Chapter 11

Identification of phenotypes with different clinical outcomes in knee osteoarthritis: data from the Osteoarthritis Initiative

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Abstract

Objective. To identify subgroups or phenotypes of knee osteoarthritis (OA) patients based on similarities on clinically relevant patient characteristics, and to compare clinical outcomes of these phenotypes.

Methods. Data from 842 knee OA patients of the Osteoarthritis Initiative were used. A cluster analysis method was performed, in which clusters were formed based on similarities in 4 clinically relevant, easily available variables: severity of radiographic OA, lower limb muscle strength, body mass index, and depression. Univariable and multivariable regression analyses were used to compare phenotypes on clinical outcomes (pain and activity limitations), taking into account possible confounders.

Results. Five phenotypes of knee OA patients were identified: 'minimal joint disease phenotype', 'strong muscle phenotype', 'non-obese and weak muscle phenotype', 'obese and weak muscle phenotype', and 'depressive phenotype'. The 'depressive phenotype' and 'obese and weak muscle phenotype' showed higher pain levels and more severe activity limitations than the other 3 phenotypes.

Conclusion. Five phenotypes based on clinically relevant patient characteristics can be identified in the heterogeneous population of knee OA patients. These phenotypes showed different clinical outcomes. Interventions may need to be tailored to these clinical phenotypes.

Introduction

The population of knee osteoarthritis (OA) patients is heterogeneous (1;2), characterized by variations in pathophysiologic etiologies (2;3), disease progression (4), underlying mechanisms of osteoarthritis pain (5), severity of pain and activity limitations (clinical outcome) (1), functional decline (6), and treatment response (1). It has been hypothesized that the heterogeneous population of knee OA patients actually consists of different subgroups or phenotypes (1;3).

The identification of different phenotypes of knee OA patients may be highly relevant to disease treatment (2). Current treatment recommendations for knee OA are intended to provide symptomatic relief (7), but not all patients respond similarly to treatment (1). Therefore, it has been theorized that treatment may need to be tailored to phenotypes of knee OA patients to optimize its effect (1-3), preferably in a cost-effective manner (8). If a treatment is exclusively effective in one particular phenotype, this effect might be missed when examined in a population consisting of more than one phenotype (3;9).

To identify clinically relevant phenotypes, phenotypes could be formed based on similarities in characteristics that: (i) are regularly assessed in clinical practice (3), (ii) show large variations between subjects (10), and (iii) have major impact on disease progression and/or clinical outcome (3). In addition, characteristics should preferably be amenable to treatment. Based on their relevance to clinical practice, we choose 4 patient characteristics to identify clinical phenotypes in a knee OA population: radiographic severity of OA (ROA), muscle strength, body mass index (BMI), and depression.

ROA is the primary modality for disease diagnosis and classification in clinical practice (11). Large variations in ROA are common among symptomatic knee OA patients ranging from no to severe structural disease (12). There is evidence for a relationship between ROA and clinical outcome, although this evidence is conflicting (4;11;12).

Muscle strength of the lower limb is an important characteristic in clinical practice in knee OA (13). Muscle weakness is highly prevalent among knee OA patients (14) and large variations in muscle strength between knee OA patients have been reported (15). Muscle weakness is a risk factor for knee OA onset (14) and progression (16), poor clinical outcome (17), and functional decline in knee OA (6).

Obesity is a common comorbidity in knee OA (18) and large variations in BMI in knee OA patients have been reported (19). High BMI is strongly related to knee OA onset and progression (18;20), poor clinical outcome (17;19), and functional decline in knee OA (6).

Depressive symptoms are more prevalent in knee OA patients than in healthy persons (21) and are varying from no depressive symptoms to major depression among knee OA patients (17). Depression is an important risk factor for poor clinical outcome (17) and functional decline (6) in knee OA.

We hypothesize that clinical phenotypes can be identified in the heterogeneous population of knee OA patients based on similarities in the 4 patient characteristics mentioned above. We hypothesize the existence of a phenotype of non-obese knee OA patients with high muscle strength, demonstrating relatively good clinical outcomes, regardless of the presence of severe ROA. In addition, we hypothesize a phenotype of obese knee OA patients with low muscle strength (i.e., dynapenic-obesity (22)), demonstrating poor clinical outcomes, even in the absence of severe ROA. Finally, we hypothesize the existence of a phenotype of knee OA patients with depressive symptoms, demonstrating poor clinical outcomes, even in the absence of severe ROA.

The first aim of the present study is to identify clinical phenotypes based on similarities on 4 patient characteristics. The second aim is to compare clinical outcomes of the identified phenotypes.

Patients and methods

We used data from the 2-year follow-up visits of the 'progression subcohort' of the Osteoarthritis Initiative (OAI) database. This database is available for public access at http://www.oai.ucsf.edu (dataset version 9, version 3.1 and 3.2.1). Subjects were eligible for the 'progression subcohort' if they have both of the following in at least 1 knee at baseline: frequent knee symptoms in the past 12 months defined as 'pain, aching or stiffness in or around the knee on most days' for at least 1 month during the past 12 months, and radiographic tibiofemoral knee OA, defined as definite tibiofemoral osteophytes (Osteoarthritis Research Society International [OARSI] atlas grades 1-3 (23)) on the baseline fixed-flexion radiograph. From a total of 1,389 participants from the 'progression subcohort', 842 participants with complete data on ROA, muscle strength, BMI, and depression at the 2-year follow-up visits were included in our study.

Measures

Clustering variables. Radiographic severity of knee OA was scored by an overall severity score (Kellgren/Lawrence [K/L] score) (24) of the most severely damaged knee ranging from 0 to 4, based on weightbearing fixed-flexion knee radiograph. Mean score of left and right lower limb isometric muscle strength (quadriceps and hamstring strength in newtons) was used as a measure for muscle strength (13;25). BMI was calculated by dividing weight (in kilograms) by squared height (in meters). A person with BMI greater than or equal to 30.0 kg/m^2 is defined as obese (26). Depression was based on the score on the Center for Epidemiologic Studies-Depression Scale (CES-D) questionnaire, which is one of the most frequently used questionnaires for depressive experiences with very strong psychometric properties (27). The CES-D is a 20-item measure with a sum score ranging from 0 to 60, in

which a score >16 is indicative of mild depression and a score ≥27 is indicative of major depression (28). Data from the 2-year follow-up visits were used.

Clinical outcome variables. Two variables for knee pain and 2 variables for activity limitations, all measured at 2-year follow-up, were used to assess clinical outcome. Knee pain was measured by an 11-point numeric rating scale (NRS) ranging from 0-10 (where 0 indicates no pain) for self-reported knee pain during the last week (29) and by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale ranging from 0-20 (where 0 indicates no pain) (30). Activity limitations were assessed by WOMAC physical function subscale ranging from 0-68 (where 0 indicates no activity limitations) (30) and by a 20-meter walking test (31). The NRS questionnaire and both WOMAC questionnaires had been obtained for each knee separately; we used the mean score for left and right knee for our analyses. The 20-meter walking test was performed twice; again we used the mean score for our analyses.

Possible confounders. Age, sex, duration of knee symptoms, bilateral knee pain, co-occurrence of hip pain, and number of comorbidities were obtained by questionnaires at the 2-year follow-up visit. Duration of knee symptoms was categorized as follows: 1 year or less, 2-5 years, and more than 5 years. Co-occurrence of hip pain was assessed as follows: any pain, aching or stiffness in the hip in the past 12 months, including pain in groin and in front and sides of upper thigh. Bilateral knee pain was present when the NRS for self-reported knee pain during the last week was 1 or higher in both knees. Number of comorbidities was assessed by the Charlson Comorbidity Index (32).

Statistical analysis

Firstly, descriptives of the total study group were analyzed on clustering variables and possible confounders.

Secondly, a cluster analysis method was used to identify relatively homogeneous phenotypes in the knee OA population. Cluster analysis is a statistical technique that identifies subgroups of individuals that are similar to each other in certain clustering variables, but different from individuals in other groups. The technique aims to achieve the highest within-group homogeneity, as well as the lowest between-group homogeneity. *K*-means clustering is a specific cluster analysis method that does not require to specify the number of clusters in advance. A *k*-means algorithm will calculate the most optimal solution with *k* number of clusters (33).

The 4 clustering variables (ROA, muscle strength, BMI, and depression) were standardized as ([score–mean]/standard deviation) before cluster analysis, because of differences in measurement unit (10). Cluster analysis techniques are sensitive to outliers

(34), therefore outliers were first identified (based on a principal component plot of the 4 clustering variables) and removed from the dataset.

The FASTCLUS procedure, i.e., a *k*-means algorithm with a nearest centroid sorting method, from the SAS package (35) was used to perform cluster analysis. Determination of the optimal number of clusters (3 or more) in the dataset was based on 2 recommended clustering criteria (36), both using a ratio of the sum of squares within clusters and sum of squares between clusters: Calinski and Harabasz *F* (37), which is suggested to be the best clustering criterion (36) and frequently used in other studies (38;39), and Beale's *F* (40;41). A cluster solution of c clusters was the most optimal solution if both *F* values were the highest and if a significant increase ($P<0.05$) in Beale's *F* after comparison with *c*-1 clusters was found. Furthermore, validity of the cluster analysis was analyzed by randomly splitting the dataset into 2 halves and repeating the same cluster analysis on each half. Similar (number of) clusters on each half indicate that the results of the cluster analysis were valid (33).

Thirdly, we compared clinical outcomes of the identified phenotypes by univariable and stepwise multivariable regression analyses in SPSS version 15.0 (SPSS, Chicago, USA). Univariable linear regression analyses were used to test the null hypothesis of similar clinical outcomes of the phenotypes, with a level of significance of 0.05. A significant regression coefficient indicates a statistical difference between 2 phenotypes. Independent variable in these analyses was the phenotype classification (by using dummy variables). Dependent variable was 1 of the 4 clinical outcome variables (NRS pain**,** WOMAC pain, WOMAC physical function and 20-meter walking test). Multivariable linear regression analyses were used to test if possible confounders were (partly) responsible for differences in clinical outcome between phenotypes. Six possible confounders (age, sex, duration of knee symptoms, bilateral knee pain, co-occurrence of hip pain, and number of comorbidities) that may affect clinical outcome were added to the multivariable regression analysis one at a time. If the addition of a possible confounder to the model resulted in a 10% change (or more) of the regression coefficient, it was kept in the model (42). After correction for possible confounders, differences between phenotypes on the clinical outcome variable were statistically tested again with a level of significance of 0.05.

Results

Identification of phenotypes. Table 1 displays the characteristics of the study sample. The mean ± SD age of the total group was 63.2 ± 9.1 years and 55% of the 842 included patients were women. Knee symptoms were present for more than 5 years in one-half of the persons (46%) and almost two-thirds of the study group had bilateral knee pain (62%). Radiographic evidence of knee OA (i.e., K/L score ≥2) was found in 84% of the persons, while 60% had evidence of moderate to severe knee OA (i.e., K/L score 3-4). Almost half of the persons

were obese (46%) and 1 out of 10 persons (10%) had mild or major symptoms of depression according to the CES-D.

We identified 1 outlier and removed this case from the dataset. As showed in Table 2, *F* values of both clustering criteria were the highest in a 5-cluster solution, indicating that the optimal number of clusters in this dataset was 5. Beale's *F* statistics also revealed that a 5-cluster solution showed a significant improvement of the model's fit compared to a 4-cluster solution, while a 6-cluster solution did not show a significant improvement of the model's fit compared to a 5-cluster solution.

Table 1. Characteristics of study group

	Value (*n*=842)
Age, mean ± SD years	63.2 ± 9.1
Women, %	55
Duration of knee symptoms, %	
Less than 1 year	15
Between 2 and 5 years	39
More than 5 years	46
Bilateral knee pain, % yes	62
Co-occurrence of hip pain, % yes	56
No. of comorbidities, median (IQR)	0 (1)
Radiographic knee OA, %	
K/L score 0	9
K/L score 1	7
K/L score 2	24
K/L score 3	40
K/L score 4	20
Muscle strength, mean ± SD N	223.8 (89.0)
BMI, mean ± SD kg/m^2	29.9 (4.8)
Obesity (BMI ≥30.0), %	46
CES-D score, median (IQR)	5 (7.5)
Depression (CES-D >16), %	10

IQR=interquartile range; OA=osteoarthritis; K/L=Kellgren/ Lawrence; BMI=body mass index; CES-D=Center for Epidemiologic Studies Depression Scale.

Table 2. Clustering criteria for solution of 3 or more clusters (5-cluster solution in bold)

number of clusters	**Calinski and Harabasz *F*** (37)	**cluster comparison**	**Beale's *F* (df[a], df[b])** (40)	**Beale's *F* (*P* value)** (41)
3	183.01	-	-	-
4	211.55	3 vs 4	1.44 (65, 419)	0.02
5	**245.77**	**4 vs 5**	**1.99 (45, 374)**	**< 0.001**
6	217.60	5 vs 6	0.61 (33, 341)	0.96

[a] numerator degrees of freedom; [b] denominator degrees of freedom.

Validity of the 5-cluster solution appeared to be good, as this solution was the most suitable solution in both (randomly split) halves of the dataset as well. Furthermore, almost all subjects (99%) were allocated in similar clusters when cluster analysis was performed in one of both halves, compared to the cluster analysis of the original dataset (data not shown).

Descriptives on the clustering variables of the 5 phenotypes and the total study group are shown in Table 3. The 5 phenotypes were characterized by: (i) mostly no or doubtful evidence of ROA, average muscle strength, and low prevalences of obesity (26%) and depression (5%) ('minimal joint disease phenotype'); (ii) high muscle strength, moderate to severe ROA, obesity in 48% of participants, and low prevalence of depression (1%) ('strong muscle phenotype'); (iii) muscle weakness, low prevalence of obesity (18%), moderate to severe ROA, and low prevalence of depression (0%) ('non-obese and weak muscle phenotype'); (iv) obesity in all participants (100%), muscle weakness, mild to moderate ROA, and low prevalence of depression (1%) ('obese and weak muscle phenotype'); and (v) prevalence of depression in almost all participants (88%), mild to moderate ROA, muscle weakness, and obesity in 58% of participants ('depressive phenotype').

The 'strong muscle phenotype' was mostly male (6% women), while the 'non-obese and weak muscle phenotype', 'obese and weak muscle phenotype' and 'depressive phenotype' were mostly female (ranging from 70-80% female) and the 'minimal joint disease phenotype' was mixed (49% women). The mean age in the 'non-obese and weak muscle phenotype' was higher (67.2 years) than in the other phenotypes (ranging from 60.0-62.1 years). Long-lasting knee symptoms (symptom duration >5 years) were less present in the 'minimal joint disease phenotype' (39%), compared to the other phenotypes (ranging from 45-52%). A majority of the persons from the 'strong muscle phenotype' ever had knee surgery or arthroscopy (56%), while prevalence of knee surgery or arthroscopy in other phenotypes ranged from 22-36%.

Differences in clinical outcomes. Figure 1 shows the 4 clinical outcome variables of each of the 5 phenotypes. Overall, the 'minimal joint disease phenotype' was clinically the least affected phenotype, followed by 'strong muscle phenotype', 'non-obese and weak muscle phenotype', 'obese and weak muscle phenotype' and 'depressive phenotype'.

Univariable regression analyses revealed 33 significant differences between phenotypes on the 4 clinical outcome variables, while 7 comparisons were not significantly different (data not shown). In the multivariable regression analyses, 31 phenotype-differences appeared to be significant after adjusting for possible confounders (age, sex, duration of knee symptoms, bilateral knee pain, co-occurrence of hip pain, and number of comorbidities) (Table 4). The clinically most affected phenotypes were the 'obese and weak muscle phenotype' and the 'depressive phenotype', with significantly worse outcomes on

Table 3. Descriptives of phenotypes on clustering variables (mean and standard deviation, unless other stated)

	'Minimal joint disease phenotype' (*n*=140)	**'Strong muscle phenotype' (*n*=189)**	**'Non-obese and weak muscle phenotype' (*n*=261)**	**'Obese and weak muscle phenotype' (*n*=168)**	**'Depressive phenotype' (*n*=83)**	**Total study group (*n*=841)**
Radiographic OA:						
K/L score 0 (%)	49	1	0	1	4	9
K/L score 1 (%)	35	2	0	2	5	7
K/L score 2 (%)	16	21	21	39	24	24
K/L score 3 (%)	0	52	47	46	47	40
K/L score 4 (%)	0	24	33	12	21	20
Muscle strength, N	241.5 (76.9)	339.1 (63.5)	170.4 (43.2)	180.6 (53.6)	188.1 (72.7)	223.8 (89.0)
Body mass index, kg/m^2	27.5 (3.9)	29.9 (3.4)	27.0 (3.0)	35.9 (3.5)	31.0 (4.6)	29.9 (4.8)
Obesity (BMI ≥30.0) (%)	26	48	18	100	58	46
CES-D score (median and IQR)	5 (6)	3 (4.5)	4 (6)	5 (6)	21 (7)	5 (7.5)
Depression (CES-D >16) (%)	5	1	0	1	88	10

IQR = interquartile range.

Table 4. Clinical outcomes of phenotypes (mean and standard deviation)

	'Minimal joint disease phenotype' (*n*=140)	**'Strong muscle phenotype' (*n*=189)**	**'Non-obese and weak muscle phenotype' (*n*=261)**	**'Obese and weak muscle phenotype' (*n*=168)**	**'Depressive phenotype' (*n*=83)**	**Total study group (*n*=841)**
Pain:						
NRS pain	2.5 (2.4)	2.8 (2.0)	3.3 (2.2)*	4.3 (2.6)*†‡	4.3 (2.6)*†‡	3.4 (2.4)
WOMAC-pain	2.1 (2.2)	2.6 (2.2)*	3.5 (3.0)*	4.5 (3.4)*†‡	5.3 (3.9)*†‡§	3.4 (3.1)
Activity limitations:						
WOMAC-physical function	6.8 (8.5)	8.1 (8.1)	11.3 (9.8)*	16.2 (12.0)*†‡	17.4 (12.5)*†‡	11.4 (10.7)
20-meter walking test, seconds	15.1 (2.0)	14.7 (1.9)	16.2 (2.6)*†	17.9 (3.4)*†‡	17.3 (5.0)*†‡	16.1 (3.1)

* significant worse clinical outcome compared to 'minimal joint disease phenotype', corrected for confounding (*P*<0.05);
† significant worse clinical outcome compared to 'strong muscle phenotype', corrected for confounding (*P*<0.05);
‡ significant worse clinical outcome compared to 'non-obese and weak muscle phenotype', corrected for confounding (*P*<0.05);
§ significant worse clinical outcome compared to 'obese and weak muscle phenotype', corrected for confounding (*P*<0.05).

both pain outcomes and both activity limitation outcomes than the other 3 phenotypes, as shown in Table 4. Furthermore, the 'depressive phenotype' demonstrated significantly higher WOMAC-pain scores than the 'obese and weak muscle phenotype' as well (5.3 versus 4.5). The 'minimal joint disease phenotype' demonstrated significantly lower pain levels and less severe activity limitations than the other phenotypes, except for the 'strong muscle phenotype'.

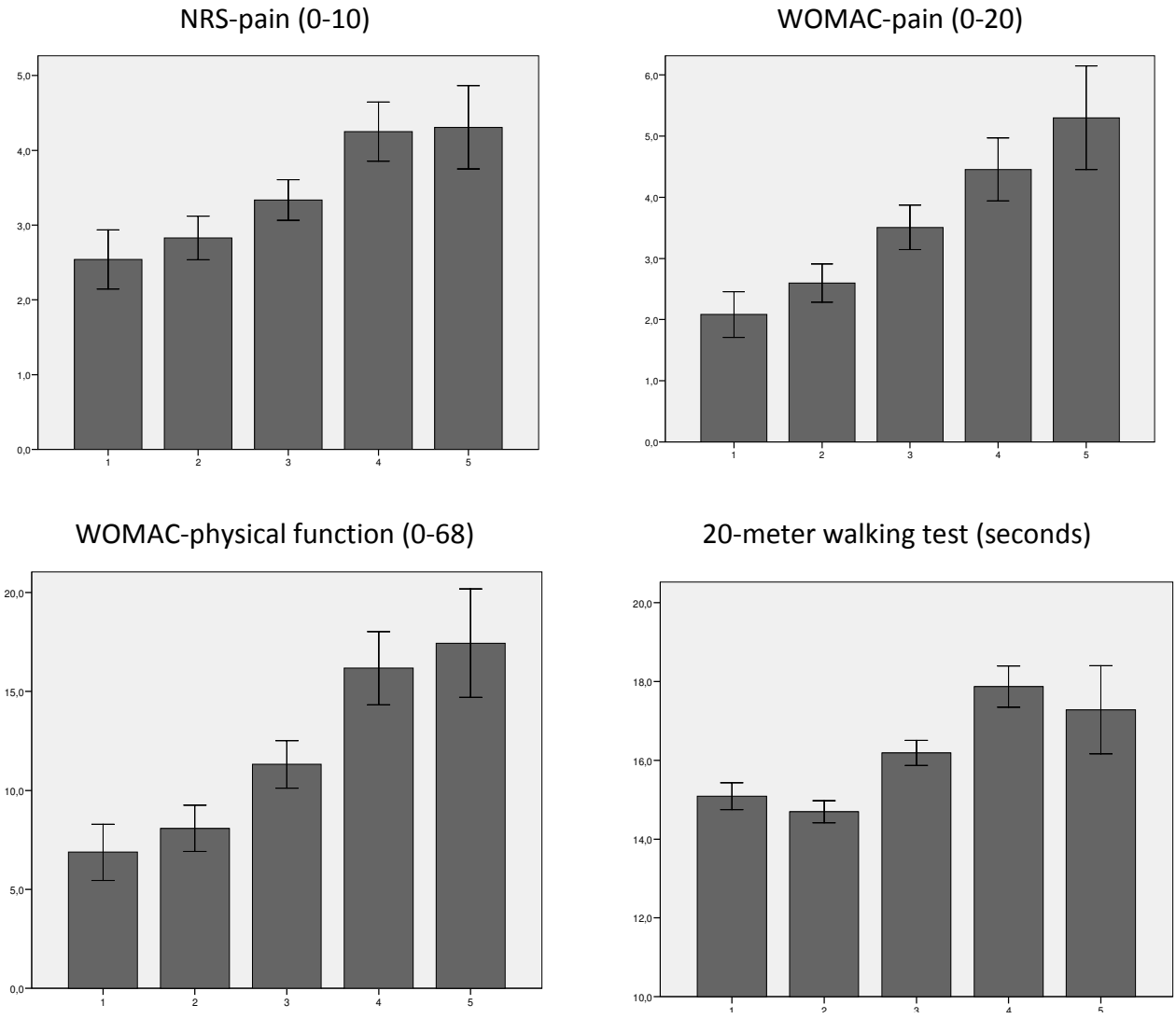

Fig. 1. Clinical outcomes of phenotypes (mean and 95% confidence interval)

Discussion

It has been suggested that the heterogeneous knee OA population can be divided into clinical phenotypes (1;3). As far as we know, we are the first to identify clinical phenotypes in a knee OA population. To identify phenotypes, we used a statistical technique, i.e., cluster analysis, that is designed to find meaningful homogeneous subgroups (10). We used 4 clinically relevant, easily available characteristics (ROA, muscle strength, BMI, and depression) to identify phenotypes. Hypothetically, the 4 characteristics could have divided the study population into numerous phenotypes. Cluster analysis revealed that in reality only 5 phenotypes exist.

Prior to the study, we hypothesized the existence of some particular phenotypes of knee OA patients. These particular phenotypes concerned a group of non-obese knee OA patients with high muscle strength, a group of knee OA patients with dynapenic-obesity (i.e., combination of low muscle strength and high BMI (22)), and a group of depressive knee OA patients. Our study demonstrated that these phenotypes actually do exist in the knee OA population, by identifying a 'strong muscle phenotype' (although this phenotype showed average BMI), 'obese and weak muscle phenotype' and a 'depressive phenotype', respectively. Furthermore, 2 other phenotypes of knee OA patients were identified: a 'minimal joint disease phenotype' and a 'non-obese and weak muscle phenotype'. This classification into 5 phenotypes reduced heterogeneity in the knee OA population, as clinical patient characteristics that were used for cluster analysis showed lower variations within each phenotype, compared to the variations in the total study group (Table 3). Almost all 5 phenotypes differed significantly from each other in their level of pain and activity limitations (Table 4). Furthermore, most of these phenotype-differences are clinically relevant and meaningful as well, based on a minimal clinically important difference of 15% (43;44). Differences between phenotypes had been analyzed based on person-specific outcomes on pain and activity limitations (i.e., mean score for both knees). Similar results were found when using knee-specific outcomes (data not shown).

The 5 identified phenotypes may represent different pathophysiologic etiological subtypes of OA. In the 'minimal joint disease phenotype', structural disease is hardly present. Furthermore, knee symptom duration is lower than in the other 4 phenotypes, which could imply an early OA subtype. The 'strong muscle phenotype' might be a subtype of severe ROA patients (76% with moderate to severe ROA) with posttraumatic OA, who are still physically active, as shown by strong lower limb muscles. In our study, history of knee surgery or arthroscopy was indeed more common in this phenotype (56%) compared to other phenotypes (22-36%). The 2 weak muscle phenotypes might consist of physically inactive persons, in which inactivity has resulted in muscle weakness only ('non-obese and weak muscle phenotype') or in dynapenic-obesity ('obese and weak muscle phenotype'). Because the age of persons from the 'non-obese and weak muscle phenotype' was on

average 6 years higher than all other phenotypes, this phenotype may represent an age-induced knee OA subtype, in which age-related changes in the musculoskeletal system (45) may have initiated knee OA development. The 'obese and weak muscle phenotype' could represent a biomechanically-induced knee OA subtype, in which overload of the knee joint may have caused OA (14;16;46). In addition, metabolic changes that are linked to obesity could have played a role in knee OA etiology in this subtype, as demonstrated by recent literature (46). Finally, persons of the 'depression phenotype', who are demonstrating highest levels of pain and activity limitations, might represent a subtype of knee OA persons in which depression have resulted in an intensified focus on pain-related stimuli (cognitive effect), increased sensitization of the central nervous system on pain stimuli (neurophysiological effect), and physical inactivity (behavioural effect) (47). These hypotheses of possible knee OA subtypes need further support from evidence.

The phenotype differences on all 4 clinical outcomes in our study may underscore the well-known importance of knee OA risk factors for clinical practice. The presence of only 1 risk factor (i.e., severe ROA in 'strong muscle phenotype' and low muscle strength in 'non-obese and weak muscle phenotype') or no risk factors at all (i.e., 'minimal joint disease phenotype') seem to result in only mild pain levels and few activity limitations. On the other hand, the presence of multiple knee OA risk factors (i.e., obesity and muscle weakness in 'obese and weak muscle phenotype') are likely to have a stronger effect on clinical outcome. Psychosocial factors seem to have even larger effects on clinical outcome in knee OA, as indicated by the outcomes of the 'depressive phenotype'.

We would like to make a number of comments on our study. Firstly, we demonstrated that the identification of 5 phenotypes was a valid result in our dataset (i.e., the same results were obtained in randomly split halves of dataset). Because our study population might not be generalizable to other knee OA populations, studies in other datasets are needed to replicate our findings. Additionally, it would be interesting to include healthy age- and sex-matched controls in these studies, to be able to compare phenotype-characteristics with normative scores. Secondly, although we explained some of the heterogeneity of the knee OA population by identifying phenotypes, there is still overlap between phenotypes, as shown by standard deviations in clustering variables and clinical outcome variables. Thirdly, we identified phenotypes based on similarities in 4 patient-specific characteristics, namely radiographic severity of OA, muscle strength, body mass index, and depression. We chose these characteristics based on their clinical relevance. Also other patient characteristics could be chosen, for example biomechanical (e.g., alignment, laxity, proprioceptive accuracy), psychosocial (e.g., anxiety, self-efficacy), or genetic factors. These characteristics could have explained some of the variation in clinical outcome within the identified phenotypes in our study. Furthermore, knee-specific or compartment-specific variables (for example, features from radiography or magnetic resonance imaging (MRI)) might be appropriate to identify meaningful phenotypes as well. MRI features may be

preferred over radiographic features, since the former have shown to be more strongly associated with clinical outcome than the latter (48). Fourthly, we included persons from the OAI study, a longitudinal cohort study. These persons could have had treatments prior or during the OAI follow-up visits. We did not adjust for differences in treatments between phenotypes, because of 'bias by indication', i.e., treatment application depends on clinical patient characteristics that have been used for cluster analysis. Consequently, it is not feasible to correct for differences in treatment. Finally, no statements can be made on causal relationships between phenotype characteristics and clinical outcome because of the cross-sectional design of our study.

Our classification into 5 phenotypes of knee OA patients may have major implications for clinical practice. Because the knee OA population is heterogeneous, interventions may need to be tailored to specific homogeneous phenotypes of knee OA patients to optimize overall effectiveness of knee OA interventions (1-3) in a cost effective manner (8). International guidelines recommend a combination of pharmacological and non-pharmacological interventions for the general knee OA population (7). Each of the 5 identified phenotypes may need to receive different tailored interventions. For example, patients from the 'depressive phenotype' may benefit most of a combination of interventions, in which an educational program, a cognitive-behavioral therapy, and an exercise therapy with graded activity levels are included (47), while in some patients the additional use of antidepressants may also be indicated. Patients from the 'obese and weak muscle phenotype' may need an intervention that focuses on both weight loss and muscle strengthening (49), while muscle strengthening exercises only could be sufficient for persons from the 'non-obese and weak muscle phenotype'. Most of the persons from the 'strong muscle phenotype' are not likely to benefit from exercise therapy. These persons, diagnosed with severe ROA, might be candidates for orthopedic surgery if pain and activity limitations are severe. Finally, persons from the 'minimal joint disease phenotype' may not be in need for specific treatment, although an educational program and instructions for home-based exercises could have beneficial effects for long-term clinical outcomes. Knowledge on tailored interventions is limited and more research will be needed to evaluate differences in response to specific interventions in various phenotypes and to evaluate the effectiveness of tailored interventions in specific phenotypes.

To conclude, 5 phenotypes can be identified in the heterogeneous population of knee OA patients based on clinically relevant patient characteristics. These phenotypes showed different clinical outcomes. Interventions may need to be tailored to these phenotypes.

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