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The role of leptin and adiponectin as mediators in the relationship between adiposity and hand and knee osteoarthritis

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SUMMARY

Objectives: To investigate associations of leptin and adiponectin levels with knee and hand osteoarthritis, and explore whether these mediate the association between adiposity and osteoarthritis.
Methods: This is a cross-sectional analysis of baseline data from the population-based Netherlands Epidemiology of Obesity study. Adiposity was assessed with body mass index (BMI) and percentage total body fat (%TBF). Osteoarthritis, defined as hand or knee osteoarthritis, was determined using American College of Rheumatology criteria. Fasting serum adipokine levels were measured using immunoassays. Associations between adiposity and osteoarthritis were examined with logistic regression, adjusted for age, sex, ethnicity and education, and additionally for leptin and adiponectin as potential mediators.
Results: In 6408 participants (56% women, median age 56 years), prevalence of osteoarthritis was 22% (10% isolated knee and 8% isolated hand osteoarthritis). Leptin levels were positively associated with osteoarthritis, while adiponectin levels were not. Leptin partially mediated the association of adiposity with osteoarthritis (OR 1.40 (95%CI 1.30; 1.52) attenuated to 1.38 (1.24; 1.54) per 5 units BMI and OR 1.25 (1.17; 1.35) to 1.20 (1.10; 1.32) per 5 units %TBF, representing 4% and 17% mediation, respectively). Larger proportion mediation by leptin was found in knee (13%/27%) than in hand osteoarthritis (9%/18%). Sex-stratified analyses generally showed stronger associations between adiposity, leptin and osteoarthritis in women than in men.
Conclusions: Serum leptin levels were associated with osteoarthritis, and partially mediated the association between adiposity and osteoarthritis, while adiponectin levels were not associated with osteoarthritis. These findings provide evidence for systemic effects of adipose tissue in osteoarthritis.

Introduction

Osteoarthritis (OA) is one of the most common musculoskeletal disorders in the developed world, and a leading cause of disability among elderly[1]. Besides a substantial individual disease burden, OA is associated with a significant socioeconomic burden[2].

Obesity is an important risk factor for OA. While this association has often been reported for weight-bearing joints, studies have also suggested a relation in non-weight-bearing joints[3,4]. However, the underlying mechanism of this association is topic of debate. While the increased mechanical stress across weight-bearing joints is thought to result in joint damage, this paradigm fails to explain the association of obesity with OA in non-weight-bearing joints[5]. It has therefore been suggested that the systemic metabolic effects of obesity also have detrimental effects on joint tissue[6]. The presence of systemic metabolic effects in OA is supported by a study in which surrogates for systemic processes (metabolic syndrome) were associated with OA, particularly in hand OA[7], although a recent

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study refuted the association between metabolic syndrome and hand OA[8]. In fact, adipose tissue is a known source of several bioactive factors, including adipokines, cytokines, chemokines, and complement factors[9]. Of these, adipokines have been postulated as a potential link between obesity and OA[10,11]. Leptin and adiponectin are among the most often studied, and have been detected in synovial fluid and the infrapatellar fat pad of knee OA patients[10,12,13]. Studies of the association of adipokines with OA, however, have led to contradictory conclusions. Most evidence is available for an association between leptin and knee OA[14–22]. Associations with adiponectin[14,15,18,21,23] or hand OA[24–27] are less consistent. However, most studies are small, and mediation is not often formally assessed.

Our aim was therefore to investigate the association of leptin and adiponectin levels with knee and hand OA, and to explore whether these adipokines play a mediating role in the association between adiposity and OA.

Methods

Study design and population

A cross-sectional analysis of baseline measurements of the Netherlands Epidemiology of Obesity (NEO) study was performed. The NEO study is a population-based cohort study, designed to investigate pathways that lead to obesity-related diseases, which recruited individuals aged 45–65 years with a self-reported body mass index (BMI) $\geq$27 kg/m^2 living in the greater area of Leiden (the Netherlands) between September 2008-2012[28]. Additionally, all inhabitants aged 45–65 years from the Leiderdorp municipality were invited to participate irrespective of their BMI, to allow for a reference BMI distribution, resulting in 6671 participants in total. The study was approved by the medical ethics committee of the Leiden University Medical Centre. All participants provided written informed consent.

After exclusion of participants with missing data for determination of OA (n = 17), adipokine measurements (n = 61) or %TBF (n = 31), and those with inflammatory rheumatic diseases (n = 154), data from 6408 participants were analysed.

Data collection

All participants completed questionnaires on demographic and clinical data, and attended the study centre for baseline measurements, including blood sampling and physical examination.

Questionnaires included questions on ethnicity (eight categories; regrouped into Caucasian vs other), educational level (ten categories; regrouped into high (higher vocational education, university degree, and postgraduate education) vs low), presence of self-reported inflammatory rheumatic diseases (including rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, and ankylosing spondylitis), and self-reported pain or stiffness of hands or knees on most days of the preceding month.

BMI (kg/m^2) was calculated from measured body weight and height. Bioelectrical impedance analysis (Tanita TBP-300 Body Composition Analyser) was used to estimate percentage total body fat (%TBF). Physical examination of knees and hands was performed by trained research nurses. In the knees, presence of tenderness of the bony margins, bony enlargement, movement restriction, crepitus and palpable warmth were assessed. In the hands, presence of bony swelling, soft swelling and deformities of the distal interphalangeal, proximal interphalangeal, metacarpophalangeal and first carpometacarpal joints were assessed. Participants were classified as having OA, defined as having hand or knee OA, according to clinical American College of Rheumatology criteria[29,30]. Participants with a knee prosthesis were classified as having knee OA.

Serum adipokine levels were measured in fasting blood samples using a latex particle-enhanced turbidimetric immunoassay (Cat A0299, Randox Laboratories Ltd) for adiponectin, and a human competitive radio-immunoassay (Cat HL-81HK, Merck Millipore, Darmstadt, Germany) for leptin. The lowest detectible levels were 0.7 mg/L (adiponectin) and 0.8 ug/L (leptin). Observations below this level (adiponectin n = 4, leptin n = 14) were recorded in the database with a value of 0.5, as recommended by the NEO study group.

Statistical analyses

To correctly represent distributions and associations in the general population[31], adjustments for oversampling of individuals with BMI $\geq$27 kg/m^2 were made by weighting towards the BMI distribution of participants from the Leiderdorp municipality (n = 1671)[32], whose BMI distribution was similar to the general Dutch population[33]. All results were based on weighted analyses. Consequently, results apply to a population-based study without oversampling of individuals with BMI $\geq$27 kg/m^2.

To investigate whether adipokines mediate the association between adiposity and OA, sequential regression analyses were performed according to the Baron and Kenny framework (Fig. 1)[34]. In this framework, pathway C represents the total effect of the exposure (adiposity) on the outcome (OA). This effect can be divided in the direct effect (pathway C'), and the indirect effect via the potential mediator (through pathway A and B). Mediation was suspected when four assumptions of the Baron-Kenny framework were satisfied: (1)adiposity was associated with OA, (2)adiposity was associated with serum adiponectin/leptin, (3)serum adiponectin/leptin was associated with OA, and (4)the association between adiposity and OA attenuated after inclusion of adiponectin/leptin into the model. Satisfaction of the first three assumptions was based on the size of the effect estimate in the regression analysis.

Logistic regression analysis was used for dichotomous endpoints. Linear regression analysis was used for continuous endpoints. Associations, expressed as ORs or betas with 95% CI, were estimated for participants with OA (knee or hand), isolated knee OA and isolated hand OA, using participants without OA as the reference group. BMI was used as measure of adiposity, and analyses were repeated using %TBF. All associations were calculated per 5 units of BMI, %TBF and adiponectin, and per 10 units of leptin. Notably, since a 5 unit increase in BMI or %TBF is not of comparable size, the point estimates of these analyses should not be directly compared and are not indicative of the relative importance of BMI or %TBF.

When the four assumptions for mediation were fulfilled, the proportion of the association between adiposity and OA mediated by the adipokine was calculated. For this, the indirect effect was estimated as the product of the regression coefficients of pathway A and B, with corresponding standard errors calculated according to the Sobel method[35]. The percentage mediation was subsequently calculated by dividing the indirect effect by the total effect (pathway C). In case not all assumptions of the Baron-Kenny framework were fulfilled, percentage mediation was not calculated. The presence of exposure-mediator interaction was explored by adding an interaction term to the model of pathway C'. No evidence of exposure-mediator interaction was found, based on statistical significance of the interaction term ($p < 0.05$), and was thus assumed absent in subsequent analyses.

In analogy with previous studies of adipokines in OA, many comparing obese to non-obese persons, and also to evaluate the

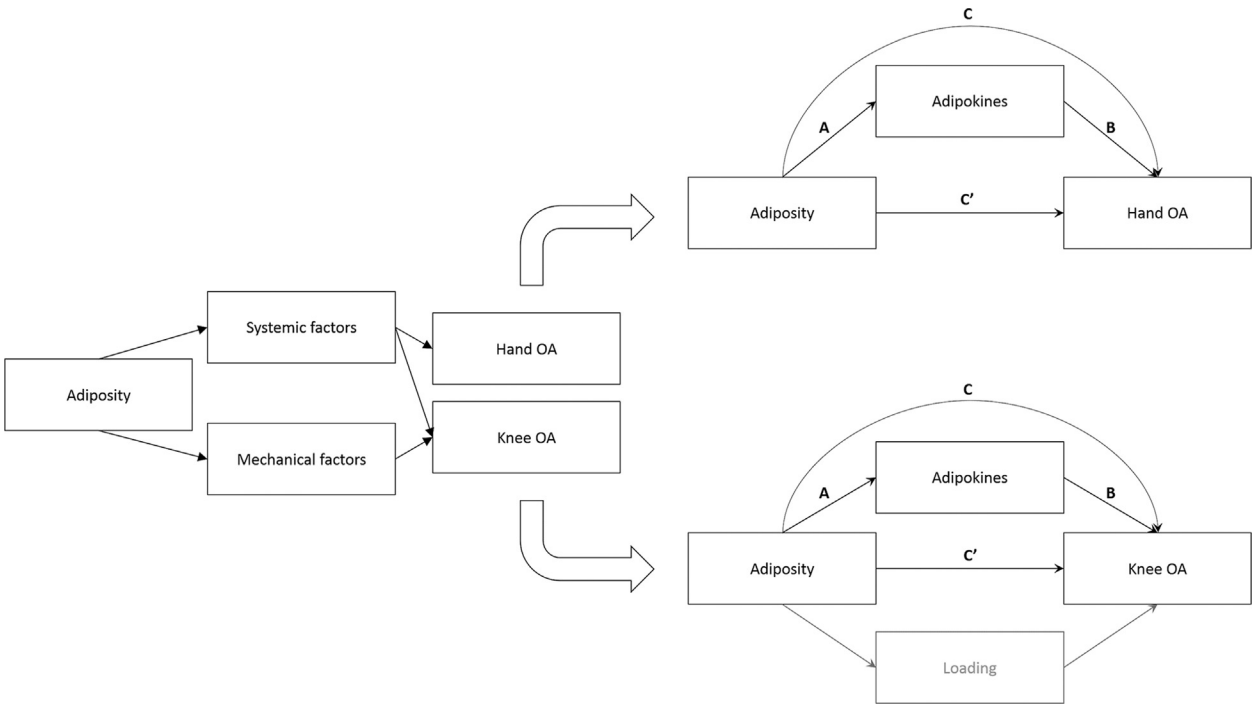

Fig. 1. Hypothesized associations between adiposity, OA and adipokines, and the Barron and Kenny framework.

robustness of our estimation of the percentage mediation, we performed sensitivity analyses, estimating the percentage mediation for BMI and %TBF high vs low. Here, besides the Sobel method, we also used the *medeff* package in Stata, which estimates mediation effects on an additive scale[36]. The cut-off was set at a BMI of 27.5 kg/m^2 or %TBF above or below the median (determined for men and women separately).

All analyses were adjusted for age, sex, ethnicity and education. Since load plays an important role in the relation between adiposity and knee OA (Fig. 1), these analyses were repeated stratified by body weight (<75 vs 75–90 vs >90 kg). We also performed sex-stratified analyses to explore differences between men and women. Analyses were performed using Stata 14 (StataCorp LP, Texas, USA).

Results

Population characteristics

Baseline characteristics are presented in Table I. In total, 22% had OA of the knee or hands (10% knee OA, 8% hand OA, 4% both knee and hand OA). OA prevalence was higher in women than in men (11% vs 9% with knee OA, 10% vs 5% hand OA, and 7% vs 1% combined OA). Adipokine levels were higher in participants with OA than in those without. On average women had higher serum leptin (mean (SD) 23.4 (18.1) vs 9.1 (7.4)) and adiponectin levels (11.3 (5.1) vs 6.6 (3.1)) than men.

Associations between adipokines and OA

Table II presents the associations between adiposity, OA and leptin or adiponectin. From left to right this table presents the association between adiposity (BMI or %TBF) and OA, the association between adiposity and the adipokine (leptin or adiponectin), the association between the adipokine and OA, and the associations with OA from the multivariable model including both adiposity and the adipokine.

First, we assessed the associations between adiposity, both adipokines and OA presence in knees or hands. While leptin levels were positively associated with OA (OR 1.16, 95% CI 1.11 to 1.22, per 10 units; Table II), adiponectin levels were not (Table II).

Table I
Characteristics of the study population (n = 6408), stratified by OA presence

	No OA (78%)	OA (22%)*			
			Knee OA (10%)	Hand OA (8%)	Knee and hand OA (4%)
Age, years	55.1 (6.1)	57.6 (5.1)	57.0 (5.2)	58.1 (5.2)	58.3 (4.6)
Sex, % women	52	71	61	74	87
Education, % high	49	38	37	40	36
Ethnicity, % Caucasian	95	94	95	94	92
BMI, kg/m^2	26.0 (4.2)	27.3 (5.1)	27.8 (5.3)	26.6 (4.7)	27.5 (5.0)
Total body fat, %	30.7 (8.4)	34.9 (8.6)	34.2 (9.3)	34.5 (7.8)	37.5 (7.4)
Adiponectin levels, mg/L	9.0 (4.8)	10.1 (5.2)	9.6 (5.3)	10.4 (5.5)	10.7 (4.6)
Leptin levels, ug/L	15.7 (14.5)	22.3 (19.9)	22.2 (20.9)	21.0 (17.6)	24.8 (21.1)

Results were based on analyses weighted towards the BMI distribution of the general population. Numbers represent mean (standard deviation) unless otherwise specified.
BMI, body mass index; OA, osteoarthritis.
* Defined as having knee or hand OA.

Table II
Associations between adiposity, OA* and leptin or adiponectin

Independent variable	Dependent variable				Mediation %
	OA OR (95% CI)	Leptin β (95% CI)	OA OR (95% CI)	OA OR (95% CI)†	
BMI	1.40 (1.30; 1.52)	1.16 (1.11; 1.20)	1.16 (1.11; 1.22)	1.38 (1.24; 1.54)	4
Leptin				1.01 (0.95; 1.07)	
%TBF	1.25 (1.17; 1.35)	0.75 (0.72; 0.78)	1.16 (1.11; 1.22)	1.20 (1.10; 1.32)	17
Leptin				1.05 (1.00; 1.11)	
	OA OR (95% CI)	Adiponectin β (95% CI)	OA OR (95% CI)	OA OR (95% CI)†	
BMI	1.40 (1.30; 1.52)	−0.23 (−0.26; −0.20)	1.02 (0.92; 1.13)	1.44 (1.32; 1.56)	N/A
Adiponectin				1.11 (1.00; 1.24)	
%TBF	1.25 (1.17; 1.35)	−0.17 (−0.19; −0.14)	1.02 (0.92; 1.13)	1.28 (1.19; 1.37)	N/A
Adiponectin				1.10 (0.99; 1.23)	

Results were based on analyses weighted by the BMI distribution of the general population. All analyses were adjusted for age, sex, ethnicity and education. Associations with adiposity measures were calculated per 5 units, associations with leptin were calculated per 10 units, associations with adiponectin were calculated per 5 units. BMI, body mass index; CI, confidence interval; N/A, not applicable; OA, osteoarthritis; OR, odds ratio; %TBF, percentage total body fat.
* Defined as having knee or hand OA.
† OR from multivariate analysis with both the adiposity measure and the adipokine included in the model.

Mediating effect of leptin

As shown in Table II, after additionally including leptin in the model, the observed association between adiposity and OA attenuated. This represented a mediating effect of leptin of 4% of the association of 5 units BMI with OA, and 17% of the association of 5 units %TBF with OA. A summary of the total, indirect and direct effects is presented in Supplementary Table 1.

Next, we explored whether the relationship between adiposity, leptin and OA differed for different OA localisations, by comparing participants with knee OA vs those with hand OA. In this analysis, participants with both knee and hand OA were not taken into account. Table III shows that adiposity and leptin were both more strongly associated with knee than with hand OA. While mediation by leptin in the association between adiposity and OA was found for both OA localisations, the effect in knee OA (13% and 27% per 5 units BMI and %TBF, respectively) was larger than in hand OA (9% and 18%).

In an attempt to account for the effect of adiposity on knee OA through increased loading, knee OA analyses were repeated stratified for weight categories. After stratification, an association between BMI and knee OA was found in the highest and the lowest weight category. However, the mediating effect of leptin on the association between BMI and knee OA only remained present in the lowest weight category. In this subgroup, the association between adiposity and knee OA was OR 1.92 (95% CI 1.22 to 3.02, per 5 units BMI; pathway C), which attenuated after inclusion of leptin into the model to 1.51 (95% CI 0.87 to 2.61; pathway C'), with an estimated 35% mediation.

Adiposity as a binary variable

Table IV presents the total, indirect and direct effects, and the percentage mediation of the sensitivity analyses where adiposity was treated as a binary variable. The estimated percentage mediation was larger than when adiposity was entered in the model per 5 units. Substantial mediation by leptin was shown for OA in general, and in both OA localisations separately. Again, the associations and estimated mediation were larger in knee OA than in hand OA. Estimation of the proportion mediation by the two different calculation methods (i.e., Sobel method vs using the *medeff* command in Stata) revealed similar results, except for the estimate of the analyses of %TBF and hand OA, likely due to a smaller number of participants in this subgroup.

Sex differences

Sex-stratified analyses (Supplementary Tables 2 and 3) showed that the association between adiposity and leptin levels was

Table III
Associations between adiposity, OA and leptin for different OA localisations

Independent variable	Dependent variable				Mediation %
	Knee OA OR (95% CI)	Leptin β (95% CI)	Knee OA OR (95% CI)	Knee OA OR (95% CI)*	
BMI	1.48 (1.34; 1.64)	1.16 (1.11; 1.20)	1.20 (1.14; 1.27)	1.41 (1.22; 1.62)	13
Leptin				1.04 (0.97; 1.12)	
%TBF	1.30 (1.18; 1.43)	0.75 (0.72; 0.78)	1.20 (1.14; 1.27)	1.20 (1.07; 1.35)	27
Leptin				1.10 (1.03; 1.17)	
	Hand OA OR (95% CI)	Leptin β (95% CI)	Hand OA OR (95% CI)	Hand OA OR (95% CI)*	
BMI	1.22 (1.09; 1.38)	1.16 (1.11; 1.20)	1.09 (1.03; 1.16)	1.20 (1.02; 1.41)	9
Leptin				1.02 (0.93; 1.11)	
%TBF	1.15 (1.04; 1.27)	0.75 (0.72; 0.78)	1.09 (1.03; 1.16)	1.12 (0.98; 1.27)	18
Leptin				1.03 (0.95; 1.12)	

Results were based on analyses weighted by the BMI distribution of the general population. All analyses were adjusted for age, sex, ethnicity and education. Associations with adiposity measures were calculated per 5 units, associations with leptin were calculated per 10 units, associations with adiponectin were calculated per 5 units. BMI, body mass index; CI, confidence interval; OA, osteoarthritis; OR, odds ratio; %TBF, percentage total body fat.
* OR from multivariate analysis with both the adiposity measure and leptin included in the model.

Table IV
Sensitivity analysis: mediation by leptin on the association of adiposity with OA, treating adiposity as a binary variable (high vs low)

	Measure of adiposity	Total effect β (SE)	Indirect effect β (SE)	Direct effect β (SE)	Mediation	
					Sobel method %	*medeff* method % (95% CI)
OA						
	BMI	0.53 (0.08)	0.14 (0.04)	0.37 (0.09)	27	28 (22; 39)
	%TBF	0.37 (0.10)	0.17 (0.03)	0.17 (0.11)	48	51 (34; 106)
Knee OA						
	BMI	0.60 (0.11)	0.21 (0.05)	0.37 (0.12)	35	35 (26; 52)
	%TBF	0.42 (0.13)	0.23 (0.04)	0.17 (0.14)	55	58 (36; 149)
Hand OA						
	BMI	0.39 (0.12)	0.07 (0.06)	0.31 (0.14)	18	18 (11; 45)
	%TBF	0.11 (0.14)	0.14 (0.05)	−0.04 (0.16)	119	66 (−993; 2070)

Results were based on analyses weighted by the BMI distribution of the general population. All analyses were adjusted for age, sex, ethnicity and education. Associations with adiposity measures were calculated for high vs low (binary), associations with leptin were calculated per 10 units. BMI, body mass index; CI, confidence interval; OA, osteoarthritis; SE, standard error; %TBF, percentage total body fat.

somewhat stronger in women than in men. Moreover, the interrelation between adiposity, leptin levels and OA, and as a consequence the mediating effect of leptin, was stronger in women, particularly in OA in general and in the knee OA subset. The subgroups of participants with isolated hand OA were even smaller, so definite conclusions on sex differences could not be drawn from these analyses.

Adiponectin

In contrast to leptin, adiponectin levels were not associated with OA (OR 1.02, 95% CI 0.92 to 1.13, per 5 units). Stratification by OA localisation revealed no differences for knee (OR 1.02, 95% CI 0.89 to 1.17) and hand OA (OR 1.03, 95% CI 0.88 to 1.21). In absence of an association between adiponectin levels and OA, we did not further explore mediation of the association of adiposity with OA by adiponectin.

Discussion

In this study, we investigated the role of systemic adipokines in OA, to gain more insight in systemic mechanisms connecting adiposity and OA. Increased leptin levels were associated with higher odds of OA, while adiponectin levels were not associated with OA. Leptin levels appeared to partially mediate the association between adiposity and OA, with larger effects in knee than in hand OA. Generally, effects were more pronounced in women than in men.

The absence of an association between adiponectin levels and OA is in accordance with most previous studies[14,15,18,21,23,24]. Only one study found a protective effect of adiponectin in a hand OA cohort of 164 patients, with a 70% decreased risk for joint space narrowing in those with the highest adiponectin levels compared to the lowest[25]. Important aspects which reduce comparability with our study include the differences in setting (population-based vs hand OA cohort) and outcome definition (presence of clinical OA vs progression of radiographic OA).

The association we found between leptin levels and OA also corresponds to previous reports. Most studies have been done in knee OA[14–22]. Fewer studies investigated the role of leptin in hand OA, and results are conflicting. The population-based Michigan SWAN study including 543 women also found a positive association between serum leptin levels and presence of radiographic hand OA, with an OR of 1.06 (1.01–1.12) per 5 ng/mL increase[26]. However, in the NHANES-III cohort, no differences were found in leptin levels between men or women with symptomatic ($n = 90$), asymptomatic ($n = 376$), and no hand OA ($n = 590$)[27]. Also in a hand OA cohort ($n = 164$) baseline leptin levels were not associated with hand OA progression after six-year-follow-up[25]. Smaller sample size, use of different outcome definitions, and differences in setting may partly explain the divergent results.

Only one previous report assessed mediation by adipokines. In a population-based study ($n = 635$) mediation by leptin in the relationship between BMI and knee OA was investigated[22]. In women, they estimated that leptin mediates approximately 49% of the total adverse effect of a high BMI on knee OA, which is similar to our finding of approximately 50% mediation in women in knee OA in the binary model. Interestingly, they found no association between leptin and knee OA in men, which corresponds to the sex-differences found in our study. Despite the resembling results, their study was tenfold smaller, comprised an elderly population (aged 70 and over), did not include measures of body composition, and did not adjust for mechanical effects of adiposity. We found no previous studies assessing mediation by adipokines in hand OA.

In an attempt to account for the mechanical component of adiposity in knee OA, we explored the effect of body weight on the analyses of leptin in knee OA, and found that the mediating effect of leptin only remained present in the lowest weight category. This may imply that in individuals with a higher weight, the detrimental effect of increased load is the most important determinant of knee OA. In contrast, in individuals with a lower weight this biomechanical effect may be smaller, and systemic effects may play a larger role, partially mediated by leptin. Since the only previous report of mediation analyses did not take body weight into account, future studies need to replicate this finding[22].

In-vitro studies have shown that human chondrocytes express functional leptin receptors[37]. It has also been shown that leptin is overexpressed in cartilage and osteophytes of OA patients, and that it can induce synthesis of growth factors in cartilage[10]. More *in vivo* support for a link between leptin and OA pathogenesis comes from a study in which female leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) mice developed extreme obesity, while the incidence of knee OA did not increase[38]. The authors of that study conclude that leptin signalling is necessary for obesity-induced OA to develop.

Most studies investigating adipokines in OA used a female study population[14,16,17,24,26], adjusted for sex or lacked power to stratify by sex[15,18–23,25]. Therefore, sex differences in the adipokine-OA relation have not often been explored. In accordance with our findings, a previous analysis in the NHANES-III cohort reports that leptin was more strongly associated with knee OA in women than in men[39]. A possible explanation for the sex differences found in the associations with and mediating effect of leptin could be that the aetiology of knee OA in men is more biomechanical in nature,

whereas the aetiology in women has a larger systemic or inflammatory component. This hypothesis is in line with a previous report showing that in men skeletal muscle mass was more strongly associated with knee OA, while in women fat mass was a more important determinant[40]. This is further supported by the finding that work-related trauma were more strongly related to knee OA in men[41]. However, the separate analyses in men and women should be interpreted with caution, especially in the participants with hand OA, due to the small size of the subgroups.

Although we found evidence for mediation by systemic leptin levels, these are likely not the sole systemic mechanisms by which adiposity contributes to OA. Rather, the systemic effects of adiposity on OA probably stem from a combination of factors, including adipokines, but also for example hypertension and dyslipidemia[6,8,42,43]. This is supported by our finding of partial, and not complete, mediation.

Notable strengths of this study include the size of the study population and its population-based design, extensive characterization of participants, and the availability of information of both weight-bearing (knee) and non-weight-bearing (hand) joints. However, there are few limitations that need to be acknowledged. The lower prevalence of OA in men resulted in less precise effect estimates in some analyses. The study had a cross-sectional design, and inherent to this design, reverse causation cannot be excluded, hampering causal inference. While we adjusted for multiple potential confounding factors, another limitation of our study design is that residual confounding by (an) unmeasured variable(s) related both to the exposure and the outcome may remain present, which may have introduced biased results. Therefore, longitudinal studies are warranted to draw more definite conclusions about the mediating role of leptin in OA. Moreover, adipokines were measured systemically, and this may not necessarily reflect intra-articular adipokine levels[44].

In conclusion, in this population-based study we demonstrated that serum leptin levels were associated with OA, and partially mediated the association adiposity and OA, while adiponectin levels were not associated with OA. These findings support the growing body of evidence for systemic effects of adipose tissue in OA.

Author contributions

RM, FR, KWD, MK participated in the conception and design of the study. KWD contributed to acquisition of data. FK, AV, SC contributed to data analysis. All authors contributed to interpretation of the data, drafting and revision of the manuscript, and approved the final version of the manuscript.

Conflicts of interest

No conflicts of interest.

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Supplementary data

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