Elsevier Editorial System(tm) for Osteoarthritis and Cartilage
Manuscript Draft

Manuscript Number: OAC1346

Title: Subclinical deformities of the hip are significant predictors of radiographic osteoarthritis and joint replacement in women. A 20 year longitudinal cohort study.

Article Type: Manuscript

Keywords: Femoroacetabular impingement, Acetabular dysplasia, Hip joint, Hip Morphology, Osteoarthritis, Risk factor

Corresponding Author: Mr. Geraint Emyr Rhys Thomas, MA, MB BS, MRCS

Corresponding Author's Institution: University of Oxford

First Author: Geraint Emyr Rhys Thomas, MA, MB BS, MRCS

Order of Authors: Geraint Emyr Rhys Thomas, MA, MB BS, MRCS; Antony J Palmer; Rajbir N Batra; Amit Kiran, PhD; Deborah Hart; Timothy Spector; M K Javaid; Andrew Judge; David W Murray; Andrew J Carr; Nigel K Arden; Sion Glyn-Jones

Abstract:

Objective
Femoroacteabular Impingement and Acetabular Dysplasia are common deformities, which have been implicated as a major cause of hip osteoarthritis (OA). We examined whether these subtle deformities of the hip are associated with the development of radiographic OA and total hip replacement.

Design
A population-based, longitudinal cohort of 1003 women underwent pelvis radiographs at baseline, 8 and 20 years. Alpha angle and Modified Triangular Index Height and Lateral Centre Edge (LCE) angle and Extrusion Index were measured. Radiographic OA and the presence of a total hip replacement were then determined at 20 years.

Results
Measures of Femoroacetabular Impingement were significantly associated with the development of radiographic OA. For each degree increase in Alpha angle above 65° there was a 5% increase in the risk of radiographic OA (OR 1.05 [95% CI 1.01-1.09], $p = 0.007$). For Acetabular Dysplasia, each degree reduction in LCE angle was associated with an increase in risk of 13.0% (OR 0.87 [95% CI 0.78-0.96], $p = 0.008$) for radiographic OA and 18% (OR 0.82 [95% CI 0.75-0.89], $p < 0.001$) for total hip replacement.

Conclusions
This study demonstrates that Cam-type Femoroacetabular Impingement and mild Acetabular Dysplasia are predictive of subsequent OA and total hip replacement. These are independent of age, BMI and joint space and significantly improve current models of hip OA development. Pincer-type Femoroacetabular Impingement was not predictive of subsequent OA or total hip replacement.

Suggested Reviewers: Andrew McCaskie
Professor, University of Cambridge
awm41@cam.ac.uk

Mike Nevitt
UCSF
MNevitt@psg.ucsf.edu

Richard Field
Professor, Imperial College, London
richard.field@eoc.nhs.uk

Opposed Reviewers:

Subclinical deformities of the hip are significant predictors of radiographic osteoarthritis and joint replacement in women.

A 20 year longitudinal cohort study.

[1]Geraint E. R. Thomas – Academic Clinical Fellow
[1]Antony J. R. Palmer – Clinical Research Fellow
[1]Rajbir.N. Batra – Statistician
[1]Amit Kiran - Statistician
[2]Deborah Hart - Executive Director TwinsUK
[2]Timothy Spector - Professor of Genetic Epidemiology
[1]M. Kassim Javaid - University Lecturer in Metabolic Bone Disease
[1]Andy Judge - Senior Statistician
[1]David W. Murray - Professor of Orthopaedic Surgery
[1]Andrew J. Carr - Nuffield Professor of Orthopaedic Surgery
[1,3]Nigel K. Arden - Professor of Rheumatology
[1]Sion Glyn-Jones - Senior Lecturer

[1]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, NIHR Musculoskeletal Biomedical Research Unit, Nuffield Orthopaedic Centre, University of Oxford, Windmill Road, Oxford, OX3 7LD
[2] Department of Twin Research & Genetic Epidemiology, King's College London, St Thomas' Hospital Campus, 3rd & 4th Floor South Wing Block D, Westminster Bridge Road, London SE1 7EH
[3] MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, SO16 6YD, United Kingdom

Corresponding author:
Geraint E. R. Thomas
geraint.thomas@ndorms.ox.ac.uk
Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, NIHR Musculoskeletal Biomedical Research Unit, Botnar Research Centre, Nuffield Orthopaedic Centre, University of Oxford, Windmill Road, Oxford, OX3 7LD
Tel: +44 1865 737902
Fax: +44 1865 227671

Keywords: Osteoarthritis, Epidemiology, Hip Osteoarthritis, Femoroacetabular impingement, Acetabular Dysplasia

Word Count: 3249

Abstract

Objective

Femoroacteabular Impingement and Acetabular Dysplasia are common deformities, which have been implicated as a major cause of hip osteoarthritis (OA). We examined whether these subtle deformities of the hip are associated with the development of radiographic OA and total hip replacement.

Design

A population-based, longitudinal cohort of 1003 women underwent pelvis radiographs at baseline, 8 and 20 years. Alpha angle and Modified Triangular Index Height and Lateral Centre Edge (LCE) angle and Extrusion Index were measured. Radiographic OA and the presence of a total hip replacement were then determined at 20 years.

Results

Measures of Femoroacetabular Impingement were significantly associated with the development of radiographic OA. For each degree increase in Alpha angle above 65° there was a 5% increase in the risk of radiographic OA (OR 1.05 [95% CI 1.01-1.09], $p = 0.007$). For Acetabular Dysplasia, each degree reduction in LCE angle was associated with an increase in risk of 13.0% (OR 0.87 [95% CI 0.78-0.96], $p = 0.008$) for radiographic OA and 18% (OR 0.82 [95% CI 0.75-0.89], $p < 0.001$) for total hip replacement.

Conclusions

This study demonstrates that Cam-type Femoroacetabular Impingement and mild Acetabular Dysplasia are predictive of subsequent OA and total hip replacement. These are independent of age, BMI and joint space and significantly improve current models of hip OA development. Pincer-type Femoroacetabular Impingement was not predictive of subsequent OA or total hip replacement.

INTRODUCTION

Osteoarthritis (OA) of the hip is a common disease, with a cumulative prevalence of up to 27%[1-4]. The mortality adjusted lifetime risk of Total Hip Replacement (THR) at age 50 is 12%[5]. Losses of earnings due to disability and direct treatment costs have made OA and other rheumatic diseases among the most expensive of all items in any healthcare budget and a major burden to society. Health expenditure towards arthritis related care represents 2.5% of the United States' entire Gross Domestic Product[6]. Hip Replacement accounts for almost half of the hospitalization costs associated with OA[7], with over three hundred thousand total hip replacements performed in the United States in 2011[8], which is projected to increase to five hundred and seventy four thousand by 2030[9].

Historically, 10% of hip OA has been termed secondary and attributed to major deformities of the hip, such as developmental acetabular dysplasia, Legg-Calvé-Perthes disease or slipped capital femoral epiphysis[10]. The remaining 90% of hip OA was termed 'primary' or 'idiopathic' and presumed some underlying abnormality of articular cartilage. For nearly 50 years authors have suggested some relationship between more subtle deformities of the proximal femur and/or acetabulum and subsequent development of OA of the hip[10-12]. More recently cross-sectional studies have supported this theory; although cannot prove causality[13]. These deformities can be broadly divided into milder forms of acetabular dysplasia, which results in a shallow hip socket, and Femoro-Acetabular Impingement, which describes morphological abnormalities of the femoral head-neck junction, acetabulum, or both[14]. Both can be quantified using measurements taken on plain radiographs. These deformities are thought to result in a focal mechanical overload of articular cartilage, leading to subsequent osteoarthritis and joint replacement[14].

Femoroacetabular impingement and acetabular dysplasia are prevalent and are common in patients with established osteoarthritis of the hip, with concomitant hip malformations seen in 36.6% of women and 71.0% of men with hip osteoarthritis[13]. However, it is not known whether these malformations pre-date or are a result of the OA pathogenic process and therefore whether they are truly causal. If the radiographic measurements of mild acetabular dysplasia and femoroacetabular impingement are predictive of developing hip OA, they may represent targets for preventative strategies and treatment. Surgical interventions, such as osteotomy and osteochondroplasty have already been developed for these conditions, though there treatment efficacy is unproven. Pharmaceutical and physical treatments may

also become available in the near future[15]. Such interventions may ultimately reduce the burden of end-stage hip osteoarthritis and THR.

The aim of this study was to determine whether subtle deformities of the hip are associated with the development of radiographic osteoarthritis and end-stage OA (defined by THR) in a population based prospective cohort. To date, no studies have been able to assess the role of hip morphology in the development of structural change and THR in a population cohort, making this a unique project. Our hypothesis was that a causal relationship exists between subtle deformities of the hip and subsequent osteoarthritis.

METHODS

Study Participants

The Chingford 1000 Women Study is a population-based cohort of 1003 women living in the United Kingdom. In 1989, women registered at a general practice in London of the age range 44-67 years (mean 54.2) were invited to participate in a study assessing musculoskeletal disease, with yearly clinic visits; morphometric, clinical, biologic, and radiographic measurements were obtained at these visits. Standardised supine Anterio-Posterior (AP) pelvis radiographs were taken at years 2, 8 and 20. The present study included all participants who had undergone an AP pelvis radiograph. The local ethics committee approved the study and written consent was obtained from each woman (Outer North East London Research Ethics Committee (formerly Barking & Havering and Waltham Forest RECs), LREC (R&WF) 96). Figure 1 shows flow of participants from the recruitment of the cohort to the final study populations.

Exclusions

Exclusion criteria were applied to ensure that year 2 radiographs were of a minimum acceptable standard. Twenty individuals were excluded due to poor radiograph quality. Poor radiograph quality was a subjective exclusion criterion applied by the principal investigator when a radiograph was either grossly over- or underexposed to the extent that constituent anatomic landmarks were not visible for the purposes of analysis. Five hip joints (3 individuals) were excluded because they already had a THR in situ. Five hip joints (5 individuals) were excluded because it had a dynamic hip screw in situ, indicating previous femoral neck fracture. Seventy-two hip joints (36 individuals) were excluded because they had excessive rotation or tilt, as measured according to the distance between the sacrococcygeal joint and the

pubic symphysis[16]. A total of 119 hips in 61 individuals were excluded. Baseline characteristics of those excluded from analysis were not significantly different from those included in the analysis.

Radiographic assessment of morphology

Hip morphology was analysed using a validated software package called HipMorf 2.0[17]. We used two radiological measurements for Acetabular dysplasia and Pincer-type femoroacetabular impingement; the LCE angle [18] and Extrusion Index[19, 20]. LCE measures acetabular coverage of the femoral head and Extrusion Index measures the proportion of femoral head located within the acetabulum. A low LCE indicates acetabular dysplasia, while a high LCE is indicative of Pincer-type femoroacetabular impingement. The converse is true with respect to Extrusion Index. Two measurements for Cam-type femoroacetabular impingement were also used; the Alpha angle[21, 22] and Gosvig's Modified Triangular Index Height[17]. These measurements are in routine clinical use and can be made on standard anterior-posterior pelvis radiographs. Each radiograph was anonymised. All morphological measurements were performed by the principal investigator (GERT), blinded to outcome. Reproducibility of hip morphology measurement was assessed with intra-observer ICC in excess of 0.75 for all measures and inter-observer ICC in excess of 0.81.

Radiographic assessment of OA

At baseline (Year 2, n=787) and at Year 20 (n=487) radiographs were scored 'blind' to clinical details according to the method of Kellgren and Lawrence (K & L)[23] using the Atlas of Standard Radiographs by a single trained clinician (GERT). OA was defined as K & L $\geq$ 2.

Total Hip Replacement (End-stage Hip Osteoarthritis)

Details of any operations undergone in the previous year are recorded at each Chingford visit. Confirming that a patient had undergone THR for end-stage OA was done by contacting the patient's general practitioner and checking the medical records at the hospital at which the surgery was performed.

Statistical Analysis

The distribution of morphological measurements (LCE, Alpha Angle, Extrusion Index and Modified Triangular Index Height) was examined using histograms and kernel density plots. Normally distributed variables were compared using the independent 2-tailed t-test; non-normally distributed variables were compared using the Wilcoxon rank sum test. Participants were only included in an analysis if they had not had the outcome at the start of the study; that is no radiographic OA (K & L < 2) or no THR at baseline. Outcomes were assessed at year 20 according to whether or not the patients had 1) Radiographic OA; 2)

THR. A sensitivity analysis was also performed for development of Radiographic OA which included only hips with baseline K & L =0.

The morphological measurements detailed above were the predictors of interest. We visually assessed evidence of linearity of continuous variables with the outcomes using fractional polynomial plots (see Figure 2). Where evidence of non-linearity was observed, variables were fitted with linear splines. Lateral Centre Edge angle was fitted as a linear spline at these points (27.96° and 33.67°). This is consistent with clinical observations, as acetabular over and under-coverage are both implicated in the development of OA. Alpha angle was fitted as a linear spline at a point of 65° which also ties in with its bimodal distribution, with a clear second peak beginning at 65°. Logistic regression analysis was performed to describe the univariate association of the predictors listed above with radiographic OA and THR as binary outcomes. Secondary analysis were performed by further adjusting for confounders of baseline age, BMI and joint space width. Interactions between the acetabular and femoral morphological measurements were explored. Logistic regression analyses were with robust standard errors and clustering by subject identifier to account for the dependency of two hips from one subject. Area Under Receiver Operating Characteristic (AUROC) as well as McFaddens's pseudo R^2 statistic were used to evaluate the discriminatory ability of the morphological measurements. The cut point for non-linearity was examined for alpha angle, as a function of radiographic osteoarthritis and THR. Logistic regression with these thresholds was performed to determine the increase in relative risk for every degree increase in alpha angle.

RESULTS

The baseline characteristics of the participants included in this study are summarised in Table 1. 358 participants (670 hips) were included in the analysis of radiographic OA and 726 (1455 hips) in the THR analysis. Participants included were younger. In the radiographic OA analysis participants included were found to be taller (Table 1).

Radiographic OA

Incident radiographic OA was seen in 14.8% of hips at Year 20.

Femoral measures

Alpha angle and modified triangular index height were significantly greater in the radiographic OA versus no OA group (p<0.001 in both cases) (Table 2), with marked differences in kernel density plots by group. Alpha angle and modified triangular index were significantly associated with the development of radiographic OA, and remained significantly associated after adjusting for confounders (Table 3).

Acetabular measures

The acetabular measures, LCE and Extrusion Index were found to be similar in those with and without radiographic OA (Table 2). Kernel density plots revealed an increased incidence of acetabular under and over coverage (i.e. acetabular dysplasia and Pincer-type femoroacetabular impingement) in those who went on to develop radiographic OA.

LCE angle was significantly associated with the development of radiographic OA, and remained significantly associated after adjusting for confounders.

When femoral and acetabular measures were included in the same model, with use of the same covariates, an alpha angle of greater than 65° was associated with a 5% increased risk of radiographic OA per degree increase in alpha angle (OR 1.05 [95% confidence interval [95% CI] 1.01-1.09], p = 0.009), the increase in risk of radiographic OA per 1° reduction in lateral centre edge angle was 14% (OR 0.86 [95% CI 0.77-0.96], p = 0.007). Over coverage, consistent with Pincer Femoroacetabular Impingement, was not significantly associated with radiographic OA.

ROC AUC statistic for non-morphological covariates (age, BMI, joint space width) alone as predictors of incident radiographic OA was 57.5% and increased significantly to 66.7% with the inclusion of both LCE and alpha angle (p<0.001). McFadden's pseudo R^2 statistic increased from 1.21% to 7.48% (Table 4).

Total Hip Replacement

Femoral measures

Alpha angle and modified triangular index height were both significantly greater in hips that went on to undergo THR.

Modified triangular index height was significantly associated with Total Hip Replacement and remained significantly associated when adjusting for the covariates (OR 1.14 [95% CI 1.00-1.30], p=0.046). Alpha angle was significant in only the univariate analysis (OR 1.04 [95% CI 1.00-1.08], p=0.038), (Table 3).

Acetabular measures

Acetabular dysplasia at baseline was significantly more common in hips that went on to undergo THR (mean LCE 25.94°, SD 7.53°, mean Extrusion Index 0.25 SD 0.09) than non-THR (LCE 30.94°, SD 6.78° Extrusion Index 0.18, SD 0.08), p<0.001 in both cases.

Univariate logistic regression showed that low lateral centre edge was significantly associated with THR and remained significantly associated when adjusting for the same covariates (OR 0.77 [95% CI 0.63-0.93], p=0.008).

When femoral and acetabular measures were included in the same model, with use of the same covariates, modified triangular index height was associated with THR with a 19% increase per unit (OR 1.19 [95% CI 1.01 -1.40], p=0.039. The increase in risk of radiographic OA per 1° reduction in lateral centre edge angle was 21% (OR 0.79 [95% CI 0.72-0.87], p < 0.001).

ROC AUC statistic for non-morphological covariates as predictors of THR was 63.73% and increased significantly to 83.36% with the inclusion of LCE, alpha angle and modified triangular index height (p<0.001). McFadden's pseudo R^2 statistic increased from 4.75% to 22.84% (Table 4).

Alpha Angle Thresholds by Outcome

The cut point for non-linearity varies according to outcome, statistically the threshold for non-linearity for Alpha Angle with Radiographic OA is 41° and with THR is 82° (Figure 2 and Table 5). Logistic regression with these thresholds showed that each degree increase in alpha angle increased the risk of developing radiographic OA by 3 % (OR 1.03 [95% CI 1.02-1.05], p<0.001) and THR by 6% (OR 1.06 [95% CI 1.01-1.11], p = 0.011).

Sensitivity Analysis

Inclusion of only hips with no signs of radiographic osteoarthritis (K&L Grade 0 – Radiographic Osteoarthritis Analysis 556 hips and Total Hip Replacement Analysis 1388 hips), resulted in no significant change to the results discussed above. (See Appendix).

DISCUSSION

This study of a population-based cohort confirms our hypothesis and demonstrates that radiographic measurements of subtle hip deformities are associated with the longitudinal development of hip osteoarthritis and THR. We found that the deformities associated with Cam-type femoroacetabular impingement and mild acetabular dysplasia of the hip were independently predictive of radiographic osteoarthritis and THR 19 years later. These measurements were independently predictive of outcome even when controlling for baseline age, BMI and joint space width and significantly increased the predictive value of the model. This is the first study to demonstrate these findings in a longitudinal population cohort.

Femoroacetabular impingement has been extensively documented as a cause of groin pain[24]. Whilst associations of abnormal morphology and OA are established[13, 25], prospective longitudinal data, which may provide more convincing evidence of a causal relationship, is lacking. Previous studies examining the development of OA have focused on acetabular dysplasia[26, 27]. Two recent studies have associated cam deformity with OA, but are limited by their cross-sectional nature and used outcome measures which may not be as relevant as using the hard endpoint of THR for example[13, 28]. Longitudinal data is limited to a nested case control using the Chingford cohort[17] and an enriched cohort of symptomatic osteoarthritis patients[29].

This work demonstrates that women with a Cam-deformity identified by an alpha angle of greater than 65 degrees have an increased risk of radiographic OA and THR with each degree increase in alpha angle conferring a 5% and 3% increase in risk respectively. More severe Cam-type deformities identified by increased modified triangular index height are predictive of THR at 19 year follow-up with each unit increase conferring a 19% increased risk.

Mild acetabular dysplasia significantly increased the risk of radiographic OA development and THR with each degree reduction in lateral centre edge angle associated with a 14% and 21% increase in risk respectively, these results are consistent with previously published evidence in relation to incident radiographic OA by Lane et al.[30]. No significant associations were seen with Pincer-type femoroacetabular impingement alone. Evaluation of the models showed statistically significant improvements in our ability to predict radiological OA and THR ($p<0.001$ in both cases) with the inclusion of morphological measurements as compared to established risk factors of age, BMI, joint space width.

Although we have chosen these thresholds for non-linearity based on the data distribution this statistically might not be the case. On further exploration it was found that the cut point for non-linearity varies according to outcome. The statistical threshold for non-linearity for Alpha Angle with Radiographic OA is 41° and with THR is 82°. When using these statistical thresholds we see a more pronounced association, with a risk increase for THR of 6% per degree when the alpha-angle is greater than 82°. These two methods for calculating the thresholds for non-linearity may have different clinical applications. The use of a threshold based on the distribution has a lower cut off with a lower specificity and a higher sensitivity for OA and THR. These lower thresholds may be used for low-risk treatments for OA. For example, a physical therapy or weight loss treatment might use the lower threshold of 65°. Conversely, a more invasive intervention, such as surgery may wish to identify those patients with a higher risk using a threshold of 80°, which has a higher specificity.

It has been proposed that FAI leads to shear forces being applied to acetabular cartilage with displacement of the labrum[31]. This may lead to delamination of the acetabular cartilage, and detachment of the labrum at the chondro-labral junction. Developmental dysplasia leads to increased contact stress and cartilage degeneration[32]. The mechanism by which morphological abnormalities lead to OA are likely to be similar in both men and women.

This study has several strengths and potential limitations. This is the only cohort study at present which includes long term follow up in a normal population with validated records to THR. Loss to follow-up appears to be non-differential, and expected with the median age of the cohort reaching seventy four. In addition only women are included in the study. Baseline characteristics of women in the study were similar to the UK general population in terms of weight (65 kg in the UK, 67 kg in Chingford), height (1.61 m v 1.62 m) and BMI (25.4 v 25.6 kg/m^2)[33]. This study did not consider a wide range or ethnic groups, as 98% of the women were white and predominantly middle class (but with a range of all social groups).

Cam-type femoroacetabular impingement appears to be twice as frequent in men as in women[25, 34], and acetabular dysplasia approximately 20% more frequent in women as in men[13]. The role of Cam-type femoroacetabular impingement in OA may therefore be underestimated in this population cohort and a long-term epidemiological study involving male subjects is needed to confirm the natural history of these anatomical

In summary this study provides longitudinal evidence in a large population cohort that measurements of hip morphology characteristic of Cam-type femoroacetabular impingement and undiagnosed dysplasia

are predictive of OA development (radiographic OA and THR), independent of age, BMI and joint space width. These measurements can be made on a simple anteroposterior pelvis radiograph, and significantly improve our ability to identify individuals at risk of hip OA development. Pincer-type Femoroacetabular Impingement was not predictive of subsequent OA or total hip replacement.

ACKNOWLEDGMENTS

We thank the staff at Chingford Hospital for their cooperation with this study, and the general practice and patients at Highams Park Medical Partnership.

CONTRIBUTIONS

All authors made substantial contributions to the conception and design of the study, or acquisition of data, or analysis and interpretation of data. GERT drafted the article and all authors were involved in revising it critically for important intellectual content as well as final approval of the version to be submitted.

FUNDING

This work was supported by the Oxford National Institute for Health Research Musculoskeletal Biomedical Research Unit. Mr Geraint E. R. Thomas is funded by The Jean Shanks Foundation and Orthopaedic Research UK. The funding bodies did not have any involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

NKA has received consultancy fees from Merck, Roche, Smith & Nephew, Q-Med, Nicox and Flexion, grants from Novartis and Schering-Plough, and payment for lectures from Novartis, Schering-Plough, Smith & Nephew, Q-med, Servier, GSK, Amgen, Schering-Plough, Rottapharm and Lilley. SGJ has received consultancy fees, grants and payment for lectures from Zimmer.

References

1. Croft P. Review of UK data on the rheumatic diseases--3. Osteoarthritis. Br J Rheumatol 1990; 29: 391-395.
2. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008; 58: 26-35.
3. Nevitt MC, Lane NE, Scott JC, Hochberg MC, Pressman AR, Genant HK, et al. Radiographic osteoarthritis of the hip and bone mineral density. The Study of Osteoporotic Fractures Research Group. Arthritis Rheum 1995; 38: 907-916.
4. Murphy LB, Helmick CG, Schwartz TA, Renner JB, Tudor G, Koch GG, et al. One in four people may develop symptomatic hip osteoarthritis in his or her lifetime. Osteoarthritis Cartilage 2010; 18: 1372-1379.
5. Culliford DJ, Maskell J, Kiran A, Judge A, Javaid MK, Cooper C, et al. The lifetime risk of total hip and knee arthroplasty: results from the UK general practice research database. Osteoarthritis Cartilage 2012; 20: 519-524.
6. Yelin E, Murphy L, Cisternas MG, Foreman AJ, Pasta DJ, Helmick CG. Medical care expenditures and earnings losses among persons with arthritis and other rheumatic conditions in 2003, and comparisons with 1997. Arthritis Rheum 2007; 56: 1397-1407.
7. Bitton R. The economic burden of osteoarthritis. Am J Manag Care 2009; 15: S230-235.
8. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project. 2011.
9. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007; 89: 780-785.
10. Harris WH. Etiology of osteoarthritis of the hip. Clin Orthop Relat Res 1986: 20-33.
11. Murray RO. The aetiology of primary osteoarthritis of the hip. Br J Radiol 1965; 38: 810-824.
12. Solomon L. Patterns of osteoarthritis of the hip. J Bone Joint Surg Br 1976; 58: 176-183.
13. Gosvig KK, Jacobsen S, Sonne-Holm S, Palm H, Troelsen A. Prevalence of malformations of the hip joint and their relationship to sex, groin pain, and risk of osteoarthritis: a population-based survey. J Bone Joint Surg Am 2010; 92: 1162-1169.
14. Leunig M, Beaule PE, Ganz R. The concept of femoroacetabular impingement: current status and future perspectives. Clin Orthop Relat Res 2009; 467: 616-622.

15. Cooper C, Reginster JY, Chapurlat R, Christiansen C, Genant H, Bellamy N, et al. Efficacy and safety of oral strontium ranelate for the treatment of knee osteoarthritis: rationale and design of randomised, double-blind, placebo-controlled trial. Curr Med Res Opin 2012; 28: 231-239.

16. Siebenrock KA, Kalbermatten DF, Ganz R. Effect of pelvic tilt on acetabular retroversion: a study of pelves from cadavers. Clin Orthop Relat Res 2003: 241-248.

17. Nicholls AS, Kiran A, Pollard TC, Hart DJ, Arden CP, Spector T, et al. The association between hip morphology parameters and nineteen-year risk of end-stage osteoarthritis of the hip: a nested case-control study. Arthritis Rheum 2011; 63: 3392-3400.

18. Wiberg G. Studies on dysplastic acetabula and congenital subluxation of the hip joint with special reference to the complication of osteoarthritis., 83: 7-38. Acta Chir Scand 1939; 83.

19. Heyman CH, Herndon CH. Legg-Perthes disease; a method for the measurement of the roentgenographic result. J Bone Joint Surg Am 1950; 32: 767-778.

20. Li PL, Ganz R. Morphologic features of congenital acetabular dysplasia: one in six is retroverted. Clin Orthop Relat Res 2003: 245-253.

21. Gosvig KK, Jacobsen S, Palm H, Sonne-Holm S, Magnusson E. A new radiological index for assessing asphericity of the femoral head in cam impingement. J Bone Joint Surg Br 2007; 89: 1309-1316.

22. Notzli HP, Wyss TF, Stoecklin CH, Schmid MR, Treiber K, Hodler J. The contour of the femoral head-neck junction as a predictor for the risk of anterior impingement. J Bone Joint Surg Br 2002; 84: 556-560.

23. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957; 16: 494-502.

24. Smith-Petersen MN. The classic: Treatment of malum coxae senilis, old slipped upper femoral epiphysis, intrapelvic protrusion of the acetabulum, and coxa plana by means of acetabuloplasty. 1936. Clin Orthop Relat Res 2009; 467: 608-615.

25. Gosvig KK, Jacobsen S, Sonne-Holm S, Gebuhr P. The prevalence of cam-type deformity of the hip joint: a survey of 4151 subjects of the Copenhagen Osteoarthritis Study. Acta Radiol 2008; 49: 436-441.

26. Cooperman DR, Wallensten R, Stulberg SD. Acetabular dysplasia in the adult. Clin Orthop Relat Res 1983: 79-85.

27. Murphy SB, Ganz R, Muller ME. The prognosis in untreated dysplasia of the hip. A study of radiographic factors that predict the outcome. J Bone Joint Surg Am 1995; 77: 985-989.

28. Doherty M, Courtney P, Doherty S, Jenkins W, Maciewicz RA, Muir K, et al. Nonspherical femoral head shape (pistol grip deformity), neck shaft angle, and risk of hip osteoarthritis: a case-control study. Arthritis Rheum 2008; 58: 3172-3182.

29. Agricola R, Heijboer MP, Bierma-Zeinstra SM, Verhaar JA, Weinans H, Waarsing JH. Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK). Ann Rheum Dis 2013; 72: 918-923.

30. Lane NE, Lin P, Christiansen L, Gore LR, Williams EN, Hochberg MC, et al. Association of mild acetabular dysplasia with an increased risk of incident hip osteoarthritis in elderly white women: the study of osteoporotic fractures. Arthritis Rheum 2000; 43: 400-404.

31. Beck M, Kalhor M, Leunig M, Ganz R. Hip morphology influences the pattern of damage to the acetabular cartilage: femoroacetabular impingement as a cause of early osteoarthritis of the hip. J Bone Joint Surg Br 2005; 87: 1012-1018.

32. Pompe B, Daniel M, Sochor M, Vengust R, Kralj-Iglic V, Iglic A. Gradient of contact stress in normal and dysplastic human hips. Med Eng Phys 2003; 25: 379-385.

33. Rosenbaum S, Skinner RK, Knight IB, Garrow JS. A survey of heights and weights of adults in Great Britain, 1980. Ann Hum Biol 1985; 12: 115-127.

34. Jung KA, Restrepo C, Hellman M, AbdelSalam H, Morrison W, Parvizi J. The prevalence of cam-type femoroacetabular deformity in asymptomatic adults. J Bone Joint Surg Br 2011; 93: 1303-1307

Figure Legends

Figure 1
Flow Diagram summarising selection for inclusion and analyses

Figure 2
Fractional polynomial plots showing probability of outcome versus Alpha Angle (95% CI) - Non-linear effect demonstrated

Figure 1
Click here to download high resolution image

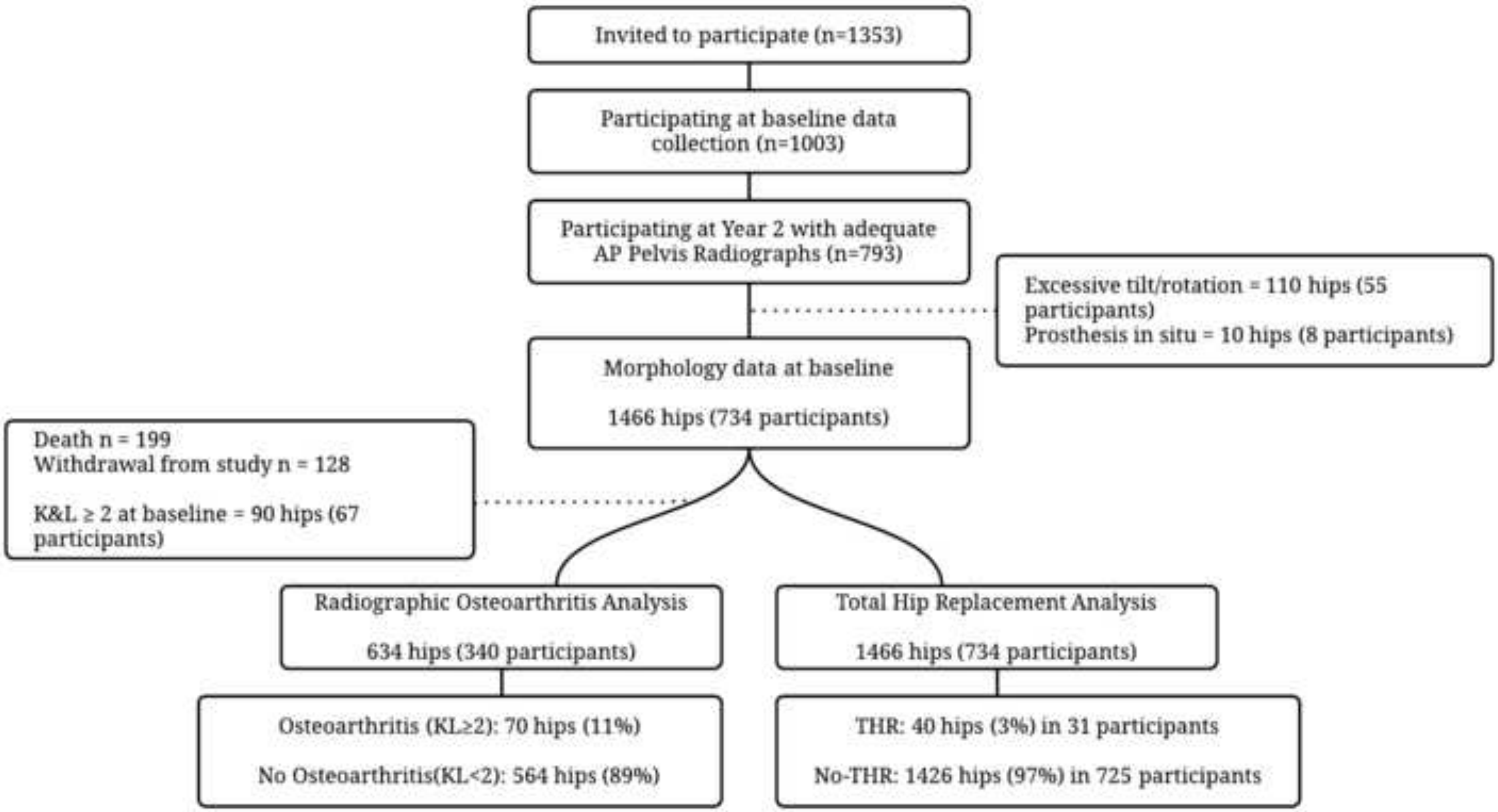

Figure 1: Flow diagram summarising selection for inclusion and analyses

Figure 2

Click here to download high resolution image

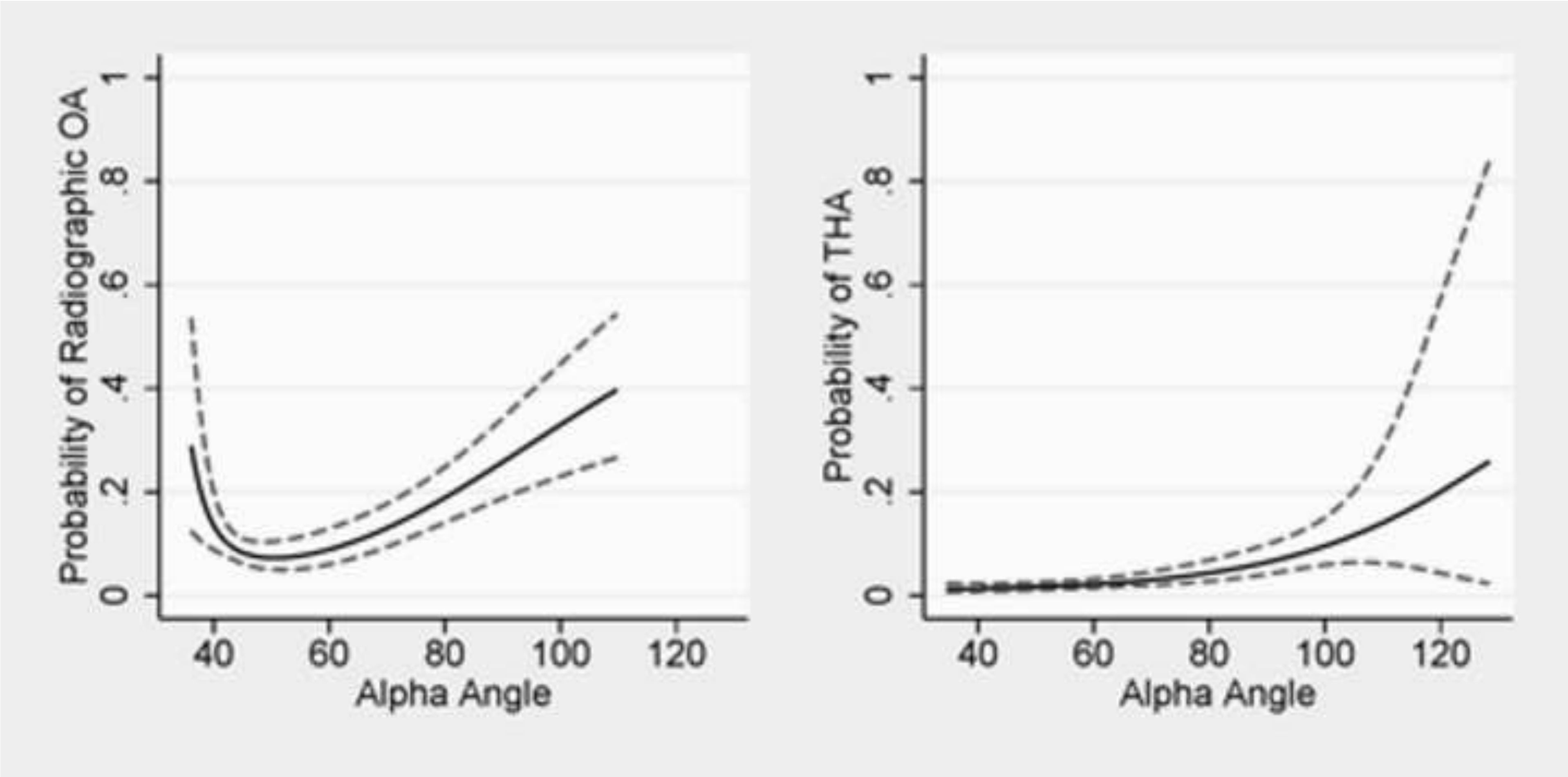

Table 1

Table 1: Baseline characteristics

Characteristics	Full cohort (n=1003)	Radiographic Osteoarthritis			Total Hip Replacement		
		Subjects not used in this analysis (n=663)	Subjects used in this analysis (n=340)	p-value	Subjects not used in this analysis (n=269)	Subjects used in this analysis (n=734)	p-value
Age (years), median (IQR)	54.00 (49.00, 60.00)	57.00 (50.50, 61.00)	52.00 (48, 56)	<0.001	54 (50,58)	54 (48,59)	0.05
Height (m), mean (s.d.)	1.62 (0.06)	1.61 (0.06)	1.62 (0.06)	0.04	1.62 (0.06)	1.63 (0.06)	0.05
Weight (kg), median (IQR)	65.00 (58.50, 73.00)	65.70 (58.45, 73.75)	64.6 (58.50, 71.80)	0.194	66.2 (58.4, 71.8)	69.4 (60.8, 71.4)	0.194
BMI (kg/m^2), median (IQR)	24.86 (22.63, 27.61)	25.15 (22.67, 28.19)	24.59 (22.60, 27.01)	0.05	25.2 (22.5, 27.0)	26.1 (23.5, 26.8)	0.05

Table 2

Table 2. Hip Morphology At Year 2

Hip Morphological Variable	Radiographic Osteoarthritis			Total Hip Replacement		
	Control	Radiographic OA at Year 20	p-value	Control	Total Hip Replacement	p-value
LCE, mean (SD)	30.56 (6.44)	30.03 (8.11)	0.456	30.94 (6.78)	25.94 (7.53)	<0.001
Extrusion Index, mean (SD)	0.25 (0.11)	0.26 (0.15)	0.4563	0.18 (0.08)	0.25 (0.09)	<0.001
Alpha angle+, median (IQR)	46.47 (43.53, 55.23)	55.81 (44.09, 87.60)	<0.001	46.75 (43.53, 58.83)	73.10 (47.47, 94.57)	<0.001
MTIH+, mean (SD)	22.90 (2.09)	23.69 (2.52)	<0.001	22.97 (2.12)	24.15 (3.13)	0.005

P-values in this analysis are a guide only, and do not account for clustering

Table 3

Table 3: Logistic regression: Hip morphology at Year 2 Predicting 20 Year Outcome, OR (95% CI)

Hip Morphological Variable		Radiographic Osteoarthritis				Total Hip Replacement			
		Univariate		Adjusted#		Univariate		Adjusted#	
		OR (95% CI)	p-val	OR (95% CI)	p-val	OR (95% CI)	p-val	OR (95% CI)	p-val
Alpha Angle	<65 (per unit)	0.99 (0.95, 1.04)	0.818	0.99 (0.95, 1.04)	0.819	1.02 (0.97, 1.08)	0.384	1.03 (0.97, 1.09)	0.326
	>65 (per unit)	1.05 (1.01, 1.09)	0.008	1.05 (1.01, 1.09)	0.007	1.04 (1.00, 1.08)	0.038	1.03 (1.00, 1.07)	0.082
LCE	<28 (per unit)	0.89 (0.81, 0.98)	0.017	0.87 (0.78, 0.96)	0.008	0.84 (0.77, 0.91)	<0.001	0.82 (0.75, 0.89)	<0.001
	28-33.7 (per unit)	1.10 (0.95, 1.27)	0.199	1.10 (0.95, 1.28)	0.194	0.91 (0.74, 1.11)	0.346	0.88 (0.72, 1.09)	0.243
	>33.7 (per unit)	1.03 (0.93, 1.15)	0.539	1.03 (0.92, 1.15)	0.641	1.00 (0.87, 1.15)	0.984	0.97 (0.84, 1.12)	0.666
Extrusion Index (per SD)		1.09 (0.74, 1.61)	0.67	1.15 (0.77, 1.72)	0.508	2.23 (1.63, 3.06)	<0.001	2.50 (1.78, 3.49)	<0.001
MTIH (per unit)		1.14 (1.03, 1.26)	0.01	1.14 (1.02, 1.27)	0.026	1.27 (1.13, 1.43)	<0.001	1.25 (1.10, 1.43)	0.001

 # adjusted for Age, BMI and Joint Space

Table 4

Table 4: Area Under Receiver Operating Characteristic (AUROC) statistic as well as McFadden's pseudo R2 statistic were used to evaluate the discriminatory ability of the morphological measurements

Radiographic Osteoarthritis				Total Hip Replacement			
Model with Age, BMI, Joint Space		Model + Morph Variables*		Model with Age, BMI, Joint Space		Model + Morph Variables*	
R2	AUC	R2	AUC	R2	AUC	R2	AUC
1.21%	57.50%	7.48%	66.70%	4.75%	63.73%	22.84%	83.36%

** Alpha Angle, LCE, MTIH*

Table 5

Table 5: Comparison of Logistic regression Analysis for association of Alpha Angle with 20 Year Outcomes using Distribution based and Statistical thresholds of non-linearity

	Distribution Threshold		OR (95% CI)	p-val	Statistical Threshold		OR (95% CI)	p-val
Radiographic Osteoarthritis	Alpha Angle	<65 (per unit)	0.99 (0.95, 1.04)	0.818	Alpha Angle	<41 (per unit)	0.55 (0.39, 0.78)	0.001
		>65 (per unit)	1.05 (1.01, 1.09)	0.008		>41 (per unit)	1.03 (1.02, 1.05)	<0.001
Total Hip Replacement	Alpha Angle	<65 (per unit)	1.02 (0.97, 1.08)	0.384	Alpha Angle	<82 (per unit)	1.02 (1.00, 1.05)	0.045
		>65 (per unit)	1.04 (1.00, 1.08)	0.038		>82 (per unit)	1.06 (1.01, 1.11)	0.011

Appendix: Sensitivity Analysis Baseline K&L Grade = 0 - Radiographic Osteoarthritis Analysis 556 hips and Total Hip Replacement Analysis 1388 hips

Logistic regression: Hip morphology at Year 2 Predicting 20 Year Outcome, OR (95% CI)

Hip Morphological variables		Radiographic Osteoarthritis (baseline KL Grade=0)			
		Univariate		Adjusted#	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Alpha Angle	<65 (per unit)	1.00 (0.95, 1.06)	0.862	1.00 (0.95, 1.06)	0.869
	>65 (per unit)	1.04 (1.00, 1.09)	0.05	1.04 (1.00, 1.09)	0.046
LCE	<28 (per unit)	0.85 (0.76, 0.95)	0.004	0.84 (0.75, 0.94)	0.002
	28-33.7 (per unit)	1.18 (1.00, 1.38)	0.044	1.18 (1.00, 1.38)	0.05
	>33.7 (per unit)	0.99 (0.88, 1.10)	0.801	0.98 (0.88, 1.10)	0.746
Extrusion Index (per SD)		1.10 (0.71, 1.71)	0.672	1.15 (0.73, 1.80)	0.553
MTIH (per unit)		1.10 (0.97, 1.23)	0.124	1.09 (0.96, 1.24)	0.18

 # adjusted for Age, BMI and Joint Space

Area Under Receiver Operating Characteristic (AUROC) statistic as well as McFadden's pseudo R2 statistic were used to evaluate the discriminatory ability of the morphological measurements

Radiographic Osteoarthritis (baseline KL Grade=0)			
Model with Age, BMI, Joint Space		Model + Morph Variables*	
R2	AUC	R2	AUC
0.69%	54.91%	7.41%	67.47%

** Alpha Angle, LCE, MTIH*

Comparison of Logistic regression Analysis for association of Alpha Angle (univariately) with 20 Year Outcomes using Distribution and Statistical thresholds of non-linearity

Radiographic Osteoarthritis (baseline KL Grade=0)	Distribution Threshold		OR (95% CI)	p-value	Outcome Threshold		OR (95% CI)	p-vauel
	Alpha Angle	<65 (per unit)	1.00 (0.95, 1.06)	0.862	Alpha Angle	<41 (per unit)	0.56 (0.40, 0.77)	<0.001
		>65 (per unit)	1.04 (1.00, 1.09)	0.05		>41 (per unit)	1.03 (1.02, 1.05)	<0.001

*Cover Letter
Click here to download Cover Letter: Cover_letter_final.doc

NIHR Musculoskeletal Biomedical Research Unit
Nuffield Department of Orthopaedics,
Rheumatology and Musculoskeletal Sciences,
University of Oxford, Windmill Road, Headington,
Oxford, OX3 7LD, UK

Tel: +44 (0)1865 737902
Fax: +44 (0)1865 227671
geraint.thomas@ndorms.ox.ac.uk

20th December 2013

Dear Professor Lohmander,

Please find enclosed an original full-length article that we would like you to consider for publication in Osteoarthritis and Cartilage, entitled "*Subclinical deformities of the hip are significant predictors of radiographic osteoarthritis and joint replacement in women. A 20 year longitudinal cohort study.*"

Osteoarthritis of the hip is a common painful disease, and among the most expensive of all items in any health budget. In the United States and Europe the expenditure on musculoskeletal disease currently exceeds US$300 Billion. Traditional risk factors of osteoarthritis, poorly predict progression. Subtle deformities of the hip joint have been implicated in the development of osteoarthritis, although there is little longitudinal evidence to support this.

This study provides longitudinal evidence in a large, population-based cohort that radiographic measurements of hip morphology are independently predictive of radiographic osteoarthritis and Total Hip Replacement 19 years from baseline. These measurements are significantly more predictive than established risk factors, such as age, sex and Body Mass Index. This has major implications for the identification of high-risk individuals in clinical practice and research and for the development of predictive models of disease development.

We believe that this research has the potential to change practice in any developed healthcare setting and will therefore be of interest to your readers.

I confirm that each individual named as an author meets the Uniform Requirements for Manuscripts Submitted to Biomedical Journals criteria for authorship and that the manuscript has is not simultaneously being submitted elsewhere, and that no portion of the data has been or will be published in proceedings or transactions of meetings or symposium volumes. No financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interests that any of the authors may have, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

Yours sincerely

Geraint E R Thomas MA, MBBS, MRCS
Academic Clinical Fellow, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford

OSTEOARTHRITIS AND CARTILAGE

AUTHORS' DISCLOSURE

Manuscript title **Subclinical deformities of the hip are significant predictors of radiographic osteoarthritis and joint replacement in women**

Corresponding author **G.E.R. Thomas**

Manuscript number ______________________________

Authorship
All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. By signing below each author also verifies that he (she) confirms that neither this manuscript, nor one with substantially similar content, has been submitted, accepted or published elsewhere (except as an abstract). Each manuscript must be accompanied by a declaration of contributions relating to sections (1), (2) and (3) above. This declaration should also name one or more authors who take responsibility for the integrity of the work as a whole, from inception to finished article. These declarations will be included in the published manuscript.

Acknowledgement of other contributors
All contributors who do not meet the criteria for authorship as defined above should be listed in an acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Such contributors must give their consent to being named. Authors should disclose whether they had any writing assistance and identify the entity that paid for this assistance.

Conflict of interest
At the end of the text, under a subheading "Conflict of interest statement" all authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and research grants or other funding.

Declaration of Funding
All sources of funding should be declared as an acknowledgement at the end of the text.

Role of the funding source
Authors should declare the role of study sponsors, if any, in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. If the study sponsors had no such involvement, the authors should state this.

Studies involving humans or animals
Clinical trials or other experimentation on humans must be in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) *and* with the Helsinki Declaration of 1975, as revised in 2000. Randomized controlled trials should follow the Consolidated Standards of

Reporting Trials (CONSORT) guidelines, and be registered in a public trials registry.

Studies involving experiments with animals were in accordance with institution guidelines

Please sign below to certify your manuscript complies with the above requirements and then upload this form at http://ees.elsevier.com/oac/

Author Signature	Date	Author Signature	Date
	4/12/13		06/12/2013
	4/12/13		9.12.13
	4/12/13		9.12.13
	4/12/13		9/12/13
	5/12/13		19/12/13
	9.12.13		
	20/12/13		

*ICMJE COI form

Click here to download ICMJE COI form: Carr ICMJE_COI_Disclosure_Form_Subclinical.pdf

*ICMJE COI form
Click here to download ICMJE COI form: Glyn-Jones ICMJE_COI_Disclosure_Form_Subclinical.pdf

*ICMJE COI form
Click here to download ICMJE COI form: ICMJE Disclosure form_AJ_Subclinical.pdf

***ICMJE COI form**

Click here to download ICMJE COI form: ICMJE Nigel Arden.pdf

*ICMJE COI form
Click here to download ICMJE COI form: ICMJE_COI_Disclosure_Form_Subclinical_deformitiesBatra.pdf

*ICMJE COI form
Click here to download ICMJE COI form: ICMJE_COI_Disclosure_Form_Subclinical_deformitiesDHart.pdf

*ICMJE COI form

Click here to download ICMJE COI form: ICMJE_COI_Disclosure_Form_Subclinical_deformitiesKiran.pdf

*ICMJE COI form
Click here to download ICMJE COI form: ICMJE_COI_Disclosure_Form_Subclinical_deformitiesPalmer.pdf

*ICMJE COI form
Click here to download ICMJE COI form: ICMJE_COI_Disclosure_Form_Subclinical_deformitiesTSpector.pdf

*ICMJE COI form
Click here to download ICMJE COI form: Javaid ICMJE_COI_Disclosure_Form_Subclinical.pdf

*ICMJE COI form
Click here to download ICMJE COI form: Thomas ICMJE_COI_Disclosure_Form_Subclinical.pdf

*ICMJE COI form

Click here to download ICMJE COI form: Murray ICMJE_COI_Disclosure_Form_Subclinical.pdf