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

Hanneke J.M. Kerkhof[1,2], **Ingrid Meulenbelt**[2,3], **Toru Akune**[4], **Nigel K. Arden**[5,6], **Arpo Aromaa**[7], **Sita M.A. Bierma-Zeinstra**[8], **Andrew Carr**[6], **Cyrus Cooper**[5,6], **Jin Dai**[9], **Michael Doherty**[10], **Sally A. Doherty**[10], **David Felson**[11], **Antonio Gonzalez**[12], **Andrew Gordon**[13,14], **Arsi Harilainen**[15], **Deborah J. Hart**[16], **Valdimar B. Hauksson**[17], **Markku Heliovaara**[7], **Albert Hofman**[2,18], **Shiro Ikegawa**[19], **Thorvaldur Ingvarsson**[20], **Qing Jiang**[9], **Helgi Jonsson**[21], **Ingileif Jonsdottir**[17,21], **Hiroshi Kawaguchi**[22], **Margreet Kloppenburg**[23], **Urho M. Kujala**[24], **Nancy E. Lane**[25], **Paivi Leino-Arjas**[26], **Stefan Lohmander**[27], **Frank P. Luyten**[28], **Konstantinos N. Malizos**[29], **Masahiro Nakajima**[19], **Michael C. Nevitt**[25], **Huibert A.P. Pols**[1], **Fernando Rivadeneira**[1,2,18], **Dongquan Shi**[9], **Eline Slagboom**[2,3], **Tim D. Spector**[16], **Kari Stefansson**[17,21], **Akihiro Sudo**[30], **Agu Tamm**[31], **Ann E. Tamm**[32], **Aspasia Tsezou**[29], **Atsumasa Uchida**[30], **André G. Uitterlinden**[1,2,18], **Jeremy Mark Wilkinson**[13,14], **Noriko Yoshimura**[33], **Ana M. Valdes**[16], and **Joyce B.J. van Meurs**[1,2]

[1]Department of Internal Medicine, Erasmus Medical Center Rotterdam, Rotterdam, the Netherlands [2]The Netherlands Genomics Initiative-sponsored Netherlands Consortium for Healthy Aging (NGI-NCHA), Rotterdam/Leiden, the Netherlands [3]Department of Molecular Epidemiology, Leiden University Medical Center, Leiden, the Netherlands [4]Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, The University of Tokyo, Tokyo, Japan [5]MRC Epidemiology Resource Centre University of Southampton, Southampton General Hospital, Southampton, United Kingdom [6]NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford England Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences University of Oxford, Oxford, United Kingdom [7]The National Institute for Health and Welfare (THL), Helsinki, Finland [8]Department of General Practice, Erasmus Medical Center Rotterdam, Rotterdam, the Netherlands [9]Center of Diagnosis and Treatment for Joint Disease, Nanjing DrumTower Hospital, The affiliated Hospital of Nanjing

Corresponding author/address for reprint requests: Hanneke JM Kerkhof, Genetic Laboratory Department of Internal Medicine Room Ee2183, Erasmus MC, MC PO Box 1738, 3000 DR Rotterdam, the Netherlands, Telephone number: +31107044292, j.m.kerkhof@erasmusmc.nl.

Author Contribution: Responsible for the integrity of the work as a whole: JBJ van Meurs and HJM Kerkhof.
Conception and design: HJM Kerkhof, TD Spector, AM Valdes, JBJ van Meurs, AG Uitterlinden, I Meulenbelt.
Analysis and interpretation of data: HJM Kerkhof, NE Lane, NK Arden, I Meulenbelt, N Yoshimura, A Tamm, MC Nevitt, UM Kujala, P Leino-Arjas, D Felson, FP Luyten, AM Valdes, JBJ van Meurs, M Kloppenburg, F Rivadeneira, S Lohmander, TD Spector.
Drafting of the article: HJM Kerkhof, AM Valdes, JBJ van Meurs
Critical revision of the article: all authors
Final approval of the article: all authors
Provision of study material or patients: I Meulenbelt, NK Arden, A Aromaa, A Carr, C Cooper, J Dai, M Doherty, SA Doherty, D Felson, A Gonzalez, DJ Hart, M Heliovaara, A Hofman, S Ikegawa, T Ingvarsson, Q Jiang, H Jonsson, I Jonsdottir, UM Kujala, NE Lane, P Leino-Arjas, S Lohmander, MC Nevitt, E Slagboom, TD Spector, K Stefansson, A Tamm, A Tsezou, JM Wilkinson, JBJ van Meurs, AG Uitterlinden, AM Valdes, N Yoshimura
Collection of data: T Akune, J Dai, A Gordon, A Harilainen, VB Hauksson, H Kawaguchi, M Kloppenburg, M Nakajima, D Shi, A Sudo, AE Tamm, A Uchida, I Meulenbelt, NK Arden, A Aromaa, A Carr, C Cooper, J Dai, M Doherty, SA Doherty, D Felson, A Gonzalez, DJ Hart, M Heliovaara, A Hofman, S Ikegawa, T Ingvarsson, Q Jiang, H Jonsson, I Jonsdottir, UM Kujala, NE Lane, P Leino-Arjas, S Lohmander, MC Nevitt, E Slagboom, TD Spector, K Stefansson, A Tamm, A Tsezou, JM Wilkinson, JBJ van Meurs, AG Uitterlinden, AM Valdes, N Yoshimura, HJM Kerkhof, JM Wilkinson.

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University Medical School, Nanjing, China [10]Academic Rheumatology, Clinical Sciences Building, Nottingham City Hospital Hucknall Road, Nottingham, United Kingdom [11]Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA, United States of America [12]Laboratorio Investigacion and Rheumatology Unit, Hospital Clinico Universitario Santiago, Santiago de Compostela, Spain [13]Academic Unit of Bone Metabolism, Department of Human Metabolism, University of Sheffield, Sheffield, United Kingdom [14]Sheffield NIHR Bone Biomedical research Unit, Centre for Biomedical Research, Northern General Hospital, Sheffield, United Kingdom [15]ORTON Orthopedic Hospital, Invalid Foundation, Helsinki, Finland [16]Department of Twin Research and Genetic Epidemiology, St. Thomas' Hospital, King's College London, London, United Kingdom [17]deCODE Genetics, Reykjavik, Iceland [18]Department of Epidemiology, Erasmus Medical Center Rotterdam, Rotterdam, the Netherlands [19]Laboratory for Bone and Joint Diseases, Center for Genomic Medicine, RIKEN, Japan [20]FSA University Hospital, Institution of Health Science, University of Akureyri, Akureyri, Iceland [21]Department of Medicine, Landspitali University Hospital and Faculty of Medicine, University of Iceland, Reykjavik, Iceland [22]Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan [23]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands [24]Department of Health Sciences, University of Jyväskylä, Jyväskylä, Finland [25]University of California at San Francisco and University of California at Davis, Sacramento, United States of America [26]Finnish Institute of Occupational Health, Helsinki, Finland [27]Department of Orthopedics, Clinical Sciences, Lund University, Lund, Sweden [28]Laboratory for Skeletal Development and Joint Disorders, Division of Rheumatology, Katholieke Universiteit Leuven, Belgium [29]Department of Biology and Genetics, University of Thessaly, Larissa, Greece [30]Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, Japan [31]Department of Internal Medicine, University of Tartu, Estonia [32]Department of Sport Medicine and Rehabilitation, Univerity of Tartu, Estonia [33]Department of Joint Disease Research, 22nd Century Medical and Research Center, The University of Tokyo Hospital, The University of Tokyo, Tokyo, Japan

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. To investigate whether different OA definitions result in different association results, we created hip OA definitions used within the consortium in the Rotterdam Study-I and tested the association of hip OA 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 ($p=3\times10^{-9}$). 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. Standardization of SOA phenotypes was not possible due to the case-control design of the studies.

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 will examine the effect of heterogeneity among symptomatic (SOA) and radiographic osteoarthritis (ROA) phenotypes and address the need for standardization of osteoarthritis phenotypes. We will 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). For the GARP Study, subjects were recruited with clinical and radiographic confirmed OA at two or more joint sites among hand, spine, knee or hip[16]. If a subject was selected on the basis of hip and hand SOA for example, but the objective of a future study is knee OA, this subject might have ROA of the knee. We can neither call this pure knee ROA nor SOA since the subject was selected on the basis of having symptoms of generalized OA, but the assessment of knee OA is radiographic. In addition, the Finnish cases consist of 2 subsets with subjects affected with SOA and ROA of the hand and affected siblings with ROA of the hand[17]. In this study, we have chosen to classify the GARP Study and the Finnish cases as studies with 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.

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%, $p=3\times10^{-9}$), 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 ($p=3\times10^{-9}$), 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.

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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.

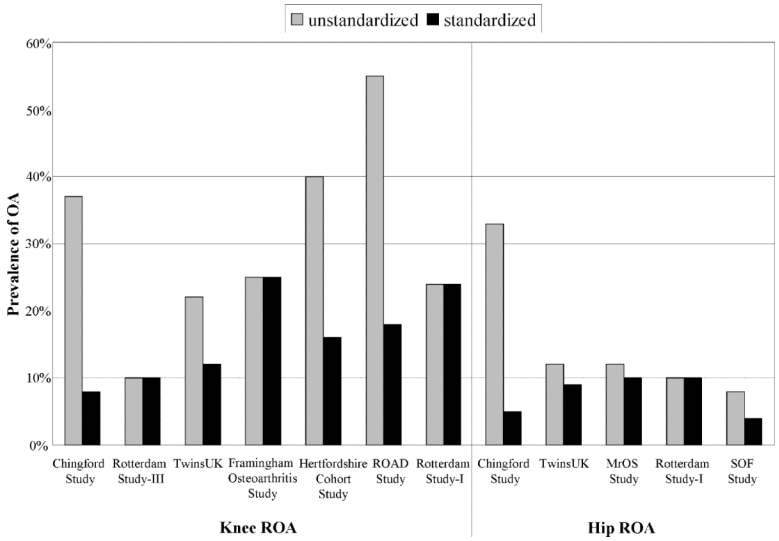

Figure 1.
Prevalence of knee and hip OA before and after standardization of the ROA phenotypes.

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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
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]

Study	Reference article	Study design	Ethnic origin	Country of origin	Joint site	ROA/SOA	Age/BMI	% women	Follow-up data
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; 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

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

[a] age is available for all subjects, BMI only for part of the subjects

[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&TStudy	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 ≥ 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	3×10^{-8}	26.3	26.3	0.99
One definite osteophyte	1906	1373	54%	64%	3×10^{-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	8×10^{-11}	26.9	26.3	0.18
ROA (original K/L ≥ 2) + pain	58	3221	79%	57%	0.001	69.9	65.8	3×10^{-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**
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	-	-

Study	Knee OA		Hip OA		Thumb OA	
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**

NA = not applicable

OA = osteoarthritis

[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

[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)