EXTENDED REPORT

Do metabolic factors add to the effect of overweight on hand osteoarthritis? The Rotterdam Study

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Background: As hand joints are non-weight bearing, the association between overweight and hand osteoarthritis (HOA) is critical to understanding how overweight may associate with osteoarthritis (OA) apart from axial load. Overweight might be associated with the occurrence of OA through other metabolic factors.
Aim: To evaluate the role of overweight in HOA, cross-sectional data of a population-based study were used (⩾55 years, n = 3585). The role of diabetes, hypertension and total cholesterol:high-density lipoprotein (HDL)-cholesterol ratio on HOA, and whether they play an intermediate role in the association of overweight/HOA was investigated. Furthermore, the prevalence of HOA in the concurrent presence of overweight and other metabolic factors was evaluated.
Results: Independently of other metabolic factors, overweight (body mass index (BMI) >27.4 kg/m^2) showed a significant association with HOA (OR 1.4, 95% CI 1.2 to 1.7). The association between diabetes and HOA was only present in people aged 55–62 years (OR 1.9, 95% CI 1.0 to 3.8), but was absent in the total population or in other age groups. The association of hypertension with HOA was weak, and disappeared after adjustment for BMI. The total/HDL cholesterol ratio showed no significant association with HOA. The concurrent presence of overweight, diabetes and hypertension resulted in an even higher prevalence of HOA (OR 2.3, 95% CI 1.3 to 3.9) compared with subjects with none of these characteristics; this prevalence increased further in the younger age group (OR 3.2, 95% CI 1.1 to 8.8).
Conclusion: No intermediate effect of metabolic factors on the association of overweight with HOA was found. An increase in the prevalence of HOA, however, seems to be present when overweight occurs together with hypertension and diabetes especially at a relatively young age.

Osteoarthritis (OA) is a slowly progressive degenerative disease affecting the cartilage and bone, whose aetiology is considered to be multifactorial.[1] It is already the most common form of arthritis and will become even more prevalent as the large cohort of baby boomers grows old.[2] To devise possible preventive strategies, researchers have focused on identifying potential risk factors. One potentially preventable risk factor for OA is overweight, which may contribute to the development of OA through various mechanisms.[3] Being overweight increases the load across weight-bearing joints and subsequent cartilage breakdown. However, this mechanism fails to explain the association between overweight and OA in non-weight-bearing joints, such as the hand. To date, reports on the association of hand OA with overweight have been inconsistent.[1] An association between overweight and hand OA, therefore, calls for a consideration of other possible explanations. Adipose tissue may produce atypical hormone or growth factor concentrations that affect the cartilage or bone.[4] Leptin secreted primarily by adipocytes has been suggested to be involved in osteophyte formation in OA.[5] It has also been suggested that overweight may be associated with the occurrence of OA through other metabolic factors, such as diabetes, hypertension, high triglycerides and total cholesterol:high-density lipoprotein (HDL)-cholesterol ratio.[1 6–12] As the hand joints are non-weight bearing, the association between overweight, and hand OA is critical for a better understanding of how overweight through the metabolic process, cause OA. The objective of this study was to evaluate the association between overweight and OA of the hand joints. In addition, we evaluated the association between other metabolic factors such as diabetes, hypertension or total cholesterol:HDL-cholesterol ratio and hand OA. Further, we investigated whether the simultaneous presence of several metabolic factors together with overweight increases the prevalence of hand OA, or whether they play an intermediary role in the association of overweight with hand OA.

SUBJECTS AND METHODS

Study population

For this study, we used cross-sectional data from the Rotterdam Study, a population-based cohort study on the determinants and prognosis of chronic diseases in elderly people. The medical ethics committee of the Erasmus Medical Centre, Rotterdam, The Netherlands, approved the study, and written informed consent was obtained from all participants. The baseline measurements were conducted between April 1990 and July 1993. The complete study design has been described previously.[13] All inhabitants of Ommoord (a suburb of Rotterdam) who were aged ⩾55 years were invited to participate in the study. In all, 7983 participants (response rate 78%) were examined. At baseline, trained interviewers performed an extensive home interview on demographic characteristics, medical history, risks factor for chronic diseases and use of medication. After the home interview, participants also visited the research centre, where, among other measurements, they underwent radiographic examination. For feasibility reasons, baseline hand radiographs of those participants who were available for follow-up 6 years later (n = 3585) were scored for OA, and were included in this study.

Abbreviations: BMI, body mass index; CMC1/TS, first carpometacarpal and trapezioscaphoid; DIP, distal interphalangeal; HDL, high-density lipoprotein; HOA, hand osteoarthritis; IGF, insulin-like growth factor; K–L, Kellgren–Lawrence; MCP, metacarpophalangeal; OA, osteoarthritis; PIP, proximal interphalangeal

Table 1 Baseline characteristics of the study population

Characteristics	Study population, n = 3585	Rotterdam Study, n = 7983
Female, %	58.2	61.1
Age, years	66.0 (6.9)	70.6 (9.8)
Body mass index, kg/m^2	26.3 (3.5)	26.3 (3.7)
Diabetes, %	7.4	10.5
Hypertension, %	30.1	36.1
Total cholesterol, mmol/l	6.7 (1.2)	6.6 (1.2)
HDL-cholesterol, mmol/l	1.4 (0.4)	1.4 (0.4)
Total cholesterol:HDL-cholesterol ratio	5.3 (1.6)	5.2 (1.6)
DIP OA, %	47.8	NA
PIP OA, %	17.6	NA
MCP OA, %	7.8	NA
Base of thumb (CMC1/TS) OA, %	35.9	NA
Hand OA, %	27.5	NA

CMCI/TC, first carpometacarpal and trapezioscaphoid; DIP, distal interphalangeal; HDL, high-density lipoprotein; MCP, metacarpophalangeal; OA, osteoarthritis; PIP, proximal interphalangeal.
OA: presence of Kellgren–Lawrence ⩾2 in right/left joint groups (DIP, PIP, MCP, CMC1/TS).
Values are mean (SD) unless otherwise specified.
Missing data: diabetes, 8; hypertension, 31; total:HDL-cholesterol ratio, 33; BMI, 19.
Hand OA, 516; DIP OA, 472; PIP OA, 486; MCP OA, 479; base of thumb, 451.
Hand OA: presence of Kellgren–Lawrence ⩾2 in two out of three hand joint groups (DIP, PIP, CMC1/TS).

Measurements

Radiographic scoring

Two trained assessors (SD and UC) scored standard anteroposterior radiographs of both hands. The readers were blind to other data, such as clinical or demographic variables. OA for each joint was defined as a Kellgren–Lawrence (K–L) Score of ⩾2. Four groups (distal interphalangeals (DIPs), proximal interphalangeals (PIPs), metacarpophalangeals (MCPs) and first carpometacarpal and trapzioscaphoid (CMC1/TS) were defined, and a group was considered positive if at least one joint in the group had a K–L Score of ⩾2. Hand OA was defined as the presence of a K–L Score of ⩾2 in two of three groups of hand joints (DIPs, PIPs and CMC1/TS). The complete scoring method has been described elsewhere.[14] To make an easy comparison with other studies, we used this definition of hand OA, in which MCP joints are not included in the definition. Further, signs of OA in MCP joints might be similar to signs of other inflammatory OA, such as rheumatoid arthritis. In the clinical definition of hand OA from the American College of Rheumatology criteria, a patient with ⩾3 swollen MCP joints is not defined as having hand OA. Therefore, we did not include the MCP joints in the definition of hand OA. Moreover, including this joint in the definition for hand OA (two of four joint groups) added only a few cases.[14]

Metabolic factors

Height and weight were measured at the research centre; the participants were wearing indoor clothes but no shoes. Body mass index (BMI) was calculated by the weight in kilograms divided by the height in metres squared. BMI >27.4 kg/m^2 was defined as overweight (highest tertile of the BMI). Blood pressure was measured twice and the average of two consecutive measurements was used to calculate the diastolic and systolic pressures. Hypertension was defined as systolic pressure ⩾160 mm Hg, diastolic pressure ⩾100 mm Hg or the use of antihypertensive medication. Blood samples were taken, and subjects not using antidiabetic medications received a drink of 75 g of glucose. Post-load glucose level was measured after 2 h. Diabetes was defined as a random or post-load blood glucose level of >11.0 mmol/l and/or the use of antidiabetic drugs (oral or insulin injection). Total serum cholesterol was determined by an automated enzymatic procedure in a non-fasting blood sample. HDL-cholesterol was measured after precipitation of the non-HDL fraction with phosphotungstate magnesium.[15] The ratio of total cholesterol to HDL-cholesterol was calculated, and used as a continuous variable in the analysis.

Statistical analysis

Univariate and multivariate logistic regression analyses (odds ratios (ORs)) were used to examine the association between radiological OA of the different hand joint groups or hand OA and overweight (BMI > 27.4 kg/m^2), adjusted for age, gender and smoking (current or past smokers vs non-smokers). We also examined these associations using a categorical variable for different cut-off points for BMI and using BMI as a continuous variable. The same analysis was performed for the association of diabetes, hypertension and total/HDL-cholesterol ratio with radiological hand OA, with additional adjustment for BMI >27 kg/m^2 as well as BMI as a continuous variable. Interaction (multiplicative effects in logistic regression models) with age or gender was tested for all the associations specified above. If present, we also presented stratified analyses. Further, using logistic regression models with respect to the presence of hand OA, we compared subjects with 2–3 metabolic factors present with subjects with none of these factors. The crude prevalences and adjusted ORs were both presented. Here, interaction was also explored (multiplicative effects in logistic regression models).

The SPSS V10 program was used for all analyses.

RESULTS

A total of 3585 elderly participants (mean age 66.0 years; 58.2% women) were evaluated. Table 1 shows the baseline characteristics of our study population compared with the total population of the Rotterdam Study.

Overweight adjusted for age, gender and smoking showed a positive association with hand OA (BMI >27.4 kg/m^2, OR 1.4; 95% CI 1.2 to 1.7). After additional adjustment for diabetes, hypertension and total cholesterol:HDL-cholesterol ratio, the association of overweight with hand OA remained significant with the same magnitude (table 2). Using a categorical variable for different cut-off points for BMI showed that the prevalence of hand OA increased in subjects with a higher BMI (fig 1). Analyses with BMI as a continuous variable indicated the same (OR 1.06, 95% CI 1.03 to 1.08; p = 0.000).

Differentiation for hand joint groups, adjusted for age, gender and smoking, showed a similar association of BMI with OA of DIP, PIP and MCP, but no association with OA of the base of the thumb (CMC1/TS).

Hypertension showed a weak association with hand OA (OR 1.2, 95% CI 1.0 to 1.4), adjusted for age, gender, smoking and overweight. This association disappeared after adjustment for overweight as a continuous variable. Evaluation with an alternative cut-off point of hypertension (130/85 mm Hg) yielded the same results.

Diabetes showed an association with the presence of hand OA (OR 1.2, 95% CI 0.9 to 1.6) adjusted for age, gender, smoking and overweight. No change was observed after using BMI as a continuous variable. Total cholesterol:HDL-cholesterol ratio showed no significant association with hand OA (OR 1.0, 95% CI 1.0 to 1.1, p = 0.119). Of the tested relationships, the association of diabetes with hand OA showed a significant interaction with age and led us to evaluate this relationship in three age groups. This showed that the prevalence of hand OA is higher in younger people with diabetes (table 3). Older

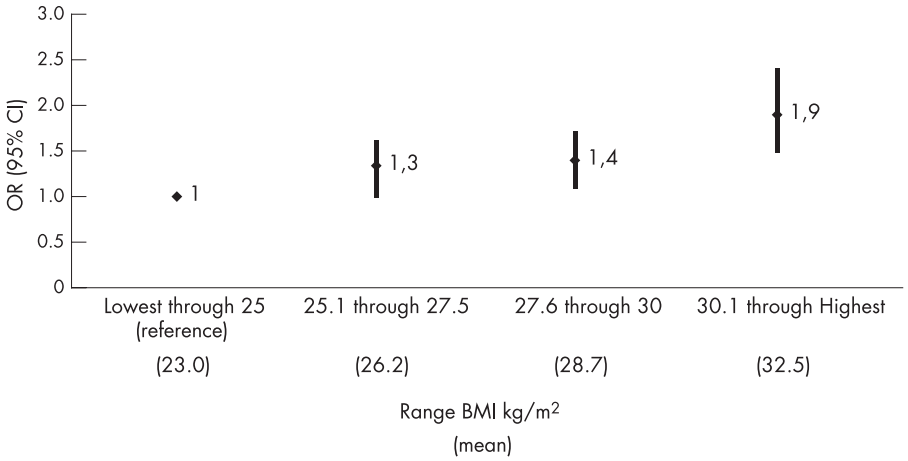

Figure 1 Association of body mass index with osteoarthritis of the hand.

people with diabetes did not have a higher prevalence of hand OA. With further adjustment for duration of diabetes or for BMI as a continuous variable, the same results were obtained.

The concurrent presence of overweight with either diabetes or hypertension led to nearly the same association with hand OA. However, adjusted for age, gender and smoking, the simultaneous presence of overweight, diabetes and hypertension (ie, these three metabolic factors together) showed higher association with hand OA than for subjects with none of these conditions (OR 2.3, 95% CI 1.3 to 3.9; table 4). This association increased further in the younger age group (55–62 years) to OR 3.2, 95% CI 1.1 to 8.8, but interaction with age could not be proven with logistic regression models. Other age groups (62.1–68.7 and >68.8 years) also showed ORs of 1.9 and 1.8, respectively, but probably because of less power in the analysis, it was no longer significant. To explore further the additional effect of diabetes and hypertension, we compared a group of overweight people with diabetes and hypertension with a group of overweight people without diabetes and hypertension (reference group), and obtained an OR of 1.6, 95% CI 0.9 to 2.7. Again, less power in the analysis resulted in a borderline significant association.

DISCUSSION

Our cross-sectional study confirms that overweight is associated with hand OA, independent of other metabolic factors. This association is stronger in subjects with a higher BMI. Differentiation for hand joint groups showed that overweight was associated with OA of the DIP, PIP and MCP, but not with OA of the base of the thumb. Although an association between diabetes and hand OA in the total population was absent, it became stronger and statistically significant independently of overweight in the younger age group. The concurrent presence of overweight with diabetes and hypertension resulted in an even higher prevalence of hand OA.

This study adds to the scattered positive associations of overweight and hand OA reported in previous studies.[1 16 17] In a large open population cohort, Carman *et al*[16] found that after 23 years of follow-up, overweight at baseline was associated with more incident hand OA. Van Saase *et al*[17] reported that overweight in men had a positive association with OA of the DIP, PIP and MCP, and in women with OA of the DIP and PIP.[12] As in our study, they did not show a positive association between overweight and OA of the base of the thumb. Studies by Hochberg *et al*[18 19] did not find any association between overweight and hand OA in men or in women.

We showed that independently of other metabolic factors, overweight contributes to the presence of hand OA; we also rule out the possible intermediary effect of metabolic factors in explaining the role of overweight on hand OA. The metabolic influence of overweight on OA may possibly be explained by leptin, which we were unable to evaluate because of lack of data. Leptin consists of small polypeptides encoded by the obese gene; it is produced by adipose tissue and was initially discovered as a central regulator of appetite and energy uptake at the hypothalamus level. Leptin may also be involved in regulating metabolic activity in the bone and cartilage. Recent studies suggest that it might promote osteophyte formation in OA by increasing the production of transforming growth factor β.[5 20] Dumond *et al*[21] additionally found that leptin levels in

Table 2 Association of overweight with osteoarthritis of the different hand joint groups

	BMI >27.4 kg/m² OR (95% CI)*	BMI >27.4 kg/m² OR (95% CI)†	BMI (continuous), OR (95% CI)†
Hand OA	1.4 (1.2 to 1.7)	1.4 (1.1 to 1.6)	1.04 (1.01 to 1.07)
OA in the hand joint groups			
DIPs	1.4 (1.2 to 1.6)	1.4 (1.2 to 1.6)	1.05 (1.03 to 1.08)
PIPs	1.4 (1.1 to 1.7)	1.3 (1.1 to 1.6)	1.06 (1.03 to 1.1)
MCPs	1.5 (1.1 to 2.0)	1.5 (1.1 to 2.0)	1.1 (1.0 to 1.1)
Base of thumb	1.1 (1.0 to 1.3)	1.1 (1.0 to 1.3)	NS

BMI, body mass index; DIP, distal interphalangeal; MCP, metacarpophalangeal; OA, osteoarthritis; PIP, proximal interphalangeal.
Hand OA: presence of Kellgren–Lawrence ≥2 in two of three hand joint groups (DIP, PIP, first carpometacarpal and trapezioscaphoid).
*Adjusted for age, gender and smoking
†Adjusted for age, gender, smoking, diabetes, hypertension and total cholesterol: high-density lipoprotein-cholesterol.

Table 3 Association of diabetes with osteoarthritis of the hand in relation to age

	Prevalence for hand OA, %		
	No diabetes	Diabetes	OR (95% CI)
*Total group	27.1	32.6	1.2 (0.9 to 1.6)
55–62 years	14.2	22.8	1.9 (1.0 to 3.8)
62.1–68.7 years	27	28.9	1.1 (0.7 to 1.8)
> 68.8 years	42.5	41.5	0.9 (0.6 to 1.4)

OA, osteoarthritis.
Age categorised in tertiles.
The associations are adjusted for gender, smoking and body mass index >27.4 kg/m^2.
*Total group additionally adjusted for age.

synovial fluid of patients with OA were significantly correlated with BMI. They also found that leptin has a peripheral function on chrondrocyte metabolism and indicate that leptin may play an important role in the pathophysiology of OA.

Earlier results on the association between diabetes and OA were inconsistent. Hart *et al*[8] showed an association of diabetes with radiological OA of the knee independent of overweight, while Frey *et al*[22] could not show any association between diabetes and clinical OA. This inconsistency may be explained by a different definition of OA (radiological OA in the first study vs clinical OA in the second study). We found only an age-dependent association between diabetes and hand OA, and then solely in the younger age group. In the study of Sturmer *et al*,[23] no significant association was shown after adjustment for age, as in our analyses for all age groups together. However, they did not analyse the association in different age groups and might have overlooked this effect.[23] One might assume that there are proportionately more patients with insulin-dependent diabetes in the younger age group, but our data did not support this. Similarly, the duration of diabetes did not show any association with hand OA.

Different mechanisms have been suggested for the association of diabetes with OA. The anabolic effect of insulin-like growth factor (IGF)I on the chondrocyte is likely to be affected by an altered serum concentration of IGF-binding proteins, which have been reported for diabetes.[24] Other explanations have also been suggested for the mechanism whereby diabetes might act through OA: increased glucose levels may lead to IGF-I resistance of the chondrocyte; diabetic microangiopathy and macroangiopathy may contribute to OA by influencing synovial tissue and subchondral bone; or increased tnon-enzymatic glycation of collagen may alter the functional properties of articular cartilage.[23] Although the underlying mechanisms of diabetes and overweight may be different, the simultaneous presence of both resulted in only a slight increase in the prevalence of hand OA.

At least two studies have reported a significant association between hypertension and knee OA independent of overweight.[8 25] It has been suggested that hypertension may be associated with atherosclerotic disease, leading to defects in the subchondral plate of the weight-bearing joints.[8] This mechanism may not be strongly involved in the non-weight-bearing joints: in our study, the association between hypertension and hand OA, which was already weak, disappeared after adjustment for BMI as a continuous variable. Nevertheless, we showed that the simultaneous presence of three metabolic factors (diabetes, hypertension and overweight) led to an increased prevalence of hand OA. One might speculate that although hypertension alone exerts no strong influence on hand OA, it might play an additional role when diabetes and overweight have already harmed the joint. In other words, a joint might be injured more seriously when two other metabolic factors also affected the joint. Still, one could suggest that the increased prevalence in the group with three metabolic factors is due to the higher BMI in this group. However, this was not the case, as the mean of the BMI in the group with three metabolic factors was lower than the mean of the BMI in the highest subgroup of people with obesity (fig 1), and the latter group showed an even lower OR. In further analysis, overweight people with diabetes and hypertension showed a borderline significant higher prevalence of hand OA compared with overweight people without diabetes and hypertension. Therefore, these results indicate that an additional effect of diabetes and hypertension together seems to be present, resulting in a higher prevalence of hand OA; however, the interaction could not be proven in logistic regression models.

Table 4 Association between concurrent presence of metabolic factors and osteoarthritis of the hand

	Hand OA		
	Mean BMI	Prevalence of hand OA, %	OR (95% CI)*
BMI ⩽27.4 kg/m^2 (reference group)	24.4	24.6	
BMI >27.4 kg/m^2	30.2	33.2	1.4 (1.2 to 1.7)
BMI ⩽27.4 kg/m^2, no diabetes (reference group)	24.3	24.4	
BMI >27.4 kg/m^2+diabetes	30.8	38.2	1.6 (1.0 to 2.4)
BMI ⩽27.4 kg/m^2, no hypertension (reference group)	24.2	23.2	
BMI >27.4 kg/m^2+hypertension	30.5	35.7	1.5 (1.2 to 2.0)
BMI ⩽27.4 kg/m^2, no hypertension, no diabetes (reference group)	24.2	22.7	
BMI >27.4 kg/m^2+diabetes+hypertension	31.2	45	2.3 (1.3 to 3.9)

BMI, body mass index; OA, osteoarthritis.
*Adjusted for age, gender and smoking.
Absolute prevalence of hand OA in our study population: 27.5%.

Although we used a huge dataset derived from the Rotterdam Study, some limitations are present. First, there might be some selection bias in our study population compared with the total Rotterdam population. Hand radiographs of the participants available for follow-up were scored 6 years later (n = 3585). The total population at baseline was older, had a higher proportion of women and a higher frequency of diabetes and hypertension. However, there were no differences for mean BMI. The lower frequency of diabetes and hypertension may be due to a selection of the older healthy survivors, which may have caused the association of metabolic disorder and hand OA to be underestimated in our data. Second, because we evaluated the association of overweight with hand OA in cross-sectional data, we were unable to show whether overweight is a cause of OA or whether the disability due to OA leads to overweight. However, prospective data presented evidence that overweight is an antecedent to the occurrence of OA rather than a subsequent event.[16 26] Third, although we were interested in the relationship of hand OA with the metabolic syndrome, we were unable to investigate this relationship in this study. The first reason was that one of the criteria (triglyceride) was not available for all subjects of our study population. The second reason was that we were obliged to define the determinants as the existing dataset allowed us. The blood sugar was measured by a non-fasting blood sample, and therefore we again could not comply with the definition of metabolic syndrome as suggested by the National Cholesterol Education Program Adult Treatment Panel III. However, we tried to capture some possible aspects of the metabolic syndrome as discussed above.

In summary, by showing that the presence of overweight with diabetes and hypertension has an additive influence on hand OA, our data support the previous suggestion that OA has a metabolic component in its aetiology.[8]

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Competing interests: None declared.

SD has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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