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Incidence, prevalence, natural course and prognosis of patellofemoral osteoarthritis: the Cohort Hip and Cohort Knee study

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SUMMARY

Objective: To examine the proportion of isolated patellofemoral osteoarthritis (PFOA) compared to tibiofemoral osteoarthritis (TFOA) in middle-aged participants with early osteoarthritis (OA) symptoms of the knee; to describe the natural course of PFOA compared with that of TFOA and to identify whether patients with PFOA have a different phenotype compared to patients with TFOA, or with combined PFOA and TFOA (combined osteoarthritis (COA)).

Design: Participants with early OA symptoms of the knee were selected, completed questionnaires, underwent physical examination, and had knee radiographs at baseline, and at 2 and 5 years follow-up. Based on radiographs, participants were classified as having isolated TFOA, isolated PFOA, COA, or no radiographic OA. Multivariate logistic regression was used to identify participant characteristics associated with a specific group of OA at 2 years follow-up.

Results: The cohort comprised 845 participants (mean age 55.9 years). At baseline, 116 had PFOA, none had TFOA or COA. Of these 116 participants, 66.3% had developed COA at 5 years follow-up. At 2 years follow-up, PFOA, TFOA and COA were present in 77 (10.8%), 39 (5.5%) and 83 (11.6%) participants, respectively. Multivariate regression analyses at 2 years follow-up showed that participants with radiographic PFOA or TFOA were not significantly different from each other with respect to signs and symptoms.

Conclusions: These results suggest that OA is more likely to start in the patellofemoral joint and then progress to COA in individuals with symptoms of early knee OA. No differences in TFOA and PFOA phenotypes were determined with respect to signs and symptoms.

Introduction

The most common condition to affect the knee joint is osteoarthritis (OA)[1,2]. The knee joint consists of two compartments the tibiofemoral (TF) and the patellofemoral (PF) compartment. OA in the knee can occur solely in the TF joint [isolated tibiofemoral osteoarthritis (TFOA)] or in the PF joint [isolated patellofemoral osteoarthritis (PFOA)] or can be present in both joints [combined TFOA and PFOA (combined osteoarthritis (COA))]. Most research on OA has focused on the TF joint, although the prevalence of isolated PFOA might be higher than isolated TFOA[3–6]. Furthermore, radiographic signs of PFOA are associated with symptoms such as pain and disability[7–10].

Although the main goal of treatment for OA is pain relief, not every participant responds equally well to treatment[11,12]. One possible reason for this difference is that the heterogeneous OA population consists of persons with different phenotypes of OA[12–14]. Identification of the distinct phenotypes in OA may help classify which preventive measures are suitable for an individual[14]. Therefore, it is suggested to target interventions to different OA phenotypes[15–18]. However, Mills and Hunter stated: '*due to the inclusion of homogenous study groups based on TFOA in clinical trials,*

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the phenotype specific effects of OA can be masked'[19]. Therefore, large cohort studies that include participants with COA and isolated TFOA and PFOA are needed to determine whether participants with PFOA have a different phenotype compared to those with TFOA or COA.

Additionally, evidence from a study including participants aged ≥50 years with knee complaints suggests that OA in the knee starts in the PF joint and subsequently progresses to the TF joint[20]. This was recently strengthened by Stefanik *et al.* (2016) who found that knees with structural damage in one compartment of the knee do not develop structural damage in another compartment. Moreover, knees that developed mixed structural damage were more likely to start with isolated to the PF joint[21]. Therefore, more insight is required in the natural course of PFOA and how its natural course differs from TFOA. The few studies describing the prevalence and natural course of TFOA and PFOA included participants with severe signs of OA on radiographs[22] or studied a general population including individuals without knee complaints[9,23]. Other studies focussing on TFOA and PFOA included participants with a relatively high age (mean age 68.4, 65.2 and 62.5 years, respectively)[20,21,24,25]. Although two studies evaluated the prevalence of PFOA in a younger population (aged 34–55 years), these participants had chronic knee complaints[26] or no baseline X-ray data of the PF joint were available so that progression could not be evaluated[27]. Thus, most research has focused on older participants with a longer symptom duration of knee pain, or on the general population and therefore little is known on the incidence and prevalence rates, as well as the natural course of PFOA and TFOA, in relatively young subjects with a recent onset of knee complaints.

Therefore, the aim of this study is to 1) determine the proportion PFOA compared to TFOA in individuals with early knee OA symptoms; 2) describe the natural course of PFOA at 2 and 5 years follow-up compared with that of TFOA; and 3) identify whether participants with PFOA have a different phenotype of signs and symptoms compared to those with TFOA, and those with COA.

Methods

Study population

The present study used baseline data, and data from 2 to 5 years follow-up of the Cohort Hip and Cohort Knee study (CHECK). A detailed description of this cohort is published elsewhere[28,29]. In brief, the cohort included 1002 participants recruited between October 2002 and September 2005. Inclusion criteria were: participants aged 45–65 years with hip and/or knee complaints (pain or stiffness) who had never visited a general practitioner (GP) for their complaints, or had visited a GP no longer than 6 months previously.

Participants were excluded if they had a pathologic disorder (based on medical history and physical examination) that also could explain the symptoms (e.g., for the knee; other rheumatic disease, ligament or meniscus injury, knee joint replacement, plica syndrome, Baker's cyst); had a serious comorbidity that did not allow physical evaluation/follow-up for up to 10 years; and did not have adequate understanding of the Dutch language[28].

For the current study only those participants that reported knee pain or knee stiffness at baseline were included ($n = 845$). Ethical approval was obtained and participants provided informed consent prior to commencement of the study[28].

Questionnaires

Self-reported questionnaires were filled in yearly by all participants. At baseline and at follow-up the following domains were assessed by questionnaires: 1) Socio-demographic characteristics: age (in years), sex (male/female), body height (m) and weight (kg), 2) Knee symptoms: duration of complaints (only assessed at baseline), side of knee pain, number of subjects with hip and knee symptoms, and the Western Ontario and McMaster Universities Index (WOMAC)[30] for knee function (higher scores indicating worse function). Moreover, information on pain when going up/down upstairs and when walking on a flat surface was obtained by means of a five-point Likert scale ('none', 'slight', 'moderate', 'severe', 'extreme')[30].

Physical examination

All participants underwent a standardised physical examination at baseline, and at 2 and 5 years follow-up. For the present study, we used data of the physical examination at baseline and data of the 2-year follow-up of the index knee (i.e., the most affected knee)[31]. Of the 845 participants with knee pain, 384 (44.5%) had unilateral symptoms. For participants with bilateral symptoms the index knee was based on the following decision tree as described by Holla *et al.*[31] 1) highest Kellgren/Lawrence score, 2) lowest degree of active knee flexion, 3) highest pain during knee flexion, and 4) crepitus during knee flexion. In participants for whom we could not define an index knee based on these signs, we randomly assigned an index joint.

Range of joint motion was measured with a goniometer (in degrees). To assess knee effusion the refill test was used (present or absent), palpable warmth was determined by comparing both knees with each other (present or absent), and bony enlargement, joint line tenderness, crepitus (during squatting) and PF grinding test were all scored for presence or absence by palpation.

Radiographs

At baseline and at 2 and 5 years follow-up, weight-bearing posterior–anterior (PA), with 7–10°; knee flexion; lateral weight-bearing radiographs with 30° of knee flexion; and skyline view with the knees in 30° flexion were made of both knees separately. For the PA radiographs individual features of OA were scored according to the atlas of Altman *et al.*[32] The following features of OA were scored: joint space narrowing (none, doubtful, mild or moderate), femoral medial and lateral osteophytes, and tibial medial and lateral osteophytes (none to moderate). The original Kellgren & Lawrence (K&L) criteria were used to score the severity of TFOA of the involved knee on the PA radiographs[33]. On the lateral views osteophytes (none to moderate) were scored and on the skyline view osteophytes (none to moderate) and joint space narrowing (none to moderate) were scored according to Burnett *et al.*[34]. All the above-mentioned features were scored by five observers independently, according to a paired reading procedure (inter-reader reliability: 0.62)[35].

Definition of radiographic OA per compartment

The type of OA was defined for the index knee of the individual. Patients were classified having no OA, isolated PFOA, isolated TFOA or combined OA. Patients classified having isolated PFOA only had signs of OA in the PF joint, patients with isolated TFOA only had signs of OA in the TF joint, and none in the PF joint. and patients with COA had signs of OA in both the TF and the PF joint (Table I). No radiographic OA was defined if none of the definitions was fulfilled. Incident cases at 2 or 5 years follow-up were defined as participants with radiographic signs of any type of OA at follow-up who did not have signs of OA at baseline or at 2 years follow-up[4,23].

Table I
Radiographic criteria for PFOA, TFOA and COA

Isolated PFOA	Isolated TFOA	Combined OA
K&L score <2 on PA radiographs and osteophytes grade ≥2 on skyline OR K&L score <2 on PA radiographs and osteophytes grade ≥2 on lateral radiographs OR K&L <2 on PA radiographs and narrowing grade ≥2 and osteophytes grade ≥1 for skyline radiographs	K&L score ≥2 on PA radiographs and osteophytes grade <2 on both skyline and lateral radiographs OR K&L score ≥2 on PA radiographs and narrowing grade <2 and osteophytes grade <1 for skyline radiographs	K&L score ≥2 on PA radiographs and skyline or lateral osteophytes grade ≥2 OR K&L score ≥2 on PA radiographs and narrowing grade ≥2 and osteophytes grade ≥1 for skyline radiographs

Statistical analyses

To determine the proportion PFOA compared to TFOA in individuals with early knee OA symptoms, descriptive statistics (mean, standard deviations [SD] and proportions) were applied. Descriptive statistics were also applied to determine the natural course of PFOA and TFOA at 2 and 5 years follow-up. Differences in characteristics between study groups at baseline and at 2 years follow-up were analysed using ANOVA tests and posthoc Bonferroni tests were performed when $P < 0.05$.

To identify whether participants with PFOA had a different phenotype of signs and symptoms compared to those with TFOA, and those with COA multivariate binary logistic regression (based on complete case analyses) ($P < 0.01$) was used. For the analyses data at 2 years follow-up were used because none of the participants had TFOA or COA at baseline so that we were unable to test for differences in phenotypes at baseline. The following variables were included in the regression analyses: gender, age, body mass index (BMI), pain when walking up/down stairs and when walking on a flat surface [both dichotomised into no pain ('none' and 'slight') and painful ('moderate', 'severe' and 'extreme')], function score (WOMAC), bony tenderness during palpation, joint line tenderness, crepitus in the knee duration flexion, degrees of knee flexion and extension, and the patellar grinding test. This selection of characteristics was based on the literature and their practicability in general practice[20,25,36]. Significance level was set at $P < 0.01$, and a significant trend was defined as a P-value >0.01 and <0.05. Analyses were based on complete case analyses (i.e., no missing radiograph and physical examination). Analyses were performed using the Statistical Package for the Social Sciences version 21.0 (SPSS Inc., Chicago IL, USA).

Results

Study population

At baseline, the total cohort comprised 845 participants (80% females) who reported knee pain or stiffness. The mean age was 55.9 (5.18) years and mean BMI was 26.3 (4.15) kg/m^2. Due to missing data, the type of OA could not be determined for 139 (16.4%), 129 (15.3%) and 150 (17.8%) participants at baseline and at 2 and 5 years follow-up, respectively.

Incidence and prevalence of different types of OA

Of the 706 participants available at baseline, 116 (16.4%) had isolated PFOA and none had TFOA or COA; 590 participants had no radiographic defined OA at baseline. The presence of isolated PFOA in those with knee pain at baseline was associated with higher age, higher BMI, hip pain at baseline, crepitus, positive PF grinding test, palpable bony enlargement, lower knee flexion range of motion (ROM) and a K&L score ≥1 (Table II).

At 2-year follow-up, isolated PFOA was found in 77 (10.8%) participants. Posthoc analyses of ANOVA showed that participants with PFOA had a significantly lower BMI, had more knee flexion and less knee effusion compared to participants with COA at 2-year follow-up (Table II). At the 5-year follow-up, 100 (14.4%) participants were diagnosed with isolated PFOA.

Natural course of PFOA and TFOA

Of the 116 participants with isolated PFOA at baseline, 63 (54.3%) had developed COA at the 2-year follow-up and 62 (53.4%) had developed COA at the 5-year follow-up. The status of five participants with PFOA at baseline was unknown due to missing data at both 2 and 5 year follow-up. Seven of the 116 participants had already progressed to COA at 2-years follow-up, but had missing data at 5-years follow-up and three participants were diagnosed with PFOA at baseline and 2-years follow-up, but had missing data at 5-years follow-up (Fig. 1).

Of the 77 participants with PFOA at 2-year follow-up, 48 (62.3%) already had PFOA at baseline, 27 were new incident cases and two PFOA patients had missing data at baseline. Isolated TFOA was present in 39 (5.5%) participants, none of them had signs of OA at baseline. COA was present in 83 (11.6%) participants at 2 years follow-up; 63 (75.9%) had PFOA at baseline, 18 patients did not have signs of OA at baseline and two patients had missing data at baseline (Fig. 1).

At the 5-year follow-up, 100 participants were diagnosed with isolated PFOA: .39 already had PFOA at baseline and 2-years follow-up, 23 had PFOA at 2-years and 30 did not have signs of OA neither at baseline and 2-years follow-up. Of the 129 participants with missing data at 2 years follow-up, eight had PFOA at 5-year follow-up.

A total of 54 patients had TFOA at 5-year follow-up: 29 already had TFOA at 2-years follow-up, 17 did not have signs of OA at baseline and 2-years follow-up and seven patients had missing data at 2-years follow-up. A total of 102 patients had COA at 5-year follow-up: 56 (54.9%) already had COA at 2-years follow-up and PFOA at baseline, while 6 (5.9%) had PFOA at baseline and 2-year follow-up and progressed to COA. Five out of the 102 patients developed COA while they were diagnosed with PFOA at 2-years follow-up, and eight progressed from TFOA at 2-year follow-up to COA. Seven patients with COA at 5-year follow-up did not have signs of OA at baseline and 2-year follow-up and three patients with COA at 5 years follow-up had missing data at 2-years follow-up (Fig. 1).

Multivariate regression analysis for different types of OA at 2-year follow-up

No significant differences in clinical signs and symptoms were found between participants with radiographic PFOA or TFOA

Table II
Patient characteristics and symptoms at baseline and at 2-year follow-up per group: variables are *n* [%] unless stated otherwise

Characteristics at baseline	Isolated TFOA	Isolated PFOA $n = 116$	Combined TFOA and PFOA	No radiographic OA $n = 590$	OA status unknown $n = 139$	Total $n = 845$	*P*-value between groups*
Age (years), mean [SD]		57.8 [4.82]		55.5 [5.16]	56.4 [5.18]	55.9 [5.18]	<**0.01**
Sex (female)		89 [76.7%]		473 [80.2%]	110 [79.1%]	672 [79.5%]	0.70
BMI (kg/m^2), mean [SD]		28.1 [4.55]		26.1 [4.00]	26.0 [4.21]	26.3 [4.15]	<**0.01**
Bilateral complaints (yes)		61 [52.6%]		324 [54.9%]	76 [54.7%]	461 [54.6%]	0.33
Hip and knee pain at baseline (yes)		42 [36.2%]		324 [54.9%]	65 [46.8%]	431 [51.0%]	**0.06**
Pain when walking on flat surface (yes)		21 [18.1%]		96 [16.3%]	26 [18.7]	143 [16.9%]	0.72
Pain when going up or down stairs (yes)		61 [52.6%]		258 [43.7%]	68 [48.9]‡	387 [45.8%]	0.13
Baseline WOMAC function (0–68), mean [SD]		25.9 [17.2]		22.7 [16.9]	27.4 [18.4]	23.9 [17.3]	<**0.01**
Crepitus (yes)		72 [62.1%]		271 [45.9%]†	55 [39.6%]†	398 [47.1%]	<**0.01**
Bony enlargement (yes)		12 [10.3%]		21 [3.6%]†	4 [2.9%]†	37 [4.4%]	<**0.01**
Patellofemoral grinding test (pos)		46 [39.7%]§		159 [26.9%]†,§	32 [23.0%]†,‖	237 [28.0%]§	<**0.01**
Knee flexion ROM (degrees), mean [SD]		130.8 [10.6]‡		135.1 [8.88]‡	133.4 [12.5]‡	134.2 [9.92]	<**0.01**
Knee extension ROM (degrees), mean [SD]		2.63 [2.68]‡		2.73 [2.77]‡	2.28 [2.46]‡	2.64 [2.74]	0.24
Knee effusion (yes)		15 [12.9]		43 [7.3]	5 [3.6%]†	63 [7.5]	0.02
Morning stiffness knee < 30 min (yes)		85 [73.3%]		356 [60.3%]†	92 [66.2%]	533 [63.1%]	0.02
Joint line tenderness (yes)		49 [42.2%]		273 [46.3%]	53 [38.1%]	375 [44.4%]	0.22
K&L score 1 (yes)		89 [76.7%]		243 [41.2%]†	5 [3.6%]†,‖	343 [46.7%]‖	<**0.01**
Characteristics at 2-year follow-up	***n* = 39**	***n* = 77**	***n* = 83**	***n* = 517**	***n* = 129**	***n* = 845**	
Age (years), mean [SD]	58.5 [5.54]	59.3 [5.39]	59.7 [4.16]	57.5 [5.21]†	56.3 [5.15]	58.1 [5.17]	<**0.01**
Sex (female)	33 [84.6]	58 [75.3]	68 [81.9]	407 [78.7]	106 [82.2%]	672 [79.5]	0.65
BMI (kg/m^2), mean [SD]	26.7 [3.81]	26.4 [4.27]	28.4 [4.67]†	25.7 [3.75]	26.3 [3.95]	26.2 [4.06]	<**0.01**
Bilateral complaints (yes)	17 [43.6]	38 [49.4]	51 [61.4]	217 [42.0]	70 [54.3%]	367 [43.4]	0.03
Pain when walking on flat surface (yes)	18 [46.2]	12 [15.6]	21 [25.3]	75 [14.5]	29 [22.5%]‡	143 [16.9]	0.07
Pain when going up or down stairs (yes)	6 [15.4]	37 [48.1]	56 [67.5]	214 [21.4]	62 [48.1%]‡	387 [45.8]	0.02
WOMAC function (0–68), mean [SD]	19.5 [16.2]	24.9 [20.1]	27.8 [17.7]	21.2 [17.1]	26.9 [18.8]	22.9 [17.8]	<**0.01**
Crepitus (yes)	18 [46.2]	40 [51.9]	49 [59.0]	201 [38.9]	54 [41.9%]	339 [40.1]	**0.03**
Bony enlargement (yes)	1 [2.6]	8 [10.4]	6 [7.2]	24 [4.6]	5 [3.9%]	43 [5.1]	0.23
Patellofemoral grinding test (pos)	4 [10.3]‖	17 [22.1]§	20 [24.1]§	88 [17.0]§	30 [23.3%]‖	142 [16.8]‖	0.28
Knee flexion ROM (degrees), mean [SD]	134.6 [8.02]‡	136.9 [9.07]‡	130.0 [10.4]†	136.1 [8.50]	133.4 [13.2]‡	135.3 [9.09]‡	<**0.01**
Knee extension ROM (degrees), mean [SD]	2.19 [2.23]‡	2.52 [3.27]‡	2.84 [2.99]	2.69 [2.63]	2.55 [2.78]‡	2.64 [2.74]‡	<**0.01**
Knee effusion (yes)	4 [10.3]	2 [2.6]	11 [13.3]†	27 [5.2]	5 [3.9%]	50 [5.9]	0.03
Morning stiffness knee < 30 min (yes)	22 [56.4]	49 [63.3]	56 [67.5]	288 [55.7]	83 [64.3%]	464 [54.9]	0.23
Joint line tenderness (yes)	6 [15.4]	15 [19.5]	28 [33.7]	164 [31.7]	53 [41.1%]	242 [28.6]	0.04

n: number, m: meter, kg: kilogram, pos: positive, OR: odds ratio.
Bold indicates: *P*-value <0.01.
**P*-value between groups using ANOVA analyses.
† Posthoc Bonferroni analysis: significant different compared to PFOA.
‡ Data missing in >5% to ≤10% cases.
§ Data missing in >10% to ≤20% cases.
‖ Data missing in >20% cases.

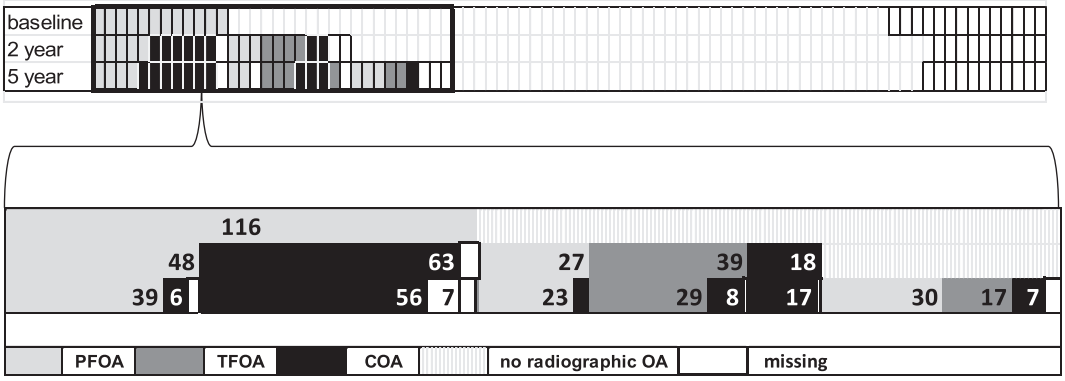

Fig. 1. The blocks with the different shades of grey indicate the number of patients with OA. At follow-up the blocks in the different shades of grey below the different blocks at the previous time point indicate the number of patients that remained the same type of OA or developed another type of OA. In the upper graphic one block is indicating 10 subjects, whereas in the enlargement one block is indicating one subject.

(Table III). Compared with participants with PFOA, those with COA were more likely to have a lower knee flexion range of motion (OR 0.94, 95% CI 0.89–0.98). Participants without radiographic knee OA had better knee function (lower WOMAC scores) compared with those with isolated PFOA (OR 0.97, 95% CI 0.95–0.99) and reported more joint line tenderness compared with those with isolated PFOA (OR 3.13, 95% CI 1.47–6.69). Participants without radiographic OA tended to be younger, were less likely to have palpable bony enlargement and were less likely to have crepitus during knee flexion compared to those with isolated PFOA (Table III).

Table III
Multivariate regression analysis for different types of OA at 2-year follow-up

	TFOA vs PFOA			COA vs PFOA			NOA vs PFOA		
	$n = 39$ vs $n = 77$			$n = 83$ vs $n = 77$			$n = 517$ vs $n = 77$		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Sex (female)	2.69	0.71–10.1	0.15	1.01	0.38–2.69	0.99	1.03	0.52–2.03	0.94
BMI (m/kg^2)	0.95	0.84–1.08	0.45	1.07	0.98–1.18	0.14	0.95	0.88–1.02	0.17
Age (years)	0.98	0.89–1.08	0.70	1.02	0.93–1.12	0.68	0.93	0.88–0.99	*0.02*
Pain when walking on flat surface (yes)	0.42	0.07–2.58	0.35	1.91	0.53–6.83	0.32	1.13	0.44–2.90	0.81
Pain when going up or down stairs (yes)	0.58	0.14–2.52	0.47	1.33	0.46–3.85	0.60	1.20	0.55–2.59	0.65
WOMAC function (0–68)	1.01	0.97–1.05	0.70	0.97	0.94–1.00	0.08	0.97	0.95–0.99	**<0.01**
Crepitus (yes)	0.47	0.16–1.38	0.17	1.04	0.45–2.41	0.92	0.54	0.30–0.97	*0.04*
Bony enlargement (yes)	0.18	0.02–1.78	0.14	0.25	0.05–1.12	0.07	0.36	0.13–0.96	*0.04*
Knee extension ROM (degrees)	0.96	0.74–1.25	0.77	0.85	0.68–1.07	0.17	1.09	0.96–1.25	0.20
Knee flexion ROM (degrees)	0.94	0.88–1.00	*0.04*	0.94	0.89–0.98	**<0.01**	0.98	0.94–1.01	0.16
Joint line tenderness (yes)	0.56	0.14–2.33	0.43	2.18	0.83–5.73	0.11	3.13	1.47–6.69	**<0.01**
Patellofemoral grinding test (pos)	0.62	0.15–2.48	0.50	1.23	0.46–3.30	0.69	0.85	0.42–1.73	0.65
R^2	0.19			0.24			0.15		

Dependent variable PFOA.
Abbreviations: m: meter, kg: kilogram, pos: positive, OR: odds ratio, NOA: no radiographic osteoarthritis, R^2: coefficient of determination.
Bold indicates: *P*-value <0.01.
Italics indicates: *P*-value >0.01 and <0.05.

Discussion

The results of this study suggest that combined OA may start in the PF joint and then progresses to COA. At baseline, 16.4% of our participants with symptoms of early knee OA were diagnosed with radiographic isolated PFOA and none with isolated TFOA and at the 2-year follow-up, half of the participants with PFOA at baseline had developed COA, and at 5-year follow-up two thirds of the participants with isolated PFOA at baseline had developed COA. The incidence of COA and TFOA in patients that presented with symptoms of knee OA was low, i.e., 3.1–6.6%, respectively at the 2-year follow-up and 1.4–4.5%, respectively, at the 5-year follow-up.

Compared to the CAS(K) studies[20,25,37,38], in the present study the prevalence of PFOA at baseline was lower (23.9% vs 16.4%, respectively) and this difference remained at follow-up (28.8% at 3 years follow-up in the CAS(K) study vs 4.6% at 2 years follow-up in the present study)[20]. These differences in prevalence and incidence are probably explained by the different populations in the studies. The CAS(K) studies[20,25] comprised older patients with a higher BMI compared to our CHECK population. However, it was notable that, compared to Thorstensson *et al.*[27] who also included middle-aged participants (age range 35–54 years) with chronic knee complaints (>3 months), we found a lower prevalence of TFOA at baseline (47% vs 0%, respectively). Therefore, the differences in prevalence and incidence might not only be due to different populations but might also be attributed to the use of inconsistent definitions for knee OA[39]. The inconsistency in definitions of radiological OA in studies evaluating different OA types may have led to misclassification into the different OA groups[40]. This emphasises the need for consensus on the radiographic classification system used for OA[39].

It is noteworthy that in the present study, none of the participants had TFOA at baseline. This can probably be explained by our study population as most participants had not visit a GP or physician for their knee symptoms yet. However, the absence of TFOA in the present study might also be explained by detectability of the abnormalities of the different radiographs. It could be possible that on skyline radiographs osteophytes are earlier detectable than osteophytes on the PA radiograph, so that PFOA is earlier detectable with radiographs compared to TFOA. This may be strengthened by the findings of Stefanik *et al.* (2016) in which isolated PFOA was already seen at baseline, though in a relatively older population[21]. Though similar to our study, knees that developed OA in both the PFJ and TFJ started with damage isolated to the PFJ. It therefore seems important to get more insight in the patient population who develop combined knee OA and develop preventative and therapeutic strategies targeting the PFJ.

In the literature, three main signs of OA that were determined on physical examination (i.e., crepitus, restricted movement, and bony enlargement) were found to be associated with the development of radiographic OA[2]. These positive physical examination findings increase the risk of radiographic OA[2]. However, the present results indicate the difficulty of discriminating between the different types of OA using the measures from clinical history and physical examination. However, the results do indicate that participants with COA had a lower knee flexion ROM compared to those with isolated PFOA, and a trend was seen in participants with TFOA; i.e., they also had a lower knee flexion ROM compared to those with isolated PFOA. Consistent results were reported in another cross-sectional study on clinical features of symptomatic OA, showing that lower knee flexion ROM was an indicator for radiographic COA and not for radiographic PFOA[25]. Furthermore, this latter study also reported that lower knee flexion ROM was an indicator for TFOA[25]. It is proposed that knee flexion ROM is an important clinical finding in (especially) participants with severe radiological signs of OA[41]. In the present cohort, the majority of the participants with knee symptoms had PFOA at baseline and this was already associated with reduced knee flexion ROM. Therefore, reduced knee flexion ROM seems to be an early sign of knee OA. However, it is questionable whether the ROM can distinguish between those with isolated PFOA, and those with TFOA and COA, in middle aged persons with knee symptoms.

It is noteworthy that participants without radiographic signs of OA were more likely to have joint line tenderness compared to those with PFOA. It could be hypothesised that joint line tenderness might be associated with other intra-articular pathologies (e.g., meniscus) that are not seen on radiographs. This hypothesis is strengthened by the fact that, when the K&L grade $\geq$1 variable was added to the multivariate regression model to test differences in phenotype between patients without radiographic signs of OA and those with PFOA, the significant association between joint line tenderness remained (data not shown).

The strength of the present study is that we were able to analyse a large cohort of relatively young subjects with early knee symptoms so that the natural course of OA could be evaluated. However,

the study also has some limitations. In this relatively young cohort of participants with symptoms of knee OA, X-rays may not be sufficiently sensitive to detect early OA features and changes that are detectable on MRI[42]. On the other hand, these participants were followed over 5 years, a period in which radiographic signs are expected to progress[43].

Due to the small number of participants with TFOA we were unable to test for differences in phenotype based on baseline characteristics; therefore, we performed a cross-sectional analysis with the 2-year follow-up data. Furthermore, a limited number of variables were included in the regression analysis. Additional variables measured in the CHECK study (including clinical hand OA, profession, and physical activity) and reported to be risk factors for knee OA, might also differ between patients with PFOA and TFOA[43]. The explained variance in the regression model was low, indicating that other factors not included in the present study (e.g., quadriceps strength, malalignment) might be able to differentiate between the different types of OA[19,25,43]. These biomechanical variables could be potential targets for specific treatments for PFOA[44].

Implications for future research

None of the participants in the present study had TFOA at baseline and 116 had PFOA. This suggests but does not prove that combined OA is more likely to start in the PF-joint. Furthermore, two-thirds of the participants that had PFOA at baseline progressed to COA at the 5-year follow-up (assuming that the status of the seven participants with COA at 2-year follow-up but missing data at 5-year follow-up did not change), whereas only 20% of the participants that had TFOA at the 2-year follow-up progressed to COA at the 5-year follow-up. This indicates that, in those who have their first signs of radiographic OA in the PF joint, they are more likely to progress to COA compared to those with isolated radiographic signs of OA in the TF joint. This is in agreement with earlier studies[20,38]. Additionally, this was recently strengthened by Stefanik *et al.* (2016) showing that patients with isolated PFOA on MRI at baseline were 2.1 times more likely to develop combined OA compared to patients with isolated TFOA at baseline[21]. However, a longer follow-up period is needed to determine whether all participants with PFOA at baseline will develop COA, or whether there are more subgroups within the PFOA population (e.g., stable PFOA, progression to COA, and progressive PFOA).

Conclusion

The results of this study suggest that combined OA seems to start in the PF joint and then progress to COA. Differences in TFOA and PFOA phenotypes could not be determined with respect to signs and symptoms. A longer follow-up is necessary to determine whether all participants with PFOA will eventually develop COA.

Contributors

N.L., J.D., E.O, J.V., M.K, S.B-Z and M.v.M. contributed to the conception and design of this study. N.L contributed to the analysis of data. J.D., E.O, J.V., M.K, S.B-Z and M.v.M. contributed to the interpretation of data. Article draughts were written by N.L. and critically revised by all authors. The final version of the article was approved by all authors. S.B-Z takes responsibility for the integrity of the work as a whole [s.bierma-zeinstra@erasmusmc.nl].

Conflict of interest

The authors declare that they have no competing interests.

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