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Recommendations for standardization and phenotype definitions in genetic studies of osteoarthritis: the TREAT-OA consortium

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Abstract:

Objective: To address the need for standardization of osteoarthritis (OA) phenotypes by examining the effect of heterogeneity among symptomatic (SOA) and radiographic osteoarthritis (ROA) phenotypes.

Methods: Descriptions of OA phenotypes of the 28 studies involved in the TREAT-OA consortium were collected. We investigated whether different OA definitions result in different association results by creating various hip OA definitions in one large population based cohort (the Rotterdam Study-I) and testing those for association with gender, age and BMI using one-way ANOVA. For radiographic OA, we standardized the hip, knee and hand ROA definitions and calculated prevalence's of ROA before and after standardization in 9 cohort studies. This procedure could only be performed in cohort studies and standardization of SOA definitions was not feasible at this moment.

Results: In this consortium, all studies with symptomatic OA phenotypes (knee, hip and hand) used a different definition and/or assessment of OA status. For knee, hip and hand radiographic OA 5, 4 and 7 different definitions were used, respectively. Different hip OA definitions do lead to different association results. For example, we showed in the Rotterdam Study-I that hip OA defined as "at least definite JSN and one definite osteophyte" was not associated with gender ($p=0.22$), but defined as "at least one definite osteophyte" was significantly associated with gender ($p=3x10^{-9}$). Therefore, a standardization process was undertaken for radiographic OA definitions. Before standardization a wide range of ROA prevalence's was observed in the 9 cohorts studied. After standardization the range in prevalence of knee and hip ROA was small.

Conclusion: Phenotype definitions influence the prevalence of OA and association with clinical variables. ROA phenotypes within the TREAT-OA consortium were standardized to reduce heterogeneity and improve power in future genetics studies.

Introduction

The Translational Research in Europe Applied Technologies for OsteoArthritis (TREAT-OA) consortium was established in January 2008 to address the generalisability and utility of genetic and biochemical risk factors (www.treatoa.eu). The two main goals of TREAT-OA are 1) to develop efficient diagnostics for risk and progression of osteoarthritis (OA) and 2) to identify new targets for therapeutic interventions. This will be done by identification of genes and biochemical markers consistently associated with risk and progression of OA, but also by defining the roles of these genes in molecular pathways involved in disease aetiology, for example by the development of *in vivo* transgenic animal OA model systems.

A major goal of the consortium is to identify new genes consistently associated with risk and progression of OA. To reach this goal, large-scale genome-wide association studies (GWASs) and meta-analyses are being performed. To date, research within the TREAT-OA consortium has resulted in the identification of a novel genetic locus on chromosome 7q22 that is associated with knee- and hand OA[1], which was confirmed by a yet unpublished GWAS meta-analysis on knee OA. In addition, the ataxin 2 binding protein 1 gene[2] and the prostaglandin-endoperoxide synthase 2 gene[3] have been found associated with respectively hand and knee OA. One of the difficulties in these genetic analyses, and also in general in epidemiological research of OA is heterogeneity of the definition of the phenotype under study. Heterogeneity of the definition of the phenotype among different studies reduces power to find consistent associations in any disease[4]. Two working groups of HuGEnet and NCI-NHGRI have published recommendations for replication studies in genetic epidemiology studies[5-7]. One of their recommendations was to try to

investigate the same or a very similar phenotype in replication studies. Specifically for OA, the American College of Rheumatology (ACR) criteria were developed to define clinical OA within a secondary care setting[8] and the OARSI-OMERACT initiative proposed definitions for radiological progression of hip and knee OA[9]. The problem of heterogeneity in genetic association studies of OA has been highlighted[10] and therefore standardized radiographic OA (ROA) phenotypes were used in our recent GWAS and subsequent meta-analysis[1]. However, symptomatic (SOA) and ROA phenotypes were both used within the same meta-analysis. For ROA, several grading systems exists, but the most widely and consistently used system is the Kellgren and Lawrence (K/L) grading system[11]. Among major cohort studies, K/L scores are interpreted differently, especially for the knee and hip, despite the fact that they all refer to the original description[12-14].

In the current study, we have examined the effect of heterogeneity among symptomatic (SOA) and radiographic osteoarthritis (ROA) phenotypes on association analyses, to address the need for standardization of osteoarthritis phenotypes to enhance power for future association studies. We further provide recommendations for standardization of OA phenotypes.

Subjects and Methods

Study Populations

We collected data for 28 studies currently involved in the TREAT-OA consortium on the following 9 items: 1) reference article, 2) study design, 3) ethnic origin, 4) country of origin, 5) joint site(s) studied 6) radiographic or symptomatic OA definition, 7) availability of age and/or BMI data, 8) percentage of women in the study and 9) availability of follow-up data. **Table 1** describes the characteristics of all

studies evaluated. A short description of each study is given in the supplementary data.

OA definitions

OA phenotypes can be categorized into symptomatic OA and radiographic OA, and this information was collected from all studies. Subsequently, we asked for the exact OA definition used in that particular study. For example, if a study used a K/L score and used the cut-off value defined by a summary grade of 2 or more to define OA cases, the exact description of a K/L of 2 was requested (e.g. definite osteophytes with possible JSN versus definite osteophyte(s) only) or a reference article was asked were the exact interpretation of the K/L score was given.

Data analysis of OA phenotypes within the Rotterdam Study I (RSI)

Within RSI radiographic features are scored separately for hip OA (such as osteophytes, sclerosis and joint space narrowing at the lateral, superior and axial site of the hip joint)[15]. In addition, total hip replacement and the presence of pain during the last month are recorded. To discover if differences in case definitions result in different association results, we created all hip OA case definitions used by studies of the consortium within RSI. Association analyses were performed to study the relationship between different OA definitions of the hip and age, gender and body mass index (BMI). One-way ANOVA was used to assess the relationship between hip OA and the clinical variables. The analyses were carried out using SPSS version 15.0.

Standardization of phenotypes

Consensus on which ROA phenotype to use within the TREAT-OA consortium was based on the ROA definition as originally described by Kellgren and Lawrence and the feasibility of its use within each of the studies[11]. Total joint replacements (TJR) due to primary OA visible on radiographs are considered as OA. TJR due to fractures and other diseases were excluded as much as possible. After a consensus was reached between consortium members, the cohort studies either shared their data with our research group (Rotterdam Study) who standardized the definitions (data of TwinsUK, Chingford Study) or performed the standardization process themselves (other replication studies) if they were able and willing to standardize their ROA definition. The prevalence of OA was calculated by dividing the number of prevalent ROA cases over controls. Before standardization, controls were defined as the absence of OA, according to the definition used by each study, at the joint site studied. After standardization, controls were defined as the absence of OA, according to the standardized definition as described in the results section, at the joint site studied.

Results

Study Populations

Since the start of the TREAT-OA consortium in 2008, the number of teams collaborating with the consortium has grown to include 28 teams participating as of April 2010. The studies originate from Europe, the United States of America and Asia. In 24 of the 28 studies (86%), the majority of subjects included are women (63% on average). With respect to genetic data, there are in total 11 studies with GWAS data, 2 studies in which part of the subjects have GWAS data and 15 studies

without GWAS data. A short description of all studies involved in the consortium is given in the supplementary data.

OA definitions

In total, there were 11 studies using a symptomatic definition of OA and 15 studies with a radiographic definition. Two studies could not be classified as completely symptomatic or radiographic (SOA/ROA).

Radiographic OA (ROA):

For knee OA, there are 14 studies using radiographic definitions of knee OA shown in **Table 2a** with a detailed description of the knee ROA definition. A total of 12 studies used the K/L score, of which 11 studies used a cut-off value of 2 to define knee ROA and 1 study used a more stringent cut-off of 3. Two studies, which are both high risk cohorts, used a definition of OA not according to a standard classification system. As is shown in **Table 2a**, four different interpretations are given for the K/L score of the knee considering a cut-off value of 2 although all studies used the original K/L atlas. In **Table 2b-c**, results are given for hand- and hip ROA respectively in a similar way as for knee ROA.

For hand ROA, most studies (7 out of 9) used the K/L score to define hand OA, with the exception of two studies[16,17]. The interpretation of this K/L score is the same for all these studies, but there are 4 different hand ROA definitions based on the number of joints included. For example, 2 studies define OA in one hand joint as at least one definite osteophyte, but hand OA is defined as "≥3 joints (DIP/PIP/CMC1) affected" in one study and "2 out of 3 hand joint groups (DIP/PIP/CMC1 or TS) affected" in another study.

Hip ROA was defined by the (modified) Croft grade in 3 studies and by the K/L score in 4 studies. Also for hip ROA there is no consensus on the interpretation of the K/L score as 2 different interpretations are present among the studies. This includes both "definite JSN and a definite osteophyte" OR "one definite osteophyte". The Croft grade cut off of 1 as a criterion for hip ROA, is defined as definite osteophytes and does not include JSN.

Symptomatic OA (SOA):

For knee OA, there are 10 studies using clinical definitions of knee OA, which are shown in **Table 3a**. In total, 4 of these 10 studies defined knee OA as ROA + symptoms, but the inclusion of patients was done in 4 different ways. For example, one study used a K/L score ≥ 2 (defined as one definite osteophyte) + medial joint space > 1 mm + pain to include patients, whilst another study used a K/L score ≥ 3 + symptomatic OA and treated on a regular basis. The other 6 studies included patients on the basis of total joint replacements due to primary OA or a combination of a TJR or ROA and clinical symptoms of OA.

In **Table 3b-c**, results are given for hand (n=2) and hip (n=8) SOA respectively in a similar way as for SOA of the knee. Also, these definitions differed for each study. In summary, hand SOA was defined by either ACR criteria or by patient records. Hip SOA was defined as a THR by 3 studies although the assessment was different for all 3 studies (i.e., based on hospital records versus based on the description of a rheumatologist). In addition, 2 studies defined SOA of the hip as symptoms of OA + ROA, but the definition of ROA is unclear and inclusion based on symptoms differs. Furthermore, there were 3 additional studies defining hip SOA again in another way (i.e., incident THR or either clinical records of SOA or a THR).

Data analysis of OA phenotypes within the Rotterdam Study I (RSI)

In **Table 4**, association results are given for the relationship between age, gender and BMI and different hip OA definitions. When hip OA was defined radiographically as "one definite osteophyte" subjects with hip OA were more frequently men compared to controls (mean difference of 10%, $p=3x10^{-9}$), whilst subjects with a THR were more frequently women compared to controls (mean difference of 21%, p=0.001). When radiographic OA definitions were compared, we observed that hip ROA defined as "one definite osteophyte" were more frequently men compared to controls ($p=3x10^{-9}$), whilst hip OA defined as "definite JSN and one definite osteophyte" was not associated with gender (p=0.22). When analyzing SOA, we did not observe clear differences in association results for the different definitions of SOA, but the number of cases for SOA is much lower than for ROA, therefore results should be taken with caution.

Standardization of phenotypes

Consensus was reached for the knee and hip OA definition based on the ROA definition as originally described by Kellgren and Lawrence[11] and at the feasibility within each of the studies. It was agreed that the knee ROA definition used within the TREAT-OA consortium is the original K/L score[11] defined as "definite osteophytes and possible joint space narrowing" at the tibio-femoral (TF) joint. If studies did not score possible JSN as a separate feature, the definition used was: "at least 2 definite osteophytes OR one definite osteophyte plus definite JSN". Hip ROA, which was the most poorly specified in the original scores, was defined as "at least definite joint space narrowing". For hand ROA, consensus was not reached within the consortium,

due to the fact that different studies graded different joints for hand OA, thus limiting the possibility to generate a single definition. As an alternative, thumb OA was put forward as an interesting phenotype to study, because of the high correlation with pain and disability[18]. Consensus was reached on a definition for thumb OA which is "at least one definite osteophyte (= original K/L grade ≥ 2) in either the left or right first carpometacarpal (CMC1) joint".

In **Table 5**, the number of cases and controls for each study are given after standardization of phenotypes (both SOA and ROA). In total, there are 13,119 knee OA cases and 61,538 controls, 9,521 hip OA cases and 59,345 controls and 4,913 hand OA cases and 41,863 controls with DNA and phenotype data within the TREAT-OA consortium.

To evaluate the effect of standardization of the ROA phenotypes, we calculated the prevalence of knee and hip ROA in 8 Caucasian and 1 Japanese cohort study before and after standardization of the ROA definition. In **Table 6**, the mean age and BMI are shown for the 9 cohorts. The Framingham Osteoarthritis Study, The Hertfordshire Cohort Study, The Osteoporotic Fractures in Men Study, The Rotterdam study I, the ROAD Study and the Study of Osteoporotic Fractures are on average 14 years older than The Chingford Study, the Rotterdam Study III and TwinsUK. The result of the standardization of knee and hip OA phenotypes is shown in **Figure 1**. Results for the thumb OA phenotype are not shown since all studies use the same definition. The standardized hip OA definition is "at least definite JSN or a THR visible on the radiograph due to primary OA". In the SOF and MrOS Study a minor adjustment was made and hip ROA was defined as: "at least medial JSN (grade≥3) or lateral JSN (grade≥2) or a THR visible on the radiograph due to primary

OA". The standardized knee ROA definition is "at least definite osteophytes and possible JSN or a TKR visible on the radiograph due to primary OA".

Before standardization the prevalence of knee OA ranged between 10-55%, of hip OA between 2-33%. After standardization the prevalence of knee OA ranged from 8-25% and hip OA between 4-10%. When comparing cohorts with the same age range, the prevalence of knee ROA was 8-12% in the younger cohorts and 16-25% in the cohorts with subjects of an older age. To show that the differences in age are indeed the cause of the lower prevalence of knee OA in 3 cohort studies, we studied the prevalence of knee ROA in one relatively young and one old cohort with a wide age range, respectively TwinsUK and RS-I. The prevalence of knee ROA ranged from 10-15% in subjects aged 65 years and younger. In subjects aged 65 years and older, the prevalence ranged from 29-34% for the 2 studies.

Discussion

A wide range of OA definitions were used in the 28 studies participating in the TREAT-OA consortium. Since heterogeneity in phenotype definitions will reduce power to find consistent associations, radiographic OA phenotypes were standardized within the consortium.

There are some research fields in which specific attention is given to phenotype definitions. This mainly concerns studies in the field of neuroscience (i.e., bipolar disorder or schizophrenia)[19] and obesity[20]. In contrast, published research involving osteoarthritis, osteoporosis and heart disease does not usually discuss phenotype definitions. Our results showed that OA definitions should be standardized since association results differ when varying ROA and SOA definitions are used within the same study. In addition, it was recently shown that the ability to detect hip

OA genetic associations is influenced by proper phenotyping[21]. We showed by standardizing of ROA phenotypes, that similar ROA prevalence's could be obtained.

For hip ROA, a distinction can be made between atrophic OA (presence of JSN without osteophytes), hypertrophic OA (presence of osteophytes without JSN) or a composite score (both JSN and osteophytes)[22]. It is known that these different forms of hip ROA have different risk factors[23,24]. In addition, atrophic OA shows to be a more progressive form of OA than hypertrofic OA[25]. Since some studies interpret a K/L score ≥ 2 as one definite osteophyte, whereas other studies interpret this as definite JSN and one definite osteophyte, a difference in association results would be expected. Although the standardized definition agreed upon by the consortium is based on JSN (hip ROA = at least definite JSN, with or without osteophytes), a majority of the subjects (78 and 80% in the Rotterdam Study-I and III, respectively) have both JSN and osteophytes. This definition can therefore also be seen as a composite score. Although less often used than the composite score of hip ROA, hypertrophic hip and atrophic hip ROA definitions should also be standardized. We suggest using "presence of at least one definite osteophyte at the femoral head without definite JSN" as preferred definition for hypertrofic OA and "definite JSN without the presence of any osteophytes at all locations" as atrophic OA which was also used in a previous study by Javaid *et al.*[22].

It was difficult to reach consensus on the hand ROA definition, since different studies scored different joints. To overcome this problem, a subtype for clinically relevant OA was suggested within the consortium: thumb OA, associated with pain and disability[18,26], will be used within the consortium. The definition of ROA of the thumb is "at least one definite osteophyte in either right or left CMC1 joint".

We recommend for future studies on ROA to always specify the exact OA definition. A statement such as "we defined OA as a K/L ≥ 2" should be avoided or the interpretation of this K/L score should be given.

Since all studies involved in the consortium defined SOA differently, or at least assessed the OA status differently, it is likely that heterogeneity is a problem in studies on SOA. Standardization of SOA would in principle be possible if studies had pain, clinical assessment data for study subjects, as well as radiographic grade for the index joints, age, BMI, for both cases and controls. The design of some studies is such however that there is no radiographic characterization for cases and controls, which is necessary if SOA would be defined based on both symptoms and radiographs, and only a diagnosis of TJR for an indication of OA is present. These are extant studies and to collect homogenous SOA studies would require a huge investment of resources as well as time. However, there remains a lack of consensus and guidelines about how SOA should be assessed. For example, the American College of Rheumatology (ACR) defines signs of OA as stiffness <30 minutes, crepitus, bony tenderness, bony enlargement, no palpable warmth and pain in or around the joint. The presence of these traits in subjects over the age of 50 (preferably accompanied by radiographic evidence of OA) is commonly used in the design of randomized clinical trials (RCTs)[27]. But these criteria were developed in a clinic setting so the sensitivity and specificity of a diagnosis based on these criteria in a community or primary care settings, are as yet unknown.

Most of the SOA cases included in the TREAT-OA consortium are total joint replacement cases with a primary indication of OA. Although it is possible to define TJR as the main clinical outcome representative of severe symptomatic large joint OA

in itself, as has been proposed for RCTs[28], this might not be the best option. Recent studies on this topic have revealed considerable heterogeneity in the radiographic severity, functional disability and pain suffered by TJR candidates[29]. In addition, the pain and disability components among subjects undergoing TJR are significantly correlated with risk factors that also impact on ROA such as BMI, age, sex, whilst being poorly correlated with radiographic severity[29,30]. Further, not all patients with severe symptomatic OA can or are willing to get a TJR either because of lack of access to healthcare, or they may be afraid of surgery, or have co-morbidities that make them ineligible etcetera[31]. TJR patients are usually recruited in secondary care settings and might in some instances represent a non-random subset of severe symptomatic OA.

In summary, additional research is needed to reach consensus for in- and exclusion criteria and definitions of clinical/symptomatic OA studies. We suggest that more thought should be given to the establishment of clear guidelines for future research using symptomatic OA cohorts, as this would have implications not just for genetic studies, but also for the assessment of biomarkers, imaging and interventional studies.

Genome-wide association studies (GWAS) and meta-analyses have been[1,32] and will continue to be performed within the TREAT-OA consortium in order to identify genes consistently associated with risk and progression of OA. Presently, there are few genes discovered for OA by means of GWAS, and this may be explained by heterogeneity of phenotypes and the limited sample size used in the discovery GWAS samples up to now. For example, in a previous GWAS, ROA and SOA definitions were used within one meta-analysis[1]. It has been shown before that

ROA shows only modest correlation with clinical features of OA[33,34]. In addition, we showed in this study that the association between SOA and age, gender and BMI is different compared to ROA. Although the sample size would decrease using stratification methods, the statistical power might increase if there is a reduction in the heterogeneity in the phenotype definition. Therefore, we recommend that for future GWASs additional work is needed to standardize or stratify on ROA and SOA. Fortunately, in the TREAT-OA consortium studies on ROA have access to the source material and individual features of ROA are scored separately. This enables us to easily establish standardized phenotypes across cohorts.

Additionally, other phenotypes or possible predictors such as hypertrophic vs. atrophic forms of OA, joint shape, MRI based features, severe ROA (K/L≥3 versus K/L=0) or generalized OA may expand our definitions of the OA phenotypes and may increase the number of consistent associations in genetic studies. However, consensus among OA epidemiologist on OA phenotypes should be reached within the OA field, prior to the performance of these association studies.

In conclusion, standardization of radiographic OA phenotypes was carried out in the TREAT-OA consortium to reduce heterogeneity as much as possible. Standardization of symptomatic OA phenotypes, although desirable, was not possible due to the case-control study design of the studies. In the future, more precise OA phenotypes and stratification according to symptomatic and radiographic OA phenotypes are highly recommended.

Recommendations

1	Future studies on OA should always **specify the exact OA definition**. A statement such as "we defined OA as a K/L ≥ 2" should be avoided or the interpretation of this K/L score should be given.
2	**The use of standardized ROA definitions is recommended** in association studies with knee ROA defined as "at least 2 moderate definite osteophytes and possible JSN at the tibio-femoral joint", hip ROA as "at least definite JSN" and thumb ROA as "at least one moderate definite osteophyte at the CMC1 joint".
3	**Atrophic hip ROA** is suggested to be defined as "definite JSN without the presence of any osteophytes at all locations" and **hypertrophic hip ROA** as "presence of at least one moderate definite osteophyte at the femoral head without definite JSN".
4	**Consensus is needed** on in- and exclusion criteria and phenotype definitions of **SOA studies**. More thought should be given to the establishment of clear guidelines for future research using clinical OA cohorts
5	For future **GWASs** additional work must be done to **stratify** on age/BMI and especially **ROA and SOA**.
6	**Expansion of OA phenotypes is not discouraged**. Other phenotypes such as joint shape, MRI based features, severe ROA (K/L ≥ 3 versus K/L = 0) or generalized SOA/ROA may expand our definitions of the OA phenotypes, but consensus among OA epidemiologist on these new OA phenotypes should be reached, prior to the performance of these association studies.

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Figure Legends

Figure 1. Prevalence of knee and hip OA before and after standardization of the ROA phenotypes.

Table 1. Overview of all studies involved in the TREAT-OA consortium

Study	Reference article	Study design	Ethnic origin	Country of origin	Joint site	ROA/SOA	Age/BMI	% women	Follow-up data
GWAS data									
arcOGEN consortium		Case-control	Caucasian	United Kingdom	Knee, hip	ROA/SOA	-	60%	Not available
- Chingford Study	Hart et al.[35]	Cohort	Caucasian	United Kingdom	Knee, hip	SOA	+	100%	Available
- Nottingham Case-Control Study	Valdes et al.[36]	Case-control	Caucasian	United Kingdom	Knee, hip	SOA	+	53%	Not available
- Oxford Study	Chapman et al.[37]	Case-control	Caucasian	United Kingdom	Knee, hip	SOA	-	55%	Not available
- Sheffield Study	Gordon et al.[38]	Case-control	Caucasian	United Kingdom	hip	SOA	+[a]	53%	Not available
- TwinsUK	Spector et al.[39]	Cohort	Caucasian	United Kingdom	Knee, hip	ROA	+	100%	Available
- VIDEO	Not available yet	RCT	Caucasian	United Kingdom	Knee	SOA	+	60%	Available in 2011
Other									
deCODE	Ingvarsson et al.[40] and Stefansson et al.[41]	Case-control	Caucasian	Iceland	Knee, hip, hand	SOA	+[a]	58%	Not available
Framingham Osteoarthritis Study	Hunter et al.[42]	Cohort	Caucasian	United States	Knee, hand	ROA	+	56%	Available
GARP	Riyazi et al.[43]	Cohort	Caucasian	Netherlands	Knee, hip, hand	SOA/ROA	+	65%	Available
Health 2000	Kaila-Kangas et al.[44]	Cohort	Caucasian	Finland	Hip, knee	SOA	+	55%	Available
RSI	Hofman et al.[45]	Cohort	Caucasian	Netherlands	Knee, hip, hand	ROA	+	59%	Available
RSII	Hofman et al.[45]	Cohort	Caucasian	Netherlands	Knee, hip, hand	ROA	+	56%	Available
RSIII	Hofman et al.[45]	Cohort	Caucasian	Netherlands	Knee, hip, hand	ROA	+	57%	Available in future
TwinsUK	Spector et al. [39]	Cohort	Caucasian	United Kingdom	Knee, hip, hand	ROA	+	100%	Available

GWAS = genome-wide association study; ROA = radiographic osteoarthritis; SOA = symptomatic osteoarthritis; BMI = body mass index; RCT = randomized clinical trial; Age/BMI +: age and BMI data are available; GARP = Genetics osteoARthritis and Progression; RS = Rotterdam Study; [a]age is available for all subjects, BMI only for part of the subjects

Table 1 continued. Overiew of all studies involved in the TREAT-OA consortium

Study	Reference article	Study design	Ethnic origin	Country of origin	Joint site	ROA/SOA	Age/BMI	% women	Follow-up data
De novo genotyping									
Chingford Study	Hart et al.[35]	Cohort	Caucasian	United Kingdom	Knee, hip, hand	ROA	+	100%	Available
Chinese Case-Control Study	Miyamoto et al.[46]	Case-control	Asian	China	Knee	SOA	+[b]	75%	Not available
D&T Study	Solovieva et al.[47]	High risk Cohort	Caucasian	Finland	Hand	ROA	+	100%	Only symptoms
Estonian Studies	Tamm et al.[48]	Cohort	Caucasian	Estonia	Knee	ROA	+	65%	Available
Finnish OA cases	Näkki et al.[49]	Case-control	Caucasian	Finland	Hand, knee	SOA/ROA	+	76%	Not available
Greek clinical cases	Fytili et al.[50]	Case-control	Caucasian	Greece	Knee	SOA	+	78%	Not available
HCS	Abdin-Mohamed et al.[16]	Cohort	Caucasian	United Kingdom	Knee, hand	ROA	+	50%	Available[c]
Japanese Case-Control Study	Miyamoto et al.[46]	Case-control	Asian	Japan	Knee, hip	SOA	+[b]	80%	Not available
Japanese Cohort Study	Miyamoto et al.[46]	Cohort	Asian	Japan	Knee	ROA	+	75%	Available[d]
KANON	Frobell et al.[51]	High risk Cohort	Caucasian	Sweden	Knee	ROA	+	26%	Available in 2011
LUMEN	Englund et al.[17]	High risk Cohort	Caucasian	Sweden	Knee	ROA	+	21%	Available
MDC study	Lohmander et al.[52]	Cohort	Caucasian	Sweden	Knee, hip	SOA	+	65%	Available
MrOS	Orwoll et al.[53]	Cohort	Caucasian	United States	Hip	ROA	+	0%	Available
Nottingham Case-Control	Valdes et al.[36]	Case-control	Caucasian	United Kingdom	Knee, hip	SOA	+	53%	Not available
Spanish clinical cases	Rodriguez-Lopez et al.[54]	Case-control	Caucasian	Spain	Knee, hip, hand	SOA	+	65%	Not available
SOF	Nevitt et al.[55]	Cohort	Caucasian	United States	Hip	ROA	+	100%	Available
The ROAD Study	Muraki et al.[56]	Cohort	Asian	Japan	Knee	ROA	+	65%	Available in 2010

GWAS = genome-wide association study; ROA = radiographic osteoarthritis; SCOA = symptomatic osteoarthritis; BMI = body mass index; Age/BMI +: age and BMI data are available for all subjects; D&T = dentists & teachers; HCS = Hertfordshire cohort study; MDC = Malmö Diet and Cancer; MrOS = Osteoporotic Fractures in Men Study; SOF = Study of Osteoporotic Fractures; [b]only for the cases data on age and BMI is available; [c] Available for clinical data, not available for x-ray data; [d] for part of the subjects follow-up data is available

Table 2a. Description of the radiographic knee OA definition according to 14 studies of the TREAT-OA consortium

Study	Classification System	Cut-off value for OA	Exact OA definition
Chingford Study	K/L score	2	One definite osteophyte
Estonian Studies	K/L score	2	Definite osteophytes
Finnish cases	K/L score	3	Definite osteophytes + definite JSN and/or joint deformation
Framingham Osteoarthritis Study	K/L score	2	Definite osteophytes and possible JSN
GARP	K/L score	2	Definite osteophytes and possible JSN
HCS	K/L score	2	Definite osteophytes
Japanese Cohort Study	K/L score	2	One definite osteophyte
KANON	-	-	JSN grade ≥ 2 or sum of 2 marginal osteophyte grades from the same compartment ≥ 2 or grade 1 JSN + grade 1 osteophytes in the same compartment
LUMEN	-	-	JSN grade ≥ 2 or sum of 2 marginal osteophyte grades from the same compartment ≥ 2 or grade 1 JSN + grade 1 osteophytes in the same compartment
RSI	K/L score	2	Definite osteophytes and possible JSN
RSII	K/L score	2	Definite osteophytes and possible JSN
RSIII	K/L score	2	Definite osteophytes and possible JSN
The ROAD Study	K/L score	2	One definite osteophyte
TwinsUK	K/L score	2	One definite osteophyte

K/L = kellgren and Lawrence; JSN = joint space narrowing; - no standard classification system is used to define OA; GARP = Genetics osteoARthritis and Progression; HCS = Hertfordshire Cohort Study; RS = Rotterdam Study

Table 2b. Description of the radiographic hand OA definition according to 9 studies of the TREAT-OA consortium

Study	Classification System	Cut-off value for OA	Exact OA definition
Chingford Study	K/L score	2	≥3 joints (DIP/PIP/CMC1) affected[a]
D&T Study	Modified K/L score	2	≥2 joints (DIP/PIP/MCP) affected[b]
Finnish OA cases and families	K/L score	2-3	K/L ≥ 3 for index cases and K/L ≥2 for their siblings (DIP bilateral)
Framingham Osteoarthritis Study	K/L score	2	K/L ≥ 2 (one definite osteophyte): joint specific definitions (i.e., DIP OA, PIP OA etcetera)
GARP	K/L score	2	≥3 joints (DIP/PIP/CMC1) affected[c]
HCS	-	-	Presence of Heberden's or Bouchard's nodes
LUMEN	-	-	Presence of OA (JSN grade ≥2 or osteophyte grade ≥2 or JSN grade 1 plus osteophyte grade 1) in at least 1 DIP or PIP joint in each hand symmetrically or at least 2 DIP/PIP joints in the same hand in a pattern consistent with primary OA (in the same row or ray) or the CMC1 joint bilaterally.
RSI	K/L score	2	2 out of 3 hand joint groups (DIP/PIP/CMC1 or TS) affected[a]
TwinsUK	K/L score	2	≥3 joints (DIP/PIP/CMC1) affected[a]

OA = osteoarthritis; K/L = Kellgren and Lawrence; - no standard classification system is used to define OA; DIP = distal interphalangeal joint; PIP = proximal interphalangeal joint; CMC1 = first carpometacarpal joint; TS = trapezioscaphoid joint; MCP = metacarpophalangeal joint; D&T = Dentists and Teachers Study; GARP = Genetics osteoARthritis and Progression; HCS = Hertfordshire Cohort Study; RSI = Rotterdam Study-I; [a] affected means K/L ≥ 2 (=definite osteophyte) in each or both hands; [b] affected means modified K/L ≥ 2 (=a single radiographic sign indicative of OA, slight to moderate lowering of the joint space, sometimes subluxation, minimal osteophytes, degeneration cysts or slight marginal sclerosis, each of the latter signs without a clear narrowing of joint space but little if any additional pathology) irrespective of right or left hand; [c] affected means K/L ≥ 2 (=definite osteophyte) irrespective of left or right hand.

Table 2c. Description of the radiographic hip OA definition according to 7 studies of the TREAT-OA consortium

Study	Classification System	Cut-off value for OA	Exact OA definition
Chingford Study	K/L score	2	Definite osteophyte
GARP Study	K/L score	2	Definite JSN + definite osteophyte
MrOS	Modified Croft grade	2	Presence of either definite JSN or definite osteophytes plus at least 1 of 5 other features: osteophytes, JSN, sclerosis, cysts or femoral head deformity
RSI	K/L score	2	Definite JSN + definite osteophyte
RSII	K/L score	2	Definite JSN + definite osteophyte
SOF	Modified Croft grade	2	Presence of either definite JSN or definite osteophytes plus at least 1 of 5 other features: osteophytes, JSN, sclerosis, cysts or femoral head deformity
TwinsUK	Croft grade	1	Definite osteophytes

OA = osteoarthritis; K/L = Kellgren and Lawrence; JSN = joint space narrowing; GARP = Genetics osteoARthritis and Progression; MrOS = Osteoporotic Fractures in Men Study; RSI = Rotterdam Study-I; RSII = Rotterdam study-II; RSIII = Rotterdam Study-III; SOF = Study of Osteoporotic Fractures

Table 3a. Description of the symptomatic knee OA definitions according to 10 studies of the TREAT-OA consortium

Study	OA definition based on:	Exact OA definition
Chinese Case-Control Study	K/L grade + symptoms	K/L ≥ 2 (=one definite osteophyte) + pain with rest and/or night pain of over 5-month duration. Exclusion of inflammatory, posttraumatic, post septic arthritis, dysplasias
deCODE	Hospital records of TJR	TKR. A clinician reviewed the patients records to verify the diagnosis
Greek clinical cases	TJR due to OA reported by specialist	TKR + K/L ≥ 2 (=definite osteophytes + possible JSN)
Health 2000	Clinical records of OA or TKR	History, records and a standardized clinical diagnosis of previously diagnosed knee OA or knee arthroplasty due to OA based on convincing findings OR at least moderately restricted mobility OR slightly restricted mobility and either of the following: documented history of previously diagnosed knee OA but not convincingly presented grounds for the diagnosis or typical symptoms of knee OA
Japanese Case-Control Study	K/L grade + symptoms	Symptomatic OA and treated on a regular basis + K/L ≥ 3
MDC Study	Incident knee arthroplasty/osteotomy from national Swedish hospital discharge register	First knee arthroplasty or high tibial osteotomy + diagnosis of OA according to the International Classification of Disease (ICD) 9 and 10
Nottingham Case-Control	Clinically severe knee OA based on hospital orthopaedic surgery lists	Referred to the hospital with symptomatic, clinically severe knee OA and the majority had undergone unilateral or bilateral TKR within the previous 5 years. Pre-operative knee radiographs were examined to confirm the diagnosis. Exclusion based on another major arthropathy, Paget's disease
Oxford Study	Severe symptomatic knee OA + K/L grade	Signs and symptoms of OA sufficiently severe to require TKR + K/L ≥ 2 (exact definition unknown). Exclusion based on dysplasia
Spanish clinical cases	TJR	TKR, a rheumatologists considered patients to suffer from severe primary OA. Exclusion based on inflammatory, infectious, traumatic or congenital joint pathology and lesions due to crystal deposition or osteonecrosis
VIDEO	K/L grade + pain	K/L ≥ 2 (=one definite osteophyte) + medial joint space width > 1mm + knee pain

OA = osteoarthritis; TJR = total joint replacement; TKR = total knee replacement; JSN = joint space narrowing; MDC = Malmö Diet and Cancer

Table 3b. Description of the symptomatic hand OA definitions according to 2 studies of the TREAT-OA consortium

Study	OA definition based on:	Exact OA definition
deCODE	Patients records at hospitals and health centres	Included on the basis of clinical examination by an experienced examiner, supported by a radiograph for >60% of the cases
Spanish clinical cases	ACR criteria	Patients were complaining of hand OA and followed in the Rheumatology Unit. The ACR criteria were used for inclusion in the study

OA = osteoarthritis; ACR = American College of Rheumatology

Table 3c. Description of the symptomatic hip OA definitions according to 8 studies of the TREAT-OA consortium

Study	OA definition based on:	Exact OA definition
deCODE	Hospital records of TJR	THR. A clinician reviewed the patients records to verify the diagnosis
Health 2000	Clinical records of OA or THR	History, records and a standardized clinical diagnosis of previously diagnosed hip OA or hip arthroplasty due to OA based on convincing findings OR at least moderate restrictions in extension or in inner rotation or in outer rotation OR slight restrictions in extension, inner rotation, outer rotation or at least moderately restricted abduction-adduction and either of the following: documented history of previously diagnosed hip OA but no grounds for the diagnosis is given or typical symptoms of hip OA
Japanese Case-Control Study	Symptoms + radiographs	Subjects are symptomatic and were treated in participating institutions on a regular basis + radiographic signs of hip OA (exact definition unknown)
MDC Study	Incident hip arthroplasty from national Swedish hospital discharge register	First hip arthroplasty in combination with a contemporaneous diagnosis of hip osteoarthritis according to the International Classification of Disease (ICD) 9 and 10
Nottingham Case-Control	Clinically severe hip OA based on hospital orthopaedic surgery lists	Referred to the hospital with symptomatic, clinically severe hip OA and the majority had undergone unilateral or bilateral THR within the previous 5 years. Pre-operative hip radiographs were examined to confirm the diagnosis. Exclusion based on another major arthropathy, Paget's disease, overt child hip disease, THR due to trauma or terminal illness
Oxford Study	Severe symptomatic hip OA + K/L grade	Signs and symptoms of OA sufficiently severe to require THR + K/L $\geq$ 2 (exact definition unknown). Exclusion based on dysplasia
Sheffield Study	THR	Subjects had undergone THR for clinical, idiopathic OA that was confirmed radiographically prior to joint replacement (exact radiographic definition uknown)
Spanish clinical cases	TJR	THR, a rheumatologists considered patients to suffer from severe primary OA. Exclusion based on inflammatory, infectious, traumatic or congenital joint pathology and lesions due to crystal deposition or osteonecrosis

OA = osteoarthritis; TJR = total joint replacement; THR = total hip replacement; MDC = Malmö Diet and Cancer

Table 4. Association results of different hip OA case definitions (prevalence) and gender, age and BMI in the Rotterdam Study I

OA phenotype	Number		Gender (%women)			Age (mean)			BMI (mean)		
	cases	*controls*	*cases*	*controls*	*p-value*	*cases*	*controls*	*p-value*	*cases*	*controls*	*p-value*
Radiographic OA											
definite JSN and one definite osteophyte (original K/L ≥ 2)	242	3037	54%	58%	0.22	68.1	65.7	$3x10^{-8}$	26.3	26.3	0.99
One definite osteophyte	1906	1373	54%	64%	$3x10^{-9}$	66.1	65.5	0.009	26.2	26.4	0.07
Symptomatic OA											
Total hip replacement	64	3215	78%	57%	0.001	71.2	65.7	$8x10^{-11}$	26.9	26.3	0.18
ROA (original K/L ≥ 2) + pain	58	3221	79%	57%	0.001	69.9	65.8	$3x10^{-6}$	26.7	26.3	0.38
ROA (original K/L ≥ 3) + pain	23	3256	70%	58%	0.26	70.0	65.8	0.003	26.4	26.3	0.88

OA = osteoarthritis; K/L = Kellgren and Lawrence score; JSN = joint space narrowing; BMI = body mass index

Table 5. Number of cases (including incident cases) and controls in each study involved in the TREAT-OA consortium according to standardized phenotypes

Study	Knee OA		Hip OA		Thumb OA	
Radiographic OA	*cases*	*controls*	*cases*	*controls*	*cases*	*controls*
Chingford Study	80	560	34	702	356	620
D&T Study	-	-	-	-	36	507
Estonian Studies	70	441	-	-	-	-
Framingham Osteoarthritis Study	419	1,674	-	-	913	2,783
HCS	156	831	-	-	78	179
Japanese Cohort Study	226[1]	486	-	-	-	-
KANON	NA[1]	NA	-	-	-	-
LUMEN	152[1]	317	-	-	55	197
MrOS	-	-	389	3,660	-	-
RSI	1,017[2]	2,452	581[2]	3,183	868[3]	2,516
RSII	NA[2]	NA	NA[2]	NA	NA[2]	NA
RSIII	136	922	NA[2]	NA	-	-
SOF	-	-	364	3,668	-	-
The ROAD Study	541	2,426	-	-	-	-
TwinsUK	149	1,436	105	1,253	393	1,565
Subtotal radiographic OA	**2946**	**11,545**	**1,473**	**12,466**	**2,699**	**8,364**
Symptomatic/Radiographic OA						
Finnish OA cases	113	210	-	-	-[4]	-[4]
GARP	161	720	106	720	151	720
Subtotal symptomatic/radiographic OA	**274**	**930**	**106**	**720**	**151**	**720**

NA = not applicable; [1]number of cases and controls unstandardized;[2]complete dataset available summer 2010; [3]scoring of radiographs in progress, complete dataset available in 2011; [4]available in the near future

Table 5 cont. Number of cases (including incident cases) and controls in each study involved in the TREAT-OA consortium according to standardized phenotypes

Study	Knee OA		Hip OA		Thumb OA	
Symptomatic OA	*cases*	*controls*	*cases*	*controls*	*cases*	*controls*
Arcogen consortium	4,287[1]	4,287	4,107[1]	4,107	-	-
Chinese Case-Control Study	1,200[1]	1,500	200	1,500	-	-
deCODE	1,033	32,482	1,571	32,482	1,822	32,482
Greek clinical cases	228	344	67	344	-	-
Health 2000	237	6,048	132	6,151	-	-
Japanese Case-Control Study	900	3,400	-	-	-	-
MDC	471	471	551	551	-	-
Nottingham Case-Control	1,355[1]	237	1,011[1]	730	-	-
Spanish clinical cases	188	294	303	294	241[2]	294
Subtotal symptomatic OA	**9,899**	**49,063**	**7,942**	**46,159**	**2,063**	**32,776**
Total	**13,119**	**61,538**	**9,521**	**59,345**	**4,913**	**41,863**

OA = osteoarthritis; [1]recruitment in progress; [2]hand OA according to ACR criteria, thumb OA definition not possible

Table 6. Baseline characteristics of 6 cohort studies with ROA phenotypes involved in the standardization process

Study	Mean age (range)	Mean body mass index (range)
Chingford Study	54 (44-67)	26 (17-47)
Framingham Osteoarthritis Study	64 (29-93)	26 (14-54)
Hertfordshire Cohort Study	65 (59-71)	27 (17-48)
Osteoporotic Fracture in Men Study	77 (69-97)	27 (18-50)
ROAD Study	70 (23-94)	23 (13-37)
Rotterdam Study I	68 (55-94)	26 (15-59)
Rotterdam Study III	57 (45-89)	28 (14-57)
Study of Osteoporotic Fractures	71 (65-91)	27 (16-59)
TwinsUK	54 (37-76)	25 (15-51)

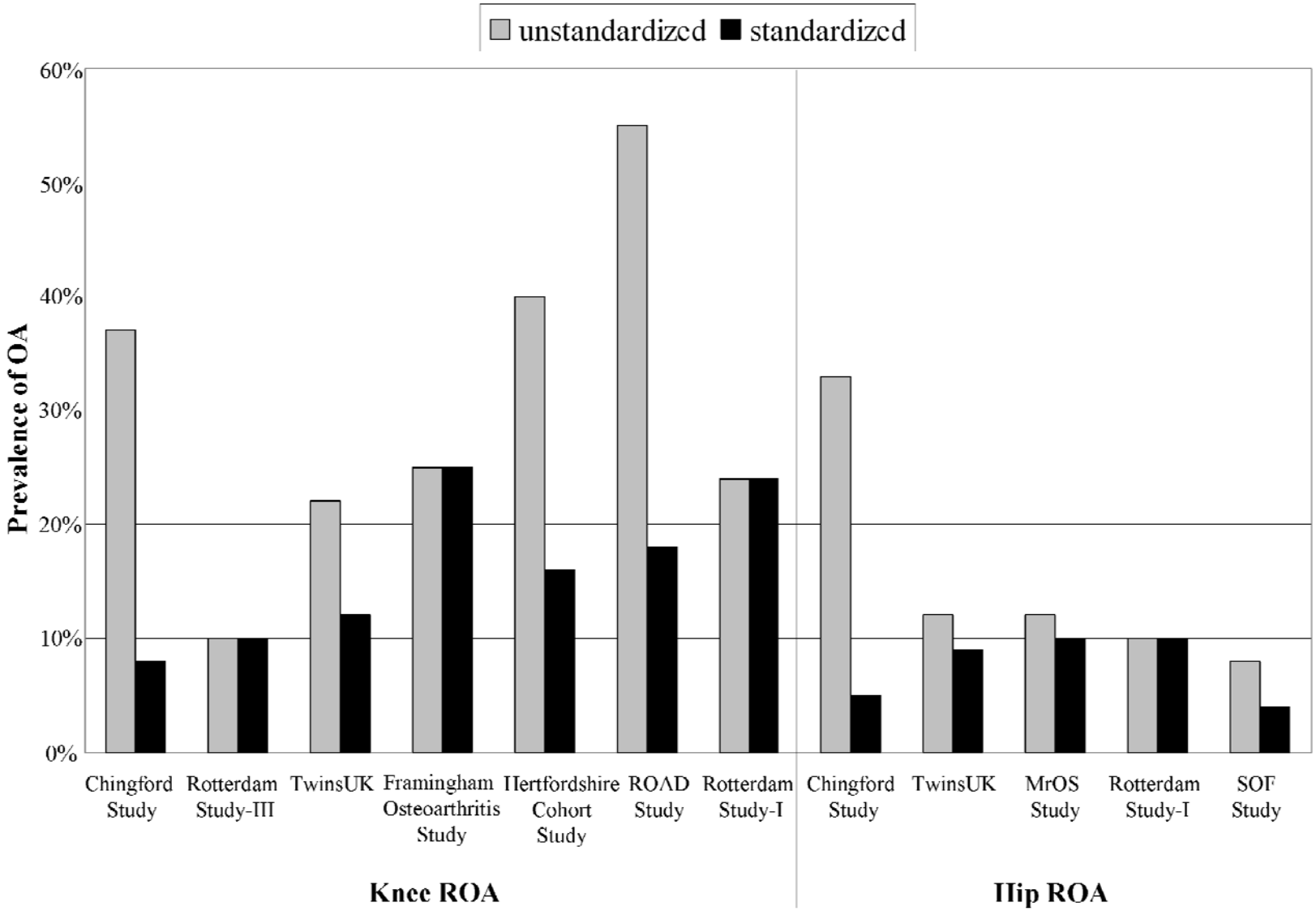

Figure 1. Prevalence of knee and hip OA before and after standardization of the ROA phenotypes

Supplementary data

Results

Description of all studies involved in the TREAT-OA consortium

Studies with GWAS data:

arcOGEN consortium:

- 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[1,2]. 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 radiological using standard X-rays of the pelvis, thoracolumbar spine, hands and weight-bearing knees[4]. 47% of the cases of the Chingford Study are involved in the arcOGEN consortium.
- 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[5]. 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. 28% of the knee OA cases and 27% of the hip OA cases are included in the arcOGEN consortium.

- Oxford study: Subjects were ascertained using the criteria of signs and symptoms of OA sufficiently severe to require joint replacement surgery in the United Kingdom[6]. The radiographic stage of the disease was a K/L grade ≥ 2 in all cases. In addition, no cases suggestive of a skeletal dysplasia or developmental dysplasia were included. The controls comprised individuals with no signs or symptoms of arthritis or joint disease (pain, swelling, tenderness or restriction of movement). Ethical approval for the Oxford collection was obtained from the Oxfordshire Clinical Research Ethics Committee, MREC 02/2/108, with each participant providing informed consent for their sample to be used in OA genetics studies.
- Sheffield Study: The Sheffield Study is a case-control study that was conducted to identify loci associated with prosthesis-related complications of total hip replacement. All subjects had undergone cemented total hip replacement for clinical, idiopathic, osteoarthritis that was confirmed radiographically prior to joint replacement. All subjects had K/L disease grade ≥ 2, and were free from any history of childhood hip disorders, inflammatory arthropathy or infection, and were not taking drugs known to affect bone metabolism. The characteristics of the subjects are described elsewhere[7]. The study was approved by the North Sheffield research ethics committee, and all subjects provided written, informed consent prior to participation.
- TwinsUK: 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[8]. These unselected twins were recruited from the general population through national media campaigns in the United Kingdom. Ethics approval was obtained from the

Guy's and St. Thomas' Hospital Ethics Committee. Written informed consent was obtained from every participant. The radiographs were taken between 1995 and 2000[9]. Anteroposterior extended-view weight-bearing radiographs of both knees were obtained at baseline and follow-up using the same protocol and a tube-to-film distance of 100 cm[10]. Pelvic radiographs with the subject in the supine anteroposterior position, with a standard tube-to-film distance of 100 cm and the feet positioned in 15 degrees of internal rotation were obtained[11]. Radiographs of both hands were taken with a standard posteroanterior view[12]. 23% of the cases of the TwinsUK Study are involved in the arcOGEN consortium.

- VIDEO: This study is a placebo-controlled randomized controlled trial of 800 unit's cholecalciferol in men and women with knee OA. In total, 477 cases are included in this trial which are classified as knee OA patients according to the Kellgren and Lawrence grading system[13] (OA defined as one definite osteophyte) and patients had to suffer from knee pain and have a medial joint space width > 1mm. The study was approved by the local research ethics committee, and all subjects provided written, informed consent prior to participation.

deCODE: Hand OA cases were obtained from patients records at hospitals and health care centers in Iceland[14]. 2754 hand OA cases were included on the basis of clinical examination by an experienced examiner, supported by radiographs in over 60% of the cases, including all doubtful cases. Assessment was based on radiologists descriptions and in doubtful cases from the radiographs. THR and TKR cases were recruited through a computer-aided search of hospital records. A clinician reviewed the patients records to verify the diagnosis[15]. Population controls were used, excluding all individuals with known signs of OA in any joint. The study was approved by the Data Protection Authority of Iceland and the National Bioethics Committee of Iceland. Informed consent was obtained from all participants.

Framingham Osteoarthritis Study: This study is a longitudinal population-based cohort study established in 1948 in Framingham, Massachusetts to examine risk factors for heart disease[16]. In addition to the original cohort, a study of the offspring and their spouses of this cohort was initiated in 1971. The Framingham OA study, which includes participants of both cohorts, was developed to study the inheritance of OA[17]. The Boston University Medical Center IRB approved the Osteoarthritis Protocol. Written informed consent was obtained from all subjects for both the osteoarthritis examination and for DNA acquisition and use. During the Framingham Offspring Cohort examination 5 visit (conducted during 1992–1994), a radiograph of both knees in full extension with weight-bearing was obtained, using a standardized protocol that included outlines of the feet in order to keep the rotation of the knee the same at follow-up evaluations. Knee radiographs were obtained at 0° and at 6° caudal, and the better of the 2 views (based on the optimal superimposition of the anterior and posterior margins of the medial tibial plateau) was selected for comparison with findings at the follow-up examination[18]. A single bone-and-joint radiologist read PA hand films according to the reading protocols of the Framingham OA Study[19].

Genetics OsteoArthritis and Progression (GARP) Study: The GARP study from Leiden, the Netherlands, consists of 192 sibling pairs concordant for clinical and radiographically (K/L score) confirmed OA at two or more joint sites among hand, spine (cervical or lumbar), knee or hip[20]. Random controls (N=720) were partners of the offspring of the Leiden longevity study[21]. Written informed consent was obtained from each subject as approved by the ethical committees of the Leiden University Medical Center. Conventional radiographs of the hands (dorso-volar), knees (posterior-anterior (PA) in weight bearing semiflexed and lateral), hips (PA), lumbar (PA and lateral), and cervical spine (anterior-posterior, lateral, and transbuccal) were obtained from all participants. They were taken in a standard manner with a fixed film focus distance and a fixed joint position. Conventional radiographs of the knees were taken using the fixed flexion radiography[20].

Health 2000: This study is a nationally representative population-based study of 8,028 persons aged 30 years or over. Of these, 78.4% participated in a health examination including standard clinical examination of the joints by a physician. In total, 2856 men and 3436 women were included. Knee- and hip OA were defined according to clinical records. Knee OA is defined as a documented history of previously diagnosed knee OA or knee arthroplasty due to OA based on convincing findings OR at least moderately restricted mobility OR slightly restricted mobility and either of the following: documented history of previously diagnosed knee OA but not convincingly presented grounds for the diagnosis or typical symptoms of knee OA[22]. Hip OA is defined as a documented history of previously diagnosed hip OA or hip arthroplasty due to OA based on convincing findings OR at least moderate restrictions in extension or outer rotation OR slight restrictions in extension, inner rotation, outer rotation or moderately restricted abduction-adduction and either of the following: documented history of previously diagnosed hip OA but no grounds for the diagnosis is given or typical symptoms of hip OA [22,23].

Rotterdam Study I, II and III (RSI, RSII, RSIII): The Rotterdam Study is a population-based prospective cohort study ongoing since 1990 to study determinants of chronic disabling disease [24]. The Rotterdam Study consists of three sub-populations. The Rotterdam Study I (RSI) is the first cohort of 7,983 persons living in the Ommoord district of Rotterdam in the Netherlands. All subjects were aged 55 years and older and recruitment started in 1990. The Rotterdam Study II (RSII) started in 1999 when 3,011 participants moved into the study since they became 55 years of age or moved into the study district. A further extension, the Rotterdam Study III (RSIII), was initiated in 2006 and to date 3,829 participants, aged 45-54 years, are included in this study. The medical ethics committee of Erasmus University Medical School approved the study and written informed consent was obtained from each participant. Weight bearing anteroposterior radiographs of the knee and hip were obtained at 70 kV, a focus of 1.8, and a focus to film distance of 120 cm, applying a Fuji High Resolution G 35x43 cm film[25]. Standard anteroposterior radiographs of both

hands were taken[26]. For RS-I 10 year follow-up data and for RS-II 5 year follow-up data is available. All three studies are ongoing and more follow-up data will be generated in the future.

TwinsUK Study: For study design and objectives please see the information under the subheading arcOGEN consortium. 77% of the cases and 100% of the controls were not part of the arcOGEN consortium, but are available for replication purposes within the TREAT-OA consortium. There is no overlap between the cases involved in the arcOGEN consortium and the cases used for replication purposes in the TwinsUK Study itself.

Replication studies using de novo genotyping:

Chinese Case-Control Study: The Han Chinese knee OA cases and controls were recruited from the Center for Diagnosis and Treatment of Joint Disease and the Center of Physcial Examination at Drum Tower Hospital. All subjects included in the study were Han Chinese living in and around Nanjing. All the patients had pain with rest and/or night pain of over 5-month duration. Other etiologies causing knee diseases such as inflammatory arthritis, posttraumatic or postseptic arthritis, skeletal dysplasia or developmental dysplasia were excluded[27]. The controls had never any signs or symptoms of arthritis or joint diseases (pain, swelling, tenderness or restriction of movement). The Study was approved by the ethical committee of the Medical School of Nanjing University and informed consent was obtained from all patients and controls.

Chingford Study: For study design and objectives please see the information under the subheading arcOGEN consortium. 53% of the cases and 100% of the controls were not part of the arcOGEN consortium, but are available for replication purposes within the TREAT-OA consortium. There is no overlap between the cases involved in the arcOGEN consortium and the cases used for replication purposes using *de novo* genotyping for the Chingford Study.

Hand OA among Finnish dentists and teachers (D&T Study): Subjects were identified through the registers of the Finnish Dental Association and the Finnish Teachers' Trade Union (comprising both the occupationally active and non-active)[28]. In 2002, a questionnaire was sent to 436 female dentists (67% participation rate) and 436 female teachers (57% participation rate) randomly selected from the registers, using the place of residence (Helsinki or its neighboring cities) and age (45 to 63 years) as inclusion criteria. The mean number of years in occupation was 26 (SD 7, range 11–40) for the dentists and 24 (SD 7, range 1–37) for the teachers. 94% of the dentists and 98% of the teachers were occupationally active at the time the study was conducted. Participation in the study was voluntary and based on informed consent; altogether 543 women participated. The Hospital District of Helsinki and Uusimaa Ethics Committee for Research in Occupational Health and Safety approved the study proposal. Both hands of the participants were radiographed. Kodak x-ray films were exposed with Siemens x-ray equipment (48 kV, 10 mAs, focus film distance 115 cm). The radiographs were evaluated by an experienced radiologist who was blind to the occupation, age, and the participants' health data. The workload on the hands during the dentists' work history was estimated in detail[29].

Estonian Studies: The primary survey was conducted in two small South-Estonian towns, Elva[30] and Võru where a postal questionnaire on knee problems was sent to all 1800 subjects aged 35-55 years (three family doctors' lists). A total of 965 responses were obtained. Of all contacted subjects 417 participated in an in-depth clinical examination (KOOS questionnaire, functional knee tests, X-ray and ultrasonography of both knees) and gave blood samples for DNA and for other biomarkers. Moreover, 94 subjects (aged 35-55 years) were included which underwent arthroscopy at the Clinic of Traumatology & Orthopaedics of the Tartu University Hospital in Estonia. In all of them radiographs of the TF joint and axial radiographs of the PF joint were taken. Two independent radiologists read the radiographs according to the grading system (0-III) of Nagaosa *et al.*[31]

Both studies were approved by the Ethics Committee of the University of Tartu and informed consent was obtained from all subjects.

Finnish OA cases: Knee OA cases were 113 patients visiting ORTON Orthopaedic Hospital, Helsinki, between 1994-2001 having primary bilateral knee OA severe enough to fulfill the criteria for knee arthroplasty: pain, walking disability and radiologically at least stage 3/4 osteoarthritic changes according to Kellgren and Lawrence (K/L) classification[32]. They had not had a major knee trauma in the aetiology of OA, their pain or other OA symptoms began at a mean age of 52 y (SD 12 y), and mean age at first arthroplasty was 67 y (SD 8). The hand OA material[32] [32] was based on the set of severe DIP OA families. Eighty-five index cases with a primary criterion of ≥ 3rd degree K/L radiographic OA in DIP joints bilaterally and siblings of index cases with ≥ 2nd degree OA in DIP joints were included as affected individuals. In total the material includes 134 affected hand OA cases and 34 unaffected family members. Subjects with rheumatoid arthritis (RA) were excluded from both OA materials. The 210 control subjects were selected from the Finnish Twin Cohort study on opposite sex twins[33]. The inclusion criteria were that they were born in 1938-1941, responded to a questionnaire in 1996-1997 and gave DNA samples for analyses. One twin from each twin pair was included in the control group if neither twin had physician diagnosed OA or RA, and neither twin reported that their mother, father, co-twin or any other sibling had OA or RA. Men and women were selected using the ratio of 1:3, similarly to our case series. The study was approved by the ethics committee of the Helsinki metropolitan hospital region and all individuals gave their informed consent.

Greek clinical cases: The individuals included in this study were of Greek origin living in the district of Thessalia in central Greece[34]. All of them had undergone a TKR/THR, meaning that all of them suffered from severe knee or hip OA, which is defined by a K/L grade ≥ 2 (defined as at least 2 definite osteophytes and possible JSN). None of the patients had evidence of arthritis due to another disease. All the controls had a K/L score of 0 and had undergone treatment for injuries or

fractures. Patients with rheumatoid arthritis and other autoimmune diseases as well achondrodysplasias, infection-induced OA, and posttraumatic OA were not included in the study. This study was approved by the ethics committee of the Larissa University Hospital and all individuals gave their informed consent.

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[35]. 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 and DXA scans for assessment of BMD. Ethical approval was obtained from East and North Hertfordshire ethical committees and all participants gave written informed consent[35]. In 2004-2005, a follow-up study was performed. There were 295 men and 288 women for whom all the relevant knee X-rays were available. 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[35]. The study was approved by the local research ethics committee, and all subjects provided written, informed consent prior to participation.

Japanese Case-Control Study: Subjects are individuals living in or around Tokyo, located in mainland Japan, and visited the participating clinical institutions. All individuals with OA were symptomatic and were treated in participating institutions on a regular basis. For each individual with knee OA, standard three-direction radiographs were taken and for each individual with hip OA, anteroposterior radiographs were taken[27].

Japanese Cohort Study: This is a population-based cohort study (n=317) from habitants of Miyagawa village in the mainland of Japan. For each individual, standard three-direction knee radiographs were taken. All individuals recruited for this study were Japanese and received clinical and radiographic examinations by orthopaedic specialists. Rheumatoid arthritis (RA) and

polyarthritis associated with auto-immune diseases were excluded, as were post-traumatic OA and infection-induced OA. Individuals who had clinical and radiographic findings suggestive of skeletal dysplasias and a definitely positive Mendelian family history of OA were also excluded from the study[27].

KANON: Subjects are from a cohort of patients with anterior cruciate ligament (ACL) injury which are part of a randomized controlled trial (RCT) (Controlled-Trials.com number, ISRCTN 84752559). Subjects were recruited and screened, at two different centers (Helsingborg hospital and University Hospital Lund), aged 18–35 years, having a high to moderate physical activity level and a not more than 4 weeks old ACL rupture. Eligible patients were randomized to surgical reconstruction or non-surgical treatment after having agreed to participate in the RCT and signed informed consent. All patients were assigned to an identical rehabilitation protocol. MRI of the knees was performed within a mean of 19 (standard deviation [SD] 6.5) days after injury using a 1.5 T imager (Gyroscan, Intera, Philips, Eindhoven, The Netherlands) with a circular polarized surface coil and at regular intervals thereafter. The MRI scans consisted of sagittal three-dimensional (3D) Water excitation fast low angle shot (FLASH) with repetition time (TR)/echo time (TE)/flip angle of 20 ms/7.9 ms/25°, sagittal T2) weighted 3D gradient echo (GRE) with TR/TE/flip angle of 20 ms/15 ms/50°. Both series were acquired with 15 cm field of view (FOV), 1.5 mm slice thickness, and 0.29 x 0.29 mm pixel size[36]. Standardized standing postero-anterior X-ray films using the MTP-view[37] were obtained at baseline and at regular intervals thereafter. The Ethics Committee of the Lund University Faculty of Medicine approved the study, and informed consent was obtained from all participating subjects.

LUMEN: Patients who underwent isolated meniscectomy at Lund University Hospital in 1973, 1978, or 1983–1985 were retrospectively identified through the surgical coding system or by manual search of surgical records. A total of 456 patients fulfilled the criteria and were invited to undergo radiographic and clinical assessment in 1994, 1995, or 2000. In total, 70% of the subjects

participated in the study (n=317). The control group comprised 68 individuals who have not undergone meniscectomy and who had no clinical meniscal or cruciate ligament injury. Controls were identified using national population records[38]. In patients and controls, standing anteroposterior images of both knees in 15 degrees of flexion were. Axial views of the patellofemoral joint were obtained with a vertical beam with the subject standing with the knee in 50° of flexion. A Siemens Basic Radiological System (Siemens, Erlangen, Germany) with a film-focus distance of 1.4m at 70 kV and 10 mA was used for patients who were followed up in 1994 and 1995, and for the control subjects. For patients who were assessed in 2000, we used a Phasix 60generator (CGR, Liege, Belgium) at 70 kV, 16 mA, film-focus distance 1.5m. The Ethics Committee of the Lund University Faculty of Medicine approved the study, and informed consent was obtained from all participating subjects[39].

Malmö Diet and Cancer Study (MDC): All men and women living in the city of Malmö in Sweden, who were born between 1923 and 1945 (men) or between 1923 and 1950 (women), were invited to participate in the MDC Study[40]. The subjects were invited by letters and advertisements in newspapers. The cohort consisted of 28 449 subjects (11 246 men and 17 203 women) from the eligible population of approximately 74 000 individuals. The research ethical committee at Lund University approved the MDC Study (LU 51–90). Each participant signed a written informed consent. All participants were followed until the first osteoarthritis surgery, emigration from Sweden, death or 31 December 2005, whichever came first. Information on knee and hip arthroplasty for osteoarthritis and mortality were based on record linkage with the national Swedish hospital discharge register and the Swedish causes of death register. Knee osteoarthritis was defined as a first knee arthroplasty or high tibial osteotomy in combination with a contemporaneous diagnosis of osteoarthritis according to the International Classification of Disease (ICD) 9 and ICD-10, respectively. Hip osteoarthritis was defined as a first hip arthroplasty in combination with a contemporaneous diagnosis of hip osteoarthritis according to ICD-9 and ICD-10, respectively[40].

Nottingham Case-Control Study: For study design and objectives please see the information under the subheading arcOGEN consortium. 72% of the knee OA cases and 73% of the hip OA cases was not part of the arcOGEN consortium, but is available for replication purposes within the TREAT-OA consortium. There is no overlap between the cases involved in the arcOGEN consortium and the cases used for replication purposes using *de novo* genotyping for the Nottingham Case-Control Study.

Osteoporotic Fractures in Men Study (MrOS): The MrOS Study is a multi-center prospective, longitudinal, observational study of risk factors for vertebral and all non-vertebral fractures in older men, and of the squealed of fractures in men[41,42]. The study population consists of community dwelling, ambulatory men aged 65 years or older and were recruited from different clinical centers in the US: Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA. Inclusion criteria were designed to provide a study cohort that is representative of the broad population of older men. The inclusion criteria were: (1) ability to walk without the assistance of another, (2) absence of bilateral hip replacements, (3) ability to provide self-reported data, (4) residence near a clinical site for the duration of the study, (5) absence of a medical condition that (in the judgment of the investigator) would result in imminent death, and (6) ability to understand and sign an informed consent. To qualify as an enrollee, the participant had to provide written informed consent.

Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) Study: The ROAD Study, started in 2005, involves the collection of clinical information from 4 cohorts with participants located in urban, mountainous and coastal areas. Currently, a baseline database including 3 cohorts with in total 3,040 participants is completed. The objectives of the study are to clarify the prevalence and estimate the number of people with musculoskeletal diseases represented by knee OA, lumbar spondylosis and osteoporosis[43]. Plain radiographs with standing on both legs and the knee extended were taken with a horizontal X-ray beam unless otherwise described, using a Fuji

5000 Plus Reader on a 36 x 46 cm Fuji ST-VI Computed Radiography (CR) imaging plate (Fuji Medical Systems, Tokyo, Japan) with a 20 x 30 mm rectangular metal plate beside it as a magnification index. Rotation of the foot was adjusted to keep the second metatarsal bone parallel to the X-ray beam[44]. The study was conducted with approval of the Institutional Review Boards (IRBs) of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology, and all participants provided written informed consent.

Spanish clinical cases: Patients were selected from consecutive patients, aged 55-75 years of age at time of the surgery, undergoing THR/TKR and patients complaining of hand OA that were followed in the Rheumatology Unit[45]. All patients were included if a rheumatologist considered them to suffer from severe primary OA. Exclusion criteria were inflammatory, infectious, traumatic or congenital joint pathology and lesions due to crystal deposition or osteonecrosis. Patients with hand OA were required to fulfill the ACR criteria[46]. Controls were recruited among subjects older than 55 years of age undergoing preoperative work-up for elective surgeries other than joint surgery and who did not show clinical manifestations of OA. This study was approved by the Ethical Committee for Clinical Research of Galicia and all cases and controls gave their written informed consent to participate.

Study of Osteoporotic Fractures (SOF): The SOF Study is a multi-center cohort study initiated in 1986 to determine risk factors for osteoporotic fractures in elderly women[47]. Participants were all age > 65 years at baseline and were recruited from population-based listings at 4 clinical centers in the US: Baltimore, MD; Minneapolis, MN; Monongahela Valley, PA (near Pittsburgh); and Portland, OR. Exclusion criteria for the parent study, the SOF, included bilateral hip replacement and an inability to walk unassisted. The study was approved by the institutional review boards at each of the institutions involved. All subjects provided written informed consent at enrollment and at each clinical examination. Hip radiographs were read for individual radiographic features (IRFs) of OA using an atlas to standardize the readings[48,49]. At each of 2 time points (the baseline and 8-

year follow-up visits), each hip was rated for joint space narrowing in 2 locations (lateral and medial) and osteophytes at 4 locations (lateral femoral, lateral acetabular, inferior femoral, and inferior acetabular)[50].

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