# Development of radiographic knee osteoarthritis and the associations to radiographic changes and baseline variables in individuals with knee pain

## a 2-year longitudinal study

Törnblom, Margareta; Bremander, Ann; Aili, Katarina; Andersson, Maria L.E.; Nilsdotter, Anna; Haglund, Emma

*Published in:*
BMJ Open

*DOI:*
10.1136/bmjopen-2023-081999

*Publication date:*
2024

*Document version:*
Final published version

BMJ Open

# Development of radiographic knee osteoarthritis and the associations to radiographic changes and baseline variables in individuals with knee pain: a 2-year longitudinal study

Margareta Törnblom ,[1,2] Ann Bremander,[1,3] Katarina Aili,[2,4] Maria L E Andersson ,[1,2] Anna Nilsdotter,[5,6] Emma Haglund [2,7]

**To cite:** Törnblom M, Bremander A, Aili K, *et al*. Development of radiographic knee osteoarthritis and the associations to radiographic changes and baseline variables in individuals with knee pain: a 2-year longitudinal study. *BMJ Open* 2024;**14**:e081999. doi:10.1136/bmjopen-2023-081999

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-081999).

Received 11 November 2023
Accepted 11 February 2024



For numbered affiliations see end of article.

**Correspondence to**
Margareta Törnblom;
margareta.tornblom@med.lu.se

## ABSTRACT

**Objectives** The aim was to study the development of radiographic knee osteoarthritis (RKOA) in individuals with knee pain over 2 years, and the associations between radiographic changes and baseline variables.

**Design** Longitudinal cohort study.

**Participants and setting** This study is part of the Halland Osteoarthritis cohort. The included 178 individuals, aged 30–67, had knee pain, without cruciate ligament injury or radiographic findings and 67% were women. The presence of RKOA was defined as Ahlbäck score of ≥1 in ≥1 knee. (Ahlbäck grade 1: joint space narrowing in the tibiofemoral joint <3 mm). Diagnosis of clinical KOA was based on the clinical guideline from the National Institute for Health and Care Excellence (NICE). Knee injury and Osteoarthritis Outcome Score (KOOS), pain intensity, physical function, body mass index (BMI) and visceral fat area (VFA) were measured. Associations to RKOA were analysed with logistic regression (OR).

**Results** In all, 13.8% (n=24) developed RKOA in 2 years whereof all had clinical KOA at baseline, as defined by NICE. Deterioration to RKOA was significantly associated with higher BMI, OR 1.119 (95% CI 1.024 to 1.223; p=0.013), and VFA, 1.008 (95% CI 1.000 to 1.016; p=0.049), worse knee pain intensity, 1.238 (95% CI 1.028 to 1.490; p=0.024), worse scores for KOOS Pain, 0.964 (95% CI 0.937 to 0.992; p=0.013) and KOOS Symptoms, 0.967 (95% CI 0.939 to 0.996; p=0.027), KOOS Activities of daily living 0.965 (95% CI 0.935 to 0.996; p=0.026) and KOOS Quality of Life 0.973 (95% CI 0.947 to 0.999; p=0.044), at baseline.

**Conclusions** One out of seven individuals with clinical KOA developed RKOA in only 2 years. Baseline variables associated with RKOA after 2 years may possibly be detected early by using the NICE guideline, assessment of obesity and self-reported data of symptoms to support first-line treatment: education, exercise and weight control.

**Trial registration number** ClinicalTrials.gov (NCT04928170)

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Longitudinal radiographic data (baseline and 2-year follow-up).
⇒ A relatively young study population (mean age 57±SD 11 years) may enhance the knowledge of early knee osteoarthritis.
⇒ Multiple data sources: self-reported, clinical examination and radiography.
⇒ Study recruitment was based on self-interest which could contribute to bias.

## BACKGROUND

Knee pain is a common musculoskeletal symptom that affects over one-fifth of the general adult population[1] and represents a frequent reason to seek healthcare.[2] Knee pain could also be the first symptoms in individuals with knee osteoarthritis (KOA).[3 4] Early symptoms of KOA are often described as episodic and activity related.[5 6] Along with knee pain, KOA manifests through symptoms such as stiffness, and signs of crepitus, joint swelling, bony enlargements, with consequences of functional impairment and activity limitations.[5 7] The burden caused by KOA, for both the individual and society, is expected to increase.[8]

Clinical KOA is based on the individual's symptoms and a clinical examination, while radiographic KOA (RKOA) requires structural changes.[9] Radiography is disputed because structural findings appear relatively late in the course of the disease and symptoms are not always associated with the structural findings.[5 9] Therefore, it is preferable to identify KOA in primary healthcare, based on symptoms and clinical examination, clinical KOA.[10 11] First-line treatment for KOA includes education, exercise and if needed weight loss.[12] Identifying KOA early has previously been described as representing a 'window of opportunity' to prevent more

severe KOA.[9] However, today, most individuals start their treatment in the later stages of the disease course.[9 13] In 2022, only 8% of individuals in the Swedish joint prosthesis register were offered first-line treatment when they sought help for the first time because of knee symptoms.[14] If treatment could start when the window is open, that is, before radiographic changes have become apparent, it will allow more proactive management.[9]

In recent years, although there has been some development in the field of early KOA concerning classification[15 16] and diagnostic criteria,[17 18] there is still no gold standard. The National Institute for Health and Care Excellence (NICE) has presented a guideline with recommendations how to clinically diagnose KOA, based on the individual's report of symptoms and without the need for radiography.[19] Previous research suggests that the NICE guideline may be relevant in identifying individuals with symptoms of KOA in primary healthcare.[11] Using clinical findings as symptoms of activity-related knee pain with no or less than 30 min morning knee stiffness to diagnose KOA will enable a greater proportion of individuals to receive first-line treatment before radiographic changes become apparent. By following a selected cohort of individuals with knee pain over time, we aimed to shed light on important factors in KOA development, from knee pain to radiographic changes. Thus, the aim was to study the development of RKOA in individuals with knee pain over 2 years, and the associations between radiographic changes and baseline variables.

## METHOD

### Study sample

The current study is part of an ongoing, 5-year longitudinal study, the Halland osteoarthritis cohort (HALLOA) ClinicalTrials.gov (NCT04928170). The study is described in detail elsewhere[20] and part of the results in this study has been published as a conference abstract.[21] Continuous enrolment took place between 2017 and 2019. Individuals, aged 30–67, who sought primary healthcare for knee pain or who responded to an advertisement in local newspapers, were included. The age cut-off was set with the aim to avoid the 'ageing phenotype'.[22] The inclusion criteria were knee pain and no former known RKOA. A general practitioner examined all individuals to rule out inflammatory rheumatic disease and previous cruciate ligament injury, that is, the exclusion criteria of the study. The general practitioner took anamnesis with questions about previous knee injuries and characteristic symptoms of inflammatory rheumatic diseases. A thorough examination of the knee joints were performed including inspection, palpation and stability testing. Furthermore, rheumatoid arthritis was ruled out with a blood sample test for anticyclic citrullinated peptide. In total, 178 individuals from the HALLOA cohort were eligible, that is, had no RKOA at baseline. They also had available radiographs at the 2-year follow-up, and self-reported baseline data from the Knee injury and Osteoarthritis Outcome Score (KOOS) (figure 1).[23 24]

### Radiography

Weight-bearing, semiflexed radiographic examination of the tibiofemoral and patellofemoral joint of both knees was conducted for all individuals[25 26] and assessed in accordance with the Ahlbäck criteria[27] at baseline and follow-up. The radiologist was unaware of the individuals' clinical status when scoring the images. The presence of RKOA in painful (index) knee or knees was defined as an Ahlbäck score of ≥1 in ≥1 knee. Ahlbäck grade 1 is defined as joint space

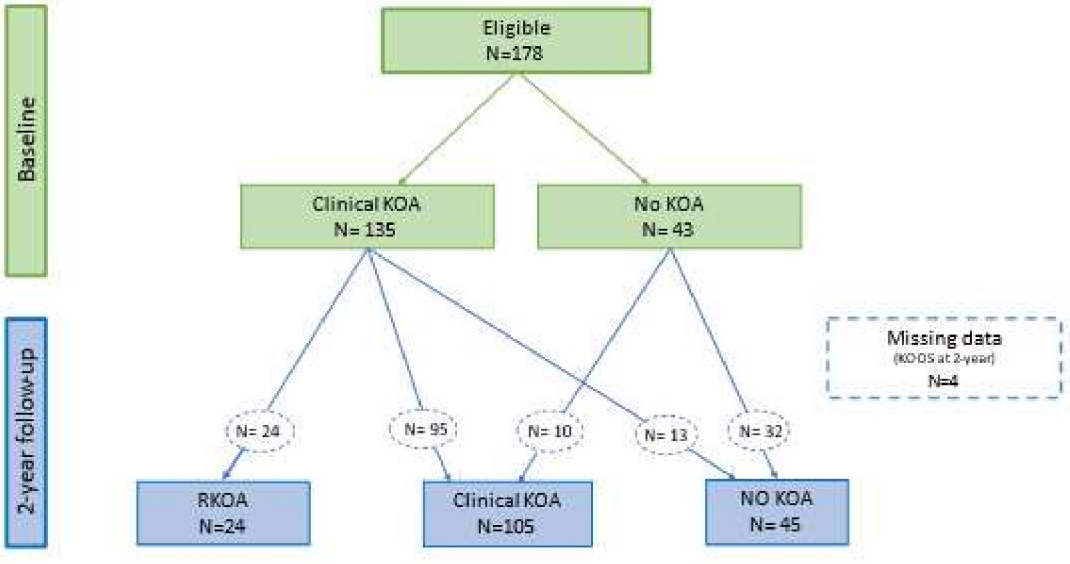


**Figure 1** Flow chart of the study population. Clinical KOA (knee osteoarthritis) was based on NICE clinical guideline. NICE, National Institute for Health and Care Excellence; RKOA, radiographic KOA.

narrowing in the tibiofemoral joint with space less than 3 mm.[26]

### Clinical KOA

Diagnosis of clinical KOA was based on the NICE guideline.[19] Clinical KOA according to NICE guideline was fulfilled if the individual was ≥45 years and had activity-related knee pain, with no or less than 30 min of morning knee stiffness.[19] The individuals were coded at baseline as either fulfilling clinical KOA according to NICE guideline or not (please see the 'Data management' section).

### Self-reported knee symptoms

The KOOS questionnaire assesses self-reported opinion about knee and associated problems[23 24] and has shown good validity, reliability and responsiveness in individuals with knee injuries and KOA.[23] KOOS has 5 subscales and gives a score of 0–100 (worst to best) in each subscale: symptoms (7 items), pain (5 items), activities of daily living, (ADL, 17 items), function in sport and recreation (Sport/Rec, 5 items) and knee-related quality of life (QOL, 4 items).[23 24] Knee pain intensity was measured with a Numerical Rating Scale from 0 'no pain' to 10 'worst imaginable pain' during the last week.[28]

### Clinical examinations

With the individual in a supine position, crepitus and the presence of palpable bony enlargement were assessed by one of four trained and experienced physiotherapists. Crepitus during passive knee movement was assessed through palpation or as a crepitus sound registered (yes/no). Bony enlargement was assessed through palpation of the knee joint line (yes/no).

Physical function in the lower extremity was assessed with the 30 s chair stand test (30 s CST),[29–31] the one-leg rising (OLR) test[32] (seat height 44 cm), and the maximal voluntary isometric contraction (MVIC) of the quadriceps muscle.[33 34] In the 30 s CST, the number of standardised sit-to-stand rises from a chair for 30 s was counted.[29–31] In the OLR test, a maximum number of rises from sitting to standing on one leg was performed and then repeated on the contralateral leg after a short rest. A light support for balance was allowed.[32] The isometric strength of the quadriceps muscle was assessed in an upright sitting position with 90° knee and hip flexion. Measurement was performed with a hand-held dynamometer (Commander Muscle Tester, 2016 JTECH Medical MN084_D. JTECH Medical Industries, Midvale, USA) held against the tibia with a strap.[33 34] The MVIC was repeated three times per side and was registered in newtons (N).

Visceral fat area (VFA) was assessed, and body weight (kg) was determined with bioelectrical impedance analysis (Inbody 770, Seoul, Korea).[35] Height (m) was measured with a stadiometer (portable stadiometer, MZ10042. ADE, Hamburg, Germany). Body mass index (BMI) was calculated (kg/m$^2$).

### Data management

The painful knee/s, set as the index knee, was identified at baseline by one or more of the following: answers from a written question (current ache or pain in right/left or both knees), the pain figure,[36] and/or an oral question during the clinical examination.

To evaluate the fulfilment of NICE clinical guideline the criteria activity-related knee pain and morning knee stiffness were assessed using self-reported data from KOOS. Thus, activity-related knee pain for clinical KOA, in accordance with NICE, was confirmed if the individual scored any pain (from mild to extreme, score 1–4) on the KOOS subscale Pain (items 2–6 and 9). The questions answering to activity-related knee pain were; if the individual had pain from the knee when twisting/pivoting (item 2), straightening or bending fully (items 3 and 4), walking on flat surface (item 5), going up or down stairs (item 6) and standing upright (item 9). Morning knee stiffness was confirmed if the individual scored any morning knee stiffness (from mild to extreme, score 1–4) on the KOOS subscale Symptoms (item 6). However, the duration of morning knee stiffness (< or >30 min) could not be considered.

Crepitus and/or bony enlargement were set as present if noted in the painful knee (index) during clinical examination. In the analysis of the MVIC and the OLR tests, various calculations were made, depending on whether the individuals reported bilateral or unilateral knee pain. For those with bilateral knee pain both knees were counted as index knees, and the peak mean values for left and right leg were used in the analysis. For those with unilateral knee pain, the peak value of the index knee was used.

### Data analysis

Non-parametric statistics were used because there was not normally distributed data. Frequency, median and IQR were used when describing the data. The $\chi^2$ test or Mann-Whitney U test was used for comparisons between groups, and logistic regression for analysis of associations between baseline variables and RKOA at follow-up, adjusted for age. All analyses were performed in IBM SPSS Statistics for Windows, V.27.0.

### Patient and public involvement

This study is part of the HALLOA cohort.[20] A patient research partner, educated by the Swedish Rheumatism Association, was involved in the development of the HALLOA cohort. Contributing to research questions, outcome measures, study design as well as the burden of the intervention and time required to participate in the research. The individuals, who are involved in this research, will have possibilities to learn more about the results through open lectures.

Table 1 Comparisons between individuals with RKOA or not at 2-year follow-up, n=174

| | All (n=174) Median (IQR) | RKOA (n=24) | No RKOA (n=150) | P value |
|---|---|---|---|---|
| Age, (years) | 53 (11) | 56 (7) | 52 (13) | 0.051 |
| Sex (women), n (%) | 116 (66.7) | 17 (70.8) | 99 (66.0) | 0.641 |
| Body mass index, (kg/m$^2$) | 25.2 (6.3) | 28.8 (9.0) | 25.1 (5.7) | **0.022** |
| Visceral fat area, cm$^2$, (n=170) | 92.9 (72.8) | 130.3 (90.6) | 86.6 (68.3) | **0.021** |
| NRS knee pain intensity, (0–10) | 4.0 (4.0) | 5.0 (5.0) | 4.0 (3.0) | **0.038** |
| Activity-related knee pain, n (%) | 164 (94.3) | 24 (100.0) | 140 (93.3) | 0.193 |
| Knee pain (duration >3 months), (n=172), n (%) | 121 (70.3) | 20 (83.3) | 101 (68.2) | 0.133 |
| Morning knee stiffness, n (%) | 120 (69.0) | 16 (66.7) | 104 (69.3) | 0.793 |
| Crepitus, n (%) | 123 (70.7) | 17 (70.8) | 106 (70.7) | 0.987 |
| Bony enlargement, n (%) | 97 (55.7) | 17 (70.8) | 80 (53.3) | 0.109 |
| 30 s chair stand test, (sit to stand) | 16 (6.3) | 15.0 (5.5) | 16.0 (7.0) | 0.726 |
| MVIC, (Newton), (n=151) | 261.5 (119.0) | 279.5 (104.8) | 252.0 (127.8) | 0.445 |
| One-leg rising, (n=171), (sit to stand) | 9.5(16) | 6.0 (12.8) | 10.0 (18.0) | 0.076 |
| Clinical KOA (NICE), n (%) | 132 (76) | 24 (100) | 108 (72) | **0.003** |
| KOOS (pain), (best to worst, 100–0) | 77.8 (20.1) | 72.2 (29.2) | 77.8 (19.4) | **0.028** |
| KOOS (symptoms), (best to worst, 100–0) | 75.0 (18.8) | 75.0 (23.2) | 78.6 (17.9) | 0.119 |
| KOOS (ADL), (n=173), (best to worst, 100–0) | 88.2 (14.7) | 85.6 (24.3) | 89.7 (14.7) | 0.079 |
| KOOS (Sport-rec), (n=173), (best to worst, 100–0) | 60.0 (40.0) | 50.0 (42.5) | 60.0 (37.5) | 0.120 |
| KOOS (QoL), (n=173), (best to worst, 100–0) | 56.3 (25.0) | 50.0 (37.5) | 56.3 (25.0) | 0.101 |

Analysed with $\chi^2$ test or Mann-Whitney U test.
P value in bold typeface <0.005.
ADL, activities of daily living; KOOS, Knee injury and Osteoarthritis Outcome Score; MVIC, Maximal Voluntary Isometric Contraction; NICE, National Institute for Health Care Excellence; NRS, Numeric Rating Scale; QOL, quality of life; RKOA, radiographic knee osteoarthritis ; Sport/Rec, sports and recreational activities.

## RESULT

Due to missing data, 59 individuals were not eligible from the HALLOA cohort. Of those, 78% were women, median age 50 (IQR 18) and median BMI 24.9 (5.4). They were younger, compared with those included in the analysis (p=0.015).

### Baseline data

Data at baseline included 178 individuals. Of those, 43 individuals (24%) did not fulfil the clinical criteria for KOA according to the NICE guideline (figure 1), 10 did not have activity-related knee pain. The rest, (33/43 individuals) did not fulfil the age criteria for clinical KOA (≥45 years). At the 2-year follow-up, KOOS data from four individuals were missed. The remaining baseline analyses were based on the 174 individuals with complete data. 67% (n=116) were women, the median age was 53 (IQR 11) and they had median BMI of 25.2 (6.3) (table 1). In total, 94% (n=164) had activity-related knee pain at baseline while the prevalence of clinical KOA was fulfilled for 76% (n=132) (table 1).

### RKOA at 2-year follow-up

In all, 24 out of 174 individuals (13.8%) developed RKOA from baseline to follow-up. The individuals with RKOA at follow-up (n=24) had significantly higher median BMI at baseline compared with those without 28.8 (9.0) vs 25.1 (5.7), p=0.022 and higher VFA 130.3 (90.6) vs 86.6 (68.3), p=0.021. Furthermore, they reported worse knee pain intensity 5.0 (5.0) vs 4.0 (3.0), p=0.038 and worse KOOS Pain 72[29] vs 78,[19] p=0.028. A higher proportion had clinical KOA, 100% vs 72%, p=0.003, at baseline (table 1).

Every individual with RKOA (n=24) at 2 years had clinical KOA according to NICE at baseline. None of the individuals classified as not having clinical KOA at baseline (n=43) developed RKOA after 2 years (figure 1).

In the logistic analysis and adjusted for age, a higher BMI (OR 1.119, 95% CI 1.024 to 1.223, p=0.013) and VFA (OR 1.008, 95% CI 1.000 to 1.016, p=0.049), worse knee pain intensity (OR 1.238, 95% CI 1.028 to 1.490, p=0.024), worse scores for KOOS Pain (OR 0.964, 95% CI 0.937 to 0.992, p=0.013), KOOS Symptoms (OR 0.967, 95% CI 0.939 to 0.996, p=0.027), KOOS ADL (OR 0.965, 95% CI 0.935 to 0.996, p=0.026) and KOOS QOL 0.973, 95% CI 0.947 to 0.999, p=0.044) at baseline, were associated with RKOA at follow-up. Tests of physical function at baseline did not associate with RKOA after 2 years (table 2).

Table 2 Associations to development of radiographic knee osteoarthritis at 2-year follow-up in individuals with knee pain, n=174

| | Univariate logistic regression | | | Adjusted for age | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P value | OR | 95% CI | P value |
| Age, years | 1.073 | 1.006 to 1.144 | **0.033** | | | |
| Sex (women) | 1.251 | 0.487 to 3.212 | 0.641 | 1.155 | 0.443 to 3.012 | 0.768 |
| Body mass index, (kg/m$^2$) | 1.114 | 1.022 to 1.214 | **0.014** | 1.119 | 1.024 to 1.223 | **0.013** |
| Visceral fat area, cm$^2$ | 1.008 | 1.001 to 1.016 | **0.036** | 1.008 | 1.000 to 1.016 | **0.049** |
| NRS knee pain intensity, (0–10) | 1.218 | 1.016 to 1.461 | **0.033** | 1.238 | 1.028 to 1.490 | **0.024** |
| Morning knee stiffness | 0.885 | 0.354 to 2.213 | 0.793 | 0.898 | 0.354 to 2.276 | 0.820 |
| Crepitus | 1.008 | 0.391 to 2.601 | 0.987 | 1.211 | 0.458 to 3.202 | 0.700 |
| Bony enlargement | 2.125 | 0.833 to 5.423 | 0.115 | 1.829 | 0.704 to 4.751 | 0.215 |
| 30 s chair stand test, (sit to stand) | 0.984 | 0.903 to 1.073 | 0.721 | 0.988 | 0.906 to 1.078 | 0.786 |
| MVIC, m. Quadriceps, (Newton) | 1.001 | 0.996 to 1.006 | 0.624 | 1.002 | 0.997 to 1.008 | 0.372 |
| One-leg rising, (n=171), (sit to stand) | 0.955 | 0.910 to 1.003 | 0.066 | 0.963 | 0.919 to 1.009 | 0.116 |
| KOOS (pain) | 0.965 | 0.938 to 0.992 | **0.011** | 0.964 | 0.937 to 0.992 | **0.013** |
| KOOS (symptoms) | 0.971 | 0.944 to 0.999 | **0.041** | 0.967 | 0.939 to 0.996 | **0.027** |
| KOOS (ADL) | 0.964 | 0.935 to 0.994 | **0.019** | 0.965 | 0.935 to 0.996 | **0.026** |
| KOOS (Sport/Rec) | 0.986 | 0.969 to 1.003 | 0.111 | 0.985 | 0.968 to 1.003 | 0.109 |
| KOOS (QOL) | 0.975 | 0.950 to 1.001 | 0.056 | 0.973 | 0.947 to 0.999 | **0.044** |

Analysed with logistic regression models. Radiographic knee osteoarthritis based on Ahlbäck grade 1 or more in painful knee.
P value in bold typeface <0.005.
ADL, activities of daily living; KOOS, Knee injury and Osteoarthritis Outcome Score; MVIC, Maximal Voluntary Isometric Contraction; NRS, Numeric Rating Scale; QOL, quality of life; Sport/Rec, sports and recreational activities.

### Clinical KOA at 2-year follow-up

The prevalence of individuals fulfilling the clinical criteria for KOA after 2 years was 60% (n=105), while 26% (n=45) did not (figure 1). Of those not fulfilling the clinical criteria for KOA at follow-up, 56% (n=25) did not due to age, while 6 (13%) were ≥45 years at follow-up, transferring them from the no KOA group at baseline to clinical KOA. 13 individuals (7%) were transferred from clinical KOA at baseline to no KOA at follow-up, due to lack of activity-related knee pain at the time (figure 1).

## DISCUSSION

Approximately one out of seven individuals with knee pain at baseline had developed RKOA within only 2 years, that is, with structural signs visible on the radiograph. Development of RKOA within 2 years was associated with higher BMI, VFA, knee pain intensity as well as worse pain, symptoms, ADL and QOL self-reported in KOOS. Furthermore, those with RKOA (n=24) at follow-up all had symptoms of clinical KOA, that is, activity-related knee pain (n=24), and morning knee stiffness (n=16) at baseline, defined according to the NICE clinical guideline.

Knee pain and ageing are associated with a more rapid development from no KOA to RKOA over a period of 4–5 years.[37 38] In our study, almost 14% with knee pain at baseline developed RKOA quite rapidly in this 2-year follow-up, and these individuals were significantly older, compared with those who did not develop RKOA. Earlier studies have shown a variation of the prevalence of development from no KOA to RKOA over 4–5 years, varying between 13% and 51%.[38 39] These varying frequencies, including the prevalence in the current study, can partly be explained by diverging methods, for example, inclusion criteria (including older individuals, with knee symptoms and/or at risk of developing KOA), or using different radiographic classification criteria and/or cut-offs to confirm RKOA, and longer time to follow-up (4–5 years). The above-mentioned studies defined RKOA according to Kellgren-Lawrence (KL).[40 41] KL is a more widely used radiographic classification criteria compared with Ahlbäck.[27] Besides joint space narrowing, KL also focuses on osteophytes (grades 1 and 2), possibly making the criterion more sensitive to find early signs of RKOA. But still, Ahlbäck grade 1 is suggested to be comparable to grade 3 defined by KL, at least in a younger population.[41] Nevertheless, activity-related knee pain in middle-aged individuals is an early sign of KOA and is thus an important clinical finding. An early identification of these individuals represents a 'window of opportunity' to start first-line treatment, including education, exercise and possibly weight loss.[12]

The association between knee pain and RKOA has been described previously.[3 4] Compared with normative age-specific and gender-specific KOOS values, the

individuals in our study scored worse on all subscales, except KOOS ADL, indicating that their knee pain had an impact on them.[42] Intermittent knee pain and pain during weight-bearing activities, for instance, using stairs, are considered to be early signs of KOA.[5 6] Activity-related knee pain forms the basis for clinical KOA, according to NICE clinical guideline.[19] At baseline, 70% of individuals in the current study reported knee pain for more than 3 months and 94% had activity-related knee pain, which may indicate intermittent knee pain as a sign of early KOA. Being younger than 45 was the main reason for not fulfilling clinical KOA, both at baseline and at follow-up. This age limit may cause younger individuals with activity-related knee pain to be misclassified as non-clinical KOA and they could thereby miss out on first-line treatment. Despite a 2-year increase in age from baseline to follow-up, we noticed a decrease in prevalence of clinical KOA from 76% at baseline to 60% at follow-up. Whether that also could be explained by intermittent activity-related knee pain is hard to answer. Part of the explanation may lie in the fact that despite the observational design of the current study, regular monitoring can influence the individuals motivation for changes. For example, it may influence their interest on regular physical activity and weight control.[43]

To our knowledge, there are few previous studies that have based their analysis on the NICE guideline for clinical KOA, meaning there is only a narrow basis for comparisons. However, Skou *et al*[11] evaluated a large set of individuals in Denmark (n=13 459) already diagnosed with clinical KOA and/or RKOA in primary healthcare. Their sample was older (mean age 65), had higher BMI (29.1, kg/m$^2$) and 4% had RKOA (self-reported radiographic findings) compared with our sample. The prevalence of clinical KOA at baseline (76%) in our sample diverged somewhat from the prevalence reported by Skou *et al* (89%), possibly because of the differences in age, BMI and inclusion/exclusion criteria. The individuals in the Skou *et al* sample were included after seeking contact with the healthcare system because of knee joint problems and almost 35% had a previous knee injury. The intention of the inclusion and exclusion criteria in the HALLOA cohort (knee pain with no previous cruciate ligament injury) was to find individuals at an early stage of KOA with risk of developing RKOA. The exclusion of individuals with cruciate ligament injury (a strong RKOA predictor)[44] was set in order to fit the aim of the HALLOA cohort.[20]

Obesity is a well-known risk factor for KOA and is also considered to be modifiable.[5 13] Decreasing BMI may prevent development or progression of KOA.[39] Visceral fat, as a variable of central obesity, may be associated with pain and possibly also radiographic findings independent of BMI.[45] A high VFA level is also considered as risk factor for development of type 2 diabetes,[46] which is also associated to KOA.[47] The threshold value considered as a raised and unhealthy VFA varies between studies. In a gender-specific study the threshold value of a high VFA was set as 80 cm$^2$ for women and 120 cm$^2$ for men[46] compared with ≥100 cm$^2$ in studies that did not differentiate between women and men.[48 49] In this aspect the VFA for those developing RKOA in our study, must be considered as high (>130 cm$^2$). According to findings in the current study, both BMI and VFA were significantly associated with development of RKOA and thus important to measure, assess and treat in clinical settings. Another known modifiable lifestyle-related factor is the level of physical activity and exercise, which in turn can impact individuals' physical function and also be beneficial in weight control. Good physical function is helpful for individuals with KOA, and physical activity and exercise are considered to reduce pain.[5] However, previous studies show diverging results in terms of associations between quadriceps strength and development of RKOA.[3 50] In our current study, neither quadriceps strength nor test of physical function were associated with RKOA at follow-up. The prediction value of measuring physical function could be questioned. The non-association between RKOA and measurement of physical function could partly be explained by a type II error.

A limitation of our study is that, in defining RKOA based on the Ahlbäck criteria,[27] the opportunity to compare our study to others' is restricted, given that classification according to KL[40] is more commonly applied. By using Ahlbäck, we might have missed out on the chance to grade potential structural changes, for example, osteophytes in a more detailed way as defined grades 1 and 2 according to KL.[40] The main inclusion criteria of individuals in the current study were knee pain, frequently occurring in a primary care setting where MRI is not recommended as a first-line management, although the method is sensitive to detect a structural damage.[5] Even so, not using MRI in the study, could be seen as a limitation since individuals with early structural changes, for example, meniscal tears as a sign of early KOA can have been missed. The small sample size is another limitation that might have influenced the result. A strength of this study is the mix of clinical and easy self-reported data, including validated, time-efficient and easy-to-use measurements. These tools could easily be implemented in the clinic and used for screening by health professionals who meet individuals with knee pain and/or clinical KOA.

Activity-related knee pain is an important early sign of KOA. The individuals who developed RKOA in only 2 years all had clinical KOA at baseline according to NICE guideline. The sensitivity and specificity for the NICE clinical guideline were 100% and 30%, respectively, using RKOA as the reference standard. This result is in line with a previous study showing 94% sensitivity and 33% specificity for NICE, with a difference that their reference standard was clinically KOA set by clinical experts.[51] The high sensitivity of the NICE guideline may indicate usefulness in the clinic. The NICE guideline excludes young adults (<45 years) despite having activity-related knee pain, which might omit them from getting the recommended first-line treatment. Besides knee pain, obesity

also appears to be of importance, as it affects the development of RKOA and should be a part of the screening in individuals, if KOA is suspected.

## CONCLUSIONS

Approximately one out of seven individuals with knee pain and clinical KOA, according to NICE clinical guideline, developed RKOA in only 2 years. In individuals with activity-related knee pain, variables associated with RKOA, such as BMI, VFA and self-reported symptoms can be detected early. An early detection is desirable as it enables a faster start to first-line treatment, including education, exercise and possibly weight loss.

**Author affiliations**
[1]Department of Clinical Sciences, Section of Rheumatology, Lund University, Lund, Sweden
[2]Spenshult R & D center, Halmstad, Sweden
[3]Department of Regional Health Research, University of Southern Denmark, Odense, Denmark
[4]Department of Health and Sports, School of Health and Welfare, Halmstad University, Halmstad, Sweden
[5]Department of Orthopaedics, Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden
[6]Department of Orthopaedics, Sahlgrenska University Hospital, Göteborg, Sweden
[7]Department of Environmental and Biosciences School of Business, Innovation and Sustainability, Halmstad University, Halmstad, Sweden

**Acknowledgements** The authors thank all individuals of the Halland osteoarthritis cohort.

**Contributors** MT and EH led the study in terms of concept, design, analysis and the writing of the manuscript. AB, KA, AN and MLEA all had an active part in the concept, design and critical review of the manuscript. All the authors read and approved the final version of the manuscript. MT is the guarantor and accepts full responsibility for the finished work and/or the conduct of the study. MT had access to the data, and controlled the decision to publish.

**Funding** The study was supported by the Swedish Rheumatism Association (grant number R-967899), recipient: Maria LE Andersson.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not applicable.

**Ethics approval** The study was conducted following the ethical principles of the Helsinki Declaration of Helsinki. All participants were provided with both oral and written information, and written consent before participation. The study was approved by the Regional Ethical Review Board in Lund, Sweden (2016/229, 2017/253).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.



**ORCID iDs**
Margareta Törnblom http://orcid.org/0000-0002-1022-3799
Maria L E Andersson http://orcid.org/0000-0002-0217-5029
Emma Haglund http://orcid.org/0000-0002-1445-5247

## REFERENCES

1 Turkiewicz A, Gerhardsson de Verdier M, Engström G, *et al*. Prevalence of knee pain and knee OA in southern Sweden and the proportion that seeks medical care. *Rheumatology (Oxford)* 2015;54:827–35.
2 Hubertsson J, Petersson IF, Thorstensson CA, *et al*. Risk of sick leave and disability pension in working-age women and men with knee osteoarthritis. *Ann Rheum Dis* 2013;72:401–5.
3 Bastick AN, Belo JN, Runhaar J, *et al*. What are the prognostic factors for radiographic progression of knee osteoarthritis? A meta-analysis. *Clin Orthop Relat Res* 2015;473:2969–89.
4 Thorstensson CA, Andersson MLE, Jönsson H, *et al*. Natural course of knee osteoarthritis in middle-aged subjects with knee pain: 12-year follow-up using clinical and radiographic criteria. *Ann Rheum Dis* 2009;68:1890–3.
5 Emery CA, Whittaker JL, Mahmoudian A, *et al*. Establishing outcome measures in early knee osteoarthritis. *Nat Rev Rheumatol* 2019;15:438–48.
6 Hensor EMA, Dube B, Kingsbury SR, *et al*. Toward a clinical definition of early osteoarthritis: onset of patient-reported knee pain begins on stairs.Data from the osteoarthritis initiative. *Arthritis Care Res (Hoboken)* 2015;67:40–7.
7 Petersson IF, Jacobsson LTH. Osteoarthritis of the peripheral joints. *Best Pract Res Clin Rheumatol* 2002;16:741–60.
8 Kiadaliri AA, Lohmander LS, Moradi-Lakeh M, *et al*. High and rising burden of hip and knee osteoarthritis in the Nordic region, 1990-2015. *Acta Orthop* 2018;89:177–83.
9 Mahmoudian A, Lohmander LS, Mobasheri A, *et al*. Early-stage symptomatic osteoarthritis of the knee - time for action. *Nat Rev Rheumatol* 2021;17:621–32.
10 Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet* 2019;393:1745–59.
11 Skou ST, Koes BW, Grønne DT, *et al*. Comparison of three sets of clinical classification criteria for knee osteoarthritis: a cross-sectional study of 13,459 patients treated in primary care. Osteoarthr Cartil 2020;28:167–72.
12 Bannuru RR, Osani MC, Vaysbrot EE, *et al*. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthr Cartil 2019;27:1578–89.
13 Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. *Nat Rev Rheumatol* 2016;12:92–101.
14 ArtrosregistretS. Årsrapport 2022, Svenska Artrosregistret. 2022. Available: https://registercentrum.blob.core.windows.net/boa/r/Svenska-artrosregistrets-rsrapport-2022-korrigerad-fotograf-REGL21F1a.pdf
15 Luyten FP, Bierma-Zeinstra S, Dell'Accio F, *et al*. Toward classification criteria for early osteoarthritis of the knee. *Semin Arthritis Rheum* 2018;47:457–63.
16 Mahmoudian A, Lohmander LS, Jafari H, *et al*. Towards classification criteria for early-stage knee osteoarthritis: a population-based study to enrich for progressors. *Semin Arthritis Rheum* 2021;51:285–91.
17 Runhaar J, Kloppenburg M, Boers M, *et al*. Towards developing diagnostic criteria for early knee osteoarthritis: data from the CHECK study. *Rheumatology (Oxford)* 2021;60:2448–55.
18 Wang Q, Runhaar J, Kloppenburg M, *et al*. Diagnosis for early stage knee osteoarthritis: probability stratification, internal and external validation; data from the CHECK and OAI cohorts. *Semin Arthritis Rheum* 2022;55:152007.
19 Osteoarthritis in over 16S: diagnosis and management [Internet]. NICE National Institute for Health Care Excellence; 2022. Available: https://www.nice.org.uk/guidance/ng226/resources/osteoarthritis-in-over-16s-diagnosis-and-management-pdf-66143839026373
20 Andersson MLE, Haglund E, Aili K, *et al*. Cohort profile: the Halland osteoarthritis (HALLOA) cohort-from knee pain to osteoarthritis: a longitudinal observational study in Sweden. *BMJ Open* 2022;12:e057086.
21 Törnblom M, Bremander A, Andersson M. Pos0797-HPR prevalence and associations with development of radiographic knee osteoarthritis in individuals with knee pain – a 2-year follow-up. EULAR 2023 European Congress of Rheumatology, 31 May - 3 June. Milan, Italy; BMJ Publishing Group Ltd, June 2023
22 Sellam J, Berenbaum F. Is osteoarthritis a metabolic disease? *Joint Bone Spine* 2013;80:568–73.
23 Roos EM, Roos HP, Ekdahl C, *et al*. Knee injury and osteoarthritis outcome score (KOOS)--Validation of a Swedish version. *Scand J Med Sci Sports* 1998;8:439–48.
24 Roos EM, Roos HP, Lohmander LS, *et al*. Knee injury and osteoarthritis outcome score (KOOS)--Development of a self-administered outcome measure. *J Orthop Sports Phys Ther* 1998;28:88–96.

25 Boegård T, Rudling O, Petersson IF, *et al*. Joint-space width in the axial view of the patello-femoral joint: definitions and comparison with MR imaging. *Acta Radiol* 1998;39:24–31.
26 Boegård T, Rudling O, Petersson IF, *et al*. Postero-anterior radiogram of the knee in weight-bearing and semiflexion: comparison with MR imaging. *Acta Radiol* 1997;38:1063–70.
27 Ahlbäck S. Osteoarthrosis of the knee. A radiographic investigation. *Acta Radiol Diagn (Stockh)* 1968.
28 Hawker GA, Mian S, Kendzerska T, *et al*. Measures of adult pain: visual analog scale for pain (VAS pain), Numeric rating scale for pain (NRS pain), McGill pain questionnaire (MPQ), short-form McGill pain questionnaire (SF-MPQ), chronic pain grade scale (CPGS), short Form-36 bodily pain scale (SF-36 BPS), and measure of intermittent and constant osteoarthritis pain (ICOAP). *Arthritis Care Res (Hoboken)* 2011;63:S240–52.
29 Dobson F, Hinman RS, Hall M, *et al*. Reliability and measurement error of the osteoarthritis research society International (OARSI) recommended performance-based tests of physical function in people with hip and knee osteoarthritis. Osteoarthr Cartil 2017;25:1792–6.
30 Gill S, McBurney H. Reliability of performance-based measures in people awaiting joint replacement surgery of the hip or knee. *Physiother Res Int* 2008;13:141–52.
31 Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport* 1999;70:113–9.
32 Larsson AC, Petersson I, Ekdahl C. Functional capacity and early radiographic osteoarthritis in middle-aged people with chronic knee pain. *Physiother Res Int* 1998;3:153–63.
33 Hirano M, Katoh M, Gomi M, *et al*. Validity and reliability of Isometric knee extension muscle strength measurements using a belt-stabilized hand-held dynamometer: a comparison with the measurement using an isokinetic dynamometer in a sitting posture. *J Phys Ther Sci* 2020;32:120–4.
34 Koblbauer IFH, Lambrecht Y, van der Hulst MLM, *et al*. Reliability of maximal Isometric knee strength testing with modified hand-held Dynamometry in patients awaiting total knee Arthroplasty: useful in research and individual patient settings? A reliability study. *BMC Musculoskelet Disord* 2011;12:249.
35 Lahav Y, Goldstein N, Gepner Y. Comparison of body composition assessment across body mass index categories by two multifrequency bioelectrical impedance analysis devices and dual-energy X-ray absorptiometry in clinical settings. *Eur J Clin Nutr* 2021;75:1275–82.
36 Bergman S, Herrström P, Högström K, *et al*. Chronic musculoskeletal pain, prevalence rates, and sociodemographic associations in a Swedish population study. *J Rheumatol* 2001;28:1369–77.
37 Driban JB, Harkey MS, Barbe MF, *et al*. Risk factors and the natural history of accelerated knee osteoarthritis: a narrative review. *BMC Musculoskelet Disord* 2020;21:332.
38 Wesseling J, Bierma-Zeinstra SMA, Kloppenburg M, *et al*. Worsening of pain and function over 5 years in individuals with 'Early'OA is related to structural damage: data from the osteoarthritis initiative and CHECK (cohort hip & cohort knee) study. *Ann Rheum Dis* 2015;74:347–53.
39 Salis Z, Gallego B, Nguyen TV, *et al*. Association of decrease in body mass index with reduced incidence and progression of the structural defects of knee osteoarthritis: a prospective multi-cohort study. *Arthritis Rheumatol* 2023;75:533–43.
40 Kellgren JH, lawrence JS. Radiological assessment of Osteo-Arthrosis. *Ann Rheum Dis* 1957;16:494–502.
41 Petersson IF, Boegård T, Saxne T, *et al*. Radiographic osteoarthritis of the knee classified by the Ahlbäck and Kellgren & Lawrence systems for the tibiofemoral joint in people aged 35–54 years with chronic knee pain. *Ann Rheum Dis* 1997;56:493–6.
42 Marot V, Murgier J, Carrozzo A, *et al*. Determination of normal KOOS and WOMAC values in a healthy population. *Knee Surg Sports Traumatol Arthrosc* 2019;27:541–8.
43 Thorstensson CA, Roos EM, Petersson IF, *et al*. Six-week high-intensity exercise program for middle-aged patients with knee osteoarthritis: a randomized controlled trial [ISRCTN20244858]. *BMC Musculoskelet Disord* 2005;6:1–10.
44 Poulsen E, Goncalves GH, Bricca A, *et al*. Knee osteoarthritis risk is increased 4-6 fold after knee injury–a systematic review and meta-analysis. *Br J Sports Med* 2019;53:1454–63.
45 Andersson M, Haglund E, Aili K, *et al*. Associations between metabolic factors and radiographic knee osteoarthritis in early disease-a cross-sectional study of individuals with knee pain. *BMC Musculoskelet Disord* 2022;23:938.
46 Kim EH, Kim H-K, Bae S-J, *et al*. Gender differences of visceral fat area for predicting incident type 2 diabetes in Koreans. *Diabetes Res Clin Pract* 2018;146:93–100.
47 Courties A, Sellam J, Berenbaum F. Metabolic syndrome-associated osteoarthritis. *Curr Opin Rheumatol* 2017;29:214–22.
48 Japan ECoCfODi. New criteria for'obesity disease'in Japan. *Circ J* 2002;66:987–92.
49 Li S, Li S, Ding J, *et al*. Visceral fat area and body fat percentage measured by bioelectrical impedance analysis correlate with Glycometabolism. *BMC Endocr Disord* 2022;22:231.
50 Øiestad BE, Juhl CB, Culvenor AG, *et al*. Knee extensor muscle weakness is a risk factor for the development of knee osteoarthritis: an updated systematic review and meta-analysis including 46 819 men and women. *Br J Sports Med* 2022;56:349–55.
51 Wang Q, Runhaar J, Kloppenburg M, *et al*. Evaluation of the diagnostic performance of ACR, EULAR and NICE criteria against clinically relevant knee osteoarthritis; data from the CHECK cohort. Osteoarthr Cartil 2023;31:S144–5.