disease (LDD) as determined by MR scan is highly heritable and is positively correlated with age. We have previously reported that our longitudinal study of LDD follow-up had confirmed deterioration in LDD over 11 years in almost all subjects. We wished to determine if progression of LDD is itself mediated by genetic factors.

Methods: Healthy twin volunteers forming the UK twin register (www.twinsuk.ac.uk) who had previously undergone spine MR scanning in 1996-9 were recalled for repeat sagittal T2-weighted MR scan. The new scans were coded for degenerative change using the same 4-point scale for disc height, disc signal, disc bulge and anterior osteophytes (Jarosz et al). An LDD summary score was derived by summing the codes at the 5 lumbar discs. A difference in LDD summary score was computed by taking the summary score for the baseline scan from that of the follow-up scan, and adjusting for time between the MR scans. Questionnaires were used, as at baseline, to determine demographic and lifestyle factors. In order to capture the variation inherent in the interval-adjusted change in summary score, principal components analysis (PCA) was performed (Stata 10) and heritability of the first component assessed using Mx.

Results: Longitudinal data were available for 403 twins, 8 (1.9%) of whom were male. Mean (range) age at baseline = 53.3 (32.3-69.5) years. The mean (range) interval between baseline and follow-up was 10.7 (7.6-13.7) years. Almost all the MR scans deteriorated with mean LDD summary score at baseline vs follow-up = 13.1 vs 22.1 ($p<0.0001$). PCA of the time-adjusted change in summary score revealed that the first 2 components accounted for 63% of the variation in MRI deterioration. Heritability of the 1st component was best explained using a model containing genetic and unique environmental factors only (AE model) - ie no detectable contribution from the shared family environment. The AE model estimated heritability (95% CIs) = 76 (65-83)%.

Conclusions: This is the first large scale, longitudinal, population-based study of LDD in healthy adult volunteers to examine the heritability of progression of LDD. This longitudinal study may identify those that deteriorate more rapidly and who may have worse symptoms. Demonstrating a genetic component to progression leads naturally to association studies - both candidate gene and genome-wide association (GWA) studies. In GWA an agnostic search of the genome would be made for variants associated with change in LDD. GWA studies have been performed with success in other complex traits and may uncover genetic variants associated with very rapid deterioration in LDD, in what is an almost universal condition. GWA studies generally require very large sample sizes and refined or enriched phenotyping methods. Using this information on heritability of LDD progression we will be able to optimise our GWA strategy to search for variants influencing LDD progression.

Joint Morphometry

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KNEE JOINT BONE SHAPE IS RELATED TO BMI BUT ONLY MARGINALLY TO EARLY SIGNS OF KNEE OSTEOARTHRITIS IN HEALTHY MIDDLE-AGED WOMEN

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Purpose: Development of primary osteoarthritis (OA) is known to be a multifactorial process. Tissue characteristics and shape of bones in the knee joint are subject to changes due to increased load across the joint caused by overweight and obesity. Changes in bone characteristics are suggested to play an initial role in the development of knee OA. Using Active Shape Models, associations between BMI and shape of femur and tibia will be studied in non-OA middle-aged women. Using MR imaging data, shape features of femur and tibia will be linked to early signs of knee OA, to evaluate whether these differences in shape features can be linked to early signs of knee OA.

Methods: Data from a sub cohort of the prospective population-based Rotterdam study was used in this study. Body length and weight were measured, and weight-bearing anteroposterior radiographs and MR images were obtained in 891 women between 45 and 60 years. Using the radiographs, OA status was scored using Kellgren and Lawrence (K&L) scale. To analyse shape variations prior to initiation of knee OA, only women with a K&L score of 0 were selected for analysis. All MR images were assessed using the semi-quantative Knee Osteoarthritis Scoring System. Focal and diffuse cartilage defect scores and bone marrow lesions scores of medial and lateral femur condyl and tibia plateau were selected to evaluate early signs of knee OA. Since MR imaging data is more sensitive to changes in cartilage and bone characteristics than radiographs, it can be used to detect early signs of OA. Even in people without any radiographic signs of OA.

Using freely available SSM software (Active Shape Models toolkit), a statistical shape model was applied to the radiographs (see Figure 1). After all contour points were applied to the radiographs, the program overlays all contours. Through Principal Component Analysis, independent modes of shape variation in femur and tibia were produced. Each mode is expressed numerically, where 0 is the mean shape and negative and positive values represent the deviation from this mean, in either direction. All femur and tibia modes of shape variation with a significant correlation to BMI were related to cartilage defect and bone marrow lesion scores using Generalized Estimating Equations.

Results: Among the 397 selected women, mean age was 53.8±3.9 years and mean BMI was 26.4±4.6 kg/m^2. Of all 18 femur modes, 5 correlated to BMI. These 5 modes described 55.6% of shape variance in the study population. In the tibia, 7 of the 27 modes correlated to BMI. These modes described 26.6% of shape variance. Femur mode 0 correlated to presence of lateral focal cartilage defects. Tibia mode 0 was related to presence of lateral diffuse cartilage defects. For tibia modes 25 and 26, BMI*mode had a significant association to presence of lateral diffuse cartilage defects.

Figure 1. Examples of femur shape (left) and tibia shape (right).

Conclusions: In middle-aged women without any signs of radiographic knee OA, BMI is related to more than 50% of femur shape variation and with more than 25% of tibia shape variation. So adaptations of bone characteristics in the knee joint due to higher loads across the joint caused by overweight and obesity take place before initiation of osteoarthritis. Our study indicates that these adaptations of bone characteristics can only be marginally linked to early signs of primary knee OA.

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ASSOCIATION OF A SINGLE NUCLEOTIDE POLYMORPHISM IN TBX4 WITH DEVELOPMENTAL DYSPLASIA OF THE HIP: A CASE-CONTROL STUDY

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Purpose: Developmental dysplasia of the hip (DDH), formerly known as congenital dislocation of the hip, comprises a spectrum of abnormalities, including abnormal acetabular shape (dysplasia) and malposition of the femoral head during embryonic, fetal and infantile growth periods. Genetic factors play a considerable role in the pathogenesis of developmental dysplasia of the hip. As a key regulator for the hindlimb outgrowth and identification, *Tbx4* may be involved in the aetiology and pathogenesis of developmental dysplasia of the hip. Our objective is to evaluate whether the *TBX4* (rs3744438 or rs3744448) SNP (single nucleotide polymorphism) is associated with DDH in the people of Chinese origin.

Methods: The *Tbx4* SNP was genotyped in 505 children with developmental dysplasia of the hip and 551 control subjects.

Results: The SNP (rs3744438) was not associated with developmental dysplasia of the hip. The SNP (rs3744438) was significantly associated with developmental dysplasia of the hip in the dominant model of males (p=0.039; odds ration (OR)=0.556; 95% confidence interval (CI)=0.318 to 0.972) and allele G was considered as a protective role (p=0.020; odds ration (OR)=0.585; 95% confidence interval (CI)=0.372 to 0.918). After adjusted for gender, we discovered a significant association with hip dislocation in the dominant model when stratified by severity (p=0.032; odds ration (OR)=0.732; 95% confidence interval (CI)=0.550 to 0.974), but not with subluxation and instability.

Conclusions: Our results indicate that *Tbx4* may play an important role in the aetiology of congenital dysplasia of the hip. To date this is the first time that the association between *Tbx4* SNP and developmental dysplasia of the hip susceptibility has been detected.