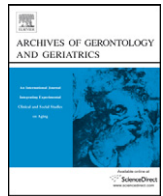




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Lower limbs composition and radiographic knee osteoarthritis (RKO) in Chingford sample—A longitudinal study

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ABSTRACT

Our aim in this longitudinal study was to evaluate to what extent fat and lean tissue mass variations are associated and can predict RKO in a large sample of British women followed-up over 10 years. Kellgren/Lawrence (K/L), joint space narrowing (JSN) and osteophyte (OSP) grades were scored from radiographs of both knees in 909 middle-aged women from the Chingford registry. Body composition components were assessed using the dual energy X-ray absorptiometry (DXA) method. In cross-sectional analysis, combined effect of age, BMI and leg tissue composition was required for best fitting model explaining variations of K/L scoring and osteophytes at lateral compartment. To explain medial osteophytes, age and BMI were sufficient to generate the best fitting model. In prediction analysis, leg lean mass was the more powerful predictor of K/L, medial osteophytes than BMI. In conclusion, BMI appears to influence the development of knee OA through both fat and/or lean mass, depending on RKO phenotype.

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1. Introduction

Knee osteoarthritis (OA) is a common, disabling condition in middle-aged and elderly and its prevalence is predicted to increase substantially over the coming decade (Acheson & Collart, 1975; Garstang & Sittik, 2006). It is characterized by pain, and affects all the structures of the knee joint. The characteristic features include low-grade inflammation, cartilage loss, sub-chondral bone changes and peri-articular soft tissue changes. Important risk factors for radiographic knee OA (RKO) include age, female sex and obesity (Abbate et al., 2006; Felson, 2004). At least 33% of people over the age of 55 have radiographic evidence of knee OA (Cooper et al., 2000; Felson & Zhang, 1998; Hart, Doyle, & Spector, 1999), and females have more severe RKO after the menopause (Srikanth et al., 2005). The prevalence of RKO in adults over the

age of 45 years among participants in Framingham study was 19.2% and 27.8% in Johnston County Osteoarthritis project (Lawrence, Felson, Helmick, et al. 2008). Because the proportion of older people in the world population is continually increasing; OA is becoming an increasingly important public health concern. With the increase in obesity and the aging of human population it is essential to understand the relationship between obesity and OA. Longitudinal data have shown that overweight/obesity is a powerful risk factor for the development of knee OA with a clear dose response relationship between excess weight and knee OA (Manek, Hart, Spector, & MacGregor, 2003). Thus 9–13% increased risk of OA occurs with every kilogram increase in body weight (Cicuttini, Baker, & Spector, 1996). Perhaps more surprisingly still, epidemiological studies show this risk to be reversible: a 5.1 kg loss in body mass over 10 years reduced the odds of developing OA by more than 50% (Felson, Zhang, Anthony, Naimark, & Anderson, 1992; Messier, Gutekunst, Davis, & DeVita, 2005).

Anthropometric measurements of central adiposity such as BMI, waist circumference and waist-hip ratio (WHR) are often used to assess risk of OA, and all are significantly associated with RKO (Hart & Spector, 1993). However, such measurements are surrogate measures of adiposity and cannot discriminate adipose from non-adipose mass. Several studies have compared the body composition measures and BMI between individuals with healthy and arthritic knee joints (Toda, Segal, Toda, Kato, & Toda, 2000; Wang et al., 2007). It was found that fat mass, lean mass of the

Abbreviations: BC, body composition; BMI, body mass index; JSN, joint space narrowing; JSN_{lt}, joint space narrowing, lateral compartment; JSN_{md}, joint space narrowing, medial compartment; K/L, Kellgren/Lawrence grading scale of osteoarthritis; LH, likelihood; OA, osteoarthritis; OSP, osteophytes; OSP_{lt}, osteophytes, lateral compartment; OSP_{md}, osteophytes, medial compartment; RKO, radiographic knee osteoarthritis.

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entire body and BMI were positively associated with RKOA (Abbate et al., 2006; Hochberg et al., 1995; Lohmander, Gerhardsson de Verdier, Rollof, Nilsson, & Engstrom, 2009; Sowers et al., 2008). However, only few studies attempted to examine the relationship between the main components of the leg soft tissue mass and RKOA. For example, association of cartilage volume and/or defect of medial-tibial cartilage volume was examined with lower limb composition components in addition to total body lean and fat mass (Cicuttini et al., 2005). This study found that muscles of legs and total body mass were positively associated with medial-tibial cartilage volume and defect. However, they found no significant association between fat mass of legs or total body and cartilage volume or defect. Other studies, nevertheless, have concluded that greater adipose mass is associated with the increased probability of cartilage defect (Teichtahl, Wang, Wluka, & Cicuttini, 2008).

The first aim of this study was therefore to replicate the previously published cross-sectional studies of association between BMI and body composition, in particular lower limb composition components, leg lean mass and leg fat mass, with the RKOA-related phenotypes in a large cohort of UK women. However, our major purpose was to evaluate the extent to which these potential risk factors predict the appearance of the disease 10-years after first measurement, which was followed-up during this time. Our additional aim in both sections of the study was to test the hypothesis that abdominal obesity (fat mass) can be an independent risk factor for knee OA.

We examined association and prediction testing specifically in RKOA the dynamics of Kellgren/Lawrence (K/L), joint space narrowing (JSN) and osteophytes' development (OSP) scores.

2. Materials and methods

2.1. Study subjects

The Chingford Study population was established in 1989 as a retrospective case-control study to determine prevalence rates of (OA) in middle-aged women in the general population, and to assess a number of known risk factors and their associations with the OA. It has since become a prospective population-based longitudinal cohort of women seen annually (Hart & Spector, 1993). The cohort consisted originally of 1003 middle-aged women aged 45–64 from a general practice in Chingford, North-East London and initial response rate of the sample was 78%.

2.2. Radiographic assessment

RKOA was classified using standard antero-posterior weight-bearing radiographs in extension position, scored by a single trained reader who was blinded to the clinical information. RKOA status was determined based on three characteristics, following Altman atlas (Berry et al., 2010): (1) the K/L scores, ranging from 0 (no evidence of bony changes or joint degradation) to 4 (definite osteophytes and increased diminution of the joint space); (2) OSP and (3) JSN score, each graded on 4-point scale (where 0 = osteophytes are not observable, and 3 = most severe status, and similarly for JSN). The assessment of OSP and JSN was done for lateral and medial compartments of each knee separately. An individual was considered "affected" if at least one knee had $K/L \geq 2$, or if OSP and/or JSN ≥ 1 . RKOA was assessed twice – first at entrance examination and then 10 years later.

2.3. Body composition measurements

The BMI (in kg/m^2) was calculated using standard formula, and was assessed twice. Body composition components were

measured by Hologic dual energy X-ray absorptiometry (DXA) scanner (Hologic Corp., Waltham, MA, USA) as described elsewhere (Altman & Gold, 2007). We used sum of legs fat and lean mass for legs composition, and abdominal fat mass as potential covariates for RKOA-related phenotypes as defined above.

2.4. Statistical analysis

This was performed using SPSS package version 19 (SPSS Inc., Chicago, IL, USA), and was conducted in two main stages: association and prediction examination. In the association study, we used Mann-Whitney analysis to determine the relationship between RKOA features and BMI, and leg mass composition, without adjusting for age with RKOA phenotypes treated as categorical variables in which non-affected individuals were contrasted with the affected individuals in the worst knee. In this analysis, both dependent and independent variables were taken at baseline examination. We next conducted a binary logistic regression analysis with adjustment for age in which RKOA-related phenotypes (dependent variables) were treated as categorical traits: affected vs non-affected and quantitative continuous traits including age, BMI, leg composition and abdominal fat mass variables as independent predictors. We implemented a maximum likelihood approach to examine the effect of each risk factor, using hierarchically nested models, and comparing their fit by likelihood ratio test (LRT). In this analysis, we started with age and gradually added other covariates, to test whether their introduction improved the model fit. For two models, 1 and 2, with likelihoods LH_1 and LH_2 , respectively, where model 1 is nested within model 2, $LRT = -2 \ln(LH_1/LH_2)$ is asymptotically distributed as a χ^2 distribution with k degrees of freedom; k is the difference, in number of estimated parameters, between the two models. However, in some instances the hierarchical comparison of the models was not possible. For example, only two parameters: age and BMI (or lower limb lean mass) were sufficient to predict appearance of K/L at visit 10. In such a case the restricted model was compared with the general model, including all the parameters.

In prediction analysis, we predicted appearance of RKOA-related phenotypes 10 years after baseline, using baseline covariates as predictors. First we excluded those with OA at baseline and individuals undergoing total knee replacement during follow-up ($N = 309$). We used binary logistic regression to compare individuals remaining unaffected with those who developed OA after 10 years. For illustrative purposes, binary logistic regression by quartiles of significant covariates (comparison of first and fourth quartiles) was used to estimate percentage of attributable risk. For the sake of convenience, some additional standard statistical tests are briefly described in the results section.

3. Results

3.1. Descriptive statistics

The basic characteristics of the sample at baseline and at 10 years are given in Table 1. Nine hundred and nine individuals had complete data available from entry examination, and two subjects were lost to follow up. Table 1 also summarizes the main results of the covariate analysis for each RKOA-related phenotype, comparing their distribution characteristics in the two RKOA groups (not affected and affected). This analysis was conducted twice, at baseline and at 10 years. The mean age at baseline of the "not affected" and "affected" was 54 and 57.7, respectively. The mean age of "not affected" at baseline and after 10 years (control) and of "not affected" at baseline and

Table 1

Descriptive statistics and univariate comparison of the affected and non-affected individuals in Chingford study. Two comparisons are provided in the table: 1. Cross-sectional design. Both RKOA-related phenotypes and potential covariates, all assessed at baseline. 2. Prediction analysis. RKOA-related phenotypes were assessed 10 years after entrance examination; all potential risk factors were assessed at baseline. In this design not-affected cohort included only individuals who were not affected at baseline and at 10 years later examinations. The affected cohort included only individuals who were not affected at baseline, but became affected after 10 years of follow-up.

Predictor variables	Cross sectional study				Mann-Whitney p	Prediction study				Incidence/1000	Mann-Whitney p
	Not affected		Affected			Not affected		Affected			
	N	Mean (SD)	N	Mean (SD)		N	Mean (SD)	N	Mean (SD)		
K/L – visit 1											
Age (years)	775	54.0(5.9)	134	57.7(5.6)	0.001	565	53.5(5.8)	208	55.5(5.8)	269	0.001
BMI (kg/m ²)	775	25.2(3.9)	134	27.8(4.6)	0.001	565	24.7(3.7)	208	26.4(4.4)	269	0.001
Lower limb fat mass (kg)	710	11.1(3.3)	117	13.0(4.4)	0.001	513	10.8(3.1)	197	12.0(3.7)	277.5	0.001
Lower limb lean mass(kg)	710	11.5(1.8)	117	12.3(2.0)	0.001	513	11.2(1.6)	197	12.2(1.9)	277.5	0.001
Abdomen fat mass(kg)	710	13.3(5.5)	117	15.7(6.7)	0.001	513	12.8(5.2)	197	14.8(6.0)	277.5	0.001
OSP_md visit 1											
Age (years)	821	54.2(5.9)	88	57.8(5.4)	0.001	641	53.7(5.9)	178	55.9(5.7)	217.3	0.001
BMI (kg/m ²)	821	25.3(4.0)	88	27.7(4.4)	0.001	641	24.9(3.9)	178	26.8(4.4)	217.3	0.001
Lower limb fat mass (kg)	751	11.2(3.5)	76	12.9(4.2)	0.001	582	11.0(3.4)	169	12.2(3.5)	225	0.001
Lower limb lean mass (kg)	751	11.5(1.8)	76	12.3(2.0)	0.001	582	11.4(1.7)	169	12.2(1.9)	225	0.001
Abdomen fat mass (kg)	751	13.4(5.6)	76	16.0(6.8)	0.001	582	12.9(5.5)	169	15.2(5.7)	225	0.001
OSP_It visit 1											
Age (years)	815	54.2(5.9)	94	58.2(5.6)	0.001	684	53.8(5.8)	128	55.6(6.0)	157.6	0.002
BMI (kg/m ²)	815	25.2(4.0)	94	28.2(4.7)	0.001	684	24.9(3.7)	128	27.1(4.7)	157.6	0.001
Lower limb fat mass (kg)	747	11.2(3.4)	80	13.3(4.4)	0.001	626	10.9(3.1)	120	12.6(4.2)	160.9	0.001
Lower limb lean mass (kg)	747	11.5(1.8)	80	12.4(2.0)	0.001	626	11.4(1.7)	120	12.3(2.0)	160.9	0.001
Abdomen fat mass (kg)	747	13.4(5.6)	80	16.2(6.9)	0.001	626	13.0(5.3)	120	15.4(6.4)	160.9	0.001
JSN_md visit 1											
Age (years)	729	54.5(6.0)	180	55.0(5.9)	0.216	638	54.4(6.0)	90	54.7(6.0)	123.6	0.674
BMI (kg/m ²)	729	25.5(4.2)	180	25.7(4.0)	0.560	638	25.4(4.0)	90	26.3(5.2)	123.6	0.268
Lower limb fat mass (kg)	663	11.3(3.5)	164	11.6(3.7)	0.338	578	11.3(3.5)	85	11.8(4.0)	128.2	0.396
Lower limb lean mass (kg)	663	11.7(1.8)	164	11.5(1.9)	0.089	578	11.6(1.8)	85	11.8(2.1)	128.2	0.849
Abdomen fat mass (kg)	663	13.6(5.7)	164	13.9(6.2)	0.835	578	13.5(5.6)	85	14.6(6.0)	128.2	0.082
JSN_It_visit 1											
Age (years)	827	54.5(5.9)	82	55.4(6.4)	0.212	792	54.4(5.9)	34	55.6(6.0)	41.2	0.229
BMI (kg/m ²)	827	25.5(4.2)	82	25.9(3.6)	0.138	792	25.4(4.2)	34	27.3(5.1)	41.2	0.024
Lower limb fat mass (kg)	749	11.4(3.6)	78	11.1(3.4)	0.618	717	11.4(3.5)	33	12.7(4.6)	44	0.139
Lower limb lean mass (kg)	749	11.7(1.8)	78	11.0(1.9)	0.001	717	11.7(1.8)	33	12.2(2.1)	44	0.115
Abdomen fat mass (kg)	749	13.6(5.8)	78	14.2(5.9)	0.345	717	13.6(5.7)	33	14.8(6.9)	44	0.385

became “affected” after 10 years (case) was 53.5 and 55.5, respectively. Comparison of the non-affected vs affected groups by RKOA phenotype in the association and prediction studies showed: age, BMI and all other body composition components were consistently significantly higher in the affected group

defined by K/L and osteophytes scoring, in lateral and medial compartments. The JSN of the lateral compartment was associated with lower limb lean mass at baseline, and with BMI at 10 years examination. No other associations were found significant.

Table 2

Cross sectional study: binary multiple logistic regression models implementing likelihood ratio tests (LRTs) to choose the best fitting combination of the potential covariates in relation to RKOA manifestation.

Covariates by RKOA phenotype	Models with BMI and body composition						
	Model 1	Model 2	Model 3	Model 4	Model 5 (the best fitting model)		
	p	p	p	p	β coefficient (SE)	Odd ratio (95%CI)	p
Knee_K/L, visit 1							
Age (years)	0.001	0.001	0.001	0.001	0.114(0.019)	1.121(1.079–1.164)	0.001
BMI (kg/m ²)		0.001	0.013	0.089	0.131(0.044)	1.140(1.046–1.243)	0.003
Lower limb fat mass (kg)			0.022	0.043	0.117(0.041)	1.124(1.037–1.219)	0.005
Lower limb lean mass (kg)				0.068	0.155(0.068)	1.167(1.022–1.333)	0.022
Abdomen fat mass (kg)					−0.091(0.034)	0.913(0.855–0.975)	0.007
−2 log LH [*]	717.2	680.8	604.8	601.4			
LRT		<0.005	<0.005	>0.05	<0.005		
Knee_OSP_It, visit 1							
Age (years)	0.001	0.001	0.001	0.001	0.140(0.024)	1.150(1.098–1.205)	0.001
BMI (kg/m ²)		0.001	0.016	0.115	0.135(0.051)	1.145(1.037–1.264)	0.007
Lower limb fat mass (kg)			0.025	0.052	0.124(0.047)	1.132(1.032–1.242)	0.009
Lower limb lean mass (kg)				0.057	0.189(0.081)	1.209(1.032–1.415)	0.019
Abdomen fat mass (kg)					−0.094(0.039)	0.910(0.843–0.983)	0.016
−2 log LH	562.9	527.4	457.6	454.0			
LRT		<0.005	<0.005	>0.05	0.025		

LRT, each model compared vs the previous one, e.g. M2 vs M1, M3 vs M2, etc.

^{*} LH: maximum likelihood estimate.

Table 3
 Prediction study for incidence: binary logistic regression models implementing likelihood ratio tests (LRTs) and comparing relative risk (RR) of the potential risk factors to choose the best predictive model for RKOA-related phenotypes.

Predictor variables by RKOA phenotype	Models with BMI and body composition						
	Model 1	Model 2	Model 3	Model 4	Best fitting model – Model 5		
	<i>p</i>	<i>p</i>	<i>p</i>	<i>p</i>	β coefficient (SE)	Relative risk (95%CI)	<i>p</i>
Knee_OSP_It, visit 10							
Age (years)	0.002	0.003	0.004	0.001	0.066(0.019)	1.068(1.030–1.108)	0.001
BMI (kg/m ²)		0.001	0.016	0.219	0.099(0.046)	1.104(1.009–1.207)	0.031
Lower limb fat mass (kg)			0.031	0.072	0.100(0.042)	1.105(1.017–1.200)	0.018
Lower limb lean mass (kg)				0.002	0.222(0.067)	1.248(1.094–1.424)	0.001
Abdomen fat mass (kg)					–0.066(0.034)	0.936(0.875–1.001)	0.055
–2 log LH	698.0	669.5	617.8	608.5	604.6		
LRT		<0.005	<0.005	<0.005	<0.05		
Knee_JSN_It, visit 10							
BMI (kg/m ²)					0.084(0.034)	1.087(1.017–1.162)	0.014

3.2. Association and prediction analyses of RKOA status

Since several covariates were associated with RKOA status, in cross sectional and prediction studies, we implemented binary logistic regression analysis starting with contribution of age, and then adding to a regression function, one by one the other covariates, for each of the RKOA-phenotypes. The results of the corresponding analyses, namely, parameter estimates, their confidence intervals and significance values are provided in (Tables 2 and 3). The tables present odds ratios (ORs) for association and relative risk (RR) for prediction, correspondingly estimated in best fitting and most parsimonious models.

As seen, in Table 2, association analysis with K/L showed that inclusion of BMI and lower limb fat mass into a logistic regression model in addition to age leads to a significant improvement of the model fitting, by LRT. Adding lower limb lean mass, does not improve the model likelihood. Interestingly, however, in combination with abdominal fat mass this model (M5) became significantly better not only in comparison to M4, but also vs M3 ($\chi^2_{(2)} = 11.0, p < 0.01$), and therefore was selected as the best fitting model. Of interest, the similar best fitting model was obtained with lateral osteophytes. Also with this phenotype, the best fitting model 5 was significantly better than model 3 ($\chi^2_{(2)} = 9.50, p < 0.01$). For medial osteophytes, only age and BMI were independently and significantly associated covariates [OR = 1.11 (95%CI 1.07–1.16) and OR = 1.12 (95%CI 1.07–1.17)], respectively. Inclusion of other covariates, did not improve the model fitting for this phenotype. Notable, exclusion of BMI from the covariates, in any of the aforementioned models led to a significant deterioration of the model likelihood.

It may also be mentioned that we performed an additional analysis to test the association of the leg fat mass/leg lean mass ratio with the RKOA affection status, as assessed by K/L scores. The main purpose here was to see whether the both leg composition components change proportionally with the RKOA appearance. We observed significant positive association ($p < 0.01$) in this analysis. Moreover, the trend remained the same even when the group of the affected individuals was subdivided into subgroups: affected, K/L = 2, and severely affected, K/L > 2 individuals. Fig. 1 shows consistent results ($p < 0.01$), and likely suggests that increase in leg fat mass outpaces the growth of leg lean mass with in association with RKOA severity.

Finally, note that in this part of analysis we found no association of JSN with any of the body composition components examined.

The main results of prediction analysis are summarized in Tables 3 and 4. At first stages, BMI (in addition to age) was clearly common predictor for K/L, osteophyte scores in both compartments and for JSN in lateral compartment. However, at following stages, when leg lean mass was introduced, it significantly improved model fitting for K/L and medial osteophyte scores, and obliterated effects of BMI, leg and abdominal fat mass variables. In fact, for fitting these two RKOA phenotypes age and either BMI or leg lean mass were sufficient by LRT. However, when compared with general model, the model including leg lean mass was superior, with following parameter estimates: $RR_{AGE} = 1.08$ (95%CI: 1.05–1.12), $RR_{LLM} = 1.36$ (95%CI: 1.12–1.53) for K/L, and $RR_{AGE} = 1.08$ (95% CI: 1.05–1.12), $RR_{LLM} = 1.25$ (95%CI: 1.11–1.40) for medial osteophytes, respectively. When lateral osteophytes were examined, the best fitting model was model 5. Similar to association analysis, it included BMI in combination with all other tested covariates (Table 3). In comparison to previous models it was significantly better than model 4 (Table 3) and even model 3 ($\chi^2_{(2)} = 13.2, p = 0.005$). We next compared first and fourth quartiles of the significant covariates in the corresponding logistic regressions (Table 4), and percentage of the attributable risk for each of the potential predictors was estimated. The provided quantities show what number of the affected women at 4th quartile would be avoided if the correspondent predictor variables (e.g. age, BMI, etc.) of the 4th quartile would be similar to the 1st quartile. For example, 47 women found with positive osteophytes at lateral compartment. If their BMI was similar to BMI of the women in 1st quartile, 62.4% of the 47 women would not be affected. The results were, in general similar with the results shown in Table 3. The data suggest 56.0%–71.2% of the affected women (new cases), at 4th quartile would not appear in the cohort if they had the same values of the predictor variables as those in 1st quartile. Interestingly, in comparison of quartiles for osteophyte's manifestation in lateral compartment, abdominal and leg

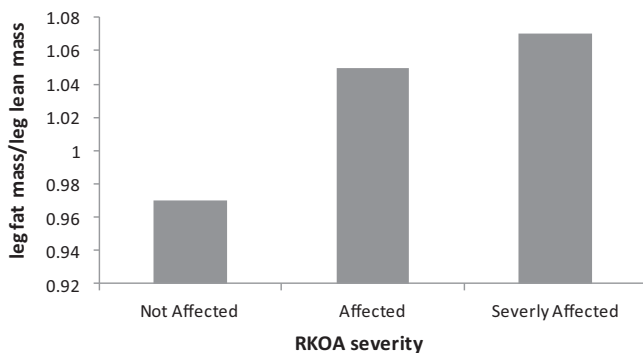


Fig. 1. Leg fat mass/Leg lean mass ratio at baseline by K/L severity at cross sectional study (after adjustment of age $p = 0.001$).

Table 4

Prediction study: binary logistic regression provides relative risk (RR) and percentage of attributable risk (%AR) of predictive covariates divided into quartiles: first versus fourth.

Predictor variables, by RKOA phenotype	Not affected N (%)	Affected N (%)	RR (95%CI) Q1 vs Q4	p	%AR = [(RR - 1)/RR] × 100
Knee_K/L, visit 10					
Age, years				0.001	68.70%
Q1: 44.6–49.1	173(30.6%)	40(19.2%)	3.197		
Q4: 60.1–67.9	100(17.7%)	58(27.9%)	(1.895–5.396)		
Lower limb lean mass, kg				0.001	65.20%
Q1: 7.5–10.3	147(28.7%)	36(18.3%)	2.875		
Q4: 12.8–21.2	91(17.8%)	72(36.5%)	(1.661–4.976)		
Knee_OSP_md, visit 10					
Age, years				0.001	71.20%
Q1: 44.6–49.1	189(29.5%)	27(15.2%)	3.471		
Q4: 60.1–67.9	128(20.0%)	50(28.1%)	(1.969–6.120)		
Lower limb lean mass, kg				0.001	63.60%
Q1: 7.5–10.3	162(27.9%)	29(17.2%)	2.751		
Q4: 12.8–21.2	113(19.4%)	65(38.5%)	(1.544–4.901)		
Knee_OSP_lt, visit 10					
Age, years				0.007	56.50%
Q1: 44.6–49.1	196(28.7%)	25(19.5%)	2.299		
Q4: 60.1–67.9	131(19.2%)	38(29.7%)	(1.253–4.017)		
BMI, kg/m ²				0.04	62.40%
Q1: 16.8–22.6	199(29.1%)	18(14.1%)	2.659		
Q4: 27.6–47.3	130(19.0%)	47(36.7%)	(1.048–6.749)		
Lower limb lean mass, kg				0.012	56.00%
Q1: 7.5–10.3	167(26.8%)	21(17.5%)	2.271		
Q4: 12.8–21.2	125(20.0%)	47(39.2%)	(1.199–4.302)		

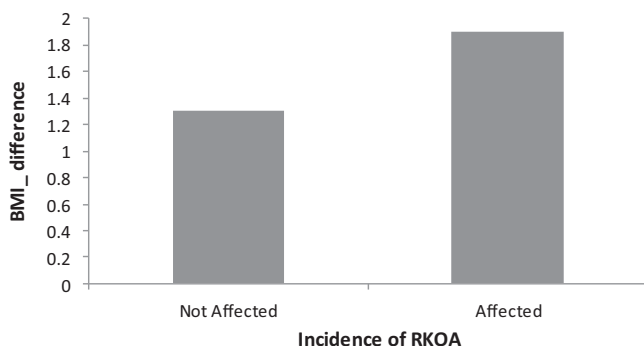


Fig. 2. BMI difference between BMI at baseline and BMI 10 years after ($\Delta\text{BMI} = \text{BMI}_1 - \text{BMI}_{10}$) by K/L of participants who were not affected at baseline and after 10 years and participants who were not affected at baseline and were affected after 10 years (affected individuals were defined by $\text{K/L} \geq 2$).

fat mass were not retained as significant predictors. In addition, to aforementioned analysis, since BMI was inconsistently significant predictor, we compared the magnitude of BMI change between the 1st measurement and after 10 years in the affected ($\text{K/L} \geq 2$) and non-affected participants. Fig. 2 presents the results. The affected women had significantly more elevated BMI in comparison to not affected women even accounting for BMI at baseline.

4. Discussion

The major aim of this study was to determine to what extent body composition components specifically, lower limb fat and lean mass are associated with signs of RKOA and to determine whether the lower limb body mass can be used as predictor for the development of RKOA. The study was therefore conducted in two stages. First, we examined the corresponding associations cross-sectionally, and in the second stage we examined prediction of incidence of RKOA 10 years after entry examination. Our main positive findings could be presented as following. In association (cross-sectional) analysis, combined effect of age, BMI and body composition is required for best fitting model explaining variations

of K/L scoring and osteophytes at lateral compartment. To fit variation of medial osteophytes, age and BMI are sufficient to generate the best fitting model. In prediction analysis, comparing the individuals that were not affected at baseline and after 10 years with those who became affected after 10 years revealed that leg lean mass was more powerful predictor of K/L and medial osteophytes than BMI. Its inclusion obliterates association with BMI, which appears as highly significant ($p < 0.001$) in univariate analyses (Table 1). For lateral osteophytes, inclusion of BMI together with leg lean and fat mass is necessary for better prediction. Abbate et al. (2006) in their cohort found that using body composition does not have an advantage over BMI in explaining RKOA, as assessed by K/L. However, contrary to this conclusion Sowers et al. (2008) reported that body composition when used in model-based analysis fitted significantly better RKOA variation (K/L and JSN), in comparison to BMI. Our analysis clarifies these contradictory results and suggests that some features of RKOA can better be explained by lower limb composition and others – by BMI. This general conclusion, of the covariate/phenotype specificity is true with respect to both association and prediction analysis. It should also be mentioned that in majority of our analyses BMI was necessary component, with or without leg composition components. Abdominal fat mass appeared as mostly negligible contributor to prediction of any of the RKOA-related phenotypes. The small, although significant regression coefficients observed in some analyses are apparently due to its high correlation with BMI ($r = 0.816$, $p < 0.001$), leg composition components ($r = 0.72$ and $r = 0.41$, $p = 0.001$ with leg fat and lean mass, respectively) and consequent collinearity, which is well known problem for the prediction ability and classification ability, using multiple regression approach (Tormod & Bjørn-Helge, 2001). The bias caused by collinearity between the predictor variables may also be responsible for appearance of leg lean mass as a better predictor than BMI. Indeed, although lower limb lean mass was better predictor of K/L scores (Table 3), when we compared BMI of new diagnosed affected participants ($\text{K/L} \geq 2$ at 10 years visit) vs control (those who remained with $\text{K/L} < 2$ during these years), we observed significantly more sizable elevation in BMI in case than in control, non-attributable to their differences at

baseline (Fig. 2). This result supports the notion that, overall BMI is a simpler, cheaper and good predictor of RKOA manifestation (Anderson & Loeser, 2010; Fuller, Laskey, & Elia, 1992; Lau et al., 2000; Sowers, Lachance, Hochberg, & Jamadra, 2000; Strumer, Gunther, & Brenner, 2000).

Nevertheless, it is not possible to exclude a possibility that the association with leg lean mass may also have a physiological component. Cicuttini et al. (2005) observed atrophy of muscle mass of lower limb with osteoarthritic knees. The authors assumed that this association was secondary to activity limitation imposed by an arthritic knee joint. The study found a decline in muscle mass with age, which may be compensated for by an increase in adipose tissue. We also expected to find similar trend, with lower lean mass than in unaffected women. However, in our study the results suggested an opposite trend. This result, suggesting that the leg lean mass is a predictor of K/L scores is seemingly in contradiction to a significant positive correlation between the leg fat mass/leg lean mass ratio and the affection status in cross-sectional analysis (Fig. 1). Such a correlation may suggest that despite the leg lean mass absolute increase, its amount relative to fat mass amount decreases, potentially leading to sarcopenia in OA, as was also recently suggested by (Scott, Blizzard, Fell, & Jones, 2012). However, our observation of leg lean mass increase with RKOA appearance is not lonely and not first. It was reported previously (Abbate et al., 2006; Sowers et al., 2008) and was explained by suggesting that muscle mass can increase not only as a result of physical activity but also because of the requirement for supporting growing adipose tissue mass (Forbes, 1987; Janssen, Heymsfield, Wang, & Ross, 2000; Srikanth et al., 2005). One of the studies (Kitagawa & Miyashita, 1978) mentioned, for example, that increase in lower extremity muscle mass in women who develop incident OA was not accompanied by an increase in low limb extensor muscles' strength. Other study (Tataranni & Ravussin, 1995) showed that in obese persons fat mass increase is accompanied by hypertrophy of lower limb muscles, which is likely required to carry the increased load. It has been suggested that such hypertrophic muscles do not generate higher force comparatively to the total body mass as could be expected, but on the contrary, there exists a 15% to 25% muscle strength deficit (Slemenda et al., 1997). It is also possible that progression of KOA is accompanied with co-contraction of muscles around the knee in response to laxity and instability of joint, which in turn could lead to elevation of muscle mass (Lewek, Ramsey, Snyder-Mackler, & Rudolph, 2005). This hypothesis could also be a plausible explanation to our results concerning positive association between leg lean fat and association and prediction of RKOA.

As other studies, the present project has also some important limitations that may have affected the interpretation of the evidence being presented. The major one is likely related to a fact that this study was focused on radiographic assessment of an individual and did not consider the pain and other symptoms of the disease. Note also that the results observed on these female samples may not necessarily be true for men. Scott et al. (2012), for example, reported substantial differences in lower-limb muscle strength decline and risk of falls in older women compared to men. The strength of the study is that the relatively large sample size at the entrance examination and 10 years follow-up make this study one of the most reliably projects in this field.

In conclusion, this study shows that obesity defined by elevated BMI or fat tissue mass is a risk factor for the development of RKOA. However, for some RKOA features, including K/L body composition variables can also serve as useful and even preferable predictors. The most remarkable and contradictory finding of this study is related to leg lean mass, which was a better predictor of K/L and osteophytes than BMI. This could be due to tight interrelationships between the body composition variables, but may also be caused

by physiological factors. This in turn may have important clinical and scientific implications, which require further exploration and clarification of a possible mechanism of this association in order to plan an efficient treatment to improve outcomes of patients with KOA.

Conflict of interest statement

The authors certify that there is no conflict of interest related to work presented.

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