CHAPTER 6

Do knee osteoarthritis and fat-free mass interact in their impact on health-related quality of life in men? Results from a population-based cohort

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ABSTRACT

Objective
To investigate whether obesity and other risk factors interact with knee osteoarthritis (OA) in its adverse impact on health-related quality of life (HRQOL).

Methods
In 1,262 participants of the Netherlands Epidemiology of Obesity study, a population-based cohort (age 45 to 65 years, 53% women, and median body mass index (BMI) 27 kg/m^2), knee OA was defined following modified American College of Rheumatology criteria. BMI and fat-free mass (FFM) (as proxy for muscle mass) were assessed by bioelectrical impedance analysis, and comorbidities by self-report. HRQOL was assessed using the Short Form 36 physical component summary (PCS) score. Linear regression analyses were performed to examine associations between knee OA and PCS score, adjusting for age and sex and stratified for BMI, FFM, and comorbidities.

Results
Knee OA (prevalence 16%) was associated with a 7.2-points lower PCS score (95% confidence interval -9.5 to -4.8). PCS score was also negatively associated with obesity and comorbidities; however, no interaction with knee OA was seen. Low FFM was associated with a lower PCS score and interacted with knee OA in men. Interaction between concurring OA and low FFM attributed to 64% of the decrease in PCS score, as compared with men without OA and with high FFM.

Conclusion
Knee OA was associated with a lower HRQOL, as were its risk factors, obesity, comorbidities, and low FFM. In men, FFM interacted with knee OA, leading to an additional decrease of HRQOL in the case of concurrence. Especially in the former, improvement of FFM may improve HRQOL in knee OA patients.

INTRODUCTION

Of the musculoskeletal disorders, osteoarthritis (OA) is the second largest contributor to disability. Knee OA has been shown to account for 83% of the global years lived with disability that were due to the presence of any OA.[1] In addition, knee OA has been associated with an impaired health-related quality of life (HRQOL).[2-4]

Several risk factors for knee OA are known;[5,6] some of these risk factors are not only associated with development of OA but also with a decreased HRQOL. It is possible that presence of knee OA together with a risk factor that is also associated with HRQOL results in strengthening of both adverse associations with HRQOL. The latter will be especially important when it concerns risk factors that can either be prevented or treated, as interventions aimed at prevention or treatment of these factors could then result in additional improvement of HRQOL in knee OA patients.

Modifiable risk factors for OA that also decrease HRQOL could be potential targets for interventions. Obesity may be one of those factors; it has been related both to development of knee OA and to impaired HRQOL.[7-9] Another risk factor for knee OA that may be a target for intervention is muscle weakness.[10] Although no studies related muscle weakness or the actual amount of muscle mass to HRQOL, physical frailty (associated with low fat-free mass (FFM), a proxy for muscle mass) has been related to decreased HRQOL.[11] A preventable risk factor is the presence of comorbidities, such as cardiovascular diseases and diabetes mellitus. Such comorbidities have been associated both with presence of knee OA and decreased HRQOL.[12-14]

Obesity, exercise (related to muscle mass), and comorbidities have been related to HRQOL, not only in the general population but also within knee OA patients.[15-18] However, the relative contributions of knee OA and these risk factors to HRQOL, as well as a possible interaction when they concur, are not clear.

To gain insight into possible targets for improvement or prevention of HRQOL in knee OA patients, we aimed to evaluate the impact of the presence of knee OA and its modifiable or preventable risk factors: obesity, FFM (as proxy for muscle mass), and comorbidities on HRQOL. In addition, we aimed to examine the presence of interaction between knee OA and these risk factors in relation to HRQOL.

PATIENTS AND METHODS

Study design and study population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based prospective cohort study including 6,673 individuals aged 45 to 65 years, with an oversampling of persons with overweight or obesity (members of the NEO Study Group are listed in Appendix A). Detailed information about the study design and data collection has been described previously.[19] In short, men and women between ages 45 to 65 years with a self-reported body mass index (BMI) of ≥27 kg/m^2 living in the greater area of Leiden (in the West of The Netherlands) were eligible to participate. In addition, all inhabitants aged 45 to 65 years from one municipality (Leiderdorp) were invited irrespective of their BMI, allowing for a reference distribution of BMI.

All participants completed questionnaires on demographic and clinical data, in addition to the Short Form 36 (SF-36) Health Survey, and visited the NEO study center between September 2008 and September 2012 for an extensive physical examination, including anthropometry and blood sampling. All medication that was used in the month preceding the study visit was recorded. A random sample of 1,285 study participants without contraindications (metallic devices, claustrophobia, body circumference >170 cm) underwent magnetic resonance (MR) imaging of the right knee. The present study is a cross-sectional analysis of baseline measurements of these 1,285 participants. The study was approved by the medical ethics committee of the Leiden University Medical Center and all participants gave written informed consent.

Data collection

Highest level of education was reported in categories according to the Dutch education system and grouped into low, medium, or high education. Reported professions were categorized into non-, light- and heavy physically demanding work, based on a classification scheme of physical work demands by De Zwart et al.[20]

MR imaging

MR imaging was performed using a dedicated knee coil in a 1.5T system (Philips, Medical Systems). Our standardized scanning protocol consisted of (1) coronal proton density (PD) turbo spin-echo (TSE), repetition time (TR)/echo time (TE) 2,335/35 msec; echo train length (ETL) 6; (2) coronal frequency selective fat-suppressed PD TSE (TR/TE 2,334/ 35 msec, ETL 6, 3 mm slice thickness); (3) sagittal PD TSE (TR/TE 2,338/35 msec, ETL 6; 3.5 mm slice thickness); (4) sagittal frequency selective fat-suppressed T1-weighted 3-dimensional gradient echo sequence (TR/TE 11/5.5, 25° flip angle, 150 mm field of view, 272 x 512 acquisition matrix, 2 mm slice thickness with a 1 mm overlap between images); and (5) axial frequency selective fat-suppressed PD TSE (TR/TE 3,225/15 msec, ETL 6, 4 mm slice thickness). In all TSE sequences we used a 150-160 mm field of view and a 304 x 512 acquisition matrix. Total acquisition time, including the initial survey sequence, was 30 minutes.

Definition of OA

Knee OA was defined, based on modified criteria of the American College of Rheumatology (ACR), as presence of osteophytes, knee pain on most days of the prior month, and at least 1 of the following criteria: age >50 years, stiffness <30 minutes duration, and crepitus on active motion.[21] Instead of the presence of radiographic osteophytes as described in the original ACR criteria, osteophytes were assessed with MR imaging.

Assessment of the MR imaging was done by a trained reader (AWV, supervised by JLB), using the validated semiquantitative knee OA scoring system, blinded to clinical data. Osteophytes were defined as focal bony excrescences extending from a cortical surface and measured from base to tip. Osteophytes were either absent (grade 0), or present (grade 1 (<3 mm), grade 2 (3-5 mm), or grade 3 (>5 mm)).[22] A random 10% of the MR images (n = 120) were scored twice to test the reproducibility; the calculated intraclass correlation coefficient was 0.97.

Physical examination of the knees was performed by trained research nurses, using a standardized scoring form. Self-reported knee pain and morning stiffness were measured using standardized questionnaires.

Body composition

Height was measured with a calibrated tape measure. Body weight, fat mass, and body fat percentage were measured using the Tanita foot-to-foot bio impedance balance (TBF-310, Tanita International Division).[23] BMI was calculated by dividing the weight in kilograms by the height in meters squared (kg/m^2). According to the classification of the World Health Organization, BMI was categorized into normal weight (BMI <25 kg/m^2), overweight (BMI 25-30 kg/m^2), and obesity (BMI ≥30 kg/m^2).

The percentage of FFM was calculated as 100 minus the percentage of body fat measured by bioelectrical impedance analysis using the Tanita balance.[23] Percentage of FFM was divided in tertiles separately in men and women because of the major difference in FFM between the sexes.[24] Low FFM was defined as the lowest tertile of percentage FFM.

Comorbidities

The presence of cerebrovascular disease, lung disease, cardiovascular diseases (myocardial infarction, angina, congestive heart failure, stroke, peripheral vascular disease), and diabetes was self-reported using a standardized questionnaire. In addition, use of glucose-lowering therapy or a measured fasting plasma glucose of ≥7.0 mmol/liter at the time of the study visit were also defined as diabetes mellitus.

HRQOL

HRQOL was assessed using the physical component summary (PCS) score of the generic SF-36. The SF-36 PCS and mental component summary scores were derived using norm-based data from the Dutch population, standardized to a mean of 50 and SD of 10.[25] The total scores range from 0 to 100, and higher scores indicate better HRQOL.26 The minimal clinical important difference is 2.5 to 5.0 points.[27]

Statistical analysis

Data were analyzed using STATA, version 12. In the NEO study there is an oversampling of persons with a BMI ≥27 kg/m^2. To correctly represent associations in the general population, adjustments for the oversampling of individuals with a BMI ≥27 kg/m^2 were made.[28] This was done by weighting individuals towards the BMI distribution of participants from the Leiderdorp municipality (n = 1,671),[29] whose BMI distribution was similar to the BMI distribution in the general Dutch population.[30] Consequently, results apply to a population-based study without oversampling of BMI ≥27 kg/m^2.

First, we performed linear regression analyses to examine the association of knee OA with the SF-36 PCS score. Regression coefficients with 95% confidence intervals (95% CI) were reported and can be interpreted as the mean difference in PCS score of participants with knee OA as compared with participants without knee OA. Adjustments were made for age, sex, BMI, FFM, and presence of comorbidities.

Second, we examined the presence of interaction of knee OA with obesity, low percentage FFM, or comorbidities in relation to HRQOL by including interaction terms between knee OA and BMI, knee OA and percentage FFM, and knee OA, and presence of comorbidities in the model. These regression analyses were performed separately for the 3 interaction terms. Interaction was considered present when the interaction term was significant ($P < 0.05$).

Finally, for a transparent presentation of the joint associations, we stratified all analyses by knee OA and categories of BMI, FFM and comorbidities to report all associations compared with the unexposed group as a joint reference category.[31,32]
For example, the adjusted difference in PCS scores were calculated for each stratum of BMI, using individuals without knee OA and with normal weight as reference. Similar analyses were performed with tertiles of FFM and presence/absence of comorbidities.
Since BMI is a cumulative measure of fat, muscle, and bone, we performed sensitivity analyses including fat mass as specific measure of adiposity instead of BMI as robust measure of obesity. Furthermore, since MR imaging is a very sensitive tool for detection of osteophytes, sensitivity analyses excluding small osteophytes (grade 1) from the knee OA definition were performed.

RESULTS

Population characteristics
After exclusion of individuals with missing SF-36 data (n = 23), data from 1,262 participants were analyzed. The unweighted baseline characteristics, i.e. without taking oversampling of BMI ≥27 kg/m^2 into account, are shown in Supplementary Table 1. Table 1 shows the weighted baseline characteristics of the total study population and stratified by knee OA. These characteristics represent the population to which all subsequent results apply. Median (25th to 75th percentiles) age of the total study population was 56 years (51 to 61 years), BMI 27 kg/m^2 (24 to 29 kg/m^2), and 56% were women.
The prevalence of knee OA, including osteophytes of at least grade 1 as assessed on MR imaging, was 16% (95% CI 13% to 19%). The prevalence of knee OA when including only osteophytes of at least grade 2 was 5% (95% CI 4% to 7%). Median age and percentage of women were higher in individuals with knee OA. Furthermore, individuals with knee OA had a higher median BMI and more comorbidities as compared with participants without knee OA. Mean SF-36 PCS score was lower in individuals with knee OA than in those without (Table 1).

Knee OA in relation to HRQOL
First, we investigated the association between knee OA and PCS score (Table 2). The crude mean PCS score in individuals with knee OA was 7.4 points lower (95% CI -9.3 to -5.4) than in individuals without knee OA. After adjustment for age, sex, and the assessed risk factors, the mean difference in PCS score between individuals with and without OA was -6.2 points (95% CI -8.0 to -4.4).
Sensitivity analysis, including fat mass as specific measure of adiposity instead of BMI as robust measure of obesity, provided the same mean difference in PCS score between individuals with and without OA (-6.2 points (95% CI -8.1 to -4.4)). Sensitivity analyses, including knee OA based on osteophytes of at least grade 2 instead of all observed osteophytes, yielded similar results.

Table 1. Baseline characteristics of the NEO study population

		Total population	Knee OA (prevalence 16%)	No knee OA (prevalence 84%)
Age (years)		56 (51-61)	57 (53-61)	56 (50-61)
Sex (% women)		56	61	55
Education (high)		38	34	39
Profession (high physically demanding)		10	10	9
BMI (kg/m^2)		26.7 (23.8-29.4)	27.1 (24.8-30.7)	26.6 (23.4-29.2)
FFM (kg)	Men	74.7 (71.2-79.3)	74.7 (71.4-79.0)	74.8 (71.2-79.3)
	Women	61.6 (57.2-66.7)	59.8 (55.2-63.7)	61.7 (57.4-67.3)
Comorbidities		14	24	13
- Cardiovascular disease		6	8	5
- Cerebrovascular accident		3	2	3
- Diabetes		7	12	6
- Lung disease		4	9	2
SF-36 MCS score		51.5 ± 8.7	51.2 ± 9.9	51.5 ± 8.5
SF-36 PCS score		53.0 ± 8.6	46.9 ± 9.5	54.2 ± 7.9

Values are the percentage, median (25th to 75th percentiles), or mean ± SD. Results are based on weighted analyses of the study population (n = 1,262).

BMI, body mass index; FFM, fat-free mass; MCS, mental component summary; NEO, Netherlands Epidemiology of Obesity; OA, osteoarthritis; PCS, physical component summary; SF-36, Short Form 36 health survey.

Table 2. Association of knee OA with PCS score in 1,262 participants of the NEO study

	Mean difference PCS score	95% CI
Crude	-7.4	-9.3, -5.4
Adjusted for age and sex	-7.2	-9.1, -5.3
Adjusted for age, sex, and BMI	-6.5	-8.3, -4.7
Adjusted for age, sex, and FFM	-6.7	-8.4, -4.9
Adjusted for age, sex, and comorbidities	-6.6	-8.5, -4.8
Adjusted for age, sex, BMI, FFM, and comorbidities	-6.2	-8.0, -4.4

Results are based on weighted analyses of the study population.

BMI, body mass index; FFM, fat-free mass; CI, confidence interval; NEO, Netherlands Epidemiology of Obesity; OA, osteoarthritis; PCS, physical component summary.

Interaction between knee OA and its risk factors in relation to HRQOL

Next, we investigated whether knee OA interacts with obesity, low FFM, or comorbidities in relation to HRQOL. In men, a significant interaction term (P = 0.002) was observed between the presence of knee OA and low FFM in relation to HRQOL. There was no interaction between knee OA and obesity and knee OA and comorbidities. When performing a sensitivity analysis including fat mass instead of BMI, again no interaction with presence of knee OA was observed in relation to HRQOL. Sensitivity analyses including knee OA based on osteophytes of at least grade 2 instead of all observed osteophytes provided similar results.

Table 3 shows the mean PCS score stratified by presence of knee OA and BMI categories, as well as the adjusted mean difference in PCS score between the strata, using individuals with a normal weight and without knee OA as reference. The adjusted mean difference in PCS score due to the presence of only knee OA (within normal weight individuals) was -5.3 points (95% CI -9.9 to -0.6), the difference in PCS score due to presence of obesity within individuals without knee OA was -2.6 points (95% CI -5.2 to -0.02). When knee OA and obesity concurred, the mean PCS score was -9.4 (95% CI -12.3 to -6.4).

Table 3. PCS mean score and difference, stratified by knee OA and BMI category

	PCS score (mean ± SD)		**Mean difference PCS score (95%CI)***	
BMI	No knee OA	Knee OA	No knee OA	Knee OA
< 25 kg/m^2	56.1 ± 6.4	50.4 ± 8.7	reference	-5.3 (-9.9, -0.6)
25-30 kg/m^2	54.2 ± 8.0	46.8 ± 9.3	-0.9 (-2.8, 1.0)	-7.5 (-10.4, -4.6)
>30 kg/m^2	50.8 ± 9.2	43.4 ± 9.7	-2.6 (-5.2, -0.02)	-9.4 (-12.3, -6.4)

Results are based on weighted analyses of the study population (n = 1,262).

* As compared with reference (BMI <25 kg/m^2, without knee OA), adjusted for age, sex, comorbidities, and percentage FFM.

BMI, body mass index; CI, confidence interval, OA, osteoarthritis; PCS, physical component summary.

Table 4 shows the mean PCS score and adjusted difference stratified by presence of knee OA and tertiles of percentage FFM, separately in men and women. In men with knee OA in the lowest tertile of FFM the mean PCS score was 10.2 (95% CI -14.6 to -5.8) points lower than in the reference category. If no interaction would have been present we would expect a lower PCS score of 3.7 points in men with knee OA (-0.7 points) and in the lowest tertile of FFM (-3.0 points). However, as illustrated in Figure 1, the decrease in mean PCS score between men with concurring knee OA and low FFM as compared with the reference category is higher (-10.2 points) than the summed decreases due to only knee OA or low FFM (-3.7 points). In absence of bias, the additional 64% (6.5 of 10.2 points) of the decrease in PCS score can be attributed to interaction between knee OA and low percentage FFM. No such association was observed in women.

Table 4. PCS mean score and difference, stratified by knee OA and percentage fat-free mass separately in men and women

	PCS score (mean ± SD)		Mean difference PCS score (95%CI)*	
FFM (%)	No knee OA	Knee OA	No knee OA	Knee OA
Men#				
Highest tertile	57.3 ± 6.1	56.3 ± 3.6	reference	-0.7 (-2.9, 1.5)
Middle tertile	54.7 ± 7.5	44.6 ± 8.3	-2.7 (-5.2, -0.1)	-11.8 (-17.1, -6.6)
Lowest tertile	53.2 ± 8.0	45.2 ± 10.7	-3.0 (-5.8, -0.2)	-10.2 (-14.6, -5.8)
Women§				
Highest tertile	55.4 ± 7.1	46.2 ± 9.8	reference	-9.5 (-18.0, -1.0)
Middle tertile	55.1 ± 7.3	48.9 ± 8.8	1.5 (-1.1, 4.2)	-4.4 (-9.1, 0.3)
Lowest tertile	51.2 ± 9.2	44.5 ± 9.5	0.7 (-2.3, 3.6)	-5.0 (-8.8, -1.3)

Results are based on weighted analyses of the study population (n = 568 for men, n = 694 for women).

* As compared with reference (BMI <25 kg/m^2, without knee OA), adjusted for age, comorbidities, and BMI.

Men: highest tertile ≥73.2%, middle tertile 68.7-73.1%, lowest tertile <68.7%.

§ Women: highest tertile ≥58.7%, middle tertile 54.5-58.6%, lowest tertile <54.5%.

BMI, body mass index; CI, confidence interval; FFM, fat-free mass; OA, osteoarthritis; PCS, physical component summary.

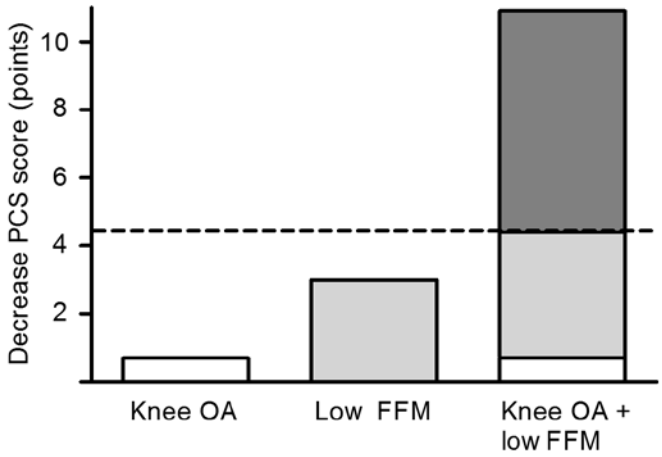

Figure 1. Adjusted decrease in mean physical component summary (PCS) score in men with knee osteoarthritis (OA), low FFM (FFM), or both, compared with men without knee OA and high FFM: decrease due to knee OA (white), decrease due to low FFM (gray), and additional decrease in PCS score due to interaction between concurring knee OA and low FFM (dark gray). The broken line indicates exact additivity of effects. Results are based on weighted analyses of the study population, adjusted for age, sex, comorbidities, and body mass index.

Finally, Table 5 shows the PCS score stratified by presence of knee OA and presence of comorbidities. The adjusted difference in mean PCS score was -6.6 points (95% CI -8.7 to -4.5) due to presence of knee OA and -4.4 points (95% CI -6.2 to -2.7) due to comorbidities. When knee OA and comorbidities concurred, mean PCS score was 9.1 points lower (95% CI -12.6 to -5.7) as compared with the reference category.

Table 5. PCS mean score and difference, stratified by knee OA and comorbidities

	PCS score (mean ± SD)		**Mean difference PCS score (95%CI)***	
Comorbidities	No knee OA	Knee OA	No knee OA	Knee OA
Absent	54.9 ± 7.5	47.7 ± 9.1	reference	-6.6 (-8.7, -4.5)
Present	49.4 ± 9.0	44.1 ± 10.5	-4.4 (-6.2, -2.7)	-9.1 (-12.6, -5.7)

Results are based on weighted analyses of the study population (n = 1,262). Comorbidities include cardiovascular disease, cerebrovascular accident, diabetes and lung disease.

*As compared with reference (BMI <25 kg/m^2, without knee OA), adjusted for age, sex, percentage FFM, and BMI.

CI, confidence interval; OA, osteoarthritis; PCS, Physical Component Summary.

DISCUSSION

This study aimed at evaluating the interaction between knee OA and its risk factors obesity, low percentage FFM (as proxy for muscle mass), and comorbidities in their association with HRQOL, measured by the PCS score. After adjusting for age and sex, the mean PCS score was observed to be 6.2 points lower in individuals with knee OA than in those without. Because 2.5 to 5.0 points difference in PCS score has been described as the minimum clinically important difference in arthritis patients,[27] the observed decrease is clinically relevant.

When knee OA concurred with obesity, low FFM, and comorbidities, interaction was observed between knee OA and low percentage FFM in men, but not with the other risk factors.

Although knee OA and its assessed risk factors have been related to impairment of HRQOL before, this study is the first showing that knee OA may interact with FFM in its relation with HRQOL in a population-based cohort. To our knowledge, an interaction of knee OA with low FFM in relation to HRQOL has not been described before.

The presence of knee OA together with low FFM was associated with a larger impairment of HRQOL than would be expected on the basis of the separate associations of knee OA and low FFM with HRQOL. This observation suggests that concurrence of knee OA and low FFM may result in strengthening of their separate adverse associations with HRQOL. Therefore, it will be of importance to increase FFM in knee OA patients. Although disease-modifying treatment is not yet available for knee OA, the decreased HRQOL in knee OA patients may be prevented by interventions aiming at obesity and the amount of FFM (i.e., reducing weight and strengthening of muscle). Although to a lesser extent, prevention, but also strict control and treatment of comorbidities may maintain or improve HRQOL in knee OA patients.

Our results are supported by a recent study of Messier et al., showing that reducing weight and performing exercises improved HRQOL within knee OA patients.[18] The knowledge that exercising reduces pain and improves physical function in knee OA patients

may provide an explanation.[33] The effect of prevention or treatment of comorbidities on HRQOL in knee OA patients has not been evaluated in a longitudinal study.

In the present study, analyses on FFM were stratified by sex because of the large differences in amount of FFM between men and women. Although previous studies on proxies for muscle mass in relation to HRQOL did not assess men and women separately, our study underscores the utility of sex-stratified analyses. Different results were observed for men and women, as percentage FFM was associated with impaired HRQOL only in men. Within women, the most impaired HRQOL was observed in individuals with knee OA in the highest tertile of FFM. The underlying mechanism for the observed difference is not clear. The amount and intensity of physical activity, probably related to the amount of muscle mass and to HRQOL, may be higher in men than in women. However, additional adjustment for physical activity did not change the results (data not shown). In addition to the observed importance of FFM for HRQOL in men, we observed a stronger association between the amount of muscle mass and presence of knee OA in men than in women in a previous study.[34] Perhaps, the role of muscle mass in both the pathogenesis of knee OA and HRQOL is different between men and women.

A strength of this study is the size of the study population. However, since this is an observational cross-sectional study, residual confounding may still be present. Since the direction of associations cannot be determined, reverse causation may be present. Although several determinants have been measured in this study, not all determinants that may affect quality of life in knee OA patients could be accounted for. An example of such a determinant is the presence and severity of chronic pain.

Knee OA was defined based on the presence of osteophytes assessed by MR imaging instead of, as incorporated in the original ACR criteria, by radiography. Since MR imaging is a more sensitive tool for detection of osteophytes,[35] it could be that we observed more osteophytes than would be detected by radiography, leading to a higher prevalence of knee OA. Therefore, we repeated all analyses including knee OA based on the presence of osteophytes of at least 3 mm (defined as grade 2 and 3) instead of all observed osteophytes. These analyses did not change the results.

We did have MR images of the right knee only. The presence of OA of the left knee (or presence of bilateral knee OA) could therefore not be assessed.

Another limitation is that we did not have information regarding the actual amount of muscle mass or muscle strength. However, FFM consists for a substantial part of muscle mass and has been shown to be correlated with both muscle mass and muscle strength.36 Therefore the percentage FFM is a valuable proxy for muscle mass.

Although we mentioned low muscle mass as a risk factor for knee OA in this study, it may also be a consequence of knee OA because of disuse of muscles due to OA associated knee pain. However, the association between low FFM and impaired HRQOL within knee OA patients applies to all men with knee OA, independent of having low muscle mass as cause or consequence of their knee OA. We also did not have information on history of knee injury, which may act as a confounder in the association between muscle mass and knee OA.

Finally, the presence of comorbidities was based on self-report; unfortunately we did not have information of medical records to check the reliability of the reported comorbidities. However, studies on agreement of self-report and medical record data showed substantial agreement for most of the assessed comorbidities.[37-39]

In conclusion, this study confirms that knee OA is associated with impaired HRQOL. Additional impairment of HRQOL was observed in men because of interaction between concurring knee OA and low FFM. No such interaction with obesity was seen. Interventions aiming at prevention or treatment of obesity or comorbidities could maintain HRQOL in knee OA patients, and interventions aiming at increasing the percentage FFM may result in additional improvement of HRQOL in men with knee OA. Longitudinal research could help to confirm and quantify the beneficial effect of these interventions on HRQOL in knee OA patients.

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Supplementary table. Unweighted baseline characteristics of 1,262 participants of the NEO study with an over-sampling of BMI ≥ 27 kg/m^2

		Total population n = 1,262	**Knee OA n = 229**	**No knee OA n = 1,033**
Age (year)		56 (50-61)	57 (53-61)	56 (50-61)
Sex (% women)		55	66	52
Education (% high)		32	31	32
Profession (% high physically demanding)		12	11	12
BMI (kg/m^2)		30.0 (27.9-33.0)	31.0 (28.3-34.3)	29.9 (27.8-32.6)
FFM (kg)	Men	71.3 (67.6-74.5)	70.6 (67.4-73.8)	71.5 (67.8-74.5)
	Women	56.6 (53.5-59.9)	55.8 (52.4-58.7)	56.8 (53.7-60.1)
Comorbidities (%)		20	30	18
- Cardiovascular disease		7	8	6
- Cerebrovascular accident		2	2	2
- Diabetes		11	15	10
- Lung disease		7	15	4
SF-36 MCS score		50.5 ± 9.5	50.8 ± 10.2	50.4 ± 9.4
SF-36 PCS score		51.2 ± 9.4	44.9 ± 9.7	52.6 ± 8.7

Values are the percentage, median (25th to 75th percentiles), or mean ± SD.

BMI, body mass index; FFM, fat-free mass; MCS, mental component summary; NEO, Netherlands Epidemiology of Obesity; OA, osteoarthritis; PCS, physical component summary; SF-36, Short Form 36 health survey.