SUPPLEMENTARY METHODS

Study cohorts

arcOGEN study. The arcOGEN cases used in this analysis are part of a GWAS that was carried out in two stages and includes a total of 7410 OA cases collected from several locations in the United Kingdom and genotyped on the Illumina HumanHap 610-Quad panel. The characteristics of the full arcOGEN GWAS dataset have been described in detail elsewhere,[1]. Briefly, subjects were unrelated and of European origin. The majority of cases (~80%) were ascertained by clinical evidence of the disease to a level requiring total joint replacement with the remainder having radiographic evidence of OA (ROA) with a Kellgren-Lawrence (K/L) grade ≥2. From the arcOGEN dataset we have excluded cases coming from the Nottingham and Chingford collections and of male gender because of the availability of female only controls with BMI info. The resulting dataset comprised 1310 cases with hip OA and 1209 cases with knee OA. We used 1671 unrelated female individuals from the OA-free TwinsUK cohort genotyped on the Illumina HumanHap 610-Quad panel as a control set. This cohort is ascertained to study the heritability of age-related diseases and contains full phenotypic information for OA status as well as age and BMI,[2]. Genotyping and QC of this dataset have been described elsewhere,[1].

Chingford Study. This study is a prospective population-based longitudinal cohort, which includes women derived from the age/sex register of a large general practice in North London. The study design and rationale have been described elsewhere in detail,[3]. The Guy’s St. Thomas’ Trust and the Waltham Forest Trust ethics committees approved the study protocol. After study procedures were explained to participants, written informed consent was given by each participant. OA was classified radiologically using standard X-rays of the pelvis, thoracolumbar spine, hands and weight-bearing knees,[4]. Hip OA was defined as definite joint space narrowing (JSN) and knee OA as at least one definite osteophyte and definite JSN or at least two definite osteophytes. Severe hip OA and knee OA were defined as a K/L score ≥ 3 or a total joint replacement (TJR).

Hertfordshire Cohort Study (HCS). The HCS is a population-based cohort study of men and women born and still resident in Hertfordshire designed to investigate the relationship between growth in infancy and the development of adult disease,[5]. In the late 1990s, 3000 men and women were recruited to this study which included a home interview and a subgroup (498 men and 468 women) underwent knee X-rays. Ethical approval was obtained from East and North Hertfordshire ethical committees and all participants gave written informed consent. Weight bearing anteroposterior and lateral semi-flexed radiographs of both knees were taken at the same hospital using the same radiographic equipment; a standard tube to film distance of 100 cm was used,[5]. Knee OA was defined as K/L≥2 at the tibiofemoral compartment.

Nottingham Case-Control Study. All individuals were affected by knee or hip OA and were recruited in Nottingham both from families with a history of OA and from clinic populations,[6]. Hip and knee OA cases were recruited from hospital orthopaedic surgery lists. All had been referred to the hospital with symptomatic, clinically severe hip or knee OA and the majority had undergone
unilateral or bilateral THR or TKR within the previous 5 years. Pre-operative knee or pelvis radiographs were examined to confirm the diagnosis. Subjects were excluded if they had another major arthropathy, Paget’s disease, overt child hip disease, THR due to trauma or terminal illness. Controls were age-matched individuals from the same catchment area free from radiographic OA and over the age of 55. All research participants gave written informed consent to take part. Approval for recruitment of index knee and hip OA cases and siblings of index hip OA cases was obtained from the research ethics committees of Nottingham City Hospital and North Nottinghamshire. For further details see [6].

**Genetics of Osteoarthritis and Lifestyle (GOAL) study.** Recruitment criteria were the same as for the Nottingham case-control study. Cases with clinically severe knee OA were recruited from hospital orthopaedic surgery TKR lists in the Nottingham area as previously described,[7]. Approval for recruitment was obtained from the research ethics committees of Nottingham City Hospital and North Nottinghamshire. Knee and hip radiographs were examined to confirm the diagnosis and to grade for changes of OA and scored for individual radiographic features of OA by a single observer and graded 0-3 according to a standard atlas using the K/L grade for each joint. Only individuals of European descent were included in the genetic study. Subjects aged 45-85 who had undergone intravenous urography (IVU) in the same hospital were recruited.

**TwinsUK study.** The study participants were white monozygotic and dizygotic twin pairs from the TwinsUK adult twin registry, a group used to study the heritability and genetics of age-related diseases,[2]. Ethics approval was obtained from the Guy’s and St. Thomas’ Hospital Ethics Committee. Written informed consent was obtained from every participant. Samples included in this study were a subset over the age of 40 who had pelvis and anteroposterior weight-bearing knee X-rays. Only one individual from each twin pair was included. Hip OA was defined as definite joint space narrowing (JSN) and knee OA as at least two definite osteophytes and possible JSN. Severe hip OA and knee OA were defined as a K/L score ≥ 3 or a total joint replacement.

**The Tasmanian Older Adult Cohort (TASOAC) study.** This is an ongoing prospective, population-based study that was initiated in 2002 and was aimed at identifying the environmental, genetic, and biochemical factors associated with the development and progression of OA at multiple sites (hand, knee, hip, and spine). Subjects between the ages of 50 and 80 years were randomly selected from the electoral roll in Southern Tasmania (population 229,000), with an equal number of men and women. The study was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee, and all subjects provided informed written consent. The overall response rate was 57%. Subjects who were institutionalized were excluded from the study. Total knee replacement was also an exclusion criterion. Details on the radiographic and pain assessment have been described elsewhere,[8]. Briefly, a standing anteroposterior semiflexed view of the right knee with 15° of fixed knee flexion was performed at baseline in all subjects. Radiographs were assessed and scored for osteophytes (OP) and joint space narrowing (JSN) on a scale of 0–3 (0 = normal, 3 = severe) according to the Osteoarthritis Research Society International (OARSI) atlas. Bilateral pelvis X-rays were also taken for all subjects and OP and JSN features were scored. A K/L score was computed using the OP and JSN scores for both hip and knee radiographs. Controls were individuals with no knee ROA and no hip ROA. 98 % of subjects reported being of white or Caucasian ethnicity. Those of other ethnicities were not included in this genetic study.
**Data analysis**

We carried out logistic regression analysis for rs8044769 under the multiplicative model (adjusting for gender and BMI where applicable) in each cohort using PLINK,[9]. We used a meta-analysis framework to combine summary statistics across all cohorts implemented in GWAMA,[10]. Combined estimates of ORs for reference alleles were obtained by weighting the logORs of each study by the inverse of their variance using a fixed effects model. We investigated evidence of heterogeneity of ORs using the Cochran’s Q and I² statistics,[11]. We additionally assessed the combined results using a random effects meta-analysis model. To evaluate the association of the *FTO* variant with risk of overweight/obese we classified all overweight/obese samples as cases and normal-weight subjects as controls in each cohort (irrespective of OA status). For the BMI-matched analyses we stratified the OA hip or knee cases and the controls into 3 categories for each cohort according to BMI: normal weight ≤25, overweight and obese >25, obese only >30. We carried out logistic regression analyses and meta-analyses for rs8044769 across the BMI-matched case/control datasets. BMI adjustment was carried out in all hip OA or knee OA cases vs controls by including BMI as a covariate in the logistic regression.

Power calculations were performed using Quanto,[12]. Power was calculated separately for the number of hip and knee individuals in each meta-analysis and separately for the number of hip and knee individuals across the 3 different BMI categories for alpha=0.05, effect size=1.1, and risk allele frequency= 0.5 as estimated in the arcOGEN replication only GWAS,[1].

**SUPPLEMENTARY REFERENCES**


Table S1. Meta-analysis summary statistics for the association of allele G at rs8044769 with hip or knee OA stratified by sex.

<table>
<thead>
<tr>
<th>OA site</th>
<th>Sex</th>
<th>Covariates</th>
<th>N cases/controls</th>
<th>¹F.E. OR (95% CIs)</th>
<th>F.E. p-value</th>
<th>²R.E. OR (95% CIs)</th>
<th>R.E. p-value</th>
<th>³q</th>
<th>⁴I²</th>
<th>⁵Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>Male</td>
<td>None</td>
<td>1238/1065</td>
<td>0.98 (0.86-1.12)</td>
<td>0.79</td>
<td>0.98 (0.86-1.12)</td>
<td>0.79</td>
<td>0.70</td>
<td>0</td>
<td>0.36</td>
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<tr>
<td>Hip</td>
<td>Male</td>
<td>BMI</td>
<td>1238/1065</td>
<td>0.98 (0.86-1.11)</td>
<td>0.72</td>
<td>0.98 (0.86-1.11)</td>
<td>0.72</td>
<td>0.59</td>
<td>0</td>
<td>0.36</td>
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<tr>
<td>Hip</td>
<td>Female</td>
<td>None</td>
<td>3117/3902</td>
<td>0.98 (0.93-1.03)</td>
<td>0.46</td>
<td>1.02 (0.89-1.17)</td>
<td>0.74</td>
<td>0.006</td>
<td>0.76</td>
<td>0.81</td>
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<tr>
<td>Hip</td>
<td>Female</td>
<td>BMI</td>
<td>3117/3902</td>
<td>1.05 (0.97-1.13)</td>
<td>0.25</td>
<td>1.05 (0.97-1.13)</td>
<td>0.25</td>
<td>0.69</td>
<td>0</td>
<td>0.81</td>
</tr>
<tr>
<td>Knee</td>
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<td>None</td>
<td>1863/1359</td>
<td>1.04 (0.94-1.14)</td>
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<td>1.04 (0.94-1.14)</td>
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<td>0.47</td>
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<tr>
<td>Knee</td>
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<td>BMI</td>
<td>1863/1359</td>
<td>1.03 (0.93-1.13)</td>
<td>0.62</td>
<td>1.03 (0.93-1.13)</td>
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<tr>
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<td>0.07</td>
<td>0.54</td>
<td>0.83</td>
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<tr>
<td>Knee</td>
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<td>BMI</td>
<td>3546/4003</td>
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<td>0.76</td>
<td>1.01 (0.94-1.09)</td>
<td>0.76</td>
<td>0.42</td>
<td>0</td>
<td>0.83</td>
</tr>
</tbody>
</table>

¹F.E. Fixed effects

²R.E. Random effects

³q_p-value Cochran’s heterogeneity statistic’s p-value
$I^2$ Heterogeneity index

Power has been calculated for alpha=0.05, risk allele frequency=0.5 and effect size=1.1, as estimated in the arcOGEN replication only GWAS,[1]