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The role of fat mass and skeletal muscle mass in knee osteoarthritis is different for men and women: the NEO study

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SUMMARY

Objective: To investigate if the amount of fat mass (FM) or skeletal muscle mass (SMM) is more strongly associated with knee osteoarthritis (OA), in both men and women.

Methods: The Netherlands Epidemiology of Obesity (NEO) study is a population-based cohort aged 45–65 years, including 5313 participants (53% female, median body mass index (BMI) 29.9 kg/m^2). FM (kg), fat percentage, SMM (kg) and skeletal muscle (SM) percentage were estimated using bioelectrical impedance analysis (BIA). Clinical OA was defined following the ACR criteria. Structural OA was defined based on magnetic resonance imaging (MRI) in 1142 participants. Logistic regression analyses were used to examine the associations of all body composition measures with clinical and structural knee OA per standard deviation (SD), stratified by sex and adjusted for age and height.

Results: Clinical or structural OA was present in 25% and 14% of women and 12% and 13% of men, respectively.

FM and fat percentage were positively associated with clinical knee OA in men and women. SMM was positively associated, while the SM percentage was negatively associated with clinical OA in both men and women. The FM/SMM ratio was positively associated with clinical OA. All determinants showed even stronger ORs for structural knee OA. In men, SMM was more strongly associated with knee OA as compared to FM whereas in women, FM was most strongly associated.

Conclusion: Especially a high FM/SMM ratio seems to be unfavorable in knee OA. In men, SMM is most strongly associated with knee OA whereas in women FM seems to be of most importance.

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Introduction

Knee osteoarthritis (OA) is a common musculoskeletal disorder and a major cause of disability, especially in the elderly[1]. Overweight or obesity, usually characterized by body mass index (BMI), is an important risk factor for knee OA[2]. However, BMI does not distinguish between fat mass (FM) and lean body mass. Therefore it remains unclear whether FM or skeletal muscle mass (SMM) is more important in knee OA.

In knee OA biomechanical pathways are thought to play an important role; excessive mechanical stress due to either a decrease in the load-bearing area on the joint surface or an increase in loading leads to a failed repair of damaged joint tissue[3]. Earlier studies showed that body weight is associated with knee OA and that especially persons with a high FM are at risk for knee OA[4,5]. However, inconsistent results have been described regarding FM in relation to knee OA. Where some studies reported a negative association between FM or fat percentage and knee OA or knee cartilage as well[6–8], other studies did not find an association[9,10].

Besides FM the body consists of lean body mass, consisting partially of SMM. SMM is important in the distribution of mechanical loading across the joint surface. Decreased muscle forces can alter the mechanical loading and ultimately result in

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degeneration of the joint. For example, quadriceps weakness has been shown to be associated with knee OA[11,12]. Conroy *et al.* confirmed this negative association between quadriceps weakness and OA, however they reported a positive association between SMM and knee OA[7]. This is remarkably since muscle mass and strength have been shown to be highly correlated[13]. Other studies on the association of SMM and knee OA show conflicting results; some observed a negative association[6,12], where others reported a positive association[5].

The present study investigates whether the amount of FM or SMM is more strongly associated with knee OA in both men and women. To this end we used two OA definitions: the partly subjective clinical criteria of the American College of Rheumatology (depending on the presence of pain) as well as an objective measure of structural OA, assessed by magnetic resonance imaging (MRI)[14,15]. We examined the associations of the relative amounts of FM and SMM with both clinical and structural knee OA.

Patients and methods

Study design and study population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based prospective cohort study in lean, overweight and obese individuals aged between 45 and 65 years. The present study is a cross-sectional analysis of the baseline measurements of the 5313 participants included in the NEO study between September 2008 and January 2012. Detailed information about the study design and data collection has been described previously[16]. Men and women with a self-reported BMI ≥ 27 kg/m^2 living in the greater area of Leiden (in the West of The Netherlands) were eligible to participate in the NEO study. In addition, in one municipality (Leiderdorp), all inhabitants aged 45–65 years were invited, irrespective of their BMI ($n = 874$).

All participants completed questionnaires on demographic and clinical data and visited the NEO study center for several baseline measurements. The study was approved by the medical ethics committee of the Leiden University Medical Center and all participants gave written informed consent.

Clinical assessment and clinical OA diagnosis

Self-reported pain and morning stiffness were measured using standardized questionnaires. Physical examination of both knee joints was performed by trained research nurses, using a standardized scoring form. Bony enlargement, tenderness of the bony margins of the joint, palpable warmth, crepitus and movement restriction were scored. Clinical OA was defined according to the clinical criteria of the American College of Rheumatology[14].

Body composition measures

Measured body weight (kg) and height (cm) were used to calculate the BMI (kg/m^2). The percentage of body fat and amount of FM (kg) were measured by bioelectrical impedance analysis (BIA) using the Tanita foot-to-foot (FF) BIA system TBF-300A Body Composition Analyzer[17]. The percentage of skeletal muscle (SM) and amount of SMM (kg) were calculated based on height, gender, age and resistance measured by the BIA[18]. To test the reliability, repeated measurements were performed in a random sample of the participants ($n = 72$); the calculated intraclass correlation coefficient was 0.98.

Since FM and SMM are positively correlated, we also calculated the FM/SMM ratio.

MRI

A random sample (about 20%) of the study participants without contraindications (metallic devices, claustrophobia, body circumference ≥ 170 cm) underwent MRI of the right knee. Imaging was performed using a dedicated knee coil in a 1.5 T system (Philips, Medical Systems, Best, the Netherlands). A standardized scanning protocol was used.

The following parameters were identical for the TSE images; a 150–160 mm field of view and a 304×512 matrix. Sequences performed were:

(1) Coronal proton density (PD) (repetition time (TR)/echo time (TE) 2335/35 ms); (2) fat-suppressed PD TSE images (TR/TE 2334/35 ms; 3 mm slice thickness; 0.6 mm interslice gap); (3) sagittal PD TSE images (TR/TE 2338/35; echo train length 6; 3.5 mm slice thickness; 0.7 mm interslice gap); (4) sagittal frequency selective fat-suppressed T1-weighted 3D gradient echo (GE) sequence (TR/TE 11/5.5; 25° flip angle; 150 mm field of view, 272×512 matrix, 2 mm slice thickness with a 1 mm overlap between images; no gap); (5) axial fat-suppressed PD (TSE) images (TR/TE 3225/15; echo train length 6, 4 mm slice thickness; 0.8 mm interslice gap). Total acquisition time, including the initial survey sequence, was 30 min.

MRI scoring and structural knee OA diagnosis

All MR images were analyzed using the validated semi-quantitative knee OA scoring system (KOSS)[19], by a trained reader (AWV), blinded to clinical data. The presence or absence of osteophytes, cartilage loss, subchondral bone marrow lesions (BMLs) and cysts were scored at four anatomic locations: the medial and lateral femoral condyle and medial and lateral tibial plateau.

Osteophytes were defined as focal bony excrescences extending from a cortical surface and measured from base to tip; ≥ 3 mm was considered a definite osteophyte.

Based on their depth, cartilage defects were classified as full- or partial thickness.

BMLs were defined as ill-defined areas of increased signal intensity in the subchondral bone extending away from the articular surface; cysts as well-defined foci of high signal intensity in the subchondral bone. Both were required not to be associated with meniscal or ligamentous attachments.

The medial and lateral menisci were reviewed for the presence of subluxation, maceration and degenerative tears. Subluxation was defined as protrusion over the edge of the tibial plateau, maceration as an intrameniscal focus of intermediate signal intensity and tears as regions of intermediate signal intensity within the meniscus, communicating with the surface or inner margin on more than one section.

A random ten percent of the MR images ($n = 120$) were scored twice to test the reproducibility; the calculated intraclass correlation coefficient was 0.61–0.97 for the different features (meniscal maceration 0.61, meniscal tear 0.87, meniscal subluxation 0.93, cyst 0.64, BML 0.93, cartilage loss 0.90, osteophyte 0.97).

Structural OA was defined based on the MRI features following the criteria recently suggested by Hunter *et al.*[15]. Structural OA was defined on the presence of a definite osteophyte and full thickness cartilage loss, or one of these features in addition to at least two of the following features: (1) subchondral BML, (2) cyst, (3) meniscal subluxation, maceration or degenerative tear, or (4) partial thickness cartilage loss. In the recommendation by Hunter *et al.* bone attrition was described as a fifth feature, since this was not scored in the KOSS it was left out of the definition.

Statistical analysis

Data were analyzed using SPSS version 20 and STATA version 12.

In the NEO study there is an oversampling of persons with a BMI of 27 kg/m^2 or higher. To correctly represent associations in the general population[20], adjustments for the oversampling of individuals with a BMI $\geq$27 kg/m^2 were made. This was done by weighting individuals towards the BMI distribution of participants from the Leiderdorp municipality[21], whose BMI distribution was similar to the BMI distribution in the general Dutch population[22]. Consequently, results apply to a population-based study without oversampling of BMI $\geq$27 kg/m^2.

Body composition measures were compared between men and women using a t-test, further analyses were stratified by sex because of the observed significant differences for all measures of body composition. Logistic regression analyses were used to calculate cross-sectional associations of BMI and body compositions with clinical and structural knee OA, and were expressed as odds ratios (OR) with 95% confidence intervals (CI). Furthermore, multivariate logistic regression analysis including both FM and SMM was performed to investigate their independent association with knee OA. All continuous variables were standardized by dividing individual values by the standard deviation (SD) to be able to compare ORs, because in this way all ORs describe the effect on the odds of OA of an increase of one SD of the corresponding variable. All analyses have been stratified by sex and adjusted for age and height. Analyses on SMM and SM percentage in relation to OA were additionally adjusted for the total level of physical activity during 1 week (assessed by the validated Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH)[23]).

Results

Population characteristics

After exclusion of individuals with missing data of the BIA ($n = 25$) or physical examination ($n = 4$) data from 5284 participants were analyzed. Table I shows the baseline characteristics of the total population and stratified by sex. Women had a lower median weight, SMM and SM percentage, but a higher FM, fat percentage and FM/SMM ratio than men ($P < 0.001$). Clinical OA was present in 25% of women and 12% of men.

MRI of the right knee was performed in a subset of 1142 participants. Except for a higher median weight in women (86.0 kg (IQR 77.6–95.4)) and SMM in women (23.3 kg (21.3–25.6)) and men (34.3 kg (31.7–36.8)), this subgroup did not differ from the total group as well as from the participants without a knee MRI in age, sex or body compositions (data not shown).

Structural OA was present in 14% of women and 13% of men. To compare this prevalence to clinical knee OA, we assessed the presence of clinical OA of only the right knee in the MRI subgroup, showing a prevalence of 18% in women and 10% in men (total population 14%). Of the individuals with structural knee OA, 39% of women and 31% of men also was defined as having clinical OA. Of the individuals with clinical OA, 31% of women and 40% of men also had structural OA.

Association of body composition measures with clinical knee OA ($n = 5284$)

Next, we investigated the associations of body composition measures with clinical knee OA in men and women, adjusted for age and height (Table II). FM and fat percentage were positively associated with knee OA in both men and women. For example, the OR of 1.34 in men for FM means that one SD increase in FM (9.39 kg) is associated with a 34% higher odds of having knee OA. SMM was positively associated with knee OA as well. On the contrary, SM percentage was negatively associated with knee OA, this was statistically significant in women only. Additional adjustment for the level of physical activity did not change the results (data not shown).

Finally, the FM/SMM ratio was positively associated with knee OA in both men and women.

Association of body composition measures with structural knee OA ($n = 1142$)

In addition to the analyses on clinical knee OA, we investigated the associations of measures of body compositions with structural knee OA (Table III). FM, fat percentage, SMM and SM percentage were even stronger associated with structural OA than with clinical OA in both men and women. However, in structural OA the association of SM percentage was statistically significant in women only. Again, additional adjustment for physical activity did not alter the observed associations of SMM and SM percentage with OA (data not shown).

The FM/SMM ratio was positively associated with structural knee OA. When comparing the ORs of the different body composition measures for knee OA as shown in Table III, in men the association of SMM (OR 1.94 (1.18–3.17)) was somewhat stronger than the association of FM (OR 1.50 (1.09–2.07)). In women this is different; the association of FM (OR 2.20 (1.41–3.43)) was stronger than the association of SMM (OR 1.86 (1.31–2.63)).

Since FM and SMM are positively correlated, we assessed the associations of both parameters with structural knee OA independently of each other in a logistic regression model including both FM and SMM (Table IV). In men, the association between SMM and OA became stronger and was the most important predictor of knee OA (OR 1.67 (1.07–2.61)). In contrast, in women the association of FM with knee OA became stronger and was the most important predictor of knee OA (OR 1.93 (1.24–3.02)), independently of SMM.

Table I
Baseline characteristics of the total NEO study population and stratified by sex

	Total population N = 5284	Men N = 2490	Women N = 2794
Age (year)	56 (51–61)	57 (51–61)	56 (51–61)
BMI (kg/m^2)	29.9 (27.8–32.8)	29.6 (27.9–32.0))	30.3 (27.8–33.5)
Height (m)	1.73 (1.66–1.80)	1.80 (1.76–1.85)	1.67 (1.62–1.71)
Weight (kg)	90.6 (80.6–100.8)	96.6 (89.2–106.0)	84.0 (75.8–94.2)
FM (kg)	32.4 (26.1–40.0)	28.1 (23.6–34.0)	36.4 (30.4–43.1)
Fat percentage (%)	37.5 (29.0–43.7)	29.0 (25.9–32.7)	43.3 (39.9–46.4)
SMM (kg)	27.7 (22.6–33.5)	33.6 (31.2–36.4)	22.8 (20.8–25.2)
SM (%)	30.7 (26.9–34.9)	34.8 (32.5–37.1)	27.2 (25.1–29.6)
FM/SMM ratio	1.22 (0.83–1.63)	0.83 (0.70–1.00)	1.59 (1.35–1.84)
Clinical knee OA, no. (%)	991 (18.8)	306 (12.3)	685 (24.5)
Structural knee OA, no. (%)*	156 (13.7)	65 (12.8)	91 (14.4)

Numbers represent medians (interquartile ranges) unless stated otherwise.
* $N = 1142$ (508 men, 634 women).

Table II
Associations of body composition measures with clinical knee OA

	SD		OR (95% CI)	
	Men	Women	Men, N = 2490	Women, N = 2794
FM (kg)	9.39	10.76	1.34 (1.12–1.59)	1.44 (1.27–1.63)
Fat percentage (%)	6.22	6.88	1.33 (1.08–1.63)	1.47 (1.21–1.77)
SMM (kg)	4.16	3.19	1.28 (1.02–1.60)	1.36 (1.19–1.56)
SM percentage (%)	4.50	4.40	0.80 (0.60–1.06)	0.74 (0.61–0.91)
FM/SMM ratio	0.26	0.40	1.30 (1.09–1.55)	1.39 (1.20–1.61)
BMI (kg/m^2)	4.01	5.19	1.38 (1.14–1.68)	1.43 (1.28–1.61)
Weight (kg)	14.49	14.73	1.42 (1.14–1.78)	1.46 (1.30–1.64)

All ORs express the increase in odds on OA per SD and are adjusted for age and height.

Table III
Associations of body composition measures with structural knee OA

	SD		OR (95% CI)	
	Men	Women	Men, N = 508	Women, N = 634
FM (kg)	9.39	10.76	1.50 (1.09–2.07)	2.20 (1.41–3.43)
Fat percentage (%)	6.22	6.88	1.42 (1.01–1.99)	2.36 (1.23–4.51)
SMM (kg)	4.16	3.19	1.94 (1.18–3.17)	1.86 (1.31–2.63)
SM percentage (%)	4.50	4.40	0.74 (0.50–1.09)	0.51 (0.29–0.88)
FM/SMM ratio	0.26	0.40	1.35 (0.99–1.85)	1.92 (1.23–3.00)
BMI (kg/m^2)	4.01	5.19	1.67 (1.15–2.42)	2.17 (1.48–3.20)
Weight (kg)	14.49	14.73	1.77 (1.19–2.65)	2.31 (1.48–3.63)

All ORs express the increase in odds on OA per SD and are adjusted for age and height.

Discussion

In this study we aimed to investigate the relative importance of FM and SMM in knee OA. Both FM and fat percentage were positively associated with knee OA in men and women. The same was observed for SMM, whereas the SM percentage was negatively associated with knee OA. This suggests that especially a high FM relative to low SMM is unfavorable. The importance of the relative amounts of FM and SMM has been confirmed by the association between the FM/SMM ratio and knee OA.

In a subpopulation we had the opportunity to assess structural knee OA by MRI, providing a purely objective outcome measure. Of the individuals with clinical or structural OA, about one third did meet both definitions. The discrepancy underscores the difference between the definitions; whereas in clinical OA objective symptoms as pain are of importance, structural OA is based only on MRI features. All parameters associated with clinical OA were observed to be associated even stronger with structural OA, especially in women. In men, this stronger OR for SM percentage was not statistically significant, this might be due to the smaller number of participants included in the analyses on structural OA.

To date, most studies on knee OA examined predominantly or only women[5–7,10,12,24,25]. Since this study comprises a large group of men as well, we were able to investigate the underlying mechanisms mediating the association between BMI and knee OA in both sexes. In men, a higher OR was observed for SMM in relation to OA whereas in women, FM showed the highest OR for knee OA. This might suggest that the pathogenesis of knee OA in men might be more biomechanical whereas the etiology in women might be more inflammatory. Differences in the pathogenesis of knee OA between the sexes have been suggested before[12,26,27]. The risk factors contributing to the development of knee OA could be different. Trauma and occupational stresses for example, which hypothetically could be associated with SMM, have been reported to be related to knee OA more strongly in men than in women[26]. A larger amount of SMM could serve as a surrogate for individuals who have been more active and therefore more prone to injury, supporting the suggestion of a more biomechanical etiology of knee OA in men. Our results stress that in studies aiming to provide insight into the pathogenesis of knee OA, both sexes should be studied and stratified analyses should be performed.

Table IV
Logistic regression analyses including both FM and SMM with structural knee OA

	SD		OR (95% CI)	
	Men	Women	Men, N = 508	Women, N = 634
FM (kg)	9.39	10.76	1.35 (0.99–1.84)	1.87 (1.18–2.95)
SMM (kg)	4.16	3.19	1.67 (1.07–2.61)	1.32 (0.98–1.78)

All ORs express the increase in odds on OA per SD and are adjusted for age and height.

In the present study, we observed a positive association between SMM and knee OA in both women and men, but when assessing the amount of SM as a percentage of the total body weight, we observed a negative association with knee OA.

The positive association between SMM and OA might be explained by differences in physical activity (and perhaps trauma) or joint loading that are associated with SMM. Although adjustment for physical activity did not alter the observed associations between SMM and OA, the questionnaire on physical activity did not assess physical activity during earlier years. However, the opposite associations of SMM and SM percentage with OA suggests that the positive relation of SMM with OA might be due to the increase of SMM in obese individuals as a consequence of increased loading (association of body weight with SMM: men $\beta = 0.19$, women $\beta = 0.15$ ($P < 0.001$)). However, this increase in SMM is not sufficient in relation to the total weight gain since FM increases more with increasing weight (association of body weight with FM: men $\beta = 0.59$, women $\beta = 0.72$ ($P < 0.001$)), resulting in a lower SM percentage in obese individuals.

An alternative explanation for the association of low SM percentage with knee OA is the metabolic syndrome, frequently occurring in individuals with greater adiposity. In obese individuals with the metabolic syndrome, insulin resistance and systemic inflammation might result in changes in striated muscle, causing loss of muscle mass and muscle weakness[28]. This is supported by a study in exercising and sedentary mice, showing that a high-fat diet induces knee OA in association with increased adiposity, glucose intolerance and systemic pro-inflammatory mediators. Exercise improved glucose tolerance and disrupted the co-expression of pro-inflammatory cytokines. Furthermore, exercise was associated with less severe OA[29].

Since a lower FM/SMM ratio seems to be beneficial, interventions aiming at improvement of SMM in addition to weight reduction might be useful in the prevention and treatment of knee OA.

This is supported by studies on the effect of weight loss and exercise on physical performance, showing that a combination of both interventions provides greater improvement in physical performance than either intervention alone. In these individuals, more FM relative to fat free mass was lost[30,31]. In addition, a study on weight loss alone observed an increase in physical function but a loss of leg muscle tissue and knee muscle strengths, supporting the need to restore or increase muscle mass during weight loss[32]. Other studies on weight reduction showed that specifically a reduction in FM reduces the risk for knee OA and relieves clinical symptoms[24,25]. This greater reduction in FM relative to loss of fat free mass has been shown to be associated with greater gains in muscle quality as well[33]. As a proxy for SMM, an increase in fat free mass has been shown to be positively associated with tibial cartilage volume[4].

There are some potential limitations of this study. We measured SMM and SM percentage by BIA and did not have information regarding muscle strength or specific lower limb SMM. However, muscle strength has been shown to be highly correlated with SMM[13]. Furthermore, since muscle parameters were measured using a FF-BIA, measurements depend predominantly on the lower limb amount of SMM.

It has been suggested that FF-BIA might overestimate the amount of FM[34], however comparative studies reported a strong correlation of the FF-BIA to hand-to-foot BIA ($r = 0.84$), and underwater weighing and dual-energy X-ray absorptiometry ($r = 0.89$)[17,35]. Structural knee OA was defined following the definition suggested by Hunter et al.[15]. Since this definition has not been applied frequently and not been validated yet like the ACR criteria for clinical knee OA, further assessment of this definition is required.

However, we observed all body composition measures to be associated similarly or even stronger with structural than clinical OA, suggesting that the structural OA definition discriminates knee OA very well.

Furthermore, since this is a cross-sectional study, causal relationships are difficult to identify.

This study suggests that the amount of SM relative to fat is of importance in knee OA and that the underlying mechanisms differ between men and women. More research is necessary to gain more insight into the precise underlying mechanisms. Future research should aim at clarifying the role of insulin resistance and inflammatory cytokines in the development of knee OA. Furthermore, research of interventions aiming at improvement of SMM in addition to weight reduction should be performed, as this may lead to potential new treatment targets in knee OA.

Contributorship

Authors made substantial contributions to the following: (1a) conception and design of the study: AWV, RM, SC, MH, JLB, MR, FRR, MK; (1b) acquisition of data: AWV, ML, JLB, MR, MK; (1c) analysis and interpretation of data: AWV, RM, ML, SC, MH, FRR, MK (2) drafting or critically revising of manuscript: AWV, RM, ML, SC, MH, JLB, MR, FRR, MK; (3) final approval of manuscript: AWV, RM, ML, SC, MH, JLB, MR, FRR and MK.

Conflicts of interest
None.

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