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SUMMARY

Objective: To improve the interpretation of the Knee injury and Osteoarthritis Outcome Score (KOOS) in individual patients, we explored associations with age, sex, BMI, history of knee injury and presence of clinical knee osteoarthritis, and developed percentile curves.

Methods: We used cross-sectional data of middle-aged individuals from the population-based Netherlands Epidemiology of Obesity (NEO) study. Clinical knee osteoarthritis was defined using the ACR classification criteria. KOOS scores were handled according to the manual (zero = extreme problems, 100 = no problems). Patient characteristics associated with KOOS were explored using ordered logistic regression, and sex and body mass index (BMI)-specific percentile curves were developed using quantile regression with fractional polynomials. The curves were applied as a benchmark for comparison of KOOS scores of participants with knee osteoarthritis and comorbidities.

Results: The population consisted of 6,643 participants (56% women, mean (SD) age 56(6) years). Population-based KOOS subscale scores (median; interquartile range) near optimum: pain (100;94–100), symptoms (96;86–100), ADL function (100;96–100), sport/recreation function (100;80–100), quality of life (100;75–100). Worse KOOS scores were observed in women and in participants with higher BMI. Clinical knee osteoarthritis was defined in 15% of participants, and was, in comparison to other patient characteristics, associated with the highest odds of worse KOOS scores. Furthermore, presence of any comorbidity and cardiovascular disease specifically, was associated with worse KOOS scores, particularly in women.

Conclusions: In the middle-aged Dutch population KOOS scores were generally good, but worse in women and with higher BMI. These percentile curves may be used as benchmarks in research and clinical practice.

Introduction

Knee complaints, such as pain and functional disability, are among the most reported complaints of the musculoskeletal system in the general practitioner's office.[1] The prevalence of knee complaints in the Dutch population is estimated to be 32.1 per 1000 persons per year. Besides injury, knee osteoarthritis (OA) is an important cause of knee complaints, especially in the elderly. Knee OA is one of the most common chronic joint disorders, with a prevalence in the Dutch general practice of 37.9 per 1000 patient years; occurring more often in women and increasing with age.[2]

To assess the patient's burden due to knee complaints the Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire was developed[3], which evaluates short-term and long-term knee symptoms, function and quality of life (QOL).[4] KOOS is a widely used patient-reported outcome measure, which underwent extensive metric testing and is considered valid, reliable and responsive across groups with knee injury and knee OA.[5]

The interpretation of the KOOS depends on relevant benchmarks. This is illustrated by previous studies on different knee-

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specific questionnaires in the general population, that show that a suboptimal score may be unrelated to musculoskeletal pathology.[6–8] Previous studies have developed reference values in population-based samples[9–11], but these studies have important limitations. Either the study populations were small, or only age-specific mean and median scores were reported[9], or they did not take into account the effect of body mass index (BMI).[9,11] Importantly, none of these studies explored how knee OA or other relevant knee-related factors or comorbidities affect KOOS scores.

Therefore, we aimed to develop percentile curves in a large population-based cohort of Dutch middle-aged individuals. We explored possible association of factors such as age, sex, BMI, history of knee injury, presence of clinical knee OA and comorbidities with KOOS scores. Furthermore, we illustrate the use of the percentile curves as a benchmark for comparison of KOOS scores of individual patients and specific patient groups.

Methods

Study design and population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based cohort study. Detailed description of study design and data collection has been provided elsewhere.[12] Briefly, men and women between 45 and 65 years with a self-reported BMI $\geq$27 kg/m^2 living in the greater area of Leiden (The Netherlands) were eligible to participate. In addition, all inhabitants aged between 45 and 65 years from one municipality (Leiderdorp) were invited to participate irrespective of their BMI, allowing for a reference BMI distribution comparable to the general Dutch population.[13] In total, 6,671 participants were included in the NEO study. The present study is a cross-sectional analysis of baseline measurements. The Medical Ethical Committee of the Leiden University Medical Center (LUMC) approved the design of the study and all participants gave written informed consent. We excluded participants with missing physical examination ($n = 14$) or missing all KOOS subscales ($n = 14$).

Questionnaires

Prior to the study visit, participants completed questionnaires on demographic and clinical information; including self-reported presence of inflammatory rheumatic disease, history of leg fractures and knee surgery, and presence of comorbidities (cardiovascular disease (CVD), liver disease, diabetes, renal disease, cancer and chronic pulmonary disease). In addition, participants completed the KOOS.[3,14] The KOOS consists of five subscales: pain (nine items), symptoms (seven items), function in activities of daily living (ADL) (17 items), sport and recreation function (five items) and knee-related QOL (four items). All patients scored the KOOS for their right knee and items were scored considering the previous week from 0 (no problems) to 4 (extreme problems), on a 5-point Likert scale. Subscale scores were calculated according to the KOOS user's guide[15] as the sum of the items included, and subsequently transformed to a 0–100 scale, with zero representing extreme knee problems and 100 representing no knee problems. A KOOS subscale score was considered valid when at least 50% of the items were completed. If more than 50% of data from a subscale was missing, the participant was excluded from analyses of that subscale.[15] The symptom scale was missing in 0.6% of participants, the pain scale in 0.8%, the ADL scale in 0.6%, the sport and recreational function scale in 2.1% and the QOL scale was missing in 0.8% of participants.

Clinical assessment

BMI was calculated from measured body weight and height (kg/m^2). Physical examination of the knees was performed by trained research nurses, using a standardized scoring form. Of both knees, presence of bony swellings, palpable pain and warmth, crepitus and movement restriction were assessed. Clinical knee OA was defined according to the American College of Rheumatology (ACR) classification criteria.[17]

Statistical analysis

In the NEO study participants were recruited in two phases. At first participants with a BMI $\geq$27 kg/m^2 were oversampled. Secondly, a reference population was recruited with a BMI distribution similar to the Dutch general population. In this study we aimed to make inferences on the associations in the general population, and the over-representation of overweight and obese participants may induce bias due to the skewed BMI distribution. To represent distributions and associations in the general population correctly, adjustment for this oversampling was made by weighting individuals towards the BMI distribution of participants from the Leiderdorp municipality ($n = 1{,}671$)[18], whose BMI distribution was similar to the general Dutch population.[13] All results were based on weighted analyses, using the Stata command *pweight,* that denotes the inverse of the probability that the participant is included because of the sampling design. Consequently, results can be interpreted as corresponding to a population-based study without oversampling. Ordinal logistic regression analyses were performed to explore determinants associated with worse KOOS subscale scores, stratified by sex. KOOS scores were categorized into three categories with cut-offs (provided in supplementary file A) chosen such that the first category contains participants with a maximum score (no complaints), and the two remaining categories were approximately equal in size. Associations were expressed as odds ratios (ORs) with 95% confidence intervals (CI), representing the OR of being in the lowest compared with the middle or highest KOOS category for a unit change in the determinant. Age and BMI were used as continuous variables, and standardized to a mean of zero and standard deviation (SD) of one prior to the analysis. Because the proportional odds assumption could not formally be tested in combination with the weight factor, we performed a multinomial logistic regression analyses as a sensitivity analyses (supplementary table A3). We explored which of the general patient characteristics influenced KOOS scores most to aid decisions about relevant subgroups for development of the KOOS percentile curves. Subsequently, we developed sex and BMI specific percentile curves for all KOOS subscales, to facilitate the interpretation of KOOS scores in patients of a particular sex and BMI. For development of the curves, BMI was included as a continuous variable. Participants with a BMI below the 1st or above the 99th percentile were excluded due to a low number of observations leading to unreliable estimations at those points. We used quantile regression with fractional polynomials[19] to derive the percentile curves as this method is suited for data that do not meet the usual regression assumptions of normality, linearity, and constant variance.[20–22] The 50th, 25th, 10th, 5th and 2.5th centiles were estimated. Powers for the fractional polynomial models were taken from a predefined set ($S = \{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$). More complicated functions were only accepted if they resulted in a substantially improved fit, aiming to improve the feasibility in practical use of the percentile curves. Goodness of fit of the curve was inspected visually. The 95% CIs of the curves are provided in supplementary file C. Subsequently, KOOS scores of participants with clinical knee OA, and with comorbidities were compared to the percentile curves developed in

the whole population. Lastly, we investigated whether there are specific items from each KOOS subscale that drive a low score. Stata V14.1 (StataCorp LP, TX, USA) was used for all analyses.

Results

Patient characteristics

After exclusion of participants with missing physical examination ($n = 14$) or missing all KOOS subscales ($n = 14$), the study population consisted of 6,643 participants with a mean (SD) age of 56 (6) years and a mean BMI of 26 (5) kg/m^2. About half of the population consisted of men (44%). As shown in Table I, general patient characteristics varied only slightly between sexes. Clinical knee OA was more common in women (18.3%) than in men (10.4%), while men more often had a history of knee surgery (20.8% in men vs 13.8% in women) and a history of leg fractures (9.3% in men vs 6.2% in women). The number and frequency of any comorbidity was equal between the sexes, while CVD occurred more often in men (7.6%) compared to women (4.1%). KOOS subscale scores (median; interquartile range) were high: pain (100; 94–100), symptoms (96; 86–100), ADL function (100; 96–100), sport and recreation function (100; 80–100), QOL (100; 75–100).

Patient characteristics associated with worse KOOS scores

Female sex was associated with an increased odds of being in a worse KOOS score category (compared to no complaints) on all subscales, with odds ratios (95% CI) ranging from 1.39 (1.22; 1.58) for the symptoms scale, to 1.63 (1.41; 1.88) for the pain subscale. Therefore, further analyses were stratified by sex. BMI was also associated with worse KOOS scores, with ORs of 1.08 (0.97; 1.21) in men and 1.46 (1.32; 1.61) in women on the KOOS subscale pain for each SD increase in BMI. For each SD increase in age, we observed ORs of 0.86 (0.77; 0.97) in men and 1.01 (0.90; 1.12) in women on the subscale pain.

Table II shows that among the patient characteristics that were investigated, clinical knee OA was associated with the highest odds of worse KOOS scores in all subscales. The largest ORs were found for the subscale pain in men 13.79 (9.61; 19.79) and for the subscale QOL in women 9.45 (7.06; 12.65). The symptom subscale was least affected by clinical knee OA (4.84 (3.48; 6.74) in men and 5.31 (4.05; 6.95) in women). Also inflammatory rheumatic diseases were positively associated with worse KOOS scores. In men the associations attenuated in the multivariable analyses, in women the OR varied between 2.07 (1.05; 4.11) for QoL and 2.85 (1.52; 5.33) for ADL function. A history of knee surgery was associated with approximately two to four times higher odds of worse KOOS scores compare to no history of knee surgery. A history of leg fractures was mostly associated with worse ADL (1.60 (1.03; 2.46)) and sport and recreation scores (1.66 (1.13; 2.46)) in women. Furthermore, each additional comorbidity increased the odds of worse KOOS scores, which was most evident for the sport and recreation scale with an OR of 1.31 (1.09; 1.57) in men, and for the ADL function subscale with an OR of 1.34 (1.13; 1.59) in women.

Percentile values

The observed KOOS subscale scores for the 50th, 25th, 10th, 5th and 2.5th percentile are presented in Table III. In Fig. 1 the KOOS percentile curves were plotted for the five KOOS subscales. The curves were derived using first-degree polynomials, as the fit of the curves did not markedly improve using higher degree fractional polynomials. Since the 50th percentile curves of the subscales sport and recreation function and QOL in men were constant at the maximum value of

	Men 44%		Women 56%	
General patient characteristics				
Age, year	56 (6)		55 (6)	
Ethnicity, % Caucasian	95		95	
Education, % high	48		44	
BMI, kg/m^2	26.9 (3.7)		25.9 (4.9)	
Clinical knee OA, %	10.4		18.3	
Inflammatory rheumatic disease, %	4.5		3.7	
History of knee surgery, %	20.8		13.8	
Knee prosthesis for OA, %	0.2		0.3	
Knee prosthesis other, %	0.4		1.3	
Arthroscopy, %	10.2		8.1	
Meniscus operation, %	11.8		7.6	
Knee surgery other, %	3.6		2.8	
History of leg fracture, %	9.3		6.2	
Any comorbidities, %	24.6		25.2	
Cardiovascular disease, %	7.7		4.2	
KOOS subscales				
Pain	95 (12)	100 (97–100)*	92 (15)	100 (92–100)*
Symptoms	92 (12)	100 (89–100)*	90 (14)	96 (86–100)*
ADL function	96 (11)	100 (97–100)*	93 (14)	100 (93–100)*
Sport and recreation function	88 (22)	100 (85–100)*	82 (28)	100 (75–100)*
Quality of life	88(18)	100 (75–100)*	84 (21)	94 (75–100)*

Results are based on analyses weighted towards the BMI distribution of the general population ($n = 6,643$). Numbers represent mean (SD) unless otherwise specified
* median (interquartile range). KOOS sub scores are transformed to a 0–100 scale, with zero representing extreme knee problems and 100 representing no knee problems.

Table I Characteristics of the weighted study population (***n*** = 6,643)

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	Univariable OR (95% CI)		Multivariable OR (95% CI)	
	Men	Women	Men	Women
Pain				
Age	0.95 (0.86; 1.06)	1.20 (1.09; 1.32)	0.86 (0.77; 0.97)	1.01 (0.90; 1.12)
BMI	1.22 (1.10; 1.35)	1.65 (1.51; 1.79)	1.08 (0.97; 1.21)	1.46 (1.32; 1.61)
Education, high vs other	0.77 (0.62; 0.96)	0.69 (0.57; 0.83)	0.93 (0.73; 1.19)	0.87 (0.69; 1.08)
Clinical knee osteoarthritis	18.10 (12.81; 25.58)	11.13 (8.56; 14.47)	13.79 (9.61; 19.79)	8.51 (6.49; 11.17)
History of knee surgery	4.33 (3.33; 5.62)	3.97 (3.04; 5.19)	3.18 (2.37; 4.25)	2.67 (1.95; 3.66)
History of leg fracture	1.09 (0.78; 1.53)	1.34 (0.93; 1.95)	0.93 (0.64; 1.36)	1.33 (0.86; 2.06)
Inflammatory rheumatic disease	1.53 (1.07; 2.18)	2.69 (1.53; 4.71)	1.17 (0.77; 1.79)	2.27 (1.24; 4.13)
Number of comorbidities	1.34 (1.14; 1.57)	1.49 (1.28; 1.74)	1.26 (1.05; 1.50)	1.20 (1.01; 1.43)
Symptoms				
Age	0.83 (0.75; 0.91)	1.05 (0.96; 1.15)	0.78 (0.71; 0.86)	0.90 (0.81; 0.99)
BMI	1.29 (1.19; 1.41)	1.57 (1.44; 1.70)	1.19 (1.08; 1.31)	1.37 (1.25; 1.51)
Education, high vs other	0.67 (0.56; 0.81)	0.67 (0.55; 0.80)	0.73 (0.60; 0.90)	0.76 (0.62; 0.94)
Clinical knee osteoarthritis	6.27 (4.54; 8.65)	6.45 (4.99; 8.33)	4.84 (3.48; 6.74)	5.31 (4.05; 6.95)
History of knee surgery	2.80 (2.22; 3.55)	3.09 (2.29; 4.17)	2.16 (1.68; 2.79)	2.16 (1.56; 2.99)
History of leg fracture	0.97 (0.72; 1.31)	1.12 (0.76; 1.64)	0.87 (0.63; 1.20)	1.07 (0.71; 1.62)
Inflammatory rheumatic disease	1.49 (1.01; 2.18)	2.51 (1.51; 4.15)	1.29 (0.83; 1.99)	2.18 (1.26; 3.77)
Number of comorbidities	1.16 (0.99; 1.37)	1.33 (1.14; 1.55)	1.11 (0.93; 1.32)	1.10 (0.93; 1.29)
ADL function				
Age	1.10 (0.99; 1.22)	1.25 (1.14; 1.38)	1.05 (0.94; 1.18)	1.05 (0.94; 1.17)
BMI	1.34 (1.21; 1.47)	1.84 (1.68; 2.01)	1.23 (1.11; 1.36)	1.63 (1.48; 1.81)
Education, high vs other	0.63 (0.50; 0.78)	0.61 (0.51; 0.74)	0.74 (0.59; 0.94)	0.77 (0.62; 0.96)
Clinical knee osteoarthritis	11.72 (8.38; 16.38)	11.08 (8.48; 14.47)	8.35 (5.83; 11.96)	8.53 (6.45; 11.28)
History of knee surgery	3.77 (2.94; 4.84)	3.65 (2.81; 4.73)	2.69 (2.03; 3.57)	2.49 (1.83; 3.40)
History of leg fracture	1.37 (0.97; 1.92)	1.50 (1.04; 2.17)	1.30 (0.89; 1.91)	1.60 (1.03; 2.46)
Inflammatory rheumatic disease	1.81 (1.23; 2.66)	3.01 (1.79; 5.07)	1.32 (0.87; 2.00)	2.82 (1.56; 5.12)
Number of comorbidities	1.40 (1.18; 1.67)	1.66 (1.43; 1.92)	1.20 (0.99; 1.46)	1.34 (1.13; 1.59)
Sport and recreation function				
Age	0.95 (0.86; 1.05)	1.27 (1.16; 1.40)	0.86 (0.77; 0.97)	1.08 (0.97; 1.20)
BMI	1.24 (1.13; 1.36)	1.80 (1.65; 1.96)	1.11 (1.01; 1.23)	1.62 (1.47; 1.79)
Education, high vs other	0.73 (0.60; 0.90)	0.73 (0.60; 0.88)	0.86 (0.69; 1.08)	0.96 (0.78; 1.19)
Clinical knee osteoarthritis	11.93 (8.66; 16.45)	11.44 (8.61; 15.22)	8.83 (6.33; 12.31)	8.33 (6.14; 11.30)
History of knee surgery	4.36 (3.34; 5.69)	4.86 (3.61; 6.53)	3.30 (2.48; 4.39)	3.54 (2.56; 4.90)
History of leg fracture	1.28 (0.92; 1.78)	1.60 (1.12; 2.29)	1.22 (0.85; 1.74)	1.66 (1.13; 2.46)
Inflammatory rheumatic disease	1.69 (1.12; 2.55)	3.37 (2.06; 5.53)	1.36 (0.88; 2.12)	2.85 (1.52; 5.33)
Number of comorbidities	1.39 (1.17; 1.64)	1.60 (1.36; 1.87)	1.31 (1.09; 1.57)	1.28 (1.07; 1.52)
Quality of life				
Age	0.92 (0.83; 1.02)	1.15 (1.05; 1.26)	0.85 (0.76; 0.95)	0.93 (0.84; 1.04)
BMI	1.25 (1.14; 1.37	1.61 (1.47; 1.75)	1.15 (1.04; 1.27)	1.40 (1.27; 1.55)
Education, high vs other	0.85 (0.69; 1.04)	0.72 (0.59; 0.86)	1.05 (0.84; 1.31)	0.87 (0.71; 1.08)
Clinical knee osteoarthritis	14.24 (10.04; 20.20)	12.15 (9.22; 16.00)	10.73 (7.48; 15.38)	9.45 (7.06; 12.65)
History of knee surgery	4.44 (3.40; 5.80)	5.21 (3.92; 6.92)	3.39 (2.54; 4.51)	3.92 (2.85; 5.40)
History of leg fracture	1.21 (0.89; 1.65)	1.19 (0.80; 1.77)	1.10 (0.79; 1.52)	1.11 (0.74; 1.66)
Inflammatory rheumatic disease	1.58 (1.13; 2.21)	2.56 (1.45; 4.50)	1.30 (0.85; 1.98)	2.07 (1.05; 4.11)
Number of comorbidities	1.23 (1.04; 1.44)	1.55 (1.33; 1.80)	1.13 (0.95; 1.34)	1.32 (1.12; 1.57)

Results are based on analyses weighted towards the BMI distribution of the general population ($n = 6,643$). Age and BMI were standardized (mean 0, SD 1), leading to odds per SD increase of the variable. Inflammatory rheumatic disease: rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis or spondyloarthritis. Comorbidities: cardiovascular disease, liver disease, diabetes, renal disease, cancer and chronic pulmonary disease. Abbreviations: CI = confidence interval, KOOS= Knee injury and Osteoarthritis Outcome Score, OR = odds ratio, SD = standard deviation.

Table II Factors associated with Knee injury and Osteoarthritis Outcome Score, stratified by sex

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100, these were fitted with linear functions. Evident from Table III and from Fig. 1 is that KOOS scores were worse in women than men and that KOOS scores were worse with higher BMI in all KOOS subscales in both men and women. Intercepts, regression coefficients and fractional polynomial powers are provided in supplementary file B, along with an example calculation.

Use of the percentile curves in practice: an example

Patient X consults her orthopaedic surgeon with longstanding knee complaints to see whether there is an indication for a total knee replacement. She is obese, with a BMI of 33 kg/m^2. Patient X completes the KOOS questionnaire. She suffers from pain in her knee on a daily basis, and experiences severe pain when she goes up and down stairs and when pivoting on her knee. She reports moderate pain in her knee when bending her knee fully and when walking on a flat surface, or when she has to stand for prolonged periods of time. She has mild pain when sitting. Her responses add up to a KOOS pain subscale score of 50. To get a better grasp of what a pain score of 50 means in comparison to the general population, the score was plotted on the percentile curves (see Fig. 1). This showed that the pain score of this particular patient is below the 10th percentile, indicating that less than 10% of the general population has a pain score this severe.

KOOS subscale	BMI	Percentiles									
		Men					Women				
		50th	25th	10th	5th	2.5th	50th	25th	10th	5th	2.5th
Pain											
	≤25	100.0	97.2	86.1	75.0	66.7	100.0	97.2	86.1	75.0	55.6
	>25 - ≤30	100.0	97.2	80.6	69.4	58.3	100.0	88.9	66.7	55.6	44.4
	>30	100.0	91.7	71.4	52.8	41.7	97.2	77.8	55.6	38.9	30.6
Symptoms											
	≤25	100.0	92.9	82.1	71.4	64.3	96.4	89.3	75.0	71.4	60.7
	>25 - ≤30	96.4	85.7	71.4	67.9	57.1	92.9	82.1	67.9	60.7	50.0
	>30	96.4	78.6	71.4	57.1	46.4	89.3	75.0	57.1	46.4	39.3
ADL function											
	≤25	100.0	98.5	89.7	76.5	70.6	100.0	98.5	88.2	79.4	66.2
	>25 - ≤30	100.0	97.1	83.8	70.6	61.8	100.0	89.7	69.1	54.4	45.6
	>30	100.0	92.6	73.5	55.9	43.8	96.3	76.5	52.9	41.2	32.3
Sport and recreation											
	≤25	100.0	90.0	65.0	45.0	25.0	100.0	85.0	55.0	30.0	20.0
	>25 - ≤30	100.0	85.0	55.0	35.0	25.0	95.0	65.0	30.0	15.0	5.0
	>30	100.0	75.0	35.0	15.0	5.0	80.0	35.0	10.0	0.0	0.0
Quality of life											
	≤25	100.0	83.3	62.5	56.3	43.8	100.0	75.0	62.5	50.0	37.5
	>25 - ≤30	100.0	75.0	62.5	43.8	37.5	87.5	68.8	50.0	37.5	31.3
	>30	100.0	75.0	50.0	37.5	25.0	81.3	56.3	37.5	31.3	18.8

Results are based on analyses weighted towards the BMI distribution of the general population ($n = 6,643$). Abbreviations: ADL = activities of daily living, BMI = body mass index, KOOS= Knee injury and Osteoarthritis Outcome Score.

Table III Observed sex and BMI specific percentile values of the Knee injury and Osteoarthritis Outcome Score

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KOOS scores in specific population groups

In Fig. 2(A), the KOOS pain subscale scores of participants with clinical knee OA were plotted over de percentile curves, which demonstrates that the KOOS scores in these participants were lower than in the reference population. The median KOOS subscale pain score in participants with clinical knee OA lay between the 25th and 5th percentile in men and between the 50th and 10th percentile in women.

In women with comorbidities, median KOOS pain scores were between the 50th and 25th percentile, and worse scores were observed in individuals with a higher BMI [Fig. 2(B)]. In contrast, in men with any comorbidity or CVD, median KOOS pain scores were at the 50th percentile, with exception of men with an extremely high BMI (above 37 kg/m2), who had worse KOOS pain scores.

Items driving low KOOS subscale scores

We investigated which items were most often reported to be at least mildly affected in patients in the worst KOOS subscale score category (category cut-offs can be found in supplementary file A) and drove worse KOOS subscale scores. In participants in the worst category of the KOOS pain subscale scores, 94% of participants reported a higher frequency of knee pain and the item "going up or down stairs" was scored positive in 91% of participants of the worst score category. Most frequent reported symptoms were feeling grinding or hearing a clicking noise when the knee moves (65%), and restrictions in movement, in particular inability to fully bend the knee (65%). A low score on the ADL function scale resulted mostly from difficulties with heavy domestic duties, which was scored positive in 92% of participants in the worst category of ADL function scores, followed by getting in and out of a car (89%) rising from sitting (88%) and ascending stairs (87%). In patients in the category with the worst sport and recreation function subscale scores all items were relevant (90–96% reported at least mild difficulty). Similarly, in patients within the worst QOL subscale scores, at least mild difficulty was reported for all items with high frequency (87–99%). Results were similar between men and women (data not shown).

Discussion

We developed percentile curves for the five KOOS subscales in a large middle-aged population-based cohort. We showed that sex and BMI were strongly associated with KOOS scores, while age was not consistently associated with the KOOS scores. Therefore, the percentile curves are sex- and BMI-specific. In addition, we illustrated possible applications of the curves, and investigated how the scores of specific subgroups related to the curves. As expected, we observed that median KOOS scores of participants with knee OA were well below the 50th percentile of the general population. In addition, we observed that in women, but not in men, with comorbidities the median KOOS scores were worse compared to the general population, especially in women with a higher BMI.

In the current study, women scored worse on all KOOS subscales, which is in line with previous research.[9–11] Furthermore, our results show that a higher BMI was associated with worse KOOS scores. The association of BMI with KOOS scores has only been briefly touched upon by a limited number of other studies.[10,11] Marot *et al.* did not find relevant differences in KOOS scores with higher BMI, however they compared KOOS scores in participants between 16 and 97 years with a BMI ≥25 kg/m^2 to participants with a BMI < 25.[10] Williamson *et al.* investigated age-related effects on KOOS and additionally compared the effects of BMI and age.

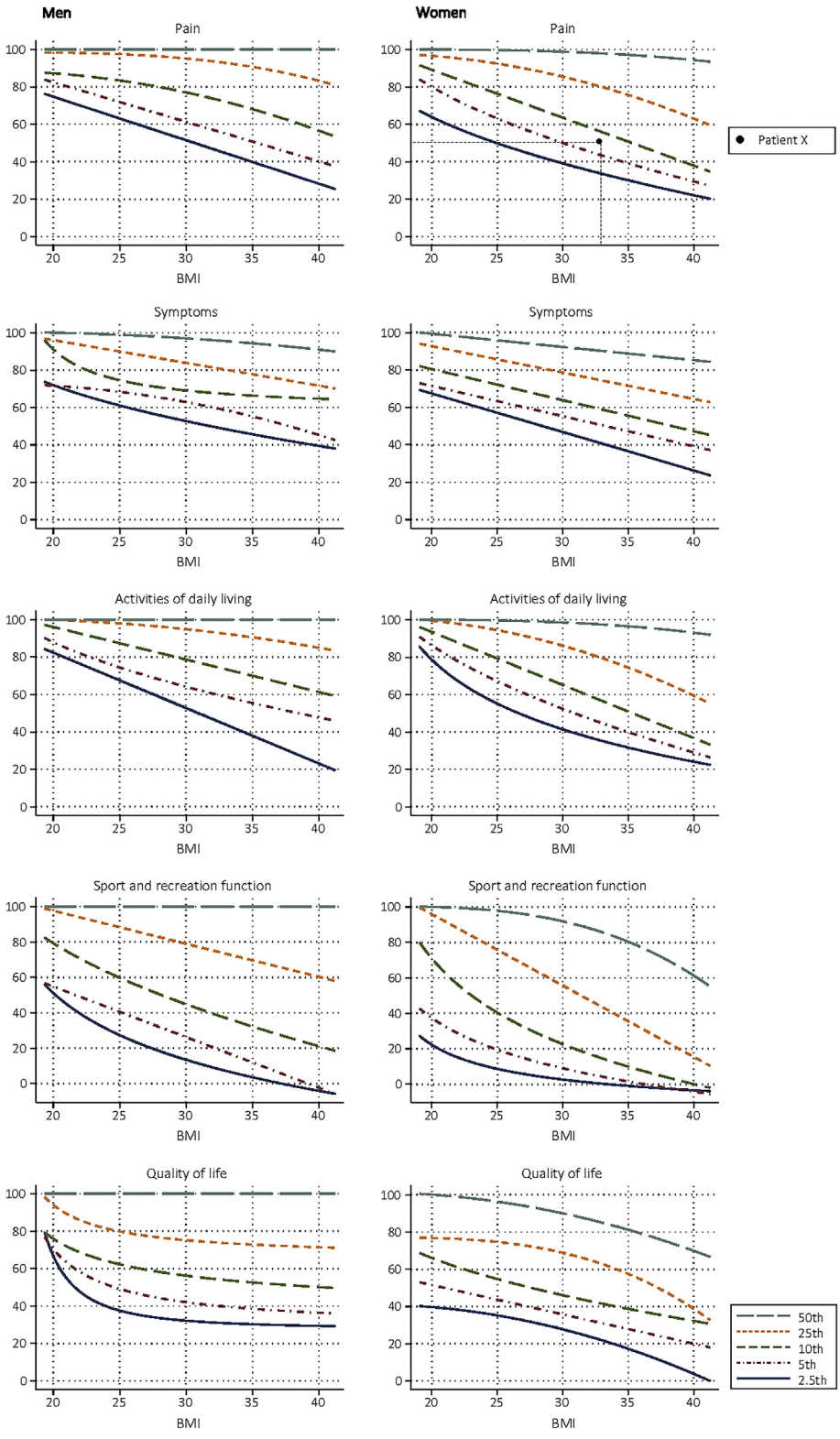

Fig. 1

Sex- and BMI- specific percentile curves for the five Knee injury and Osteoarthritis Outcome Score subscales. Results are based on analyses weighted towards the BMI distribution of the general population (***n*** = 6,438). Participants with a BMI below the 1st or above the 99th percentile were excluded (***n*** = 205). Patient X is included for illustrative purposes; see text for a more detailed explanation.

Osteoarthritis and Cartilage

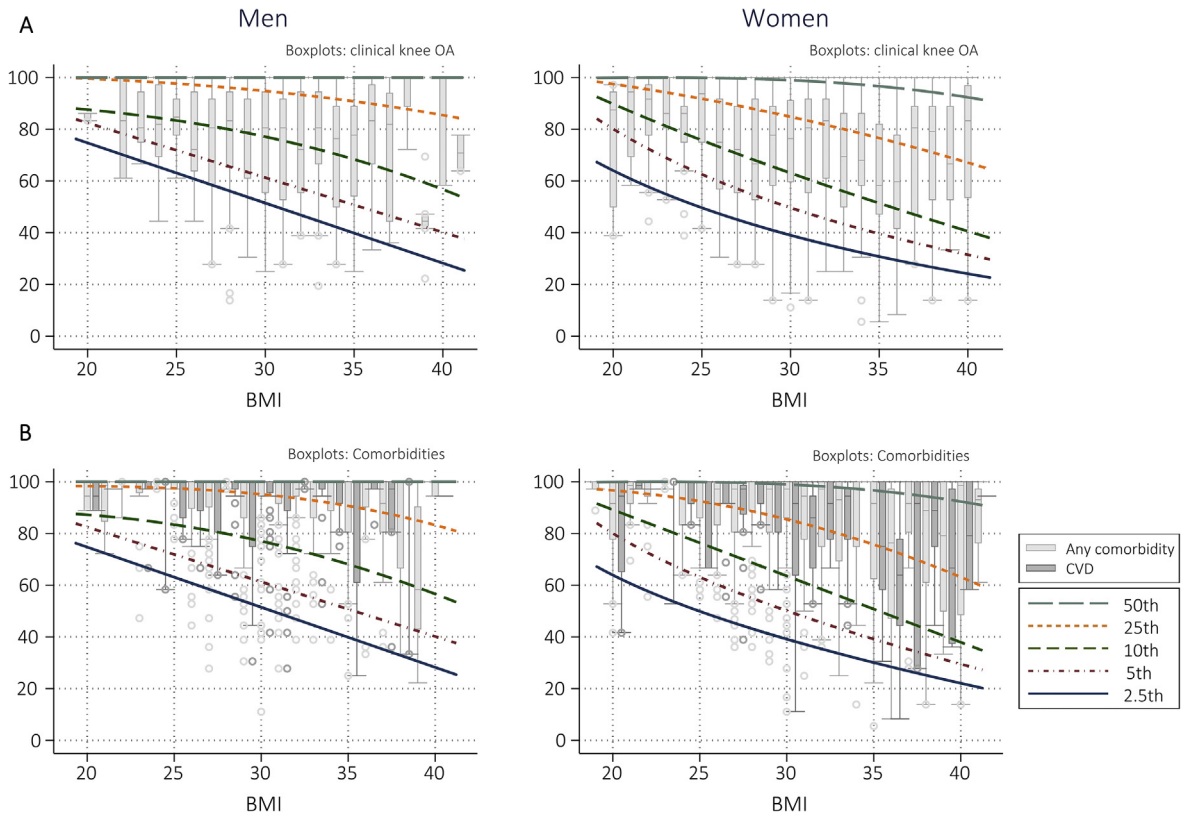

Fig. 2 Percentile curves of the Knee injury and Osteoarthritis Outcome Score subscale pain compared to scores of participants classified with knee OA [A] and presence of any comorbidity and cardiovascular disease (CVD) [B]. Results are based on analyses weighted towards the BMI distribution of the general population (***n*** = 6,438). Participants with a BMI below the 1st or above the 99th percentile were excluded (***n*** = 205).

Osteoarthritis and Cartilage

Compared to age, they observed a stronger effect of BMI on the subscale sport and recreation function, and a smaller effect of BMI on the QoL subscale. Unfortunately, results regarding the effect of BMI on the other subscales were not mentioned.[11] Our results indicate that increasing BMI may play an important role in the interpretation of KOOS scores, and the limited number of studies available underscore the necessity to further explore the role of BMI on pain, function and QOL.

In our population between 45 and 65 years of age, we found no associations of age with KOOS subscale scores in the multivariable analyses. Previous population-based studies have included populations with participants between 18 and 84 years[9], 16 and 97 years[10] and between 18 and 64 years[11], and found varying results for the effect of age on the different KOOS subscales. Discrepancies with, and between, these studies may be explained by treating age as a continuous or categorical variable, or the different age ranges investigated. Of note, the population of interest should kept in mind when interpreting these results. One of the major patient groups in which the KOOS is used are middle-aged patients with osteoarthritis. Previous studies have used study populations which for a considerable part consisted of participants who are not part of the target population. Our study is the first to focus on the effect of age on KOOS scores in the middle-aged population.

Furthermore, we have illustrated possible applications of the percentile curves. The curves may be used to determine how the KOOS scores of individual patients relate to the reference population, but could also be used to track changes in scores following for example physical therapy or knee surgery. In addition, the curves may be used to get more insight in how the scores of specific patient groups relate to the scores in the general population. We plotted the scores participants with knee OA on the percentile curves. As expected, in both sexes KOOS scores of participants with knee OA were below the 50th percentile curves. In men, median scores were around the 10th percentile and in women around the 25th percentile, which constitute clinically relevant reductions.[3] Furthermore, we investigated the association of other comorbidities with KOOS scores. The presence of any comorbidity was associated with worse KOOS scores, most notably in women. On the percentile curves, median scores of women with comorbidities were between the 50th and 25th percentile, while median scores of men were above or just below the 50th percentile. This demonstrates that these curves can be used to visualize to what extent scores of specific patient groups deviate from the general population. Our results further imply that while knee OA was strongly associated with worse KOOS scores compared to the general population, it is important to realize that a lot of different factors, such as presence of comorbidities or a history of knee surgery, may influence these results.

To our knowledge, we are the first to develop and apply KOOS percentile curves to investigate knee OA disease burden in a population-based study sample of considerable size. Another strength of our study is that we have accounted for the non-normal

distribution of the KOOS subscales scores by using non-parametric tests. Previous studies have used parametric statistical methods, which might be less suited for the investigation of KOOS percentile values, as KOOS scores are very skewed towards high scores in population-based studies. To overcome this problem, we used quantile regression with fractional polynomials to develop the percentile curves. Furthermore, while tables provided by previous studies may give detailed information, we deemed that curves, similar to the growth curves extensively used in paediatrics, facilitate the interpretation and use of these benchmarks. The rather narrow age range in our study might be seen as a limitation. However, as discussed above, we believe that the age range of our population is representative for patients most at risk for developing symptomatic knee OA, and may therefore be the most relevant age group to investigate. A further limitation is that individuals willing to participate may be more mobile and healthier, which could have led to a healthy-candidate bias. In addition, the history of other musculoskeletal conditions, among which inflammatory rheumatic diseases, and comorbidities was obtained by questionnaire, which could be subject to recall bias and misclassification.

To conclude, we have developed sex- and BMI-specific percentile curves for the five KOOS subscales. As we have shown, these curves can be used to help interpretation of KOOS scores of individual patients, as well as to assess the deviation of KOOS scores of specific patient groups from the general population. These charts may be used as benchmarks to improve interpretation of KOOS scores in research and daily clinical care.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2020.03.014.

Author contribution

ML was the principle investigator and contributed to design of the study, data analysis, data interpretation and drafting of the article. SB provided statistical support, contributed to data interpretation and critically revising of the article. FPBK, EMR, FR and MK contributed to design of the study, data interpretation and critically revising of the article. All authors give final approval of the submitted article.

Conflict of interest

MK has received financial support from the Dutch Arthritis Society. All other authors have declared no conflicts of interest.

Role of funding source

None.

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