for OAI and Most Study, version 1.0, 14.08.2013

These have been reviewed and are satisfactory and the study amendment no 1: 14 August 2013 is approved.

Approval is given on the understanding that the Conditions of Approval set out below are followed.

1. You must follow the protocol agreed and inform the Committee of any changes using a notification of amendment form (please request a form).

2. You must notify the Chair of any serious or unexpected event.

3. This study is approved for the period of active recruitment requested. The Committee also provides a further 5 year approval for any necessary work to be performed on the study which may arise in the process of publication and peer review.

4. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely

Dr Clodagh Dugdale
Chair, Nottingham University Medical School Research Ethics Committee

Appendix 2: The survey package

- Invite letter
- Participant's information sheet
- Questionnaire booklet

School of Medicine,
Division of Rheumatology,
Orthopaedics & Dermatology

«Title» «Surname»
«Addr1»
«Addr2»
«Addr3»
«Town»
«Postcode»

Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
Floor C, West Block
Queen's Medical Centre
Nottingham, NG7 2UH

Email: kneestudy@nottingham.ac.uk
Tel: 0115 823 1412
Mobile: 07840 380010

Dear «Title» «Surname»,

I am writing to you about a survey we are undertaking, which is seeking to find out information about peoples' knees. We want to understand how knees vary in the general adult population; from pain-free knees to knees that cause pain and disability.

We would be very grateful if you would please read the enclosed 'Participant Information Sheet' which explains why we are doing this questionnaire survey and what it would involve if you were to participate. If you have any questions about the study, we would be happy to answer them. Please feel free to contact us.

Then, if you wish, please complete the enclosed questionnaire booklet. After the first page it is all tick-type answers and should take about 20 minutes to complete. A pre-paid postage, addressed envelope has been provided for you to return the questionnaire booklet. Thank you for taking time to read this letter.

Yours sincerely,

Dr Kim Edwards, BSc (Hons); MMedSci; PhD; PGCAP

Chief investigator

School of Medicine, Division of Rheumatology, Orthopaedics & Dermatology

Participant Information Sheet

Title of Study: Collecting data to find out what normal knees are like

Short title: Knee; Normative data survey

Research Team: Dr Kim Edwards, Dr Lisa Hodgson, Professor Brigitte E Scammell, Mr Hessam Soutakbar

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?

The purpose of the study is to collect information on knees. This will be done using a questionnaire normally used with people who have suffered a painful knee due to injury or osteoarthritis. Currently, we do not know what is normal, so it is not possible to gauge how badly or how well recovered someone might be following a treatment.

Why have I been invited?

All adults are eligible to take part in our study, whether you have 'good' or 'bad' knees!

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to complete a questionnaire. Some people have already completed this questionnaire and reported taking about 20 minutes to do so.

If you decide to take part you are still free to withdraw, without giving a reason. This would not affect your legal rights. We have built in a one week 'cooling-off' period in case you wish to withdraw. This means that if you let us know that

you no longer wish to participate in the study at any time up to a week after we receive your completed questionnaire, we will return your questionnaire to you (or destroy it if you have not provided a postal address) and not use your data in our study.

What will happen to me if I take part?

You will be provided with a questionnaire to complete. The questions are mainly tick-box styled questions, therefore quick to complete. Once completed please return them, using the pre-paid postage, addressed, envelope provided.

What are the possible disadvantages and risks of taking part?

There are no risks or disadvantages from completing the questionnaire.

What are the possible benefits of taking part?

There are no physical benefits from taking part. But your help may help future knee studies, because at the moment it is unclear what '*normal'* really is. We will not be diagnosing any health problems in participants.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers' contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you should then contact the Research Ethics Committee Administrator, c/o The University of Nottingham, School of Medicine Education Centre, B Floor, Medical School, Queen's Medical Centre Campus, Nottingham University Hospitals, Nottingham, NG7 2UH. E-mail: louise.sabir@nottingham.ac.uk.

Will my taking part in the study be kept confidential?

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

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

The completed questionnaires will be kept securely for 7 years after the end of the study in line with standard practice. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality. Only members of the research team will have access to your personal data.

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

Your participation is voluntary and you are free to withdraw at any time, without giving any reason. If you do not want to complete the questionnaire then do not. Please feel free to dispose of it.

If you complete the questionnaire and send it to us, then we will store them securely under lock and key for one week before processing it. If you wish to withdraw during that time, simply let us know (contact details at the bottom of this document) and we will return your questionnaire to you (or destroy it if no postal address provided). After this time (one week) your results will be entered onto the University's computer system. Once that has happened, due to anonymisation and analyses/backup processes, we will not be able to remove your data from the system.

What will happen to the results of the research study?

The information this study gathers may be used to develop reports and presentations for professional journals, academic conferences etc., as well as at local professional and public presentations. It will also inform future studies about what is 'normal' in a knee. All results will be presented anonymously.

Who is organising and funding the research?

This research is being organised and funded by the University of Nottingham

Who has reviewed the study?

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

Further information and contact details:

For further information please contact us using the following:

Knee: Normative data survey
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
F Floor, West block
Queen's Medical Centre
Derby Road, Nottingham, NG7 2UH
E-mail: kneestudy@nottingham.ac.uk
Tel: 0115 823 1412 Mobile: 07840 380010

The chief investigator for this study is:
Dr Kim Edwards
Course Director MSc Sport and Exercise Medicine
Academic Orthopaedics, Trauma and Sport Medicine University of Nottingham
Floor C, West Block, Queens Medical Centre
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Email: kneestudy@nottingham.ac.uk
Tel: 0115 823 1114

The University of Nottingham

Knee Survey

An anonymous postal survey enquiring about the health of your knees

For assistance or any queries, please contact the research team:

Tel: 0115 823 1412 or 07840 380010

E-mail: kneestudy@nottingham.ac.uk

For office use only:

Participant ID Number								
Return date	D	D	M	M	Y	Y	Y	Y

Please complete this anonymous postal survey enquiring about the health of your knees even if they are both normal. If one or both of your knees cause you a problem, please complete the questionnaire for your worst knee. It will take 15-20 minutes. Please place a tick in the appropriate box.

Background Information Section

How old are you today? …….years What is your post code? …….

Are you:	Male ☐	Female ☐
How tall are you:	. . . ft, . . . inches, or	. . . . . cm
How much do you weigh:	. . . st, . . . lb, or	. . . . . kg

Do you have activity related joint pain
in one or both knee(s)? ☐ Yes ☐ No

Do you have morning stiffness
in one or both knee(s)? ☐ Yes ☐ No

If yes, does this morning knee stiffness
last for **more than** 30 minutes? ☐ Yes ☐ No ☐ Not applicable

Have you ever had a knee joint replacement
in one or both knee(s)? ☐ Yes ☐ No

Have you ever had surgery/arthroscopy for ligament or meniscal repair in
one or both knee(s)? ☐ Yes ☐ No

Do you have a current significant knee injury (for example, one that you
have sought medical treatment for)? ☐ Yes ☐ No

If yes, please provide details here:
_____
_____
_____

Questionnaire Section

Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms

Questions 1-5 should be answered thinking of your knee symptoms during the **last week**.

1. Do you have swelling in your knee?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

3. Does your knee catch or hang up when moving?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

4. Can you straighten your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

5. Can you bend your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

Stiffness

Questions 6-7 concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

6. How severe is your knee joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain *(Questions 8-16)*

8. How often do you experience knee pain?

Never	Monthly	Weekly	Daily	Always
☐	☐	☐	☐	☐

What amount of knee pain have you experienced in the **last week** during the following activities?

9. Twisting/pivoting on your knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

10. Straightening knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

11. Bending knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

12. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

13. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

14. At night while in bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

15. Sitting or lying

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

16. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

Questions 17-33 concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

17. Descending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

18. Ascending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

19. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

20. Standing

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

21. Bending to floor/pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

22. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

23. Getting in/out of car

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

24. Going shopping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

25. Putting on socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

26. Rising from bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

27. Taking off socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

28. Lying in bed (turning over, maintaining knee position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

29. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

30. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

31. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

32. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc.)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

33. Light domestic duties (cooking, dusting, etc.)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

Questions 34-38 concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

If you **have not done these activities**, please leave the corresponding question blank.

34. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

35. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

36. Jumping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

37. Twisting/pivoting on your injured knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

38. Kneeling

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of life *(Questions 39-42)*

39. How often are you aware of your knee problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

40. Have you modified your life style to avoid potentially damaging activities to your knee?

Not at all	Mildly	Moderately	Severely	Totally
☐	☐	☐	☐	☐

41. How much are you troubled with lack of confidence in your knee?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

42. In general, how much difficulty do you have with your knee?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Problems with your knee during the past 4 weeks... *(Questions 43-54)*

Tick (✓) one box for every question.

43. During the past 4 weeks… How would you describe the pain you usually have from your knee

None	Very mild	Mild	Moderate	Severe
☐	☐	☐	☐	☐

44. During the past 4 weeks… Have you had any trouble with washing and drying yourself (all over) because of your knee?

No trouble at all	Very little trouble	Moderate trouble	Extreme difficulty	Impossible to do
☐	☐	☐	☐	☐

45. During the past 4 weeks… Have you had any trouble getting in and out of a car or using public transport because of your knee? (Whichever you tend to use)

No trouble at all	Very little trouble	Moderate trouble	Extreme difficulty	Impossible to do
☐	☐	☐	☐	☐

46. During the past 4 weeks… For how long have you been able to walk before pain from your knee becomes **severe**? (With or without a stick)

No pain/ More than 30 minutes	16 to 30 minutes	5 to 15 minutes	Around the house only	Not at all/ pain severe when walking
☐	☐	☐	☐	☐

47. During the past 4 weeks… After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?

Not at all painful	Slightly painful	Moderately painful	Very painful	Unbearable
☐	☐	☐	☐	☐

48. During the past 4 weeks… Have you been limping when walking, because of your knee?

Rarely/ never	Sometimes, or just at first	Often, not just at first	Most of the time	All of the time
☐	☐	☐	☐	☐

49. During the past 4 weeks… Could you kneel down and get up again afterwards?

Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
☐	☐	☐	☐	☐

50. During the past 4 weeks… Have you been troubled by pain from your knee in bed at night?

No nights	Only 1 or 2 nights	Some nights	Most nights	Every night
☐	☐	☐	☐	☐

51. During the past 4 weeks… How much has pain from your knee interfered with your usual work (Including housework)?

Not at all	A little bit	Moderately	Greatly	Totally
☐	☐	☐	☐	☐

52. During the past 4 weeks… Have you felt that your knee might suddenly 'give way' or let you down?

Rarely/ never	Sometimes, or just at first	Often, not just at first	Most of the time	All of the time
☐	☐	☐	☐	☐

53. During the past 4 weeks… Could you do the household shopping on your own?

Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
☐	☐	☐	☐	☐

54. During the past 4 weeks… Could you walk down one flight of stairs?

Yes, easily	With little difficulty	With moderate difficulty	With extreme difficulty	No, impossible
☐	☐	☐	☐	☐

Your general health today *(Questions 55-60)*

Under each heading, please tick the ONE box that best describes your health **TODAY**

55. MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

56. SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

57. USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

58. PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

59. ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

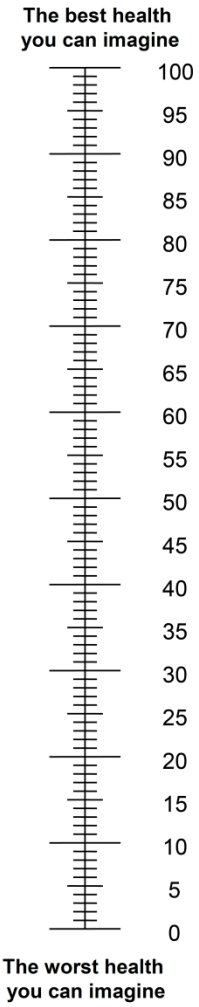
We would like to know how good or bad your health is **TODAY**. This scale is numbered from **0** to **100**.

- **100** means the best health you can imagine.
- **0** means the worst health you can imagine.

- Mark an X on the scale to indicate how your health is **TODAY**.

- Now, please write the number you marked on the scale in the box below.

60. YOUR HEALTH TODAY **=** ☐



Please think of the last 7 days when answering questions 61-62.
We are interested in any physical activity that you have undertaken in the last seven days, that lasted at least ten minutes at a time and was 'moderate' or 'vigorous' in nature (see definitions below):

MODERATE physical activity: any activity that gets you mildly sweaty and out of breath, (e.g. brisk walking, carrying loads, digging, climbing ladders)

VIGOROUS physical activity: any activity that involves hard physical effort and makes you breathe much harder than normal (e.g. heavy lifting, aerobics, or fast bicycling)

Please tick here if you **did not** undertake **any** moderate or vigorous physical activity in the last seven days ☐

61.	**Part A:** at work/college	Days	Moderate	Vigorous
How much time do you spend doing physical activity **at work/college** every week?		Monday	Minutes……	Minutes……
		Tuesday	Minutes……	Minutes……
		Wednesday	Minutes……	Minutes……
The activity must be done for at least **10** minutes at a time.		Thursday	Minutes……	Minutes……
		Friday	Minutes……	Minutes……
Please include time spent travelling to/from work or college (if **moderate or vigorous** in nature)		Saturday	Minutes……	Minutes……
		Sunday	Minutes……	Minutes……

62.	**Part B:** at home/ leisure time	Days	Moderate	Vigorous
How much time do you spend doing sport/exercise when **not at** work or college?		Monday	Minutes……	Minutes……
		Tuesday	Minutes……	Minutes……
		Wednesday	Minutes……	Minutes……
The activity must be done for at least **10** minutes at a time.		Thursday	Minutes……	Minutes……
		Friday	Minutes……	Minutes……
Please include time spent travelling to/from events (if **moderate or vigorous** in nature)		Saturday	Minutes……	Minutes……
		Sunday	Minutes……	Minutes……

Please provide your name and address (or email) only if you wish us to contact you with the results from this study or future studies:
Name: _____ Address: _____ _____ _____ Email: _____

Thank you very much for completing this questionnaire

Please return the questionnaire using the pre-paid envelope provided

If you have any queries, please contact the team at:

Knee: Normative data survey
Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
Floor F, West Block
Queen's Medical Centre
Nottingham NG7 2UH

E-mail: kneestudy@nottingham.ac.uk
Tel: 0115 823 1412 Mobile: 07840 380010

Please return the questionnaire (using the stamped-addressed-envelope) to:

Academic Orthopaedics, Trauma and Sports Medicine
University of Nottingham
Floor C, West Block
Queen's Medical Centre
Nottingham NG7 2UH

Appendix 3: Ethical approval for Nottingham Knee Study

Direct line/e-mail
+44 (0) 115 8232561
Louise.Sabir@nottingham.ac.uk

The University of Nottingham

Faculty of Medicine and Health Sciences

Research Ethics Committee
School of Medicine Education Centre
B Floor, Medical School
Queen's Medical Centre Campus
Nottingham University Hospitals
Nottingham
NG7 2UH

25th November 2014

Hessam Soutakbar
PhD Student
Orthopaedics Trauma and Sport Medicine
Division of Rheumatology, Orthopaedics and Dermatology
School of Medicine
C Floor, West Block
QMC Campus
Nottingham University Hospitals
NG7 2UH

Dear Hessam

Ethics Reference No: F14082014 SoM ROD PhD
Study Title: Collecting data to find out what normal knees are like
Short Title: Knee: Normative data survey
Chief Investigator/Supervisor: Dr Kimberley Edwards, Course Director for MSc in Sport & Exercise Medicine, Dr Lisa Hodgson, Lecturer in Sport and Exercise Medicine, Professor Brigitte Scammell, Professor of Orthopaedic Sciences, Orthopaedics, Trauma and Sports Medicine, School of Medicine.
Lead Investigator/Student: Hessam Soutakbar, PhD Student,Orthopaedics, Trauma and Sports Medicine School of Medicine
Duration of Study: 09/14-04/2015 6mths **No of Subjects:** 192+ (18-69 yrs)

Thank you for your letter dated 19th November 2014 notifying the Committee of amendment no 3 19/11/2014 as follows:

1. A change in Contact with Participants' GP. As this study is not diagnostic participants will now not be asked to provide their GP's contact details and this has been removed from the questionnaire.

2. Postal Recruitment: change to include all information (invite letter, PIS and questionnaire) in the initial round of posting to improve recruitment.

3. Change of signatory for the invite cover letters from the Student: Hessam Soutakbar to the Chief Investigator: Dr Kim Edwards to improve recruitment.

The following revised documents with corrections marked were received:

Knee; Normative data survey:
- Ethics Form V5 17/11/14
- Study Protocol v5 17/11/14
- Recruitment Poster v3 24/10/14 (no changes)
- Participant Invite Letter v3 17/11/2014
- Participant Cover Letter v3 17/11/2014
- Participant Information Sheet v3 17/11/2014
- Participant Questionnaire Booklet, v5 17/11/2014

These have been reviewed and are satisfactory and the study amendment no 3: 19/11/2014 is approved.

Approval is given on the understanding that the Conditions of Approval set out below are followed.

1. You must follow the protocol agreed and inform the Committee of any changes using a notification of amendment form (please request a form).

2. You must notify the Chair of any serious or unexpected event.

3. This study is approved for the period of active recruitment requested. The Committee also provides a further 5 year approval for any necessary work to be performed on the study which may arise in the process of publication and peer review.

4. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely

Dr Clodagh Dugdale
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee