PART I

Mechanisms underlying the association between risk factors and osteoarthritis

CHAPTER 2

The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study

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ABSTRACT

Objective
To study the relative contribution of surrogates for mechanical stress and systemic processes with osteoarthritis (OA) in weight-bearing and non-weight-bearing joints.

Methods
The Netherlands Epidemiology of Obesity (NEO) study is a population-based cohort including 6,673 participants (range 45 to 65 years, 56% women, median BMI 26 kg/m^2). Weight (kg) and fat mass (FM) (kg) were measured, fat-free mass (FFM) (kg) was calculated. The metabolic syndrome was defined following the Adult Treatment Panel III criteria. Knee and hand OA were defined according to the American College of Rheumatology clinical criteria.
Logistic regression analyses were performed to associate surrogates for mechanical stress (such as weight, FFM) and systemic processes (such as metabolic syndrome) with OA in knees alone, knees and hands or hands alone, adjusted for age, sex, height, smoking, education and ethnicity, and when appropriate for metabolic factors and weight.

Results
Knee, knee and hand, and hand OA were present in 10%, 4% and 8% of the participants, respectively. Knee OA was associated with weight and FFM, adjusted for metabolic factors (OR 1.49 (95% CI 1.32 to 1.68) and 2.05 (1.60 to 2.62) respectively). Similar results were found for OA in knees and hands (OR 1.51 (95% CI 1.29 to 1.78) and 2.17 (1.52 to 3.10) respectively). Hand OA was associated with the metabolic syndrome, adjusted for weight (OR 1.46 (95% CI 1.06 to 2.02)).

Conclusion
In knee OA, whether or not in co-occurrence with hand OA, surrogates for mechanical stress are suggested to be the most important risk factors, whereas in hand OA alone, surrogates for systemic processes are the most important risk factors.

INTRODUCTION

Overweight and obesity are well-known risk factors for osteoarthritis (OA) in weight-bearing and non-weight-bearing joints.[1,2] Several mechanisms are thought to explain the association between obesity and OA. First, increased mechanical stress can result in damaged joint tissue.[3] Second, systemic processes seem to be involved. Adipose tissue is known as a source of proinflammatory and anti-inflammatory adipokines, which have been suggested to play a role in OA pathogenesis.[4-7] Furthermore, hyperglycaemia and diabetes have been related to OA,[8-12] possibly via insulin-like growth factor I resistance of chondrocytes,[13] via changes in striated muscles due to insulin resistance,[14] or via formation of advanced glycation end products.[15,16] The association of OA with measures of atherosclerosis suggests another systemic link with OA,[17,18] possibly via systemic inflammation or pathology of subchondral bone vasculature.[19]

The relative contribution of mechanical stress and systemic processes to different types of OA remains unclear. In OA of weight-bearing joints as the knees, the concept of excessive mechanical stress leading to OA is supported by previous reported associations of weight or lean body mass with knee OA.[20-23] The role of systemic processes in OA of weight-bearing joints is questionable, and difficult to identify since in obese individuals increased mechanical stress and systemic processes frequently occur together. Two recent studies on the metabolic syndrome, as surrogate for systemic processes, in relation to knee OA reported conflicting results. One observed an association between the metabolic syndrome and increased OA incidence even after adjustment for BMI, whereas the other did not.[24,25] So far, no studies examined knee OA in the presence of OA of non-weight-bearing joints as the hands, while this type of polyarticular OA might be particularly driven by systemic processes.

In hand OA, being non-weight-bearing joints, systemic processes may be most important in the association between obesity and OA. Although a number of studies assessed individual metabolic factors in relation to hand OA,[8,17,18] the association between the metabolic syndrome and presence of hand OA has not been investigated.

To gain more insight into the relative contribution of mechanical stress and systemic processes to OA of both weight-bearing and non-weight-bearing joints, we examined the association of surrogates for both mechanisms with OA of knees, hands or both. We hypothesized that surrogates for mechanical stress associate predominantly with knee OA, whereas surrogates for systemic processes associate predominantly with presence of hand OA, whether or not co-occurring with knee OA.

METHODS

Study design and study population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based prospective cohort study with an oversampling of persons with overweight or obesity, aiming to investigate pathways leading to obesity-related diseases. The present study is a cross-sectional analysis of baseline measurements of the NEO study. Detailed information about the study design and data collection has been described previously.[26] In short, men and women between 45 years to 65 years of age 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, resulting in 5,002 participants. In addition, all inhabitants aged 45 to 65 years from one municipality (Leiderdorp) were invited irrespective of their BMI, resulting in 1,671 participants (including 605 with BMI ≥27 kg/m^2) allowing for a reference distribution of BMI.

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

Measures of body composition

Measured weight (kg) and height (cm) were used to calculate the BMI (kg/m^2). Fat mass (FM) (kg) was measured by bioelectrical impedance analysis (BIA) using the Tanita foot-to-foot BIA system TBF-300A Body Composition Analyzer.[27] Fat-free mass (FFM) (kg) was calculated on weight and FM. Waist circumference (cm) was measured midway between the lower costal margin and iliac crest with a precision of 0.1 cm.

Measurement of metabolic factors

Blood pressure was measured three times, the average was used as diastolic and systolic pressures. Serum concentrations of triglycerides (mmol/L), high density lipoprotein (HDL) cholesterol (mmol/L) and glucose (mmol/L) were measured after an overnight fast.

The metabolic syndrome was defined according to the Adult Treatment Panel III criteria, based on presence of at least three of the following: (1) elevated waist circumference (men ≥102 cm, women ≥88 cm), (2) elevated triglycerides (≥1.7 mmol/L or drug treatment for elevated triglycerides), (3) reduced HDL cholesterol (men <1.03 mmol/L, women <1.3 mmol/L or drug treatment for reduced HDL cholesterol), (4) elevated blood pressure (systolic ≥130 mm Hg, diastolic ≥85 mm Hg or antihypertensive medication), (5) elevated fasting glucose (≥5.6 mmol/L or glucose lowering medication).[28]

Clinical assessment and OA diagnosis

Self-reported pain on most days of the prior month and presence of morning stiffness with ≤30 minutes duration were measured using standardized questions. Physical examination of knees and hands was performed by trained research nurses, using a standardized scoring form. Bony swelling, palpable pain and warmth, crepitus and movement restriction of both knees were assessed. Regarding the hands, bony and soft swellings as well as deformities of the distal interphalangeal, proximal interphalangeal, metacar-

pophalangeal, carpometacarpal and wrist joints were assessed. Clinical OA was defined according to the American College of Rheumatology clinical criteria.[29,30] Presence of a knee prosthesis was considered as knee OA.

Statistical analysis

Data were analyzed using SPSS V.20 and STATA V.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,[31] adjustments for this oversampling were made by weighting individuals towards the BMI distribution of participants from the Leiderdorp municipality (n = 1,671),[32] whose BMI distribution was similar to the BMI distribution in the general Dutch population.[33] All results were based on weighted analyses. Consequently, results apply to a population-based study without oversampling of BMI ≥27 kg/m^2.

Based on OA diagnosis, four groups were defined: (1) individuals without knee or hand OA, (2) individuals with only knee OA, (3) individuals with knee and hand OA, and (4) individuals with only hand OA. We performed logistic regression analyses to examine cross-sectional associations of each of the surrogates for mechanical stress (weight, FFM, FM) and systemic processes (FM, metabolic syndrome) with each of the three OA types, using individuals without knee or hand OA as reference group. FM probably is a surrogate for mechanical stress and systemic processes. To approximate FM as surrogate for mechanical stress, adjustment for metabolic factors was performed, and adjustment for weight was performed to approximate FM as surrogate for systemic processes. Associations were expressed as odds ratios (OR) with 95% confidence intervals (CI).

All continuous variables were standardized by dividing individual values by the standard deviation (SD) to be able to compare ORs. Consequently, all ORs describe the risk of OA associated with an increase of 1 SD of the studied variable. All analyses have been adjusted for age, sex, height, smoking, education and ethnicity. Analyses on surrogates for mechanical stress were additionally adjusted for metabolic factors (presence of metabolic syndrome, hypertension, hyperglycaemia, hypertriglyceridaemia and reduced HDL cholesterol) and analyses on surrogates for systemic processes were adjusted for weight. Finally, to illustrate the relative importance of mechanical stress and systemic processes, age, sex, height, smoking, education and ethnicity adjusted ORs were calculated for presence of each OA type in three weight categories (based on tertiles of weight of the total study population: <75 kg, 75-90 kg, >90 kg), stratified by the metabolic syndrome. Participants in the lowest weight category without metabolic syndrome served as reference.

RESULTS

Population characteristics

After exclusion of individuals with missing data of BIA (n = 31) or physical examination (n = 14), data from 6,628 participants were analyzed. Unweighted baseline characteristics, that is, without taking the oversampling into account, are shown in the online supplementary table. Table 1 shows the weighted baseline characteristics stratified by OA; these characteristics represent the population on which all subsequent results apply. Median (25th to 75th centiles) age of the total study population was 56 years (50 to 61 years), BMI 26 kg/m^2 (23 to 28 kg/m^2), 56% women.

The prevalence of knee OA alone was 10% (95% CI 9% to 11%), knee and hand OA 4% (95% CI 4% to 5%) and hand OA alone 8% (95% CI 7% to 8%). The prevalence of a knee prosthesis was 1% (95% CI 1% to 1%).
The percentage of women and median age were higher in individuals with knee, knee and hand, or hand OA as compared with individuals without OA. Furthermore, individuals with knee, hand or knee and hand OA had a higher median FM and metabolic syndrome prevalence than individuals without OA.

Table 1. Baseline characteristics of the NEO study population, stratified by OA status

Prevalence	**No knee/hand OA 78%**	**Knee OA 10%**	**Knee and hand OA 4%**	**Hand OA 8%**
Age (year)	55 (49-61)	58 (53-61)	59 (55-62)	59 (55-63)
Sex (% women)	52	63	86	76
Smoking (% current)	12	11	9	8
Education (% high)	39	28	25	32
Ethnicity (% Caucasian)	95	96	92	95
BMI (kg/m^2)	25.5 (23.2-28.0)	26.9 (24.6-30.3)	26.7 (24.6-29.8)	25.9 (23.0-28.8)
Height (m)	1.74 (1.67-1.81)	1.71 (1.66-1.79)	1.68 (1.63-1.73)	1.68 (1.63-1.75)
Weight (kg)	77.8 (67.6-88.8)	80.4 (70.8-92.8)	75.6 (66.8-86.8)	73.4 (63.8-85.6)
Fat-free mass (kg)	51.8 (44.0-64.6)	49.2 (44.2-64.0)	45.9 (43.2-50.3)	45.1 (41.8-54.4)
Fat mass (kg)	22.7 (18.2-29.0)	27.5 (21.0-34.7)	27.5 (22.4-35.0)	24.4 (19.8-31.9)
Metabolic syndrome (%)	28	39	36	38

Results are based on weighted analyses of the study population (n = 6,628).

Numbers represent medians (25th-75th centiles) or percentages.

BMI, body mass index; NEO, Netherlands Epidemiology of Obesity; OA, osteoarthritis.

Surrogates for mechanical stress and different OA types

First, we investigated associations of surrogates for mechanical stress with the OA types (Table 2).
Weight, FFM and FM were positively associated with all OA types. The ORs were highest for presence of knee OA and OA in knee and hand. The ORs per SD weight for example, were 1.55 (95% CI 1.39 to 1.73) for knee OA and 1.52 (1.31 to 1.76) for knee and hand OA, meaning that 1 SD of weight (15.95 kg) was associated with a 55% higher odds of having knee OA and a 52% higher odds of having knee and hand OA. The OR for hand OA was 1.25 (1.09 to 1.42).
After additional adjustment for metabolic factors, weight, FFM and FM remained associated with knee OA and with OA in knee and hand. The associations with hand OA on the contrary decreased.
In addition, we assessed if associations between surrogates for mechanical stress and knee OA were stronger for bilateral than for unilateral knee OA. Fully adjusted ORs of weight, FFM and FM were higher for bilateral OA (OR 1.68 (1.44 to 1.97), 2.29 (1.58 to 3.34) and 1.54 (1.36 to 1.75), respectively), than for unilateral OA (OR 1.38 (1.19 to 1.59), 1.92 (1.44 to 2.57) and 1.27 (1.12 to 1.44), respectively).

Table 2. Associations of surrogates for mechanical stress with different types of OA (individuals without OA served as reference)

		OR (95% CI)					
		Knee OA		**Knee and hand OA**		**Hand OA**	
	SD	Adjusted*	Adjusted incl. metabolic factors#	Adjusted*	Adjusted incl. metabolic factors#	Adjusted*	Adjusted incl. metabolic factors#
Weight (kg)	15.95	1.55	1.49	1.52	1.51	1.25	1.12
		(1.39-1.73)	(1.32-1.68)	(1.31-1.76)	(1.29-1.78)	(1.09-1.42)	(0.96-1.32)
Fat-free mass (kg)	11.68	2.33	2.05	2.29	2.17	1.43	1.17
		(1.83-2.96)	(1.60-2.62)	(1.63-3.22)	(1.52-3.10)	(1.06-1.93)	(0.83-1.63)
Fat mass (kg)	9.97	1.43	1.37	1.42	1.41	1.21	1.11
		(1.30-1.57)	(1.24-1.52)	(1.25-1.61)	(1.22-1.63)	(1.09-1.35)	(0.97-1.27)

Results are based on weighted analyses of the study population.

All ORs express the risk of OA per SD of the independent variable.

* Adjusted for age, sex, height, smoking, education, ethnicity.

Adjusted for age, sex, height, smoking, education, ethnicity, metabolic syndrome, hypertension, hyperglycaemia, hypertriglyceridaemia, low high density lipoprotein cholesterol. CI, confidence interval; OA, osteoarthritis; OR, odds ratio; SD, standard deviation.

Surrogates for systemic processes and different OA types

Next, we assessed associations of surrogates for systemic processes with OA (Table 3). Although the OR of FM for hand OA was higher (1.17 (0.74 to 1.86)) than for knee OA or OA in knee and hand (OR 0.88 (0.61 to 1.26) and OR 1.03 (0.51 to 2.11), respectively), the associations were not statistically significant after adjustment for weight.

The metabolic syndrome, surrogate for systemic processes particularly, was associated with all OA types. However, after additional adjustment for weight the associations with knee OA and knee and hand OA disappeared whereas the metabolic syndrome remained associated with hand OA (OR 1.46 (1.06 to 2.02).

Table 3. Associations of surrogates for systemic processes with different types of OA (individuals without OA served as reference)

		OR (95% CI)					
		Knee OA		**Knee and hand OA**		**Hand OA**	
	SD	Adjusted*	Adjusted incl. weight#	Adjusted*	Adjusted incl. weight#	Adjusted*	Adjusted incl. weight#
Fat mass (kg)	9.97	1.43 (1.30-1.57)	0.88 (0.61-1.26)	1.42 (1.25-1.61)	1.03 (0.51-2.11)	1.21 (1.09-1.35)	1.17 (0.74-1.86)
Metabolic syndrome		1.56 (1.24-1.97)	1.08 (0.85-1.39)	1.48 (1.07-2.05)	1.03 (0.72-1.46)	1.62 (1.23-2.13)	1.46 (1.06-2.02)

Results are based on weighted analyses of the study population.

The OR of fat mass expresses the risk of OA per SD.

* Adjusted for age, sex, smoking, education, ethnicity, height.

Adjusted for age, sex, smoking, education, ethnicity, height, weight.

CI, confidence interval; OA, osteoarthritis; OR, odds ratio; SD, standard deviation.

Relative contribution of weight and metabolic syndrome to different OA types

Figure 1 illustrates the relative contribution of weight as surrogate for mechanical stress and metabolic syndrome as surrogate for systemic processes to the OA types.

The ORs for knee OA were stronger in higher weight categories as compared with the lowest weight category. In addition to the depicted OR representing the highest weight category compared with the lowest in individuals without metabolic syndrome 2.62 (1.77 to 3.88), we calculated the OR of highest versus lowest weight category in individuals with metabolic syndrome (2.30 (1.29 to 4.12)). Presence of metabolic syndrome, adjusted for the weight categories, did not result in a higher OR for knee OA (OR 1.16 (0.91 to 1.47). The same was observed in relation to OA in knee and hand.

In hand OA on the contrary, ORs did not increase with increasing weight (highest vs. lowest weight category: OR 1.40 (0.89 to 2.21) in individuals without metabolic syndrome (Figure 1) and 0.77 (0.39 to 1.51) in individuals with metabolic syndrome. The metabolic syndrome on the other hand was associated with presence of hand OA, adjusted for the weight categories; individuals with metabolic syndrome had a higher OR for hand OA as compared with individuals without metabolic syndrome (OR 1.52 (1.10 to 2.09)).

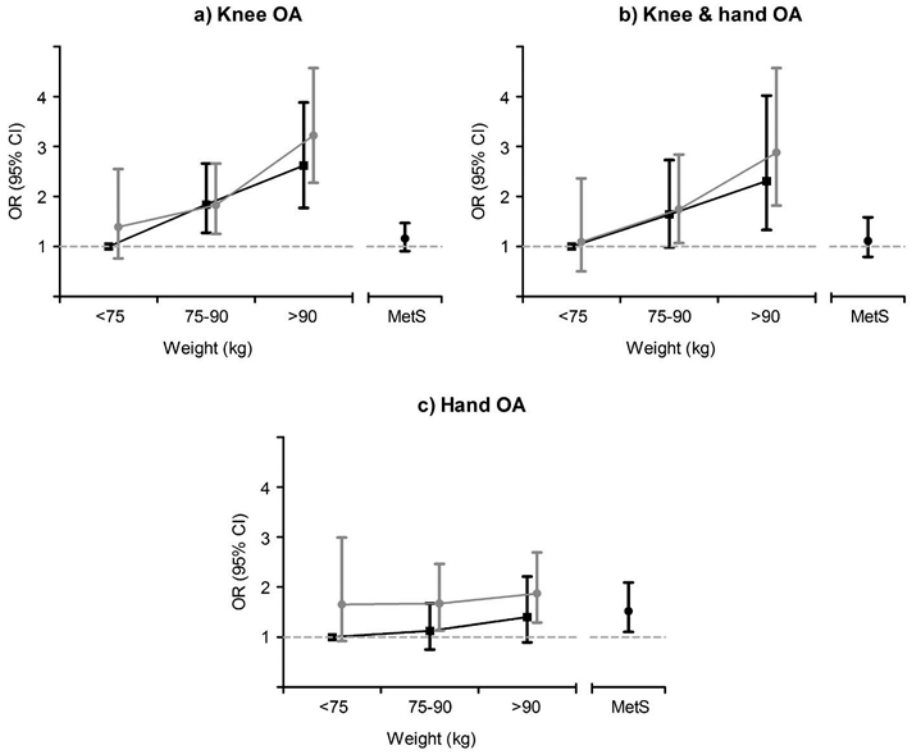

Figure 1. The adjusted ORs and corresponding 95% CIs for osteoarthritis (OA) stratified by weight and metabolic syndrome. Participants in the lowest weight category without metabolic syndrome served as reference. Gray connected lines represent individuals with metabolic syndrome, black connected lines represent individuals without metabolic syndrome. Results are based on weighted analyses of the study population, adjusted for age, sex, smoking, education, ethnicity and height. MetS, metabolic syndrome, representing the odds ratio of the metabolic syndrome for OA, adjusted for the weight catagorie

DISCUSSION

This study aimed to increase insight into the relative contribution of mechanical stress and systemic processes in the relation between overweight or obesity and OA of weight-bearing and non-weight-bearing joints. Knee OA was associated with surrogates for mechanical stress, adjusted for metabolic factors. Similar results were found for OA in knees and hands. Hand OA was associated with the metabolic syndrome, adjusted for weight.

A growing body of literature exists on mechanical stress and systemic processes in OA pathogenesis, however innovative in this study is the investigation of the relative contribution of both mechanisms to OA of weight-bearing and non-weight-bearing joints, or of both.

The association of surrogates for mechanical stress with knee OA has been described previously,[20-23,34] supporting the concept of excessive mechanical stress on the joint surface of obese individuals resulting in damaged joint tissue. Compression of cartilage might activate mechanoreceptors on chondrocytes, inducing signaling cascades leading to synthesis of inflammatory mediators and tissue remodeling.[35,36] It is unclear which biomechanical factors are involved in the relation between weight and OA, since a recent study showed that neither a decrease nor increase in knee peak compression force was associated with OA progression.[37]

Our finding regarding the metabolic syndrome in relation to knee OA is in accordance with a recent study of Han et al.,[24] reporting no association between metabolic syndrome and knee OA. Another recent study, by Monira Hussain et al.,[25] did report an association between metabolic syndrome and knee OA, adjusted for BMI. This discrepancy might be due to differences in OA definition. Where in this study clinical knee OA was assessed following the ACR criteria, Monira Hussain et al. defined severe knee OA requiring total knee replacement as OA. Han et al. defined knee OA by self-reported physician-made diagnosis. The strength of our study is that knee OA was assessed in all 6628 patients by physical examination. Consequently, OA was diagnosed following the ACR criteria, providing an objective and well validated definition.

Presence of knee and hand OA has not been investigated before. Our hypothesis was that this type of polyarticular OA might be driven by systemic processes, however we observed no association with surrogates for systemic processes after adjustment for weight. Presence of knee and hand OA was associated with surrogates for mechanical stress, even after adjustment for metabolic factors, like presence of knee OA alone. This observation suggests that co-occurrence of knee and hand OA may not be based on a common underlying pathogenic mechanism, but may represent presence of two different types of OA. Since the association between mechanical stress and knee OA was relatively strong, this association could dominate the association with OA at both sites.

The association between metabolic syndrome and hand OA, adjusted for weight, has not been reported before. A number of studies assessed individual metabolic factors in relation to OA, however the metabolic syndrome, as composition of different metabolic processes, might act as risk factor beyond the risk of its individual components.[38]

The association between metabolic syndrome and hand OA might be explained by systemic inflammation, a main characteristic of the metabolic syndrome. Adipose tissue is known as source of proinflammatory and anti-inflammatory cytokines, which have been related to the metabolic syndrome[39] and have been suggested to affect joint tissues.[4,6,7] Visceral fat has been described as the most actively secreting type of adipose tissue,[40] and has been associated with the metabolic syndrome.[41-45] In addition, in a recently performed study we associated visceral fat with hand OA in men.[46]

Strengths of this study are the large study population, extensive characterization of participants and availability of information of both weight-bearing and non-weight-bearing joints.

However, there are a number of potential limitations. The observed associations were not very strong, however since this study aimed to assess the relative contribution of mechanical stress and systemic processes to the OA types the different ORs provide valuable insight.

Increased mechanical stress and systemic processes are highly correlated in overweight or obese individuals. Therefore, we adjusted for surrogates for mechanical stress in our analyses on systemic processes and vice versa. Although these analyses identified the relative contribution of both mechanisms for OA, residual confounding may still be present in this observational study. We further minimized residual confounding by adjusting for possible confounders as age, sex and surrogates for socioeconomic status (education, smoking, ethnicity). Unfortunately we did not have information on previous knee injury, which may be a confounder in the associations with knee OA.

Furthermore, since this is a cross-sectional study, causality is difficult to identify. Since the direction of associations cannot be determined, reverse causation may be present. Longitudinal studies are needed to confirm and further explore associations of mechanical stress and systemic processes with OA.

Knee and hand OA were diagnosed based on clinical criteria, no X-rays were available. However, the ACR clinical criteria are well validated and have high sensitivity and specificity in diagnosing OA.[29,30] This criteria include findings at physical examination and presence of symptoms as pain. Since it is known that obese individuals are more likely to report pain,[47] they could be more prone to be diagnosed as having OA than non-obese individuals. However, the OA prevalence observed in this study is comparable with the prevalence observed in other population-based studies.[18,48]

Furthermore, FM was measured using foot-to-foot BIA. Although this method has been suggested to overestimate FM,[49] studies comparing foot-to-foot BIA with hand-to-foot BIA, underwater weighing and dual-energy X-ray absorptiometry reported strong correlations.[27,50]

We assessed all body composition measures in relation to OA per SD to be able to compare strength of associations observed in this study. It must be noted that the OR of the metabolic syndrome, analysed dichotomously, cannot be directly compared to the ORs of the body composition measures.

This study suggests that in knee OA, whether or not co-occurring with hand OA, mechanical stress is the most important underlying mechanism, whereas in hand OA alone, systemic processes might contribute most. To gain more insight into the underlying mechanisms, longitudinal research could help to understand how excessive mechanical stress leads to degeneration of joint tissue. In hand OA, the role of the metabolic syndrome might be explored by studying the contribution of the different components of the metabolic syndrome to OA development. Furthermore, future research should focus on the role of systemic inflammation.

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Supplementary table. Unweighted baseline characteristics of 6,628 participants of the NEO study with an over-sampling of BMI ≥ 27 kg/m^2, stratified by OA status

	No knee/hand OA n = 4,890	**Knee OA n = 854**	**Knee and hand OA n = 339**	**Hand OA n = 545**
Age (year)	55 (50-61)	57 (53-61)	59 (55-62)	58 (54-62)
Sex (% women)	47	62	84	70
Smoking (% current)	12	12	8	8
Education (% high)	32	25	20	24
Ethnicity (% Caucasian)	95	94	94	95
BMI (kg/m^2)	29.3 (27.1-32.0)	30.8 (28.2-34.1)	30.5 (27.9-34.0)	29.8 (27.6-33.2)
Height (m)	1.74 (1.67-1.81)	1.71 (1.65-1.79)	1.68 (1.63-1.73)	1.69 (1.63-1.76)
Weight (kg)	89.6 (79.4-99.8)	91.6 (81.4-102.4)	87.6 (78.2-96.4)	86.2 (76.6-98.0)
Fat free mass (kg)	58.6 (47.5-68.3)	52.9 (47.0-66.5)	48.6 (45.4-54.3)	49.8 (45.0-61.5)
Fat mass (kg)	30.2 (24.0-37.8)	35.0 (28.2-42.5)	36.1 (29.9-43.8)	33.4 (26.9-40.8)
Metabolic syndrome (%)	48	57	55	56

Numbers represent medians (25th to 75th percentiles) or percentages.

BMI, body mass index; NEO, Netherlands Epidemiology of Obesity; OA, osteoarthritis.