The Association of Obesity with Osteoarthritis of the Hand and Knee in Women: A Twin Study

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ABSTRACT. ***Objective.*** To examine the association of obesity and osteoarthritis (OA) at various sites in middle aged women and to estimate the magnitude of the weight difference associated with OA.

Methods. A co-twin control study was performed within a population based twin study of women aged 48–70. OA was defined radiologically using site specific features and a standard atlas. Twin pairs discordant for OA disease traits were analyzed.

Results. The mean weight differences (95% CI) within twin pairs discordant for different OA traits were: tibiofemoral osteophytes 3.75 (1.29, 6.21) kg; patellofemoral osteophytes 3.05 (0.96, 5.15) kg; carpometacarpal (CMC) osteophytes 3.06 (0.83, 5.28) kg. There was no significant difference in weight within twin pairs discordant for osteophytes at the distal interphalangeal (DIP) or proximal interphalangeal (PIP) joints or for joint space narrowing at all sites examined except the patellofemoral joint, 4.73 (1.61, 7.84) kg. For each kg increase in weight the increased likelihood of developing different OA traits [OR (95% CI)] was: tibiofemoral osteophytes 1.14 (1.01–1.28), patellofemoral osteophytes 1.32 (1.09–1.59), patellofemoral narrowing 1.15 (1.01–1.30), and CMC osteophytes 1.09 (1.02–1.17).

Conclusion. Obesity is an important risk factor for development of OA at the tibiofemoral and patellofemoral joints of the knee and CMC joints of the hands, with significant increases of 9–13% in risk of OA per kg increase in body weight. This emphasizes the potential importance of even minor weight reduction as a preventive health measure for OA. (*J Rheumatol 1996:***23:1221–6**)

Key Indexing Terms:
EPIDEMIOLOGY OSTEOARTHRITIS OBESITY TWINS

Osteoarthritis (OA) is an enormous public health problem in developed countries[1]. It is the most common single cause of disability[1] and the major reason for hip and knee replacements[2]. The combination of its effect on patients and the therapeutic procedures used produce a large burden on society[3]. Recently, efforts have been focused on potential risk factors for OA to identify possible preventive measures.

Obesity is likely the most important preventable risk factor for OA. Overall, results to date suggest the link between obesity and OA is more consistent in women, and is strongest in OA tibiofemoral joint of the knees and less conclusive in other joints[4-13]. In contrast, a recent study showed only a weak association with patellofemoral joint disease[14]. A few studies have also shown a slight increase in risk of distal interphalangeal (DIP) disease[4-6], but this has not been consistent[15].

Twin studies provide a special research methodology that, as well as assessing the relative contributions of genetic and environmental factors to a disease, may also be used to examine environmental risk factors in twin pairs discordant for that disease trait. This so called co-twin control method[16] can provide information about the way genes and relevant environmental factors may interact. We performed such a co-twin control study within a population based twin study. Our aim was to examine the association of obesity with OA at various sites in middle aged women and to estimate the magnitude of the weight difference associated with the development of OA.

MATERIALS AND METHODS

Subjects. The study population consisted of female twins aged 48–69 years selected from 2 sources of volunteers: a normal twin register held in the Institute of Psychiatry, London, and directly through an advertising campaign. A twin register has been held in the Institute of Psychiatry since 1969 for research into a range of fields, principally behavioral and psychiatric genetics. Registration of twins had been through advertisements and publicity calling for twins of all ages to help with medical research without mention of any specific disease. The advertising campaign group were recruited via a set of articles placed in a high circulation daily newspaper, on local and national radio, and a national news program. The articles concerned osteoporosis and did not mention arthritis. Twins were asked to phone or write for more details. Information was given on the telephone and the procedures explained. Ethical approval was obtained from the hospital ethical committee and full informed written consent was obtained at the first visit. Zygosity was determined by a standard questionnaire[17] and confirmed by multiplex DNA fingerprinting using variable tandem repeats performed at the Institute of Molecular Medicine, Oxford.

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Procedures. Each pair of twins was interviewed with a standard questionnaire for arthritis and joint symptoms. Pain was defined as ever having a previous episode of pain in the knee lasting longer than 15 days. Heights were recorded using a wall mounted stadiometer and weight with an electronic balance. Radiographs of the hands were obtained with a standard posteroanterior view and the knees with (1) a weight bearing anteroposterior view in full extension, (2) a lateral view in 30° flexion, and (3) a skyline view in 45° flexion using a perspex positioning wedge.

All radiographs were independently assessed by 2 trained observers who were blind to the pairings, zygosity, and clinical findings. Using an atlas of individual features[18], the radiological features of knee OA in both the tibiofemoral (TFJ) and patellofemoral joint (PFJ) were graded on a 4 point scale (0–3) for individual features that included osteophytes and joint space. The individual features of OA (the presence of definite osteophytes or joint space narrowing) were examined separately in this study and used to classify disease. In some analyses, the disease outcome OA, which consisted of having either osteophytes or joint space narrowing, was used as the disease definition. Grade 1 disease on our scale, which indicated a definite feature, was equivalent to the grade 2 score of the original Kellgren and Lawrence classification[19]. Classification of TFJ disease was based on the radiological findings on anteroposterior knee views. Although both the skyline and lateral views of the PFJ were available, classification of PFJ disease was based on radiological findings on the skyline view, as we have shown that this is the optimal method for defining PFJ OA in epidemiological studies[20]. Classification of hand OA including the distal interphalangeal (DIP), proximal interphalangeal (PIP), and first carpometacarpal joint (CMC) of the thumb was based on a similar validated 4 point scoring system[21].

After the initial scoring the results of the 2 observers were compared and (in the case of disagreement) the radiographs were reviewed by the 2 observers together with a 3rd independent observer. The intraobserver and interobserver reproducibility of the observations was tested on a subgroup of the twins; 50 knees and hands were selected to include the full range of radiological features and read twice by 2 observers 2 weeks apart. For all the sites intra and interobserver agreement was good, with kappa statistics ranging from 0.68 to 0.96 for intraobservers and 0.70 to 0.88 between observers for both the presence of narrowing and osteophytes. These results were comparable to our findings in similar studies[22].

Statistical analysis. The demographic variables of the monozygotic (MZ) and dizygotic (DZ) twins were initially compared using Student's t test and chi-squared test. In subsequent analyses, twin pairs discordant for the feature of OA under investigation were used, as these were the most informative. To improve power, MZ and DZ twins were combined in the analyses. Paired analyses were then performed in a way analogous to a case–control study, with the twin with the disease feature being treated as the case and the co-twin as the control. The mean body mass index (BMI) (weight/height^2) and body weight were examined using a paired t test.

Conditional logistic regression was used to estimate the odds ratio and 95% test based confidence intervals for developing a radiological feature of OA for different levels of weight and BMI. In these analyses, weight and BMI were entered as continuous variables. Adjustment for other confounding variables (menopausal status, age of menopause, hysterectomy, use of hormone replacement therapy, smoking, and total activity) was performed using conditional logistic regression with the PC software package STATA. Total activity was a composite score of amount of walking (1–4), where the range was 1 (less than 0.5 miles/week) to 4 (10+ miles/week); activity at work and home (1–4), where the range was 1 (sedentary) to 4 (predominantly manual, active all day); and sporting activity (1–4), where the range was 1 (none) to 4 (2+ h of keep fit, squash, aerobics).

RESULTS

Four hundred three twin pairs contacted our unit to enquire about the study, 125 from the normal twin register and 278 from the media campaign. After explanation of the procedures and the need to travel to London for the examination and radiographs, 335 pairs attended. Of these, 6 pairs were excluded as one of the pair had a disabling disease, one for multiple sclerosis, 3 for recently diagnosed cancer, and one for morbid obesity. The characteristics of the individuals making up the 158 MZ and 171 DZ pairs in the study are presented in Table 1. There was no significant difference in mean age (57.76 ± 0.33 and 57.80 ± 0.38), weight, height, cigarette use, age at menopause, estrogen use, and current or past physical activity scores between the 2 groups. When we examined the subgroups of twins discordant for disease, defined as either osteophytes or joint space narrowing at the different sites (TFJ, PFJ, DIP joint, PIP joint, CMC joint), the characteristics in the different subgroups did not differ significantly from the total population (separated as MZ and DZ or combined), although in some groups the numbers were small (data not shown).

For the analysis of risk factors for OA, the informative twins were the twin pairs discordant for the disease trait. The number of informative twin pairs are presented in Table 2. Overall, discordant twin pairs ranged from 13.1% of the

Table 1. Characteristics of monozygotic (MZ) and dizygotic (DZ) twins examined as individuals.

Variable Means (± SEM) or %	MZ (n = 316)	DZ (n = 342)*	Total (n = 658)
Age (yrs)	57.76 ± 0.33	57.80 ± 0.38	57.79 ± 0.25
Weight (kg)	63.91 ± 0.55	64.60 ± 0.58	64.39 ± 0.40
Height (cm)	161.90 ± 0.32	162.11 ± 0.32	161.94 ± 0.23
Current total activity**	7.36 ± 10.11	7.36 ± 0.10	7.36 ± 0.07
Age at menopause (yrs)	47.8 ± 0.99	48.7 ± 0.98	48.2 ± 0.87
No. ever used ERT (%)	128 (40.5)	127 (37.0)	255 (37.8)
No. ever smoked (%)	148 (46.7)	170 (49.6)	318 (48.3)
No. postmenopausal (%)	284 (89.9)	309 (90.3)	593 (90.1)

* Independent t test for continuous variables, chi-squared for discrete variables; all variables $p > 0.05$.

** A composite score of total amount of walking (1–4) + activity at work and home (1–4) + sporting activity (1–4).

ERT: estrogen replacement therapy.

Table 2. MZ and DZ twin pairs discordant for OA at different sites.

	Total MZ Pairs = 158 No. (%) Discordant	Total DZ Pairs = 171 No. (%) Discordant	Total Twin Pairs = 329 No. (%) Discordant
TFJ OA*	35 (22.2)	35 (20.5)	70 (21.3)
TFJ osteophytes	25 (15.8)	33 (19.3)	58 (17.6)
TFJ narrowing	25 (15.8)	25 (14.6)	50 (15.2)
PFJ OA*	39 (24.7)	52 (30.4)	91 (27.7)
PFJ osteophytes	37 (23.4)	49 (28.7)	86 (26.1)
PFJ narrowing	19 (12.0)	28 (16.4)	47 (14.3)
DIP osteophytes	31 (19.6)	47 (27.5)	78 (23.7)
PIP osteophytes	19 (12.0)	24 (14.0)	43 (13.1)
CMC osteophytes	23 (14.6)	59 (34.5)	82 (24.9)

* Either joint space osteophytes or narrowing.

total for PIP osteophytes to 24.9% of the total for CMC osteophytes. MZ and DZ twins were combined in the analyses. When analyzed as separate groups, the magnitude and direction of the effects obtained were similar to the combined analyses. However, in general, the small numbers in each group reduced power and the results were, therefore, pooled.

Twin pairs discordant for each OA disease trait were used to examine whether there was a difference in weight (Table 3) or BMI (Table 4) in the twin with disease compared to the co-twin without disease. On average, twins with knee OA were heavier than their co-twins. When OA was defined as the presence of osteophytes and/or narrowing, the twins with TFJ OA were 2.93 (0.94, 4.90) kg [mean weight difference and (95% CI)] heavier than their co-twins, while those with PFJ OA were 3.50 (1.52, 5.49) kg heavier. When osteophytes were examined, twins with TFJ osteophytes were 3.75 (1.29, 6.21) kg heavier than their co-twins without, while those with PFJ osteophytes were 3.05 (0.96, 5.15) kg heavier. In contrast to the TFJ, where no significant weight difference was observed between twins with TFJ narrowing and co-twins without, the twins with PFJ narrowing were 4.73 (1.61, 7.84) kg heavier than their co-twins. At the hand, a significant difference in body weight was only observed in twins that were discordant for CMC osteophytes, 3.06 (0.83, 5.28) kg.

For both knee and hand OA traits, similar patterns in the difference in BMI within twin pairs discordant for disease were observed (Table 4). The mean difference (95% CI) in BMI ranged from 1.31 kg/m^2 (0.56, 2.06) for TFJ osteophytes and/or narrowing to 2.08 (0.91, 3.25) for PFJ narrowing. There was no difference in weight or BMI in the twin pairs discordant for DIP or PIP osteophytes.

As one possible interpretation of the results for knee OA traits was that pain due to OA may have resulted in limitation of movement and subsequent weight gain, we per-

Table 3. Mean body weight in twin pairs discordant for different OA disease traits.

	No. Pairs	Weight Twin 1 (Disease)	Weight Twin 2 (No Disease)	Mean Difference	95% CI	p
All twins						
TFJ OA*	70	67.01 ± 1.45	64.09 ± 1.30	2.93 ± 0.99	0.94, 4.90	0.004
TFJ osteophytes	58	68.54 ± 1.72	64.79 ± 1.53	3.75 ± 1.23	1.29, 6.21	0.003
TFJ narrowing	50	65.69 ± 1.62	64.57 ± 1.59	1.12 ± 1.22	–1.34, 3.57	0.37
PFJ OA*	91	67.35 ± 1.121	63.84 ± 0.99	3.50 ± 1.0	1.52, 5.49	0.001
PFJ osteophytes	83	67.68 ± 1.16	64.62 ± 0.98	3.05 ± 1.05	0.96, 5.15	0.005
PFJ narrowing	47	68.64 ± 1.82	63.91 ± 1.52	4.73 ± 1.55	1.61, 7.84	0.004
DIP osteophytes	78	64.53 ± 1.09	64.07 ± 1.12	0.47 ± 1.14	–1.81, 2.74	0.69
PIP osteophytes	43	66.53 ± 1.50	65.48 ± 1.57	1.04 ± 1.45	–1.87, 3.96	0.47
CMC osteophytes	82	66.77 ± 1.23	63.71 ± 0.93	3.06 ± 1.12	0.83, 5.28	0.008
Asymptomatic twins						
TFJ osteophytes	35	67.33 ± 2.22	63.91 ± 2.00	3.41 ± 1.45	1.46, 6.37	0.025
PFJ osteophytes	57	67.29 ± 1.37	64.18 ± 1.08	3.11 ± 1.24	0.62, 5.60	0.015

* Either osteophytes or joint space narrowing.

Table 4. Mean BMI in twin pairs discordant for the OA disease trait.

	No. Pairs	Weight Twin 1 (Disease)	Weight Twin 2 (No Disease)	Mean Difference	95% CI	p
All twins						
TFJ OA*	70	25.52 ± 0.53	24.21 ± 0.43	1.31 ± 0.38	0.56, 2.06	0.001
TFJ osteophytes	58	26.21 ± 0.66	24.49 ± 0.55	1.73 ± 0.46	0.81, 2.41	0.000
TFJ narrowing	50	25.14 ± 0.56	24.66 ± 0.52	0.48 ± 0.43	–0.38, 1.33	0.27
PFJ OA*	91	25.78 ± 0.451	24.33 ± 0.36	1.45 ± 0.43	0.60, 2.29	0.001
PFJ osteophytes	83	25.89 ± 0.48	24.54 ± 0.37	1.35 ± 0.46	0.43, 2.26	0.004
PFJ narrowing	47	26.62 ± 0.74	24.54 ± 0.57	2.08 ± 0.58	0.91, 3.25	0.001
DIP osteophytes	78	24.66 ± 0.40	24.55 ± 0.42	0.01 ± 0.42	–0.58, 1.20	0.81
PIP osteophytes	43	25.62 ± 0.52	25.09 ± 0.57	0.53 ± 0.52	–0.52, 1.59	0.31
CMC osteophytes	82	25.47 ± 0.48	24.24 ± 0.38	1.24 ± 0.43	0.36, 2.11	0.006
Asymptomatic twins						
TFJ osteophytes	35	25.96 ± 0.90	24.44 ± 0.76	1.52 ± 0.55	0.40, 2.65	0.009
PFJ osteophytes	57	25.70 ± 0.59	24.55 ± 0.44	1.15 ± 0.54	0.06, 2.24	0.039

* Either joint space osteophytes or narrowing.

formed a subgroup analysis where only asymptomatic twins pairs were included. These analyses showed similar findings, with a mean weight difference of 3.41 (1.46, 6.34) kg between twins discordant for TFJ osteophytes and 3.11 (0.62, 5.6) kg for twins discordant for PFJ osteophytes (Table 3). This was consistent with the differences in BMI observed in twins discordant for the different OA traits (Table 4).

The crude and adjusted OR for developing different radiological OA traits are presented in Table 5. After adjustment for possible confounding variables, for each kg increase in weight the risk of developing the following OA traits [OR (95% CI)] was: TFJ osteophytes 1.14 (1.01–1.28), PFJ osteophytes 1.32 (1.09–1.59), PFJ narrowing 1.15 (1.01–1.30), and CMC osteophytes 1.10 (1.02–1.19). There was no difference in the OR when analysis was restricted to those twins with no knee pain (Table 5). When BMI was used as the measure of obesity, similar relationships were found between change in BMI and the OR of having the radiological features of OA (Table 6). The association of BMI appeared stronger than the association with weight because the BMI scale required a larger jump in BMI to get one unit change in BMI than it did for one kg of weight. For example, if the weight and BMI scales are made roughly equivalent by using the standard deviation of weight and BMI, the crude and adjusted OR were similar. The crude OR (95% CI) per unit change in body weight was 2.49 (1.28, 4.83), while the adjusted OR was 3.53 (1.19, 10.53), and the crude OR (95% CI) per unit change in BMI was 2.57 (1.33, 4.94) and the adjusted OR was 4.02 (1.29, 12.54).

As it was possible that the findings at the CMC joint may have been confounded by an association between CMC osteophytes and disease of the TFJ, adjustment for the presence of TFJ osteophytes and/or narrowing was included in

Table 5. Odds ratios for developing a radiological feature of OA per kg change in weight.

Radiological Feature of OA	Crude OR (95% CI)	p	Adjusted OR* (95% CI)	p
All twins				
TFJ osteophytes	1.10 (1.02–1.17)	0.009	1.14 (1.01–1.28)	0.03
TFJ narrowing	1.35 (0.97–1.10)	0.36	1.06 (0.96–1.18)	0.24
PFJ osteophytes	1.07 (1.02–1.13)	0.006	1.12 (1.04–1.20)	0.002
PFJ narrowing	1.09 (1.02–1.17)	0.01	1.15 (1.01–1.30)	0.03
CMC osteophytes	1.06 (1.01–1.11)	0.01	1.11 (1.02–1.19)	0.02
DIP osteophytes	1.01 (0.97–1.06)	0.68	1.02 (0.96–1.08)	0.47
PIP osteophytes	1.02 (0.96–1.09)	0.47	1.05 (0.96–1.13)	0.28
Asymptomatic twins				
TFJ osteophytes	1.11 (1.00–1.24)	0.05	1.23 (0.97–1.31)	0.111
TFJ narrowing	1.05 (0.96–1.34)	0.28	1.31 (0.93–1.84)	0.13
PFJ osteophytes	1.08 (1.01–1.15)	0.024	1.15 (1.03–1.29)	0.013
PFJ narrowing	1.06 (0.99–1.14)	0.077	1.13 (0.96–1.33)	0.132

* OR adjusted for menopausal status, age of menopause, hysterectomy, use of hormone replacement therapy, smoking, and physical activity.

Table 6. Odds ratios for developing a radiological feature of OA per unit of BMI.

Radiological Feature of OA	Crude OR (95% CI)	p	Adjusted OR* (95% CI)	p
All twins				
TFJ osteophytes	1.38 (1.12–1.71)	0.003	1.63 (1.09–2.44)	0.02
TFJ narrowing	1.11 (0.92–1.35)	0.27	1.27 (0.95–1.71)	0.11
PFJ osteophytes	1.17 (1.04–1.32)	0.01	1.32 (1.09–1.59)	0.004
PFJ narrowing	1.37 (1.09–1.70)	0.006	1.57 (1.04–2.36)	0.03
CMC osteophytes	1.18 (1.04–1.33)	0.01	1.30 (1.06–1.59)	0.01
DIP osteophytes	1.02 (0.90–1.15)	0.80	1.07 (0.91–1.25)	0.41
PIP osteophytes	1.10 (0.92–1.35)	0.31	1.15 (0.91–1.45)	0.24
Asymptomatic twins				
TFJ osteophytes	1.38 (1.03–1.86)	0.03	1.48 (0.92–2.37)	0.11
TFJ narrowing	1.17 (0.91–1.51)	0.22	2.10 (0.92–4.80)	0.08
PFJ osteophytes	1.16 (1.00–1.34)	0.05	1.37 (1.04–1.79)	0.02
PFJ narrowing	1.22 (1.00–1.50)	0.05	1.38 (0.91–2.08)	0.13

* OR adjusted for menopausal status, age of menopause, hysterectomy, use of hormone replacement therapy, smoking, and physical activity.

the analysis. There was no change in the OR (1.10, 1.02–1.19), suggesting that the association of weight with CMC OA is independent of any association between TFJ and CMC OA.

DISCUSSION

This twin study confirms that obesity is a strong risk factor for OA of the TFJ and PFJ of the knee and CMC joints of the hands in women. Overall, twins with OA of the knee tended to be 3–5 kg heavier than their co-twin. This weight difference was also observed in asymptomatic women, suggesting that obesity is a cause of OA rather than the converse. No effect of obesity was found at the DIP and PIP joints.

As with all surveys of OA, classification of disease remains a problem. Epidemiological studies of OA require explicit diagnostic criteria to classify the disease in the general population. There is no absolute clinical, radiological, or pathological standard against which the epidemiology of OA can be tested[23]. To avoid misclassification of OA in those experiencing symptoms only, the women were classified as having disease on the basis of radiographs. The available evidence would suggest that radiography is less subject to bias than clinical examination in defining OA in population based epidemiological studies[24,25]. The relative importance of the 2 major features of OA, namely osteophytes and joint space narrowing, has not been resolved. Our group have found osteophytes in the hand and knee to be better predictors of joint pain than narrowing[22]. In this study, TFJ narrowing was not significantly affected by obesity, although narrowing at the PFJ and osteophytes at the TFJ and PFJ was. It may be that TFJ narrowing is a relatively poor way to define or classify disease at the knee joint compared to the other methods.

Studies suggest a link between obesity and OA. Overall, this has been more consistent in women[5,12], strongest in OA of the TFJ of the knees, and less conclusive in other joints[6–13]. Few studies have examined whether obesity has a role in PFJ OA. One recent case–control study did not show a significant effect of obesity on the PFJ, but showed an effect at the TFJ[14]. However, this study was based on very few subjects with isolated PFJ disease. Our study argues against the hypothesis that risk factors for PFJ disease are markedly different from TFJ disease. As in our study, the link between CMC OA and obesity was observed in 2 other population based studies[12,13]. However, in contrast to our negative findings, DIP joints have also been associated with obesity in some studies[4–6], but not all[15].

The twin model used in this study enables close matching of the diseased and nondiseased twin for genetic similarity and many known or unknown environmental factors when examining the role of other potential risk factors. It thus provides a useful tool to quantify the magnitude of the difference in obesity between the twin with disease and the co-twin with no disease. For example, after adjustment for other potential risk factors, our results show that for every kg increase in weight a twin has a 14% increased risk of developing TFJ osteophytes, a 32% increased risk of developing PFJ osteophytes, and a 10% increased risk of developing CMC osteophytes compared to their co-twin. Furthermore, in an alternative way of examining the data, twins with knee disease were generally 3–5 kg heavier than the co-twin with no disease. These results are consistent with a population study in a similar age group of women that showed the risk of knee OA increased by 35% for every 5 kg of weight gain[6]. These results suggest that, in this age group of women, even small increases in body weight are associated with significant increases in risk of developing OA. Reduction or maintenance of weight may play an important part in the prevention of knee and CMC OA. There is a lack of data examining the effect of weight loss in subjects who have established disease, although one population based study suggests that the risk could be halved by losing weight[26]. Risks in men, however, cannot be extrapolated from these results and separate studies are needed.

This population survey confirms that obesity is an important risk factor for development of OA, especially in the TFJ, PFJ, and CMC joints. Twins with disease were generally 3–5 kg heavier than their co-twin with no disease. Significant increases in risk of developing radiological features of OA were observed for every kg increase in body weight (14% for TFJ osteophytes, 32% for PFJ osteophytes, 10% for CMC osteophytes). Further work is needed to determine whether intervention for obesity in younger life may affect the outcome of disease.

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