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Lifecourse influences on osteoarthritis of the knees, hips and hands as defined by musculoskeletal ultrasound

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Abstract

Aims: There has been very little lifecourse research looking at the risk of osteoarthritis (OA). A lifecourse analysis of risk factors for knee, hip and hand OA (defined using features on ultrasound) acting at different stages of life, including early life factors, was performed among members of the Newcastle Thousand Families birth cohort.

Methods: Potential risk factors for OA (including birth weight, breast feeding data and socioeconomic status) have been collected prospectively in this birth cohort of subjects aged 63 (born in May-June 1947) and an a priori conceptual framework was developed. Subjects had both knees, hips and the dominant hand scanned with ultrasound. These data were analysed in relation to a range of factors from across the lifecourse using logistic and linear regression models.

Results: Among 316 participants, duration of exclusive breast feeding showed a significant inverse association with knee osteophytes while BMI and total hip bone mineral density at age 50 increased the risk of knee osteophytes. The univariate effect of social class at birth on knee osteophytes was found to be mediated by its subsequent effect on breast feeding and total hip bone mineral density. The multivariate model for hip OA had three risk factors; BMI, physical activity and pack years of smoking at age 50. Smoking at age 50 and increased infections in childhood appeared to confer protection from hand OA.

Conclusions: This is the first study to perform a lifecourse analysis of OA risk using prospectively collected data. The majority of the risk of OA at the three joint sites seemed to occur through factors acting in adulthood. However, breast feeding protected subjects from knee OA while infections in childhood decreased hand OA risk. These results suggest that modification of OA risk factors acting in adulthood would probably be more beneficial than intervening in early life.

Dedication

I would like to dedicate this thesis to a few people who have inspired and supported me through various stages of my life. This is for my parents, Babu and Nirmala Abraham, who set me an example in the way that they have lived and worked hard through difficult times. I would like to thank my wife, Maria, for her encouragement, support and perseverance at times when it was difficult for her to manage a full time job and look after two children on her own while I was away in Newcastle. I have also taken inspiration from my two little girls, Lara and Debra, who have shown great resilience and patience while I was away for three years. Most importantly, I would like to thank my Lord Jesus Christ for the past, the now and the ever after.

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Chapter 1 Introduction

Osteoarthritis (OA) or degenerative joint disease is the most common form of arthritis in developed countries (Kelsey and Hochberg, 1988). Some of the pathological features of this condition include loss of articular cartilage, attrition of subarticular bone, osteophytes, ligamentous laxity, weakening of periarticular muscles and inflammation (Hutton, 1989). OA is no longer considered a natural process of ageing alone or "wear and tear", but is now recognised to involve dynamic biological and biochemical processes, characterised by tear, flare & repair (Birrell et al., 2011). Although OA has been traditionally considered to be a "non-inflammatory illness", to separate it from conditions like rheumatoid arthritis, inflammation is being increasingly recognised as a feature of OA and is also associated with progression (Spector et al., 1997a). Symptomatic OA is increasing in western countries like the US and UK, most likely as a result of increasing obesity and the ageing population (Reginster, 2002). It is unsurprising then that the numbers of hip and knee joint replacement surgeries in the UK, calculated as over 150,000 in England and Wales in 2008 (2010), have far exceeded the estimated projections from less than a decade ago (Dixon et al., 2004, Birrell et al., 1999). This is likely to have a huge impact on health care utilisation and service provision, with the added burden of significant economic costs to society (Lawrence et al., 2008).

OA is the most common form of arthritis and affects 12.1% of the adult population in the United States; a total of 27 million Americans (Lawrence et al., 2008). This is significantly higher than the prevalence estimate for rheumatoid arthritis which is 0.6% of the adult American population; a total of 1.3 million affected (Helmick et al., 2008).

Lawrence et al reviewed the important prevalence studies of OA (Lawrence et al., 2008) in the US and reported the age standardised prevalence of radiographic knee OA. In the

Framingham Osteoarthritis study of adults between 63 and 94 years of age, the prevalence of symptomatic OA was 19.2% (Felson et al., 1987), while it was 16.7% in the Johnston County Osteoarthritis Project in subjects aged more than 45 years (Jordan et al., 2007). The prevalence of radiographic OA was 37% in the National Health and Nutrition Examination Survey (NHANES) III of subjects more than 60 years old (Dillon et al., 2006).

The prevalence of hand OA was 27.2 % in the Framingham study (Age > 45) (Zhang et al., 2002). Symptomatic hand OA prevalence was 6.8% in this cohort (age more than 26 years).

In general, previous estimates suggest that the prevalence of radiographic hip OA is less than that at the knee and the hand. All of these studies demonstrated variations in prevalence of OA with age, with the general trend being an increase in prevalence with age (Lawrence et al., 2008).

In the UK, symptomatic knee OA was found to be 13% in a community study of 513 men and women aged over 55 years. Even within this sample, there was significant variation in the rates between the sexes and the different joint compartments within the knee (McAlindon et al., 1992). Men were found to have a higher prevalence of patello-femoral joint (PFJ) knee OA when compared to the medial tibio-femoral compartment (12% vs 23%) as opposed to women who were noted to have the reverse pattern (26% vs 14%).

Another group in Nottingham that looked at 459 men and women aged 40-79 years in the community reported a prevalence of symptomatic radiographic knee OA as 11%. This study showed that the prevalence could vary depending on the question asked for knee pain as well as the threshold used for defining radiographic knee OA (O'Reilly et al., 1996). The estimate of prevalent knee pain was lowest (19.3%) when using the American College of Rheumatology (ACR) criteria question which asked participants about knee pain on most days of the last month. The estimate was higher (28%) for pain in or around

the knee on most days for at least a month and if so, if they experienced any pain in the previous year. A modified version of the above question resulted in a drop in estimate to 25%; “Have you had pain within the last year in or around the knee that occurred on most days for at least a month?” It is not unexpected to see that the ACR criteria question has lower prevalence estimates since it requires current symptoms. However, it was interesting to see that the subtle change in wording between the other 2 questions also resulted in a change in prevalence estimates. There was a poor correlation between pain and the presence of radiographic osteophytes seen in this study; which highlights the need for an imaging modality with better correlation with symptomatic knee OA.

A study using the general practice research database examined the trends of hip and knee replacement surgery in the UK between 1991 and 2006 (Culliford et al., 2010). This database provides computerised routine information on general practice morbidity and prescribing in the UK and contains data from 1987 onwards. In 1994, this covered 5.6% of the population of England and Wales. The authors found that there was a steady rise in the rates of primary total hip replacement surgery; the estimated age-standardised rates (per 100,000 person years) increasing from 60.3 (95% CI 53.7, 67) to 144.6 (95% CI 138.1, 151.1) for women and from 35.8 (95% CI 30.4, 41.3) to 88.6 (95% CI 83.4, 93.7) in men. While the rates of primary hip replacements doubled during this period, the rates of primary knee replacement surgeries were found to treble in the same period. Women had consistently higher proportion of hip and knee replacement surgeries, compared to men; although the mean age at which they had the surgery was 70 years for the knee and hip in women compared to 67 years and 69 years for hip and knee surgery respectively, in men.

Attempts to calculate the economic burden of OA have been made. An analysis in 1997 found that the prevalence of OA was the highest among musculoskeletal conditions in five countries, namely, Australia, Canada, France, UK and United States (March and Bachmeier, 1997). The authors reported that musculoskeletal conditions (predominantly

OA) accounted for between 1.1 (UK) to 2.5% (United States) of gross national product in these countries.

OA is known to have an impact on individuals in various domains including (March and Bachmeier, 1997):

- Difficulty with activities of daily living
- Disability
- Limitations to social and leisure activities
- Problems with personal relationships
- Requirement of assistance and decreased independence
- More psychological issues such as anxiety and depression
- Out of pocket costs due to health care, non-medical needs and loss of predicted earnings.

A study that assessed the loss of income in people affected by asymmetric oligoarthritis (a surrogate for OA) found that that men and women with arthritis earned only 63% and 30% respectively, of incomes of people without arthritis (Pincus et al., 1989). While two-thirds of this difference was explained by factors such as age, lower education and co-morbidity, arthritis in itself was responsible for about a third of the observed difference in incomes. An analysis of 1258 Canadian participants in 1997 (mean age 73) found that the mean annual cost to individuals with OA was 12,200 Canadian dollars (Gupta et al., 2005). 80% of this cost was due to time lost from employment and leisure by participants and unpaid caregivers. Those with greater disability from lower limb OA (WOMAC $\geq$55) were 15 times more likely to report costs than those with less disability (WOMAC <15) and their costs were three times higher (both $p < 0.0001$).In an analysis of various epidemiologic studies and surveys in the United States, OA was found to be the fifth leading cause of disability in those aged 65-74; ahead of dementias, diabetes mellitus and breast and prostate cancer (Michaud et al., 2006). In fact, OA came third on the list of causes of "years of life lost due to disability"; ahead of ischaemic heart disease,

cerebrovascular disease and COPD. The Johnston County Osteoarthritis Project demonstrated a high level of functional impairment in participants with knee OA, especially those with knee pain (Jordan et al., 1997). Participants with moderate to severe knee pain showed high disability in all 20 tasks of the disability score ($p<0.001$ for all).

Despite the increase in prevalence, OA remains a poorly understood condition with relatively few effective therapies. A lot of effort has gone into trying to modify the structural progression of OA, but this has been hampered by the heterogeneity of the clinical manifestations of the disease and the need to follow patients for many years to observe meaningful structural changes in subjects with OA. A significant limitation in the epidemiological study of OA in the past has been the use of radiographs to define OA which is considered to be an insensitive imaging modality due to its inability to visualise soft tissue structures and due to its poor correlation with symptoms and disability. Ultrasound imaging of joints for features of OA has distinct advantages in that it does not involve ionising radiation, is easy to use and can identify soft tissue features of OA such as cartilage thickness and synovial effusion (Grassi et al., 2005). The reliability and validity of the use of ultrasound in OA has already been demonstrated in previous studies (Abraham et al., 2011, Naredo et al., 2009, Qvistgaard et al., 2006).

Epidemiological studies of OA have so far looked at cross sectional associations with risk factors or performed relatively short term prospective studies, with a few years of follow up, to assess risk of prevalent OA. However, it is now widely accepted that OA has a multifactorial aetiology and develops as a consequence of a variety of systemic and local factors throughout the lifecourse (Zhang and Jordan, 2008). Early life factors such as birth weight and socioeconomic status have been found to influence the adult risk of many chronic diseases such as hypertension (Lackland et al., 2003), diabetes (Barker, 2005) and osteoporosis (Cooper et al., 2009). David Barker and his team proposed the hypothesis that there were critical periods in intra-uterine life for the development of chronic diseases later in life and that these periods could “program” subsequent body

structure and function (Barker, 1998). Barker did not have a significant amount of prospective early life data on the original Hertfordshire cohort with which he initially constructed his hypothesis and sampled only those with available records. However, there have subsequently been a large number of epidemiological studies using birth cohorts, such as the 1946 National Birth Cohort (Wadsworth et al., 2006) and the Newcastle Thousand Families cohort (Pearce et al., 2009), which have looked at the lifecourse risk of chronic illnesses such as hypertension, coronary heart disease and osteoporosis. The lifecourse approach to chronic disease epidemiology was defined as "the study of long term effects of physical and social exposures in gestation, childhood, adolescence and adulthood" (Ben-Shlomo and Kuh, 2002). The lifecourse approach to epidemiology does not accept merely collecting various exposures and entering these data in to a multivariable model. This approach takes in to consideration, the temporal associations between the risk factors across the different stages of the lifecourse, both directly and through mediating variables, with the outcome being studied.

To my knowledge, there have been no lifecourse studies performed to look at OA risk factors in a prospectively followed birth cohort. A rigorous and prospective lifecourse study of the influence of social and physical exposures in gestation, infancy, childhood, adolescence and later adult life, on the development of OA is needed. The potential factors include variables operating over the whole lifecourse such as birth weight, duration of breast feeding, socioeconomic circumstances and physical activity. The Newcastle Thousand Families cohort (discussed in chapter 5) presents unique opportunities to address these issues, using the existing data and that collected at the 62/63 year review.

This thesis will provide unique ultrasound defined OA prevalence data in a prospective population cohort, allowing for the hypotheses mentioned below, to be tested.

1.1 Hypotheses

[1] Early life influences are an important cause of the structural changes of OA in the knees, hips and hands as determined by ultrasound (US).

[2] OA identified on US will be associated significantly with radiographic OA as well as clinical symptoms.

1.2 Aims

To conduct a life course analysis to assess the relationship and impact of potential risk factors for OA operating at various stages of life to ultrasound features of OA at the hand, knee and hip in a population based cohort who have been prospectively followed up from birth and to estimate the prevalence of structural and inflammatory parameters, as determined by US evaluation of the hand, knee and hip in this cohort.

1.3 Primary objective

To determine the relative impact of factors operating at various stages of the life course, with the structural parameters of OA found on US evaluation of the hand, knee and hip of these subjects.

1.4 Secondary objectives

[1] To determine the prevalence of inflammatory and structural parameters of OA in the knees, hips and hands and their association with potential risk factors for OA.

[2] To ascertain the relationship between US findings and radiography, pain and disability.

Chapter 2 provides details of prevalence rates of OA at the knee, hip and hand using radiographic outcomes in previous studies. It outlines some of the limitations in the epidemiological study of OA in the past and provides justification for the use of a more sensitive imaging modality to define OA for epidemiological studies. The reliability and validity of ultrasound in OA has also been discussed in this chapter. Chapter 3 provides evidence of previous epidemiological studies that have assessed the magnitude of risk of various risk factors for OA. It also describes Barker's hypothesis and lifecourse epidemiology and their relevance to musculoskeletal health; leading on to the conceptual framework of this analysis. Chapter 4 describes the Newcastle Thousand Families Birth Cohort and outlines results of some of the previous epidemiological studies that have been performed on this cohort. Chapter 5 provides details of the methods used in this study including ultrasound protocols, radiographic protocols and the collection and validity of questionnaire data. It also describes details of the pilot study that was performed to demonstrate the reliability and validity of use of ultrasound in OA. Chapter 6 states the results of the analyses that were performed while Chapter 7 moves in to the discussion of the results that were found, comparing these results with previous studies. Chapter 8 provides a summary of the results of this study and its implications for the future of OA research.

Chapter 2 Osteoarthritis Prevalence & Imaging

2.1 Definition

There is more than one accepted epidemiological definition of OA: as structural defects on imaging, by joint symptoms or as a combination of both. While there are multiple grading systems for radiographic OA, the one devised by Kellgren and Lawrence is the one that has been used most frequently (Kellgren and Lawrence, 1963). These criteria (K-L score) include a global score that ranged from 0 to 4 and most studies use grade 2 changes and above as the definition of radiological OA. However, one of the limitations with this global score is that it excludes subjects with joint space narrowing (JSN) and no osteophytes. This led to the development of modified atlases which were based on individual radiographic features (IRF) for the hand (Kallman et al., 1989), hip (Lane et al., 1993) and the knee (Scott et al., 1993). These atlases show better reliability within and between trained readers in some studies and there is recent evidence suggesting they are more valid than the global K-L score (see ADD). However, the K-L score still remains the most extensively used epidemiological tool for the assessment of radiographic OA.

Croft et al (Croft et al., 1990) demonstrated that the radiographic feature most strongly associated with hip pain was minimal joint space, in a study of 1315 men aged 60-75 in Stoke-on-Trent, who had undergone intravenous urograms. They also found that measures of joint space were the most reproducible radiographic feature and related best to other radiographic features. It was therefore felt that this was the best radiologic criterion for epidemiologic definitions of hip OA in men. However, a more recent study of 5839 women from the Study of Osteoporotic fractures demonstrated that composite definitions of radiographic hip OA, which included both osteophytes and JSN, displayed the best construct validity (as determined by association with pain and functional limitation) and predictive validity (determined by subsequent total hip replacements). It was able to validate existing definitions that were being used for prevalent OA and also some new definitions for epidemiological studies of incident hip OA (Arden et al., 2009).

The Chingford study assessed IRF of OA in the knee and used antero-posterior weight bearing radiographs while utilising various quantitative and qualitative tools to read these radiographs. This study found that the presence of definite osteophytes was the feature most strongly associated with reported knee pain in 1003 women aged between 45 to 65 years (Spector et al., 1993).

The definition of OA began to include clinical criteria in 1981 when the American College of Rheumatology classified symptomatic OA using joint pain as an inclusion parameter (Altman et al., 1983).

2.2 Prevalence

The prevalence of OA has been described extensively in the past using radiographic studies. The inability of radiographs to view soft tissue structures relevant to OA pathology and the reduced sensitivity of radiographs when compared to ultrasound in identification of osteophytes in OA (Keen et al., 2008b), demonstrates the need for the use of ultrasound to define features of OA for epidemiological studies. However, there have been no previous population-based estimates of OA prevalence using a more sensitive imaging modality such as ultrasound.

The prevalence of radiographic OA has been reported in numerous population-based epidemiological studies across the world. These results have been tabulated by joint site in the tables below: knee (Table 1), hip (Table 2) & hand (Table 3).

2.2.1 Studies estimating prevalence of knee OA

As seen in Table 1, the prevalence of radiographic knee OA was more common in women than in men, particularly for symptomatic knee OA. The prevalence of OA increased with age and was higher among African Americans when compared to Caucasians in the Johnston County cohort (Jordan et al., 2007).

Table 1 Studies demonstrating prevalence of radiographic knee OA

Author	Sample size	Population studied	Age/ sex	Site of OA	Diagnostic method	Prevalence (total)	Prevalence (male)	Prevalence (female)
McAlindon (McAlindon et al., 1992)	513	Bristol, England	55+ M+F	knee (incl PFJ)	Radiographic (R) + symptoms (S)	R : 36.3% R+S : 13%		
O'Reilly (O'Reilly et al., 1996)	459	Nottingham, England	40-79 M+F	knee	Radiographic + symptoms	11%		

Table 1 Studies demonstrating prevalence of radiographic knee OA

Author	Sample size	Population studied	Age/ sex	Site of OA	Diagnostic method	Prevalence (total)	Prevalence (male)	Prevalence (female)
Felson (Felson et al., 1987)	1424	Framingham, USA	63-94 M+F	knee	Radiographic + symptoms	R: 33% R+S : 9.5%	R : 30.9% R+S : 6.8%	R : 34.4% R+S : 11.4%
Jordan (Jordan et al., 2007)	3018	Johnston County, North Carolina, USA	45+ M+F	knee	Radiographic + symptoms	R : 27.8 R+S : 16.4% Caucasian R : 26.8% African-American R : 32.4%	R : 23.7% R+S : 13.5%	R : 31% R+S : 18.7%

Table 1 Studies demonstrating prevalence of radiographic knee OA

Author	Sample size	Population studied	Age/ sex	Site of OA	Diagnostic method	Prevalence (total)	Prevalence (male)	Prevalence (female)
Dillon (Dillon et al., 2006)	2415	NHANES III, USA	60+ M+F	Knee	Radiographic (non weight bearing) + symptoms	R : 37.4% R+S : 12.1%	R : 31.2% R+S : 10%	R : 42.1% R+S : 13.6%
Neame (Neame et al., 2004)	1729	Nottingham, England	40+ M+F	Knee (incl PFJ)	Radiographic	TFJ : 12% PFJ : 13.7%		

Table 1 Studies demonstrating prevalence of radiographic knee OA

Author	Sample size	Population studied	Age/ sex	Site of OA	Diagnostic method	Prevalence (total)	Prevalence (male)	Prevalence (female)
Van Saase (Van Saase et al., 1989) (6585 inhabitants of a Dutch village)	465 participants >60 yrs of age	Zoetermeer, Netherlands	60+ M+F	Knee	Radiographic		R ~ 20% (60-64 yr age group)	R ~ 25% (60-64 yr age group)
Odding (Odding et al., 1998)	2895	Rotterdam, Netherlands	55+ M+F	Knee	Radiographic+ symptoms		R : 16.3% R+S : 4.2%	R : 29.1% R+S : 9.9%

Table 1 Studies demonstrating prevalence of radiographic knee OA

Author	Sample size	Population studied	Age/ sex	Site of OA	Diagnostic method	Prevalence (total)	Prevalence (male)	Prevalence (female)
Duncan (Duncan et al., 2006)	777 (with knee pain)	North Staffordshire, England	50+ M+F	Knee (incl PFJ)	Radiographic (all had symptoms)	TFJ : 4% PFJ : 24% TFJ+PFJ : 40%		

R = radiographic knee OA; R+S = radiographic and symptomatic knee OA; TFJ = tibio-femoral joint; PFJ = patella-femoral joint

2.2.2 Studies estimating prevalence of hip OA

Hip OA prevalence was lower than that seen in the knee as seen in Table 2. The prevalence among the Chinese was particularly low at about 1% (Nevitt et al., 2002) while in contrast, the prevalence was much higher in an American (Johnston County) cohort (Jordan et al., 2009) which included a large proportion of African American participants.

Table 2 Studies demonstrating prevalence of radiographic hip OA

Author	Sample size	Population studied	Age/ sex	Site of OA	Diagnostic method	Prevalence (Male)	Prevalence (Female)	Prevalence (total)
Jordan (Jordan et al., 2009)	2637	Johnston County, North Carolina, USA	45+ M+F	Hip	Radiographs + symptoms	R (Caucasian) : 23.8% R+S (Caucasian) : 7.6 % R (African-American) : 33.2%	R (Caucasian) : 29.1% R+S (Caucasian) : 10.8 % R (African-American) : 31.2%	R : 27.6% R+S : 9.7% R (Caucasian) : 26.6%

Table 2 Studies demonstrating prevalence of radiographic hip OA

Author	Sample size	Population studied	Age/ sex	Site of OA	Diagnostic method	Prevalence (Male)	Prevalence (Female)	Prevalence (total)
Neame (Neame et al., 2004)	1715	Nottingham, England	40-85 M+F	Hip	Radiographs			3.5% -right 3.9% - left 6% - overall
Nevitt (Nevitt et al., 2002)	1506	Beijing, China	60+ M+F	Hip	Radiographs + symptoms	R : 1.1% R+S : 0%	R : 0.9% R+S : 0.1%	
Van Saase (Van Saase et al., 1989) (6585 inhabitants of a Dutch village)	465 participants >60 yrs of age	Zoetermeer, Netherlands	60+ M+F	Hip	Radiographs	R : 10.1% (right) R : 10.7% (left) 60-64 yr	R : 3.8% (right) R : 3.8% (left) 60-64 yr	R- 7% (60-64) R – 15.4% (80+)

Table 2 Studies demonstrating prevalence of radiographic hip OA

Author	Sample size	Population studied	Age/ sex	Site of OA	Diagnostic method	Prevalence (Male)	Prevalence (Female)	Prevalence (total)
Jacobsen (Jacobsen et al., 2004) (3807 in whole study)	2344 participants >60 yrs of age	Copenhagen, Denmark	60+ M+F	Hip	Radiographs	R : 5.6-6.7% Bilateral : 3.1%	R : 3.0-3.3% Bilateral : 1%	
Odding (Odding et al., 1998)	2895	Rotterdam, Netherlands	55+ M+F	Hip	Radiographic + symptoms	R : 14.1% R+S : 2.2%	R : 15.9% R+S : 5.3%	
Ingvarsson (Ingvarsson et al., 1999)	1517	Iceland	35+ M+F	Hip	Radiographs (<2.5 mm)	R : 12%	R : 10%	R – 10.8%

R = radiographic hip OA; R+S = Radiographic and symptomatic hip OA

2.2.3 Studies estimating prevalence of hand OA

The prevalence of hand OA varied between studies and across joint sites as seen in Table 3. The DIP joint was found to have the highest prevalence of OA. Joints that were thought to go through higher mechanical forces among the Chinese (due to chopstick use) were found to have a higher prevalence of OA (Hunter et al., 2004).

Table 3 Studies demonstrating prevalence of radiographic hand OA

Author	**Sample size**	**Population studied**	**Age/ sex**	**Site of OA**	**Diagnostic method**	**Prevalence (Males)**	**Prevalence (Females)**	Prevalence
Acheson (Acheson et al., 1970)	1127	New Haven, Connecticut, USA	21+ M+F	Hand	Radiographs	Right index: DIP : 44.4% PIP : 7.4 % MCP : 16.0% CMC : 8.2%	Right index: DIP : 45.0% PIP :13.8 % MCP : 9.7% CMC : 10.1%	

Table 3 Studies demonstrating prevalence of radiographic hand OA

Author	**Sample size**	**Population studied**	**Age/ sex**	**Site of OA**	**Diagnostic method**	**Prevalence (Males)**	**Prevalence (Females)**	Prevalence
Niu (Niu et al., 2003)	976	Framingham, USA	71-99 yrs M+F	Hand	Radiographs + symptoms	Overall(R+S): DIPs: 2.9% PIPs: 2.5% MCPs: 0.1% CMCs: 2.7%	Overall(R+S): DIPs: 9.4% PIPs: 7.3% MCPs: 0.7% CMCs: 5.0%	Radiographic OA: Men – 22.1% Women – 32.7%
Wilder (Wilder et al., 2006)	3327	Florida, USA	40 + M+F	Index DIP, Middle PIP, 1st CMC	Radiographs	Index DIP : 35.1% Middle PIP :17.6% 1st CMC : 19.7%	Index DIP : 35.4% Middle PIP :18.5% 1st CMC : 20.9%	Index DIP – 35.3% Middle PIP – 18.2% 1st CMC – 20.5%

Table 3 Studies demonstrating prevalence of radiographic hand OA

Author	**Sample size**	**Population studied**	**Age/ sex**	**Site of OA**	**Diagnostic method**	**Prevalence (Males)**	**Prevalence (Females)**	Prevalence
Hunter (Hunter et al., 2004)	2507	Beijing, China	60 + M+F	Hand	Radiographs	Overall: DIP : 15.6% PIP : 7.0% CMC : 19.5%	Overall: DIP : 23.1% PIP : 13.4% CMC : 14.5%	
Egger (Egger et al., 1995)	967	Chingford, England	45-64 F	Hand (MCPs not included)	Radiographs		DIP : 14.4% PIP : 3.4% CMC :11.5%	

Table 3 Studies demonstrating prevalence of radiographic hand OA

Author	**Sample size**	**Population studied**	**Age/ sex**	**Site of OA**	**Diagnostic method**	**Prevalence (Males)**	**Prevalence (Females)**	Prevalence
Poole (Poole et al., 2003)	2986	National birth cohort, UK	53 yrs M+F	Hand (MCPs not included)	Clinical assessment	Overall: DIP : 14 % PIP : 8 % CMC : 4 %	Overall: DIP : 21 % PIP : 12 % CMC : 8%	Any joint: Men – 19% Women – 30%
Neame (Neame et al., 2004)	489	Nottingham, England (Hospital referred with OA in hand/other sites + siblings)	Mean age 66 yrs M+F	Hand (MCPs, 1st CMC not included)	Radiographs			DIP – 46.0% PIP – 17.2%

Table 3 Studies demonstrating prevalence of radiographic hand OA

Author	**Sample size**	**Population studied**	**Age/ sex**	**Site of OA**	**Diagnostic method**	**Prevalence (Males)**	**Prevalence (Females)**	Prevalence
Van Saase (Van Saase et al., 1989) (6585 inhabitants of a Dutch village)	465 participants >60 yrs of age	Zoetermeer, Netherlands	60+ M+F	Hand	Radiographs	1st CMC ≥20% MCP ≥40% PIP ≥20% DIP ≥50%	1st CMC ≥50% MCP ≥40% PIP ≥30% DIP ≥70%	Results of those >60 years of age are shown

DIP = Distal interphalangeal joint; PIP = Proximal interphalangeal joint; MCP = Metacarpophalangeal joint; CMC = Carpometacarpal joint

Epidemiological studies look to ascertain the causes and risk factors for OA. However, there have been many barriers to the epidemiological study of OA. The most significant problem was in defining OA cases. The three main domains of OA, namely pain, structural change and disability, have been interpreted differently in the epidemiological studies in the past. To add to this, there is significant discordance in the relationship between each of these domains (Hannan et al., 2000, Odding et al., 1998).

The next problem is that different joints need to be studied separately, as each joint shows different risk factor profiles and associations, which has led to the suggestion that they may represent different disease entities (Felson, 2010).

It has been suggested frequently in the past that the relationship between radiographic OA and symptoms has been weak(Dieppe, 2004, Hannan et al., 2000), probably due to the inability of radiographs to view soft tissue structures; but these differences could also be due to other patient factors like psycho-social environment and previous experiences. Nevertheless, a study of 745 participants from a community cohort in North Staffordshire, UK demonstrated a significant increase in the prevalence of radiographic arthritis with increasing duration of pain, severity of pain and stiffness as well as degree of disability as measured by the WOMAC tool (Duncan et al., 2007).

A more recent study by Neogi(Neogi et al., 2009) using a within person, knee matched, case control design, demonstrated excellent correlation between radiographic severity and severity of knee pain. If these results are in fact a true description of the association between imaging and symptoms, it can be expected that imaging modalities with a higher sensitivity, such as ultrasound, will correlate even better with symptoms and explain the mechanisms by which pain occurs; due to the ability to visualise structures like synovium, ligaments and meniscus, which may be responsible for some of the pain in OA.

It has therefore now been recognised that we require more sensitive outcome measures in order to produce meaningful results from prospective cohort studies. Magnetic Resonance imaging (MRI) and ultrasound imaging are gaining popularity in the assessment of OA, but these modalities require further prospective studies to establish construct validity with radiographs and symptoms.

2.3 Reliability and validity of the use of ultrasound imaging in OA

Ultrasound is non invasive, involves no radiation, is a dynamic evaluation and significantly easier and cheaper to use than MRI (Grassi et al., 2005). It allows for comparison with the opposite side and has been described as an extension of the clinical examination.

2.3.1 Ultrasound assessment of the knee:

Significant correlation has been seen between MRI and ultrasound imaging techniques for evaluating cartilage and soft tissue changes in patients with knee OA (Tarhan et al., 2003). Hyaline cartilage (McCune et al., 1990, Grassi et al., 1999) and menisci (Ko et al., 2007) of the osteoarthritic knee have been successfully visualised ultrasonographically, although doubt still remains as to its reliability, validity and response to change.

Ko et al (Ko et al., 2007) demonstrated a significantly higher grade of medial meniscal subluxation in patients with radiographic OA when compared to patients with painful knees without radiographic OA, in a cross sectional study. Furthermore, a higher degree of subluxation was seen with higher grades of radiographic OA, suggesting a strong association of medial meniscal subluxation with OA. Further longitudinal studies are required to assess the nature of this relationship of the meniscus to OA.

Naredo demonstrated excellent agreement between ultrasonographic and histological measurements of femoral cartilage thickness, with ICCs ranging from 0.73 to 0.88 (Naredo et al., 2009). The macroscopic anatomic findings from seven cadaveric knees were used as the comparator in this study. Since histological assessment is the gold standard for the measurement of cartilage thickness, ultrasound can be considered a highly valid tool for this purpose. In the same study, the ICCs for inter-rater reliability for ultrasound measurements of cartilage thickness ranged from 0.75 to 0.96. Martino et al also found significant correlation between ultrasound and histological measurements of femoral cartilage thickness in 18 patients with severe knee OA and 10 controls (Martino et al., 1993). Comparison of femoral cartilage thickness between ultrasound and MRI in a Danish study showed a Spearman correlation coefficient of 0.82 among 20 subjects with various arthritides, including OA (Ostergaard et al., 1995).

Ultrasound has been found to be more sensitive than clinical examination in detecting knee effusions in patients with rheumatoid arthritis (Kane et al., 2003). D'Agostino et al in their European League Against Rheumatism (EULAR) report, demonstrated that ultrasound prevalence of either synovitis or effusion was high at 47% in hospital outpatient subjects with symptomatic, primary, chronic knee OA, despite using quite strict definitions for the above two parameters (D'Agostino et al., 2005) A higher prevalence of effusions (70%) was detected in the study by Tarhan et al (Tarhan et al., 2003) but their definition of effusion and synovitis was >2mm compared to D'Agostino's definition of the same parameters as >4mm. The sensitivity of machines has been gradually improving over the years, which makes it difficult to compare studies using different machines. The EULAR group found no correlations between ultrasound inflammation and pain intensity, which suggests that non-synovial structures may also be implicated in the causation of pain in subjects with OA (D'Agostino et al., 2005). The main limitation to this study was that no attempt was made to assess inter observer reliability among the 29 ultrasonographers.

A recent paper by Iagnocco et al demonstrated a high prevalence of effusions (43%) among 82 patients with knee OA in Italy and also noted a high correlation between the

total ultrasound score and the Lequesne index (a validated measure of severity of knee OA) as well as the patient's global assessment of knee pain, providing further evidence of the construct validity of ultrasound in OA (Iagnocco et al., 2010)

Karim et al provided evidence for the validity and reliability of ultrasound in detecting synovitis in the knee, when compared with macroscopic arthroscopic findings, in patients with various arthritides. They also demonstrated higher accuracy when compared to clinical examination. However, while they used both a semi quantitative and dichotomous grading for synovitis, the presence or absence of synovial fluid was only stated as dichotomous. There was high intra and inter observer reliability using the dichotomous scale for presence or absence of synovitis and high intra observer reliability for the semi quantitative grading of synovitis (Karim et al., 2004). Lindblad et al demonstrated that arthroscopic and histologic evaluation of knee synovitis in OA is subject to the possibility of sampling error, since the synovitis in OA is more focal than in RA and more prominent in the juxtachondral areas (Linblad and Hedfors, 1987). Ultrasound imaging has the advantage of being able to sweep the probe across the entire surface of the joint, in real time and a three dimensional manner, while focussing on the area of interest.

2.3.2 Ultrasound assessment of the hip:

There is little evidence of the use of ultrasound imaging of the hip in OA, despite its important role in mobility. Qvistgaard et al (Qvistgaard et al., 2006) developed a semi-quantitative scoring system for ultrasound evaluation of hip OA and were able to demonstrate good intra-observer correlation (Interclass correlation coefficients [ICC] of 0.69 -0.80) and moderate inter-observer correlation between two observers (ICC of 0.45-0.65) for the parameters tested. Four parameters namely, osteophytes, femoral head score, effusion and synovial profile, were tested in 100 patients with radiographic hip OA

according to ACR criteria. In addition, a global osteoarthritis and synovitis score was also made. The bony parameters had slightly better correlation than those for soft tissue. The distribution of the frames that were chosen by the two observers in the study showed good concordance between them and a secondary analysis of the outliers showed changes of similar magnitude, which reduced concern about misinterpretation due to frame selection. It was the global osteoarthritis score that was most strongly associated with the patient's pain (VAS score), although the authors recognise that further studies need to be done to establish the validity of the score in clinical situations.

Atchia et al demonstrated that the training period required for a "trainee" with no previous experience in musculoskeletal ultrasound to obtain images of the hip, of a standard that was acceptable for routine clinical use, was remarkably low at 75 minutes (Atchia et al., 2007). The trainee was able to also demonstrate high inter-observer agreement with an expert (ICC 0.93, 95% CI 0.83 to 0.98) on the assessment of hip effusion in 17 subjects with hip OA. The trainee also achieved 96% accuracy in injecting the hip joint under ultrasound guidance, confirmed by radiopaque contrast. This suggests that regional ultrasound training for non-radiologists, of a limited number of joints looking for specific features, is certainly possible in a short span of time.

2.3.3 Ultrasound assessment of the hands:

Keen et al (Keen et al., 2008b) compared ultrasound and radiography in the assessment of OA of the hands, specifically comparing osteophytes and joint space narrowing (JSN). 1106 joints of the 37 subjects with clinical OA were imaged. Both osteophytes and JSN were detected more frequently by ultrasound than radiography. They further classified osteophytes as proximal or distal to the joint and found that ultrasound improved detection of osteophytes proximal to the joint when compared with radiography and suggested that radiography may underestimate the prevalence of proximal osteophytes. They also found a high prevalence of ultrasound detected osteophytes in the first and

second MCP joints. An arbitrary definition of JSN was made where it "appeared reduced" or "was assumed to be reduced due to overlying osteophytes". Erosions were not looked at and neither were synovitis or effusion.

Keen also went on to perform a case-control study (Keen et al., 2008c) on thirty six subjects with symptomatic radiographic OA (SOA group) and nineteen controls. The controls were recruited from rheumatology clinics and had other rheumatic complaints, not affecting the hands. This study looked not only at osteophytes and JSN, but also at gray-scale synovitis and Power Doppler signal. Semi quantitative scales based on the OMERACT definition and a previous paper by Keen (Keen et al., 2008a) were used to define gray scale synovitis (GS) and Power Doppler signal (PDS) respectively. The intra reader reliability for osteophytes (Kappa 0.83) and PDS (Kappa 0.87) was excellent, while it was also substantial for GS (Kappa 0.62) and JSN (Kappa 0.64). Joints that were reported as painful and those that were tender were found to have a higher prevalence of US pathology in all four domains. An interesting point to note is that there was a high prevalence of synovitis (GS) of ~45% in the cases but a significant proportion (~35%) of controls, albeit smaller, was also found to have synovitis. This high prevalence of synovitis in controls could have resulted from the fact that they were recruited from rheumatology clinics, which makes them more likely to have sub-clinical inflammatory disease. Another explanation would be that the semi quantitative scale that was used for GS was too sensitive. The lack of correlation between pain and AUSCAN sub-scales with ultrasound detected severity or extent in an individual subject was attributed to the possibility of other factors that may influence these outcomes, like mental state and socio-economic factors.

Iagnocco et al (Iagnocco et al., 2005b) investigated 110 female patients with clinical hand OA and divided them into two groups based on the presence or absence of erosions on conventional radiography (CR) - Erosive OA and Classical hand OA. Their findings suggest ultrasound is less sensitive than CR in detecting central erosions. They did not

look at marginal erosions which, it could be reasonably expected, may be picked up more often with ultrasound.

Chapter 3 Risk factors across the lifecourse & conceptual framework

Due to the differences in the risk factors, prevalence and clinical presentation of the individual joint regions affected by OA, epidemiologists have tended to look at each joint separately. The following sections (3.1 to 3.10) look at epidemiological studies of the hands, hips and knees, grouped together by individual and shared risk factors for the incidence and progression of OA.

3.1 Age

There is extensive evidence that increasing age is the greatest risk factor for the development of OA in susceptible joints (Anderson and Loeser, 2010). OA is known to be a multifactorial condition and the current concept is that ageing contributes to, but is not sufficient on its own, for the development of OA.

Epidemiological studies of knee OA have consistently demonstrated an increasing prevalence of OA with age. Data from the Framingham Osteoarthritis Study of 1424 participants aged more than 60 years, demonstrated that the prevalence of OA increased from 27.4% in those aged <70 to 43.7% in those aged ≥80 years old (Felson et al., 1987). Similarly, the prevalence of radiographic knee OA increased from 26.2% in those aged 55-64 to 49.9% in participants aged >75 years old, in the Johnston County Osteoarthritis project (Jordan et al., 2007). The prevalence of symptomatic knee OA increased from 16.3% to 32.8% in the same age groups in the Johnston County study. Data from the NHANES III survey also demonstrated a consistent increase in the prevalence of both radiographic and symptomatic knee OA in older age groups (Dillon et al., 2006). Similar increases in prevalence of OA with age has also been noted in the hips (Dagenais et al., 2009) and hand (Van Saase et al., 1989).

It is now clear that this relationship of OA to ageing is not a simple process of "wear and tear" over time, but in fact, a number of biological processes associated with ageing might in fact increase susceptibility to OA in older joints. Bone is one of the sites implicated in this process where an increase in bone turnover or local bone remodelling (potentially affected by ageing) might influence the progression of OA. Bone marrow lesions seen on MRI might represent these areas of remodelling and these lesions have been shown to be associated with increasing age (Baranyay et al., 2007) and knee pain (Felson et al., 2001). Changes in the hyaline cartilage have also been noted with age related senescence of the chondrocytes (Dai et al., 2006) and age related changes to cartilage matrix (DeGroot et al., 2004) which contribute to the development of OA. Other processes such as reduced muscle strength (Hurley, 1999) and reduced joint proprioception (Sharma, 1999) are known to be associated with ageing and to the incidence and progression of OA.

3.2 Gender

Women have been found to have a higher prevalence of radiographic and symptomatic OA in the hands and knees in previous epidemiological studies. A recent meta-analysis reported that males had significantly reduced rates of prevalent knee (RR 0.63, 95% CI 0.53, 0.75) and hand OA (RR 0.81, 95% CI 0.73, 0.90) but this gender difference was not seen at other joint sites (Srikanth et al., 2005). Males were also found to have decreased rates of incident OA at the knee (RR 0.55, 95% CI 0.32, 0.94) and hip (RR 0.64, 95% CI 0.48, 0.86) in the same meta-analysis.

It is thought that this sex difference seen in the prevalence and incidence of OA might be due to the effects of oestrogen. Oestrogen use has been associated with lower prevalence of knee (Hannan et al., 1990) and hip (Nevitt et al., 1996) OA in epidemiological studies. However, sex hormone levels (Sowers et al., 1996) and reproductive history (Samanta et al., 1993) did not appear to have an association with prevalent OA.

3.3 Obesity

Obesity has been considered to be one of the strongest risk factors, for OA, particularly of the hand (Carman et al., 1994) and the knee (Felson et al., 2000), but less strongly for the hip (Cooper et al., 1998).

A cross sectional study of the Chingford cohort of 1003 women aged 45 to 64, confirmed a strong association of obesity with radiographic knee OA when comparing the high and low tertile of BMI (age adjusted OR 6.17, 95% CI 3.26 to 11.71) and CMC joint OA (OR 1.71, 95% CI 1.05 to 2.78) and an insignificant association with DIP and PIP joint OA. The weight was calculated as BMI, but the authors also looked at body fat distribution by undertaking measurements of the hip, waist and thigh. They did not see an association between radiographic OA and body fat distribution (Hart and Spector, 1993b).

A case control study of men and women in the UK where the 611 cases were identified as subjects who were awaiting a hip arthroplasty, showed a positive association of obesity (BMI) with hip osteoarthritis. When comparing the highest to the lowest third of BMI categories, the odds ratio for radiographic hip OA was 1.7 (95% CI 1.3 to 2.4) which is not as high as seen in the knee, especially considering that this was a group of patients with severe disease. The risk was higher in obese subjects who also had heberden's nodes in the hands (OR 3.2, 95% CI 1.9 to 5.4) (Cooper et al., 1998).

The NHANES 1 case control study in 2490 subjects aged 55 – 74 years, did not find an association between radiographic hip OA and obesity, but there was however a near significant relationship of obesity with bilateral hip OA (Adjusted OR 2.00, 95% CI 0.97 to 4.15) (Tepper and Hochberg, 1993). A BMI threshold of 27.3 for females and 27.8 for males was used to define presence or absence of obesity in this study; this arbitrary cut off might have contributed to the lack of association of obesity with hip OA in this study.

Obesity was found to be significantly associated with radiographic and symptomatic knee OA in the Framingham study (Felson, 1990), more so in women than in men. For the heaviest fifth (crude weight) in this cohort of 1424 participants, the relative risk of severe radiographic OA was 1.86 for men and 3.16 for women, $p<0.01$ for both. This association remained significant even after controlling for potential confounders such as age, physical activity, presence of diabetes and uric acid levels.

The Rotterdam study prospectively followed 3585 men and women aged 55 years or more for a mean duration of 6.6 years, to look at the relationship of BMI to the incidence and progression of knee and hip OA (Reijman et al., 2007). Since both the joints were looked at in the same study, it eliminated the possibility of any difference being attributed to different study populations, study methodology or different definitions for radiographic OA. The results of this study showed that BMI >27.5 was associated with both incidence (OR 3.3, 95% CI 2.1 to 5.3) and progression (OR 3.2, 95% CI 1.1 to 9.7) of knee OA, but was not associated with the incidence or progression of hip OA. The possible reasons for this difference are discussed in Chapter 8 (Reijman et al., 2007).

A systematic review in 2002 which assessed the influence of obesity on the development of hip OA found moderate evidence for a positive association (Lievense et al., 2002). However, this was a synthesis of only 12 studies of which only one had a prospective cohort design (which was limited by hip OA being defined by self-report),while the remaining studies were small case-control and a few large cross-sectional studies.

Although there have been a number of studies that have shown no association between hip OA and obesity (Reijman et al., 2007, Sturmer et al., 2000, Tepper and Hochberg, 1993), there are a few that do show a positive association (Jarvholm et al., 2005,

Lohmander et al., 2009). Jarvholm et al studied 320,192 Swedish male construction workers to look at the association of bodyweight and the risk of severe OA in the hip and knee, which was defined as arthroplasty of the joint; this was traced by linkage with the Swedish hospital discharge register (Jarvholm et al., 2005). The participants were aged between 15 and 67 years, which made it a very heterogeneous age structure of the cohort. A baseline assessment obtained information on measured heights and weights. Participants were followed up for a period of about 12 years. BMI was found to a strong predictor for joint replacement in this study. After adjusting for age and smoking, the relative risk of knee OA was 0.50 (95% CI 0.19, 1.36), 2.39 (95% CI 1.93, 2.94) and 4.82 (95% CI 3.65, 6.38) in the BMI categories of 17-19, 25-29 and 30-35 respectively, in relation to the BMI 20-24 reference group. A similar but weaker association was seen in the hip with relative risks of 0.35 (95% CI 0.20, 0.61), 1.54 (95% CI 1.38, 1.72) and 2.02 (95% CI 1.68, 2.43) in the same BMI categories. This study was limited by the fact that it used arthroplasty as the definition of OA and included only male construction workers, who may have different levels of physical activity at work and for recreation. Physical activity was not measured and adjusted for in this study.

Another recent and large population based prospective cohort study in Sweden among 18000 participants (mean age 55 years), assessed the relationships between different measures of body mass and the incidence of knee and hip OA, defined as first arthroplasties or osteotomies identified by the Swedish hospital discharge register (Lohmander et al., 2009). BMI, waist circumference, waist-hip ratio, weight and percentage body fat (calculated by bioelectrical impedance method) were used as different measures of body mass at baseline and participants were followed up for a mean of 11 years. The relative risks of knee OA when comparing fourth to first quartiles were 8.1 (95% CI 5.3, 12.4) for BMI, 6.7 (95% CI 4.5, 9.9) for waist circumference, 6.5 (95% CI 4.6, 9.43) for weight, 3.6 (95% CI 2.6, 5.0) for percentage body fat and 2.2 (95% CI 1.7, 3.0) for waist-hip ratio. The relative risks of hip OA were also significant but less in magnitude than that in the knee. The fact that BMI had a much higher association with

knee and hip OA than measures of adiposity such as percentage body fat and waist-hip ratio, led the authors to conclude that biomechanics related to overweight might have a stronger impact than metabolic factors (which are closely related to measures such as percentage fat and waist-hip ratio) in the development of severe OA. They also felt that the lack of association between weight and OA of the hip in other studies might have been due to underpowered studies, since this study showed a small association among 18000 participants. This was a study that used the end point of arthroplasty for the definition of knee and hip OA, which might have the disadvantage of selection bias for surgery and the exclusion of less severe grades of OA.

The mechanism by which obesity is associated with OA is thought to be due to a combination of biomechanical factors as well as metabolic components related to adipose tissue, as described by Pottie et al (Pottie et al., 2006). Adipose tissue is known to be metabolically active and releases various chemokines such as leptin which may be involved in the pathogenesis of OA.

The role of mechanical overload on the joint has been suggested as one of the mechanisms by which obesity increases the risk of OA. The discovery of "mechanoreceptors" on the surface of chondrocytes has shown that compression and stretching forces can induce intra-cellular signalling cascades through these mechanoreceptors and eventually cause the release of various cytokines that could potentially influence matrix and cartilage structure and function (Pottie et al., 2006). Although both the knee and the hip have to withstand high mechanical loads during weight bearing tasks, the hip is constructed in a way that provides better stability and fewer demands on the capsule, ligaments, cartilage and muscles, when compared to the knee. This difference in the mechanical stresses around these two joints may explain the difference in the risk of obesity in causing OA at these two sites. Malalignment of the knee seems to be an especially strong factor involved in the progression of knee OA (Sharma and Chang, 2007).

However, systemic factors may well be involved as suggested by the relationship with hand OA (non weight bearing joints) and the strong association of obesity with bilateral joint OA (Hart and Spector, 1993b). The inverse relationship with osteoporosis (discussed in section 3.4), the unequal effect of obesity on knee and hip OA and the association with estrogens add further support to the notion that OA is influenced by systemic factors.

Adipose tissue contains adipocytes, which have a common mesenchymal stem cell precursor with osteoblasts, chondroblasts and myoblasts, which suggests a potential link between lipid metabolism and musculoskeletal disease. Adipocytes are also known to release various hormones like adiponectin and leptin. Leptin is a small polypeptide that regulates food intake and energy expenditure via its actions on the hypothalamus. Leptin deficient mice have been shown to have a high bone mass, despite the mice being hypogonadal, demonstrating its ability to inhibit bone formation (Ducy et al., 2000). Leptin expression has been shown to be upregulated in osteoarthritic cartilage, osteophytes and sub-chondral bone and this is also related to the grade of cartilage destruction, suggesting that it may be responsible for cartilage destruction. Although the ratio of leptin to adiponectin in the synovial fluid of OA subjects is higher than controls, the mechanisms for this finding have not been identified (Pottie et al., 2006). There certainly is a need to investigate the temporal relationship of these adipocytokines with OA, so as to explore the systemic and metabolic mechanisms by which obesity causes OA.

3.4 Bone density

Osteoarthritis and osteoporosis have long been thought to have an inverse relationship (Sowers et al., 1996, Hart et al., 1994). Cross-sectional studies have demonstrated a higher bone mineral density (BMD) in subjects with radiographic OA of the hand and knee (even after controlling for spinal osteophytes) (Hart et al., 1994) as well as hip OA (Nevitt et al., 1995) in women, when compared to subjects without OA at these joints. A prospective study of 473 elderly women in the Framingham cohort showed that higher bone density at the femoral neck increases the risk of incident knee OA (predominantly due to osteophytes) over an 8 year period, although this did not reach statistical significance (Zhang et al., 2000). The adjusted OR of incident OA for each quartile increase of BMD were 1.0, 2.5, 2.0 and 2.3 respectively ($p=0.222$). This study showed however, that a higher BMD was associated with a significantly ($p<0.001$) decreased likelihood of progression of existing knee OA (mainly due to decreased risk of joint space narrowing). Compared to the lowest quartile of BMD, adjusted OR for progressive OA were 0.3, 0.2 and 0.1 respectively.

The large MEDOS case-control study of 2816 patients in the Mediterranean region and 5369 age-matched controls, showed that previously diagnosed OA subjects were protected from femoral neck fracture, when compared to non OA subjects, among both men and women (Dequeker and Johnell, 1993). The age adjusted relative risk was 0.68 ($p<0.001$) and remained significant (0.74, $p<0.001$) after adjusting for BMI. The limitations of the study were that it defined OA based on self report of subjects from a questionnaire and there was lack of clarity as to how the cases of hip fracture were identified. Self reported OA could lead to errors in either direction as symptomatic

patients might not have imaging features of OA while participants without symptoms but imaging features of OA might have been missed as OA cases in this study.

A prospective study followed up 830 women (with a mean age of 54 years) over four years in the Chingford cohort (Hart et al., 2002) and reported a 70% reduction in the risk of developing incident knee OA, defined by osteophytes but not JSN, in those subjects who sustained a self-reported fracture at interview (OR 0.30, 95% CI 0.11 to 0.84). The fractures were unrelated to trauma and at any site; fracture information was collected at annual interviews from participants. There was no association of fractures with OA progression, although the numbers were small for this sub-group. A sub-analysis found a significant trend towards protection [OR 0.26, 95% CI 0.06-0.89] from incident knee osteophytes if the fracture was recent (during follow-up period), with this protection disappearing [OR 1.04, 95% CI 0.25-4.21] for fractures sustained in the 10 years before baseline. The data did not include drugs that patients were taking, which may have influenced the above results, as patients with older fractures were more likely to have had the influence of the "bone forming" effects of bisphosphonates. The study did however confirm the findings of the Framingham cohort by demonstrating a significantly higher baseline BMD in women with incident knee osteophytes. Contrary to the Framingham study, there was no association between BMD and progression of knee OA in the Chingford cohort. This may have been due to the shorter period of follow up in the Chingford cohort. A limitation in both the Framingham and Chingford cohorts is the radiographic protocol (knee in full extension), which is not as sensitive and accurate as the use of positioning frames or fluoroscopic techniques.

In the recent and large Multicentre Osteoarthritis study (Nevitt et al., 2010), 1754 subjects with a mean age of 63.2 years and a mean BMI of 29.9 kg/m^2 were followed up for 30 months, to look at the association of baseline whole body and high femoral neck BMD on the incidence and progression of radiographic knee OA. They found that subjects in the highest quartiles of BMD had ORs of 2.3 to 2.9 (significant CIs) compared

to the lowest quartile, of developing incident knee OA, defined by K-L score, osteophytes and JSN. They did not find a significant association of BMD with knee OA progression. The strengths of this study were that it had many subjects and also that there were a large number of them who had progressive OA. The use of a positioning frame for radiographs would have helped to increase the robustness of the data. However, an important point was that this was a selected group of participants who were selected because of their high risk of developing OA; this meant that they were more likely to be overweight, have knee pain, previous injury or surgery. Although BMI was adjusted for in the analysis, it may be possible that systemic factors (such as leptin and other adipocytokines) due to a high BMI could have affected the risk of incident and progressive OA (Sowers and Karvonen-Gutierrez, 2010). As strengths, the authors were able to adjust for potential confounders like physical activity, smoking, knee injury, quadriceps strength, bisphosphonate and oestrogen use.

An Australian study by Jones et al (Jones et al., 1995) reported no significant association between OA of any joint and subsequent fracture. This was a prospective study of 1753 men and women based in the community, aged over 60 who were followed up for 5 years. They found that there was an increase in the BMD in women with self-reported OA, but this did not translate into a reduced risk of fracture at any site. These findings led the authors to suggest that the OA subjects were more likely to fall, possibly due to postural instability, which would explain the lack of reduction in fracture rates in this group, despite a higher BMD. This study was again limited by the fact that OA was defined by self report and no radiographic data were available. A case-control study of 368 elderly men and women (mean age 82) did in fact find, that OA subjects were more likely to fall (OR 2.3, $p<0.003$), when compared to controls, after matching for their length of stay in the care home. The cases however, were also taking more medications and were more ambulatory than controls; hence these results might be an overestimate (Granek et al., 1987).

The prospective study by Arden et al in the Study of Osteoporotic Fractures, (Arden et al., 1999) showed a lack of association for OA of the hand or hip to subsequent vertebral or non-vertebral fractures in elderly women, despite BMD being 10% higher in women with hip OA than in those without. This was a large study of 5552 women with radiographic and self reported OA and although there was a low concordance between the two definitions, neither of the two definitions of OA were associated with fractures. They were able to demonstrate that self reported OA was associated with a 40-50% increased risk of falls but subjects with radiographic hip OA had a 30% reduced risk of falls. The difference remained even after controlling for exercise, muscle strength, use of sedatives, health status, visual acuity, walking aids and hip pain (other factors associated with falls). Previous studies reporting that radiographic hip OA was associated with a trend to decreased femoral neck fractures but increased inter-trochanteric fractures, led the authors to postulate that it is possible that radiographic OA, despite being associated with a reduced risk of falls, could adversely affect the type and the severity of falls sustained. One of the mechanisms suggested was decreased muscle strength and joint proprioception which could increase the proportion of falls leading to inter-trochanteric hip fractures. Differences in the quality of the bone, bone turnover and its micro-architecture may be another explanation for this lack of reduction in fracture risk, despite a high BMD.

The prospective Michigan Bone Health study of 482 women (aged 28-48 years) reported that women with radiographic knee and/or hand OA had lower bone turnover (measured by cross-sectional serum osteocalcin concentrations) than women without OA. In addition they also found that this turnover continued to remain low over a 3 year period, compared to subjects without OA; after adjusting for BMI, age, and injury. These findings in younger women, which contradict other studies involving older subjects, suggest that there is a possibility that bone turnover could vary depending on the stage and severity of OA (Sowers et al., 1999). The limitations of the study were that there were only a small number of incident cases of OA; serum (and not synovial) osteocalcin

was measured, which may be released into the serum by bone and other tissues and therefore may not be specific to the joint.

In summary, the results of the Framingham, Chingford and MOST studies suggest that higher femoral neck BMD is a predictor of incident knee OA but does not necessarily predict progression of existing knee OA.

3.5 Inflammation

The population based study of 662 men and women aged 45 years and above in the Johnston County OA project evaluated the association of high sensitivity CRP (hsCRP) with radiographic hip and knee OA and the applicability of hsCRP for CHD risk prediction. The authors found a strong correlation of hsCRP with all definitions of radiographic knee ($p<0.0001$) and hip OA ($p<0.05$) and found a linear increase with increased severity of OA and number of joints affected. For example, an increase in one K-L grade of knee OA resulted in an average increase of 1.10 mg/L hsCRP (range 0.54 to 1.54 mg/L change in hsCRP per K-L grade over the range of K-L grades 0 to 4). However, these relationships were no longer significant after controlling for BMI. There was no association between hsCRP and self-reported CHD or CHD risk. The authors point out the complex interaction of obesity, OA and inflammation. This cross sectional study was unable to tease out the relationship between hsCRP, OA and CHD but was able to inform us that interpretation of hsCRP for CHD risk can be confounded by variables like OA, race, lung disease, obesity and sex. It should however be noted that the authors did not have information about recent infections and exclude these patients from analyses (Kraus et al., 2007). Nevertheless, this suggests that any study attributing risk of a disease to CRP levels should ideally control for the above variables.

In a multi-centre hospital based longitudinal study, 422 patients with primary knee OA were followed for a period of one year, to assess the relationship of baseline synovitis (detected by arthroscopy) to the progression of medial cartilage damage (seen on arthroscopy**)** (Ayral et al., 2005). The mean age of the subjects was 61 years and they had been symptomatic for an average of four years. The study revealed that inflammatory changes in the medial perimeniscal synovium was associated with a significantly higher chance of developing medial cartilage damage on macroscopic evaluation via arthroscopy after a period of one year ($p<0.0001$). The OR for progression among those with an inflammatory synovium was 3.11 (95% CI 1.07 to 5.69) when compared to those without inflammation. Limitations to the study included the lack of data on intra and inter-observer reliability of synovial evaluation using arthroscopy in different centres. It should also be borne in mind that there was no adjustment for important confounding factors like the stage of disease and BMI. There was a higher prevalence of cartilage abnormalities at baseline in those subjects with synovial inflammation; the initial severity of cartilage disease would have further confounded this association. It should also be noted that this study only looked at a small portion of the cartilage and synovium in the medial compartment of the knee using arthroscopy without biopsy.

The use of C-reactive protein (CRP) as a bio-marker of incident knee OA was tested by Sowers et al (Sowers et al., 2002). A population sample of 1025 women with a mean age of 43 at baseline in Michigan, were followed up for 2.5 years. Prevalent and incident knee OA were defined by radiographs using K-L criteria, although a limiting factor was that no positioning frame was used to standardise image acquisition. CRP was measured using an ultra-sensitive rate immunonephelometry technique. In this relatively young cohort, mean CRP levels were found to be significantly higher (by a factor of more than two) in prevalent as well as incident OA participants ($p<0.0001$). However, CRP had a high correlation with BMI ($r=0.58$) and the association of CRP with increasing radiographic grades of OA severity, incident and prevalent OA was lost after controlling for BMI. This led the authors to suggest that the association of CRP with prevalent and

incident radiographic knee OA was probably mediated by BMI. Presence of inflammatory conditions or malignancies were not identified and controlled for, in the analysis.

In the study of 845 participants from the Chingford cohort, the longitudinal relation between CRP and progressive radiographic knee OA was observed (Spector et al., 1997a). The subjects were women aged between 44 to 67 years, who had radiographic assessment at baseline; 70 of the 105 women with prevalent OA had repeat radiographs after four years. Baseline CRP was assayed by an automated monoclonal antibody microparticle enzyme immunoassay method. In contrast to the Michigan study (Sowers et al., 2002), the authors reported a significant association of CRP with progressive knee OA in this cohort even after controlling for age, height, weight, smoking and knee pain. The median CRP was 2.6 mg/l (IQR 1.9 to 4.6) in the 31 subjects with progressive OA compared to 1.3 mg/l (IQR 0.6 to 2.4) in the 39 subjects without progression (p=0.006). The significance of this association persisted when radiographic disease was assessed by K-L criteria, osteophytes only or joint space narrowing only. The difference in this study when compared to that in Michigan was that this looked at progressive rather than incident knee OA. Furthermore, height and weight were controlled for separately in this study while BMI (as a binary variable) was used in the Michigan study; and the participants were older than in the Michigan cohort. This study suggests that low-grade inflammation is a predictor of progressive knee OA in four years time.

3.6 Achieved education level

A cross sectional study of 2572 men and women in Finland found higher mobility limitations in those with less educational attainment, than those with a higher level of education (Sainio et al., 2007). This was partly mediated by the presence of OA in the knee and hip. This study was limited by the fact that it did not use radiographic outcomes

to define OA at the joint sites; using clinical definitions by field doctors without calculating inter-rater reliability between observers.

A recent cross-sectional review of 2627 participants of the Johnston County Osteoarthritis project studied the association between educational attainment and prevalence of radiographic and symptomatic knee OA (Callahan et al., 2010). Educational attainment was dichotomised at the point of completion of high school at 12 years of age (<12 years vs. ≥12 years). Radiographic OA was defined as K-L score of ≥2 of the tibio-femoral joint, while symptomatic knee OA required the presence of pain, aching or stiffness on "most days" in addition to the radiographic definition above. The mean age of the sample was 61 years and 37% of women and 38 % of men were found to have low educational attainment. 29% had radiographic OA while 16% had symptomatic OA. The authors adjusted for risk factors such as BMI, age, race, knee injury, current smoking and current alcohol use and occupational factors. In women, there was a significant association of low educational attainment with radiographic OA with an OR of 2.30 (95% CI 1.84, 2.86) and this remained significant even after adjustment for lifestyle, clinical and occupational factors with an OR of 1.48 (95% CI 1.12, 1.96) in the fully adjusted model. In men however, although there was a significant association in the unadjusted model (OR 1.65; 95% CI 1.25, 2.17), the association was explained by age and race. There was a significant association of low educational attainment with symptomatic knee OA in both the sexes with an OR of 1.86 (95% CI 1.20, 2.87) in men and 1.64 (95% CI 1.16, 2.31) in women, in the fully adjusted models. Current HRT use in the sub-set of post-menopausal women was found to be protective for radiographic knee OA with an OR of 0.58 (95% CI 0.41, 0.83). An important characteristic of this sample is that there is a high proportion of African-American participants accounting to nearly one-third of the cohort. African-American participants are likely to have differences in diet and physical activity leading to alterations in the manner in which achieved education level might affect the risk of OA.

The only other study that measured the association of educational status with radiographic knee OA was the NHANES I survey (Hannan et al., 1992). This was also a cross-sectional study which found that in men and women, symptomatic knee OA was significantly associated with low educational status, even after controlling for known risk factors. However, the association with radiographic knee OA lost its significance after controlling for risk factors such as age, race, obesity, knee injury and occupation.

3.7 Smoking

An early analysis from the Framingham Osteoarthritis study identified risk factors for knee OA; it had the advantage of having followed up patients from an early age, at which the prevalence of OA was likely to be minimal (Felson, 1990). They found that smoking had a protective effect that was found to be significant even after controlling for age, sex, physical activity, knee injury history, weight change since the first examination and alcohol consumption. After these adjustments, the OR for OA in smokers was 0.74 ($p<0.05$).

A study of 320,192 Swedish male construction workers assessed the relationship of smoking habits and the risk of severe OA in the hip and knee, which was defined as arthroplasty of the joint; this was traced by linkage with the Swedish hospital discharge register (Jarvholm et al., 2005). A baseline assessment obtained information on smoking habits and participants were followed up for a period of about 12 years. Smoking was shown to have a protective effect on hip OA after adjusting for age and BMI. The relative risk for non smokers when compared to current smokers was 1.37 (95% CI 1.22, 1.54). However this protective effect of smoking did not extend to the knee joint which showed no significant difference between non smokers and current smokers. The mechanism for the association between smoking and OA has not been explored in any detail to date.

3.8 Physical activity

The association of physical activity and OA has been studied often but the direction of this association has often been difficult to ascertain. Physical activity can broadly be divided in to occupational physical activity, which one would expect to increase load on the joints and recreational physical activity which would be expected to protect joints, if done in a controlled manner.

Occupational physical activity

The relationship between physical activity and OA is still currently far from clear. An initial analysis from the Framingham Osteoarthritis study assessed the risk factors for knee OA (Felson, 1990). Patients were followed from an early age and hence the authors made the reasonable assumption that information on the risk factors was likely to have been collected prior to the onset of OA. This is necessary to consider as the possibility of reverse causation remains; i.e. prevalent OA could lead to decreased levels of physical activity. They found a strong association between radiographic knee OA and knee-bending jobs in both men (OR 6.0, $p<0.05$) and women (OR 12.0, $p<0.05$), which lends credibility to the theory of mechanical stress being a risk factor. However, the classification of knee bending jobs was not clear, there could have been recall and misclassification bias and the time spent in these jobs was not ascertained, making the interpretation of these results difficult. The results did however confirm the association that was found previously by the NHANES 1 survey (Anderson and Felson, 1988). The NHANES 1 survey split the knee bending demand of a job and the "strength" demand of a job in to three categories each. The authors reported an association of self reported knee OA in the 55-64 year age group with knee-bending demands in men (OR 2.45 per category; 95% CI 1.21,4.97) and in women (OR 3.49 per category; 95% CI 1.22,10.52) and "strength" demands in women (OR 3.13 per category; 95% CI 1.04, 9.39) but not in men (OR 1.88 per category; 95% CI 0.88, 3.99).

A subsequent longitudinal study of participants from the Framingham cohort with a mean age of 70.1 years at baseline followed up 470 men and women over a period of about 9

years (McAlindon et al., 1999). Physical activity was measured using the "Framingham Physical Activity index" which is a measure of metabolic work in a usual day. The activities were divided into classes namely heavy, moderate and light and the number of hours of each class of activity per day was recorded. One of the limitations was that this information was only collected at one time point; this was between 3 and 4 years after the baseline radiographs, which weakens the interpretation of this longitudinal data. As a strength, this study was able to perform radiographs at the start and end of the long follow up period. It demonstrated that heavy physical activity (>4 hours a day) was associated with an OR of 7.2 (95% CI 2.5 to 21) for incident radiographic knee OA, compared to those performing no heavy physical activity at all. Among those performing three or more hours of heavy physical work per day, the risk of incident OA was higher in individuals in the highest tertile of BMI (OR 13.0, 95% CI 3.3 to 51) compared to those in the lowest tertile for BMI (OR 2.1, 95% CI 0.5 to 9.7). It was also interesting to note that the results remained significant even after adjusting for knee injury and for unemployment (suggesting that physical activity outside of normal employment is also a risk factor for incident OA).

1410 participants of the Framingham study were assessed to delineate the association of habitual physical activity with radiographic knee OA (Hannan et al., 1993). Knee OA was defined radiologically using the Kellgren and Lawrence criteria. Physical activity was measured by weighting and adding the number of hours of reported daily physical activity of different intensities. Data on physical activity had been collected about 30 years and 12 years prior to the baseline radiographs and the average of these values were taken and divided into quartiles for the analysis. After adjustment for age, BMI, previous knee injury, high school education (yes, no) and cigarette use, there was no positive association between habitual physical activity and knee OA. Physical capacity measures such as Forced Expiratory Volume in the first second (FEV1) and resting pulse rate also showed no significant association. Interestingly, men in the highest quartile of physical activity had a higher rate of osteophytes (but not in OA); this feature was not seen in

women. The difference between the sexes might have been due to the fact that men had on average, higher levels of physical activity. The authors surmised that high levels of physical activity might induce osteophytes at joint margins which are the sites of traction of ligaments and tendons. The other possibility stated by them was that osteophytes develop to provide joint stability in the larger male knee, which is more likely to be overused. The difference in this study when compared to previous studies of the Framingham cohort looking at the association of physical activity with knee OA is that this study looked at habitual physical activity and not at specific occupational activities. The authors felt that certain occupational activities might increase the overload on the knees specifically but habitual activities were not knee specific and therefore did not confer a risk of increased knee OA. It should be remembered that the measure of physical activity that was used in this study (24 hour weighted score) was different to those in other studies. However, the likelihood of misclassification is unlikely to be any more than any other method of calculation.

Rossignol et al performed a study in France to look at the association between occupational exposure and OA of the hand, knee and hip (Rossignol et al., 2005). The cases of OA were identified by 1394 different physicians and this is a significant limitation of the study, since there was no effort made to check the reliability of these diagnoses between observers, although they state that 90.7% of patients had the diagnosis confirmed on radiographs. The strength was that this study was large with 2834 patients. In addition to their longest held occupation, the participants also reported on whether they had to perform the following five biomechanical stresses in their entire professional lives: lift heavy objects, keep affected joint in uncomfortable positions, work with vibrating tools/vehicles, repeat movements continuously and work at a pace set by a machine. While an uncomfortable position of the affected joint had an OR of 2.5 (95% CI 1.6 to 4.1) in those with knee and hip OA, repetitive movements and working at machine pace were associated with hand OA; the relationship being stronger in women (OR 3.6, 95% CI 2.4 to 5.7) than in men (OR 1.5, 95% CI 0.9 to 2.5). Female cleaners were found to have an OR of 6.2 for OA (in all three sites) when compared to the "expected" value. This was in part explained by the exposure to "uncomfortable positions" in this group,

but this was not sufficient to explain the magnitude of this association. The higher prevalence of hand OA in the self employed when compared to salaried persons made the authors postulate that better regulations of working hours and similar factors may help decrease the likelihood of hand OA among the salaried workers. Masons and construction workers were found to have the highest prevalence among males, once again showing a higher prevalence among self employed when compared to salaried workers. The authors queried whether a lack of variety of tasks among the self employed led to greater repetitive stresses to the joints involved, although this hypothesis has not been tested yet.

A systematic review by Jensen in 2008 highlighted the difficulties in analysing the relationship between occupational activity and hip OA. The main problem was that the definitions of OA that were used in the various studies were extremely heterogeneous, using multiple radiographic and symptom definitions. The next issue was the measurement of the exposure variable, which is a difficult area to standardise since there is a wide variation in the amount and duration of exposure in different occupations, often with a long duration between the onset of the exposure and onset of OA. The results were then adjusted for potential confounders such as BMI and trauma. Despite these limitations, it is interesting to note that the majority of studies did show a significantly increased risk of hip OA in subjects who did jobs involved with heavy lifting and in farmers. There was no information as to whether there was an added risk associated with kneeling or squatting with the heavy lifting. The author also stated the need to identify pathophysiological mechanisms leading to the development of OA (Jensen, 2008).

Recreational physical activity

A retrospective case control study of 216 cases and 864 controls looked to assess the potential association between self-reported “recreational” physical activity and self reported knee OA; this was an analysis from the Allied Dunbar National Fitness Survey in England (Sutton et al., 2001). Physical activity was graded into three groups based on

the likelihood of each activity to increase the quadriceps strength; this was decided by a consensus of seven physiotherapists. The outcome was self reported OA, which had a relatively "loose" definition. In this study, no association was seen between any of the grades of reported recreational physical activity and self reported knee OA. This may be a true result, but may have also resulted from the lack of validated tools for assessment of physical activity, lack of radiographic outcome data and lack of information on work related physical activity. The authors themselves state that it has been previously found that high work related physical activity can be associated with low participation in recreational physical activities, therefore acting as a confounder that was not measured in this study. Knee injuries were found to have a six fold increase in risk of OA, but recall bias is a likely problem here with the use of only self report to diagnose OA, since it is likely that those with symptoms are more likely to remember previous knee injuries.

The definition of physical activity has been poor and variable in most studies that have looked at this risk factor. A longitudinal study of 224 women from a population based cohort in Melbourne, simply asked the participants to state how often they "participated in physical activities or sports for recreational or fitness purposes" (Szoeke et al., 2006). The participants had a mean age of 49.7 at baseline and were followed up for 11 years. There was no association of recreational physical activity with radiographic hand OA, but found an OR of 10.1 ($p<0.03$) among those who exercised daily at ages 20-29 compared to those who did not exercise, for radiographic knee OA (radiographs only performed at 11 year follow up). This study was significantly limited by a very broad definition of physical activity. The lack of association in the other age groups is difficult to explain. The authors surmised that structured team physical activities are more likely to be remembered by participants at a later stage, but this theory should have meant that an association should have also been found in the 9-19 year age group when it is likely that they participated in school sports programmes, which was not the case. An interesting point from this study, was that compared to baseline, the participants were more likely to report exercising frequently at the 11^{th} year follow up. This could be due to the fact that

they many were in the retirement age group at follow up and therefore have more time for leisure activity but this could also reflect the changing trends regarding the benefits of exercise, over time.

Panush and Holtz, in their review of the relationship between exercise and arthritis summarised that the balance of evidence suggested that running was not associated with a higher risk of lower limb OA (Panush and Holtz, 1994). They hypothesised that putting a joint through its normal range of movement on a regular basis was not necessarily a risk factor for subsequent OA, although the evidence for this still remains controversial. It is possible that this association between exercise and OA is a U shaped curve where either excess activity or too little activity could lead to increased OA, while normal levels of activity might be protective. The inability to adequately classify different forms of activity and quantify them appropriately for epidemiological purposes has meant that the relationship between physical activity and OA is still open to debate.

A study of 2049 male athletes and 1403 controls in Finland demonstrated that athletes from different types of competitive sports were all at a higher risk of OA of the lower limb joints requiring hospitalisation, when compared to controls (Kujala et al., 1994). The study was performed by comparing the incidence of admissions to hospital for OA of the hip, knee and ankle between the athletes and the controls, from a national database. Athletes involved in endurance sports had an OR of 1.73 (95% CI 0.99 to 3.01) for OA admissions to hospital, OR in mixed sports athletes was 1.90 (95% CI 1.24 to 2.92) and 2.17 (95% CI 1.41 to 3.32) in power sports athletes. Endurance athletes tended to have a later age of onset of hospitalisations, which was thought to be in part due to their lower BMI and physically active lifestyle. Results from questionnaire data on the same group showed that over 60% of athletes engaged in regular recreational physical activity throughout life compared to only 17% of controls. It may have therefore been possible that the athletes were more likely to seek hospital help in order to be able to continue their greater activity level.

A case control study of 970 subjects in Tehran, Iran, assessed the relation between life-long daily activities, occupations, sports and clinical knee OA defined by the ACR criteria (Dahaghin et al., 2009). 480 cases (mean age of 57 years) were randomly selected from 1532 participants with clinical knee OA, who had already been identified from 50 clusters in Tehran, as part of a larger study. 490 controls were selected by matching for age decade, sex and region (therefore matched for socio-economic class). Occupations since leaving school were categorised into three groups: sedentary work, laborious jobs and housewives (among women). Sports activities performed for at least 6 months were recorded and collapsed in to four categories: running/jogging, fitness/body-building, football/volleyball and other sports. Life-long daily activities performed for at least one year were ascertained by trained interviewers using a standardised questionnaire. Generalised estimating equation technique was used to account for the correlation between both knees but also to calculate the contribution of each knee as a unit of analysis. After adjusting for age, sex and BMI, the two activities that were significantly associated with clinical knee OA were prolonged (>30 minutes) squatting (OR 1.51; 95% CI 1.12, 2.04) and prolonged (>30 minutes) cycling (OR 2.06; 95% CI 1.23, 3.45) when compared to those who performed these activities for <30 minutes a day. Knee bending activities (>30 minutes) showed a near significant relationship with an adjusted OR of 1.98 (95% CI 0.98, 3.99). Knee bending was only reported by a few participants and this might have led to the lack of statistical significance in this study. The odds of a housewife having knee OA was 1.68 (95% CI 0.93, 3.03) when compared to women who did not work. The authors felt that technological advances leading to reduced strain in performing household tasks might have diluted the effect of housework on clinical knee OA. Heavy lifting was not associated with knee OA, which was hypothesised to be due to the fact that there were hardly any high rise buildings in Tehran at the time of the study and therefore it was unlikely that any of the participants lived in a multi storey building. Being in a laborious or a sedentary job did not seem to affect the risk for developing knee OA; further adjustment for knee injuries did not change the results either. None of the sports categories showed a significant relationship with knee OA but this is probably due

to the very broad categories that were used in the study which were unlikely to detect any definite associations between specific sports and knee OA.

Physical activity and weight gain

Physical activity might exert its influence on the prevalence and incidence of OA by its confounding effect on an important risk factor for OA, namely obesity.

There is evidence that physical activity can modulate changes in weight from various prospective studies. A ten year follow-up of 5115 mean and women aged 18-30 years at baseline demonstrated that decreasing levels of physical activity was associated with higher levels of weight gain (Schmitz et al., 2000). A small study involving 97 members (aged 3-5 years) of the Framingham Children's Study examined the longitudinal relationship between preschool physical activity (measured with an electronic motion sensor) and change in body fatness (measuring the slopes of triceps and subscapular skinfolds and BMI) (Moore et al., 1995). Inactive preschoolers had a relative risk of 3.8 (1.4-10.6) when compared to their active counterparts to having an increase in the triceps slope (as opposed to a stable or decreased slope) over the follow up period, after controlling for age, television viewing, energy intake, baseline triceps and parents BMI. A large study of the Growing Up Today cohort followed 11887 boys and girls aged 10-15 years for a period of one year (Berkey et al., 2003). An increase in physical activity over the course of the year was associated with reducing BMI in girls (-0.06 kg/m^2 per hour increase in daily activity; CI: -0.11, -0.01) and in overweight boys (-0.22 kg/m^2; CI: -0.33, -0.10). An increase in inactivity was associated with increasing BMI in girls (+0.05 kg/m^2 per hour increase in daily TV/videos/video games; CI: +0.02, +0.08). However, these prospective studies were able to only look at specific time-periods in the participants' life, while the risk of accumulation of these exposures over the lifecourse into late adult life has yet to be determined.

We know that the association of physical activity and obesity is bi-directional. A prospective study followed 1213 black girls and 1166 white girls in America for a period of eight years during the adolescent period (Kimm et al., 2002). Black girls were found to have a 100 percent drop in leisure-time physical activity between the ages of 9-10 to 18-19 years ($p<0.001$). Similarly, white girls also showed a significant drop in activity during this period of 64 percent ($p<0.001$). Baseline BMI ($p=0.05$) was associated with decline in physical activity among white girls. The habitual activity questionnaire was used as the instrument to measure leisure time physical activity, in addition to the sports activities in school. This instrument does not take into account the duration of activities.

In summary, excessive physical activity appears to have a consistent association with OA. However, the possibility of a bidirectional association exists and further research is needed to elucidate the magnitude of each of these directions of associations. Also, it is important to consider the confounding effect of obesity in this relationship.

3.9 Diet

A prospective analysis of participants (without knee OA) from the Melbourne Collaborative Cohort Study analysed the relationship of dietary intake of anti-oxidants on knee cartilage and bone parameters (Wang et al., 2007). The participants were aged between 50 and 79 years and did not have ACR defined knee OA at baseline. They had an MRI at baseline and 2 years later. A limitation of the study was that the questionnaire data were collected ten years prior to the baseline assessment and it is possible that the dietary patterns of the participants might have changed in that time. A total of 293 participants were analysed and it was found that vitamin C and fruit intake were inversely associated with bone marrow lesions and tibial plateau bone area. For every standard deviation increase in vitamin C intake, the OR for bone marrow lesions was 0.50 (95% CI 0.29, 0.87) and the regression co-efficient for reduced tibial plateau bone area was -

35.5 (95% CI -68.8, -2.3; p=0.04). The corresponding values for increase in one serving per day for fruit intake were OR 0.72 (95% CI 0.52, 0.99) for bone marrow lesions and regression co-efficient of -27.8 (95% CI -54.9, -0.7, p=0.04). No association was seen between vitamin C and fruit intake with cartilage volume or cartilage defects. Intake of vitamin E had the opposite (detrimental) effect where a positive association was found with tibial plateau bone area, after adjusting for vitamin C intake. The carotenoids, lutein and zeaxanthin, were associated with decreased risk of cartilage defects (OR 0.71 per standard deviation increase; 95% CI 0.51, 0.99). This suggests that the effect of vitamin C and fruit intake might be through effects on bone rather than cartilage. The fact that vitamin E had an adverse effect on tibial bone area suggests that the anti-oxidant effect might not be the important mechanism in this situation, as both vitamin C and E had anti-oxidant properties but very different effects on bone.

An analysis of the same participants from the Melbourne Collaborative Cohort Study looked at the relationship of fatty acid intake with subsequent development of bone marrow lesions on MRI (Wang et al., 2009a). Fatty acid intakes were derived from a food frequency questionnaire using Australian food composition data and were adjusted for energy intake. The dietary intake was ascertained ten years prior to the collection of the MRI of the knees for features of OA. Higher intake of saturated fatty acids was associated with a significant increased risk of developing bone marrow lesions after adjusting for energy intake. For each SD increase in intake of saturated fatty acids, the odds of developing bone marrow lesions over two years was 2.62 (95% CI 1.11, 6.17). The results were similar after adjusting for age, gender and BMI. A previous cross sectional study on the same cohort had demonstrated that high intakes of monounsaturated and n-6 rather than n-3 polyunsaturated fatty acids were associated with higher levels of bone marrow lesions (Wang et al., 2008). However, the intake of fatty acids was unrelated to cartilage volume and cartilage defects.

The Framingham study demonstrated the association of antioxidant nutrient intake with incident and progressive radiographic knee OA (McAlindon et al., 1996b). 640

participants were included in the analysis. Radiographs were obtained at baseline and at follow up about eight years after, while dietary intake was obtained using a validated food frequency questionnaire about five years after the baseline radiographs. Supplement use was calculated and adjusted for in the analysis. The multivariate analysis was also adjusted for age, sex, BMI, level of physical activity and total energy intake. No association was seen between any of the antioxidant nutrients and incident knee OA. However, there was found to be a significant reduction in the risk of progressive knee OA in the middle tertile (OR = 0.32, 95% CI 0.14, 0.77) and the highest tertile (OR=0.26, 95% CI 0.11, 0.61) of vitamin C intake, which was found to be mainly due to reduced risk of joint space loss. Beta carotene was found to be associated with a reduced risk of progressive knee OA with an OR of 0.42 (95% CI 0.19, 0.94) in the highest intake tertile. Other nutrients such as vitamin E, B1, B6, niacin and folate did not have any association with incident or progressive knee OA. This study used radiographic knee OA using the Kellgren and Lawrence system of analysis as the outcome which is different to the MRI based outcomes of the Melbourne study. It should also be noted that the nutrient intake in this study was analysed in tertiles and this might have led to insufficient variability of specific nutrient intake and reduced sensitivity of different diets. There were a number of non-responders in this sample and they were found to be older and less active than the participants and therefore likely to have poorer nutrient intakes and higher incidence and prevalence of OA. This might have led the results to move closer towards the null.

Vitamin D and OA

Bischoff-Ferrari et al found that there was a positive association of serum 25-Hydoxyvitamin D level and bone density in 228 members of the Framingham cohort (Bischoff-Ferrari et al., 2005). The mean age of the participants was 74.4 years; vitamin D replete subjects had an 8.5% higher BMD when compared to those with vitamin D deficiency (p=0.02). The role of vitamin D and it's relationship with knee(McAlindon et al., 1996a) and hip(Lane et al., 1999) OA has been studied previously.

In the study of osteoporotic fractures(Lane et al., 1999), 237 women with a mean age of 70 were followed for an average of eight years. Subjects in the lowest tertile of 25 (OH) vitamin D levels had an OR of 3.34 (95% CI 1.13 to 9.86) for incident radiographic hip OA, when compared to the highest tertile. The radiographic definition above was characterised by JSN; however, there was no association of vitamin D levels to incident osteophyte growth at the hip. Progression of hip OA was not assessed in this study.

The Rotterdam study of 1248 men and women aged more than 55 years at baseline, looked to assess the relationship of vitamin D intake and serum levels with the subsequent incidence and progression of radiographic knee OA (Bergink et al., 2009). The participants were followed up for a mean of 6.5 years. The vitamin D intake was measured at baseline using a validated food frequency questionnaire and was adjusted for calorific intake. The Vitamin D levels were also adjusted for time of season. The limitation to the study was that duration and amount of sunlight exposure could not be determined and use of vitamin D supplementation was not ascertained. However, the results were adjusted for a variety of important confounding factors including age, sex, baseline JSN, BMI and health status. Those in the lowest tertile of vitamin D intake had an OR of 7.7 (95% CI 1.3 to 45) for knee OA progression; there was no relation of vitamin D intake to the incidence of knee OA. Similarly, those in the lowest tertile of vitamin D serum levels had a crude OR of 2.9 (95% CI 1.0 to 8.3) for knee OA progression, but this association lost significance after adjustment of the above confounders. The authors were surprised however to find that adjustment for bone mineral density did not change any of the risk estimates of vitamin D intake or serum levels for the incidence and progression of knee OA. They suggested that the above relationship of low vitamin D intake and progression of OA was mediated through mechanisms other than bone density. A hypothesis proposed by the authors was that decreased vitamin D led to increased parathyroid hormone release, causing increased bone turnover which is known to be associated with knee OA (Hunter et al., 2003).

The Framingham study also found a similar association of vitamin D status with knee OA progression (McAlindon et al., 1996a). 126 OA knees and 788 normal knees were included in this analysis, where vitamin D intake and serum levels were collected in a similar manner to the Rotterdam study; the follow up period being 8.5 years. Those in the lowest tertile of vitamin D intake had an OR of 4.05 (95% CI 1.40 to 11.6) for progression of radiographic knee OA when compared to the highest tertile; similarly those in the lowest tertile of serum vitamin D levels (compared to highest) had an OR of 2.89 (95% CI 1.01 to 8.25) for knee OA progression. Low serum vitamin D level also predicted loss of joint space on radiographs where the OR for lower to upper tertile was 2.3 (95% CI 0.9 to 5.5) and increased osteophytes, OR 3.1 (95% CI 1.3 to 7.5). No such association of vitamin D intake or serum levels were noticed for incidence of radiographic knee OA in this study. The association between vitamin D intake and serum levels of vitamin D was moderate ($r = 0.24$, $p<0.001$). The strength of this study was that it adjusted for important confounders such as age, sex, BMI, physical activity, knee injury and health status. They were also able to ascertain the use of vitamin D supplementation by the participants. An attempt was made to control for sunlight exposure by asking the participants about the number of months they spent in a "Sunbelt state" each year. The authors noted that there was no significant alteration of the results even after adjusting for Vitamin D supplement use, Vit C intake and also bone mineral density. The limitation to this study was that the numbers were fewer than the Rotterdam study and that the serum levels of vitamin D were taken at the mid point of follow up, which could potentially affect the magnitude of the observed association in either direction.

In contrast, a recent study by Felson et al using MRI showed no association between vitamin D status and cartilage or joint space loss in knee OA (Felson et al., 2007a). This study followed two cohorts namely the Framingham offspring cohort of 715 subjects (mean age 53.1 years) and the Boston Osteoarthritis of the Knee Study, which had 215 subjects with pre-existing OA (mean age 66.2 years). The Framingham cohort had

baseline and follow up radiographs (mean interval of 9 years) using fluoroscopic positioning, while serum vitamin D levels were checked at the mid point of follow up. The lack of baseline bloods is a limitation as it means that the lack of association found in this study may have been due to taking the blood samples at a later stage of the follow up. The participants of the Boston cohort also had MRI of the knees (at baseline and at 15 and 30 months) which evaluated cartilage loss in a semi-quantitative manner. The results showed that there was no association of vitamin D levels with worsening of radiographic OA in either cohort and to cartilage loss on MRI in the Boston cohort. Surprisingly, there was a modest but insignificant protective effect of the lowest tertile of serum levels of vitamin D (compared to the highest tertile) for joint space loss in both cohorts and a similar pattern for cartilage loss in the Boston cohort. This study did not calculate vitamin D intake which was found to have a stronger association than serum levels in the Rotterdam (Bergink et al., 2009) and the Framingham (McAlindon et al., 1996a) studies. The authors argued that the original Framingham cohort had not used fluoroscopic positioning which makes interpretation of joint space loss over time more difficult to interpret reliably. Furthermore, the radiographs in this study were read without blinding for sequence, which the authors' state is a more accurate method of assessing progression. The small numbers and the young age of the offspring cohort could have also decreased the power of the study, but the narrow confidence intervals suggest that this may not be a big limitation to the study. It is also important to note that there was selective inclusion into the study of only 715 of the original 1200 subjects from the Framingham offspring cohort, as only 715 of these subjects had their vitamin D status measured; which could have influenced the association in either direction. This study did not look at osteophyte progression on MRI or radiographs; while both the Framingham and the Rotterdam studies had looked at the global K-L scoring as the outcome measure. It is entirely possible that the main action of vitamin D is to produce its effects on the bone (rather than cartilage), as evidenced by the twin study by Hunter et al (Hunter et al., 2003). For these reasons, this isolated lack of association of vitamin D status with knee OA progression should not be presumed to be a true one yet, until further studies have looked at both cartilage as well as bone parameters of imaging.

3.10 Barker hypothesis

It was the geographical distribution of coronary heart disease (CHD) and its close association with that of infant mortality in paralleled previous years, early in the 20th century in England and Wales which provided the first indication that there may be a relation between impaired foetal growth and CHD, since infant mortality was regarded as an index of deprivation at the time (Barker and Osmond, 1986). Forsdahl suggested that poor standards of living and nutritional deprivation in childhood were related to arteriosclerotic heart disease (Forsdahl, 1977). Adverse effects of maternal nutrition and lactation due to lower socioeconomic status, was identified as the main cause for differences in neonatal mortality rates in Britain (Woolf, 1947).

This and similar such findings led Barker to suggest the hypothesis that "poor nutrition" to the foetus during critical periods of development, as manifest in patterns of foetal and infant growth, can permanently "program" the body's structure and function (Barker, 1998). He proposed that individuals with low birth weight, poor nutrition and growth in infancy, are more likely to develop certain illnesses such as coronary heart disease, stroke and non-insulin dependant diabetes. This was in line with animal studies, which showed the "programming" of similar outcomes. Snoek et al demonstrated that rat foetuses that were under-fed protein, had a long term reduction in the number of pancreatic cells and also in insulin secretion (Snoek et al., 1990). Japanese physiologists gave further credence to this idea by demonstrating that the number of functioning sweat glands was "programmed" and was subject to change depending on the temperature to which a child was exposed during the first 3 years of life, but thereafter remained constant (Diamond, 1991). These findings led to the idea that there was a "critical period" in the various systems in the body, where they are subject to change and any insult during this period could lead to permanent damage. Furthermore, since there was no increase in the number

of cells after this period, this would result in a fixed functional capacity after the critical period (Barker, 1998). It is therefore important, in the context of chronic disease, to separate the effects of exposure on structure from the effects on function.

The association of small birth size with adult impaired glucose tolerance led Hales and Barker to propose the "thrifty phenotype" hypothesis (Hales and Barker, 1992). This hypothesis states that a poorly nourished foetus has the need to be nutritionally thrifty and therefore develops insulin resistance and deficiency which then leads to subsequent disease in adulthood.

~~Barker studied 449 men and women born in hospital in Preston during 1935-43 and calculated the association between birth and placental weight with blood pressure at age 46 to 54 years . Both systolic and diastolic blood pressures were found to be related strongly to both birth and placental weights. Mean systolic pressure was found to increase by 15 mm as placental weight increased from <1 lb to >1.5 lbs with an OR of 3.0 (95% CI 0.8, 11.3) and fell by 11mm as birth weight increased from <5.5 lbs to >7.5 lbs. The above relations were independent of each other and of other confounders such as BMI, alcohol intake and social class at birth and adulthood. The length of gestation did not have any significant effect on systolic or diastolic blood pressure.~~

~~Barker further studied the same cohort in Preston to look at the association of other anthropometric measures at birth with blood pressure at age 50 . They identified 327 men and women who were born after 38 weeks gestation. They analysed the above relations within two groups of placental weight, with an arbitrary cut-off of 1.25 lbs. This categorisation into two groups of placental weight was done because the authors had noted a strong positive association of birth weight, length and head circumference with placental weight. They found that in persons with a placental weight of 1.25 lbs or less, mean blood pressure rose by 13 mm Hg as ponderal index fell from >14.75 to 12 or less~~

(p=0.0001). Mean blood pressure increased 14 mm Hg as head circumference to length ratio increased from <0.65 to 0.7 or more, in those with placental weights above 1.25 lbs (p=0.02). Barker deduced that this study identified two groups of babies with high risk of hypertension at age 50. The first group had low placental weights with low ponderal indices (thin), low birth weight and head circumference but increased length. The second group had high placental weights, were short in relation to head size, with higher birth weight and head circumference and below average length.

A study by Barker's team of 239 men from Preston (born between 1935-43) and 845 men from Hertfordshire (born between 1920-30) assessed the relationship of waist to hip ratio (a measure of abdominal fatness) in adulthood to fetal and infant growth . They found that after controlling for adult BMI, there was an inverse association of adult waist to hip ratio with birth weight in both cohorts: regression coefficient of -0.56 (95% CI -1.12, 0.00) for Preston and -0.29 (95% CI -0.52, -0.05) for Hertfordshire. They also found that this association was independent of the duration of gestation and hence argued that this might be due to reduced fetal growth. They also noticed that the waist to hip ratio increased with increased placental weight to birth weight ratio, although this association did not reach significance: regression coefficient of 1.76 (95% CI -0.73, 4.24) in the Preston cohort. According to the authors, this provided further evidence for proof of the fetal under-nutrition theory, since high placental weight to birth weight ratio is considered to be a feature of fetal growth failure.

As can be seen from the above studies, Barker's team tended to perform studies in small cohorts with the view to assess correlations between variables, but tended to extrapolate a lot when making further hypotheses. For example, Barker's team studied 63 primigravid women in Southampton to assess the relation between fetal heart rate in early and late pregnancy and various anthropometric measures at birth . They only found an association of fetal heart rate at 18 weeks of gestation (but not at 36 weeks) with the measures of ponderal index, head circumference and birth weight. This was partly explained by shorter

~~gestational periods in the babies with higher heart rates; but the authors assumed that the remaining association was due to retarded fetal growth. There was a lack of association of fetal heart rate with placental weight and placental: birth weight ratio, which would go against the fetal under-nutrition hypothesis; but this, was not mentioned in the discussion. Instead the authors focussed on the limited explanation of gestation on the relation between fetal heart rate and head circumference and assumed that the remaining association must be due to growth retardation.~~

Huxley et al had reported in a systematic review in 2000 that birth weight and head circumference at birth are both inversely related to systolic blood pressure, after adjustment for current weight (Huxley et al., 2000). This review involved 80 studies from all over the world, including a total of 440,000 participants. However, the size of the effect was extremely small; approximately 2mm Hg fall in blood pressure per kg increase in birth weight while it was about 0.5mm Hg with each cm increase in head circumference. There was no association of ponderal index and birth length with systolic blood pressure; while there was no "consistent" relationship with gestational age, placental weight or placental: birth weight ratio. This contradicts many of the associations seen in Barker's studies and goes against the foetal under-nutrition hypothesis. They showed a consistent positive association of catch-up growth with subsequent blood pressure, although it was not possible to ascertain whether this was independent of pre-natal growth since birth weight was always used in the calculations for post-natal catch up growth. A recent analysis of the Thousand Families cohort demonstrated that the effect of birth weight on adult systolic blood pressure was small and far less significant, when compared to the effect of modifiable factors in adulthood such as BMI (Mann et al., 2011).

Barker showed a direct association between foetal size and hypertension (Barker et al., 1990) but needed to adjust for adult weight to show this association with diabetes (Fall et al., 1998b). Adjusting for current size or weight was found to be necessary according to

Barker and his colleagues, since current size has been found to be positively associated with birth weight and may well be related to the outcome of interest. However, there has been uncertainty as to whether the relation between adult health outcomes and birth weight is significant without this adjustment for current size. The notion that adult health could be related to postnatal changes in body size, rather than foetal size, is therefore perfectly plausible.

Lucas et al (Lucas et al., 1999) describe the lack of clarity in the justification and interpretation for adjusting for current size, in studies looking at the association between birth weight and various health outcomes. The authors highlight the flaws in statistical interpretation of such study results. They propose the notion that if size in early life is related to an outcome in adulthood only after adjustment for current size, it is this change in size between the two time points (the centile crossing of size of the child/adult for the particular age) that should be implicated, rather than foetal factors alone. While it is important to control for anthropometric measures at various stages in the lifecourse, it is also imperative that these results are interpreted appropriately. Although early life may be the "critical" period for the observed outcome, it should be acknowledged that any stage in life between the periods of change in size may be responsible for the outcome. The authors go on to recommend the use of 4 different regression models, which would help to tease out the relationship between exposures in the different life-stages and the final outcome.

~~Another study measured deprivation in adulthood in Scotland, England and Wales and demonstrated that this measure was strongly associated with mortality from all causes. They found that the effect of deprivation and affluence on mortality was much more significant than the effect of social class. (Carstairs and Morris, 1989). Ben Shlomo looked to clarify the issue of whether it was deprivation in adult life or as a child that had a greater influence on mortality. His study measured the past infant mortality rates with contemporary causes of adult mortality and adjusted for social class and social deprivation~~

~~at the time of their death. Although the correlation between infant and adult mortality was high, this association was significantly attenuated after controlling for contemporary social circumstances (Ben-Shlomo and Smith, 1991). This contradicted Barker's theory which stated that it was factors in early life that had a significant impact on adult CHD risk and the authors argued that this was because Barker had not controlled for the confounding effect of adult deprivation. It helped confirm the findings of Williams et al who found a correlation between CHD mortality and contemporary infant mortality and also found that the rank order of counties by infant mortality rate had not changed significantly between around 1900 to 1970 (Williams et al., 1979).~~

A study of 1500 members of the Hertfordshire cohort born in the 1930's demonstrated an independent association of birth weight and weight at one year with bone mineral content in men and women in their seventh decade of life (Dennison et al., 2005). 18% of the overall variance of bone mineral content in the proximal femoral bone area was explained by a model including birth weight (2.8%), weight at one year (6.8%) and adult weight (8.2%) in men. In women, a similar model produced values of 6.7%, 4.2% and 3.9%; producing an overall variance of 15% in proximal femoral bone area. However, the relationship between early life factors and bone density were found to be insignificant in this study which led the authors to hypothesise that lifestyle and genetic factors might be more important determinants of age related bone loss than early life factors. The authors addressed the issue of selection bias in this cohort by demonstrating that the weights at birth and one year of those who did participate did not differ significantly from those who did not. Similarly, at the adult stage, they noted no differences in anthropometric measures, cigarette and alcohol consumption, or physical activity levels in those who did or did not elect to have a bone density assessment.

In a recent analysis of a small proportion of the Hertfordshire cohort including 99 men, those with low birth weight were found to have significantly lower muscle fibre scores ($p=0.04$, unadjusted) on vastus lateralis muscle biopsy at age 72 years (Patel et al., 2012).

This association was found to be attenuated after adjustment for current age, height and physical activity (p=0.09). There was a trend towards reduced total type 1 (slow twitch) and type 2 (fast twitch) fibre densities in men with lower birth weight (≤3.18 kg) when compared to those with higher birth weight (≥3.63 kg), although this did not reach statistical significance. The type 1 (4903 vs 4644 μm^2) and type 2 fibres (4046 vs 3859 μm^2) were larger in those with low birth weight individuals, but this association was also statistically insignificant. Weakness of the quadriceps is a recognised association in subjects with knee OA. The quadriceps specific torque (a measure of muscle quality) was significantly reduced in knee OA subjects with a mean age of 73 years when compared to those without knee OA, even after adjustment for knee pain (1.92 vs 2.02 strength per unit area of quadriceps; p=0.002) (Conroy et al., 2012).

A large study involving 6370 women born in Helsinki, Finland looked to assess the influence of early life anthropometry on hip fractures in adulthood (Javaid et al., 2011). 49 hip fractures were identified through the National Finnish Hospital discharge register, over 187,238 person years of follow up. A decline in Z scores for BMI between the ages of 1 and 12 years was associated with an increased risk of hip fractures. Women in the lowest quartile of change in BMI Z scores had an OR of 8.2 (95% CI 1.9, 35) when compared to those in the highest quartile. This study suggested that it is the rate of change of BMI in childhood rather than the absolute BMI at a particular age that was the main determinant of later hip fractures. The mechanism for this association might be due to differences in timing of puberty or due to slowing of growth due to other environmental insults but is eventually likely to reflect the effect of low fat mass on bone mineralisation.

Limitations of Barker's hypothesis

While Barkers' work has been very useful in addressing a very important public health issue, there has been significant discussion and critique of his studies and hypothesis.

1. Selection bias: Paneth and Susser provided arguments to question the validity of two studies performed by Barker and his colleagues to test his hypothesis. For example, they pointed out that there may well be a significant selection bias in the Hertfordshire cohort, since they tested only a small proportion of the original birth cohort (Paneth and Susser, 1995). However, in defence of the hypothesis, further studies involving a larger proportion of the Hertfordshire Cohort born in the 1930's showed similar results to that of the earlier studies by Barker's team (Dennison et al., 2005).

2. Lack of adjustment for potential confounders: Paneth and Susser also stated the importance of smoking in the mother as being a key factor in determining birth weight as well as smoking in the offspring and therefore, also of CHD. Maternal smoking was not assessed in Barker's studies. They felt that the social status of the subjects throughout the lifecourse and that of their parents could have been important confounders that were not addressed by Barker (Paneth and Susser, 1995).

Indeed, analyses of the Thousand Families cohort found that while birth weight had a weak inverse relationship with insulin resistance at age 50 (using the homeostasis model assessment of insulin resistance) in men on univariate analysis (co-efficient -0.12 per standard deviation increase; 95% CI -0.22, -0.02), this association did not retain significance after adjusting for factors in adulthood such as percent body fat (Pearce et al., 2006). Furthermore, birth weight did not predict insulin secretion at age 50 in men or women in this study.

3. Use of proxy measure for foetal nutrition: Another limitation with these studies is that infant anthropometry was taken as a surrogate measure for foetal nutrition, but it would have been ideal to actually calculate maternal nutrition itself (Paneth and Susser, 1995). This is a valid argument against the Barker hypothesis, which is strengthened by the results of a study which showed that even extremes of nutritional

intake and childhood growth, in pre-term babies, had no significant effect on blood pressure at 8 years of age (Lucas and Morley, 1994). Walker and Walker provided evidence to suggest that maternal nutrition was not even really a significant factor influencing foetal growth, in western countries (Walker and Walker, 1993).

Infant weight and growth have been used as proxy measures by Barker and his colleagues, as markers of foetal and infant nutrition, respectively. Although Barker felt that proxy measures are only likely to weaken any associations (Barker, 1998), it could be argued that this is likely to depend on the variables, outcome and hypothesis being studied. Actual dietary intake and the effects of dietary manipulation need to be studied to further consolidate this hypothesis.

A study of subjects exposed to the Dutch famine concluded that prenatal exposure to the famine, especially in mid to late gestation, was associated with poor glucose tolerance in adults, even after controlling for adult SES, smoking status, maternal age and parity. There was a small decrease in birth weight among the exposed compared to the non-exposed subjects, but the difference in the two hour glucose and insulin concentrations was much higher, which led the authors to state that poor nutrition in utero may lead to permanent changes in glucose metabolism, even if the effect on birth weight was small. This study was limited by the fact that the actual nutritional intake of the mothers was not known as there were other sources of food available at the time in addition to the official rations. It is therefore possible that factors operating at the time of the famine other than nutritional intake, were responsible for this effect, although the likelihood of any such significant factor, is difficult to imagine (Ravelli et al., 1998). It was interesting to note Lumey's reservations on the presentation of results of the above study. He states that the initial hypothesis had "early to mid gestation" as the time period where nutrition was expected to increase the risk of blood pressure. He also suggested that the exposure groups in the study differed from previous studies of the same cohort and expressed

concerns that the authors were aiming to obtain results which fit their hypothesis (Lumey, 2001).

4. Lack of coherence among studies: There have been many studies that do not support the views of the foetal origins hypothesis (Matthes et al., 1994, Lucas and Morley, 1994, Williams et al., 1992, Lamont et al., 2000) and some that come to the entirely opposite conclusion (Ben-Shlomo and Smith, 1991). A study of 8495 Danish twins born between 1870 and 1900 and followed up till 1991, demonstrated that the mortality between twins (as a whole) and the general population after the age of six, was not significantly different (Christensen et al., 1995). They also reported that the difference in mortality between monozygotic and dizygotic twins, after age six, was not significant. Since it is known that twins, and in particular monozygotic twins, undergo more growth retardation than singletons, the result of this study goes against Barker's hypothesis as you would have expected monozygotic twins to have a particularly high mortality risk, considering their significantly reduced intra-uterine growth compared to dizygotic twins. A limitation to this study was that it assessed only one third of all twin pairs, in those twins that survived to age 6. The resulting selection bias might have potentially resulted in the lack of difference in mortality between the groups.

This lack of coherence among studies also provides evidence that the relationship is not as simple as described by Barker and the hypothesis therefore needs further investigation with lifecourse studies that have more detailed information on the risk factors across the different life stages. However, in defence of the Barker hypothesis, other large cohorts such as the Helsinki cohort of 6370 women born between 1934 and 1944, have also shown the detrimental effect of low birth weight and other childhood anthropometric

measures on the risk of fractures (Javaid et al., 2011) and intake of food and macronutrients in adulthood (Perala et al., 2012).

5. Publication bias: Huxley et al showed that the association between birth weight and subsequent blood pressure was significantly over-estimated, due to biases in reporting (Huxley et al., 2002). They noticed that the adjustment for current weight may have exaggerated the association, along with the failure to adjust for potential confounders such as parental and current socioeconomic status, parental blood pressure, alcohol consumption, race and gestational age. This analysis of the association between birth weight and subsequent blood pressure suggested that there was a clear trend towards weaker associations in larger studies when compared to the smaller ones. In particular, there was a significantly higher association seen in the studies done by the team that generated the fetal origin hypothesis, when compared to the remaining studies. They highlighted that this was a result of publication bias, driven by the trend to report extreme results. They also demonstrated that there was no clear evidence of amplification of the association with increasing age (Huxley et al., 2002).

Life course analysis

Kuh and Ben-Shlomo identified the need for a lifecourse approach to chronic disease aetiology which would take into account, the information from various stages in a person's life, so as to provide estimates of the proportion of risk that exposures acting at each stage of life, bring (Kuh and Ben-Shlomo, 2004). This does not just mean the collection of exposure data across the whole lifecourse and multivariate analysis being performed, but requires a temporal relationship to be defined between the exposure variables and their direct and indirect relationships with the final outcome measure. This would require understanding in the natural course and physiological trajectory of systems, like the joints, bone, muscle, etc. The authors explain the importance of constructing a

conceptual life course model in a lifecourse study, which would vary, depending on the exposures, the individual's response to these exposures, the outcomes being used and the question that is asked.

Kuh and Ben- Shlomo identified four models to explain the ways in which exposures act over the life course to affect disease risk (Kuh and Ben-Shlomo, 2004). The "critical period model" is when an exposure acts during a specific time period that has long lasting effects on later disease risk and is not modified by any later experience. This was used to explain the "fetal origins of adult disease" hypothesis. The second model called the "critical period model with later effect modifiers" allows for factors in later life to interact with exposures in early life to increase or decrease the likelihood of the chronic disease in adulthood. The "accumulation of risk" model suggests that the risk of chronic disease is gradually accumulated over the life course; with cumulative damage as the frequency, duration and severity of exposures increase. A "chain of risk" or "pathway" model refers to a sequence of linked exposures that ultimately results in increased disease risk, due to one exposure leading to the next. They explain that these models are not mutually exclusive and can act together at the same time. There are limitations in trying to distinguish between these models and to find appropriate methods to combine cumulative exposures.

3.11 Early life factors and Osteoarthritis

There is very limited research on the relationship between early life factors and OA in adulthood. However, certain studies have explored the relationship between potential risk factors for OA such as birth weight, socio-economic status and duration of breast feeding

with outcomes such as obesity, inflammatory markers and bone density in adulthood, which are known to affect the subsequent incidence and progression of OA.

3.11.1 Birth weight and subsequent health

There have been only two previous studies that have looked at the association of birth weight with OA in adulthood. However, both of these studies had significant limitations as described below.

A longitudinal birth cohort study of 2986 subjects aged 53 in the UK, suggested that there was an inverse association between birth weight and clinical hand OA in men; men with a birth weight <3100 grams had an 80% increased risk of hand OA at age 53 ($p=0.004$). However, there was no such relationship of birth weight and hand OA in women (Aihie Sayer et al., 2003). This relationship was independent of adult weight, height and social class; although a higher adult weight further increased prevalence of hand OA in men. The reason for this sex difference is not known and might be due to the propensity for male foetuses to be at higher risk of joint damage in early life due to their faster intra-uterine growth rates. As limitations, the study did not use radiographs as the outcome measure and the clinical assessments were performed by nurses without documentation of inter-rater reliability results. The numbers of symptomatic OA patients were too few to gain meaningful results.

In the study of a large cohort of 4008 British female twins, there was no influence of birth weight on the future development of radiographic OA in women (Antoniades et al., 2003) while it showed a clear association of birth weight with BMD and BMC. Twins who were

discordant for radiographic OA at the knees, hips and hands were found to have no evidence of significant intra-pair differences in birth weight, using matched logistic regression. However, there were significant positive associations of intra-pair differences in bone mineral content and bone mineral density at the spine, hip and fore-arm with intra-pair differences in birth weight in this study. A strength of this twin study is that it controls for the potential confounding of genetic and shared early life factors. However, the birth weight in this study was self reported and therefore subject to the possibility of recall bias. This analysis was restricted to females only. Furthermore, the participants were twins, who might have a different risk for adult disease from low birth weight when compared to singleton babies.

Both of the above studies did not have exposure data of the subjects during childhood and subsequent years when it is possible that a significant number of confounders could have been acting, to influence the prevalence of OA as an adult.

Other studies have studied the association of birth weight with outcomes such as BMD (Gale et al., 2001), obesity (Kuh et al., 2002b) and muscle strength (Aihie Sayer et al., 2004), which might influence the development and progression of OA.

A small study of 143 men and women in Sheffield aged 70 to 75 years, demonstrated significant ($p<0.01$) positive associations between birth weight and adult whole body, bone and lean mass, as measured by DEXA scanning (Gale et al., 2001). It also showed significant ($p<0.03$) associations of birth weight and bone mineral content at the lumbar spine and femoral neck. The associations for lean mass and bone mineral content were significant even after controlling for smoking, alcohol intake, calcium intake and physical activity. The association of birth weight with fat mass was weak and insignificant, which led the authors to hypothesise that these different tissues may have differential intra-uterine metabolic programming, due to the effects of early nutrition. However, it is also

entirely possible that the differences noted above could result from different environmental risks during adult life, which were not ascertained in this study.

The MRC birth cohort study of 1589 men and 1585 women (60% of the original cohort) who were born in 1946 in England, Scotland and Wales looked to examine the relationship of abdominal obesity to birth weight, childhood growth and socio-economic circumstances over the lifetime (Kuh et al., 2002b). The authors found a small inverse effect of birth weight on waist-hip ratio ($p=0.037$) in women after adjustment for current BMI; there was however no effect of birth weight on waist circumference. A limitation of this analysis is that adjustment for current BMI when waist-hip ratio is the outcome is not necessarily appropriate, since BMI does not confound the relationship, but is actually very similar to (i.e. measures a construct very similar to) the waist-hip ratio. Nevertheless, this lack of association with waist circumference suggested that women of low birth weight were more likely to have a smaller pelvis (hip circumference) than higher abdominal obesity. Relative weight (weight expressed as a percentage of standard weight for age, height and sex in this general population sample) at age seven was inversely related to waist-hip ratio and waist circumference in men ($p<0.001$) and waist circumference in women ($p=0.007$) after adjusting for adult BMI. The stronger impact of childhood relative weight compared with birth weight on waist-hip ratio in men and on waist circumference in men and women suggests that it is post-natal growth that has a greater effect on abdominal obesity than factors acting at birth. It was observed that the risk of adult abdominal obesity was high in those who had a low birth weight and remained light in childhood; there was no variation in the effect of childhood relative weight on adult waist-hip ratio or waist circumference across the birth categories, which suggests that the link between decreased childhood growth and adult abdominal obesity is independent of foetal growth. These relationships were found to be independent of childhood socio-economic circumstances. The lack of an association between social position and abdominal obesity was in contrast to the general view that there is an inverse association between the two in both men and women (Brunner et al., 1998).

A prospective study of 10683 participants from the 1958 British birth cohort (Parsons et al., 2001) examined the relationship between birth weight and BMI at age 33. BMI was also calculated at the ages of 7, 11, 16, 23 and 33 years. There was a weak and positive relationship (with a J shaped curve) between birth weight and adult BMI in men and women, which disappeared after adjustment for maternal weight. The relation between birth weight and adult BMI was unaffected however, by gestational age, the mother's height, age, parity, smoking habits and father's weight or social class (defined as father's occupational class at birth). Fetal growth, which was estimated by relating parental body size with birth weight, was found to have no relation to obesity in adulthood. Participants who achieved a higher percentage of their adult height by the age of seven, tended to have both a higher birth weight and an increased risk of obesity at age 33. This effect of childhood growth was more distinct among men than women and especially among men with low birth weight. This relationship of childhood growth and adult obesity, in men, also varied with maternal weight where members with lighter mothers (and faster childhood growth) were found to be at increased risk of obesity in adulthood. In summary, maternal weight explained the (weak) positive association between birth weight and adult BMI, suggesting that intergenerational associations exist; fetal growth was unlikely to explain this association of birth weight and subsequent obesity. It should be noted that this cohort had a high mean birth weight of 3380 grams (males) and 3250 grams (females). They were born 11 years after the Thousand Families Cohort, by which time the socio-economic conditions had improved considerably in the United Kingdom. The feeding habits are also likely to have been significantly different as there were no restrictions imposed on this cohort.

A longitudinal study of 6280 men and women from the northern Finland birth cohort evaluated the association between BMI at age 31 and social class in early childhood (based on father's occupation and its prestige), maternal BMI, BMI at birth and ages 1, 14 and 31 (Laitinen et al., 2001). A limitation was that 30 percent of participants in the study

had self-reported their BMI at age 31, which might have led to misclassification bias. In contrast to the 1958 British birth cohort study, the Finnish study reported a significantly lower BMI at age one and 31 in the higher social classes; while the BMI was significantly higher among the higher social classes at birth. This effect was seen in both men and women. However, similar to the 1958 British birth cohort, they reported higher levels of overweight and obesity at age 31, in members who had mothers who were overweight or obese ($p<0.001$). They also found that BMI at age 14 was a better predictor of obesity at age 31, than BMI at birth or age one. The use of BMI is considered by some to be an inappropriate measure of body fatness in infancy; weight or waist circumference might have been better ways of measuring fatness at these early ages. Early menarche was also associated with higher BMI at ages 14 and 31, while there was no association of age at menarche with BMI at birth and age one.

854 men and women aged between 21 to 29 years in America had their case records examined to ascertain the relationship of obesity as a young adult to obesity in various stages in childhood as well as parental obesity (Whitaker et al., 1997). The participants in the study were selected because they had attended the out patient department of the hospital and this could have introduced selection bias by including a higher proportion of either unhealthy or "health seeking" participants. Obesity was defined as being between 85^{th} to 95^{th} percentiles of age-adjusted weight, while very obese was defined as 95^{th} percentile or more. After adjustment for parental obesity, the OR for obesity as adult versus childhood obesity was 1.3 (95% CI 0.6, 3.0) at 1-2 years of age and 17.5 (95% CI 7.7, 39.5) at 15-17 years of age. The results suggested that there was tracking of obesity in childhood after the age of three years (regardless of parental obesity), but obese children under three years of non-obese parents, are at low risk of obesity in childhood. After adjustment for childhood obesity, OR for obesity as adults with one obese parent versus none was 3.2 (95% CI 1.8, 5.7) at 1-2 years and 2.2 (95% CI 1.1, 4.3) at 15-17 years. This parental risk transfer to the offspring may be mediated through genes or through behaviours learned across the life course. Limitations to this study included the potential

for selection bias of the participants as described above and a lack of information on important confounders such as physical activity, diet and SES across the life course. The heights and weights were collected as routine clinical information and the possibility of measurement error is much higher when using different instruments without any attempt to calibrate them. The definition of obesity used 85th percentile of age-adjusted weight as the cut-off; this has varied between studies.

The predictors of postnatal catch-up growth from birth to two years and its relation to obesity and size at age five was evaluated among 848 children in the Avon longitudinal study in Bristol (Ong et al., 2000). The authors reported that the children who showed catch-up growth were lighter, shorter and thinner at birth than those who showed no change or catch-down growth. Catch-up growth in this period was also associated with taller fathers, low maternal birth weight, maternal smoking and primiparous pregnancy. However, there was no association with maternal height or BMI. Furthermore, these children were found to be heavier and taller at age five and had higher measures of fatness (BMI, percentage body fat and waist circumference), even after adjustment for breast or bottle feeding. The authors postulate that this catch-up growth is due to foetal growth restraint, which in turn may be influenced by maternal and paternal genetic traits. The maternal diets in this cohort were likely to have been adequate and it was unlikely that there was any significant difference in the incidence of hypertension or other illnesses among the mothers as the population was recruited from healthy singletons at full term. Socioeconomic factors can also be expected to play a significant part in this association, which was not measured in this study.

Aihie Sayer et al conducted a study to look at the association of birth weight, weight at one year and infant growth (independent of birth weight) with grip strength adjusted for adult height, in 730 men and 673 women from the Hertfordshire cohort, who had a mean

age of 65 years (Aihie Sayer et al., 2004). They adjusted for certain confounders such as age, current physical activity, adult social class and smoking, but were unable to measure confounders such as SES at birth and childhood, other illnesses in childhood and physical activity in earlier years. They found that birth weight was associated with height adjusted grip strength (p=0.001 in men; p=0.03 in women). Weight at one year was associated with height adjusted grip strength only in men (p=0.02); this was a weaker association than that seen with birth weight. No significant association was seen between infant growth and adult grip strength in this cohort. None of the confounding factors above seemed to change the effect of the associations seen. The authors concluded that there was a strong relation of birth weight with adult grip strength; while the weak relation of weight at one year of age was probably only due to the strength of effect of birth weight with grip strength. This is an interesting result which seems to suggest that early life factors (possibly prenatal) are strong predictors of future muscle strength. However, due to the lack of sufficient information on other early life confounders as detailed above, the underlying pathways of this association between birth weight and grip strength require further evaluation.

The MRC Birth Cohort Study looked at the association of birth weight, growth at various stages in early life, cognitive ability at age eight and motor development milestones in infancy with adult grip strength in 2815 men and 2547 women, aged 53 years (Kuh et al., 2006). Growth was divided in to pre-pubertal (0-7 years), pubertal (7-15 years) and adult (15-53 years) growth. The results were adjusted for the potential confounders of current physical activity, lifetime SES and "health status" at age 53. They found that birth weight (adjusted regression co-efficient = 0.67; 95% CI 0.17, 1.18) and pre-pubertal weight gain (adjusted regression co-efficient = 0.93, 95% CI 0.19, 1.68) were associated with adult grip strength (in both sexes), conditional on later weight and height gain, but independent of other determinants of grip strength. In men only, pubertal weight gain was associated with grip strength (adjusted regression co-efficient =2.05; 95% CI 1.11, 2.99) while in women only pubertal height gain was associated with grip strength (adjusted regression

co-efficient =1.74; 95% CI 0.98, 2.49). This difference in the sexes at puberty was thought to be due to either the male sex hormone effects on muscle mass and strength or the differences in the ratio of lean to fat mass between the sexes. Boys gain less fat at puberty than girls and so weight is likely to be a better predictor of muscle mass in boys than in girls. Early motor milestones predicted higher grip strength, but this association was lost after adjusting for weight gain over the lifecourse.

Kuh et al examined the relation between birth weight and hand grip strength in a prospective national birth cohort of 1371 men and 1404 women aged 53 (Kuh et al., 2002a). They found a significant ($p = 0.006$ for men and $p = 0.01$ for women) positive association between birth weight and grip strength even after adjusting for variables such as social class and heights and weights in childhood and adulthood. The authors state that a potential mechanism for this observation was that birth weight is related to the number of muscle fibres established at birth and any compensatory hypertrophy in middle age may be insufficient to maintain strength.

This was similar to the results of the Hertfordshire cohort study (Aihie Sayer et al., 1998) which also found an association of birth weight and weight at 1 year, with adult grip strength, after adjustment for age, sex and adult height and adult socio-economic status. The latter study was different in that it was smaller (717 men and women) with older participants (aged 60-74 years) and did not control for weight and height through their childhood years.

The first musculoskeletal study to perform a lifecourse analysis was the Newcastle Thousand Families study of 171 men and 218 women aged 49-51 years. Measurements included BMD, bone area and femoral neck-shaft angle using DEXA imaging. The authors used a conceptual framework to apply the lifecourse approach to assess the effects of risk factors in the different stages of life on bone health and found that the

effects of fetal life on bone health in adulthood is mediated through achieved adult height. In men, factors in fetal life accounted for 5.2 to 7.7% of the variation in outcome measures while fetal life factors explained less than 1% of the variation in BMD in women. Adult lifestyle was the important determinant of bone health in middle age in this cohort, over 10% of variation in density for men and 6% in women. A univariate effect of birth weight was seen on bone area, but the association was not independent of adult size. The authors acknowledge that genetic factors, lifetime exercise and sunlight exposure may have contributed to variance in bone health which was not calculated by the statistical model that was used. Another limitation was that the risk of fracture was not assessed(Pearce et al., 2005a).

The mechanisms by which birth weight affects bone health in later life have not been fully understood. However, physiological studies have noted that low birth weight predicted increased adult cortisol levels in 670 participants from England and Australia (Phillips et al., 2000), while low weight in infancy predicted decreased median growth hormone levels in 37 Hertfordshire men aged 63 to 73 years (Fall et al., 1998a). Cortisol is known to be a determinant of prospective bone loss (Dennison et al., 1999) and it is therefore possible that the intra-uterine programming of bone health may be mediated in part by hormones in the hypothalamic-pituitary-adrenal axis. Godfrey et al demonstrated that maternal factors such as smoking, skinfold thickness and birth weight were associated with neonatal bone mineral content, which adds to the list of factors responsible for the programming of bone health (Godfrey et al., 2001).

3.11.2 Socio-economic status and later health

A study of 9377 members of a birth cohort, who were born in one week of March 1958 in England, Scotland and Wales, looked at the association of socio-economic situation in childhood and adulthood with various measures of morbidity at age 45 (Power et al., 2007). An impressive 53% of the original birth cohort was followed up at age 45. Socio-economic position in childhood was defined by the father's occupation at birth, while that in adulthood was based on the participant's current or most recent occupation. The classification was based on the Registrar General's occupational groups, graded from I to V. After adjusting for adult social position and for sex, there was a significant association of childhood social class on systolic and diastolic blood pressure, BMI, glycosylated haemoglobin, HDL cholesterol, triglycerides, fibrinogen, forced expiratory volume in one second, hearing threshold at 4 kHz, depressive symptoms and chronic widespread pain. The trend was generally that of deteriorating risk from class I to V. However, there was an attenuation of the effect of childhood socio-economic position after adjusting for adult position. The SD scores and ORs for the outcomes suggested that associations for childhood class were at least as good as that for adult class. Mutually adjusted models of both childhood and adult class showed that the same outcomes showed associations for social class at both stages, suggesting that socio-economic position at both these life stages had an influence on these outcomes. On looking at the combined effect of class over both life stages, the trend was for participants with a manual class at both stages to have higher morbidity.

The association between lifetime socio-economic position and self reported limiting longstanding illness at age 50 has been reported on the members of the Thousand Families Cohort (Adams et al., 2004). Long standing illness was measured by asking the question: "do you have any long term illness, health problem or handicap which limits your daily activities in any way?" Socio-economic position was available for birth (collected contemporaneously) and age 25 and 50 (collected at age 50). The registrar

general's social class of the head of the household using the 1990 classification of occupations collapsed into either manual or non-manual classes. Data were available for 202 men and 243 women (39% of original cohort). The results showed that there were significant associations between socio-economic positions at all three life stages with self reported long term illness among men, but not women. There were similar associations when the trajectory of socio-economic position through the lifecourse was looked at; with those having a stable non-manual occupation having the least likelihood to report long term illness. The authors suggest that men carry the experience of socio-economic deprivation with them throughout the course of their life and this fits with the "accumulative model" of lifecourse effects. The authors suspect that there was no such association seen in women due to the manner in which socio-economic position is classified; using the head of the household rather than the individual. Equally, it may have been possible that women report long term illness in a manner that is different to men.

A study by Wright and Parker assessed the effect of deprivation on the heights and weights of subjects from two birth cohorts in Newcastle: The 1947 Thousand Families Cohort and the 1987 Growth and Development Study (Wright and Parker, 2004). Social class was defined by the Registrar General's occupational classification of the head of household at birth in the 1947 birth cohort while it was defined by the census-data-based Townsend score approach (Townsend et al., 1988) in the 1987 cohort. The Townsend scores were ranked and grouped into four categories to correspond with the four social categories in the 1947 cohort. The authors noted that there was a gain of 0.7 SDS which was equivalent to 4cm in height in the subjects of the 1987 cohort when compared to the 1947 cohort, at the age of 9 years. The expected increase in height over this period was of similar magnitude between the social classes, with no evidence of a decrease in the gradients over this period. This suggests that there is no diminution in the effect of deprivation on growth during this 40 year period. Both cohorts also showed significant and consistent gradients in height by deprivation strata in childhood, which widened up to

age 9 years (4 cm between highest and lowest social strata) and then narrowed into adulthood (in the 1947 cohort).

Interestingly, there was no evidence of a socio-economic gradient in birth and infant weights in the 1947 cohort, while this gradient was significant in the 1987 cohort. The authors suggest that this is possibly due to the change in smoking habits between social classes from 1947 (where the affluent women smoked more) to 1987 (where smoking among women from lower social classes reached a peak and those from higher classes diminished). Maternal smoking is known to play a large influence in birth weight (Goldstein, 1981). In addition, the rationing of food in the post war period is also likely to have led to the lack of the gradient in socio-economic status in birth and infant weights in the 1947 cohort. Although the 1946 and 1958 longitudinal British birth cohort studies showed a gradient for birth weight between the social classes, both those studies included pre-term infants; which were excluded from this particular study in Newcastle.

The lack of gradient at birth (for weight) with a wide gradient (for height) at age 9 in the Thousand Families Cohort, suggests that it is factors in childhood that affect this gradient; probably of nutritional origin. The initial years of food rationing and the British Welfare Food safety net in infancy would strengthen the nutritional basis for the observed social gradient. Similarly, in the 1987 cohort the gradient (for weight) present at birth and infancy was about half that seen in the gradient (for height) at age 9; once again suggesting that the genetic or inter-generational factors were less predominant than the factors (probably nutritional) acting during the childhood years.

An analysis of 4418 men and 1710 women in the Whitehall II study assessed the relation between socio-economic exposure over the lifecourse and health outcomes such as coronary heart disease, poor physical and mental functioning and minor psychiatric disorders in adulthood (Singh-Manoux et al., 2004). The participants were London based office staff aged 35-55 years during 1985-88, working in 20 civil service departments. Men with the highest summary score for socio-economic exposure through the lifecourse had increased odds of coronary heart disease (2.53, 95% CI: 1.3, 5.1), poor physical

functioning (2.19, 95% CI: 1.4, 4.1) and poor mental functioning (2.60, 95 % CI: 1.4, 4.9) compared to men with the lowest summary score. Similarly, in women there was an accumulation effect of socio-economic status for coronary heart disease and physical functioning. However, no cumulative effect was seen for the effect of socio-economic position on minor psychiatric disorder, which was assessed by using the General Health Questionnaire. However, when the analysis was stratified by adult socio-economic status, the graded linear relationship was lost. The authors suggest that this finding implies that the pathway models and critical models of lifecourse research could also fit with these associations. These models of causation in lifecourse research are discussed later in more detail. The limitation of this study was that it relied on retrospective data collection and was therefore subject to the possibility of recall bias. Furthermore, the authors used different measures of socio-economic position to construct summary scores and trajectories, although they may not all measure the same construct. This is a study of only office based workers in London and therefore might have limited external validity.

A study of 8795 members of the 1958 British birth cohort study at age 45, examined the effects of lifecourse socio-economic position on inflammatory and hemostatic markers namely, fibrinogen, C-reactive protein, von Willebrand factor antigen and tissue plasminogen activator antigen. Socio-economic position was determined at three time periods: birth, age 23 and age 42. A cumulative score was calculated from 0 (always in highest class) to 9 (always in lowest class). The results demonstrated that increased adverse socio-economic exposure over the lifecourse was associated with higher levels of inflammatory markers (i.e. fibrinogen and C-reactive protein) at age 45. The size of the difference between people with highest and lowest cumulative scores of social class was 1.01 g/litre for fibrinogen and 1.05 mg/litre for C-reactive protein, in unadjusted analyses; these are therefore large effects. While it was found that socio-economic circumstances at different stages of the life course showed independent associations with fibrinogen and C-reactive protein, the hemostatic factors were only influenced by early life conditions, after adjustment for current and early adult socio-economic position. An

explanation offered by the authors was that this relation of the hemostatic factors to childhood class was possibly due to poorer childhood circumstances leading to endothelial dysfunction, which is a feature of early atherosclerosis. However, it is poor conditions in middle age that were found to be strongly associated with fibrinogen and C-reactive protein; markers of later atherosclerosis, which has a greater inflammatory component. The biomarkers did not always retain the significant associations after mutual adjustment for socio-economic position at the three time points; this went against the idea that this was an entirely accumulative model and the authors proposed that the critical period model could also explain part of these results. They conclude that socio-economic exposure risks accumulate across the whole lifecourse and contribute to higher levels of fibrinogen and C-reactive protein, while it was only childhood social class that mainly influenced the levels of hemostatic markers.

Ben-Shlomo and Davey Smith explain the importance of studying the lifecourse effects of socio-economic risk by using cohorts which have sufficient numbers of socially mobile individuals (Ben-Shlomo and Smith, 1991). Since socio-economic status tends to correlate highly between childhood and adult life, it is necessary for individuals to be socially mobile to disentangle the relationship of early and later socio-economic status to the outcome in question.

3.11.3 Breastfeeding and subsequent health

A systematic review of 28 observational studies (298,900 subjects) investigated the association between infant feeding and a measure of obesity in later life (Owen et al., 2005). The measurement of obesity was conducted in infants in four studies, in children

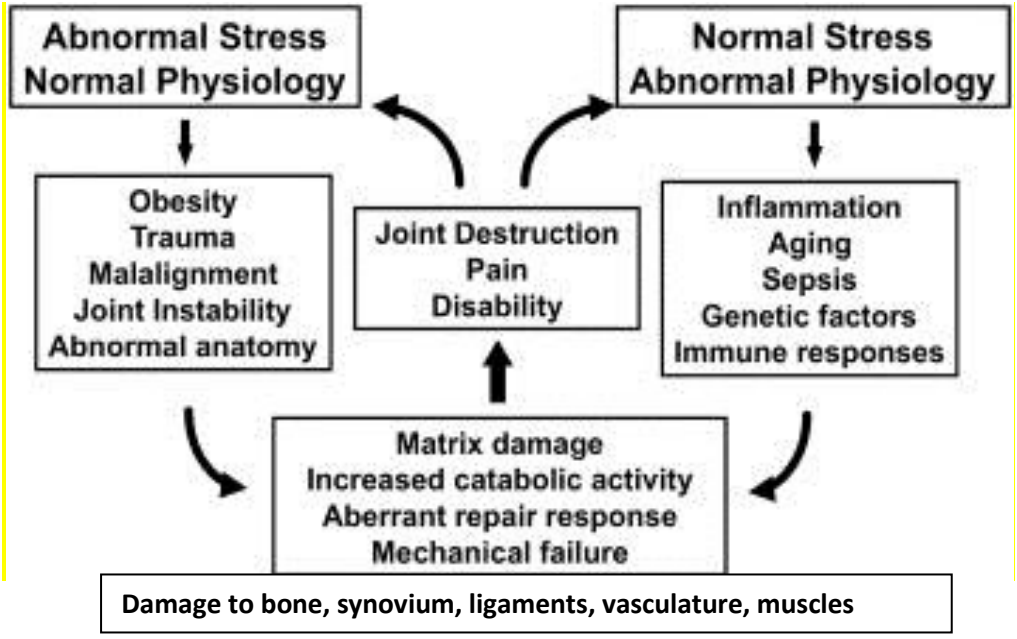
in 22 studies and in adults in two studies. 28 of the 29 estimates from the above studies showed a lower risk of obesity in breast fed compared to bottle fed infants (OR 0.87; 95% CI 0.85, 0.89). The estimate was the same after excluding the 4 studies that measured for obesity in infancy. Exclusion of the largest study which accounted for 73 % of the statistical weight, led to a higher protective effect of breast feeding (OR 0.73; 95% CI 0.70, 0.77). There was a reduction in the strength of effect of breast feeding with an increase in the participant size of the studies, with ORs of 0.43 (95% CI 0.33, 0.55) for 11 small studies, 0.78 (95% CI 0.69, 0.89) for 7 intermediate sized studies and 0.88 (95% CI 0.86, 0.90) in 10 large studies (more than 2500 subjects). This suggests an element of publication bias, although the same effect was still present (albeit at a weaker level) in the large studies. Interestingly, the authors stated that there was no clear trend for the protective effect of breast feeding to be altered with increasing age of obesity measurement. The ORs were 0.50 (95% CI 0.26, 0.94) for infants, 0.90 (95% CI 0.87, 0.92) for young children, 0.66 (95% CI 0.60, 0.72) for older children and 0.80 (95% CI 0.71, 0.91) for adults. This might suggest that the programming effect of breast feeding on adult obesity influences most of its effects in early life. However, it could be argued the other way, since the higher OR in young children was predominantly caused by one study (Grummer-Strawn and Mei, 2004) which was the largest and it had a small effect. Removal of this study would result in a dose-response relationship of breast feeding with age at measurement of obesity. In the four studies where exclusive breast feeding was reported, the protective effect of breast feeding was found to be stronger with the OR dropping to 0.76 (95% CI 0.70, 0.83). In six studies which adjusted for confounders such as socio-economic status (Grummer-Strawn and Mei, 2004, Toschke et al., 2002), parental BMI and current maternal smoking (Toschke et al., 2002), or maternal smoking in early life (Grummer-Strawn and Mei, 2004, Gillman et al., 2001, Li et al., 2003, Bergmann et al., 2003, Parsons et al., 2003), the protective effect of breast feeding seemed to weaken from 0.86 (95% CI 0.81, 0.91) to 0.93 (95% CI 0.88, 0.99). This appears to suggest that confounding possibly plays an important role in the relation between breast feeding and subsequent obesity. This needs further evaluation by adjusting for confounders, such as socio-economic status, physical activity and diet

across the lifecourse. The adjustment for birth weight or prevalence of low birth weight in ten studies did not show any sizeable effect on the estimate.

3.12 Proposed pathophysiology of Osteoarthritis

It is clear that the pathophysiology of OA is complex and involves the combination of one or more biomechanical insults along with other systemic factors that ultimately results in the failure of the various structures that assist joint function.

Figure 1: Pathophysiology of Osteoarthritis



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3.13 Proposed mechanisms/systems for lifecourse effects in musculoskeletal health

The musculoskeletal system consists primarily of three main tissues, namely muscle, bone and joints. The relationship between early life characteristics and adult outcomes has best been studied on bone, while such studies on muscle and joints are few.

Cooper et al reviewed the developmental origins of osteoporosis and fractures (Cooper et al., 2006). They state the differential growth that occurs between the axial and appendicular skeleton from birth to the post pubertal stage. This implies that adverse environmental exposures during specific periods could cause greater deficits in growth in different areas of the skeleton. Chondrocytes need to proliferate and differentiate for the process of enchondral ossification, which is the manner in which long bones develop in the embryonic period, where a cartilaginous model eventually becomes ossified and then subsequently mineralised. The former process is under the control of PTHrP, cytokines of the GH-IGF axis, vitamin D and triiodothyronine ,while the hormones involved in the regulation of placental calcium transport include parathyroid hormone (PTH), parathyroid hormone related peptide (PTHrP), Vit D and calcitonin.

They also summarise the results of studies that demonstrate the modification of osteoporosis risk by environmental influences acting in early life. They categorised these studies into four groups namely:

(1) Bone mineral measurements taken in cohorts of adults whose birth and/or childhood records are available. In one such study, Cooper et al (Cooper et al., 1997) were able to show a significant, albeit mild, relationship between weight at 1 year and Bone mineral content (BMC) at age 65, in 413 men and women of East Hertfordshire. Women in the highest third of the weight categories had 11% higher BMC at the spine ($p<0.01$) and 8% higher BMC in the femoral neck ($p<0.01$). Birth weight did not have a significant

relationship with BMC, suggesting that programming in early post natal life is probably more significant than the combined effect of programming in the gestational period and genetic influences, for this particular outcome. However, when adult height was added to a multiple regression model, the effect of weight at 1 year lost its significant effect on BMC, suggesting that the above effect was mediated through achieved adult height. The caveat for this conclusion is that some of the eventual height is determined by early growth.

(2) Physiologic studies that investigated the relationship between bone loss and endocrine systems that may be "programmed" namely GH/IGF 1; hypothalamic pituitary adrenal axis and gonadal steroid.

(3) Studies detailing the nutrition, body structure and lifestyles of pregnant women and their relationship with the bone mass of their offspring.

(4) Studies that related childhood growth to the future risk of hip fracture.

A Finnish study of 3639 men and 3447 women, whose birth and childhood growth data were linked to hospital discharge records, showed that tall maternal height and low rate of childhood growth were the two major determinants of subsequent hip fracture risk, after age and sex adjustment (Cooper et al., 2001). The hazard ratio was 1.9 (95% CI 1.1 to 3.2) among those whose growth rate was below the lowest quartile in the cohort, compared to those in the highest quartile of growth. Childhood growth could be a function of childhood lifestyle, genetic influences and intra-uterine programming due to a combination of nutritional and maternal factors, but the authors stated the need for preventive strategies to improve growth during this period to prevent fractures.

A systematic review and meta-analysis in 2011 which assessed the strength of association between birth weight and adult bone mass found 14 studies that met the inclusion criteria (Baird et al., 2011). A 1 kg increase in birthweight was associated with an increase of lumbar spine BMC by 1.49 grams (95% CI 0.77, 2.21) and hip BMC by 1.41 grams (95% CI 0.91, 1.91). However, birthweight was not associated with lumbar spine BMD (11

studies) and with hip BMD (7 studies). Three studies assessed the association of weight at one year with adult BMC and all these showed a positive association. The consistency of association between birth weight and adult BMC provides strong evidence the programming of skeletal development in utero. The mechanism of this association has been thought to be due to the effects of programming on the metabolic and endocrine systems as described earlier in this section. The lack of association of birth weight with BMD suggests that this aspect might be determined by other factors in later life such as age at puberty, physical activity or indeed even by fixed genetic variation.

A systematic review and meta-analysis of the association of birth weight and muscle strength in adulthood was published recently (Dodds et al., 2012). Of the 19 studies that met inclusion criteria, 17 showed that a higher birth weight was associated with increased muscle strength. Grip strength was the measure used most frequently (in 15 studies). The results of the meta-analysis showed that a 0.86 kg increase in muscle strength (95% CI 0.58, 1.15) occurred with every one kg increase in birth weight among >20,000 participants with mean ages ranging from 9 to 68 years, after adjustment for age, gender and height at the time of strength measurement.

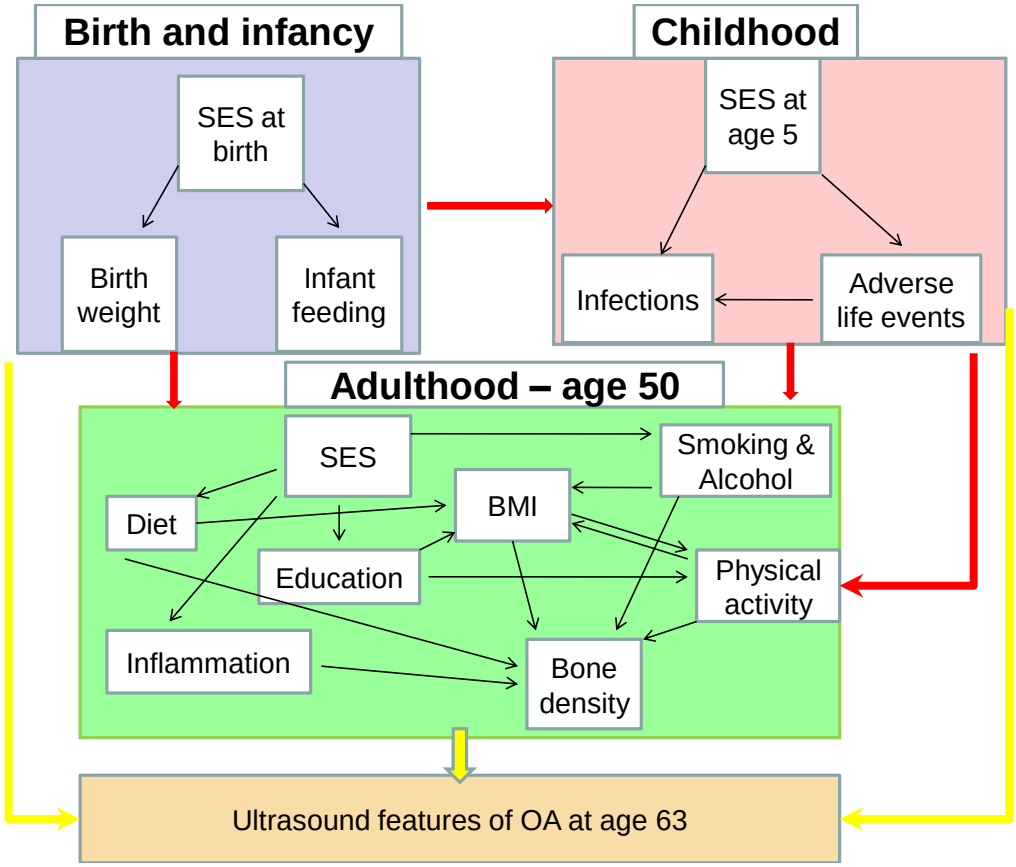
To my knowledge, there have been no reported studies that have investigated the mechanisms of programming in joint health.

There have been no studies to date that have applied the lifecourse approach to assessing the factors that influence OA.

3.14 Conceptual framework

Potential risk factors were grouped within a conceptual framework according to the stage in the life course that they would be expected to impact features of OA in the knees, hips and dominant hand. A schematic representation of this framework (see Fig 2) is given below.

Fig 2 Conceptual framework



Chapter 4 The Newcastle Thousand Families Birth Cohort

4.1 Origin of the study

The Newcastle Thousand Families Study was commenced in response to the finding by Spence that the higher rates of infant mortality in Newcastle upon Tyne in the 1930's was due to higher mortality from acute infections (Spence and Miller, 1941). The study commenced when 1142 babies born in the city of Newcastle upon Tyne in May and June 1947 were recruited into the study (Spence et al., 1954).This was an entirely unselected group and represented the entire social strata. Although the study was initially planned to confirm this finding of Spence by following participants for one year, it continued through the childhood years and is now into its seventh decade of follow up (Pearce et al., 2009).

This was a period in time that occurred just two years after the 2nd world war ended. As a result, families were small and nearly 75 % of the children in this cohort were members of 1 or 2 child families. The estimate of the population in mid-1947 was 290,470; there had been a period of sustained population growth in the city due to the combination of a high birth rate and more importantly, large-scale immigration to the city from neighbouring regions due to a demand for unskilled labour. The rate of marriage rose sharply after the war and the birth rate was also at a high 22 per thousand in Newcastle in 1947 (Miller et al., 1974).

Housing was a significant problem in Newcastle; in 1865 a detailed inquiry by the Town Council revealed that a large proportion of the families lived in single rooms and there were a significant number of people in the city without "water closet or privy

accommodation of any sort". The death rate in the city was the highest in the country at 36.7 per 1000. The infant mortality rate had dropped from 186 per 1000 births in 1873, to 44 per 1000 in 1947.

The exposures collected during the first 15 years of the study are described in 3 books (Spence et al., 1954, Miller et al., 1960, Miller et al., 1974). The investigation required the investigators to observe, visit and talk to the parents of this group of children initially (Spence et al., 1954). The initial investigators showed great foresight by demonstrating the need to follow these children in the community context. The investigators went on to study the relationships of height, weight, socio-economic circumstances, housing conditions and subsequent health. Of the 1142 babies, 967 were followed up till the age of 1 year, 847 to the age of 5 and 750 were followed during their school years (Pearce et al., 2009).

During the first five years of their lives, all participants had frequent follow up visits by the study team. The study team comprised of health visitors and paediatricians. The collection of data began with charting of the antenatal records of those mothers who attended clinics and this was followed up with the reports of midwives at birth. The families were visited at home up to every six weeks during infancy and at least every three months until the age of five years. A summary of the circumstances of the family (including socio-economic circumstances) was made at the start of the study and this was regularly updated by the health visitors at the time of routine visits. Participants were formally examined by a paediatrician at the end of year one, three and five. Once they reached school age, visits were made to the school on at least a yearly basis to record demographics such as height, weight and any specific illnesses. The health records of these participants were flagged up in primary care and in the hospitals, so that all health care episodes could be identified and coded appropriately by the study team. This enabled the team to ensure that all data were collected in a prospective and detailed manner. A red spot was placed on each participant's general practice record so that the general

practitioner could inform the study team as soon as a health event occurred. The children were subsequently known to be called “Red spot babies” and even today refer to themselves as “Red spots”. The collected data were stored in the Newcastle City Archive during the early and middle adult period when the study went through a dormant period (Pearce et al., 2009).

In 1997, all members of the cohort that had been traced till then were sent a lengthy health and lifestyle questionnaire (completed by 574 participants) and were also invited to attend a clinical examination (completed by 412 participants) which included serum, bone density and other clinical assessments. These participants followed up at age 49-51 years were shown to be representative of the original cohort for all early life characteristics except for gender (Lamont et al., 2000). It was noted that 18% of participants attending the clinical examination at age 49-51 years, were outside the North of England region, providing further evidence of the representativeness of the sample studied at that time point.

The Thousand Families Study is unique in that it followed up all the children born in a single city in the UK immediately after the Second World War. The focus on one city meant that the follow up was comprehensive and that attrition was minimised, especially during the childhood years.

One of the strengths of this study is that the majority of participants have remained in contact with the study team. The contact status of participants in the study from the previous health assessment is summarised in Table 4 below.

Table 4 Contact status of Thousand Families Study members in 1997

Contact status of Thousand Families Study members in 1997	Numbers
Traced – contactable directly or through a relative	785
Traced – contactable via GP	81
Total contactable sample on 11th November 1997	**866**
At unknown locations abroad or in armed forces	35
Untraced	31
Died	91
Total lost to follow up	**157**

Table adapted from Lamont et al (Lamont et al., 1998)

Data were collected prospectively across the lifecourse among participants in the Newcastle Thousand Families Birth Cohort at different stages of life and this has been summarised below in Table 5.

Table 5 Summary of data collected on participants of the Newcastle Thousand Families Cohort (adapted from Pearce et al (Pearce et al., 2009))

Years	Cohort ages (years)	Data collected
1947	Birth	Antenatal charts
		Midwives reports (including birth weight, gestational age and infant feeding)
		SES of the family
1947-62	Birth to the age of 15	SES of main wage earner in the household
		Measures of height and weight at ages 9 and 13 years
		Infections
		Adverse events (reported by health visitors)
1997-99	49-51	SES of main wage earner in the household
		Education history
		Smoking and alcohol history
		Diet (EPIC food frequency questionnaire) and exercise (MRC physical activity questionnaire) at age 50
		Anthropometric measures (height, weight, BMI, percent body fat using bioelectrical impedance)
		Bone mineral density using DEXA
		Serum fibrinogen
2005	58	Reproductive history

4.2 Epidemiological studies performed previously

There have been numerous previous epidemiological studies that have been reported on the Thousand Families cohort. The general theme that has been observed in these studies is that early life factors appear to play a far smaller role than risk factors in adulthood in the development of a multitude of disease outcomes at age 50 (Pearce et al., 2006, Pearce et al., 2005a, Parker et al., 2003, Pearce et al., 2005b).

A study of 388 members of the cohort at age 50 found that birth weight had an inverse association with fasting and two hour glucose levels in men ($p=0.03$), but not women (Pearce et al., 2005b).However, it was also noted that the overall contribution of early life factors (including those mediated through adult factors) could explain only about 5% of the variation in blood glucose levels measured at age 50, while factors acting in adulthood explained 10-14% of the variation in blood glucose levels.

An investigation of 379 members of this cohort at age 50 also showed an inverse relationship between birth weight and insulin resistance in men ($p=0.02$) but not women (Pearce et al., 2006). However, on multivariate analysis, only breast feeding (co-efficient -0.11 per SD increase; 95% CI -0.20, -0.02, $p=0.02$), percent body fat (co-efficient 0.23 per SD increase; 95% CI 0.13, 0.32, $p<0.001$) and waist-hip ratio (co-efficient 0.16 per SD increase; 95% CI 0.06, 0.25, $p=0.001$) remained significant explanatory variables for insulin resistance in men. Similarly, only adult risk factors were associated with insulin resistance in women; namely self-reported alcohol consumption, percent body fat and waist-hip ratio.

The life course analysis of bone health among 389 participants of The Newcastle Thousand Families cohort demonstrated that early life variables such as birth weight, breast feeding and socioeconomic status accounted for 6.7% of the variation of total hip

BMD in men and 3% of the variation in women at age 49-51 years (Pearce et al., 2005a). However, adult life factors such as adult body size and lifestyle accounted for 13.9% of the variation of total hip BMD in men and 6.1% of the variation in women. Factors acting in foetal life alone accounted for between 5.2 and 6.9 % of BMD in men, compared to less than 1% in women. It was striking to note that adult weight in particular, accounted for nearly a quarter of the variation in hip BMD in women. In summary, while birth weight did not appear to demonstrate a significant effect on subsequent bone mineral density, adult lifestyle and body size seemed to be its major determinants (Pearce et al., 2005a).

Another analysis of 412 participants of this cohort investigated the effects of childhood obesity and underweight on adult obesity and other adverse health outcomes in adulthood (Wright et al., 2001). BMI at age 9 years was significantly associated with BMI at age 50 years ($r=0.24$, $p<0.0001$) but no such association of childhood BMI was noted with percentage body fat at 50 years ($r=0.10$, $p=0.07$). There was no evidence of tracking noted between any level of BMI at age 9 years and percentage body fat at age 50 years. Children in the highest tenth of BMI at age 13 years were twice as likely as the rest of the cohort to be in the top quartile of adult percentage body fat. However, most of those in the top quartile of adult percentage body fat had not been overweight in childhood; 94% being below the 90^{th} percentile of BMI at age 9 years and 79% at age 13 years (Wright et al., 2001). Being thin in childhood did not appear to confer any protection against being fat in adulthood, as measured by percentage body fat.

Similarly, a lifecourse analysis of predictors of plasma fibrinogen (a marker of systemic inflammation) at age 49-51 years in the Newcastle Thousand Families cohort was published recently (Pearce et al., 2011). Current smokers and those with higher percentage body fat showed the most significant association with increased fibrinogen levels, while early life factors such as housing conditions at birth and duration of breast feeding had inverse associations of smaller magnitude. Further details of the results of this study are stated in section 5.5.11.

The main weakness of this cohort is the sample size which is relatively smaller than other cohorts such as the 1946 British Birth Cohort (Wadsworth et al., 2006) and the Hertfordshire Cohort study (Syddall et al., 2005). However, there are many relative strengths of this cohort as evidenced by the relatively low levels of attrition in the Newcastle Thousand Families cohort (Pearce et al., 2009) and the representativeness of the population studied, which included the entire social spectrum of the city of Newcastle upon Tyne at birth. Inclusion of cohort members who had moved out of the region at the time of assessments at ages 49-51 years and 62-63 years further validates the representativeness of the samples studied in adulthood. Data for variables such as birth weight, duration of breast feeding, socioeconomic status and childhood infections have been collected prospectively since birth. While the results from the Newcastle Thousand Families cohort did not always corroborate the findings from other cohorts, the magnitude of association of crude birth weight with systolic blood pressure seen in the Newcastle Thousand Families cohort was found to be similar to the pooled results of other existing meta-analyses on this subject (Pearce et al., 2012). The reasons for differences in results when compared to older cohorts such as the Hertfordshire cohort (Syddall et al., 2005) might be due to the specific circumstances that operated in the Newcastle Thousand Families cohort such as food rationing in the post war period, leading to less variability in diets between participants in early life. The age at which subjects were assessed might have also played a part in this difference; where the assessments of the Newcastle cohort at age 49-51 years might have been too early to pick up the associations seen in older participants of the Hertfordshire cohort.

The above studies in members of the Newcastle Thousand Families cohort suggest that while early life factors might predict disease outcomes in adulthood, their effect may in part be mediated by adult risk factors and also that the direct effect of adult risk factors on the disease outcomes is probably of greater impact than the impact of early life factors.

Chapter 5 Methods

Participants of the current analysis at age 62-63 years were members of the cohort who were either traced through the NHS Central Register or contacted the study team in response to media publicity. Between January 2010 and March 2011, health and lifestyle questionnaires were sent out for completion and return and study members invited to attend for ultrasound and clinical examination that took place over the same time period.

The ultrasound examination was performed using an Esaote Mylab 70 machine, with a 10-18 Mhz high frequency linear array transducer with a 4 cm footprint for the knees and hands and a 6-10 Mhz linear transducer with a 9cm footprint for the hips.

5.1 Ultrasound protocols for knees, hips and hands

5.1.1 Ultrasound of knees

The knee and probe positions were based on the EULAR guidelines suggested by Backhaus et al (Backhaus et al., 2001).

The presence or absence of osteophytes was assessed at the tibial and femoral sites in both knees, with 30 degrees of knee flexion. 30 degrees flexion of the knees was standardised by using the same wedge for all ultrasound assessments (see Fig 3). While there are no comparison studies to assess the validity of using 30 degrees of knee flexion (against other angles), the EULAR guidelines (Backhaus et al., 2001) and recent inter-rater reliability studies for knee OA (Iagnocco et al., 2012) affirm the reliability of this angle for assessment of knee osteophytes and effusion. Femoral and tibial osteophytes were assessed in the medial and lateral compartments using medial and lateral

longitudinal scan positions, respectively. The probe was placed in a longitudinal position anteriorly on the lateral border of the patella and then moved posteriorly in a dynamic manner to the level of the biceps femoris to assess for lateral osteophytes both at the femur and the tibia. Similarly, the probe was moved longitudinally from the medial border of the patella on the anterior aspect to the semitendinosus posteriorly to assess for medial osteophytes at the femur and tibia. Osteophytes were defined as cortical protrusions at the joint margin seen in two planes (Iagnocco et al., 2010). A very recent study published in 2013, has produced a novel atlas in an attempt to quantify the grade of osteophyte in a semi-quantitaive manner in patients with hand OA (Mathiessen et al., 2013). However, at the time of the Newcastle Thousand Families assessments, there was no specific size cut-off to define a knee osteophyte, which could be considered a limitation of this study. Nevertheless, there are no community data to date to suggest the prevalence of osteophytes at any specific size cut-off.

Prevalent knee OA was defined as the presence of at least one osteophyte in the knee joint (see Fig 4). Knees that were replaced were not scanned but marked as having prevalent knee OA.

Fig 3 Acquisition of image for knee osteophytes (knee in 30 degree flexion)

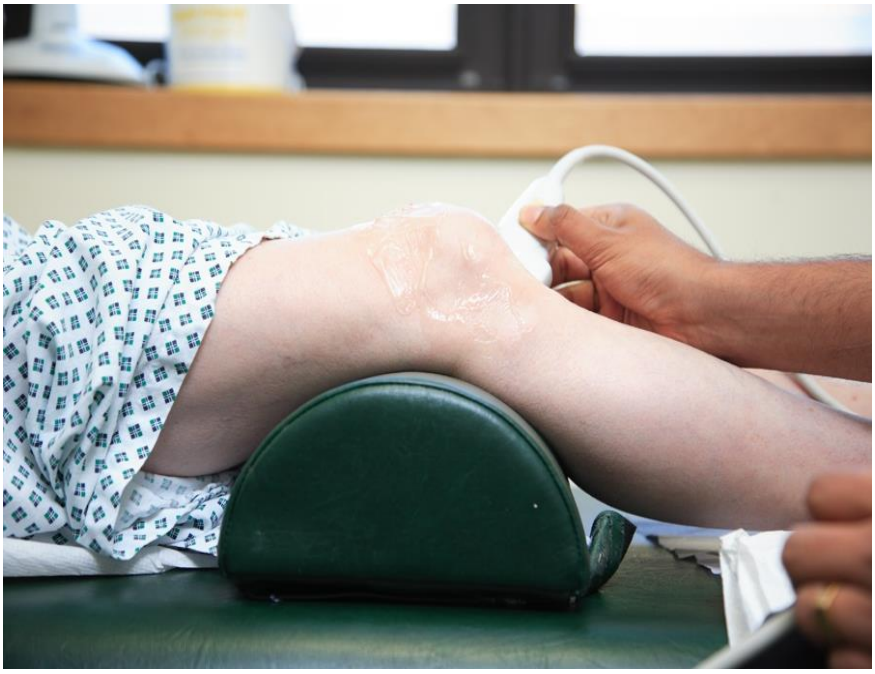
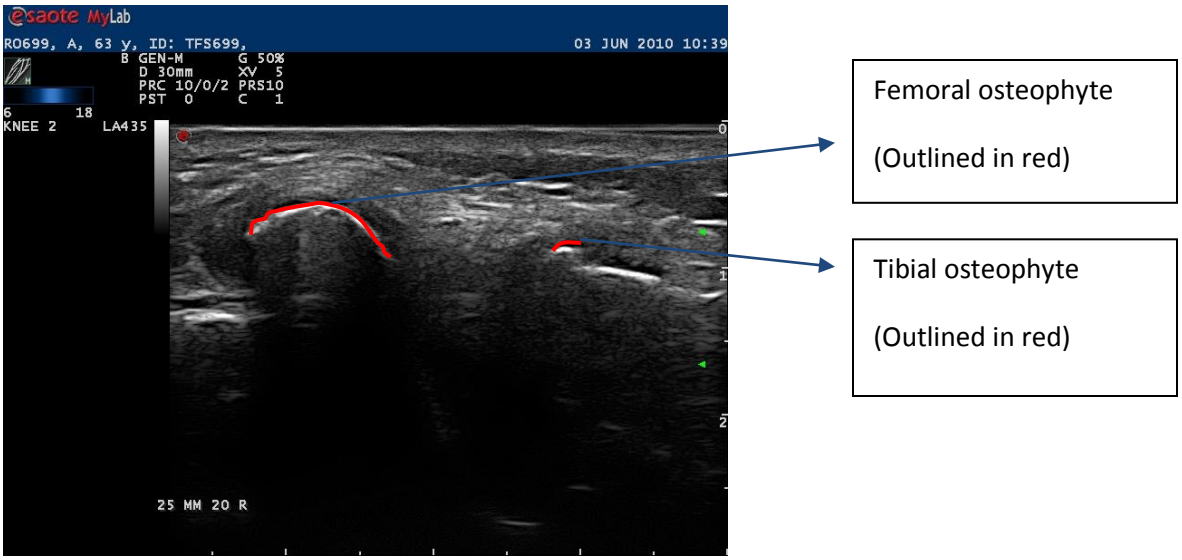


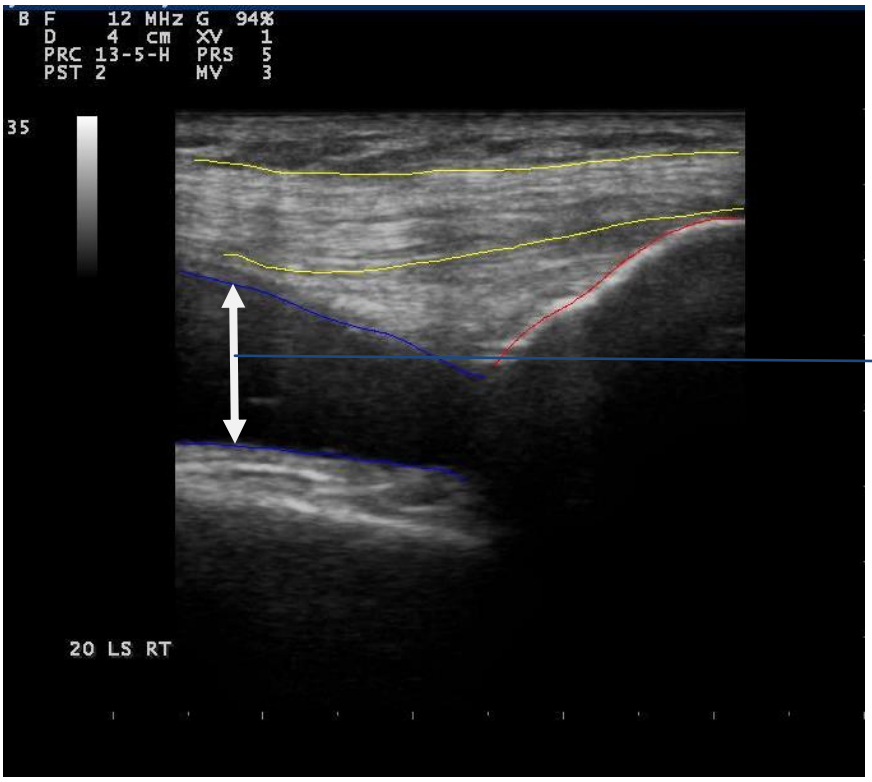
Fig 4 Knee osteophytes on ultrasound (cortical irregularity)



The size of effusions was measured in the longitudinal supra-patellar position, with the knee in 30 degrees of flexion (see Fig 5). A multi-planar approach was used to identify the effusion in the longitudinal view with the probe being swept from the lateral to the medial recess in a dynamic fashion across the supra-patellar pouch. The presence of an effusion was confirmed by the compression test to look for displacement of the fluid (Moller et al., 2008, Wakefield et al., 2005). Multiple readings were then taken to estimate the maximum diameter of the effusion (see Fig 6). Knee effusion was defined (on a dichotomous scale) as being present if the size was ≥4mm, as this definition has previously demonstrated significant association with knee pain (Naredo et al., 2005) and significant correlation with advanced radiographic knee OA in a multi centre European study of knee OA (D'Agostino et al., 2005).

Fig 5 Acquisition of image for knee effusion (knee in 30 degree flexion)

Fig 6 Knee effusion on ultrasound (hypoechoic area)



The thickness of the femoral condylar cartilage was measured in the medial and lateral condyles and in the notch of the right knee, with the knee in maximum flexion. All knees were flexed beyond 90 degrees, which is necessary to view the weight bearing portion of articular cartilage (Iagnocco, 2010). However, the specific angle of flexion was not ascertained for articular cartilage thickness measurements and it is possible that the mild variation in maximal flexion angles between participants might have led to a small measurement error. The probe was placed transversely to the leg and perpendicular to the bone surface, just above the superior margin of the patella; this technique being derived from the methods described by Aisen (Aisen et al., 1984) and Iagnocco

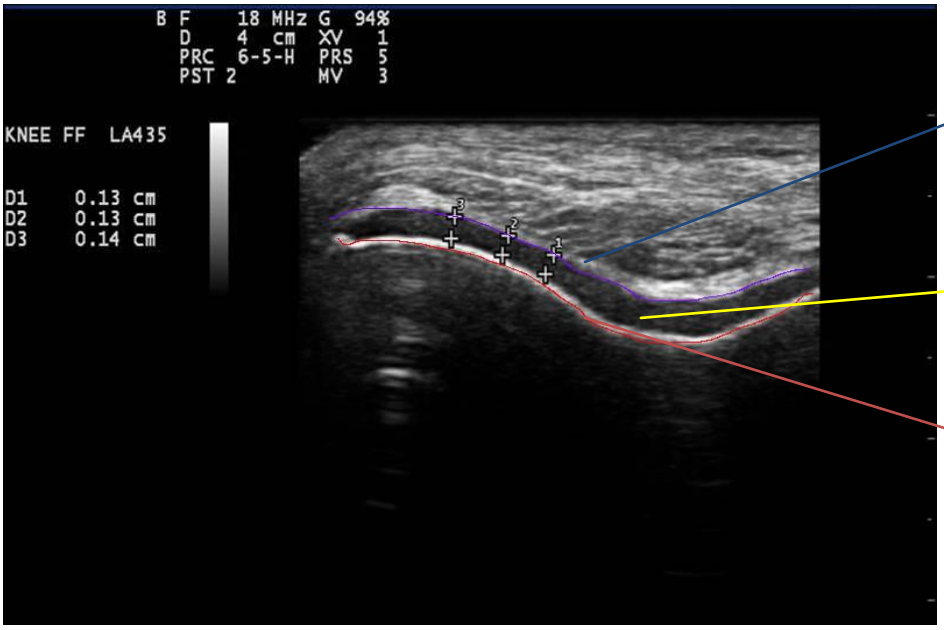
(Iagnocco et al., 1992) (see Fig 7). This position allows the ultrasonographic beam to pass through the ideal acoustic windows. There were no other lines drawn to demarcate the probe position.

The anterior margin of the cartilage should be sharp, regular and continuous and this represents the interface between cartilage and soft tissue structures (Meenagh et al., 2007, Moller et al., 2008). The posterior margin is more echoic and thicker and represents the interface between cartilage and bone (see Fig 8).

Articular cartilage thickness was measured at three sites (see Fig 8) and both mean and minimum cartilage thickness was used as an outcome.

Fig 7 Acquisition of image for femoral condyle cartilage thickness (knee in maximal flexion)

Fig 8 Femoral condyle cartilage thickness on ultrasound (three measurements taken)



Cartilage-soft tissue interface

Femoral hyaline cartilage seen as a hypoechoic area

Femur

5.1.2 Ultrasound of hips

The hip was imaged in the anterior longitudinal plane (oblique sagittal plane along the axis of the femoral neck) as described by Backhaus et al (Backhaus et al., 2001). The curved profile of the femoral head and the linear hyper echoic bony profile of the neck is seen well in this plane (Iagnocco et al., 2006) (see Fig 9). As described by Iagnocco et al (Iagnocco et al., 2006), the joint capsule inserts onto the acetabular rim and the femoral surface and appears as a thin concave echoic line which is parallel to the bone surface on ultrasound.

The pathology identified was presence of osteophytes and femoral head abnormality as described by Qvistgaard et al (Qvistgaard et al., 2006). The probe was placed in the anterior longitudinal plane and moved from a medial to lateral position in a dynamic

fashion till the optimum image was identified. Osteophytes were defined as a definite irregularity in the bone cortex of the femoral head or neck (see Fig 10) while femoral head abnormality was present if there was flattening or loss of contour of the femoral head (see Fig 11). Hips were classified as having prevalent OA if there was presence of either osteophytes or femoral head abnormality. Hips that were replaced were not scanned but marked as having prevalent hip OA.

Fig 9 Normal hip on ultrasound (smooth curve of the femoral head and neck)

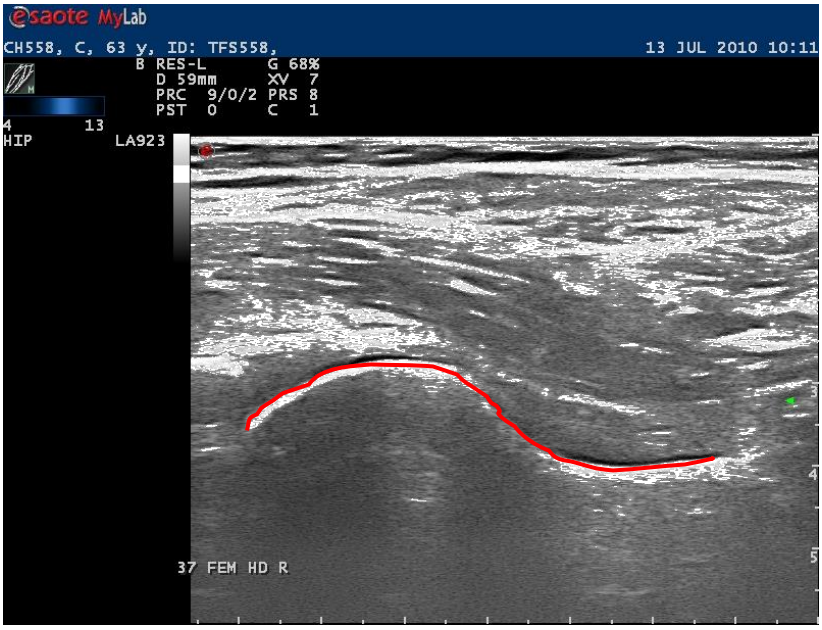


Fig 10 Femoral osteophyte on ultrasound (cortical irregularity of femoral head)

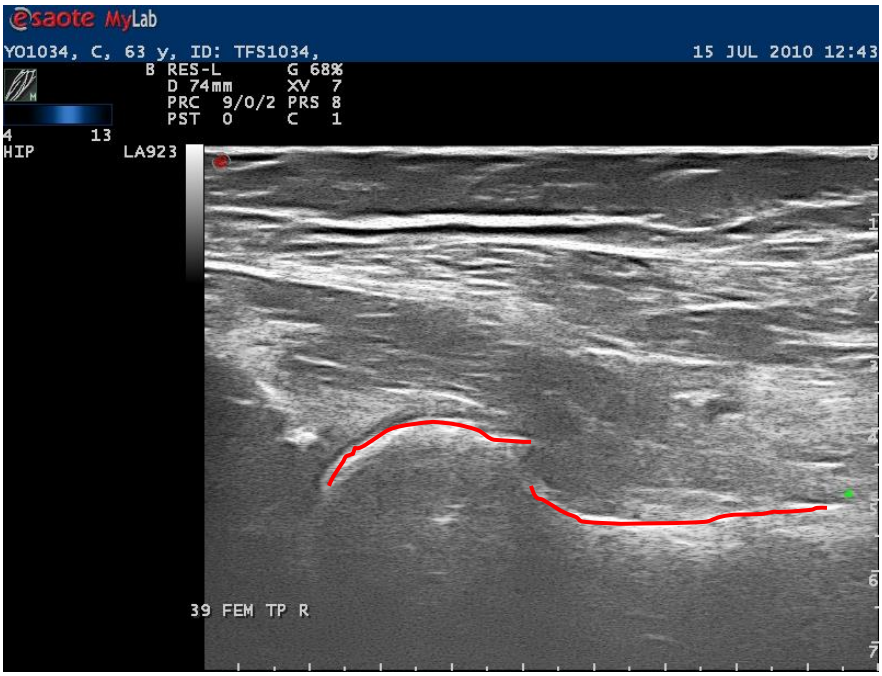
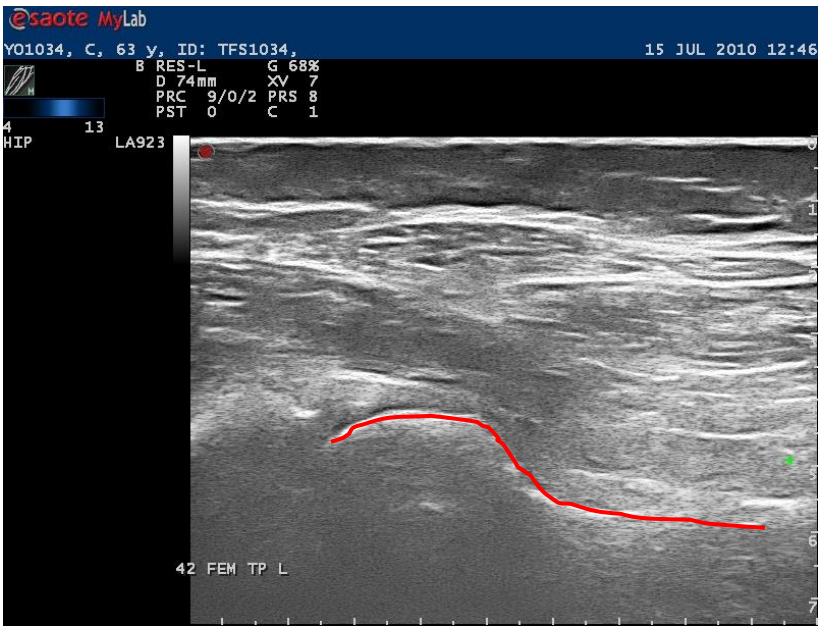


Fig 11 Flattening of femoral head on ultrasound



5.1.3 Ultrasound of hands

Ultrasound of the hand identified osteophytes in the MCP, PIP and DIP of the index finger and 1st CMC joint of the dominant hand.

Generous amounts of ultrasonographic gel were used in addition to a gel stand off, for all ultrasound assessments of the hand joints. This allowed for accurate identification of the target structures with minimal artefacts in the image.

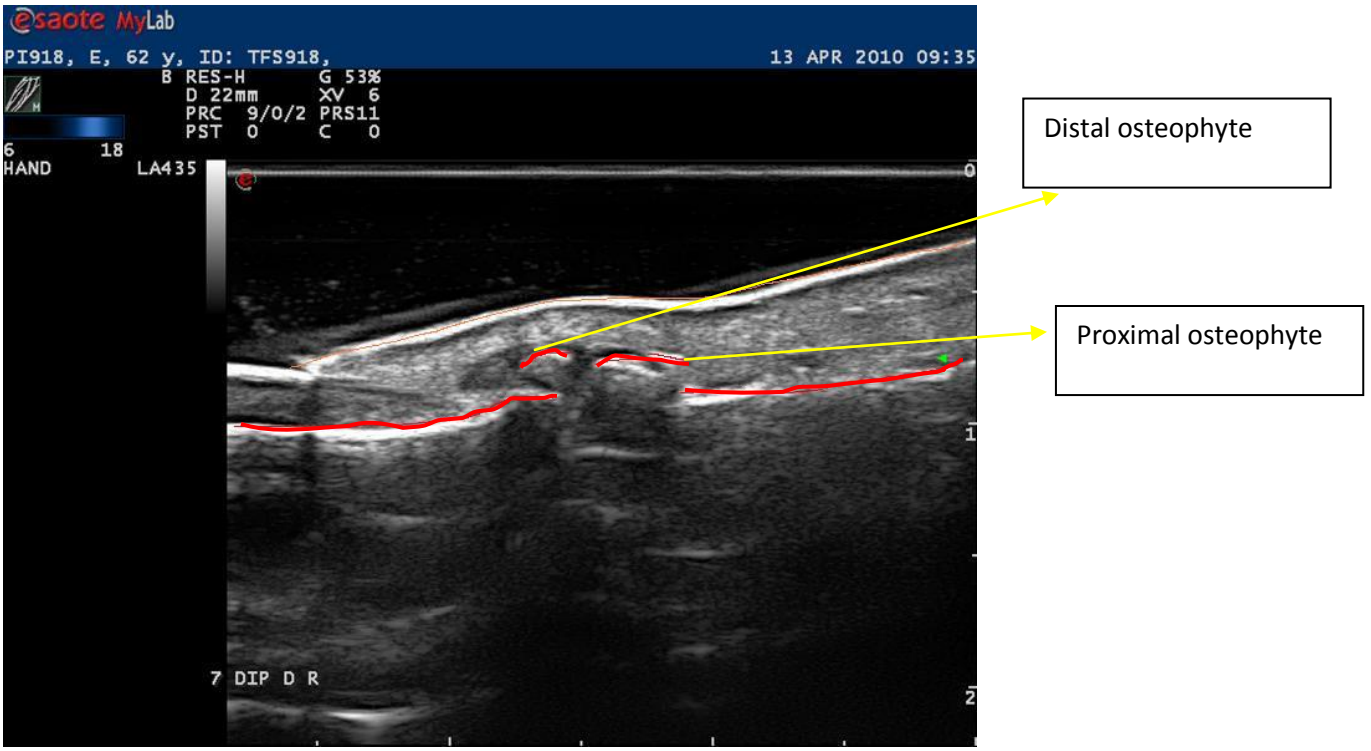
The position of the probe was based on EULAR guidelines (Backhaus et al., 2001). The MCP, PIP and DIP joints of the index finger and CMC joint of the thumb were imaged using a dynamic approach with the probe in a longitudinal position and being swept across the whole of the joint for DIP and PIP joints from the anterior to posterior aspect; and across accessible areas for the MCP and CMC joints (see Fig 12). The hand joints were placed in a neutral position for all of the scans.

Osteophytes were identified as cortical protrusions of the bone surface using a multi-planar approach (see Fig 13). In case of doubt, a transverse view was obtained to confirm the presence of the osteophyte. Ultrasound has previously been found to be more sensitive than radiography in the detection of osteophytes in the hands (Keen et al., 2008b).

Power doppler signal (PDS) was defined as a colour signal within the joint capsule which was present even after the gain was adjusted to exclude background noise, with minimal pressure of the probe on the skin. This was defined dichotomously (present vs absent).

Fig 12 Acquisition of image for osteophytes in CMC joint (Lateral view)

Fig 13 Osteophytes in DIP joint of the hand on ultrasound



Erosions were not assessed in this study. Iagnocco suggested that ultrasound was less sensitive than radiographs in detecting erosions of OA (Iagnocco et al., 2005a). It is thought that OA erosions might be in the central part of the joint and therefore inaccessible to ultrasound imaging, when compared to the erosions of rheumatoid arthritis which are peri-articular and therefore more accessible to ultrasound (Keen et al., 2009). Furthermore, the prevalence of erosive hand OA in a community cohort was likely to be significantly low to make this a feasible feature to assess from a statistical standpoint.

Given that it is technically difficult to obtain valid and reliable images of cartilage thickness in the hand joints, no attempt was made to quantify it in this study. There are a number of issues which make it difficult to visualise cartilage in the hands. Although

maximum flexion of the fingers is advised, there have been no studies to date that have demonstrated sufficient reliability or validity of this feature. Keen et al (Keen et al., 2008c) provided an arbitrary definition of joint space narrowing where they state that it was classified as present if the space "appeared reduced" or assumed to be reduced if "osteophytes prevented visualisation". Keeping this vague definition in mind, they were able to demonstrate a higher number of joints with reduced space when compared to radiographs. Since the joint space in the central portion of the hand joints can be obscured by osteophytes (Keen et al., 2008a), this might reduce the ability of ultrasound in assessing this feature in any detail.

In summary, prevalent OA in each hand joint represented the presence of at least one osteophyte in the individual joint while prevalent hand OA was defined as OA in at least one hand joint.

5.2 Radiographs of hands, knees

AP (standing), lateral (lying) and skyline (standing) views of both knees were obtained. PA films of both hands were also obtained with the palmar aspect of the hands placed on the film and the fingers extended and spaced evenly.

All radiographs were read consecutively by a single trained observer (IG), using the Kellgren and Lawrence (K-L) criteria (0-4, 0=none, 4=severe). Only definite osteophytes (grade $\geq$2) were classified as present, while grade 0 and 1 were classified as absent osteophytes, on radiographs.

5.3 Measurement of pain, stiffness and function

5.3.1 The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

It was recognised in the early 1980's that the clinical assessment of outcome measures in OA clinical trials were diverse and lacked consistency and standardisation in content, format and scaling (Bellamy, 1995). Despite several decades of investigation and numerous clinical trials in OA, there was a need at that time for a disease specific clinical outcome measure that would have the attributes of reliability, validity and sensitivity to change. With this in mind, the WOMAC instrument was developed to rationalise the measurement of clinical OA in clinical trials. Nick Bellamy proposed an item inventory in 1982 and the instrument was subsequently validated and implemented in OA research across the world and in different languages over the next three decades (Bellamy, 2005). WOMAC is currently the most widely used tool to evaluate the extent of self-reported pain, stiffness and physical disability in patients with hip or knee OA. This tool was developed after a review of the clinimetric properties of previously used instruments in OA literature (Bellamy and Buchanan, 1984) and was also based on the opinion of 100 patients with symptomatic OA who assigned dimensions to their symptoms and importance scores for each item within a dimension (Bellamy and Buchanan, 1986).

WOMAC demonstrated evidence for face, content and construct validity in a study of 57 patients with radiographic knee or hip OA (mean age 66.5) who had entered a randomised controlled study of two non-steroidal anti inflammatory drugs (Bellamy et al., 1988). This study demonstrated good correlation of three items in the WOMAC scale with other selected instruments. Pain was compared with the Doyle and Lequesne-pain index; stiffness with Lequesne-stiffness index; physical function with Lequesne- physical function index; emotional function with Bradburn index and social function with MHIQ-Social index. Pain, stiffness and physical function dimensions in WOMAC showed good

correlation with the other instruments that probed the same dimensions. The emotional and social dimensions were removed from the original instrument due to poor validity. The instrument also demonstrated excellent internal consistency with reliability co-efficients of ≥0.85. The test-retest reliability was somewhat lower but was considered sufficient, especially because the time interval of one week was considered high for OA patients, who could have variable symptom severity over this time period. Furthermore, a high degree of responsiveness was also noted within all the items of the instrument.

The WOMAC (version 3.1) has three dimensions; pain (five questions), stiffness (two questions) and physical disability (seventeen questions). It asks the patients to report symptoms that they are "currently" experiencing. It therefore has an advantage of being a short questionnaire with only 24 questions. The division into three sub-scales prevents loss of information by aggregation of data.

The questionnaire was delivered on a numerical scale ranging from 0 to 10, with descriptors at the extremes. The range of scores was 0-50 for pain, 0-20 for stiffness and 0-170 for disability. An ordinal variable was created by splitting each WOMAC sub-scale in to four categories. Comparison between ultrasound features of OA at the knee and hip was made with WOMAC sub-scales, using logistic regression. BMI, sex, knee effusion and presence of OA in the knee or hip were adjusted for in subsequent models as appropriate.

5.3.2 The Australian/Canadian (AUSCAN) Osteoarthritis hand index

This is a self reported tool which is used as a clinical outcome measure in clinical trials and epidemiological studies of hand OA. It was initially developed at the turn of the century by Bellamy et al after interviewing 50 patients with hand OA and identifying 39 items on three dimensions (pain, stiffness and function) which characterised the clinical presentation of the condition and also specified the clinical importance of each of these items (Bellamy et al., 2002a). The instrument was subsequently refined to a set of 15 questions after conducting further evaluation of the instrument for reliability, validity and responsiveness (Bellamy et al., 2002b). All the questions probe the severity of symptoms in various commonly encountered situations.

The clinimetric properties of AUSCAN were evaluated in a study of 50 patients with ACR defined hand OA (mean age 60.4)(Bellamy et al., 2002b). The test-retest correlation co-efficients were ≥0.70 for all dimensions, while the Cronbach's alpha to assess internal consistency was ≥0.90 for all dimensions. Validity was also demonstrated by showing that there were higher levels of correlation between AUSCAN scores and measures that assessed the same dimension than the correlation of AUSCAN with measures assessing different dimensions of health. Several commonly used measures of hand pain, function and OA were used as comparators to obtain criterion validity of the instrument. As a continuation of this study, the responsiveness of AUSCAN was also evaluated. Participants were asked to discontinue their current NSAID for a period of 3-7 days (washout period) and then to re-start the same treatment (re-treatment); this model having the benefit of testing the instrument in the "real world" scenario. It was found that all the three subscales of AUSCAN showed highly significant changes at all post-washout time points (Bellamy et al., 2002b).

The AUSCAN questionnaire (version 3.1) was delivered on a numerical scale ranging from 0 to 10, with descriptors at the extremes. The possible range of scores was 0-50 for pain, 0-10 for stiffness and 0-90 for physical function. An ordinal variable was created by

splitting each AUSCAN sub-scale in to four categories. Comparison between ultrasound features of OA at the knee and hip was made with AUSCAN sub-scales, using logistic regression. BMI and sex were adjusted for in a subsequent model since they are considered as potential confounders.

5.4 PILOT STUDY: Northumberland over 85 cohort

As the main concern with the use of ultrasound is that it is an operator dependent imaging modality, a pilot study was performed to compare the agreement between myself and a second sonographer in the acquisition and reading of ultrasound images for features of OA. The validity of ultrasound to detect knee osteophytes has not been demonstrated elsewhere and hence this issue was also addressed in the pilot study.

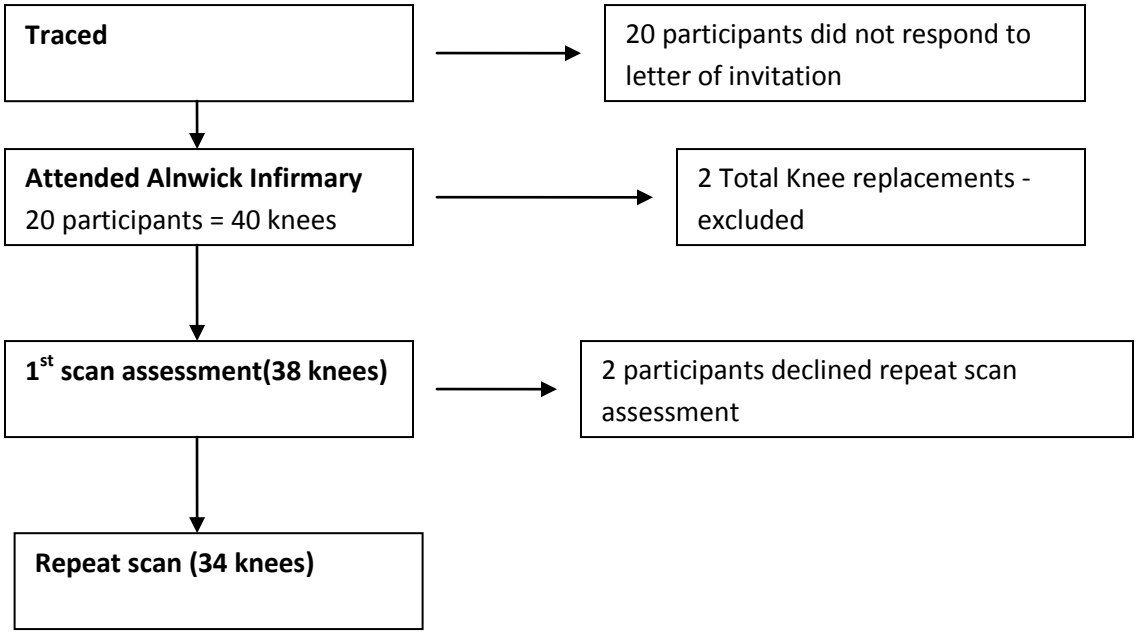
Study population

Forty surviving participants from the Northumberland Over 85 cohort (Abraham et al., 2011) were invited to participate in this study by sending a request letter in the post. This is a prospective community study of subjects aged 85 years or older from one General Practice in Northumberland, UK, that commenced in 2006. Twenty participants volunteered to participate and were invited to attend the Alnwick Infirmary in August 2009, to undergo weight bearing antero-posterior radiographs of both knees and also had ultrasound assessment of both knees for features of OA, by a trained ultrasonographer (AA). Two replaced joints were not imaged.

18 of these participants (34 knees) were re-examined using ultrasound up to six weeks later for the same features by a different trained sonographer in September 2009 (see Figure 13). Two participants declined the repeat scan. Five subjects opted to have the repeat scan at home.

A local research ethics committee (Northumberland Research Ethics Committee, Tyne and Wear, UK) approved the study, which fulfilled the requirements of the Declaration of Helsinki of 1975, as revised in 2000 and the procedures followed were in accordance with the ethical standards of the committee on human experimentation. Written informed consent was obtained from all participating individuals.

Figure 14 Flow chart to show numbers of knees scanned for inter-rater reliability at the first and the repeat scan assessments



Ultrasound assessment

All ultrasound assessments were performed using the same machine with a 10-18MHz linear transducer (Mylab 5; ESAOTE, Genoa, Italy). Both sonographers had spent time together, comparing their acquisition and reading techniques on a separate cohort of patients, to arrive at a consensus prior to the commencement of this study.

The scans were based on a protocol derived from EULAR guidelines (Backhaus et al., 2001) while the OMERACT guidelines for synovial effusion (Wakefield et al., 2005) were also met. The presence or absence of osteophytes was assessed at the tibial and femoral sites in both knees, with 30 degrees of knee flexion. Osteophytes were defined as cortical protrusions at the joint margin seen in two planes (Keen and Conaghan, 2009). Femoral and tibial osteophytes were assessed in the medial and lateral compartments

using medial and lateral longitudinal scan positions, respectively. 30 degrees flexion of the knees was standardised by using the same wedge for all ultrasound assessments. Synovial effusion was defined as an abnormal anechoic or hypoechoic area in the joint that is displaceable and compressible and lacks Doppler signal; as per the OMERACT guidelines (Wakefield et al., 2005). The size of effusions was measured in the longitudinal supra-patellar position, with the knee in 30 degrees of flexion. The maximum diameter of the effusion in the longitudinal view was used to quantify it. Joint effusion was defined by using a cut off of ≥4 mm effusion depth, as seen in a previous multi-centre European study (D'Agostino et al., 2005). The thickness of the femoral condylar cartilage was measured in the medial and lateral condyles and in the notch, with the knee in maximum flexion. Cartilage thickness was measured from the thin hyper-echoic line at the soft tissue-cartilage interface to the hyper-echoic line at the cartilage-bone interface. The probe was placed transversely to the leg and perpendicular to the bone surface, just above the superior margin of the patella; this technique being derived from the methods described by Aisen (Aisen et al., 1984) and Iagnocco (Iagnocco et al., 1992). There were no other lines drawn to demarcate the probe position.

Radiographs

All radiographs were read consecutively by a single trained observer (IG), using the Kellgren and Lawrence (K-L) criteria (0-4, 0=none, 4=severe) (Kellgren and Lawrence, 1963). Grading included the presence of osteophytes and minimal joint space (Brandt et al., 1991) in the medial and lateral tibio-femoral compartments of the knees. Only definite osteophytes were classified as present, with absent or possible osteophytes classified as not present. The images from all 20 participants (38 knees) were used for comparison between ultrasound and radiographs.

Statistical analysis

Reliability

The thickness at the medial and lateral condyles was measured by taking the mean of three measurements at each site. Intra-class correlation coefficients (ICCs) were calculated to assess the agreement between observers on the size of effusions and the thickness of the femoral condylar cartilage in the notch, medial and lateral sites. Kappa statistics (κ) (Landis and Koch, 1977) and corresponding 95% confidence intervals (95% CI) were calculated for the agreement between observers on the presence or absence of osteophytes at each site.

Validity – Unweighted κ was calculated for the agreement between US and radiographs on osteophytes.

5.5 Measurement of risk factors & analysis

5.5.1 Weights/heights

Birth weight and gestational age were prospectively obtained from antenatal charts and midwives reports routinely recorded at the time of birth (Spence et al., 1954). In order to give a better measure of fetal growth than birth weight alone, birth weights were standardised for gestation and sex, using British weight reference curves (Freeman et al., 1995). Standardised and crude birth weights were used as continuous measures; as potential risk factors for ultrasound features of OA.

Weight and height at age 49-51 years were measured using a digital weighing scale and stadiometer, respectively, during their visit to the research facility at the Wellcome Labs in Newcastle. BMI was calculated by using the formula: mass (kilograms)/height (m^2) and used as a continuous variable. Percent body fat was estimated from impedance measured using a Holtain body composition analyser (Holtain Ltd, Crymych, Wales, UK).

At age 62/63, weight was measured using the SECA digital weighing scale, with the measurement rounded to one decimal point. The participants wore light indoor clothing without jackets or shoes. Heights were measured using a SECA digital stadiometer. Callibrations for the above equipment were carried out according to the manufacturer's recommendations. Participants stood upright without shoes and measurements were made to the nearest centimetre. BMI was calculated by using the formula mass (kilograms)/height (m^2) and used as a continuous variable.

5.5.2 SES/Occupation

SES, welfare of the family, housing surveys and changes in family environments were recorded frequently between birth and age 15. Health visitors who were assigned to these children would regularly update details of the family prospectively, during their routine visits.

It was a good time for employment and only 14 fathers had no work at all during the first year. The investigators noticed that none of the families of the unemployed moved out of Newcastle to seek work elsewhere.

Only 7% of the mothers were employed in the first year; almost always due to a significant financial need in the family. This low figure was thought to be due to the cultural ideas that were prevalent in the city at the time. However, this helped the research team to gain excellent access to the houses, potentially making the advice given to the mothers, more effective.

At birth, only 10% of families were in the top two social classes while group 3 had the highest proportion with 55% of families, which demonstrated the high number of skilled artisan workers in an industrial city. It is pertinent to note that there was a higher proportion of migration out of the city from families of "better" classes; 18.4 % of total (from groups 1 and 2) compared to 10.4% from group 5.

The SES was measured as the registrar general's social class (RGSC) of the father at birth and the main wage earner of the household at ages 5 and 49-51 years. The 1990 classification of occupations was used and collapsed in to three categories: most advantaged (I, II), middle (III Manual) and least advantaged (III Non-manual, IV, V); for all three time points. These were therefore ordinal variables.

5.5.3 Adverse life events

The occurrence of adverse life events from birth to age 15 years was collected prospectively (Lamont et al., 2000).

The list of adverse events is stated below:

parental divorce or separation

death of a parent

parental incapacity through illness

serious debt

parental criminal activity or cruelty.

Adverse events were used as a dichotomous explanatory variable where presence of any one of the above events led to presence (vs absence) of an adverse life event.

5.5.4 Physical activity

Physical activity can be measured using various methods, which are broadly classified in the following five domains: behavioural observation, questionnaires, physiological indices (such as heart rate), calorimetry and motion sensors (Westerterp, 1999).

Physical activity at age 49-51 years was assessed using the MRC's National Survey of Health and Development and split into four domains of activity; sport, occupational, commuting (walking and cycling) and household (housework, gardening and DIY) (Kuh and Cooper, 1992). Three categories of activity levels were derived in each domain: inactive, less active and most active.

The criteria used to classify physical activity are stated in Table 6 below.

Table 6 Criteria used to classify physical activity (adapted from Kuh et al (Kuh and Cooper, 1992)):

Type of physical activity	***Most active***	***Less active***	***Inactive***
Physical activity during the working day (occupational activity)	Either: (1) over half the day spent walking or (2) frequently lifts and carries heavy things	Not classified in the most active or inactive groups	At least half the day sitting down
Sports and recreational activities: List of 27 activities (eg: swimming, badminton, yoga, football, jogging, etc)	Five or more times in the previous month	1-4 times in the previous month	No reported activity in the previous month

Table 6 Criteria used to classify physical activity

Type of physical activity	*Most active*	*Less active*	*Inactive*
Cycling and walking	Either: (1) Normally rides or walks to work for at least half an hour (round trip) Or (2) 12 rides or walks of half hour in leisure time in previous month	Either: (1) Normally rides or walks for less than half an hour Or (2) 1-11 rides or walks of half hour in leisure time in previous month	Does not normally ride or walk and no reports of riding or walking in leisure time in previous month
Heavy gardening and DIY: List of 10 heavy activities (eg: digging, chopping wood, brick laying, moving heavy objects etc)	Five or more times in the previous month	1-4 times in previous month	No reported activity in previous month

Using factor analysis, a two factor model was found to explain the majority of the variation between all the four physical activity domains described above (Mann et al, unpublished data). Orthogonally rotated factor loadings were high in sport activity (0.87) for factor 1 (labelled PAF1) and high in work (0.64), household (0.64) and commuting

activities (0.74) for factor 2 (labelled PAF2). PAF1 and PAF2 were also used as continuous explanatory variables for the purpose of this assessment.

5.5.5 Diet

Cross sectional self reported dietary data were obtained at age 49-51 years using the European Prospective Investigation of Cancer (EPIC) food frequency questionnaire (Bingham et al., 1997), which was included in the self-completion questionnaire given to participants at this age. Food frequency questionnaires aim to assess the habitual food and nutrient intake of participants. The EPIC food frequency questionnaire asks participants how frequently they have consumed certain food and drink items over the previous year. The responses are then converted to nutrient values.

It is recognised that there are obstacles in the measurement of dietary intake in epidemiological studies (Kaaks and Riboli, 1997). The measurement of a person's habitual, long term intake of food using structured questionnaires tends to have an element of measurement error. There is no definite gold standard measure of dietary intake; so food frequency questionnaires therefore need to be validated against different methods of diet measurement. The random errors of measurements between various methods should ideally be independent of each other, so that correlations between measurements can be regarded as purely due to the association with the same (true) intake variable. The likelihood of this independence (of errors between different methods) can be increased by using methods which have different (predicted) sources of error (Kaaks and Riboli, 1997).

A validation study of the EPIC food frequency questionnaire was performed among 156 women aged 50 to 65 years in Cambridge, UK (Bingham et al., 1997). Three different

methods of dietary assessment were compared with 16 day weighed records of food intake over the course of one year, as well as various biomarkers of food intake including urinary nitrogen, potassium and serum vitamin C and carotenoids. Of the three methods (food frequency questionnaire, 24 hour recall and the 7 day diary), it was found that the unstructured 7-day food diary had the best correlation with urinary nitrogen (r=0.65) while the food frequency questionnaire had a lower correlation of 0.24. However, the correlation of the questionnaire increased markedly to 0.49 after adjusting for energy intake which is known to correlate with 24 hour urine nitrogen. The correlation coefficients between various nutrients measured by the questionnaire and from the weighed food records showed values ranging from 0.4 to 0.6, which compares well with other similar instruments. It was however noted that the questionnaire resulted in significantly higher values for many nutrients than the other two methods and the weighed records, particularly for vegetable and milk intake. These levels of correlation were reported by the authors to be comparable to other studies that reported on instruments directed to assess habitual dietary intake.

For the purpose of this assessment, total dietary energy intake, fat intake, saturated fat intake and dietary intake of vitamin D were used as continuous explanatory variables, based on the literature review assessment of dietary intake and risk of OA which was presented in section 3.9.

5.5.6 Educational status

Educational status was reported by participants in the self-completion questionnaire that was obtained at age 49-51 years. Four categories of highest educational level achieved were derived: incomplete schooling; completed O level; completed A level and degree/post graduate qualification. These data were used to create an ordinal explanatory variable.

5.5.7 Bone density

DEXA imaging was used to measure bone mineral density and bone mineral content at the age of 49-51 years among the Thousand Families Study participants (Pearce et al., 2005a). The lifecourse study of these data found that the majority of variation in bone density was explained by factors acting in adult life. Furthermore, the authors report that the effect of early life factors appear to be mediated through height achieved in adulthood.

The DXA imaging at age 49-51 was performed using a Hologic QDR 2000 machine (Hologic instruments, Waltham, MA). The lumbar spine (L1 to L4) and all regions of the hip (total hip, femoral neck, trochanteric and inter-trochanteric) were imaged. Measurements of area, bone mineral content and bone mineral density were made at these sites. In order to correct for size differences, an estimate of volumetric density was made ($g\ cm^{-3}$); called the bone mineral apparent density (BMAD). This was calculated by using the formulae of Katzman where:

Lumbar spine BMAD = $BMC/area^{3/2}$

Femoral neck BMAD = $BMC/area^{2}$

where the area at the lumbar spine or femoral neck was the projected bone area, determined from the BMD scan (Tuck et al., 2005).

The results from this assessment demonstrated that the BMAD at both sites was significantly lower for men when compared to women. The authors suggested that this result, which was the converse of what was expected, may be due to the fact that the

women were at a perimenopausal age, where the effects of menopausal bone loss would not have occurred yet (Tuck et al., 2005).

For the purpose of the present assessment, BMD at the spine and total hip was used as a continuous explanatory variable.

5.5.8 Smoking & Alcohol

Smoking history was obtained at the age 49-51 year review by asking the participants about their smoking habits at age 15, 25, 35 and 49-51 years. The number of pack years of cigarettes smoked was estimated from the self-reported smoking habits at the ages mentioned above. One pack year = one pack of cigarettes smoked per day for one year. The type of instrument that was used to smoke was recorded, as was the duration, age of onset and quantity. The pack year history was then used as a continuous variable.

Current smoking status at age 49-51 years was also derived: never, ex-smoker and current smoker; a categorical variable.

Self reported levels of alcohol intake were obtained from questionnaire data at age 49-51 years. Four categories were subsequently derived: No drinking; light drinking (up to ten units of alcohol/week for males and 5units/week for females); moderate drinking (11-28 units for males and 6-21 units for females) and heavy drinking (>28 units for males and >21 units for females) (Power et al., 1998).

5.5.9 Infant feeding

Prospective details of infant feeding were initially obtained from midwives reports. This was then followed up by the health visitors who recorded whether infants were wholly breast fed, partly breast fed or wholly bottle fed at regular intervals (up to six times a year) in the first two years of life.

A little more than half of infants were wholly breast fed at the end of the first month, which dropped to one-third at the end of the third month and only one-fifth at the end of the sixth month (see Table 7).

Table 7 Feeding of infants in the first six months (Spence et al., 1954)

	End of 1st month		End of 3rd month		End of 6th month	
Wholly breast-fed	635	58.8%	352	33.3%	228	22.2%
Partly breast-fed, partly bottle-fed	203	18.8%	153	14.4%	86	8.4%
Wholly bottle-fed	242	22.4%	553	52.3%	711	69.4%
Unknown (removed, died, insufficient data)	62		84		117	
	1142		1142		1142	

Two variables were used to describe duration of breast feeding as a potential protective factor for prevalent OA at age 62/63. Firstly, duration of breast feeding (with or without

bottle feeds) was measured in days; as a continuous variable. Secondly, duration of exclusive breast feeding, was measured in months; as a continuous variable.

5.5.10 Infections in childhood

Each family was visited up to six times a year in the first year and between four and five times a year until the age of five, by a team of five health visitors (Lamont et al., 1998). Infections occurring between these visits were notified to the study team by the use of reply-paid postcards given to the parents. In addition, the families were visited by a paediatrician at the end of the first, third and fifth years of the study. Further information was obtained from local GPs and hospital staff who had been given notification of the commencement of this study; a red spot on their medical records helped to further remind caregivers of the study. The City Health Department provided details of attendances of these children to child welfare centres in the city.

During the first year, there was 1625 illness episodes recorded, of which the majority (1393) were infections, of which the majority (799) were respiratory. Minor colds, mild skin infections and sticky eyes were not included in this list. 44 infants died during the first year, which reflected the infant mortality rate in the region at the time.

114 children were found to have episodes of infective diarrhoea and vomiting during the first year. There were no known epidemic illnesses during this period. Four infants were diagnosed to have meningitis in the first year while 15 children were infected with tuberculosis during the first 15 months. Summaries of infections by age distribution in the first five years (see Table 8) and the distribution of the major groups of infections (see Table 9) is shown below.

Table 8 Age-distribution of infective illnesses in 847 children from birth to 5 years (adapted from Miller et al (Miller et al., 1960))

	Year 1	Year 2	Year 3	Year 4	Year 5	Total episodes
Severe colds	236	375	427	344	237	1619
Bronchitis	227	100	150	94	57	628
Pneumonia	35	15	19	6	7	82
Undifferentiated respiratory infections	197	95	80	103	109	584
Whooping cough	89	60	65	97	81	392
Tonsillitis and otitis	91	108	232	196	215	842
Acute infectious fevers	91	216	145	236	339	1027
Herpetic stomatitis	4	62	26	14	12	118
Primary tuberculosis	11	12	19	13	6	61

Table 9 Distribution of 6845 incidents (major groups) of infective illness in 847 children from birth to 5 years (adapted from Miller et al (Miller et al., 1974))

Infective illness	Number of episodes
Respiratory infections	3755
Whooping cough	392
Measles	540
Chicken Pox and Zoster	240
Rubella	134
Mumps	113
Alimentary infections	793
Staphylococcal infections	341
Acute infections of unknown origin	221
Herpetic stomatitis	118
Conjunctivitis	79
Tuberculosis	61
Infective hepatitis	24

Data on infections from birth to age five years were used; the total number of infections during this period were recorded and used as a continuous variable.

5.5.11 Inflammation

Levels of plasma fibrinogen, which is known to be an acute phase reactant, was measured at the age of 49-51, as a proxy measure for inflammation. This was derived from prothrombin time using an automatic coagulator (Lamont et al., 2000). Plasma fibrinogen was measured in grams/L and used as a continuous variable.

A lifecourse analysis of predictors of plasma fibrinogen at age 49-51 years was performed in the Newcastle Thousand Families Study (Pearce et al., 2011). Current smokers (β=0.32, 95% CI 0.21, 0.42) and percentage body fat (β=0.30, 95% CI 0.21, 0.39) had the greatest positive association with fibrinogen in this study, while factors in early life such as housing conditions at birth (β= -0.20, 95% CI -0.31, -0.10) and duration of breast feeding (β= -0.10, 95% CI -0.19, 0.001) had an inverse association of less magnitude. Several indirect associations were also identified, particularly the influence exerted by social class at birth through variables in adult life.

5.5.12 Statistical analyses:

The agreement between ultrasound observers for binary outcomes such as presence/absence of osteophytes and effusions was calculated using kappa statistic (Landis and Koch, 1977) and the corresponding 95% confidence intervals were calculated. The agreement between observers for continuous outcomes such as cartilage thickness was measured using intra-class correlation co-efficients (ICCs).

For the categorical early life characteristics, chi-squared tests were carried out to assess the statistical differences between proportions in the ultrasound cohort compared to the rest of the original birth cohort. For continuous variables, student t tests were performed to ascertain statistical differences between the means of the ultrasound cohort and the rest of the cohort. The level of significance was documented as p-values and the cut off used for significance was 0.05 (Sterne and Davey Smith, 2001).

5.5.12.1 Regression analyses

Univariate and multivariate regression was performed to test for relationships between potential risk factors acting throughout the lifecourse and ultrasound features of OA at the knees, hips and dominant hand at age 62/63 years.

Logistic regression

Logistic regression was used to assess the relationship of each potential risk factor (independent variable) on binary dependant variables such as knee osteophytes, hip OA and hand osteophytes. Logistic regression is based on the logistic transformation:

$$\text{Logit}(p) = \log(p/1-p) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 \ldots\ldots + \beta_m x_m = X\beta$$

where p is the probability of the binary outcome and each of the x_i are independent variables.

Logistic regression assumes that all the observations are independent of each other.

Logistic regression is the method used to analyse epidemiological data when the dependant variable is binary (Hosmer and Lemeshow, 1989). Binary outcomes can take only one of two values, such as presence or absence of knee osteophyte and presence or absence of hip OA. Logistic regression differs from linear regression as it gives predicted values between 0 and 1 when compared to linear regression which can produce innumerable predicted values of the dependant variable (between $-\infty$ to $+\infty$).

The estimated coefficients from each logistic regression model were exponentiated to produce estimated odds ratios which state the influence of each independent variable on the risk of ultrasound features of OA at the knees, hips and dominant hand. The interpretation of the odds ratio for categorical independent variables, such as educational status, is that the odds represent a measure of the odds of OA in one group when compared to that in a reference group. For continuous independent variables, such as duration of breast feeding, the odds ratio implies that the risk of OA increases by a factor of the odds ratio with each unit increase in the continuous variable. 95% confidence intervals are provided for each odds ratio estimate.

Multivariate logistic regression, using a non-automated forward stepwise approach was performed in order to control for potential confounding factors. Initially, all univariate associations of independent variables with the dependant outcome were performed. All univariate associations with a significance of $p<0.15$ were then added in a stepwise fashion in to the multivariate model. The cut off for significance of independent variables in the final multivariate model was $p<0.05$.

The goodness of fit of the final models were checked using Hosmer-Lemeshow deciles of risk goodness-of-fit test. The deciles of risk version of the test used in this investigation formed ten groups which were ranked in order of increasing probability of OA. Grouping data in this manner meant that there were approximately the same number of participants in each group and also that no group had too few participants. A χ^2 test was subsequently performed on eight degrees of freedom.

Linear regression

Linear regression was used to quantify the impact of each independent variable on femoral cartilage thickness in the right knee.

Simple linear regression relates the expected value of the dependent variable, y, to the continuous independent variable, x, using a straight line. This is depicted by the equation:

$$E(y) = \alpha + \beta_i x_i + \varepsilon$$

where α, the constant, is the intercept of the straight regression line with the y-axis when $y = 0$, and β_i, the regression coefficient, is the slope of the regression line. The distribution of ε is referred to as the error distribution; one of the assumptions in linear regression is that the error distribution is normally distributed.

The simplest form of linear regression is the least squares approach where the regression line is constructed to minimise the distance of the sum of the squared distances of the observed responses from the regression line.

Univariate associations of each independent variable on femoral cartilage thickness were identified. All independent variables with significant associations ($p<0.15$) were then added in a stepwise forward manner in to the multivariate adjusted model. The cut off for significance in the final multivariate model was $p<0.05$.

Chapter 6 Results

6.1 Results of pilot study in Northumberland over 85 cohort

The median age of the 20 participants in this study was 89.5 years (88-99 years); 60% (n=12) were female. For right femoral osteophytes, sonographer 1 (AA) had 37% prevalence while sonographer 2 (GM) had 53%. On the left, AA had 47% and GM had 53% prevalence of femoral osteophytes. AA had 32% right tibial osteophytes while GM had 41%. On the left, AA had 42% and GM had 35%.

The prevalence of effusions (≥4 mm) is as follows: AA had 53% prevalence on the right, while GM had 47%. On the left, AA had 47% and GM had 41%.

The prevalence of radiographic abnormalities defined by K-L criteria is as follows: K-L 1 = 17.5%, K-L 2 = 24%, K-L 3 = 41%, K-L 4 = 17.5%. Definite radiographic osteophytes were present in 44% of subjects.

The results of the inter-rater reliability between the two ultrasound observers and that of the validity of ultrasound imaging when compared to radiographs, are stated below.

Reliability

κ for osteophyte presence was in the range of 0.65 to 0.88. ICCs for effusion size were 0.70 (right) and 0.85 (left). Similar high kappa values for presence/absence of effusion were found; 0.65 (right) and 0.77 (left). Moderate to substantial agreement was found in cartilage thickness measurements except for the lateral femoral cartilage thickness on the right, which had a raw κ value of 0.06. However, after the exclusion of two outlying

values, that had been prospectively flagged (prior to analysis) as being particularly difficult to read by the more experienced ultrasonographer, the ICC for this region was 0.67 (see Table 10).

Table 10 Inter-rater reliability: results of comparison between two ultrasound observers in Northumberland over 85 study

	Kappa (95% CI)	**ICC (95% CI)**
Osteophyte (right femur)	0.77 (0.31,1.23)	
Osteophyte (left femur)	0.65 (0.41,1.35)	
Osteophyte (right tibia)	0.88 (0.18,1.12)	
Osteophyte (left tibia)	0.88 (0.41,1.35)	
Effusion size (right)		0.70 (0.45,0.95)
Effusion size (left)		0.85 (0.72,0.98)
Effusion presence (right)	0.65 (0.21, 1.1)	
Effusion presence (left)	0.77 (0.31, 1.23)	
Notch thickness (right)		0.68 (0.43,0.94)
Notch thickness (left)		0.62 (0.32,0.92)

Table 10 Inter-rater reliability: results of comparison between two ultrasound observers in Northumberland over 85 study

	Kappa (95% CI)	ICC (95% CI)
Lateral femoral cartilage thickness (right)		0.06 (0.00,0.54) *
Lateral femoral cartilage thickness (left)		0.50 (0.14,0.86)
Medial femoral cartilage thickness (right)		0.57 (0.25,0.90)
Medial femoral cartilage thickness (left)		0.42 (0.02,0.82)

*after removing the 2 identified outliers, ICC was 0.67 (0.38,0.95)

Validity

For osteophytes, κ was moderate to substantial at 0.52 (95% CI 0.06, 0.98) (right) and 0.75 (95% CI 0.28, 1.22) (left) when comparing radiograph results with those of the first sonographer (AA). When the results of the second sonographer (GM) were used in the comparison, the corresponding kappa values were 0.45 (95% CI -0.04, 0.94) on the right and 0.57 (95% CI 0.05, 1.09) on the left; demonstrating moderate agreement.

In summary, the results of this pilot study demonstrated substantial to excellent agreement between two ultrasonographers for the presence of osteophytes and effusion at the knee and moderate to substantial agreement for the measurement of femoral cartilage thickness. The validity of ultrasound was also noted as seen by the moderate to substantial agreement between ultrasound and radiographs for the presence of knee osteophytes.

6.2 Descriptive results

6.2.1 Comparison of current cohort with original birth cohort

A comparison was made between the early life characteristics of study members who attended the ultrasound assessment and that of the remainder of the Thousand Families cohort; a measure of the selection bias within the study.

There was a higher proportion of women in the ultrasound cohort when compared to the rest of the original cohort (see Table 11); women representing 55.5% in the ultrasound sample compared to 44.5% in the rest of the cohort ($p=0.007$). This could be due to the fact that the retirement age for women at present is 60 compared to 65 for men. This meant that women are less likely to be in employment and therefore might be more able to make time to attend the ultrasound assessment. It might also be related to intrinsic personality differences between the sexes that make women more likely to participate in research studies. The assessment of the cohort at age 49-51 years demonstrated the same difference in participation rates between the sexes.

There were a lower proportion of participants in lower social classes ($p<0.001$) and decreased educational status ($p=0.005$) in the ultrasound cohort, when compared to the rest of the original cohort (see Table 11). This is not entirely unsurprising as those from more advantaged social classes and higher educational status are more likely to have retired by the age of 62/63 years or might have a certain level of job flexibility that would allow them to attend the hospital for the ultrasound assessment. Higher educational status might also enable participants to have a deeper understanding of the importance of the Thousand Families Study and help foster a higher commitment to the study.

Nevertheless, there were no significant differences between the ultrasound sample and the rest of the original cohort in terms of other early life characteristics such as standardised birth weight, duration of breast feeding and adverse life events in childhood (see Table 11).

Table 11 Representative checks of early life variables

	Original cohort	Ultrasound sample	Test statistics
	n (%)	n (%)	
Sex	n = 1142	n = 316	**p = 0.007**
Male	583 (51.05)	141 (44.62)	
Female	559 (48.95)	175 (55.38)	
SES at birth	n = 1062	n = 306	**p < 0.001**
I,II	125 (11.77)	36 (11.76)	
III M	602 (56.69)	200 (65.36)	
III NM, IV, V	335 (31.54)	70 (22.88)	
Standardised birth weight	n = 1030	n = 311	p = 0.40
Mean	-0.178	-0.135	
Standard deviation	1.086	1.089	

Table 11 Representative checks of early life variables

	Original cohort	Ultrasound sample	Test statistics
	n (%)	n (%)	
Adverse life events	n = 502	n = 271	p = 0.55
Present	204 (40.64)	101 (37.27)	
Absent	298 (59.36)	170 (62.73)	
Duration of breast feeding	n = 396	n = 240	p = 0.36
Mean	2.181	2.107	
Standard deviation	1.994	1.940	
Education level	n = 539	n = 272	**p = 0.005**
Incomplete schooling	191 (35.44)	78 (28.68)	
Passed O level	174 (32.28)	99 (36.40)	
Passed A level	103 (19.11)	52 (19.12)	
Graduate or higher	71 (13.17)	43 (15.81)	

6.2.2 Validity of US with radiographs

Most previous epidemiology studies have used radiological criteria for OA definition. The validity of ultrasound defined osteophytes was therefore assessed by comparing it to radiographic osteophytes, using the kappa test statistic (Landis and Koch, 1977) (and

corresponding 95% confidence intervals) to measure the level of agreement between the two modalities.

Moderate to substantial agreement was found between radiographs and ultrasound in the detection of osteophytes, with kappa values ranging from 0.49 to 0.68 (see Table 12).

Table 12 Validity of ultrasound defined knee osteophytes in TFS: comparison with radiographs

	Kappa value (95% CI)
Right knee osteophyte	0.68 (0.39, 0.97)
Left knee osteophyte	0.49 (0.14, 0.84)
Femoral osteophyte	0.61 (0.32, 0.91)
Tibial osteophyte	0.59 (0.28, 0.90)

It was noted that there were tibial spikes reported on knee radiographs that were not identified on ultrasound; thus increasing sensitivity of radiographs in identification of tibial osteophytes (see Table 13). Ultrasound is unable to identify central lesions in the joint due to inaccessibility to this region. It is also possible that the method of ultrasound evaluation (where the probe was not taken around the entire joint circumferentially) might have reduced the sensitivity of ultrasound in identifying knee osteophytes, in this study.

Table 13 Comparison of ultrasound and radiographs - tibial osteophytes

		Ultrasound Tib osteophyte	
		Absent	Present
Radiographic tibial osteophyte	Absent	18	1
	Present	4	6

Ultrasound was found to be more sensitive than radiographs at identifying osteophytes in the femoral aspect of the joint, since these lesions occur around the periphery of the joint (see Table 14).

Table 14 Comparison of ultrasound and radiographs - femoral osteophytes

		Ultrasound Femoral osteophyte	
		Absent	Present
Radiographic femoral osteophyte	Absent	17	4
	Present	1	7

These results suggest that ultrasound and radiographs are complimentary in their ability to image the knee joint.

With regards to the hand, there was no agreement between ultrasound and radiographs at the MCP joint, while the agreement was only slight to fair in the other three joint sites in the hand (see Table 15).

There was a higher prevalence of osteophytes on ultrasound at the DIP joint when compared to radiographs (p=0.09). However, there was no significant difference in prevalence of osteophytes between the two modalities at the other three joint sites.

Table 15 Validity of ultrasound defined hand osteophytes in TFS: comparison with radiographs

	Kappa value (95% CI)
CMC joint	0.19 (-0.16, 0.54)
MCP joint	-0.03 (-0.37, 0.30)
PIP joint	0.14 (-0.28, 0.57)
DIP joint	0.24(-0.01, 0.48)

6.2.3 Inter-rater reliability of US

Inter reader reliability for ultrasound scoring was performed by analysing the scores of a second trained musculoskeletal ultrasonographer, who scored the images for the same

pathologies in all joint sites among 82 participants for the knee and 25 participants for the hand and hip joints. Kappa test statistic and intra class correlation coefficients (ICC) were used, as appropriate, to measure the agreement between the two observers.

The inter reader reliability for osteophytes at the knee was moderate to excellent with values ranging from 0.49 to 0.92. Presence of effusion had excellent agreement between the two sonographers (0.79-left and 0.92-right). Agreement at the hand was moderate to substantial (0.50, 0.69). The kappa value for presence of hip OA at either joint was 0.47, showing moderate agreement at this site. Moderate to substantial agreement was found between observers (ICC 0.43 to 0.61) in the measurement of femoral cartilage thickness at the knee (see Table 16).

Table 16 (Inter rater reliability of ultrasound features of OA at knee, hand and hip joints): comparison with second reader

	Kappa (95% CI)	ICC (95% CI)
Right medial femoral knee osteophyte	0.86 (0.72, 0.99)	
Right lateral femoral knee osteophyte	0.92 (0.82, 1.00)	
Left medial femoral knee osteophyte	0.77 (0.60, 0.93)	
Left lateral femoral knee osteophyte	0.79 (0.62, 0.95)	
Right medial tibial knee osteophyte	0.75 (0.54, 0.96)	
Right lateral tibial knee osteophyte	0.49 (0.18, 0.81)	
Left medial tibial knee osteophyte	0.73 (0.53, 0.93)	
Left lateral tibial knee osteophyte	0.65 (0.42, 0.88)	

Table 16 (Inter rater reliability of ultrasound features of OA at knee, hand and hip joints): comparison with second reader

	Kappa (95% CI)	ICC (95% CI)
Right knee effusion	0.92 (0.82, 1.00)	
Left knee effusion	0.79 (0.61, 0.96)	
CMC OA	0.69 (0.42, 0.95)	
MCP OA	0.50 (0.02, 0.99)	
PIP OA	0.62 (0.30, 0.93)	
DIP OA	0.69 (0.39, 1.00)	
Right hip OA	0.69 (0.36, 1.00)	
Left hip OA	0.40 (0.07, 0.74)	
Any hip OA	0.47 (0.19, 0.75)	
Mean right medial cartilage thickness		0.43 (0.16, 0.70)
Mean right lateral cartilage thickness		0.61 (0.40, 0.82)

6.2.4 Prevalence and pattern of ultrasound features of OA

Prevalence of osteophytes in the dominant hand was high at the DIP joint at 70% while it was 23%, 10% and 41% for index PIP, index MCP and thumb base CMC joints, respectively. Hand OA prevalence was higher among females compared to males (p=0.005). (see Table 17)

Prevalence of knee osteophytes was 22%, 25% and 30% for right, left and "any" knee, respectively. There was no significant difference of knee osteophyte prevalence between males and females (p=0.8) (see Table 17).

The prevalence of knee effusions was 24% and 20% in right and left knees, respectively; with males showing a higher prevalence (p=0.1).

The prevalence of hip OA was higher than described in radiographic surveys, with 26%, 30% and 41% in right, left and "any" hip, respectively. Males had higher prevalence of hip OA (p=0.2). (see Table 17)

Ultrasound evidence of generalised OA (48%) and isolated hand OA (31%) were common, compared to isolated hip or knee OA (5%) and both hip and knee OA (3%). (see Fig 15)

The high prevalence of isolated hand OA suggests that ultrasound defined hand OA precedes the development of generalised OA and may, therefore, be a clinical predictor of generalised OA.

Table 17 Prevalence of ultrasound features of OA in knee, hip and hand

	Total: n=316	Male: n=139	Female: n=177
	Proportion (95% C.I)	Proportion (95% C.I)	Proportion (95% C.I)
OA any knee	30% (0.25, 0.35)	28% (0.20, 0.36)	32% (0.25, 0.39)
OA right knee	22% (0.17, 0.27)	20% (0.13, 0.26)	24% (0.17, 0.30)
OA left knee	25% (0.20, 0.30)	23% (0.16, 0.30)	27% (0.20, 0.33)
OA any hip	41% (0.35, 0.46)	44% (0.36, 0.53)	38% (0.30, 0.45)
OA right hip	26% (0.21, 0.31)	26% (0.19, 0.34)	26% (0.19, 0.33)
OA left hip	30% (0.25, 0.35)	34% (0.26, 0.42)	26% (0.19, 0.33)
OA hand	78% (0.73, 0.82)	67% (0.60, 0.75)	86% (0.81, 0.91)
OA CMC	41% (0.35, 0.46)	33% (0.25, 0.40)	47% (0.40, 0.55)
OA MCP	10% (0.07, 0.13)	9% (0.04, 0.13)	11% (0.06, 0.16)
OA PIP	23% (0.18, 0.28)	21% (0.14, 0.28)	25% (0.18, 0.31)
OA DIP	70% (0.65, 0.75)	56% (0.48, 0.64)	81% (0.75, 0.86)

Fig 15 Venn diagram detailing pattern of OA (%)

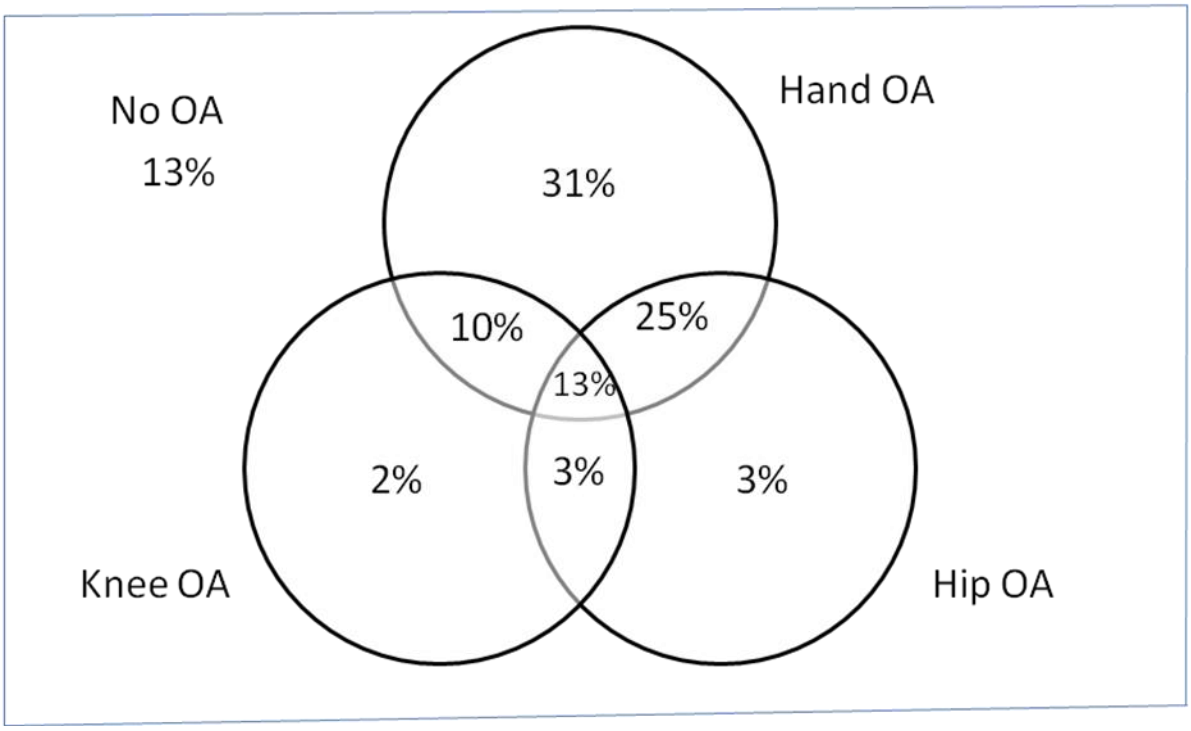


Table 17A Prevalence of power doppler signal in the hand

	Prevalence % (95% CI)
PDS CMC	1.9% (0.01, 0.04)
PDS MCP	4.5% (0.03, 0.07)
PDS PIP	3.9% (0.02, 0.07)
PDS DIP	5.5% (0.03, 0.09)

The prevalence of power doppler signal in the hand joints was low ranging from 1.9% in the CMC joint to 5.5% in the DIP joints.

6.3 Association of ultrasound features of OA with clinical symptoms

The association between ultrasound features of OA in the knee and hip and self-reported clinical symptoms on the WOMAC questionnaire was measured, as was the association between ultrasound defined hand osteophytes and self-reported symptoms on the AUSCAN questionnaire.

For the purpose of these comparisons, the participants were divided in to four categories of severity of pain, stiffness and physical dysfunction and logistic regression was used to calculate the odds ratios of each category of severity when compared to the reference category (those with no symptoms).

6.3.1 WOMAC subscale scores in relation to ultrasound defined knee osteophytes

Those participants who reported most severe pain on the WOMAC questionnaire had the highest odds of knee osteophytes on ultrasound (OR 4.42; 95% CI 2.17, 8.98) when compared to those who reported no pain. Similarly, those with severe stiffness had an OR of 4.21 (95% CI 2.01, 8.83) and those with severe physical difficulties using lower limbs had odds of 4.15 (95% CI 1.96, 8.80) when compared to those with no such symptoms (see Table 18). There was a linear increase in odds of knee osteophytes across the categories of pain and function subscales. These results suggest a high level of association between symptoms and ultrasound defined osteophytes at the knee. When using pain as a linear variable, a one unit increase in pain on the WOMAC subscale increased the odds of ultrasound defined osteophytes by 5% (OR 1.05; 95% CI 1.02, 1.07: $p<0.001$). Similarly, the odds of knee osteophytes for every unit increase in stiffness was 1.10 (95% CI 1.05, 1.16; $p<0.001$) and for one unit increase in physical dysfunction was 1.02 (95% CI 1.01, 1.02: $p<0.001$). After adjustment for sex, BMI and presence of knee effusion, the above estimates remained significant; suggesting that age,

sex, BMI and presence of knee effusion do not appear to confound this association between clinical symptoms and ultrasound defined osteophytes (see Table 18).

Table 18 Association of ultrasound defined knee osteophytes with WOMAC subscale scores

		Patients with knee OA			
Variable	**Total**	**N (%)**	**OR (95% CI)**	**Adjusted OR* (95% CI)**	**Adjusted OR[#] (95% CI)**
Pain subscale score (0-50)					
0	130	24 (18)	1 (ref)	1(ref)	1(ref)
1-9	84	25 (30)	1.87 (0.98, 3.56)	1.82 (0.93, 3.56)	1.93 (0.97, 3.83)
10-19	50	20 (40)	2.94 (1.44, 6.04)	2.33 (1.09, 4.99)	2.19 (0.98, 4.89)
20-50	50	25 (50)	4.42 (2.17, 8.98)	3.30 (1.52, 7.16)	2.74 (1.22, 6.16)

Table 18 Association of ultrasound defined knee osteophytes with WOMAC subscale scores

Variable	Total	N (%)	OR (95% CI)	Adjusted OR* (95% CI)	Adjusted OR# (95% CI)
Stiffness score (0-20)					
0	155	31 (20)	1 (ref)	1 (ref)	1 (ref)
1-4	69	26 (38)	2.42 (1.29, 4.52)	2.27 (1.18, 4.37)	2.26 (1.14, 4.48)
5-10	51	17 (33)	2.00 (0.99, 4.04)	1.59 (0.76, 3.33)	1.81 (0.83, 3.93)
11-20	39	20 (51)	4.21 (2.01, 8.83)	2.65 (1.16, 6.04)	2.37 (1.00, 5.59)
Physical function score (0-170)					
0	134	25 (19)	1 (ref)	1 (ref)	1 (ref)
1-19	81	22 (27)	1.63 (0.84, 3.13)	1.49 (0.75, 2.93)	1.61 (0.80, 3.24)
20-59	50	24 (48)	4.02 (1.99, 8.14)	3.01 (1.43, 6.35)	3.05 (1.39, 6.71)
60-170	41	20 (49)	4.15 (1.96, 8.80)	2.76 (1.20, 6.35)	2.27 (0.94, 5.48)

* = Adjusted for BMI and sex

[#] = Adjusted for BMI, sex and presence of knee effusion on ultrasound

Those in the highest category of weight bearing pain had a significantly higher prevalence of knee osteophytes (OR 3.34; 95% CI 1.61, 3.94) while those in the highest category of non-weight bearing knee pain had a non-significant trend towards increased prevalence of knee osteophytes, when compared to those with no pain (see Table 19). Furthermore, there was a linear trend of increase in knee osteophyte prevalence with increase in weight bearing pain but no such trend was seen with non-weight bearing pain, after adjustment for the potential confounders of BMI and sex. These results provide further evidence of the construct validity of ultrasound evaluation of the knee for presence of osteophytes.

Table 19 Association of knee osteophytes with weight bearing and non weight bearing pain

	Presence of knee osteophytes	
Weight bearing pain score (0-30)	Odds ratio (95% CI)	Adjusted for BMI and sex
0	Ref	Ref
1-5	1.37 (0.67, 2.79)	1.35 (0.65, 2.82)
6-10	2.17 (1.05, 4.50)	1.77 (0.82, 3.81)
11-30	4.72 (2.43, 9.18)	**3.34 (1.61, 6.94)**

Table 19 Association of knee osteophytes with weight bearing and non weight bearing pain

	Presence of knee osteophytes	
Non -weight bearing pain score (0-20)	Odds ratio (95% CI)	Adjusted for BMI and sex
0	Ref	Ref
1-4	2.48 (1.33, 4.61)	2.17 (1.12, 4.20)
5-9	2.90 (1.35, 6.21)	2.51 (1.13, 5.57)
10-20	3.41 (1.55, 7.47)	**2.29 (0.96, 5.48)**

6.3.2 WOMAC subscale scores in relation to mean right medial cartilage thickness on ultrasound

Both the mean and the minimum right medial femoral cartilage thickness were measured among participants.

While there was no association between mean cartilage thickness and the stiffness subscale of WOMAC after adjustment for sex, BMI and presence of knee effusion, there appeared to be a significant trend towards decreasing cartilage thickness with worsening pain and function subscales (see Table 20).

Table 20 Association of mean right medial cartilage thickness with WOMAC subscale scores

		Mean right medial cartilage thickness on ultrasound			
Variable	Total	Mean (SD)	Coefficient (95% CI)	Adjusted coefficient* (95% CI)	Adjusted coefficient[#] (95% CI)
Pain score (0-50)					
0	131	1.61 (0.273)	0 (ref)	0 (ref)	0 (ref)
1-9	85	1.59 (0.281)	-0.01 (-0.09, 0.07)	-0.01 (-0.09, 0.07)	-0.02 (-0.10, 0.05)
10-19	53	1.55 (0.336)	-0.05 (-0.15, 0.04)	-0.07 (-0.16, 0.03)	-0.03 (-0.12, 0.07)
20-50	46	1.49 (0.314)	-0.11 (-0.21, -0.02)	-0.10 (-0.20, 0.00)	-0.10 (-0.19, 0.00)

Table 20 Association of mean right medial cartilage thickness with WOMAC subscale scores

Variable	Total	Mean (SD)	Coefficient (95% CI)	Adjusted coefficient* (95% CI)	Adjusted coefficient[#] (95% CI)
Stiffness(20)					
0	156	1.62 (0.266)	0 (ref)	0 (ref)	0 (ref)
1-4	70	1.55 (0.334)	-0.07 (-0.15, 0.01)	-0.07 (-0.15, 0.01)	-0.06 (-0.13, 0.02)
5-10	53	1.55 (0.281)	-0.07 (-0.16, 0.02)	-0.07 (-0.16, 0.02)	-0.07 (-0.15, 0.02)
11-20	36	1.52 (0.336)	-0.10 (-0.21, 0.01)	-0.08 (-0.19, 0.03)	-0.09 (-0.20, 0.01)
Physical function (170)					
0	135	1.61 (0.266)	0 (ref)	0 (ref)	0 (ref)
1-19	82	1.61 (0.255)	-0.01 (-0.09, 0.07)	0.00 (-0.07, 0.08)	0.01 (-0.07, 0.08)
20-59	52	1.49 (0.365)	-0.12 (-0.21, -0.03)	-0.13 (-0.22, -0.03)	-0.11 (-0.20, -0.02)
60-170	38	1.47 (0.333)	-0.14 (-0.24, -0.03)	-0.13 (-0.23, -0.02)	-0.12 (-0.23, -0.02)

* = Adjusted for BMI and sex

[#] = Adjusted for BMI, sex and presence of knee effusion on ultrasound

6.3.3 WOMAC subscale scores in relation to minimum right medial cartilage thickness on ultrasound

There was a significant inverse association between minimum medial femoral cartilage thickness and pain and physical dysfunction subscales on WOMAC. The relationship remained significant even after adjustment for presence of knee effusion or osteophytes (see Table 21 and Table 22).

Table 21 Association between minimum right medial cartilage thickness on ultrasound and WOMAC scores

		Minimum right medial cartilage thickness on ultrasound			
Variable	Total	Mean (SD)	Coefficient (95% CI)	Adjusted coefficient* (95% CI)	Adjusted coefficient[#] (95% CI)
Pain (0-50)					
0	131	1.50 (0.270)	0 (ref)	0 (ref)	0 (ref)
1-9	85	1.47 (0.289)	-0.03 (-0.11, 0.05)	-0.03 (-0.10, 0.05)	-0.04 (-0.11, 0.04)
10-19	53	1.44 (0.336)	-0.06 (-0.15, 0.04)	-0.07 (-0.16, 0.02)	-0.03 (-0.12, 0.06)
20-50	46	1.38 (0.327)	-0.12 (-0.22, -0.02)	-0.11 (-0.21, -0.01)	-0.11 (-0.20, -0.01)
Stiffness(20)					
0	156	1.51 (0.263)	0 (ref)	0 (ref)	0 (ref)
1-4	70	1.43 (0.344)	-0.08 (-0.16, 0.00)	-0.08 (-0.16, 0.00)	-0.07 (-0.15, 0.01)
5-10	53	1.44 (0.287)	-0.07 (-0.16, 0.02)	-0.07 (-0.16, 0.02)	-0.06 (-0.15, 0.03)
11-20	36	1.41 (0.339)	-0.10 (-0.20, 0.01)	-0.08 (-0.19, 0.03)	-0.09 (-0.19, 0.02)

Table 21 Association between minimum right medial cartilage thickness on ultrasound and WOMAC scores

Variable	Total	Mean (SD)	Coefficient (95% CI)	Adjusted coefficient* (95% CI)	Adjusted coefficient[#] (95% CI)
Physical function (170)					
0	135	1.51 (0.262)	0 (ref)	0 (ref)	0 (ref)
1-19	82	1.49 (0.261)	-0.02 (-0.10, 0.06)	-0.01 (-0.09, 0.07)	-0.01 (-0.08, 0.07)
20-59	52	1.38 (0.373)	-0.13 (-0.22, -0.03)	-0.13 (-0.22, -0.04)	-0.12 (-0.21, -0.03)
60-170	38	1.36 (0.344)	-0.14 (-0.25, -0.04)	-0.13 (-0.24, -0.03)	-0.13 (-0.24, -0.02)

* = Adjusted for BMI and sex

[#] = Adjusted for BMI, sex and presence of knee effusion on ultrasound

Table 22 Association between minimum cartilage thickness and pain after adjustment for knee osteophytes

		Minimum right medial cartilage thickness		
Pain (0-50)	Mean (SD)	Co-efficient (95% CI)	Adjusted co-efficient* (95% CI)	Adjusted co-efficient# (95% CI)
0	1.50 (0.27)	0 (Ref)	0 (Ref)	0 (Ref)
1-9	1.47 (0.29)	-0.03 (-0.11, 0.05)	-0.03 (-0.10, 0.05)	-0.03 (-0.10, 0.05)
10-19	1.44 (0.34)	-0.06 (-0.15, 0.04)	-0.07 (-0.16, 0.02)	-0.02 (-0.11, 0.07)
20-50	1.38 (0.33)	**-0.12 (-0.22, -0.02)**	**-0.11 (-0.21, -0.01)**	**-0.11 (-0.21, -0.01)**

* = Adjusted for BMI and sex

= Adjusted for BMI, sex and presence of knee osteophytes on ultrasound

There was a significant inverse association of minimum right medial femoral cartilage thickness with weight bearing pain while this association was not significant with non-weight bearing pain. Furthermore the magnitude of the association was greater with weight bearing pain when compared to non-weight bearing pain (see Table 23). The linear trend of the inverse association (across the categories of pain severity) was found with weight bearing pain but was not as clear with non-weight bearing pain.

Table 23 Association between minimum cartilage thickness and weight bearing and non weight bearing pain

	Minimum right medial femoral cartilage thickness on ultrasound			Minimum right medial femoral cartilage thickness on ultrasound	
Weight bearing pain (0-30)	Co-efficient (95% CI)	Adjusted for BMI and sex	**Non weight-bearing pain (0-20)**	Co-efficient (95% CI)	Adjusted for BMI and sex
0	Ref	Ref	0	Ref	Ref
1-5	-0.02	-0.03	1-4	-0.01	-0.01
	(-0.11, 0.07)	(-0.11, 0.06)		(-0.10, 0.07)	(-0.11, 0.09)
6-10	-0.04	-0.06	5-9	-0.10	-0.08
	(-0.13, 0.06)	(-0.15, 0.04)		(-0.20, 0.01)	(-0.19, 0.03)
11-30	-0.16	**-0.15**	10-20	-0.12	**-0.08**
	(-0.25, -0.06)	**(-0.25, -0.06)**		(-0.24, -0.01)	**(-0.20, 0.04)**

6.3.4 WOMAC subscale scores in relation to ultrasound defined knee effusion

Contrary to what was expected, the presence of knee effusions on ultrasound did not appear to confer a risk for increasing pain, stiffness or physical dysfunction on WOMAC (see Table 24).

Table 24 Association between knee effusion on ultrasound and WOMAC scores

		Patients with knee effusion (one or both knees)			
Variable	Total	N (%)	OR (95% CI)	Adjusted OR* (95% CI)	Adjusted OR[#] (95% CI)
Pain (0-50)					
0	126	43 (34)	1 (ref)	1 (ref)	1 (ref)
1-9	82	26 (32)	0.90 (0.50, 1.62)	0.97 (0.52, 1.78)	0.87 (0.47, 1.63)
10-19	46	13 (28)	0.76 (0.36, 1.59)	0.92 (0.43, 1.99)	0.86 (0.39, 1.87)
20-50	44	15 (34)	1.00 (0.48, 2.06)	1.58 (0.71, 3.50)	1.37 (0.60, 3.11)

Table 24 Association between knee effusion on ultrasound and WOMAC scores

Variable	Total	N (%)	OR (95% CI)	Adjusted OR* (95% CI)	Adjusted OR[#] (95% CI)
Stiffness (0-20)					
0	149	53 (36)	1 (ref)	1 (ref)	1 (ref)
1-4	65	22 (34)	0.93 (0.50, 1.71)	1.07 (0.56, 2.02)	0.94 (0.49, 1.81)
5-10	49	9 (18)	0.41 (0.18, 0.90)	0.46 (0.20, 1.05)	0.43 (0.19, 1.00)
11-20	35	13 (37)	1.07 (0.50, 2.30)	1.91 (0.82, 4.48)	1.70 (0.71, 4.06)
Physical function (0-170)					
0	129	42 (33)	1 (ref)	1 (ref)	1 (ref)
1-19	79	25 (32)	0.96 (0.53, 1.75)	1.12 (0.60, 2.08)	1.04 (0.55, 1.96)
20-59	46	13 (28)	0.82 (0.39, 1.71)	1.10 (0.50, 2.40)	0.96 (0.43, 2.12)
60-170	37	14 (38)	1.26 (0.59, 2.70)	2.29 (0.96, 5.47)	2.02 (0.82, 4.99)

* = Adjusted for BMI and sex

[#] = Adjusted for BMI, sex and presence of knee osteophytes

6.3.5 WOMAC subscale scores in relation to ultrasound defined hip OA

There was no significant association between ultrasound features of hip OA and any of the three subscales of WOMAC. However, there was a near significant association in those with the most severe physical dysfunction when compared to no physical dysfunction (OR 2.34; 95% CI 0.98, 5.57) and a linear increase in odds ratios across the categories of physical dysfunction, after adjustment for potential confounders (see Table 25).

Table 25 Association between hip OA on ultrasound and WOMAC scores

		Patients with hip OA			
Variable	Total	N (%)	OR (95% CI)	Adjusted OR* (95% CI)	Adjusted OR[#] (95% CI)
Pain subscale score (0-50)					
0	129	44 (34)	1 (ref)	1 (ref)	1 (ref)
1-9	83	35 (42)	1.41 (0.80, 2.49)	1.29 (0.72, 2.33)	1.30 (0.71, 2.35)
10-19	48	20 (42)	1.38 (0.70, 2.72)	1.08 (0.52, 2.21)	1.05 (0.50, 2.21)
20-50	46	25 (54)	2.30 (1.16, 4.56)	1.63 (0.77, 3.46)	1.87 (0.87, 4.05)

Table 25 Association between hip OA on ultrasound and WOMAC scores

Variable	Total	N (%)	OR (95% CI)	Adjusted OR* (95% CI)	Adjusted OR[#] (95% CI)
Stiffness (0-20)					
0	150	54 (36)	1 (ref)	1 (ref)	1 (ref)
1-4	70	33 (47)	1.59 (0.89, 2.82)	1.41 (0.77, 2.57)	1.43 (0.77, 2.66)
5-10	49	19 (39)	1.13 (0.58, 2.19)	0.83 (0.41, 1.68)	0.84 (0.41, 1.74)
11-20	37	18 (49)	1.68 (0.82, 3.48)	1.07 (0.47, 2.42)	1.15 (0.50, 2.66)
Physical function (0-170)					
0	133	43 (32)	1 (ref)	1 (ref)	1 (ref)
1-19	80	33 (41)	1.47 (0.83, 2.61)	1.38 (0.76, 2.50)	1.39 (0.76, 2.54)
20-59	49	25 (51)	2.18 (1.12, 4.25)	1.74 (0.86, 3.52)	1.66 (0.80, 3.43)
60-170	37	21 (57)	2.75 (1.30, 5.79)	1.94 (0.84, 4.44)	2.34 (0.98, 5.57)

* = Adjusted for BMI and sex

[#] = Adjusted for BMI, sex and presence of knee effusion on ultrasound

6.3.6 AUSCAN subscale scores in relation to ultrasound defined hand OA

There was no evidence of association between ultrasound defined osteophytes and any of the three subscales in the AUSCAN questionnaire, after adjustment for BMI and sex (see Table 26).

Table 26 Association between hand OA on ultrasound and AUSCAN scores

		Patients with hand OA		
Variable	Total	N (%)	OR (95% CI)	Adjusted OR* (95% CI)
Pain subscale score (0-50)				
0	161	120 (75)	1 (ref)	1 (ref)
1-9	50	37 (74)	0.97 (0.47, 2.01)	0.74 (0.33, 1.67)
10-19	46	42 (91)	3.59 (1.21, 10.62)	4.53 (1.31, 15.74)
20-50	50	39 (78)	1.21 (0.57, 2.58)	0.87 (0.39, 1.96)

Table 26 Association between hand OA on ultrasound and AUSCAN scores

Variable	Total	N (%)	OR (95% CI)	Adjusted OR* (95% CI)
Stiffness (0-10)				
0	189	140 (74)	1 (ref)	1 (ref)
1-2	46	35 (76)	1.11 (0.53, 2.36)	1.04 (0.45, 2.41)
3-5	40	37 (93)	4.32 (1.27, 14.63)	3.61 (1.04, 12.53)
6-10	31	25 (81)	1.46 (0.56, 3.77)	1.59 (0.55, 4.56)
Physical function (0-90)				
0	151	108 (72)	1 (ref)	1 (ref)
1-9	66	56 (85)	2.23 (1.04, 4.77)	2.11 (0.91, 4.92)
10-29	54	43 (80)	1.56 (0.73, 3.30)	1.22 (0.56, 2.67)
30-90	36	31 (86)	2.47 (0.90, 6.77)	2.13 (0.68, 6.68)

* = Adjusted for BMI and sex

6.4 Lifecourse models for knee osteophyte

Among early life factors, higher standardised birth weight (OR 1.29 per sd unit, p=0.03) was associated with a significantly higher risk of knee OA on univariate analysis (see Table 28). However, the significance of this relationship was lost in the multivariate analysis. Similarly there was a univariate association between social class at birth and knee OA (OR 3.1 [3M-5 vs 1-2], p=0.03) (see Table 27) which was lost after multivariate analysis. Exclusive breast feeding (in months) was associated with a protective effect on knee OA; this association remaining significant even after multivariate analysis (OR 0.81, p=0.02) (see Table 29).

Other univariate associations for knee OA included educational status (OR 0.35 [graduate vs school dropout], p=0.02), BMI at age 50 (OR 1.17, p<0.001) and total hip bone mineral density at age 50 (OR 1.58 per 0.1 g/cm^2, p<0.001) (see Table 28). After multivariate analysis, BMI (OR 1.11, p=0.01) and total hip bone mineral density (OR 1.37 per 0.1 g/cm^2, p=0.02) remained significant associations with knee OA (see Table 29).

Table 27 Risk Factors for Knee Osteophytes (Categorical Variables)

	Knee osteophyte				Odds ratio	95% CI	p value
	Present		Absent				
	No	%	No	%			
	94	30.1	218	69.9			
Male	39	28.1	100	71.9			
Female	55	31.8	118	68.2			
Social class at birth	N = 91		N = 211				0.06
1-11	6	6.6	30	14.2	1.0		
111 (NM)	59	64.8	139	65.9	2.12	0.84, 5.37	
111 (M) - V	26	28.6	42	19.9	3.10	1.13, 8.45	
Social class at age 5 years	N = 81		N = 181				0.95
1-11	23	28.4	49	27.1	1.0		
111 (NM)	37	45.7	82	45.3	0.96	0.51, 1.80	
111 (M) - V	21	25.9	50	27.6	0.89	0.44, 1.82	

Table 27 Risk Factors for Knee Osteophytes (Categorical Variables)

	Knee osteophyte				Odds ratio	95% CI	p value
	Present		Absent				
Educational attainment	N = 80		N= 188				0.12
Below "O" level	29	36.3	45	23.9	1.0		
"O" level	28	35.0	71	37.8	0.61	0.32, 1.16	
"A" level	15	18.7	37	19.7	0.63	0.29, 1.35	
Graduate or higher	8	10.0	35	18.6	0.35	0.14, 0.87	
Adverse life events	N = 75		N = 179				0.19
No	42	56	116	64.8	1.0		
Yes	33	44	63	35.2	1.45	0.84, 2.50	
Cigarette smoking at age 50	N = 72		N = 167				0.85
Non-smokers	33	45.8	79	47.3	1.0		
Ex-smokers	28	38.9	59	35.3	1.14	0.62, 2.08	
Current smokers (age 50)	11	15.3	29	17.4	0.91	0.41, 2.03	

Table 27 Risk Factors for Knee Osteophytes (Categorical Variables)

	Knee osteophyte				Odds ratio	95% CI	p value
	Present		Absent				
Physical activity at age 50	N = 72		N = 167				0.34
Inactive	6	8.3	16	9.6	1.0		
Light activity	38	52.8	70	41.9	1.45	0.52, 4.0	
Moderate activity	14	19.4	49	29.3	0.76	0.25, 2.31	
Heavy activity	14	19.4	32	19.2	1.17	0.38, 3.61	
Sport activity at age 50	N = 83		N = 189				0.03
Inactive	53	63.9	96	50.8	1.0		
Light activity	3	3.6	23	12.2	0.24	0.07, 0.82	
Heavy activity	27	32.5	70	37.0	0.70	0.40, 1.22	
Walking/cycling at age 50	N = 82		N = 190				0.81
Inactive	10	12.2	19	10.0	1.0		
Light activity	31	37.8	78	41.1	0.76	0.32, 1.80	
Heavy activity	41	50.0	93	48.9	0.84	0.36, 2.0	

Table 27 Risk Factors for Knee Osteophytes (Categorical Variables)

	Knee osteophyte				Odds ratio	95% CI	p value
	Present		Absent				
House work activity at age 50	N = 83		N = 190				0.41
Inactive	16	19.3	25	13.2	1.0		
Light activity	12	14.5	33	17.4	0.57	0.23, 1.41	
Heavy activity	55	66.3	132	69.5	0.65	0.32, 1.31	
Occupational activity at age 50	N = 82		N = 189				0.25
Inactive	46	56.1	126	66.7	1.0		
Light activity	26	31.7	47	24.9	1.52	0.84, 2.72	
Heavy activity	10	12.2	16	8.5	1.71	0.73, 4.04	
Social class at age 50	N = 78		N = 185				0.26
1,11,III(NM)	51	65.4	134	72.4	1.0		
111 (M)	19	24.4	29	15.7	1.72	0.88, 3.34	
IV-V	8	10.3	22	11.9	0.96	0.40, 2.28	

Table 27 Risk Factors for Knee Osteophytes (Categorical Variables)

	Knee osteophyte				Odds ratio	95% CI	p value
	Present		Absent				
Self reported alcohol intake at age 50	N= 81		N= 189				0.61
None	10	12.4	15	7.9	1.0		
1	32	39.5	75	39.7	0.64	0.26, 1.58	
2	32	39.5	86	45.5	0.56	0.23, 1.37	
3	7	8.6	13	6.9	0.81	0.24, 2.73	

Table 28 Risk Factors for Knee Osteophytes (continuous variables)

	n	Mean (SD)	Odds ratio	95% CI	p value
Standardised birth weight	307	-0.139 (1.094)	1.29	1.02, 1.62	0.03
Exclusive breast feeding (months)	236	2.087 (1.917)	0.86	0.73, 1.00	0.04
Age at menarche (years)	149	12.98 (1.463)	0.89	0.70, 1.13	0.34
Body fat % at age 50 years (impedance)	245	39.11 (8.288)	1.04	1.00, 1.08	0.03
BMI at age 50 years	246	26.46 (4.159)	1.17	1.09, 1.25	<0.001
Weight at age 50 years (kg)	246	73.73 (13.782)	1.04	1.02, 1.06	<0.001
Height (cm) at age 50 years	246	166.73 (8.381)	1.00	0.97, 1.03	0.95
Total hip bone density at age 50 (dgm/cm2)	230	9.83 (1.280)	1.58	1.25, 2.00	<0.001
Total spine density at age 50 (gm/cm2)	231	1.050 (0.1310)	8.97	1.03, 78.3	0.05
Pack years of smoking (aged 50)	273	9.26 (13.647)	1.00	0.98, 1.02	0.90

Table 28: Risk Factors for Knee Osteophytes (continuous variables)

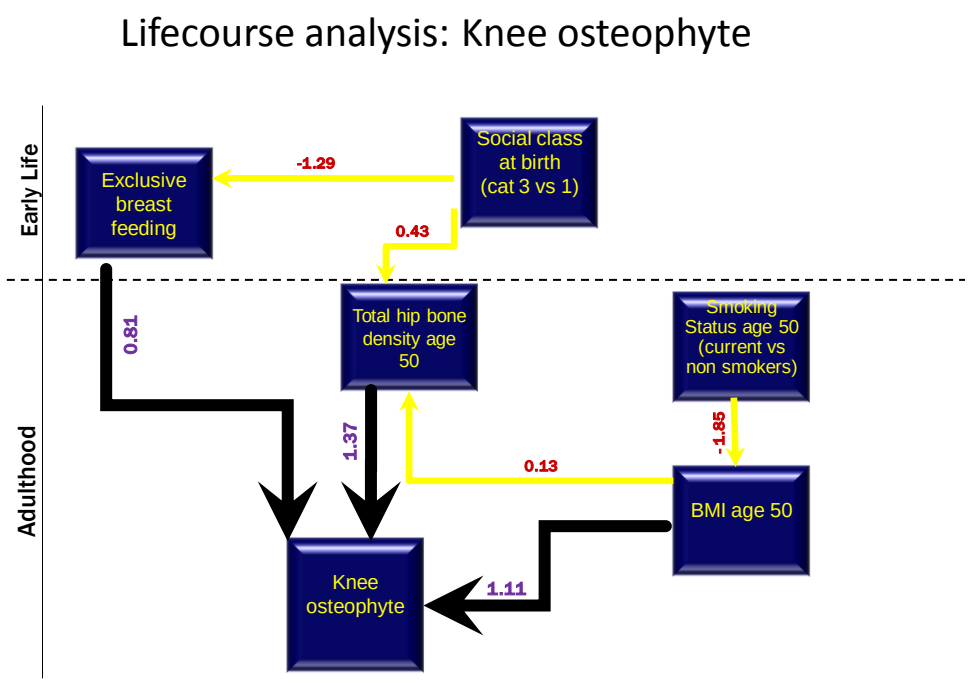
	n	Mean (SD)	Odds ratio	95% CI	p value
Vitamin D dietary intake at age 50 years (micrograms/day)	268	3.53 (2.030)	1.00	0.88, 1.14	0.95
Dietary intake of saturates at age 50 years (grams/day)	268	27.63 (12.852)	1.01	0.99, 1.03	0.37
Dietary intake of total fat at age 50 years (grams/day)	237	75.09 (31.587)	1.00	0.99, 1.01	0.33
Dietary intake of total energy (kilocals) at age 50 years	237	1984.58 (578.827)	1.00	1.00, 1.00	0.19
Total infections from age 0 to 5 years	305	10.22 (5.945)	0.98	0.94, 1.03	0.48
Sport related physical activity (aged 50)	271	0.150 (1.055)	0.76	0.59, 0.98	0.03
Non sport related physical activity (aged 50)	271	-0.048 (0.982)	1.03	0.79, 1.34	0.83

Table 29 Adjusted multivariate model for knee osteophyte

	Odds ratio (95% CI)	p value
Exclusive breast feeding (months)	0.81 (0.68, 0.97)	p = 0.02
BMI at age 50	1.11 (1.02, 1.19)	p = 0.01
Total Hip BMD (in dg/cm^2 at age 50)	1.37 (1.06, 1.78)	p = 0.02

There were indirect relationships seen between the identified direct risk factors for knee OA and other variables studied. A lower social class at birth was associated with decreased duration of exclusive breast feeding (Coef = -1.29 [3B-5 vs 1-2], p=0.01) and increased total hip bone mineral density (Coef = 0.43 [3B-5 vs 1-2], p=0.03). Smoking at age 50 was inversely associated with BMI (Coef = -1.85 (current vs non), p=0.01). A higher BMI had a positive association with total hip bone mineral density (Coef = 0.13, p<0.001). The above results explain the univariate association seen between social class at birth and knee OA which was mediated by the effect of social class on exclusive breast feeding and total hip bone mineral density. While BMI had a direct effect on knee OA, it also exerted an indirect effect through its association with total hip bone mineral density (see Fig 16).

Fig 16 Schematic representation of lifecourse risk of knee osteophytes



The black and bold arrows represent the effect of direct risk factors for knee osteophytes at age 62/63 years, while the yellow arrows represent the indirect risk factors affecting knee osteophytes through their mediating effects on the direct risk factors.

Serum fibrinogen at age 50 years demonstrated borderline significance in the multivariate model for knee osteophyte with a 67% increase in risk of knee osteophyte per 1 g/L increase in serum fibrinogen level (95% CI 0.99, 2.85) (see Table 30).

Table 30 Alternative adjusted multivariate model for knee osteophyte (with fibrinogen included)

	Odds ratio (95% CI)	p value
Exclusive breast feeding (months)	0.82 (0.68, 0.98)	p = 0.03
BMI at age 50	1.09 (1.01, 1.18)	p = 0.03
Total Hip BMD (in dg/cm^2 at age 50)	1.40 (1.08, 1.82)	p = 0.01
Fibrinogen level (in g/L at age 50)	1.67 (0.99, 2.85)	p = 0.056

Further analyses were performed to assess the risk of knee osteophyte among males and females.

6.4.1 Risk of knee osteophytes among males

On univariate analysis, males had a positive association for knee OA with total hip BMD (OR 1.56 per 0.1 g/cm^2, p=0.01), a near significant inverse relationship with exclusive breast feeding (OR 0.79, p=0.06) (see Table 32) and a positive relationship with occupational physical activity (OR 3.02 [heavy vs none], p=0.03) (see Table 31).

On multivariate analysis, total hip BMD (OR 1.72 per 0.1 g/cm^2, p=0.01) and occupational physical activity (OR 4.26 [light vs none], p=0.02) had a significant positive association with knee OA in men while exclusive breast feeding had a near significant inverse association (OR 0.75 per month, p=0.06).

Table 31 Risk factors among males for knee osteophytes (categorical variables)

	Knee osteophyte				Odds ratio	95% CI	p value
	Present		Absent				
	No	%	No	%			
Social class at birth	N = 38		N = 95				0.07
1-11	2	5.3	15	15.8	1.0		
111 (NM)	22	57.9	60	63.2	2.75	0.58, 13	
111 (M) - V	14	36.8	20	21.0	5.25	1.03, 27	
Social class at age 5 years	N = 32		N = 80				0.47
1,11,III(NM)	7	21.9	24	30.0	1.0		
111 (M)	15	46.9	39	48.8	1.32	0.47, 3.70	
IV-V	10	31.2	17	21.3	2.02	0.64, 6.36	
Educational attainment	N = 31		N = 79				0.15
Below “O” level	8	25.8	14	17.7	1.0		
“O” level	13	41.9	23	29.1	0.99	0.33, 2.98	
“A” level	7	22.6	21	26.6	0.58	0.17, 1.97	
Graduate or higher	3	9.7	21	26.6	0.25	0.06, 1.11	

Table 31 Risk factors among males for knee osteophytes (categorical variables)

	Knee osteophyte				Odds ratio	95% CI	p value
	Present		Absent				
Adverse life events	N= 31		N = 80				0.35
No	18	58.1	54	67.5	1.0		
Yes	13	41.9	26	32.5	1.50	0.64, 3.52	
Cigarette smoking at age 50	N = 28		N = 68				0.33
Non-smokers	8	28.6	28	41.2	1.0		
Ex-smokers	15	53.6	34	50.0	1.54	0.57, 4.17	
Current smokers (age 50)	5	17.9	6	8.8	2.92	0.70, 12.1	
Physical activity at age 50	N = 28		N = 68				0.61
Inactive	2	7.1	4	5.9	1.0		
Light activity	17	60.7	32	47.1	1.06	0.18, 6.40	
Moderate activity	5	17.9	18	26.5	0.56	0.08, 3.97	
Heavy activity	4	14.3	14	20.6	0.57	0.08, 4.35	

Table 31 Risk factors among males for knee osteophytes (categorical variables)

	Knee osteophyte				Odds ratio	95% CI	p value
	Present		Absent				
Sport activity at age 50	N = 33		N = 80				0.17
Inactive	23	69.7	41	51.3	1.0		
Light activity	2	6.1	11	13.8	0.32	0.07, 1.59	
Heavy activity	8	24.2	28	35.0	0.51	0.20, 1.30	
Walking/cycling at age 50	N = 32		N = 80				0.57
Inactive	2	6.3	10	12.5	1.0		
Light activity	11	34.4	28	35.0	1.96	0.37, 10.4	
Heavy activity	19	59.4	42	52.5	2.26	0.45, 11.3	
House work activity at age 50	N = 33		N = 80				0.22
Inactive	13	39.4	20	25.0	1.0		
Light activity	4	12.1	18	22.5	0.34	0.09, 1.24	
Heavy activity	16	48.5	42	52.5	0.59	0.24, 1.45	

Table 31 Risk factors among males for knee osteophytes (categorical variables)

	Knee osteophyte				Odds ratio	95% CI	p value
	Present		Absent				
Occupational activity at age 50	N = 32		N = 80				0.03
Inactive	13	40.6	54	67.5	1.0		
Light activity	11	34.4	15	18.8	3.05	1.14, 8.16	
Heavy activity	8	25.0	11	13.8	3.02	1.01, 9.0	
Social class at age 50	N = 32		N = 78				0.02
1,11,III(NM)	15	46.9	55	70.5	1.0		
111 (M)	14	43.8	14	18.0	3.67	1.44, 9.34	
IV-V	3	9.4	9	11.5	1.22	0.29, 5.1	
Self reported alcohol intake at age 50	N = 32		N = 80				0.74
None	2	6.3	4	5.0	1.0		
1	13	40.6	34	42.5	0.76	0.12, 4.7	
2	12	37.5	35	43.8	0.69	0.11, 4.23	
3	5	15.6	7	8.8	1.43	0.18, 11.1	

Table 32 Risk factors among males for Knee Osteophytes (continuous variables)

	n	Mean (SD)	Odds ratio	95% CI	p value
Standardised birth weight	138	-0.27 (1.039)	1.22	0.85, 1.76	0.28
Exclusive breast feeding (months)	97	1.99 (1.958)	0.79	0.61, 1.03	0.06
Body fat % at age 50 years (impedance)	101	36.74 (6.926)	0.97	0.91, 1.03	0.29
BMI at age 50 years	101	27.16 (3.463)	1.10	0.97, 1.25	0.13
Weight at age 50 years (kg)	101	82.17 (11.727)	1.02	0.98, 1.06	0.32
Height (cm) at age 50 years	101	173.86 (5.556)	0.97	0.90, 1.05	0.43
Total hip bone density at age 50 (dgm/cm2)	94	10.28 (1.282)	1.56	1.09, 2.24	0.01
Total spine density at age 50 (gm/cm2)	94	1.04 (0.124)	3.22	0.09, 113.8	0.52
Pack years of smoking (aged 50)	113	12.40 (16.541)	1.00	0.97, 1.02	0.96
Vitamin D dietary intake at age 50 years (micrograms/day)	112	3.73 (2.255)	1.00	0.88, 1.14	0.95

Table 32 Risk factors among males for Knee Osteophytes (continuous variables)

Dietary intake of saturates at age 50 years (grams/day)	112	31.49 (13.977)	1.02	0.99, 1.05	0.11
Dietary intake of total fat at age 50 years (grams/day)	96	84.33 (35.678)	1.01	1.00, 1.02	0.18
Dietary intake of total energy (kilocals) at age 50 years	96	2133.29 (647.211)	1.00	1.00, 1.00	0.15
Total infections from age 0 to 5 years	137	9.91 (6.515)	0.98	0.92, 1.04	0.54
Sport related physical activity (aged 50)	112	-0.07 (1.094)	0.58	0.38, 0.88	0.01
Non sport related physical activity (aged 50)	112	-0.12 (1.131)	1.21	0.83, 1.76	0.32

6.4.2 Risk of knee osteophytes among females

On univariate analysis, females showed a positive association of knee OA with BMI at age 50 (OR 1.21, p<0.001) and total hip BMD (OR 1.70 per 0.1 g/cm^2, p=0.002). Standardised birth weight had a near significant positive univariate association with knee OA in women (OR 1.32 per sd unit, p=0.06) (see Table 34).

On multivariate analysis, BMI (OR 1.22, p<0.001) and standardised birth weight (OR 1.43, p=0.05) had a significant association with knee OA in women.

Table 33 Risk factors among females for Knee Osteophytes (categorical variables)

	Knee osteophyte				Odds ratio	95% CI	p value
	Present		Absent				
	No	%	No	%			
Social class at birth	N = 53		N = 116				0.53
1-11	4	7.6	15	12.9	1.0		
111 (NM)	37	69.8	79	68.1	1.76	0.55, 5.66	
111 (M) - V	12	22.6	22	19.0	2.05	0.55, 7.6	
Social class at age 5 years	N = 49		N = 101				0.37
1-11	16	32.7	25	24.8	1.0		
111 (NM)	22	44.9	43	42.6	0.80	0.36, 1.8	
111 (M) - V	11	22.5	33	32.7	0.52	0.21, 1.3	
Educational attainment	N = 49		N = 109				0.27
Below “O” level	21	42.9	31	28.4	1.0		
“O” level	15	30.6	48	44.0	0.46	0.21, 1.03	
“A” level	8	16.3	16	14.7	0.74	0.27, 2.03	
Graduate or higher	5	10.2	14	12.8	0.53	0.16, 1.7	

Table 33 Risk factors among females for Knee Osteophytes (categorical variables)

	Knee osteophyte				Odds ratio	95% CI	p value
	Present		Absent				
Adverse life events	N = 44		N = 99				0.36
No	24	54.5	62	62.6	1.0		
Yes	20	45.5	37	37.4	1.40	0.68, 2.87	
Cigarette smoking at age 50	N = 44		N = 99				0.40
Non-smokers	25	56.8	51	51.5	1.0		
Ex-smokers	13	29.6	25	25.3	1.06	0.47, 2.42	
Current smokers (age 50)	6	13.6	23	23.2	0.53	0.19, 1.47	
Physical activity at age 50	N = 44		N = 99				0.46
Inactive	4	9.1	12	12.1	1.0		
Light activity	21	47.7	38	38.4	1.66	0.47, 5.79	
Moderate activity	9	20.5	31	31.3	0.87	0.23, 3.37	
Heavy activity	10	22.7	18	18.2	1.67	0.42, 6.56	

Table 33 Risk factors among females for Knee Osteophytes (categorical variables)

	Knee osteophyte				Odds ratio	95% CI	p value
	Present		Absent				
Sport activity at age 50	N = 50		N = 109				0.09
Inactive	30	60.0	55	50.5	1.0		
Light activity	1	2.0	12	11.0	0.15	0.02, 1.23	
Heavy activity	19	38.0	42	38.5	0.83	0.41, 1.67	
Walking/cycling at age 50	N = 50		N = 110				0.34
Inactive	8	16.0	9	8.2	1.0		
Light activity	20	40.0	50	45.5	0.45	0.15, 1.33	
Heavy activity	22	44.0	51	46.4	0.49	0.17, 1.42	
House work activity at age 50	N = 50		N = 110				0.85
Inactive	3	6.0	5	4.6	1.0		
Light activity	8	16.0	15	13.6	0.89	0.17, 4.72	
Heavy activity	39	78.0	90	81.8	0.72	0.16, 3.17	
Occupational activity at age 50 years	N = 50		N = 109				0.98
Inactive	33	66.0	72	66.1	1.0		
Light activity	15	30.0	32	29.4	1.02	0.49, 2.14	
Heavy activity	2	4.0	5	4.6	0.87	0.16, 4.73	

Table 33 Risk factors among females for Knee Osteophytes (categorical variables)

	Knee osteophyte				Odds ratio	95% CI	p value
	Present		Absent				
Social class at age 50	N = 46		N = 107				0.83
1,11,III(NM)	36	78.3	79	73.8	1.0		
111 (M)	5	10.9	15	14.0	0.73	0.25, 2.17	
IV-V	5	10.9	13	12.2	0.84	0.28, 2.55	
Self reported alcohol intake at age 50	N = 49		N = 109				0.69
None	8	16.3	11	10.1	1.0		
1	19	38.8	41	37.6	0.64	0.22, 1.84	
2	20	40.8	51	46.8	0.54	0.19, 1.54	
3	2	4.1	6	5.5	0.46	0.07, 2.89	

Table 34 Risk factors among females for Knee Osteophytes (continuous variables)

	n	Mean (SD)	Odds ratio	95% CI	p value
Standardised birth weight	169	-0.03 (1.130)	1.32	0.98, 1.78	0.06
Exclusive breast feeding (months)	139	2.15 (1.891)	0.90	0.74, 1.09	0.28
Age at menarche (years)	149	12.98 (1.463)	0.89	0.70, 1.13	0.34
Body fat % at age 50 years (impedance)	144	40.78 (8.770)	1.08	1.03, 1.13	0.002
BMI at age 50 years	145	25.98 (4.530)	1.21	1.11, 1.32	<0.001
Weight at age 50 years (kg)	145	67.85 (11.953)	1.08	1.05, 1.12	<0.001
Height (cm) at age 50 years	145	161.76 (6.128)	1.03	0.97, 1.09	0.40
Total hip bone density at age 50 (dgm/cm2)	136	9.53 (1.191)	1.70	1.22, 2.35	0.002
Total spine density at age 50 (gm/cm2)	137	1.06 (0.136)	16.8	1.07, 263.3	0.04
Vitamin D dietary intake at age 50 years (micrograms/day)	156	3.38 (1.844)	1.00	0.88, 1.14	0.95

Table 34 Risk factors among females for Knee Osteophytes (continuous variables)					
Dietary intake of saturates at age 50 years (grams/day)	156	24.86 (11.230)	1.00	0.97, 1.03	0.88
Dietary intake of total fat at age 50 years (grams/day)	141	68.80 (26.829)	1.00	0.99, 1.01	0.93
Dietary intake of total energy (kilocals) at age 50 years	141	1883.33 (505.026)	1.00	1.00, 1.00	0.61
Total infections from age 0 to 5 years	168	10.46 (5.443)	0.99	0.93, 1.05	0.65
Sport related physical activity (aged 50)	159	0.30 (1.001)	0.89	0.63, 1.24	0.48
Non sport related physical activity (aged 50)	159	0.002 (0.862)	0.85	0.58, 1.26	0.42

These results suggest that early life factors have an important direct (breast feeding) and indirect (social class at birth) role in the development of knee OA at age 63 years. They act independent of the previously known adult risk factors of BMI and BMD. There appear to be sex differences as well where breast feeding, BMD and occupational physical activity play important roles in the development of knee OA in men while BMI and standardised birth weight play the main role in women.

6.5 Lifecourse models for knee cartilage thickness

Sex was the most important predictor for mean medial cartilage thickness at the right knee; women having a significantly decreased mean cartilage thickness (coeff -0.18; 95% CI -0.25, -0.10: p<0.001). Those in less advantaged social classes at birth had a reduced mean cartilage thickness at age 63; those in category 3 when compared to category 1 had a coefficient of -0.17 (95% CI -0.30, -0.05: p=0.007). Heavy alcohol intake (when compared to no alcohol intake) at age 50 appeared to have a protective effect on mean cartilage thickness at age 63, even after controlling for smoking and other variables in the adjusted multivariable model (coeff 0.25; 95% CI 0.07, 0.43: p=0.007). Nevertheless, smoking had a deleterious effect on mean thickness of cartilage where current smokers had thinner mean cartilage when compared to never smokers (coeff -0.11; 95% CI -0.22, -0.01: p=0.03) (see Table 36).

The predictors of minimum right medial femoral cartilage thickness were the same as that of mean cartilage thickness, with similar estimates of magnitude (see Table 38).

Table 35 Linear regression (univariate analysis) – mean thickness right medial femoral cartilage

		Mean right medial cartilage thickness			
	n	Co-efficient	95% CI	P value	R^2 (%)
Gender					
Male (Reference)	142				
Female	173	-0.18	-0.24, -0.12	<0.001	9.30
Standardised birth weight	307	0.00	-0.03, 0.03	0.95	0.00
Social class at birth	305			0.16	1.19
I-II (Reference)					
III (NM)		-0.06	-0.16, 0.05	0.29	
III (M) - V		-0.11	-0.23, 0.01	0.07	
Exclusive breast feeding (months)	236	0.00	-0.02, 0.02	0.88	0.01
Social class at age 5 years	264			0.71	0.26
I-II (Reference)					
III (NM)		-0.04	-0.12, 0.05	0.43	
III (M) - V		-0.03	-0.13, 0.07	0.53	

Table 35 Linear regression (univariate analysis) – mean thickness right medial femoral cartilage

	n	Co-efficient	95% CI	P value	R^2 (%)
Age at menarche (years)	147	-0.01	-0.04, 0.02	0.40	0.49
Educational attainment	266			0.10	2.33
Below "O" level (Reference)					
"O" level		0.07	-0.02, 0.16	0.12	
"A" level		0.11	0.00, 0.21	0.04	
Graduate or higher		0.12	0.01, 0.23	0.04	
Adverse life events	255			0.24	0.54
No (Reference)					
Yes		-0.05	-0.12, 0.03		
Body fat % at age 50 years (impedance)	245	-0.004	-0.01, 0.00	0.11	1.04
BMI at age 50 years	246	-0.003	-0.01, 0.01	0.50	0.19
Weight at age 50 years (kg)	246	0.003	0.00,0.01	0.04	1.74
Cigarette smoking at age 50 years (pack years)	273	0.00	0.00, 0.00	0.85	0.01

Table 35 Linear regression (univariate analysis) – mean thickness right medial femoral cartilage

	n	Co-efficient	95% CI	P value	R^2 (%)
Cigarette smoking at age 50 years	239			0.05	2.49
Non-smokers (Reference)					
Ex-smokers		0.03	-0.05, 0.11	0.51	
Current smokers (age 50)		-0.11	-0.21, 0.00	0.05	
Height (cm) at age 50 years	246	0.01	0.01, 0.02	<0.001	9.64
Total hip bone density at age 50 (g/cm^2)	229	0.18	-0.12, 0.48	0.24	0.61
Total spine bone density at age 50 (g/cm^2)	230	-0.13	-0.42, 0.16	0.37	0.35
Physical activity at age 50 years	238			0.45	1.12
No activity (Reference)					
Light activity		0.01	-0.13, 0.14	0.94	
Moderate activity		0.08	-0.07, 0.22	0.30	
Heavy activity		0.04	-0.12, 0.19	0.65	

Table 35 Linear regression (univariate analysis) – mean thickness right medial femoral cartilage

	n	Co-efficient	95% CI	P value	R^2 (%)
Sport activity at age 50 years	272			0.17	1.32
No activity (Reference)					
Light activity		0.10	-0.02, 0.22	0.09	
Heavy activity		0.05	-0.03, 0.12	0.22	
Walking/Cycling at age 50 years	272			0.06	2.03
No activity (Reference)					
Light activity		0.13	0.01, 0.25	0.04	
Heavy activity		0.07	-0.05, 0.19	0.27	
Housework activity at age 50	273			0.56	0.43
No activity (Reference)					
Light activity		-0.06	-0.19, 0.06	0.33	
Heavy activity		-0.05	-0.15, 0.05	0.32	

Table 35 Linear regression (univariate analysis) – mean thickness right medial femoral cartilage

	n	Co-efficient	95% CI	P value	R^2 (%)
Occupational activity at age 50	270			0.98	0.02
No activity (Reference)					
Light activity		0.00	-0.08, 0.08	0.94	
Heavy activity		0.01	-0.12, 0.14	0.86	
Vitamin D intake at age 50 years (micrograms/day)	267	0.00	-0.02, 0.02	0.86	0.01
Social class at age 50 years	263			0.47	0.58
I-II (Reference)					
III (NM)		-0.01	-0.11, 0.08	0.78	
III (M) - V		-0.07	-0.18, 0.04	0.22	
Dietary intake of saturates at age 50 years (grams/day)	267	0.001	-0.002, 0.003	0.70	0.06
Dietary intake of total fat at age 50 years (grams/day)	236	0.000	-0.001, 0.001	0.68	0.07

Table 35 Linear regression (univariate analysis) – mean thickness right medial femoral cartilage

	n	Co-efficient	95% CI	P value	R^2 (%)
Dietary intake of total energy (kilocals) at age 50 years	236	0.000	0.000, 0.000	0.41	0.30
Self reported alcohol intake at age 50 years	270			0.07	2.63
None (Reference)					
1		0.11	-0.02, 0.24	0.08	
2		0.12	-0.01, 0.25	0.07	
3		0.24	0.06, 0.41	0.008	
Total infections from age 0 to 5 years	304	-0.003	-0.009, 0.002	0.22	0.50
Sport related physical activity	270	0.01	-0.02, 0.05	0.45	0.21
Non-sport related physical activity	270	-0.01	-0.04, 0.03	0.68	0.06

Table 36 Adjusted multivariate model for mean right medial cartilage thickness

		coefficient	S.E.	95% CI	p value
sex		**-0.18**	**0.038**	**-0.25, -0.10**	**<0.001**
Social class at birth	I-II (Reference)				
	III (NM)	**-0.08**	**0.055**	**-0.19, 0.03**	**0.17**
	IIIM - V	**-0.17**	**0.064**	**-0.30, -0.05**	**0.007**
Alcohol intake	None (Reference)				
	Light	**0.08**	**0.065**	**-0.05, 0.21**	**0.21**
	Moderate	**0.08**	**0.064**	**-0.05, 0.20**	**0.23**
	Heavy	**0.29**	**0.092**	**0.08, 0.44**	**0.005**
Smoking habit	Never (Reference)				
	Ex-smoker	**0.00**	**0.042**	**-0.08, 0.08**	**1.00**
	Current smoker	**-0.11**	**0.052**	**-0.22, -0.01**	**0.04**
	(aged 50)				

Table 37 Linear regression – minimum thickness right medial femoral cartilage

		Minimum right medial cartilage thickness			
	n	Co-efficient	95% CI	P value	R^2 (%)
Gender					
Male (Reference)	142				
Female	173	-0.18	-0.24, -0.11	<0.001	8.85
Standardised birth weight	307	-0.01	-0.04, 0.03	0.74	0.04
Social class at birth	305			0.20	1.05
I-II (Reference)					
III (NM)		-0.04	-0.15, 0.06	0.42	
III (M) - V		-0.10	-0.22, 0.02	0.09	
Exclusive breast feeding (months)	236	0.00	-0.02, 0.02	0.84	0.02
Social class at age 5 years	264			0.86	0.11
I-II (Reference)					
III (NM)		-0.02	-0.11, 0.06	0.59	
III (M) - V		-0.01	-0.11, 0.09	0.82	

Table 37 Linear regression – minimum thickness right medial femoral cartilage

	n	Co-efficient	95% CI	P value	R^2 (%)
Age at menarche (years)	147	-0.01	-0.04, 0.02	0.47	0.35
Educational attainment	266			0.11	2.27
Below "O" level (Reference)					
"O" level		0.07	-0.02, 0.16	0.11	
"A" level		0.11	0.00, 0.21	0.04	
Graduate or higher		0.11	0.00, 0.23	0.04	
Adverse life events	255			0.25	0.53
No (Reference)					
Yes		-0.05	-0.12, 0.03		
Body fat % at age 50 years (impedance)	245	-0.004	-0.008, 0.001	0.10	1.08
BMI at age 50 years	246	-0.004	-0.01, 0.01	0.42	0.27
Weight at age 50 years (kg)	246	0.002	0.000, 0.005	0.07	1.32
Cigarette smoking at age 50 years (pack years)	273	0.000	-0.003, 0.003	0.93	0.00

Table 37 Linear regression – minimum thickness right medial femoral cartilage

	n	Co-efficient	95% CI	P value	R^2 (%)
Cigarette smoking at age 50 years	239			0.04	2.73
Non-smokers (Reference)					
Ex-smokers		0.03	-0.05, 0.11	0.45	
Current smokers (age 50)		-0.11	-0.22, -0.01	0.04	
Height (cm) at age 50 years	246	0.01	0.006, 0.015	<0.001	8.78
Total hip bone density at age 50 (g/cm^2)	229	0.14	-0.16, 0.44	0.35	0.38
Total spine bone density at age 50 (g/cm^2)	230	-0.15	-0.44, 0.15	0.33	0.42
Physical activity at age 50 years	238			0.47	1.07
No activity (Reference)					
Light activity		0.01	-0.13, 0.16	0.84	
Moderate activity		0.08	-0.06, 0.23	0.26	
Heavy activity		0.04	-0.11, 0.20	0.57	

Table 37 Linear regression – minimum thickness right medial femoral cartilage

	n	Co-efficient	95% CI	P value	R^2 (%)
Sport activity at age 50 years	272			0.11	1.62
No activity (Reference)					
Light activity		0.12	0.00, 0.24	0.06	
Heavy activity		0.05	-0.02, 0.13	0.18	
Walking/Cycling at age 50 years	272			0.08	1.81
No activity (Reference)					
Light activity		0.13	0.00, 0.25	0.04	
Heavy activity		0.07	-0.05, 0.19	0.27	
Housework activity at age 50 years	273			0.56	0.43
No activity (Reference)					
Light activity		-0.06	-0.18, 0.07	0.39	
Heavy activity		-0.06	-0.16, 0.05	0.29	

Table 37 Linear regression – minimum thickness right medial femoral cartilage

	n	Co-efficient	95% CI	P value	R^2 (%)
Occupational activity at age 50 years	270			0.89	0.09
No activity (Reference)					
Light activity		-0.01	-0.09, 0.07	0.83	
Heavy activity		0.03	-0.10, 0.15	0.70	
Vitamin D intake at age 50 years (micrograms/day)	267	-0.003	-0.020, 0.014	0.75	0.04
Social class at age 50 years	263			0.35	0.79
I-II (Reference)					
III (NM)		-0.01	-0.11, 0.08	0.82	
III (M) - V		-0.08	-0.20, 0.03	0.15	
Dietary intake of saturates at age 50 years (grams/day)	267	0.000	-0.003, 0.003	0.90	0.01
Dietary intake of total fat at age 50 years (grams/day)	236	0.000	-0.001, 0.001	0.78	0.03
Dietary intake of total energy (kilocals) at age 50 years	236	0.000	0.000, 0.000	0.50	0.19

Table 37 Linear regression – minimum thickness right medial femoral cartilage

	n	Co-efficient	95% CI	P value	R^2 (%)
Self reported alcohol intake at age 50 years	270			0.06	2.66
None (Reference)					
1		0.14	0.01, 0.27	0.03	
2		0.14	0.01, 0.26	0.04	
3		0.23	0.06, 0.41	0.01	
Total infections from age 0 to 5 years	304	-0.003	-0.009, 0.003	0.29	0.37
Sport related physical activity	270	0.01	-0.02, 0.05	0.42	0.24
Non-sport related physical activity	270	-0.01	-0.04, 0.03	0.70	0.06

Table 38 Adjusted multivariate model for minimum right medial cartilage thickness

		coefficient	S.E.	95% CI	p value
sex		**-0.17**	**0.039**	**-0.25, -0.09**	**<0.001**
Social class at birth	I-II (Reference)				
	III (NM)	**-0.06**	**0.057**	**-0.18, 0.05**	**0.26**
	IIIM - V	**-0.16**	**0.065**	**-0.29, -0.03**	**0.015**
Alcohol intake	None (Reference)				
	Light	**0.10**	**0.066**	**-0.03, 0.23**	**0.21**
	Moderate	**0.09**	**0.065**	**-0.04, 0.21**	**0.23**
	Heavy	**0.25**	**0.094**	**0.06, 0.43**	**0.009**
Smoking habit	Never (Reference)				
	Ex-smoker	**0.00**	**0.043**	**-0.08, 0.09**	**0.94**
	Current smoker	**-0.12**	**0.054**	**-0.22, -0.01**	**0.03**
	(aged 50)				

6.6 Lifecourse models for hip OA

On univariate analysis, BMI at age 50 (OR 1.08, p=0.02) and pack years of smoking (OR 1.03, p=0.009) were the only significant variables associated with hip OA (see Table 40). However, occupational and DIY related physical activity showed a near significant association (OR 1.25, p=0.09).

The multivariable model included three risk factors: BMI at age 50 was the strongest predictor (OR 1.11, p=0.003) followed by occupational and DIY related physical activity (OR 1.48, p=0.008) and pack years of smoking (OR 1.02, p=0.02) (see Table 41).

Table 39 Risk factors for hip OA (univariate analysis) – categorical variables

	Hip OA				Odds ratio	95% CI	p value
	Present		Absent				
	No	%	No	%			
	N = 123		N = 181				
Male	59	44.0	75	56.0			
Female	64	37.6	106	62.4			
Social class at birth	N = 120		N = 175				0.14
1-11	9	7.5	26	14.9	1.0		
111 (NM)	81	67.5	111	63.4	2.11	0.94, 4.74	
111 (M) - V	30	25.0	38	21.7	2.28	0.93, 5.59	
Social class at age 5	N = 107		N = 150				0.14
1-11	31	29.0	41	27.3	1.0		
111 (NM)	54	50.5	62	41.3	1.15	0.64, 2.08	
111 (M) - V	22	20.6	47	31.3	0.62	0.31, 1.23	

Table 39 Risk factors for hip OA (univariate analysis) – categorical variables

	Hip OA				Odds ratio	95% CI	p value
	Present		Absent				
Educational attainment	N = 112		N = 150				0.21
Below "O" level	36	32.1	41	27.3	1.0		
"O" level	41	36.6	53	35.3	0.88	0.48, 1.61	
"A" level	23	20.5	26	17.3	1.01	0.49, 2.07	
Graduate or higher	12	10.7	30	20.0	0.46	0.20, 1.02	
Adverse life events	N = 106		N = 144				0.20
No	60	56.6	93	64.6	1.0		
Yes	46	43.4	51	35.4	1.40	0.84, 2.34	
Cigarette smoking at age 50	N = 100		N = 134				0.08
Non-smokers	39	39.0	72	53.7	1.0		
Ex-smokers	42	42.0	42	31.3	1.85	1.04, 3.29	
Current smokers (age 50)	19	19.0	20	14.9	1.75	0.84, 3.67	

Table 39 Risk factors for hip OA (univariate analysis) – categorical variables

	Hip OA				Odds ratio	95% CI	p value
	Present		Absent				
Physical activity at age 50 years	N = 100		N = 134				0.82
Inactive	9	9.0	12	9.0	1.0		
Light activity	48	48.0	58	43.3	1.10	0.43, 2.84	
Moderate activity	23	23.0	38	28.4	0.81	0.29, 2.2	
Heavy activity	20	20.0	26	19.4	1.03	0.36, 2.9	
Sport activity at age 50 years	N = 114		N = 152				0.52
Inactive	66	57.9	80	52.6	1.0		
Light activity	8	7.0	16	10.5	0.61	0.24, 1.5	
Heavy activity	40	35.1	56	36.8	0.87	0.51, 1.46	
Walking/cycling at age 50 years	N = 113		N = 153				0.20
Inactive	10	8.9	18	11.8	1.0		
Light activity	41	36.3	68	44.4	1.09	0.46, 2.58	
Heavy activity	62	54.9	67	43.8	1.67	0.71, 3.9	

Table 39 Risk factors for hip OA (univariate analysis) – categorical variables

	Hip OA				Odds ratio	95% CI	p value
	Present		Absent				
House work activity at age 50	N = 114		N = 153				0.58
Inactive	13	11.4	24	15.7	1.0		
Light activity	19	16.7	26	17.0	1.35	0.55, 3.31	
Heavy activity	82	71.9	103	67.3	1.47	0.71, 3.06	
Occupational activity at age 50	N = 113		N = 152				0.07
Inactive	73	64.6	94	61.8	1.0		
Light activity	25	22.1	48	31.6	0.67	0.38, 1.19	
Heavy activity	15	13.3	10	6.6	1.93	0.82, 4.55	
Social class at age 50	N = 109		N = 149				0.24
1-11	72	66.1	107	71.8	1.0		
111 (NM)	19	17.4	28	18.8	1.01	0.52, 1.94	
111 (M) - V	18	16.5	14	9.4	1.91	0.89, 4.08	

Table 39 Risk factors for hip OA (univariate analysis) – categorical variables

	Hip OA				Odds ratio	95% CI	p value
	Present		Absent				
Self reported alcohol intake at age 50	N = 112		N = 152				0.21
None	14	12.5	11	7.2	1.0		
1	49	43.8	56	36.8	0.69	0.29, 1.65	
2	42	37.5	73	48.0	0.45	0.19, 1.09	
3	7	6.3	12	7.9	0.46	0.13, 1.56	

Table 40 Risk factors for hip OA (univariate analysis) – continuous variables

	n	Mean (SD)	Odds ratio	95% CI	p value
Standardised birth weight	300	-0.13 (1.09)	0.91	0.73, 1.12	0.36
Exclusive breast feeding (months)	231	2.14 (1.958)	0.92	0.80, 1.05	0.23
Age at menarche (years)	147	12.99 (1.469)	1.11	0.88, 1.39	0.37
Body fat % at age 50 years (impedance)	240	39.18 (8.308)	1.03	1.00, 1.06	0.09
BMI at age 50 years	241	26.49 (4.174)	1.08	1.01, 1.15	0.02
Weight at age 50 years (kg)	241	73.75 (13.842)	1.02	1.00, 1.03	0.11
Height (cm) at age 50 years	241	166.65 (8.403)	0.99	0.96, 1.02	0.56
Total hip bone density at age 50 (dgm/cm2)	226	9.82 (1.269)	1.03	0.84, 1.27	0.77
Total spine density at age 50 (gm/cm2)	227	1.05 (0.131)	0.29	0.04, 2.25	0.24
Pack years of smoking (aged 50)	267	9.17 (13.547)	1.03	1.01, 1.04	0.009

Table 40 Risk factors for hip OA (univariate analysis) – continuous variables

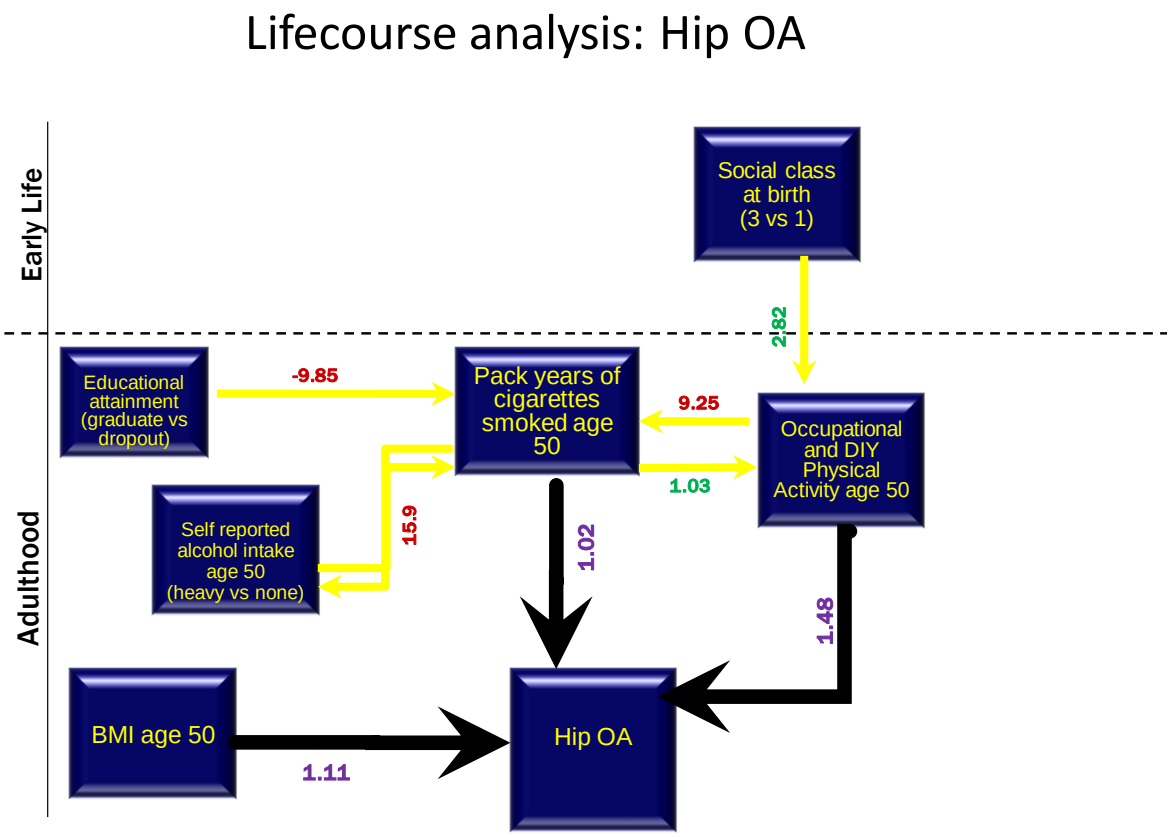
	n	Mean (SD)	Odds ratio	95% CI	p value
Vitamin D dietary intake at age 50 years (micrograms/day)	262	3.54 (2.015)	0.98	0.86, 1.11	0.72
Dietary intake of saturates at age 50 years (grams/day)	262	27.73 (12.969)	1.01	0.99, 1.03	0.53
Dietary intake of total fat at age 50 years (grams/day)	232	75.28 (32.052)	1.00	0.99, 1.01	0.85
Dietary intake of total energy (kilocals) at age 50 years	232	1989.33 (580.615)	1.00	1.00, 1.00	0.74
Total infections from age 0 to 5 years	298	10.43 (6.051)	0.99	0.96, 1.03	0.75
Sport related physical activity (aged 50)	265	0.156 (1.043)	0.96	0.76, 1.21	0.70
Non sport related physical activity (aged 50)	265	-0.040 (0.980)	1.24	0.96, 1.59	0.10

Table 41 Adjusted multivariate model for hip OA

	Odds ratio (95% CI)	p value
BMI at age 50 years	1.11 (1.04, 1.18)	p = 0.003
Physical activity (occupational and DIY) at age 50 years	1.48 (1.11, 1.98)	p = 0.008
Smoking (pack years) at age 50 years	1.02 (1.00, 1.05)	p = 0.02

Indirect pathways which occurred through the direct risk factors of hip OA were also identified (see Fig 17). Lower social class at birth was associated with higher levels of occupational physical activity. There was an inverse association between educational attainment and amount of smoking. There was a correlation between amount of smoking and alcohol intake. There was also a positive association between cigarette smoking and occupational physical activity.

Fig 17 Schematic representation of lifecourse risk of hip OA



6.6.1 Risk of hip OA among males

On univariate analysis, exclusive breast feeding had a protective effect on hip OA in males (OR 0.79 per month, p=0.03) (see Table 43) while the occurrence of an adverse

event in childhood increased risk of hip OA in men (OR 2.71, p=0.01) (see Table 42). Increased height at age 50 was found to be highly protective (OR 0.89 per cm, p=0.007) (see Table 43).

Multivariate analysis revealed two models with nearly similar significance values and pseudo R^2 values. The first model has height (OR 0.88 per cm, p=0.006) and adverse life events (OR 3.15, p=0.02) while the second model also has height (OR O.89 per cm, p=0.009) with exclusive breast feeding (OR 0.77 per month, p=0.03) as the significant predictors of hip OA in men.

Table 42 Risk factors among males for hip OA (Categorical variables)

	Hip OA				Odds ratio	95% CI	p value
	Present		Absent				
	No	%	No	%			
Social class at birth	N = 57		N = 72				0.50
1-11	5	8.8	11	15.3	1.0		
111 (NM)	36	63.2	44	61.1	1.80	0.57, 5.66	
111 (M) - V	16	28.1	17	23.6	2.07	0.59, 7.29	
Social class at age 5 years	N = 50		N = 59				0.68
1-11	14	28.0	18	30.5	1.0		
111 (NM)	26	52.0	26	44.1	1.29	0.53, 3.12	
111 (M) - V	10	20.0	15	25.4	0.86	0.30, 2.48	
Educational attainment	N = 51		N = 55				0.21
Below “O” level	12	23.5	12	21.8	1.0		
“O” level	15	29.4	19	34.6	0.79	0.28, 2.25	
“A” level	16	31.4	9	16.4	1.78	0.57, 5.58	
Graduate or higher	8	15.7	15	27.3	0.53	0.16, 1.72	

Table 42 Risk factors among males for hip OA (Categorical variables)

	Hip OA				Odds ratio	95% CI	p value
	Present		Absent				
Adverse life events	N = 50		N = 59				0.01
No	26	52.0	44	74.6	1.0		
Yes	24	48.0	15	25.4	2.71	1.21, 6.07	
Cigarette smoking at age 50	N = 47		N = 45				0.25
Non-smokers	15	31.9	20	44.4	1.0		
Ex-smokers	28	59.6	19	42.2	1.96	0.81, 4.77	
Current smokers (age 50)	4	8.5	6	13.3	0.89	0.21, 3.72	
Physical activity at age 50	N = 47		N = 45				0.96
No activity	3	6.4	2	4.4	1.0		
Light activity	24	51.1	22	48.9	0.73	0.11, 4.77	
Moderate activity	11	23.4	12	26.7	0.61	0.09, 4.37	
Heavy activity	9	19.2	9	20.0	0.67	0.09, 4.99	

Table 42 Risk factors among males for hip OA (Categorical variables)

	Hip OA				Odds ratio	95% CI	p value
	Present		Absent				
Sport activity at age 50	N = 53		N = 56				0.59
No activity	31	58.5	29	51.8	1.0		
Light activity	7	13.2	6	10.7	1.09	0.33, 3.63	
Heavy activity	15	28.3	21	37.5	0.67	0.29, 1.54	
Walking/cycling at age 50	N = 52		N = 56				0.14
No activity	4	7.7	6	10.7	1.0		
Light activity	15	28.9	25	44.6	0.90	0.22, 3.72	
Heavy activity	33	63.5	25	44.6	1.98	0.50, 7.77	
House work activity at age 50	N = 53		N = 56				0.62
No activity	12	22.6	17	30.4	1.0		
Light activity	12	22.6	10	17.9	1.7	0.56, 5.20	
Heavy activity	19	54.7	29	51.8	1.42	0.58, 3.49	

Table 42 Risk factors among males for hip OA (Categorical variables)

	Hip OA				Odds ratio	95% CI	p value
	Present		Absent				
Occupational activity at age 50	N = 52		N = 56				0.48
No activity	30	57.7	36	64.3	1.0		
Light activity	11	21.2	13	23.2	1.02	0.40, 2.59	
Heavy activity	11	21.2	7	12.5	1.89	0.65, 5.47	
Social class at age 50	N = 52		N = 55				0.37
1-11	32	61.5	35	63.6	1.0		
111 (NM)	12	23.1	16	29.1	0.82	0.34, 2.00	
111 (M) - V	8	15.4	4	7.3	2.19	0.60, 7.97	
Self reported alcohol intake at age 50	N = 53		N = 55				0.81
None	3	5.7	3	5.5	1.0		
1	25	47.2	21	38.2	1.19	0.22, 6.5	
2	20	37.7	25	45.5	0.80	0.15, 4.4	
3	5	9.4	6	10.9	0.83	0.11, 6.1	

Table 43 Risk factors among males for hip OA (Continuous variables)

	Hip OA	Odds ratio	95% CI	p value	p value
Standardised birth weight	133	-0.254 (1.035)	0.74	0.52, 1.04	0.08
Exclusive breast feeding (months)	93	2.039 (1.997)	0.79	0.64, 0.98	0.03
Body fat % at age 50 years (impedance)	97	36.80 (6.912)	1.03	0.97, 1.09	0.39
BMI at age 50 years	97	27.17 (3.450)	1.09	0.96, 1.22	0.17
Weight at age 50 years (kg)	97	82.28 (11.722)	1.00	0.96, 1.03	0.79
Height (cm) at age 50 years	97	173.95 (5.537)	0.89	0.83, 0.97	0.007
Total hip bone density at age 50 (dgm/cm2)	91	10.25 (1.231)	0.91	0.65, 1.27	0.58
Total spine density at age 50 (gm/cm2)	91	1.036 (0.121)	0.08	0.00, 2.83	0.17
Pack years of smoking (aged 50)	109	12.16 (16.399)	1.02	1.00, 1.05	0.11
Vitamin D dietary intake at age 50 years (micrograms/day)	108	3.837 (2.452)	1.05	0.90, 1.22	0.55

Table 43 Risk factors among males for hip OA (Continuous variables)

	Hip OA	Odds ratio	95% CI	p value	p value
Dietary intake of saturates at age 50 years (grams/day)	108	31.613 (14.113)	0.99	0.97, 1.02	0.64
Dietary intake of total fat at age 50 years (grams/day)	92	84.686 (36.606)	1.00	0.98, 1.01	0.41
Dietary intake of total energy (kilocals) at age 50 years	92	2146.0 (658.32)	1.00	1.00, 1.00	0.59
Total infections from age 0 to 5 years	132	10.31 (6.760)	1.00	0.95, 1.06	0.92
Sport related physical activity (aged 50)	108	-0.019 (1.076)	0.84	0.59, 1.19	0.32
Non sport related physical activity (aged 50)	108	-0.097(1.121)	1.32	0.93, 1.87	0.12

6.6.2 Risk of hip OA among females

On univariate analysis, body fat percentage at age 50 (OR 1.05, p=0.03) was the only significant predictor of hip OA in women (see Table 45). However, there was a trend towards increased hip OA with increasing levels of occupational physical activity (OR 1.80 [heavy vs none], p=0.15) (see Table 44). On multivariate analysis, non-sport related physical activity (OR 1.55, p=0.05), impedance at age 50 years (OR 1.06, p=0.02) and

vitamin D intake at age 50 years (OR 0.78 per microgram per day, p=0.04) were the significant independent predictors of hip OA.

Table 44 Risk factors among females for hip OA (Categorical variables)

	Hip OA				Odds ratio	95% CI	p value
	Present		Absent				
	No	%	No	%			
Social class at birth	N = 63		N =103				0.25
1-11	4	6.4	15	14.6	1.0		
111 (NM)	45	71.4	67	65.1	2.52	0.78, 8.08	
111 (M) - V	14	22.2	21	20.4	2.50	0.69, 9.12	
Social class at age 5 years	N = 57		N = 91				0.18
1-11	17	29.8	23	25.3	1.0		
111 (NM)	28	49.1	36	39.6	1.05	0.47, 2.34	
111 (M) - V	12	21.1	32	35.2	0.51	0.20, 1.26	
Educational attainment	N = 61		N = 95				0.16
Below “O” level	24	39.3	29	30.5	1.0		
“O” level	26	42.6	34	35.8	0.92	0.44, 1.9	
“A” level	7	11.5	17	17.9	0.50	0.18, 1.4	
Graduate or higher	4	6.6	15	15.8	0.32	0.09, 1.1	

Table 44 Risk factors among females for hip OA (Categorical variables)

	Hip OA				Odds ratio	95% CI	p value
	Present		Absent				
Adverse life events	N = 56		N = 85				0.72
No	34	60.7	49	57.7	1.0		
Yes	22	39.3	36	42.4	0.88	0.44, 1.75	
Cigarette smoking at age 50	N = 53		N = 89				0.17
Non-smokers	24	45.3	52	58.4	1.0		
Ex-smokers	14	26.4	23	25.8	1.32	0.58, 3.00	
Current smokers (age 50)	15	28.3	14	15.7	2.32	0.97, 5.56	
Physical activity at age 50	N = 53		N = 89				0.86
No activity	6	11.3	10	11.2	1.0		
Light activity	24	45.3	36	40.5	1.11	0.36, 3.46	
Moderate activity	12	22.6	26	29.2	0.77	0.23, 2.61	
Heavy activity	11	20.8	17	19.1	1.08	0.30, 3.82	

Table 44 Risk factors among females for hip OA (Categorical variables)

	Hip OA				Odds ratio	95% CI	p value
	Present		Absent				
Sport activity at age 50	N = 61		N = 96				0.07
No activity	35	57.4	51	53.1	1.0		
Light activity	1	1.6	10	10.4	0.15	0.02, 1.19	
Heavy activity	25	41.0	35	36.5	1.04	0.53, 2.03	
Walking/cycling at age 50	N = 61		N = 97				0.82
No activity	6	9.8	12	12.4	1.0		
Light activity	26	42.6	43	44.3	1.21	0.40, 3.61	
Heavy activity	29	47.5	42	43.3	1.38	0.47, 4.10	
House work activity at age 50	N = 61		N = 97				0.14
No activity	1	1.6	7	7.2	1.0		
Light activity	7	11.5	16	16.5	3.06	0.31, 29.8	
Heavy activity	53	86.9	74	76.3	5.01	0.60, 42.0	

Table 44 Risk factors among females for hip OA (Categorical variables)

	Hip OA				Odds ratio	95% CI	p value
	Present		Absent				
Occupational activity at age 50	N = 61		N = 96				0.15
No activity	43	70.5	58	60.4	1.0		
Light activity	14	23.0	35	36.5	0.54	0.26, 1.12	
Heavy activity	4	6.6	3	3.1	1.80	0.38, 8.46	
Social class at age 50	N = 57		N = 94				0.49
1-11	40	70.2	72	76.6	1.0		
111 (NM)	7	12.3	12	12.8	1.05	0.38, 2.9	
111 (M) - V	10	17.5	10	10.6	1.80	0.69, 4.7	
Self reported alcohol intake at age 50	N = 59		N = 97				0.16
None	11	18.6	8	8.3	1.0		
1	24	40.7	35	36.1	0.50	0.17, 1.42	
2	22	37.3	48	49.5	0.33	0.12, 0.94	
3	2	3.4	6	6.2	0.24	0.04, 1.5	

Table 45 Risk factors among females for hip OA (Continuous variables)

	n	Mean (SD)	Odds ratio	95% CI	p value
Standardised birth weight	167	-0.036 (1.134)	1.06	0.80, 1.39	0.70
Exclusive breast feeding (months)	138	2.209 (1.936)	1.03	0.87, 1.24	0.70
Age at menarche (years)	147	12.99 (1.469)	1.11	0.88, 1.39	0.37
Body fat % at age 50 years (impedance)	143	40.79 (8.797)	1.05	1.00, 1.09	0.03
BMI at age 50 years	144	26.04 (4.553)	1.07	0.99, 1.15	0.08
Weight at age 50 years (kg)	144	68.00 (12.108)	1.02	0.99, 1.05	0.23
Height (cm) at age 50 years	144	161.73 (6.114)	0.96	0.91, 1.02	0.17
Total hip bone density at age 50 (dgm/cm2)	135	9.531 (1.214)	1.04	0.78, 1.38	0.80
Total spine density at age 50 (gm/cm2)	136	1.057 (0.137)	0.69	0.05, 8.76	0.77
Pack years of smoking (aged 50)	158	7.111 (10.745)	1.03	1.00, 1.06	0.07

Table 45 Risk factors among females for hip OA (Continuous variables)

	n	Mean (SD)	Odds ratio	95% CI	p value
Vitamin D dietary intake at age 50 years (micrograms/day)	154	3.332 (1.618)	0.83	0.67, 1.03	0.08
Dietary intake of saturates at age 50 years (grams/day)	154	25.01 (11.382)	1.01	0.98, 1.04	0.40
Dietary intake of total fat at age 50 years (grams/day)	140	69.10 (27.074)	1.00	0.99, 1.02	0.67
Dietary intake of total energy (kilocals) at age 50 years	140	1886.36 (499.586)	1.00	1.00, 1.00	0.53
Total infections from age 0 to 5 years	166	10.53 (5.441)	0.98	0.93, 1.04	0.57
Sport related physical activity (aged 50)	157	0.277 (1.006)	1.11	0.81, 1.53	0.51
Non sport related physical activity (aged 50)	157	0.000 (0.870)	1.17	0.80, 1.70	0.41

6.7 Lifecourse models for hand OA

On univariate analysis, height at age 50 years (OR 0.93, p=0.001) and total infections from age 0 to 5 years (OR 0.95, p=0.01) were significant risk factors for development of hand OA (see Table 47). Cigarette smoking was found to have a nearly significant protective effect (OR 0.38 [current vs non], p=0.07) while total physical activity showed a trend towards increased hand OA (OR 4.90 [heavy vs none], p=0.08). Social class at birth showed a weaker trend towards increased risk in the lower social classes (OR 1.69 [3M-5 vs 1-2], p=0.20) (see Table 46).

In the multivariate analysis, sex (OR 4.13[females vs males], $p < 0.001$), smoking category (OR 0.31 [current vs non], p= 0.01) and total infections from age 0 to 5 years (OR 0.93 per infection, p= 0.01) were the significant predictors of hand OA.

Table 46 Risk factors for hand OA (univariate analysis) – Categorical variables

	Hand OA				Odds ratio	95% CI	p value
	Present		Absent				
	No	%	No	%			
Gender	N =246		N = 70				
Male	95	67.4	46	32.6			
Female	151	86.3	24	13.7			
Social class at birth	N = 239		N = 67				0.20
1-11	24	10.0	12	17.9	1.0		
111 (NM)	161	67.4	39	58.2	2.06	0.95, 4.49	
111 (M) - V	54	22.6	16	23.9	1.69	0.69, 4.11	
Social class at age 5 years	N = 206		N = 60				0.34
1-11	52	25.2	21	35.0	1.0		
111 (NM)	96	46.6	24	40.0	1.62	0.82, 3.18	
111 (M) - V	58	28.2	15	25.0	1.56	0.73, 3.34	

Table 46 Risk factors for hand OA (univariate analysis) – Categorical variables

	Hand OA				Odds ratio	95% CI	p value
	Present		Absent				
Educational attainment	N = 215		N = 57				0.31
Below "O" level	64	29.8	14	24.6	1.0		
"O" level	82	38.1	17	29.8	1.06	0.48, 2.30	
"A" level	38	17.7	14	24.6	0.59	0.26, 1.38	
Graduate or higher	31	14.4	12	21.1	0.57	0.23, 1.37	
Adverse life events	N = 199		N = 59				0.68
No	124	62.3	35	59.3	1.0		
Yes	75	37.7	24	40.7	0.88	0.49, 1.60	

Table 46 Risk factors for hand OA (univariate analysis) – Categorical variables

	Hand OA				Odds ratio		95% CI	p value
	Present		Absent					
Cigarette smoking at age 50 years	N = 197		N = 46					0.07
Non-smokers	98	49.8	15	32.6	1.0			
Ex-smokers	69	35.0	19	41.3	0.56		0.26, 1.17	
Current smokers (age 50)	30	15.2	12	26.1	0.38		0.16, 0.91	
Physical activity at age 50 years	N = 197		N = 46					0.08
No activity	15		7.6	7	15.2	1.0		
Light activity	91		46.2	20	43.5	2.12	0.77, 5.88	
Moderate activity	49		24.9	15	32.6	1.52	0.52, 4.43	
Heavy activity	42		21.3	4	8.7	4.90	1.25, 19.1	

Table 46 Risk factors for hand OA (univariate analysis) – Categorical variables

	Hand OA			Odds ratio	95% CI		p value
	Present	Absent					
Sport activity at age 50	N = 219	N = 57					0.59
No activity	118	53.9	34	59.7	1.0		
Light activity	20	9.1	6	10.5	0.96	0.36, 2.58	
Heavy activity	81	37.0	17	29.8	1.37	0.72, 2.62	
Walking/cycling at age 50	N = 219	N = 57					0.68
No activity	22	10.1	8	14.0	1.0		
Light activity	88	40.2	23	40.4	1.39	0.55, 3.53	
Heavy activity	109	49.8	26	45.6	1.52	0.61, 3.81	

Table 46 Risk factors for hand OA (univariate analysis) – Categorical variables

	Hand OA			Odds ratio	95% CI		p value
	Present	Absent					
House work activity at age 50	N = 219	N = 58					0.15
No activity	29	13.2	13	22.4	1.0		
Light activity	34	15.5	11	19.0	1.39	0.54, 3.56	
Heavy activity	156	71.2	34	58.6	2.06	0.97, 4.36	
Occupational activity at age 50	N = 219	N = 56					0.03
No activity	142	64.8	32	57.1	1.0		
Light activity	62	28.3	13	23.2	1.07	0.53, 2.19	
Heavy activity	15	6.9	11	19.6	0.31	0.13, 0.73	
Social class at age 50	N = 212	N = 55					0.47
1-11	151	71.2	35	63.6	1.0		
111 (NM)	38	17.9	11	20.0	0.80	0.37, 1.72	
111 (M) - V	23	10.9	9	16.4	0.59	0.3, 1.4	

Table 46 Risk factors for hand OA (univariate analysis) – Categorical variables

	Hand OA			Odds ratio	95% CI		p value
	Present	Absent					
Self reported alcohol intake at age 50	N = 217	N = 57					0.49
None	19	8.8	6	10.5	1.0		
1	90	41.5	18	31.6	1.58	0.55, 4.50	
2	94	43.3	27	47.4	1.10	0.40, 3.03	
3	14	6.5	6	10.5	0.74	0.20, 2.77	

Table 47 Risk factors for hand OA (univariate analysis) – Continuous variables

	n	Mean (SD)	Odds ratio	95% CI	p value
Standardised birth weight	311	-0.135 (1.089)	1.02	0.80, 1.30	0.88
Exclusive breast feeding (months)	240	2.107 (1.940)	0.97	0.83, 1.15	0.75
Age at menarche (years)	151	12.97 (1.466)	1.08	0.77, 1.50	0.66
Body fat % at age 50 years (impedance)	249	39.14 (8.288)	1.01	0.97, 1.05	0.59
BMI at age 50 years	250	26.49 (4.163)	0.96	0.89, 1.03	0.29
Weight at age 50 years (kg)	250	73.78 (13.743)	0.96	0.94, 0.99	0.002
Height (cm) at age 50 years	250	166.71 (8.344)	0.93	0.89, 0.97	0.001
Total hip bone density at age 50 (dgm/cm2)	234	9.838 (1.285)	0.98	0.76, 1.26	0.87
Total spine density at age 50 (gm/cm2)	235	1.050 (0.131)	3.56	0.29, 43.2	0.32
Pack years smoked at age 50 years	277	9.354 (13.625)	0.98	0.96, 1.00	0.03

Table 47 Risk factors for hand OA (univariate analysis) – Continuous variables

	n	Mean (SD)	Odds ratio	95% CI	p value
Vitamin D dietary intake at age 50 years (micrograms/day)	272	3.549 (2.099)	0.97	0.84, 1.11	0.63
Dietary intake of saturates at age 50 years (grams/day)	272	27.74 (12.912)	0.98	0.96, 1.00	0.08
Dietary intake of total fat at age 50 years (grams/day)	241	75.43 (31.873)	0.99	0.98, 1.00	0.03
Dietary intake of total energy (kilocals) at age 50 years	241	1988.94 (581.527)	1.00	1.00, 1.00	0.04
Total infections from age 0 to 5 years	309	10.31 (6.050)	0.95	0.91, 0.99	0.01
Sport related physical activity (aged 50)	275	0.145 (1.052)	1.40	1.05, 1.87	0.02
Non sport related physical activity (aged 50)	275	-0.053 (0.982)	1.09	0.81, 1.47	0.56

6.7.1 Risk of hand OA among males

On univariate analysis, cigarette smoking category (OR 0.17 [current vs non], p=0.04), total physical activity at age 50 (OR 25.0 [heavy vs none], p=0.02) (see Table 48) and total infections from birth to age 5 (OR 0.94, p=0.03) (see Table 49) were the significant predictors of hand OA in males.

On multivariate analysis, cigarette smoking demonstrated a protective effect (OR 0.19 [current vs non], p=0.03) and total physical activity at age 50 (OR 18.8 [heavy vs none], p=0.02) had a detrimental effect on risk of hand OA in males.

Table 48 Risk factors among males for hand OA (Categorical variables)

	Hand OA				Odds ratio	95% CI	p value
	Present		Absent				
	No	%	No	%			
Social class at birth	N = 91		N = 44				0.15
1-11	8	8.8	9	20.5	1.0		
111 (NM)	57	62.6	26	59.1	2.47	0.86, 7.11	
111 (M) - V	26	28.6	9	20.5	3.25	0.96, 11.0	
Social class at age 5 years	N = 74		N = 40				0.42
1-11	18	24.3	14	35.0	1.0		
111 (NM)	38	51.4	16	40.0	1.85	0.74, 4.59	
111 (M) - V	18	24.3	10	25.0	1.40	0.49, 3.97	
Educational attainment	N = 76		N = 36				0.68
Below “O” level	15	19.7	9	25.0	1.0		
“O” level	27	35.5	9	25.0	1.80	0.59, 5.5	
“A” level	19	25.0	9	25.0	1.27	0.4, 4.0	
Graduate or higher	15	19.7	9	25.0	1.00	0.31, 3.2	

Table 48 Risk factors among males for hand OA (Categorical variables)

	Hand OA				Odds ratio	95% CI	p value
	Present		Absent				
Adverse life events	N = 73		N = 40				0.45
No	49	67.1	24	60.0	1.0		
Yes	24	32.9	16	40.0	0.73	0.33, 1.63	
Cigarette smoking at age 50	N = 68		N = 30				0.04
Non-smokers	29	42.7	7	23.3	1.0		
Ex-smokers	34	50.0	16	53.3	0.51	0.19, 1.42	
Current smokers (age 50)	5	7.4	7	23.3	0.17	0.04, 0.71	
Physical activity at age 50 years	N = 68		N = 30				0.02
No activity	1	1.5	5	16.7	1.0		
Light activity	37	54.4	13	43.3	14.2	1.52, 133.4	
Moderate activity	15	22.1	9	30.0	8.33	0.84, 83.2	
Heavy activity	15	22.1	3	10.0	25.0	2.10, 298.3	

Table 48 Risk factors among males for hand OA (Categorical variables)

	Hand OA				Odds ratio	95% CI	p value
	Present		Absent				
Sport activity at age 50	N = 78		N = 37				0.91
No activity	43	55.1	22	59.5	1.0		
Light activity	9	11.5	4	10.8	1.15	0.32, 4.16	
Heavy activity	26	33.3	11	29.7	1.21	0.51, 2.89	
Walking/cycling at age 50	N = 78		N = 36				0.12
No activity	5	6.4	7	19.4	1.0		
Light activity	30	38.5	11	30.6	3.82	1.00, 14.6	
Heavy activity	43	55.1	18	50.0	3.34	0.94, 11.9	
House work activity at age 50	N = 78		N =37				0.64
No activity	21	26.9	13	35.1	1.0		
Light activity	16	20.5	6	16.2	1.65	0.51, 5.30	
Heavy activity	41	52.6	18	48.7	1.41	0.58, 3.42	

Table 48 Risk factors among males for hand OA (Categorical variables)

	Hand OA				Odds ratio	95% CI	p value
	Present		Absent				
Occupational activity at age 50	N = 78		N = 36				0.54
No activity	48	61.5	21	58.3	1.0		
Light activity	19	24.4	7	19.4	1.19	0.43, 3.25	
Heavy activity	11	14.1	8	22.2	0.60	0.21, 51.71	
Social class at age 50	N = 76		N = 36				0.39
1-11	50	65.8	21	58.3	1.0		
111 (NM)	20	26.3	9	25.0	0.93	0.37, 2.38	
111 (M) - V	6	7.9	6	16.7	0.42	0.12, 1.45	
Self reported alcohol intake at age 50	N = 78		N = 36				0.59
None	5	6.4	1	2.8	1.0		
1	35	44.9	13	36.1	0.54	0.06, 5.05	
2	30	38.5	18	50.0	0.33	0.04, 3.08	
3	8	10.3	4	11.1	0.40	0.03, 4.68	

Table 49 Risk factors among males for hand OA (Continuous variables)

	n	Mean (SD)	Odds ratio	95% CI	p value
Standardised birth weight	140	-0.265 (1.032)	0.82	0.58, 1.16	0.26
Exclusive breast feeding (months)	99	2.013 (1.958)	0.98	0.79, 1.21	0.84
Body fat % at age 50 years (impedance)	103	36.71 (6.916)	0.98	0.92, 1.04	0.42
BMI at age 50 years	103	27.13 (3.454)	0.91	0.80, 1.03	0.11
Weight at age 50 years (kg)	103	82.02 (11.699)	0.96	0.93, 1.00	0.03
Height (cm) at age 50 years	103	173.79 (5.524)	0.97	0.89, 1.04	0.37
Total hip bone density at age 50 (dgm/cm2)	96	10.26 (1.275)	1.04	0.74, 1.46	0.81
Total spine density at age 50 (gm/cm2)	96	1.039 (0.124)	3.34	0.10, 113.5	0.50
Pack years smoked at age 50 years	115	12.60 (16.468)	0.99	0.96, 1.01	0.29
Vitamin D dietary intake at age 50 years (micrograms/day)	114	3.794 (2.406)	1.04	0.87, 1.23	0.69

Table 49 Risk factors among males for hand OA (Continuous variables)

	n	Mean (SD)	Odds ratio	95% CI	p value
Dietary intake of saturates at age 50 years (grams/day)	114	31.50 (14.102)	0.98	0.95, 1.01	0.13
Dietary intake of total fat at age 50 years (grams/day)	98	84.38 (36.117)	0.99	0.98, 1.00	0.13
Dietary intake of total energy (kilocals) at age 50 years	98	2134.83 (652.267)	1.00	1.00, 1.00	0.19
Total infections from age 0 to 5 years	139	10.05 (6.713)	0.94	0.90, 1.00	0.03
Sport related physical activity (aged 50)	114	-0.061 (1.089)	1.24	0.86, 1.80	0.25
Non sport related physical activity (aged 50)	114	-0.136 (1.129)	1.14	0.80, 1.62	0.47

6.7.2 Risk of hand OA among females

On univariate analysis, there were no significant associations seen at the 5% level among women. However, total infections from birth to age 5 (OR 0.94, p=0.09) (see Table 51) and occupational activity at age 50 (OR 0.16 [heavy vs none], p=0.11) (see Table 50) were nearly significant univariate associations.

On multivariate analysis, total infections from birth to age 5 years was found to have a protective effect in women (OR 0.91, p=0.02) while occupational physical activity at age 50 also showed a similar protective effect (OR 0.11 [heavy vs none], p=0.01).

Table 50 Risk factors among females for hand OA (Categorical variables)

	Hand OA				Odds ratio	95% CI	p value
	Present		Absent				
	No	%	No	%			
Social class at birth	N =148		N = 23				0.40
1-11	16	10.8	3	13.0	1.0		
111 (NM)	104	70.3	13	56.5	1.50	0.38, 5.85	
111 (M) - V	28	18.9	7	30.4	0.75	0.17, 3.31	
Social class at age 5 years	N = 132		N = 20				0.69
1-11	34	25.8	7	35.0	1.0		
111 (NM)	58	43.9	8	40.0	1.49	0.50, 4.48	
111 (M) - V	40	30.3	5	25.0	1.65	0.48, 5.67	

Table 50 Risk factors among females for hand OA (Categorical variables)

	Hand OA				Odds ratio	95% CI	p value
	Present		Absent				
Educational attainment	N = 139		N = 21				0.57
Below "O" level	49	35.3	5	23.8	1.0		
"O" level	55	39.6	8	38.1	0.70	0.22, 2.29	
"A" level	19	13.7	5	23.8	0.39	0.10, 1.49	
Graduate or higher	16	11.5	3	14.3	0.54	0.12, 2.53	
Adverse life events	N = 126		N = 19				0.89
No	75	59.5	11	57.9	1.0		
Yes	51	40.5	8	42.1	0.94	0.35, 2.49	
Cigarette smoking at age 50	N = 129		N = 16				0.52
Non-smokers	69	53.5	8	50.0	1.0		
Ex-smokers	35	27.1	3	18.8	1.35	0.34, 5.42	
Current smokers (age 50)	25	19.4	5	31.3	0.58	0.17, 1.94	

Table 50 Risk factors among females for hand OA (Categorical variables)

	Hand OA				Odds ratio	95% CI	p value
	Present		Absent				
Physical activity at age 50	N = 129		N = 16				0.44
No activity	14	10.9	2	12.5	1.0		
Light activity	54	41.9	7	43.8	1.10	0.21, 5.90	
Moderate activity	34	26.4	6	37.5	0.81	0.15, 4.51	
Heavy activity	27	20.9	1	6.3	3.86	0.32, 46.3	
Sport activity at age 50	N = 141		N = 20				0.72
No activity	75	53.2	12	60.0	1.0		
Light activity	11	7.8	2	10.0	0.88	0.17, 4.5	
Heavy activity	55	39.0	6	30.0	1.47	0.52, 4.2	
Walking/cycling at age 50	N = 141		N = 21				0.30
No activity	17	12.1	1	4.8	1.0		
Light activity	58	41.1	12	57.1	0.28	0.03, 2.35	
Heavy activity	66	46.8	8	38.1	0.49	0.06, 4.15	

Table 50 Risk factors among females for hand OA (Categorical variables)

	Hand OA				Odds ratio	95% CI	p value
	Present		Absent				
House work activity at age 50	N = 141		N = 21				0.25
Inactive	8	5.7	0	0			
Light activity	18	12.8	5	23.8	1.0		
Heavy activity	115	81.6	16	76.2	2.00	0.65, 6.12	
Occupational activity at age 50	N = 141		N = 20				0.11
No activity	94	66.7	11	55.0	1.0		
Light activity	43	30.5	6	30.0	0.84	0.29, 2.42	
Heavy activity	4	2.8	3	15.0	0.16	0.03, 0.79	
Social class at age 50	N = 136		N = 19				0.89
1-11	101	74.3	14	73.7	1.0		
111 (NM)	18	13.2	2	10.5	1.25	0.26, 5.96	
111 (M) - V	17	12.5	3	15.8	0.79	0.20, 3.03	

Table 50 Risk factors among females for hand OA (Categorical variables)

	Hand OA				Odds ratio	95% CI	p value
	Present		Absent				
Self reported alcohol intake at age 50	N = 139		N = 21				0.21
None	14	10.1	5	23.8	1.0		
1	55	39.6	5	23.8	3.93	1.00, 15.5	
2	64	46.0	9	42.9	2.54	0.74, 8.75	
3	6	4.3	2	9.5	1.07	0.16, 7.15	

Table 51 Risk factors among females for hand OA (Continuous variables)

	n	Mean (SD)	Odds ratio	95% CI	p value
Standardised birth weight	171	-0.029 (1.125)	1.18	0.79, 1.75	0.41
Exclusive breast feeding (months)	141	2.172 (1.932)	0.93	0.72, 1.21	0.61
Age at menarche (years)	151	12.97 (1.466)	1.08	0.77, 1.50	0.66
Body fat % at age 50 years (impedance)	146	40.85 (8.758)	1.00	0.95, 1.07	0.87
BMI at age 50 years	147	26.04 (4.552)	1.04	0.92, 1.17	0.53
Weight at age 50 years (kg)	147	68.00 (12.041)	1.01	0.96, 1.05	0.73
Height (cm) at age 50 years	147	161.74 (6.101)	0.97	0.89, 1.06	0.55
Total hip bone density at age 50 (dgm/cm2)	138	9.547 (1.213)	1.40	0.85, 2.31	0.16
Total spine density at age 50 (gm/cm2)	139	1.057 (0.136)	2.30	0.05, 114.1	0.67
Pack years smoked at age 50 years	162	7.048 (10.645)	0.98	0.94, 1.02	0.27

Table 51 Risk factors among females for hand OA (Continuous variables)

	n	Mean (SD)	Odds ratio	95% CI	p value
Vitamin D dietary intake at age 50 years (micrograms/day)	158	3.372 (1.835)	0.91	0.72, 1.14	0.43
Dietary intake of saturates at age 50 years (grams/day)	158	25.03 (11.267)	1.02	0.97, 1.07	0.42
Dietary intake of total fat at age 50 years (grams/day)	143	69.30 (27.069)	1.00	0.98, 1.02	0.83
Dietary intake of total energy (kilocals) at age 50 years	143	1889.0 (506.143)	1.00	1.00, 1.00	0.58
Total infections from age 0 to 5 years	170	10.52 (5.460)	0.94	0.87, 1.01	0.09
Sport related physical activity (aged 50)	161	0.290 (1.004)	1.38	0.85, 2.25	0.20
Non sport related physical activity (aged 50)	161	0.005 (0.862)	0.85	0.49, 1.48	0.57

The above results suggest that increased infections in early life might have a protective effect on subsequent hand OA. In fact, this protective effect occurs particularly in women, rather than men. Adult factors related to hand OA include adult height achieved,

which was found to have a significant protective effect and smoking category at age 50, which suggested that current smokers (at age 50) were protected from subsequent hand OA. This effect of smoking was found to be significant particularly in men but not in women.

Occupational physical activity:

There was a protective effect of heavy occupational activity on hand OA in females (see Table 50) and a non-significant effect towards protection was also seen in males (OR 0.60 [heavy vs none], 0.21, 51.71) (see Table 48). This protective effect might only reflect selection of occupational activity at age 50 due to prevalent OA at that age where those already with hand OA are less likely to take on large amounts of work related activity.

This protective effect of heavy occupational activity might also be mediated by grip strength. Those doing heavy work are likely to have higher grip strength. Cross sectional studies have shown a negative association between grip strength and radiographic hand OA.

In contrast, there was an increased risk of hand OA in males with heavy "total physical activity" (see Table 48).

Chapter 7 Discussion

The above results provide evidence for the reliability and construct validity of ultrasound imaging in the evaluation of features of OA. The population based estimates of prevalence of ultrasound features of OA were higher than previous radiographic estimates, suggesting a higher sensitivity of ultrasound when compared to radiographs. This is the first study to perform a lifecourse analysis of risk factors in OA at the three different joint sites. Factors acting in adulthood were the predominant predictors of OA. Nevertheless, a few associations were found with early life risk factors such as the inverse association of breast feeding with ultrasound defined knee osteophytes at age 62/63 years.

The following aspects of the results require further consideration.

7.1 Reliability and validity of US in OA – the Northumberland over 85 pilot study

There were some important methodological considerations to note in this pilot study. Assessment of the whole process of both acquisition and reading of ultrasound images was performed: thereby including the main potential sources of variation. Some previous studies have only looked at the reliability in reading images between observers (Qvistgaard et al., 2006), but it is important to measure the differences in the acquisition of images, especially considering the dynamic nature of US imaging. The results of this study are therefore likely to be closer to the true value. Intra-rater reliability was not measured in this study but is likely to be as good as, if not better than, inter-rater reliability.

There was a time interval of up to six weeks between the two ultrasound observations, which might have altered the magnitude (size) of effusions. However, the participants were recruited from the community and not from attendance at either primary or secondary care. Therefore, it is unlikely that they had any significant steroid or other specific therapy in hospital for the incidental effusions that were picked up on the first ultrasound. As effusion size within participants might still have changed during this period, this interval could only have served to decrease the agreement between the two sonographers. The inter-rater agreement for size of effusions found in this study therefore is also likely to be conservative. When effusion was considered as a binary variable (using a cut off of ≥4 mm depth), the κ was 0.65 (right) and 0.77 (left); which remains very close to the ICC values obtained when effusion was used as a continuous variable.

Power Doppler assessment of synovitis (PDS) was not conducted in this study as the machine used for the study did not appear to have adequate sensitivity, based on images acquired prior to the study. PDS has been found to be a valid (Walther et al., 2001) method of detection of synovitis in the knees, although its reliability is still to be established. A EULAR group that assessed ultrasound features of inflammation decided not to evaluate PDS due to their concern that this was highly machine dependant (D'Agostino et al., 2005).

The Northumberland pilot study did not seek to confirm that the osteophytes seen on ultrasound were the same ones on the radiographs, as the presence of any bone response is likely to be clinically important. The kappa values for validity were comparable when either sonographer's osteophyte results were compared with radiographic osteophytes. The confidence intervals of these values between the sonographers overlap significantly; which is reassuring. Previous methods evaluating femoral condylar cartilage (McCune et al., 1990, Grassi et al., 1999), have used semi-quantitative scores to assess the clarity and sharpness of cartilage, but this has the disadvantage of losing precision due its ordinal scale. In addition, the features of sharpness and clarity are quite likely to differ between

the subjective assessments of observers. These features are also susceptible to change as more advanced ultrasound machines with better resolution are created.

The two sonographers agreed on a consensus for the acquisition and reading of images, prior to the commencement of the pilot study. This would have decreased the learning curve that otherwise might have been seen. However, the scanning protocols did not include restrictive methods such as the use of grid lines to assist the placement of the probe for cartilage thickness measurement, as has been seen with previous studies (Aisen et al., 1984, Iagnocco et al., 1992). It is important that sonographers refer to the guidelines suggested by Backhaus et al (Backhaus et al., 2001) so that consistency can be achieved in future studies using ultrasound as an outcome measure in OA.

There has been a concern that ultrasound is a very "operator dependant" imaging modality; this study provides evidence that high inter-rater reliability can be achieved between observers for the features of osteophytes, synovial effusion and femoral cartilage thickness. Osteophytes have been known to be an integral part of the pathophysiology of OA and shown in some studies to be significantly associated with pain in the knee (Spector et al., 1993, Cicuttini et al., 1996), although other studies (Muraki et al., 2009) have been unable to find this association.

The Northumberland over 85 pilot study is the first study to assess inter-rater reliability and validity of ultrasound features of OA in the community, where ultrasound is a reliable tool. This was also the first study to demonstrate the validity of the use of ultrasound to detect knee osteophytes in OA.

7.2 Prevalence results compared to previous radiographic estimates

7.2.1 Prevalence of Knee OA

The prevalence of knee osteophytes in the Newcastle Thousand Families sample was comparable to some of the previous studies using radiographic criteria to define OA. This is in contrast to the hip and hand, where ultrasound appeared to be more sensitive than previous radiographic studies. It is possible that the method of ultrasound evaluation (where the probe was not taken circumferentially around the joint) might have led to reduced sensitivity of ultrasound in identifying more central knee osteophytes. There were a higher proportion of women with knee osteophytes, as found in previous studies (Felson et al., 1987, Jordan et al., 2007, Dillon et al., 2006, Van Saase et al., 1989, Odding et al., 1998).

A study of 1424 participants with a mean age of 73 years (58.4% women), measured the prevalence of radiographic knee OA in the Framingham cohort between 1983 and 1985 (Felson et al., 1987). K-L grading ≥ 2 was used to define radiographic knee OA. There was evidence of slightly higher prevalence of knee OA among females (34%) compared to males (31%); however, this did not reach statistical significance. In fact, the authors report equal prevalence of radiographic changes between the sexes among the younger members of the cohort. The overall prevalence was 33% in the Framingham cohort which is similar to the estimate in the Newcastle Thousand Families Study. Of note, the Framingham cohort had subjects with a mean age of 73 years; which is ten years older than the Newcastle Thousand Families cohort currently. It is equally possible that the healthier lifestyles that might have been prevalent at the time of the Framingham assessment (~ 30 years ago) would have brought the prevalence estimate of OA down in this cohort.

A study of 3018 participants (aged 45 and older) from the Johnston County Osteoarthritis Project calculated the prevalence of radiographic knee OA in this cohort comprising 33%

African-Americans and 62.1% females (Jordan et al., 2007). Participants were recruited between 1991 and 1997 and K-L score ≥2 was used to define radiographic knee OA. 74% of this cohort were classified as overweight or obese (BMI ≥ 25); a particularly high proportion. African-Americans had a higher prevalence of knee OA at 32% compared to Caucasians who had a prevalence of 27%. The prevalence increased with age; the figures reported as 26%, 36% and 50% for 55-64, 65-74 and ≥75 year age groups respectively. The overall prevalence of knee OA was 28%, with a higher prevalence in women (31%) compared to men (24%). When compared to the Newcastle Thousand Families Study, the Johnston County cohort had more obese and a high proportion of African-American participants, who would be at higher risk of knee OA. Hence, the similar estimates of prevalence in these two cohorts which used two different imaging modalities to classify OA would suggest that ultrasound might be more sensitive than radiographs in the detection of osteophytes.

The NHANES III study assessed 2415 participants aged ≥ 60 years from across the USA between 1991 and 1994, for prevalence of radiographic knee OA (Dillon et al., 2006). The limitation of this study is that the radiographs were non-weight bearing and hence likely to under report knee OA using a K-L score definition of ≥2. The overall prevalence was found to be 37%, with 42% prevalence in women compared to 32% in men. The prevalence of osteophytes in the right knee were documented by compartment; 13% in the medial femoral, 24% in the medial tibial, 12% in the lateral femoral and 17% in the lateral tibial compartments.

A study of 1729 community dwelling individuals from Nottingham with a mean age of 64 years assessed the prevalence of radiographic knee OA (Neame et al., 2004). 63% of participants were female and the mean BMI was 26.8. An overall prevalence of 12% was found in this cohort, when using the K-L score ≥2, to define tibiofemoral knee OA. It was a low estimate particularly as the Nottingham cohort was identified by having participated in a previous study on knee pain. Unmeasured confounders such as BMD

and physical activity might be responsible for the observed difference in the Nottingham estimate of prevalent knee OA.

A sub-study of 465 participants more than 60 years of age in a Dutch village (a sub-urban metropolitan area near the Hague), established the prevalence of radiographic knee OA in the 1970s (Van Saase et al., 1989). The prevalence in the 60-64 year age group was 20% in men and 25% in women; while the prevalence in the ≥60 year group was 20% in men and 40% in women. The Rotterdam study of 2895 participants with a mean age of 69 years studied the prevalence of radiographic knee OA between 1990 and 1992 (Odding et al., 1998). 60% of participants were women in this community cohort. Women had almost twice the prevalence of knee OA in this cohort at 29% compared to 16% in men. The prevalence of knee OA in both of these Dutch studies was quite similar to that seen in the Newcastle Thousand Families study.

7.2.2 Prevalence of Hip OA

Hip OA was defined by the presence of either a femoral head osteophyte or femoral head abnormality. Using this definition, there was a relatively high prevalence of hip OA in this cohort, when compared to other studies using radiographic criteria (Neame et al., 2004, Nevitt et al., 2002, Van Saase et al., 1989, Jacobsen et al., 2004, Odding et al., 1998).

A recent publication from The Johnston County Osteoarthritis Project studied the prevalence of radiographic hip OA among 2637 community dwelling men and women aged 45 years and older (Jordan et al., 2009). One third of this cohort was of African-American descent and they had a higher prevalence of hip OA than the Caucasians in the cohort. The overall prevalence of radiographic hip OA was 27.6 %. On comparison with

race and sex, Caucasian men had 23.8% while African-American men had 33.2% prevalence of radiographic hip OA. The corresponding figures for women in the cohort were 29.1% and 31.2% respectively. The prevalence among all Caucasians was 26.6% while it was 32.1% among all African-Americans. The prevalence increased with age; 55-64 year group had a prevalence of 23% and this increased to 31.1% in the 65-74 year age group. These estimates are higher than previously published radiographic studies. The authors suggested that this might have been due to a higher prevalence among rural (vs urban) participants. Other reasons include the possibility of changes in hip OA risk factor profiles over time as well as variation in radiographic techniques and interpretation. As strengths, this study excluded participants with inflammatory arthritis. The results are likely to be conservative considering the fact that participants with hip replacements were also excluded; most of them were likely to be due to severe OA.

The results of a study of 1715 community dwelling participants from Nottingham, aged between 40 and 85 years of age (mean age 69) assessing radiographic hip OA prevalence and symmetry, was published in 2004 (Neame et al., 2004). The participants had a mean BMI of 26.3 and 57.1% were female. This study demonstrated significantly lower estimates of radiographic hip OA than our current study, with 3.5% (right) and 3.9% (left) and 6% (overall) prevalence. The radiographs were urograms with views of both hips and this technique of image acquisition is different to other radiographic studies. Furthermore, these estimates were based on a global OA score (≥3 on the Croft scale) which is different (and probably less sensitive) when compared to other methods of reading hip radiographs. Nevertheless, this is unlikely to have reduced the prevalence estimates considerably. As seen with the knee, it is likely that other unmeasured confounders such as BMD, diet and physical activity might have led to the lower prevalence of hip OA in this Nottingham cohort, when compared to even other radiographic studies.

A study of 1506 men and women recruited from a population-based sample in Beijing, China demonstrated an extremely low prevalence of radiographic hip OA (Nevitt et al., 2002). The mean BMI was 25.7 The crude prevalence rate in this sample was 0.9% in women and 1.1% in men. The authors suggested that the low prevalence in this study could be due to a combination of genetic influences, decreased obesity among the Chinese and increased range of movements of the hip (eg: while squatting in toilets) possibly stimulating unused areas of cartilage in the hip. Furthermore, the definitions of radiographic hip OA used in this study were different to those used in most other epidemiological studies, but the same as that used in the Study of Osteoporotic Fractures.

A sub-study of 465 participants more than 60 years of age in a Dutch village (a sub-urban metropolitan area near the Hague), established the prevalence of radiographic hip OA in the 1970's (Van Saase et al., 1989). This study found a higher prevalence of hip OA in males (10.4%) compared to females (3.8%); overall prevalence of 7%. It is likely that there has been a change in trends of underlying risk factors over the course of time, which might explain the lower overall prevalence of radiographic hip OA in this cohort when compared to the Thousand Families Study.

A Danish study in the early 1990s assessed the prevalence of radiographic hip OA among 3807 community participants from the county of Österbro in Copenhagen (Jacobsen et al., 2004). They used various definitions to classify radiographic hip OA, including Croft score, K-L score and minimum joint space width. Among the 2344 participants more than 60 years of age, the prevalence ranged from 5.6% (left) to 6.7% (right) in men and 3% (left) to 3.3% (right) in women; using the K-L score. Similar rates of prevalence were found if the Croft score was employed to define radiographic OA. Interestingly, this study also found that 75% of osteophytes in males and 60% in females were found in isolation (without other radiological features of OA).

An analysis of 2895 participants of the Rotterdam study between 1990 and 1992 was performed to estimate the prevalence of radiographic hip OA (Odding et al., 1998). The participants had a mean age of 69 years with 60% being female. Using the K-L scoring system, the prevalence of hip OA was found to be 14.1% in men and 15.9% in women. The authors acknowledge that there might have been an element of selection bias in this study due to issues with refusal to visit the research centre and exclusion due to missing data.

The increasing levels of obesity and reduced recreational physical activity over the past few decades are likely to have increased the prevalence estimates of hip OA, which is apparent in the higher prevalence of radiographic hip OA in the recent Johnston County Study when compared to previous radiographic estimates of hip OA.

7.2.3 Prevalence of Hand OA

There was an extremely high prevalence of index finger DIP joint involvement of the dominant hand, with a high prevalence also found in the CMC joint of the thumb (see Table 17). The prevalence was higher in females compared to males, as found in a few of the previous studies (Niu et al., 2003, Poole et al., 2003, Van Saase et al., 1989).

A study of 1467 men and 1519 women of the Medical Research Council's National Survey of Health and Development followed the participants from their birth in 1946 (Poole et al., 2003). At age 53, a clinical hand assessment was performed and identified a prevalence of 21%, 12% and 8% in any of the DIP, PIP and CMC joints, respectively, among women. In men, the corresponding values were 14%, 8% and 4%. This cohort was

10 years younger than the Thousand Families cohort and therefore likely to have lower estimates. Nevertheless, it also points towards a higher sensitivity of ultrasound in picking up osteophytes, when compared to clinical examination.

The Chingford study (Egger et al., 1995) performed hand radiographs on 967 women from a population cohort and found a prevalence of OA (defined as K-L score ≥2) of 14.4%, 3.4% and 11.5 % in the index finger DIP, PIP and first CMC joints of the right hand. These women were aged between 45 and 64 years; mean age was not specified. Even accounting for the likely increased age in the Thousand Families cohort, there was a far higher prevalence rate of ultrasound defined osteophytes within this cohort, compared to the Chingford study.

The prevalence rates in the Beijing Osteoarthritis study (Hunter et al., 2004) were similarly less than that seen in our study. OA was defined by a K-L score ≥2 on hand radiographs. The use of chopsticks and a different race of the participants might have played a part in the difference observed. The mean age of the men was 68.4 and that for women was 67.5, in this cohort.

In the New Haven Survey conducted between 1963 and 1967 in Connecticut, USA, hand OA was defined as K-L score ≥2 on radiographs (Acheson et al., 1970). This study had a much higher prevalence of OA in the hand joints when compared to subsequent studies. Interestingly, this was a much younger cohort, with a mean age of 47.3 among males and 46.1 among females. It is unclear as to how this particular survey has a higher estimate, but after adjustment for age, it is likely that these estimates would be in line with those in our study.

In a more recent survey of 3327 participants from Florida, USA, the prevalence of radiographic hand OA was found to be moderately high (Wilder et al., 2006). The mean age of the participants was 62 years, which is similar to our study. A K-L score of ≥2, was taken as evidence of radiographic OA at each joint site within the hands.

Prevalence rates were also high among the 465 participants older than 60 years of age in Zoetermeer, Netherlands (Van Saase et al., 1989). In fact, the prevalence rates in this cohort were similar to the findings of our study, which had particularly high rates in the DIP joints and the first CMC joint.

A cohort of 489 participants from a family study of nodal OA in Nottingham in 2004, had a prevalence estimate for radiographic OA of 46% in the right index finger and 73.3% for overall hand OA (Neame et al., 2004). The mean age of the cohort was 65.7 years with a higher proportion of women (82.6%). It should be stressed that this was not a random population sample and these participants were selected for their higher risk of prevalent hand OA. OA was defined as a K-L score of ≥2 at each joint site.

In addition to the differences in measurement and study design in the studies described above, factors such as occupation (Rossignol et al., 2005), grip strength (Chaisson et al., 2000) and other systemic factors such as use of oestrogen (Spector et al., 1997b) and obesity (Carman et al., 1994) might be responsible for some of the differences observed between these cohorts.

7.2.4 Pattern of OA

In contrast to the Nottingham radiographic study (Neame et al., 2004), we did not find any significant differences between the right and left knee for osteophyte detection using ultrasound. Similar to their findings though, there was no significant difference between the right and left hip osteophyte prevalence. Our findings are however in line with the Zoetermeer Survey which showed no evidence of any right-left differences of radiographic OA at the knee and hip joints (Van Saase et al., 1989). This suggests that bio-mechanical stresses act equally on both sides of the lower limb joints. Equally, it might also suggest that genetic and systemic factors such as oestrogen (Spector et al., 1997b) and obesity (Carman et al., 1994) might play a larger role in the pathophysiology of OA at the knee and hip, than bio-mechanical stress. In further validation of these hypotheses, we report that the prevalence of isolated knee and/or hip OA was extremely low in this cohort (8%); while isolated hand OA was particularly high (31%) (see Fig 13). This high prevalence of hand OA suggests that ultrasound defined hand osteophytes might be a predictor of a more generalised form of OA affecting the knee and the hip.

The prevalence of knee effusions was remarkably high in this study (just under a quarter of participants' had ≥4mm knee effusion on ultrasound), considering the subjects were a population sample, not selected for symptoms. It was also interesting to note that males had a higher prevalence of knee effusions than females, although this did not quite reach statistical significance (p=0.1). Since there is increasing evidence that inflammation predicts knee OA progression (Ayral et al., 2005, Spector et al., 1997a), this would suggest that males in this cohort might be at a higher risk of rapidly progressive OA. Further longitudinal follow up should help to provide more detail on this issue.

The higher prevalence of OA in the hand and hip in this study, when compared to previous radiographic studies, supports the hypothesis that ultrasound is more sensitive than radiography in detecting OA, particularly for osteophytes, although imaging only the dominant hand determines that this might be an underestimate. The high prevalence of isolated hand OA suggests that ultrasound defined hand OA may be a predictor of the

development of generalised OA. The increased sensitivity of ultrasound to detect features of OA might be due to its multi-planar capability.

7.3 Clinical symptoms as predictors of ultrasound features of OA

Self-reported clinical symptoms demonstrated good correlation with ultrasound detected knee osteophytes and femoral cartilage thickness. However, there did not appear to be a significant association of symptoms with knee effusion, hip OA and hand OA.

7.3.1 Association of symptoms with knee osteophytes

There was a consistent association of pain, stiffness and disability on the WOMAC questionnaire with knee osteophytes detected on ultrasound in the Thousand Families Study (see Table 18).

Duncan et al recently concluded that there was a consistent association between severity of pain, stiffness and physical function and the presence of radiographic knee OA in a population based study of 745 participants in North Staffordshire, UK with a mean age of 65 years (Duncan et al., 2007). Duncan's study split the pain and function subscales of WOMAC in to five categories and the stiffness subscale in to three categories. The estimates obtained by Duncan were in fact lower than that seen in the Thousand Families Study. Compared to those with no symptoms, those with severe pain had an OR of 3.8 (95% CI 2.1, 6.9), severe stiffness (OR 3.1; 95% CI 2.1, 4.7) and severe physical difficulty (OR 3.1; 95% CI 1.8, 5.3) for presence of radiographic knee OA. The higher association of clinical symptoms and OA seen in the Thousand Families Study might be partly due to the fact that only osteophytes were used in the definition of knee OA in the

Thousand Families Study; as changes in cartilage volume (on MRI) did not show any evidence of correlation with changes in either of the three subscales of WOMAC in a study of 32 patients with symptomatic knee OA (Raynauld et al., 2004).These results from the Thousand Families Study provide further construct validity for the use of ultrasound to define OA at the knee.

The NHANES I cross-sectional study did not find concordance between radiographic knee OA (defined by KL score) and knee pain (Hannan et al., 2000).They reported that only 47% of subjects with radiographic knee OA reported symptoms of pain while a meagre 15% of participants with knee pain were found to have radiographic knee OA. This discordance remained obvious in different age group categories. The lack of association in the NHANES study might have been due to knee pain and radiographic knee OA being characterised as dichotomous variables and hence lacking the sensitivity to detect an association.

A more recent study by Neogi et al (Neogi et al., 2009) using a within person, knee matched, case control design, demonstrated excellent correlation between radiographic severity measured by Kellgren and Lawrence grades and joint space narrowing with the presence and severity of knee pain. This was a study of 1032 patients from two separate American cohorts, one of which included patients who were recruited into the cohort because of their high risk of developing knee OA. Compared to knees with no pain, knees with pain had high odds of increased severity of radiographic knee OA measured by KL score; OR 5.5 (95% CI 2.7, 11.1) for KL score 2, OR 10.0 (95% CI 4.8, 20.4) for KL score 3 and a very large OR of 317 (95% CI 40, 2523) for KL score 4, when compared to a KL score of zero. Although one strength of the study was that the control knees were from the same patients (and therefore removed previously unmeasured confounding factors), there is a possibility of "overmatching" using this technique. This might explain part of the high correlation between symptoms and radiographs in their study. Furthermore, all these patients had asymmetrical knee joint symptoms; which raises the

concern that there may have been specific secondary causes like injury, which would cause such asymmetry. Nevertheless, if less sensitive modalities such as radiographs can demonstrate good correlation with clinical symptoms, it might be assumed that imaging modalities with greater sensitivity of identifying features of OA (such as ultrasound) will demonstrate even higher association with clinical symptoms of OA.

A study of 783 participants from randomly selected GP practices in south-west England assessed the cross-sectional association of radiographic bone attrition (vertical loss of bone volume) and clinical symptoms of knee pain, stiffness and disability (Reichenbach et al., 2011). The authors report a significant association of radiographic bone attrition with pain (OR 2.22; 95% CI 1.29, 3.80), stiffness (OR 3.23; 95% CI 1.85, 5.64) and disability (OR 2.09; 95% CI 1.19, 3.68), even after controlling for confounders such as age, sex, BMI, presence of joint effusion and K-L score. A limitation of this study was that it used pain, stiffness and disability as dichotomous variables and was therefore unable to demonstrate an increased prevalence of attrition with increasing severity of clinical symptoms. Another limitation of the study was that selection bias could not be excluded in this sample as there was only a small proportion of the original cohort that was assessed by radiographs; furthermore the authors report that non-attendees for radiographs had much lower proportions of pain, stiffness and disability than those who had radiographs performed in the study.

A cross sectional MRI study of 401 participants with radiographic knee OA in Boston, USA, demonstrated the association of bone marrow lesions on MRI (a feature more prevalent in OA subjects than controls) and self-reported knee pain (Felson et al., 2001).After adjustment for potential confounders such as effusion, sex, age and individual radiographic features, bone marrow lesions were significantly associated with knee pain (OR 3.31; 95% CI 1.54, 7.41). Furthermore, large bone marrow lesions had an even greater magnitude of association (OR 5.78; 95% CI 1.04, 111.11). As a limitation, this study analysed only patients with radiographic knee OA and did not include

participants with no evidence of radiographic OA. Similar results were also noted in a study of 143 participants with symptomatic knee OA in USA where bone marrow lesions on MRI were significantly associated with knee pain (co-efficient 3.72; 95% CI 1.76, 5.68) (Torres et al., 2006). This co-efficient depicted the increase in median knee pain severity associated with one unit increase in lesion score and was adjusted for age and BMI. The coefficients were also significantly positive but of lower magnitude for bone attrition (co-efficient 1.91; 95% CI 0.68, 3.13) and osteophytes (co-efficient 0.50; 95% CI 0.07, 0.94) in this study.

The presence of an osteophyte in the patellofemoral compartment of the knee on MRI was associated with presence of knee pain (OR 2.25; 99% CI 1.06, 4.77) but not stiffness (OR 1.83; 99% CI 0.88, 3.81) in a cross-sectional study of 205 participants with radiographic knee OA (Kornaat et al., 2006). However, osteophytes in the tibiofemoral compartment, bone marrow edema and sub chondral bone cysts were not significantly associated with knee pain or stiffness in their study. The participants included 100 sibling pairs and five non siblings and despite the efforts of the authors to adjust for the intra-family effect on the estimates of this study, there is likely to have been a residual effect of confounding by selection bias.

In further evidence of this association, a longitudinal study of 110 cases and 220 controls with knee OA or at high risk of knee OA in the USA, looked at the association between incident knee pain over a period of 15 months follow up and incremental changes to bone marrow lesions on MRI (Felson et al., 2007b). An increase of one in the bone marrow lesion score resulted in an insignificant OR of 1.5 (95% CI 0.8, 3.1) for incident knee pain but an increase of ≥2 in the bone marrow lesion score resulted in an odds of 3.2 (95% CI 1.5, 6.8) for incident knee pain in this cohort.

The above studies suggest that structural changes in the bone are highly correlated with clinical symptoms. However, ultrasound imaging is a far cheaper and easier modality to use than MRI, in population based studies of OA. The high correlation of ultrasound detected knee osteophytes and pain, stiffness and disability improves our understanding of the relationship of symptoms and structural changes on imaging. This also demonstrates the potential utility of ultrasound in prospective population based epidemiological studies of knee OA as well as clinical practice.

7.3.2 Association of symptoms with right medial cartilage thickness

Articular cartilage is not usually innervated by pain fibres and nociceptors and hence the finding of a lack of significant association of symptoms between mean femoral cartilage thickness on ultrasound and knee symptoms (see Table 20) is not surprising. However, when minimum cartilage thickness was used as an outcome measure (see Tables 21 and 22), there was a significant association with pain and physical function. The above results would suggest that minimum cartilage thickness has more clinical relevance than mean cartilage thickness at the femoral condyle.

Previous MRI studies have either shown a weak association (Torres et al., 2006, Wluka et al., 2004) or no significant association (Pelletier et al., 2007, Kornaat et al., 2006) of cartilage changes on MRI and knee pain.

Indeed, a cross-sectional study on 143 participants with symptomatic knee OA found only a weak association of cartilage morphology on MRI and knee pain (Torres et al., 2006). Cartilage morphology was graded on an ordinal scale from 0 to 6 (for thickness and signal). For one unit increase in cartilage score, there was an increase in median knee pain severity score of 0.53 (95% CI 0.08, 0.98), after adjusting for age and BMI. These estimates were much lower than the associations of knee pain seen for bone marrow lesions and synovitis score in the same study.

An Australian study of 132 subjects with symptomatic knee OA followed up over a period of two years found a borderline significant inverse association between baseline tibial cartilage volume on MRI and baseline pain (r= -0.17; p=0.05) and disability (r= -0.20; p=0.03) measured by WOMAC (Wluka et al., 2004). While baseline pain (r= 0.13; p=0.14) and disability (r= 0.15; p=0.10) did not have a correlation with loss of tibial cartilage volume over two years, there appeared to be an association of change in symptoms of knee OA with loss of cartilage volume over time. Increased pain was significantly associated with cartilage loss (r= -0.28; p=0.002) and so was increased disability (r= -0.21; p=0.02). This study did not adjust for potential confounders such as age, sex, BMI and presence of effusion. It is possible that these confounders, especially the presence of effusion, might have reduced the association that was seen between tibial cartilage volume and knee symptoms in this study.

An American study of 107 participants with radiographic knee OA did not find any association between cartilage volume on MRI (global or medial compartment) at baseline and baseline WOMAC pain ((p>0.5) and function (p>0.3) (Pelletier et al., 2007). There was a weak significant association between increasing pain over 24months and cartilage loss over the same period (r= -0.21; p = 0.03). However this association was even weaker than that seen between radiographic joint space loss over 24 months and increased WOMAC pain (r= -0.29; p = 0.002) in the same study.

A cross sectional study of 205 participants with radiographic knee OA found no association between focal (OR 1.07; 95% CI 0.50, 2.28) or diffuse (OR 1.79; 95% CI 0.70, 4.55) cartilage defects on MRI and presence of knee pain on most days of the previous month (Kornaat et al., 2006). The associations remained insignificant when cartilage defects were measured by compartment in the knee; (OR 1.52; 95% CI 0.64, 3.61) in patellofemoral compartment and (OR 1.47; 95% CI 0.68, 3.17) in the tibiofemoral compartment. Similarly, no associations were seen between self reported knee stiffness and the above measures of cartilage morphology.

A systematic review of the association between MRI detected cartilage defects and knee pain in OA concluded that the level of evidence on this association was conflicting (Yusuf et al., 2011). The authors reviewed a total of 12 studies that assessed this relationship; although only two studies had attempted to adjust for potential confounders (and none of the studies adjusted for presence of knee effusion). They reported that three of the five high quality studies had noted a significant, albeit weak, association of cartilage abnormalities and knee pain.

MRI studies have used various scoring systems to measure cartilage abnormalities such as cartilage volume, cartilage thickness, cartilage signal as well as scoring the number of cartilage "defects". As with any new imaging modality, the validity of these outcome measures requires further study. Based on the results of the Thousand Families Study, minimum cartilage thickness on US appears to demonstrate higher construct validity than mean cartilage thickness at the femoral condyle; due to the significant association of pain and physical dysfunction seen with minimum (but not mean) cartilage thickness.

7.3.3 Association of symptoms with knee effusion

Contrary to what was expected, the presence of knee effusions on ultrasound did not appear to confer a risk for increasing pain, stiffness or physical dysfunction on WOMAC in the Thousand Families Study (see Table 24).

In addition, prevalent knee effusions showed poor correlation with prevalent osteophytes at the knee; right knee (r=0.04; p=0.53), left knee (r=0.10; p=0.10) and "any knee" (r=0.06; p=0.29).

A number of MRI studies have in fact shown a high correlation of synovitis and/or effusion on MRI with knee pain (Torres et al., 2006) (Lo et al., 2009, Kornaat et al., 2006). However, there are some noticeable exceptions to this (Hill et al., 2007).

A study of 143 participants with symptomatic knee OA noted a high level of association between synovitis/effusion (combined score) and knee pain (Torres et al., 2006). The co-efficient for the association of grade 2 or 3 synovitis/effusion vs grade 0 for knee pain was 9.82 (95% CI 0.38, 19.27); where the co-efficient represented an increase in median knee pain severity on a 100 mm visual analogue scale associated with one unit increase in lesion score, adjusted for age and BMI.

There was significant correlation between effusion on MRI and weight bearing pain on WOMAC in a study of 160 participants with radiographic knee OA in a cross-sectional analysis of the Osteoarthritis Initiative study (Lo et al., 2009). Effusion was graded on a semi-quantitative ordinal scale from 0 to 3. The risk ratios of weight bearing knee pain for higher levels of effusion score were 1.0, 1.7, 2.0 and 2.6 (p for trend = 0.0004). The authors did not adjust for sex, age and BMI in this analysis although presence of synovitis

and bone marrow lesions was adjusted for. Importantly, there appeared to be no significant correlation between synovitis and effusion (r=0.10; p=0.20). This suggests that synovitis and effusion might not necessarily represent the same pathology in OA. Indeed, the authors of the Osteoarthritis Initiative study hypothesised that synovial effusion might indicate fluid that has extravasated from bone in those with bone marrow lesions; since there was a weak correlation between effusion score and maximal bone marrow lesions in their study (r=0.21; p=0.007).

A study of 270 participants with symptomatic knee OA from the Boston Osteoarthritis of the Knee Study demonstrated no correlation between baseline synovitis and baseline pain score (r=0.09; p=0.17) (Hill et al., 2007). Synovitis was graded on a scale from 0 to 9 using MRI and participants were subsequently followed up for 30 months. The authors noted a significant correlation between change of pain and change of synovitis score (r=0.21; p=0.0003), adjusted estimate of 3.15 VAS score increase (on 0-100 scale) per unit increase in synovitis score; 95% CI 1.04, 5.26. Confounders such as age, sex, BMI, cartilage score at baseline and change in effusions scores over 30 months were adjusted for in this analysis. Interestingly, the authors noted that there was no association between change in effusion score and change in pain score over 30 months (adjusted odds 1.19; 95% CI -8.08, 10.46). The Boston study suggests that there is a longitudinal (but not cross-sectional) relationship between change in synovitis score on MRI and change in pain scores over time; although effusions did not appear to share this relationship.

A study of 205 participants with radiographic knee OA found an extremely strong cross-sectional association between a large knee effusion on MRI and presence of knee pain (OR 9.99; 99% CI 1.13, 149) and stiffness (OR 4.67; 95% CI 1.11, 26.14) (Kornaat et al., 2006). A semi-quantitative ordinal scale was used to quantify effusions on MRI in this study; knee pain was defined as presence of knee pain for “most days of the prior month”. The participants for this study were recruited primarily to identify genetic susceptibility determinants of OA and hence included patients and their siblings with

radiographic knee OA (100 sibling pairs and five non siblings). Although the authors attempted to adjust for this intra-family effect using statistical methods, it is possible that an element of selection bias remained.

The scoring criteria for effusion and synovitis on MRI appear to have certain differences while pain and stiffness also appeared to have different definitions, in the above studies. Hence, despite the fact that a recent systematic review found moderate level of evidence to support the association between effusion/synovitis on MRI and knee pain (Yusuf et al., 2011), it must be remembered that the criteria for defining these pathologies on MRI have not been standardised across studies and hence there is still some difficulty in comparing estimates between studies.

The results of the Thousand Families Study suggest that knee effusions on ultrasound in OA might not have prevalent association with knee symptoms. However, longitudinal follow up of these participants is needed to ascertain whether there might be an increased incidence of knee OA in this group of participants.

7.3.4 Association of symptoms with hip OA

Although there were no significant statistical associations of hip OA with any of the three subscales of WOMAC in the Newcastle Thousand Families Study, there was a near significant association with physical dysfunction (Adjusted OR 2.34; 95% CI 0.98, 5.57) and a trend towards a positive association with pain (Adjusted OR 1.87; 95% CI 0.87,

4.05), when comparing those with severe symptoms to those with no symptoms (see Table 25).

Patients with radiographic OA of the hip were found to report significantly higher WOMAC scores on the function subscale (but not pain and stiffness subscales) when compared to those with radiographic knee OA in a hospital based Italian study of 244 symptomatic patients (836.8 vs 692.3; p=0.001) (Salaffi et al., 2005). The authors also demonstrated the increasing scores on the function subscale (but not pain and stiffness subscales) of WOMAC with increasing severity of radiographic hip OA and mention a lower magnitude of effect in the hip when compared to the knee (only figure provided in article; no values stated). The Thousand Families study demonstrates increased pain (OR 2.30; 95% CI 1.16, 4.56) and loss of function (OR 2.75; 95% CI 1.30, 5.79), but not stiffness (OR 1.68; 95% CI 0.82, 3.48) are associated with ultrasound defined hip OA, when comparing those with severe symptoms to no symptoms. The magnitude of these associations in the hip is lower than that seen in the knee; which is opposite to the results of the Italian study. This might be due to the difference in the participants in the two studies; the Italian study recruited symptomatic patients attending hospital while the Thousand Families Study included members of a birth cohort who were unselected and from the community.

The association of pain with radiographic hip OA was demonstrated in a population based study of 1067 participants from Manchester, England (Birrell et al., 2005). Severe hip OA had a very strong association with pain (OR 17.4; 95% CI 3.0, 102) while mild/moderate OA did not have such an association (OR 1.4; 95% CI 0.4, 4.7). Pain was considered present if participants responded to having pain in the hip for >24 hours in the previous month and indicated the same by shading a pre-specified area of a manikin in the questionnaire. This is in line with the results of the Thousand Families study which shows an association with the pain subscale of the WOMAC instrument.

7.3.5 Association of symptoms with hand OA

None of the subscales of the AUSCAN instrument were found to be associated with ultrasound defined hand OA in the Thousand Families Study (see Table 26). This might be due to the possibility that symptoms in the hands are more transient than those in the lower limbs; there was a time lag of a few weeks between filling the questionnaire and the ultrasound assessment. Considering the high prevalence of hand OA in this study, it is also possible that ultrasound was extremely sensitive and picked up osteophytes at a very early stage; prior to the development of clinical symptoms.

The large Rotterdam study of 3430 participants from the community noted that hand pain (OR 3.6; 95% CI 2.4, 5.6) and hand disability (2.4; 95% CI 1.1, 5.4) were significantly associated with erosive radiographic hand OA (Kwok et al., 2011). However, erosive OA is regarded as the severe end of the OA spectrum and hence these estimates would be expected to be higher than that seen in pooled (erosive and non-erosive) radiographic OA.

Jones et al demonstrated that pain and function are significantly associated ($p<0.01$ for all questions of the two subscales in AUSCAN) with severity of radiographic hand OA in a cross-sectional study of 522 patients from Tasmania, Australia (Jones et al., 2001). They noted that OA at the DIP joints (beta 0.15; $p=0.012$) and CMC joints (beta 0.19; $p<0.001$) were both associated significantly with hand function and OA at the DIP (beta 0.17; $p=0.003$) and CMC (beta 0.14; $p=0.02$) joints were also associated with hand pain.

Similarly, an assessment of 3902 participants from the Rotterdam study demonstrated a significant association of radiographic hand OA with pain in the previous month (OR 1.9; 95% CI 1.5, 2.4) while hand disability (measured by the health assessment questionnaire) was also associated with hand OA (OR 1.5; 95% CI 1.1, 2.1) (Dahaghin et al., 2005).

The modest association of symptoms with hand OA in the above radiographic studies may have been masked by the use of a more sensitive tool to image for presence of osteophytes (namely ultrasound) in a small sample of participants.

7.4 Direct and indirect risk factors for OA at each joint site

7.4.1 Predictors of knee osteophytes

7.4.1.1 Obesity:

BMI at age 49-51 was most significantly associated with knee osteophytes at age 62/63 on multivariate analysis in the Thousand Families Study (OR 1.11; 95% CI 1.02, 1.19) (see Table 29). This was an expected finding with the magnitude of effect being large.

While the association of obesity with knee OA has been consistently noted in studies over the years, the mechanism through which this occurs might not be as simple as that of increased load on joints leading to increased joint damage. Indeed the effects of adipose tissue as an endocrine organ which releases adipocytokines such as leptin and adiponectin is increasingly being recognised as an additional potential pathway by which obesity exerts its influence on knee OA (Aspden, 2011, Pottie et al., 2006). BMI is a measure of obesity that includes both fat and lean mass and it is unable to disentangle the relative contribution of muscle mass and adipose tissue to the risk of knee OA.

A recent cross sectional study of 76 patients with knee OA and 24 controls in Thailand demonstrated an inverse relationship between plasma adiponectin ($r = -0.68$, $p < 0.001$) and synovial fluid adiponectin ($r = -0.47$, $p<0.001$) concentrations and severity of radiographic knee OA (Honsawek and Chayanupatkul, 2010). The reason for the lower levels of adiponectin in synovial fluid when compared to plasma adiponectin levels in diseased joints found in this study is not clear. One possibility is that it is destroyed within the diseased joint at higher rates than it is produced; possibly driven by inflammation. Another hypothesis is that the transport of this cytokine in to the joint

might be reduced in OA; although you would then expect the plasma levels of adiponectin to be within normal limits in OA patients, if this were the case.

An ex-vivo study of 35 knees of obese patients (mean BMI of 28) with severe OA, found high concentrations of leptin in osteophytes, synovium and the infra-patellar fat pad (Gegout et al., 2008). The authors also noted higher levels of resistin and adiponectin in the serum when compared to synovial fluid; while leptin levels were higher in synovial fluid (compared to serum) in females with no significant difference seen in males. The authors also noted a high leptin/adiponectin ratio in synovial fluid of these obese OA patients; with females having a higher concentration of free leptin in the joint fluid. There was no comparator group (without OA) in this study but the authors did however believe that these results suggest a possible explanation for the higher prevalence of OA in obese and female participants.

A recent review on this topic explained that adipocytokines exhibit pleiotropic functions related to glucose and lipid metabolism, inflammation and bone formation and hence could be considered as systemic factors that link the association of obesity with OA (Hu et al., 2011).Most studies seem to confirm a pro-inflammatory role of leptin in OA while adiponectin might play an anti-inflammatory (hence a protective) role in OA; however the authors of the review also describe studies that contradict this general view and conclude that the role of adipocytokines in OA is yet to be clarified (Hu et al., 2011).

In addition to its effects through adipocytokines, obesity might also exert its influence on knee OA through other mechanisms such as dysregulation of glucose and lipid metabolism (Sowers and Karvonen-Gutierrez, 2010). Obesity results in a change in metabolic milieu characterised by insulin resistance and increased glucose levels which are known to be associated with pro-inflammatory cytokines seen in chronic inflammatory conditions (Sowers and Karvonen-Gutierrez, 2010). In a study of 482

women with a mean age of 47 years, obese women (BMI ≥ 30 kg/m^2) with less than 2 cardiovascular risk factors were three times more likely to have prevalent radiographic knee OA (OR 3.00; 95% CI 1.03, 8.71) when compared to non obese women with less than two cardiovascular risk factors (Sowers et al., 2009). However, the risk of prevalent knee OA was even higher among obese women with two or more cardiovascular risk factors (OR 6.20; 95% CI 2.93, 13.07) when compared to non obese women with low cardiovascular risk. It is therefore possible that any of the components of the metabolic syndrome (such as hypercholesterolemia and impaired glucose tolerance) might exert additional influence on the risk of knee OA in obese individuals.

Importantly, there are mechanical factors that are likely to mediate the relationship between obesity and knee OA. In a study of 300 participants with knee OA in Chicago, USA, BMI was found to have a significant correlation with knee OA severity (measured as narrowest joint space width) in those participants with varus malalignment (r = -0.29; 95% CI -0.43, -0.14) (Sharma et al., 2000). However, in a sex adjusted model, adjustment for varus malalignment reduced the correlation between BMI and knee OA severity from 0.24 (95% CI 0.16, 0.31) to 0.04 (95% CI -0.04, 0.12). This cross sectional study suggests that malalignment might play an important role (which could be confounding or mediating) in the association between obesity and knee OA. Furthermore, quadriceps muscle strength is also likely to play an important role in the biomechanical link between obesity and knee OA; quadriceps weakness shown to be associated with knee OA in some longitudinal studies (Sowers and Karvonen-Gutierrez, 2010). Roubenoff proposed the term "sarcopenic obesity" at the turn of the century and hypothesised that in OA "loss of muscle mass occurs as a primary event…this loss is a major contributor to fat gain, which in turn reinforces the muscle loss" (Roubenoff, 2000).

While BMI alone is insufficient (as a marker of obesity) to explain the complex relationship between obesity and knee OA, the results of the Thousand Families Study

serves to provide further evidence of the positive association between knee OA and obesity.

7.4.1.2 Bone density:

The increased risk of knee OA with higher bone density seen in this study has been noted in previous studies (Hart et al., 1994, Zhang et al., 2000, Hart et al., 2002, Nevitt et al., 2010).

The MOST study followed 1754 participants with a mean age of 63 years (similar to our study cohort) and a mean BMI of 29.9 kg/m^2 (higher than our study cohort) for 30 months (Nevitt et al., 2010). They found that subjects in the highest quartile of baseline femoral neck BMD had an OR of 2.3 (95% CI 1.2, 4.5) for development of incident radiographic knee OA, when compared to those in the lowest quartile. The corresponding OR for incident knee osteophytes was 1.9 (95% CI 1.1, 3.1). These results were adjusted for age, BMI, physical activity and knee injury.

In order to compare the magnitude of this risk with the MOST study, femoral neck BMD measurements were split in to quartiles. Univariate analysis showed an OR of 4.05 (95% CI 1.75, 9.39) for knee OA in the highest quartile when compared to the lowest quartile of femoral neck BMD in the Thousand Families Study. In the adjusted model, using BMD as an ordinal variable, the OR for knee OA was 2.51 (95% CI 0.99, 6.38) when comparing the highest to the lowest quartiles; this showed borderline significance.

A cohort of younger women (n=830; mean age 54 years) in the Chingford study were followed up over a period of four years and it was noted that baseline BMD at the lumbar spine (1.01 g/cm^2 versus 0.95 g/cm^2; p = 0.002) and femoral neck (0.79 g/cm^2 versus 0.76 g/cm^2; p = 0.02) were higher in the women who developed incident knee osteophytes (Hart et al., 2002). These results were not adjusted for confounders such as age and BMI. These results are also similar to those seen in our study, where a univariate association was seen with BMD at the femoral neck as well as at the spine.

The Framingham study of 473 women (mean age 70 years; mean BMI ~ 26) also showed a trend towards higher baseline femoral neck BMD in women who developed incident knee OA over 8 years of follow up (Zhang et al., 2000). Multivariate adjusted OR (adjusted for age, BMI, estrogen use, smoking status and physical activity) of incident OA for those in the highest quartile of BMD when compared to those in the lowest quartile was 2.3 (95% CI 0.8, 6.6).

All the above results are in line with the results seen in the Thousand Families Study. The mechanisms of this observed relationship between bone mineral density and OA have been hypothesised previously. OA is known to involve bony changes; in particular the hypertrophic bone changes with osteophyte formation and subchondral plate thickening (Hunter and Spector, 2003). Bone volume is known to be substantially higher in OA subjects (Beuf et al., 2002) but subchondral bone in those with OA is less dense and also demonstrates increased porosity and reduced mineralisation (Li and Aspden, 1997). At a molecular level, there is an increased level of metabolism in the subchondral bone collagen in the femoral head in OA, which eventually leads to reduced mineral content (Mansell and Bailey, 1998).

It is also known that larger bones have a higher apparent areal BMD (Looker et al., 2001) and the association of high BMD with knee OA seen in our study might be due, in part, to the increased bone dimensions that occur in those participants with knee OA (Wang et al., 2006). Adjustment was performed for BMI (a measure of body size) but there is the likelihood of further effects of bone size on areal BMD which could not be adjusted for in our study.

It has been suggested that TGF-β1 and other growth factors might play a role in the association of OA with high bone mineral density; through its bone-forming effects (Keen et al., 2001). A female twin study showed that subjects (mean age 48 years) who were homozygous for the presence of a polymorphism within the TGF-β1 gene had a 4% reduction ($p=0.04$) in femoral neck BMD (compared to two other genotypes); this association being particularly apparent in pre-menopausal women (Keen et al., 2001). There was a trend towards increased risk of osteoporosis (T score < -2.5) at the femoral neck in this genotype, when compared to the other two genotypes studied (OR 1.69; 95% CI 0.94, 3.04). In particular, there was a significantly increased risk noted in pre-menopausal women (OR 5.38; 95% CI 1.96, 14.89) while there was no such risk in post-menopausal women (OR 1.09; 95% CI 0.52, 2.56). This suggests that this polymorphism had a deleterious effect on the attainment of peak femoral neck BMD in this cohort of women. This might be one of the mechanisms by which BMD is associated with increased knee osteophytes.

Thirdly, BMD and the development of OA might be influenced by common genetic factors. Polymorphisms in the genes encoding Wnt antagonists are associated with knee OA (Valdes et al., 2007) and also with bone density (Ai et al., 2005).

The effect of BMD on knee OA did not appear to be mediated through vitamin D intake in the study, since adjustment for vitamin D intake did not appear to affect the magnitude

and significance of the effect of femoral neck BMD on knee OA. Sunlight exposure and serum vitamin D levels were not checked in this study. The main source of vitamin D is through sunlight and hence it is not possible to exclude the effect of vitamin D as a mediator in the association between BMD and knee OA. Nevertheless, total intake of dietary vitamin D did not appear to play a role in the above association in the Thousand Families Study.

Another limitation of this analysis is that it was not possible to look at the BMD within sub-regions of bone such as the sub-chondral bone which might have provided further information regarding the association between BMD and OA. One of the pathological hallmarks of OA includes sub-chondral sclerosis and indeed it is likely that the association of OA and BMD within this sub-region is likely to be stronger and might explain the lack of association of hip OA with BMD in this study.

7.4.1.3 Breast feeding:

This is the first study to demonstrate a protective effect of exclusive breast feeding on the development of knee OA. The results of the Thousand Families Study demonstrated that breast feeding asserts a protective effect on knee OA which is independent of the effect of BMI (see Table 29). Another hypothesis for this relationship could be that breast feeding reduces the number of infections in childhood (Howie et al., 1990); thus reducing the burden of inflammation (a known predictor of knee OA prevalence (Ledingham et al., 1995) and progression (Ayral et al., 2005)) across the lifecourse. However, the protective effect of breast feeding remained significant even after adjustment for total infections in childhood up to the age of 5 years in our study (OR 0.86; 95% CI 0.73, 1.00; p =0.05). It should however be noted that breast feeding did not appear to have a protective effect on infections up to the age of 5 years in this birth cohort (β coefficient = 0.04; 95% CI -0.26, 0.34).

A previous assessment of the Thousand Family Study participants had noted that duration of breast feeding had a protective effect on plasma fibrinogen levels measured at age 49-51, as a surrogate marker for inflammation (β= -0.10, 95% CI -0.19, 0.001) (Pearce et al., 2011). However, the protective effect of breast feeding on knee OA remained significant even after adjusting for plasma fibrinogen levels at the age of 49-51 years in the multivariate model (OR 0.82; 95% CI 0.68, 0.98; p = 0.03). SES was a potential confounder that was adjusted for in this study. However, it was not possible to adjust for another potential confounder, namely maternal smoking.

It is possible that the protective effect of breast feeding could be mediated by other unmeasured factors across the lifecourse, including factors such as cognitive development (Anderson et al., 1999) and other psychological and social factors (Fergusson and Woodward, 1999). This could be pursued further in future birth cohort studies.

7.4.1.4 Inflammation:

The Thousand Families Study demonstrates an independent positive association of fibrinogen with knee osteophytes, even after adjustment for BMI (see Table 30).

Previous studies on the association between markers of inflammation and OA have been contradictory where some population based studies have shown no association after controlling for BMI (Kraus et al., 2007, Sowers et al., 2002) while an association was found in others (Spector et al., 1997a).

The Johnston County OA project studied the association of hsCRP with radiographic knee and hip OA in 662 participants (mean age 61 years) (Kraus et al., 2007). They noticed a strong correlation of hsCRP with radiographic knee and hip OA; with a linear increase with increasing severity and extent of OA. However they noted that this association lost its significance after adjustment for BMI and also noted a significant and moderate correlation between hsCRP and BMI ($r=0.40$, $p<0.001$). This study might suggest that the effect of BMI on knee OA was mediated by hsCRP.

In contradiction to the above study, the Thousand Families Study has demonstrated an independent effect of fibrinogen (after adjustment for BMI) on the development of knee OA. However, it did show a correlation of fibrinogen with BMI as seen in the Johnston County study, albeit a weaker correlation ($r=0.15$, $p=0.02$). The results of the Thousand Families Study suggest that hsCRP and BMI confound each other but also have independent effects on the development of knee OA.

Similar to the Johnston County study, the Michigan study of 1025 women (mean age 43) noticed a higher mean CRP (>twice) in those with prevalent knee OA when compared to those without radiographic knee OA ($p<0.0001$) (Sowers et al., 2002). In addition they followed participants for 2.5 years and noted a significantly higher mean CRP in those with incident knee OA as well. Similar to the Johnson County study, they also reported a high correlation of CRP with BMI ($r=0.58$) and also noticed a lack of association of CRP with knee OA after adjustment for BMI. Further evidence of this association of CRP, knee OA and BMI comes from a Swedish study of participants with a mean age of 58 years (Engstrom et al., 2009). It showed that baseline CRP was significantly associated with severe knee OA in women (defined as arthroplasties) after 12 years of follow up, but this significance was lost after adjustment for BMI.

The reason for the independent effect of fibrinogen on knee OA (after adjustment for BMI) in the Thousand Families Study which was not seen when using CRP (as a measure

of inflammation) in the above studies is not clear. The obvious difference is that CRP and fibrinogen might work through different mechanisms in the pathway that links inflammation and OA. CRP is considered to work purely via inflammatory pathways while fibrinogen has inflammatory and vascular mechanisms of action. In addition, there were differences in the age groups of the cohorts with the Michigan cohort being particularly young (mean age of 43 years) and might therefore have picked up different phenotypes of OA, such as early OA or secondary forms of OA.

In the Thousand Families Study ultrasound was used to identify osteophytes (and not joint space). The lack of confounding by BMI of the association of inflammation and OA in our study might suggest that BMI can confound this association through effects on cartilage rather than bone. Adipose tissue releases adipocytokines such as adiponectin which has been shown to be associated with important pathways in the degradation of the cartilage matrix (Ehling et al., 2006).

A cross sectional study of 1235 participants of the Framingham Offspring cohort found no definite association between 17 markers of systemic inflammation (including fibrinogen and CRP) and radiographic knee and hand OA, after adjustment for age, sex and BMI (Vlad et al., 2011). The odds of radiographic OA for one standard deviation increase in fibrinogen was 0.94 (0.94; 95% CI 0.85, 1.03). It is possible that the lack of cross-sectional association between inflammatory markers and prevalent OA is because the longitudinal relationship between inflammation and OA is mediated by other factors such as BMI.

Similar to the findings of the Thousand Families Study, a longitudinal study of the Chingford cohort of 845 women demonstrated a significantly increased baseline CRP ($p=0.006$) among those participants with radiographic knee OA progression after four years of follow up, when compared to those without progression (Spector et al., 1997a). This association remained significant even after adjustment for age, height, weight and

smoking. The results of the Chingford study are more in line with the results of the Thousand Families Study; suggesting that there is a link between inflammation and progression of OA and possibly even incident OA, although this cannot be inferred from the results of the Thousand Families Study alone, since ultrasound features of OA were identified only at the 62/63 year review.

A longitudinal study of 188 participants with knee OA showed that knee effusion (a clinical measure of inflammation) at baseline predicted an increase in KL grade of knee OA over a median period of follow up of two years (OR 1.03; 95% CI 1.01, 1.05) (Ledingham et al., 1995). Warmth at the knee (another clinical measure of inflammation) was also associated with detrimental change in at least one radiographic feature (OR 2.22; 95% CI 1.19, 4.14). These estimates were obtained after adjusting for confounders such as BMI, stage of disease and age. A more recent multi-centre arthroscopic study has helped to demonstrated the longitudinal association of synovitis (local inflammation in the joint) with progression of cartilage damage over a period of just one year (Ayral et al., 2005). The OR for progression of cartilage damage in participants with synovitis was 3.11 (95% CI 1.07, 5.69) in this study. However, there was no adjustment for BMI and stage of disease in this study.

In summary, while cross-sectional studies have shown a lack of association between measures of inflammation and OA, longitudinal studies have shown an increased progression of knee OA with higher levels of inflammation. It would be interesting to study the factors that mediate this relationship; in particular measures of obesity such as BMI, waist circumference, leptin, adiponectin, etc.

7.4.2 Predictors of minimum medial cartilage thickness (right knee)

7.4.2.1 Social class at birth

The thinning of femoral cartilage in those from a lower social class at birth is another novel finding of the Thousand Families Study. Lower social class is known to be associated with a number of deleterious outcomes such as coronary heart disease, poor physical and mental functioning (Singh-Manoux et al., 2004). It is plausible that social class leads to intermediate outcomes that are risk factors for cartilage thinning; factors that were not assessed in the Thousand Families Study.

The inverse association of social class at birth with BMI, fibrinogen, depression and chronic widespread pain at age 45, was demonstrated in a birth cohort study of 9377 participants (Power et al., 2007). All the above factors are known to potentially increase the risk of knee OA. While BMI and fibrinogen were adjusted for in the Thousand Families Study, depressive symptoms and chronic widespread pain were not assessed. It is possible that such psychological factors could mediate the association between social class at birth and cartilage thinning at age 63. Indeed, presence of a depressive illness was associated with an increased risk of symptomatic knee OA in a study of 660 elderly Korean patients (OR 5.87; 95% CI 3.01, 11.44) (Kim et al., 2011).

A recent population based study of 7076 Dutch participants found an association between self reported "arthritis" and psychiatric disorders (Land et al., 2010). Arthritis had a cross-sectional association with mood disorders (OR 1.48; 95% CI 1.09, 1.99) and with anxiety disorders (OR 1.42; 95% CI 1.11, 1.81) after adjusting for age, sex and education level. The odds of arthritis were even higher for presence of two or more psychiatric illnesses (OR 1.78; 95% CI 1.33, 2.39). On longitudinal follow up for three years, baseline arthritis predicted an increased incidence of mood disorders (OR 2.06; 95% CI 1.31, 3.22) in this cohort. A limitation of the study was that the outcome was a loose definition of "self reported arthritis". Nevertheless, OA is the most common cause for

joint pain in the elderly and this Dutch study provides evidence of an association of OA with mood disorders.

One of the confounders in the association between negative affect and disability in OA was found to be muscle strength in a small study of 58 Dutch participants with physician reported knee or hip OA (Dekker et al., 1993). This was a cross sectional study where there was a significantly higher correlation between negative affect and disability in patients with muscle weakness, compared to those without muscle weakness ($p<0.001$).

It is therefore possible that a large number of factors might mediate this association between social class at birth and cartilage thinning in adulthood. Some of these factors might include educational level, use of healthcare facilities, smoking patterns, muscle strength, psychiatric illnesses and perception of pain. Studies of younger birth cohorts might help to identify the role of these factors and the temporal associations between these factors and OA.

7.4.2.2 Alcohol

It was surprising to note that heavy alcohol intake had a protective effect on minimum femoral cartilage thickness in the Newcastle Thousand Families Study, when compared to no alcohol intake (adjusted co-efficient 0.25; 95% CI 0.06, 0.43).

A small cross sectional Japanese study of 109 men with recently diagnosed radiographic knee OA noted an inverse association between current alcohol consumption and

functional status (Kondo et al., 2007). Compared to past or never drinkers, current alcohol consumers had a lower risk of reduced walking distance (OR 0.34; 95% CI 0.14, 0.84: P=0.02) and help for climbing stairs (OR 0.21; 95% CI 0.09, 0.51: p=0.001) even after controlling for age, height, weight, smoking and occupation status. The authors wondered if this effect was due to confounding co-morbidities such as diabetes, hypertension and cardiovascular disease where participants might have been advised to stop drinking alcohol. However, even after adjustment for the above co-morbidities, the estimates of protection remained significant for current alcohol consumers.

A cross sectional study of 8740 participants based in the population in Greece found a protective effect of modest alcohol consumption (when compared to no alcohol intake) on symptomatic hand OA (OR 0.50; 95% CI 0.3, 0.9) but not knee (OR 1.1; 95% CI 0.8, 1.4) or hip OA (OR 0.8; 95% CI 0.4, 1.7) (Andrianakos et al., 2006). While potential confounders such as BMI, level of education, smoking status and socioeconomic status was controlled for in this study, there was no adjustment for co-morbidities such as diabetes and cardiovascular disease.

It is not clear as to whether this protective effect of alcohol on knee cartilage thickness seen in the Thousand Families Study is indeed a true effect or simply an association which is due to an unexplored confounder. It is certainly possible that members of the Thousand Families Study that did not drink alcohol at all were in fact unable to drink higher amounts of alcohol due to associated co-morbidities or other unmeasured risk factors. While smoking was a potential confounder that was adjusted for in the study, there might have been a host of other factors that could have potentially confounded this association of alcohol and cartilage thickness.

If a true relationship exists, there does not appear to be a biologically plausible explanation for the protective association of alcohol on knee cartilage. However, further studies to explore this association and its mechanism would be helpful.

7.4.2.3 Smoking

Current smokers (at age 50 years) in the Newcastle Thousand Families Study had statistically significant reductions in minimum femoral cartilage thickness when compared to non smokers (Adjusted co-eff -0.12; 95% CI -0.22, -0.01).

Previous studies have suggested that smoking confers a protective effect on knee OA (Samanta et al., 1993, Felson et al., 1989). In contradiction to this, other studies have shown no association between smoking and knee OA (Hart and Spector, 1993a, Wilder et al., 2003). However, these studies have used radiographs as outcomes which are less sensitive measures of cartilage thickness (as radiographs can only measure joint space).

The decreased cartilage thickness in current smokers (when compared to never smokers) seen in the Thousand Families Study is in line with the results of an MRI based study (Amin et al., 2007). This was a study of 159 men with symptomatic knee OA in Boston, USA, who were followed up for a period of 30 months to look at the association of smoking with incidence of cartilage loss on MRI. After adjustment for baseline cartilage score, age and BMI, male current smokers were at an increased risk of cartilage loss in the medial tibiofemoral joint (OR 2.3; 95% CI 1.0, 5.4). Furthermore, they were also found to have higher pain scores at baseline and at 30 months follow up than never smokers ($p<0.05$). This study used a sensitive measure of cartilage thickness in comparison to previous studies which used radiographic(Felson et al., 1989) or surgical measures(Sandmark et al., 1999) to define the outcome of OA. However, this was a small study that remained limited to men; furthermore, only a small proportion of men were current smokers (12%).

The authors of the above study reveal numerous mechanisms by which smoking might lead to cartilage loss. Firstly, they describe the damaged chondrocytes in the intervertebral discs of smoke exposed rats on histopathology when compared to controls. They also mention the increased oxidant stress associated with smoking which in turn is associated with cartilage loss (Tiku et al., 2000). Smokers also have increased levels of carboxyhaemoglobin in arterial blood which leads to tissue hypoxia and can possibly play a part in reducing cartilage repair (McDonough and Moffatt, 1999).

The mechanism by which smoking affects articular cartilage homeostasis requires further study, especially in view of the contradictory results seen in previous studies on this issue.

7.4.3 Risk of hip OA

7.4.3.1 Obesity:

Among the variables studied in the Thousand Families Study, a raised BMI posed the greatest risk for hip OA in the adjusted model (OR 1.11; 95% CI 1.04, 1.18) (see Table 41). Obesity has been shown to be a consistent risk factor for hip OA in previous studies (Cooper et al., 1998, Lievense et al., 2002, Jarvholm et al., 2005, Lohmander et al., 2009)

although exceptions to this association have been found (Tepper and Hochberg, 1993, Reijman et al., 2007).

A large Swedish study of male construction workers found an association between baseline BMI and subsequent hip replacement after 12 years of follow up(Jarvholm et al., 2005). After adjusting for age and smoking habits, the relative risk of hip OA was 0.35 (95% CI 0.20, 0.61), 1.0, 1.54 (95% CI 1.38, 1.72) and 2.02 (95% CI 1.68, 2.43) in the BMI categories of 17-19, 20-24, 25-29 and 30-35 respectively. To compare these results with the Thousand Families Study, BMI was divided in to similar categories. After adjustment for pack years of smoking, the ORs for hip OA in the same categories of BMI were 1.0, 0.81 (95% CI 0.07, 9.45), 1.37 (95% CI 0.12, 15.7) and 2.66 (95% CI 0.23, 31.3). The reason for the lack of significance in these results is likely to be due to the small numbers of participants in the Thousand Families Study (as evidenced by the large confidence intervals); where too few participants were present in each of the four BMI categories. Nevertheless, using BMI as a continuous variable helped to demonstrate the association of obesity with hip OA in the Thousand Families Study. In contrast, the Swedish study had 320,192 participants and were able to demonstrate a relatively small, yet significant association of obesity to subsequent hip OA. Baseline BMI was a much stronger predictor of knee arthroplasty (when compared to the hip) in this study.

Another large Swedish study of nearly 28000 men and women from the community noticed a similar magnitude of positive association between baseline BMI and incident hip arthroplasty after 11 years of follow up (Lohmander et al., 2009). When compared to subjects with a BMI <25, the RR of hip OA for men with a BMI >30 was 3.3 (95% CI 2.2, 5.0) while the RR for women was 2.1 (95% CI 1.6, 2.7). The magnitude of the association of obesity with OA was far higher at the knee in the same study; RR for men in the above BMI categories was 4.4 (95% CI 2.6, 7.5) and for women it was 6.9 (95% CI 5.0, 9.6). Another large population based study of 39,023 participants from Melbourne, Australia demonstrated a similar positive association of BMI and other measures of

adiposity (fat mass, percentage fat, waist circumference and waist-to-hip ratio) with hip and knee arthroplasty, the association being stronger at the knee (Wang et al., 2009b). The authors concluded that adipose mass (leading to biomechanical stress) as well as central adiposity (acting via metabolic pathways) contribute to the risk of lower limb joint replacement.

A systematic review of the association of obesity with hip OA concluded that there was moderate evidence of a positive association; a pooled OR in the region of 2.0 (comparing BMI ≥25 with BMI <25) (Lievense et al., 2002). The estimate was finally based on four high quality studies; one cohort and three case-control studies. This review included 12 studies in all; most of which were cross-sectional associations and only half had radiographic outcome data. A more recent systematic review on the same subject reviewed a total of 14 epidemiological studies (Jiang et al., 2011). An increase of 5 units in the BMI scale led to an increased risk of hip OA (RR1.11; 95% CI 1.07, 1.16). They noted no significant difference in the magnitude of the association between the two sexes. Similarly, the estimates were not particularly different for case-control studies (RR 1.12; 95% CI 1.02, 1.24) when compared to cohort studies (RR 1.11; 95% CI 1.06, 1.16). Studies using radiological and clinical outcomes had lower estimates (RR 1.04; 95% CI 1.00, 1.07) when compared to studies that defined OA using surgical end-points (RR 1.16; 95% CI 1.11, 1.22), although this difference was not statistically significant. This is not surprising as surgical definitions include the severe end of the OA spectrum.

The results of the Thousand Families study provide further evidence of the positive association between a measure of obesity (namely BMI) and hip OA. The mechanism of this association has been a matter of great interest recently (Pottie et al., 2006).

The universally accepted mechanism for this association of obesity with lower limb joint OA is that of increased biomechanical stress in obese persons, leading to joint damage.

However, the high concentrations of leptin and other adipocytokines in the synovium of OA patients has led researchers to hypothesise that the adipose tissue produces systemic factors that might also alter the risk of OA via metabolic pathways (Pottie et al., 2006).

A histological study of five patients with hip OA and five with osteoporotic hip fracture requiring replacement surgery, noted that bone in OA patients had twice the amount of fat per unit volume when compared to those with osteoporosis (0.22 g/cm^3 vs 0.10 g/cm^3; p=0.002) (Plumb and Aspden, 2004). The authors noted that there was a particularly high level of omega-6 fatty acids in OA, which are precursors to pro-inflammatory eicosanoids (such as prostaglandin E_2), albeit quite further upstream in the prostaglandin pathway. This suggests that altered lipid metabolism might have a role to play in the pathogenesis of hip OA, in some part possibly mediated by inflammatory pathways.

This was the first assessment for hip OA in the Newcastle Thousand Families cohort at age 62/63 years. The association between hip OA and obesity can be bi-directional and hence it would be incorrect to derive a causative link between obesity and hip OA based on these results alone.

7.4.3.2 Smoking:

The Thousand Families Study is the first study to demonstrate a higher risk of prevalent hip OA with increased levels of smoking (OR 1.02 per pack year; 95% CI 1.00, 1.05; p = 0.02) (see Table 41). This is in contradiction to a large study in Sweden of 320,192 Swedish male construction workers where it was found that non smokers (OR 1.37; 95% CI 1.22, 1.54) and ex-smokers (1.21; 95% CI 1.05, 1.39) had a higher risk of hip OA than current smokers (Jarvholm et al., 2005). However this study defined hip OA as those requiring arthroplasty; data obtained by linkage with the Swedish hospital discharge

register. Smokers are more likely to have associated co-morbidities and the threshold for surgical intervention in these subjects is likely to be higher. This might explain the protective effect of smoking on hip OA seen in this study, since OA was defined by the occurrence of arthroplasties and there was no adjustment for the likely confounding effect of co-morbidities in the Swedish study. A part of the difference observed between the Thousand Families Study and the Swedish study might also be explained by the fact that the Swedish OA phenotype represents the severe end of the OA spectrum (requiring joint replacement) and would not have included more mild cases. In the Swedish cohort, 0.47% of participants developed hip OA while the Thousand Families study had a prevalence of 41%; demonstrating a marked variation in the phenotype of hip OA cases between the two cohorts.

A study of 611 patients listed for hip replacement and an equal number of controls (in two districts in England) found a protective effect of smoking in men but not women (Cooper et al., 1998). There was a significant protection against hip OA in current smokers when compared to non smokers (OR 0.40; 95% CI 0.20, 0.90) in men in this study. Once again, the confounding effect of co-morbidities was not adjusted for in this study and hence the protective effect of smoking might have resulted from a selection bias for surgical intervention among non-smokers (with less co-morbidity).

Evidence for the protective effect of smoking on lower limb OA comes from the Framingham cohort, although this effect was seen on radiographic knee OA (Felson et al., 1989). Participants of the study had knee radiographs taken in 1983-85 and had their smoking history recorded 36 years previously. They demonstrated that heavy smokers were less likely to develop knee OA than non smokers (RR 0.81) after adjustment for age, sex and weight. They even adjusted for other potential confounders such as knee injury history, sports activity history, physical activity level, coffee and alcohol consumption but found that smoking continued to confer protection from knee OA. A concern with this study is that it obtained smoking history 36 years prior to knee

radiographs being obtained and it is possible that smoking habits might have changed considerably during this period; for example non-smokers could have become heavy smokers and vice versa. In any case, the Framingham study is confined to the assessment of knee OA and is unable to answer the same question with regards to hip OA.

A study of 690 subjects in a case control study in Nottingham, UK, noted a negative association of ever smokers and lower limb joint OA (OR 0.43; 95% CI 0.25, 0.72)(Samanta et al., 1993). Once again, knee OA appeared to confer most of this protective effect (OR 0.29; 95% CI 0.14, 0.62). In contrast to the Thousand Families Study, this was a study of hospital referred patients with symptomatic knee OA and the analysis was restricted to women.

A recent met-analysis which looked at the association of smoking and osteoarthritis concluded that the protective effect of smoking in OA in many studies was probably false and might have been caused by selection bias. It demonstrated that the inverse association was only noted in case-control studies (OR 0.82; 95% CI 0.70, 0.95) but not in cohort studies (0.92; 95% CI 0.81, 1.06) or cross sectional studies (OR 0.89, 95% CI 0.78, 1.01). Even within case-control studies, the association was only seen in hospital based studies (OR 0.65; 95% CI 0.52, 0.81) but not in population based studies (OR 0.90; 95% CI 0.75, 1.08).

There are several possible mechanisms for the increased risk of hip OA in smokers, which are described below:

Immune insults caused by smoking might lead to an inflammatory phenotype of hip OA. A large cross sectional study of 6902 men and 8405 women in the UK (EPIC-Norfolk cohort) demonstrated higher total white cell counts in smokers (particularly current

smokers) when compared to non-smokers (Smith et al., 2003). However, the authors noted that smokers who had recently given up smoking (in the previous 12 months) had significantly reduced white cell counts when compared to current smokers; thus concluding that smoking cessation might have an immediate benefit in reducing the inflammatory burden associated with smoking. In the large population based NHANES III study conducted between 1988 and 1994, there were strong associations between self-reported cigarette smoking and peripheral blood inflammatory markers, even after adjustment for conventional cardiovascular risk factors (Bazzano et al., 2003). When compared to non-smokers, smokers had higher levels of elevated CRP (defined as ≥10 mg/L) with an OR of 1.98 (95% CI 1.57, 2.51) and elevated fibrinogen (≥11.1 μmol/L) with an OR of 2.15 (95% CI 1.65, 2.80). Furthermore, there was a significant dose-response relationship of cigarette smoking (including serum cotinine levels) with these measures of inflammation in this study.

The British Regional Heart Study also demonstrated a significantly higher level of CRP (2.53 vs 1.35 mg/L), fibrinogen (3,51 vs 3.13 g/L) and white cell count (7.92 vs 6.42 x 10^9/L) in current smokers compared to non-smokers (Wannamethee et al., 2005). However, compared with non-smokers, the levels of the above inflammatory markers remained significantly higher in ex-smokers even after 10-19 years of stopping smoking (all $p<0.05$); levels (in ex-smokers) reaching equilibrium (compared with non-smokers) only after 20 years of smoking cessation. This study suggests that there might be a cumulative effect of cigarette smoking on the markers of inflammation.

Smoking is also associated with abnormal and increased numbers of T-lymphocytes (Hughes et al., 1985), decreased levels of NK cells (Ginns et al., 1985) and reduced humoral and cell mediated immunity (Harrison, 2002). Another possibility includes deleterious effects of smoking on adipocytokines (Al-Daghri et al., 2009, Iwashima et al., 2005) and estrogen (Tanko and Christiansen, 2004).

A cross-sectional study of 154 diabetic men in Saudi Arabia demonstrated hyperleptinemia (OR 2.15), hypoadiponectinemia (OR 2.05) and hyperresistinemia (OR 3.05) among current smokers when compared to non-smokers (Al-Daghri et al., 2009). However, they noted that ex-smokers had similar leptin and adiponectin levels when compared to non-smokers and hypothesised that smoking cessation might help improve the adipocytokine profile. This study was limited by the lack of appropriate confidence intervals and significance levels being stated in the article.

A study of 331 Japanese men also showed a significantly lower ($p=0.01$) plasma adiponectin level in current smokers compared to never smokers; the significance of the relationship remained even after controlling for potential confounders such as age, BMI, hypertension, diabetes and hyperlipidaemia (Iwashima et al., 2005). The study also noted an acute drop in adiponectin levels ($-14.5 \pm 0.6\%$; $p<0.01$) in five never smokers (and co-authors in the study) 12 hours after they smoked a cigarette.

A review article of the association of smoking with estrogens detailed the consistency of evidence showing a negative effect of smoking on serum estrogen levels (Tanko and Christiansen, 2004). The review also drew attention to the studies that demonstrated lower estradiol and estrone levels in smokers (compared to non-smokers) receiving hormone therapy; suggesting that cigarette smoking might reduce the effectiveness of hormone therapy in women.

In summary, the mechanisms by which smoking exerts its influence on OA of the hip needs further study. This is the first study to demonstrate a higher risk of hip OA with increasing pack years of cigarettes smoked.

7.4.3.3 Physical activity:

The existing evidence on the relationship between physical activity and OA is limited and potentially complex, because it is hypothesised that a certain amount of mechanical joint stress is necessary for ideal functioning of the joint while excessive stresses on the joint might lead to OA (Stevens-Lapsley and Kohrt, 2010).

A case-control study of 138 patients with radiographic hip OA identified from a hospital in Hong Kong (and age/sex matched controls from the community) noted a higher risk of hip OA in men (OR 8.7; 95% CI 1.8, 42.7) and women (OR 2.5; 95% CI 1.0, 5.9) who climbed stairs (>15 flights per day) in their main paid occupation, when compared to those who did not (Lau et al., 2000). Lifting weights of ≥10 kg more than 10 times a week showed hip OA odds ratios of 5.3 (95% CI 1.8, 15.8) in men and 3.0 (95% CI 1.8, 5.1) in women, when compared to those who lifted no weights. Similarly, lifting weights of ≥50 kg led to hip OA odds ratios of 9.6 (95% CI 2.2, 42.2) in men and 2.9 (95% CI 1.5, 5.6) in women. Potential confounders such as joint injury, weight, height and sports activities were adjusted for. The authors also tried to ascertain the relationship of sport activity with hip OA and found that there was no significant protective or adverse effect of sport on hip OA. However, it is likely that the numbers in the study were too few and it therefore lacked power to demonstrate a true relationship, if present.

Yoshimura performed a case control study of 114 Japanese patients listed for hip replacement for primary OA and found similar results for the relationship of hip OA with occupational activity (Yoshimura et al., 2000). Occupational activity relating to joint loading was ascertained using structured interviews. Participants were mostly women (90%) and odds for hip arthroplasty when lifting weights more than 50 kg (more than

once a week) in their main job was 4.1 (95% CI 1.1, 15.2) and regular lifting more than 25 kg in their first job conferred odds of 3.5 (95% CI 1.3, 9.7) when compared to participants who did not lift such weights. These results were obtained after controlling for knee pain and educational attainment which were considered potential confounders. On the other side of the coin, those who spent more than two hours a day sitting in their first job were significantly less likely to require hip arthroplasty (OR 0.6; 95% CI 0.3, 1.0).

Croft et al performed a case control study of 167 male farmers and 83 controls working in sedentary jobs in Staffordshire and Cheshire, England to confirm the association of farming with hip OA (defined as hip replacement for OA or joint space ≤ 1.5 mm) (Croft et al., 1992a). They reported that farmers with more than 10 years of experience in the profession had odds of 9.3 (95% CI 1.9, 44.5) for prevalent hip OA; even after controlling for confounders such as age, height, weight and presence of heberden's nodes in the hands. Possible explanations for this relationship include the burden of heavy lifting, exposure to vibration from agricultural machinery and walking for prolonged periods over rough surfaces.

Croft et al in a separate study demonstrated that severe hip OA (defined as hip replacement for OA or joint space ≤ 1.5 mm) in men was more common in farmers with more than 10 years experience (OR 2.0; 95% CI 0.9, 4.4), prolonged standing at work for > 2 hours a day (OR 2.7; 95% CI 1.0, 7.3) and heavy lifting of > 25.4 kg for ≥20 years (OR 2.5; 95% CI 1.1, 5.7) (Croft et al., 1992b). This was a case control study of 245 cases and 434 controls recruited from the community in North Staffordshire and Shrewsbury, England. Climbing > 30 flights of stairs (OR 1.2; 95% CI 0.6, 2.5), kneeling

for > 30 minutes a day (OR 1.0; 95% CI 0.3, 3.2) and squatting for >30 minutes a day (OR 1.3; 95% CI 0.4, 3.6) did not appear to confer a risk of severe hip OA.

As previous studies have used different measures and definitions of physical activity, it is difficult to compare these results with one another and also with the results of the Thousand Families Study. However, it is reasonable to suggest that a variety of physical activities have been shown to demonstrate a positive relationship with hip OA in the past and the results of the Thousand Families Study adds further evidence to this association. However, further longitudinal studies using standardised measures of physical activity would provide more evidence for the magnitude and consistency of these findings.

The differential effect of physical activity on knee and hip OA is not easily explained. While physical activity was a risk factor for hip OA in the Thousand Families Study, there was no association seen with knee OA. One of the reasons for this difference might be that there are different types of physical activities that lead to OA at the knee and hip. A review on this topic noted that while kneeling and squatting were important risk factors for knee OA, it was climbing stairs and lifting heavy objects that conferred a higher risk of hip OA (Schouten et al., 2002). This in turn, might be due to the differences in local factors affecting mechanical loading at the joints, such as malalignment at the knee.

It is not known from the results of the Thousand Families study as to whether exceeding a specific threshold will lead to increased hip OA. However, this issue is still not clear from any of the previous studies and will require strict and consistent definitions of physical activity in future studies. It is also important to point out that an international systematic review recommends that “healthy subjects and patients with OA can pursue a high level of physical activity, provided the activity is not painful and does not

predispose to trauma" (Vignon et al., 2006). It is therefore important to try and work out whether there are specific physical activities that particularly predispose to hip OA, especially if regular physical activity is being recommended as a therapeutic strategy in OA. However, the data obtained from the Thousand Families Study to date does not help to answer that question at present.

7.4.3.4 Educational attainment:

A Japanese case control study of 114 cases (103 women) and 114 controls found that low educational status (leaving school at age 14 vs 18 years) increased the risk of severe hip OA (being listed for hip arthroplasty) even after controlling for BMI and previous knee pain (OR 2.3; 95% CI 1.0, 5.2) (Yoshimura et al., 2000). This study had predominantly women participants with a mean age of 64 years. The Thousand Families Study noticed the same trend; compared to school dropouts, graduates had a near significant lower prevalence of hip OA in the total sample (OR 0.46; 95% CI 0.20, 1.02) and a strong trend to protection from hip OA in the female sample (OR 0.32; 95% CI 0.09, 1.10) on univariate analysis. However, this univariate relationship in the total sample was lost after adjusting for pack years of smoking (OR 0.57; 95% CI 0.25, 1.31). This suggests that the effect of higher education on hip OA is mediated by smoking; where educated persons were less likely to smoke and therefore had a decreased prevalence of hip OA at age 63. BMI (at age 50 and age 63) and physical activity at age 50 did not appear to play a significant mediating role in the association between educational status and hip OA in the Thousand Families Study.

In summary, the risk of hip OA appears to be predominantly influenced by adult lifestyle factors such as obesity, physical activity and smoking. This suggests that intervention in

early adult life might be the most effective time to help reduce the burden of hip OA in the community.

7.4.4 Predictors of hand OA

7.4.4.1 Smoking

Current smokers at age 50 years were found to have a lower prevalence of hand osteophytes on ultrasound in the Newcastle Thousand Families Study (OR 0.31, p= 0.01) when compared to non smokers.

Some studies have shown previously that smoking might confer a protective effect on hand OA (Haara et al., 2003, Wilder et al., 2003), although there are studies that suggest that there is no overall association (Hart and Spector, 1993a, Szoeke et al., 2006).

A cross sectional study of 985 women in Chingford, England with a mean age of 54 years assessed the association between smoking and hand OA (Hart and Spector, 1993a). After adjustment for age and BMI, current smokers had a nearly significant increased risk of radiographic DIP OA with an RR of 1.49 (95% CI 0.92, 2.41) and a significantly higher risk of radiological and clinical DIP OA (RR 2.13; 95% CI 1.18, 3.85) compared to never smokers. However, no such increased risk was seen at the PIP and CMC joints in the hand in the Chingford study. The opposite effect was seen in the Thousand Families Study which showed a significant protective effect in current smokers from prevalent DIP

OA (OR 0.44; 95% CI 0.20, 0.95) when compared to non smokers; and no evidence of a significant association in the PIP (OR 0.60; 95% CI 0.25, 1.42), the MCP (OR 0.47; 95% CI 0.13, 1.69) and CMC (OR 0.95; 95% CI 0.46, 1.96) joints in the hand. The reason for the different results in the two studies could be due to a list of factors. The Chingford study had only women participants and when this relationship in the Thousand Families Study was restricted only to women, current smokers had no evidence of a protective effect at the DIP joint when compared to non smokers (OR 0.61; 95% CI 0.21, 1.73). OA was defined radiologically in the Chingford study while it was defined using ultrasound (a more sensitive measure) in the Thousand Families Study. Indeed, the prevalence rate of DIP OA in the Chingford Study was 14% compared to 70% in the Thousand Families Study. This difference in prevalence rate at the DIP joint would have also reflected the increased age of the participants in the Thousand Families Study. The Thousand Families Study adjusted for other variables such as socioeconomic status and occupational activity, which are likely to have confounded the association of smoking with hand OA. The timing of the smoking exposure was 13 years prior to assessment for hand OA in the Thousand Families study, compared to the cross sectional Chingford study.

A cross sectional study of 227 women in Melbourne, Australia found no association between smoking (ever vs none) and hand OA (RR 1.01; 95% CI 1.0, 5.7; p = 0.35) (Szoeke et al., 2006). Ever smokers had no association with osteophytes at the DIP (RR 0.8; 95% CI 0.4, 1.8), PIP (RR 0.7; 95% CI 0.3, 1.5) and CMC (RR 0.9; 95% CI 0.4, 2.2) joints. The prevalence of radiographic hand OA was 44.5% in this study; which is still markedly lower than the prevalence estimate in the Thousand Families Study. The mean age of this cohort was 60 years and the mean BMI was 27.7; which is comparable to the Thousand Families Study.

A large Finnish population based study of 3595 men and women found a protective effect of smoking (≥20 cigarettes a day currently vs never smoked) on symmetrical DIP joint OA in men (OR 0.40; 95% CI 0.18, 0.86) but not in women (OR 0.66; 95% CI 0.18,

2.45) (Haara et al., 2003). The prevalence of radiographic OA in any finger joint and at least two symmetrical pairs of DIP joints was 45% and 16%, respectively. Current male smokers (≥20 cigarettes a day) had near significant protection for OA in any finger joint (OR 0.72; 95% CI 0.48, 1.09) while female smokers did not appear to have a significant association with OA in any finger joint (OR 0.81; 95% CI 0.32, 2.04) when compared to non smokers. These associations were adjusted for potential confounders such as age, BMI, educational level and physical activity. It is entirely possible that this inverse association of smoking and hand OA is due to an unmeasured confounder such as bone mineral density; where smokers are known to have lower bone mineral densities, which in turn is known to be associated with a lower prevalence of hand OA (Sowers et al., 1996, Marcelli et al., 1995). The Finnish study also suggests that smoking appears to have a protective effect from hand OA in men but not women; this observation does not seem to have a clear explanation. The Thousand Families study also noticed the same pattern where current (at age 50) male smokers had significant protection from prevalent hand OA (OR 0.17; 95% CI 0.04, 0.71) while female smokers did not have such protection (OR 0.58; 95% CI 0.17, 1.94) when compared to non smokers.

Another large cohort study in Clearwater, Florida, USA examined 1531 men and women to delineate the relationship of smoking (current vs never) with subsequent radiographic hand OA over a mean period of follow up of 5.5 years (Wilder et al., 2003). From the original cohort who had no evidence of OA at baseline, 49% developed hand OA (KL grade ≥ 2) and 17% developed severe hand OA (KL grade ≥ 3) at follow up. The authors noted a significant protective effect of current smoking (at study entry) with radiographic hand OA (KL grade ≥ 2) in the unadjusted analysis (RR 0.71; 95% CI 0.54, 0.92) when compared to those who never smoked. The level of protection was even grater for severe hand OA (KL grade ≥ 3) where current smokers had a RR of 0.38 (95% CI 0.22, 0.67) compared to non smokers. These estimates lost their significance after adjusting for potential confounders such as age, BMI, gender, occupation, physical activity and presence of OA at three other joint sites. The RR estimates in the adjusted analysis were

0.99 (95% CI 0.75, 1.31) for radiographic (KL grade ≥ 2) hand OA and 0.60 (95% CI 0.33, 1.08) for severe radiographic (KL grade ≥ 3) hand OA. It is possible that the adjustment for OA at the other three joint sites resulted in the loss of the significance seen in the adjusted estimates in the Clearwater study; since smoking was not associated with severe OA at the other joints while OA at the hand is likely to have been positively associated with OA at the other joints.

Further evidence for the protective effect of smoking on hand OA comes from the cross-sectional study of 174 men and 348 women in a Tasmanian study (Jones et al., 2002). Ever smokers had less frequent (OR 0.6; 95% CI 0.4, 0.9) and less severe Heberden's nodes (beta -0.60; 95% CI -1.03, -0.17), when compared to never smokers. However, there was no association of smoking with radiographic hand OA. The authors suggest that this might be due to smoking having an effect on Heberden's nodes by an anti-angiogenic effect at an earlier stage in the disease process of OA; prior to the development of radiographic changes.

In summary, the two largest studies which examined the relationship between smoking and hand OA did in fact show a protective effect of smoking; which is in line with the results seen in the Thousand Families Study.

7.4.4.2 Infections

The protective effect of infectious burden in childhood from subsequent hand OA in adulthood is a novel finding of the Thousand Families Study. The mechanism for this association is not clear and can only be hypothesised.

OA is known to involve auto immune processes (Du et al., 2005, Doherty et al., 1990) and shares common features with an auto immune disease like rheumatoid arthritis (Yuan et al., 2003). It was Strachan who suggested the idea of the "hygiene hypothesis" which claims that the increasing incidence of various autoimmune diseases in the western world is partly due to better hygiene and declining infections (Strachan, 1989). This inverse association of various auto immune diseases (such as multiple sclerosis, insulin dependant diabetes mellitus and inflammatory bowel disease) and infections in childhood has been demonstrated in several studies as described by Kivity et al (Kivity et al., 2009).

The hygiene hypothesis is considered a reasonable explanation for the apparent inverse association seen between certain childhood infections and subsequent onset of atopy and asthma (von Hertzen, 2000). Asthma is suggested to occur as a consequence of an imbalance between the Th1 and Th2 type immune response. However, while asthma is known to induce a predominantly Th2 type immune response with low levels of Th1 type of cytokines, patients with OA are known to have a predominance of Th1 cytokines in their synovial membranes (Ishii et al., 2002, Sakkas and Platsoucas, 2007). Nevertheless, Kero et al found that Th1 and Th2 diseases could coexist by noting an increased incidence of asthma in children with celiac disease and rheumatoid arthritis during the first seven years of their life (Kero et al., 2001). This was a study of a Finnish birth cohort of 60,254 children where the diseases were identified by linking with several national health registers.

Doherty et al, as early as 1990, discussed the hypothesis of generalised nodal (hand) OA as an autoimmune disease (Doherty et al., 1990). Indeed, nodal generalised OA, like other autoimmune diseases, is more prevalent in women. Doherty et al also noted the reported association of OA with other autoimmune diseases such as autoimmune thyroid disease and Sjogren's syndrome.

While the precise sequence and mechanism of immune events leading to cartilage destruction is not known in OA, there is sufficient evidence for humoral and cellular immunity to components of cartilage in OA which play a key role in the process of cartilage degeneration (Yuan et al., 2003). Yuan et al in an elegant review describe the numerous studies which have reported increase levels of T cells in OA synovial tissues; which are even comparable to that seen in rheumatoid synovium (Yuan et al., 2003). They suggest that a Th1 cell-mediated specific immune response occurs in the synovium in OA; similar to that seen in other auto immune diseases. They also noted the presence of antibodies and components of the complement system in OA cartilage in various studies. The imbalance between catabolic and anabolic pathways in OA joints is due to dysregulation of the cytokine network. Catabolic cytokines such as IL-1β are seen to be upregulated in OA probably even more than that seen in RA (Yuan et al., 2003).

Edwards et al found that sharing a bedroom in childhood (a proxy for burden of infection) conferred a lower risk of developing a positive rheumatoid factor in adulthood (OR 0.48; 95% CI 0.30, 0.78) among 675 men and 668 women in Hertfordshire, England (Edwards et al., 2006). The authors concluded that a "developing immune system exposed to fewer infectious micro-organisms through improved standards of hygiene may be more likely to produce rheumatoid factor and perhaps begin the pathological process that leads to rheumatoid arthritis". It is therefore quite plausible that infections in childhood might cause favourable changes to the immune milieu of an individual to help protect from an auto immune phenotype (the generalised form) of hand OA.

In summary, the predictors of hand OA in the Thousand Families Study were smoking status and number of infections in early childhood; both novel predictors for hand OA. The mechanisms of these associations need further investigation.

7.4.5 Role of early life factors in OA

There was a lack of association of birth weight with ultrasound features of OA at any of the three joint sites in this study, on multivariate analysis. ~~This suggests that the Developmental Origins of Health and Disease hypothesis does not appear to stand up to scrutiny in this particular study.~~ Apart from the protective effect of breast feeding on knee osteophytes, there did not appear to be a significant direct association of early life factors with OA. The results of the Thousand Families Study suggest that it is environmental exposures, particularly in adult life, that play a major part in the risk of developing OA at the knee, hip and hand.

However, it was noted that early life factors might play an indirect role in OA development, where adult risk factors played mediating roles in this association. These results support a "pathway" model of risk exposure across the lifecourse, ultimately leading to OA. There does not appear to be a significant "critical period" in infancy or foetal life that influences the prevalence of OA, in the Thousand Families Study. These results are contradictory to those found in relation to other outcomes such as coronary heart disease, diabetes, obesity and osteoporosis.

The potential reasons for these differences are many. Firstly, OA is a separate disease entity to the above illnesses and might therefore have a different risk factor profile across the lifecourse. The inverse association between osteoporosis and OA is evidence in favour of this possibility. Indeed, while obesity has a positive association with OA,

osteoporosis appears to have an inverse association with measures of weight and obesity. Contrary to this view, an inverse association between birth weight and clinical hand OA was found in men (but not women) in the MRC birth cohort study (Aihie Sayer et al., 2003) . Crude birth weight was used as an explanatory variable in the MRC study, with no adjustment for gestational age. Furthermore, the outcome used was clinical (and not image based) and the prevalence of hand OA was far lower in the MRC cohort (19% in men and 30% in women) when compared to the Thousand Families Study.

Secondly, birth weight was adjusted for gestation and sex in this study while not all studies supporting the Barker hypothesis did the same. Hence it is possible that the associations seen previously are limited to those with low birth weight due to prematurity rather than being small for gestational age. Furthermore, there were multiple relevant risk factors that were adjusted for in this analysis, using an a priori conceptual framework defining the temporal relationships between the selected variables. This provided a more rigorous approach to answering the question about lifecourse risk factors of OA, than studies which had only limited data on risk factor profiles across the lifecourse.

Only a very small part of the Hertfordshire cohort was sampled and did not have sufficient information about the non-participants to exclude the possibility of selection bias. In contrast, the Thousand Families Study has sufficient information on the non-attendees to assess the differences between those who participated and those who did not. Apart from sex and social class at birth, there were no significant differences between the sampled cohort at age 62/63 years and the rest of the original birth cohort in the Newcastle Thousand Families Study.

It is also possible that the relationship between birth weight and OA is a weak one and was therefore not identified in the Thousand Families Study which has a relatively small sample size. While it might not be possible to use ultrasound to define OA in larger birth

cohort studies due to feasibility, it will be interesting to observe the association of birth weight with radiographic OA in studies of larger birth cohorts.

Lastly, it is important to recognise that as with most epidemiological studies, the Thousand Families Study does not have information on certain risk factors that might have been relevant to test the foetal under-nutrition hypothesis; such as maternal smoking habits, alcohol intake and nutritional intake. This lack of adequate collection of relevant data might be an important reason why there was limited association between early life factors and OA in adulthood.

In summary, while it is not possible to refute the Barker hypothesis based on the results of the Thousand Families Study, there did not appear to be any data that would support this view either. The majority of the risk of OA conferred to these participants appeared to be acting through factors in adulthood.

Strengths of study

- Longitudinal design with prospectively collected data (exposures) over the whole lifecourse
- Important risk factors for OA have been collected previously (especially weight, physical activity, bone density)
- Incorporates social context of participants
- Used a community cohort of participants, which is important in epidemiological studies of OA since it helps to determine the burden of disease from a public health perspective. This is the largest cohort in OA using ultrasound as the

imaging modality and the first to report the prevalence of US defined OA in a community cohort.

- US is a sensitive, reliable and valid imaging modality. Inter-rater reliability and validity had already been established in a pilot study on the Northumberland over 85 cohort and further validity was established by comparison with radiographs and with self-reported symptoms of participants in the Thousand Families Cohort.
- Good follow up of cohort with very little attrition considering the long period of follow up. The study included about 30% of original birth cohort which is comparable to other birth cohort studies.
- Other outcomes (chronic conditions such as ischaemic heart disease, lung disorders and metabolic syndrome) have already been studied successfully in this cohort, using a lifecourse analysis.
- Conceptual framework had been developed prior to the assessment of participants and analysis of the data.

Weaknesses of study

- The study was not originally set up to specifically assess OA as an outcome, so certain risk factors (like alignment, muscle strength) have not been collected until the current assessment. Hence, only cross sectional associations can be made with some of the risk factors for the current analysis. Since this is the first assessment of joint disease in this cohort, only prevalent (and not incident) OA was used as the outcome measure.
- Not large numbers in this cohort, when compared to other epidemiological studies of OA using radiographs.
- The study assesses the lifecourse of this cohort born in 1947. There are likely to be significant "cohort" effects involved in the accumulation of OA risk and the

results may not necessarily apply to cohorts that have been born since then. Birth in the post war era; the demographic and working conditions at the time, diet, physical activity might have been different then when compared to current times.

- Only white Caucasian participants in this study; therefore may limit external validity.
- Recurrent assessments of health status in this cohort may introduce a bias which tends to make them develop healthier habits as they have been made more aware of their health during their lifecourse.

Chapter 8 Conclusions

This is the first population based study to describe the prevalence of ultrasound features of OA in the knee, hip and hand. Moderate to substantial agreement was noted between two observers for ultrasound features of OA. Validity of the use of ultrasound was demonstrated by comparison with radiographs at the knee and the hand. In addition, correlation of ultrasound features of OA with clinical symptoms reported by the participants served to provide a clinical perspective to the study. Indeed, certain ultrasound features of OA at the knee and hip had strong correlation with clinical symptoms of pain and disability; higher than that reported in previous radiographic studies of OA.

The risk factor profiles for OA across the lifecourse for the three joint sites varied; this suggests that the mechanism of OA varies between the different joint sites. It was found that obesity played a large role in OA of the weight bearing joints (knee and hip) as would be expected. However, there were a few novel associations found; such as the inverse association between breast feeding and the development of knee osteophytes.

~~The majority~~A large proportion of the risk of OA at the three joint sites seemed to occur through factors acting in adulthood. It should also be noted that while factors acting in adulthood had a strong association with OA in this study, some of the associations were mediated by early life factors (eg: social class at birth had an indirect effect on knee OA through mediators later on in the lifecourse). Nevertheless, early life factors such as breast feeding appeared to have a strong independent protective effect on the development of knee OA.

These results have implications from a public health perspective and would suggest that while modification of factors acting in adulthood ~~would probably be more beneficial than~~is very important, there is a also a key role for intervening in early life. The results also provide evidence of the complexity surrounding the etiopathogenesis of OA at the knee, hip and hand.

8.1 Implications for the future:

Further work to demonstrate reliability between observers will help to improve standardisation of ultrasound measurements in OA. Predictive validity of the use of ultrasound in OA will be demonstrated by longitudinal follow up of these participants to assess the risk factors for progression and incidence of OA.

Other birth cohort studies with larger numbers should use a similar conceptual framework to describe the risk factors acting across the lifecourse to influence OA in adulthood. Whilst it may be logistically difficult to perform ultrasound imaging in very large birth cohorts, it might be possible to perform scans on a significant proportion of the cohort to test the same hypothesis.

This study provides evidence that modification of lifestyle factors in adulthood, such as smoking, physical activity and obesity, are likely to play a major role in the prevention of OA in the community. Furthermore, interventions in early life, such as prolonging the duration of breast feeding among mothers, might also help to decrease the burden of knee OA in the community.

Further epidemiological studies to explore the mechanism of some of these associations are in order. The protective effects of breast feeding on knee OA and of infections in childhood on hand OA are novel findings that deserve further study.

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