

The Association of Body Mass Index and Osteoarthritis of the Knee Joint

An Examination of Genetic and Environmental Influences

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Objective. To examine the genetic and environmental influences on the known association between body mass index (BMI) and knee osteoarthritis (OA), using adult twin data.

Methods. Bilateral knee radiographs were obtained from 785 pairs of healthy female twins (mean age 54.5 ± 7.8 years) from the St. Thomas' Hospital Adult Twin Registry (261 monozygotic [MZ] and 524 dizygotic [DZ] twin pairs). Tibiofemoral knee OA was graded according to the Kellgren and Lawrence (K/L) scoring system on an ordinal scale of 0–4. Presence of knee OA was defined as a K/L grade of ≥ 2 on either side of the knee joint. Body weight and height were measured and the subjects were stratified into quartiles of BMI. Cross-trait cross-twin association of BMI and knee OA was assessed by logistic regression, to assess whether genetic or environmental influences explain the BMI–knee OA link. The genetic (heritability) and environmental contributions to each of the measures were estimated using path modeling.

Results. A strong association was found between high BMI and the presence of knee OA (odds ratio 3.90 for highest versus lowest quartile of BMI; $P = 0.0001$). The heritability of knee OA was 50.4% (95% confidence interval [95% CI] 34–62%) and that of BMI was 55.7% (95% CI 35–72%). However, cross-trait cross-twin associations were not significantly different from unity in either the MZ or DZ twin pairs, indicating that shared

genetic influences were unlikely to explain the association. Path modeling showed that the model containing additive genetic factors, common environmental factors, and unique environmental factors had the best fit to the data overall. The shared genetic path between BMI and knee OA could be dropped without deterioration in the fit of the model.

Conclusion. The strong association between high BMI and knee OA is not likely to be mediated by shared genetic factors. The results imply that environmental modification of BMI can influence knee OA.

Osteoarthritis (OA) is a multifactorial disease with both genetic and environmental determinants. Obesity is most strongly linked to OA at the knee joint (1). Many population studies to date have found a cross-sectional association between obesity and OA of the tibiofemoral joint of the knee (2–10). Radiographic knee OA is increased 4-fold in obese women, with a range of odds ratios (ORs) between 2 and 9 in different studies. There is a dose-response relationship between excess weight or obesity and knee OA (5). These cross-sectional data have been confirmed by longitudinal data from the Framingham Study (11,12), the Chingford study (13), as well as the Baltimore Longitudinal Study of Aging (14).

How obesity causes OA at the knee joint has been the subject of considerable debate. Two major theories have been proposed to explain this association: biomechanical (6,15,16) and systemic/metabolic (3) mechanisms. The biomechanical theory concludes that obesity leads to repetitive application of increased axial loading at the knee joint with consequent degeneration of articular cartilage and sclerosis of subchondral bone. This could explain the excess of knee OA in overweight subsets. However, obesity is not consistently associated

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with an excess of hip OA (6). Furthermore, the modest excess of OA of the non-weight-bearing joints (the distal interphalangeal joints of the hands) does not support this mechanical theory (3,17). An alternative explanation is that excess fat may have a direct metabolic effect on cartilage over and above the effects of stress (18). The metabolic theory proposes that some metabolic factor, or factors, correlated with obesity adversely affect cartilage and other joint structures, suggesting that obesity acts indirectly to increase the risk of knee OA. Proposed metabolic conditions associated with obesity and OA, which arose from positive findings in the New Haven Study (4), include hypertension, hyperuricemia, diabetes, and hypercholesterolemia. However, in subsequent studies, none of these metabolic correlates remained independently significant after adjusting for obesity (5,6,16,19).

There is considerable evidence indicating that genetic factors play an important role in the determination of OA. Twin studies have estimated that up to 65% of the population variance of OA is attributable to genetic factors (20). Similarly, obesity, or high body mass index (BMI), also has a strong genetic basis (21). It is plausible therefore that the positive association between BMI and knee OA is the result of shared genetic determinants of these 2 traits.

The study of twins is a useful approach for the separation of genetic and environmental influences. By studying 2 traits that are associated in individuals, the design can be readily extended to quantify the role of genetic and environmental factors in determining the association. Using a large group of twins, this study was thereby undertaken to examine the extent to which shared genetic and environmental factors explain the BMI and knee OA association.

SUBJECTS AND METHODS

Twin subjects. The analysis was carried out on data from female twins who were enrolled with the United Kingdom Adult Twin Registry at St. Thomas' Hospital, London. These twin subjects were healthy volunteers recruited through media campaigns, and they were not aware of the objective of the study. The study group comprised 261 monozygotic (MZ) and 524 dizygotic (DZ) female twin pairs. Zygosity was determined by a standardized questionnaire (22). If the responses were ambiguous, zygosity was confirmed by DNA fingerprinting.

Measurements of knee OA. Anterior-posterior, weight-bearing, bilateral radiographs of the knees were read on the basis of a standardized atlas of radiographic features of OA, by 2 trained readers who were blinded to the pairings and zygosity (23). The presence of definite osteophytes or joint space

narrowing was used to classify tibiofemoral disease. The overall status of knee OA was determined based on the Kellgren and Lawrence (K/L) system, in which grade 0 (no evidence of bony changes or joint space narrowing) and grade 1 (small osteophytes of doubtful significance) were considered normal, while grades 2, 3, or 4 (definite osteophytes and increasing diminution of the space) were defined as OA. The patellofemoral joint compartment was graded on skyline views of the knee joint for the presence of joint space narrowing and osteophytes, graded on a 4-point scale (range 0–3). Both intraobserver and interobserver reproducibility were tested on a subgroup of twins, and the kappa statistic exceeded 0.70 for both.

Measurement of BMI. The height in meters and weight in kilograms was measured with each subject in a standing position, and the BMI (in kg/m^2) was calculated. The distribution of BMI was subdivided according to 4 quartiles.

Analytic approach. We compared the strengths of association of each BMI quartile by computing ORs for the presence of radiographic knee OA in an individual in comparison with the group classified as having no knee OA. The association between BMI and OA of the knee was performed by logistic regression, with BMI and age included as explanatory variables and presence of knee OA as the outcome variable. Definite knee OA was defined as a K/L score ≥ 2 on either side of the knee joint. The analysis took into account the paired nature of the data.

The analysis then examined if the association could be explained by shared genetic factors. Insight into the nature of the association is gained by examining the strength of the association between knee OA in one twin and BMI in the other twin, which must be due to determinants shared by the twins. Thus, the pattern of strength of the OR for the cross-trait cross-twin association can help determine if genetic and/or environmental influences explain the association. This informative approach of cross-twin ORs in bivariate twin analysis has been discussed elsewhere (24). There are 2 main possible scenarios. 1) A cross-trait cross-twin association is present if the association is greater in MZ twin pairs than in DZ twin pairs. This would be evidence for a genetic influence between obesity and knee OA, because MZ twins share 100% of their genes. If, however, the association is of a similar magnitude in both MZ and DZ twin pairs, then this would imply that factors in the shared environment of the twins could explain the association. 2) A cross-trait cross-twin association is absent if both the MZ and the DZ pairs do not show any evidence of an association. This would be evidence for unique environmental influences.

The nature of the association was further explored by path modeling, in which the observed phenotypic correlation structure was separated into additive (A) and dominant (D) genetic components and into common (C) and unique (E) environmental variance components (25). The data used as the basis for modeling comprised matrices of tetrachoric correlations (BMI as a continuous variable and knee OA status as a binary [0,1] variable) between the phenotypes of twin and co-twin for each zygosity group. The model was constructed to allow for unique genetic and environmental influences, together with shared genetic and environmental influences that might explain the association using standard variance decomposition methods (25). The common environmental compo-

nent estimates the effect of shared family environment, whereas the unique component applies to the individual subject. Since age is a risk factor for knee OA, it was incorporated into all models.

The significance of A, D, C, and E components was assessed by removing each sequentially and testing the change in the chi-square statistic of the model. Parameters were removed from the model if found to have no significant contribution, using a threshold of P less than 0.05. Heritability was computed as the ratio of genetic variance over total phenotypic variance from the final selected model. The significance of indirect or shared paths of the final model was also tested using a similar approach. All genetic modeling was carried out with Mx software (26) (see Figure 1).

RESULTS

Characteristics of study sample. The MZ and DZ twins were comparable with respect to age, weight, and BMI, with a mean \pm SD age of 54.5 ± 7.8 years (range 24–79 years), weight of 65.0 ± 11.5 kg, and BMI of 24.8 ± 4.3 kg/m² (Table 1). One hundred thirty-four subjects (8.5%) with a BMI in the highest quartile had definite radiographic knee OA, compared with 43 subjects (2.7%) in the lowest quartile of BMI (Table 2). As

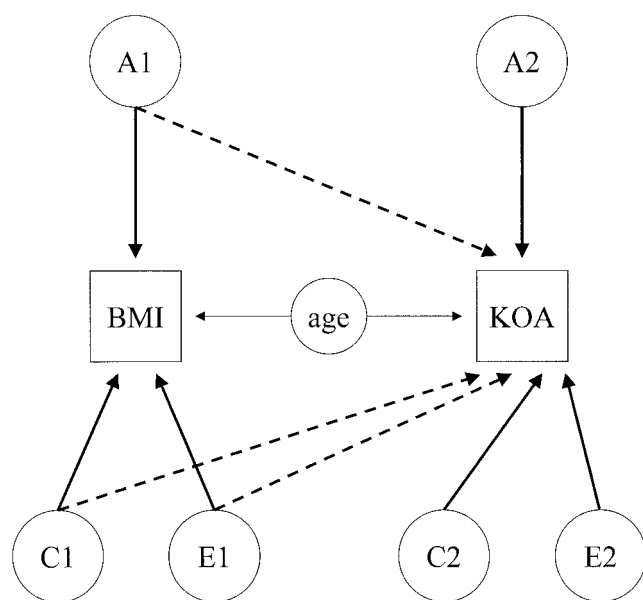


Figure 1. Path analysis of a single twin. Path diagrams show the unique and shared factors for genetic and environmental sources of variance for body mass index (BMI) and knee osteoarthritis (KOA). BMI and KOA have influences from additive genetic factors (A1, A2), common environmental factors (C1, C2), and unique environmental factors (E1, E2). The shared pathways are depicted by dotted lines. In this ACE model, the shared genetic pathway A1 to KOA can be dropped without deterioration in the fit of the model. Shared C (C1–KOA) and shared E (E1–KOA) paths have to be retained.

Table 1. Demographic and clinical characteristics of twin subjects*

	Monozygotic	Dizygotic
No. of pairs	261	524
Age, years	56.8 ± 7.0	53.8 ± 7.8
Weight, kg	63.7 ± 10.6	65.8 ± 11.9
Height, cm	161.2 ± 6.1	162.3 ± 5.9
BMI, kg/m ²	24.5 ± 3.8	25.0 ± 4.4
Knee OA prevalence, no. (%)	126 (24)	214 (20)
Postmenopausal, %	84	67
Smoker (current + past), %	45	49
Estrogen replacement, %	33	37

* Except where otherwise indicated, values are the mean \pm SD. BMI = body mass index; OA = osteoarthritis.

expected, subjects in the second and third BMI quartiles also had a significantly increased risk of radiographic knee OA when compared with those in the lowest BMI quartile. As shown in Table 2, the age-adjusted OR for developing knee OA in an individual in the second BMI quartile compared with individuals in the lowest BMI quartile was 1.74 (95% confidence interval [95% CI] 1.12–2.69), which increased to an OR of 2.26 (95% CI 1.45–3.52) for those in the third BMI quartile. The OR was 3.90 (95% CI 2.56–5.93) for subjects in the highest BMI quartile. The range of BMI in the highest quartile was 27–51 kg/m², with 60% of the twins in this quartile having a BMI >25 kg/m² but ≤ 30 kg/m², 26% having a BMI >30 kg/m² and ≤ 35 kg/m², and 14% having a BMI >35 kg/m². The number of subjects with only patellofemoral knee OA was 72 (4.6% overall); the analysis was carried out on those with tibiofemoral knee disease regardless of whether there was concurrent disease in the patellofemoral knee joints.

Table 2 also shows the cross-twin cross-trait association for MZ and DZ twin pairs. The cross-trait cross-twin association for MZ twins in the highest BMI quartile was indicated by an OR of 1.25 (95% CI 0.53–2.98), and for DZ twins in this quartile, an OR of 1.77 (95% CI 0.92–3.42) was found. These results were not significantly different from zero and were therefore not compatible with the hypothesis of shared genetic factors as an explanation for the BMI–knee OA association.

Path model. Comparison of a sequence of models (Table 3) showed the model with additive genetic (A), common environmental (C), and unique environmental (E) effects to be the most appropriate model (ACE) for the data overall. Dropping the shared additive (A) genetic path between BMI and knee OA did not result in a significant change in the model chi-square statistic. However, dropping either the shared common environ-

Table 2. Body mass index (BMI) and presence of radiographic knee osteoarthritis (OA)*

BMI (kg/m ²)	Knee OA, no. (%)	OR (95% CI)		
		All twin pairs	Cross MZ	Cross DZ
First quartile (15–22)	43 (2.7)	Reference		
Second quartile (22–24)	76 (4.7)	1.74 (1.12–2.69)†	0.90 (0.37–2.17)	1.00 (0.49–2.03)
Third quartile (24–27)	87 (5.4)	2.26 (1.45–3.52)‡	1.25 (0.54–2.90)	1.61 (0.83–3.14)
Fourth quartile (27–51)	134 (8.5)	3.90 (2.56–5.93)‡	1.25 (0.53–2.98)	1.77 (0.92–3.42)

* OR = odds ratio (adjusted for age); 95% CI = 95% confidence interval; MZ = monozygotic; DZ = dizygotic.

† *P* = 0.013 versus first quartile.

‡ *P* = 0.0001 versus first quartile.

mental (C) or shared unique environmental (E) paths resulted in a significant change in the model chi-square values, and both paths had to be retained to adequately explain the data (*P* < 0.05 for both comparisons). The proportion of variance of knee OA accounted for by environmental factors, that is, both the unique and the common paths, was 17.9%. Age accounted for 12.3% of the variance. In the final model, the heritability of knee OA was estimated to be 50.4% (95% CI 34–62%), and heritability of BMI was 55.7% (95% CI 35–72%).

DISCUSSION

The data demonstrate and lend support to what is a well-known observation: leaner subjects have a smaller risk of radiographic knee OA compared with subjects with a high BMI. We have confirmed previous study findings in these analyses, indicating that a high BMI is strongly associated with knee OA in women. The 4-fold increase in risk of radiographic knee OA in overweight persons in the present study is comparable with that observed in other population studies to date (2,3,5).

This study is unique in being able to discern the genetic and environmental components that might determine the association between these 2 traits. The cross-twin cross-trait analysis results were not compatible with a genetic explanation for the association between BMI and knee OA, since the results in MZ and DZ twins did not differ significantly from unity. Path modeling not only confirmed this result, but also allowed for a more detailed examination in which the significance of shared paths could be tested. The analysis does not, however, resolve the debate regarding the mechanism of association between BMI and knee OA, but it does indicate that shared genetic susceptibility is unlikely. Our data demonstrated that both unique and shared environmental factors contribute to BMI, and both appear to account for the environmental influence on knee OA. Examples of common or familial environmental factors are dietary intake, levels of physical activity, and occupations. Risk factors that are not shared by family members, such as knee injury or operations, may represent examples of the individual-specific source of variance in susceptibility to knee OA. Environmental risk factors for the development of knee OA, such as occupations and exercise, are factors that are modifiable and thereby attenuate the obesity risk factor for knee OA.

As indicated in the First National Health and Nutrition Examination Survey (5), we found a dose-response effect of increasing BMI and age-adjusted OR for the development of knee OA in an individual. The OR of knee OA comparing the second quartile with the lowest quartile was 1.74, which increased to an OR of 2.26 for the third quartile. In the highest BMI quartile, the OR was 3.90. The range of BMI in the highest quartile was 27–51 kg/m², and so it included “overweight subjects.” Overweight is defined herein as a BMI of 25–29.9 kg/m² and obesity as a BMI of ≥30 kg/m² (27). However, overweight and obesity are not mutually ex-

Table 3. Results of path modeling*

	χ ²	df	<i>P</i>
Model components			
ACE	69.98	8	–
ADE	81.36	8	–
AE	83.13	11	–
CE	146.28	11	–
E	612.03	14	–
Best model (ACE)			
Drop A	1.56	9	NS
Drop C	11.07	9	<0.001
Drop E	78.73	9	<0.001

* Genetic variance has contributions from additive (A) and dominant or nonadditive (D) variance components. In twins, environmental variance can be divided into variance shared within twin pairs (C) and environment that is unique to each twin in a pair (E). df = degrees of freedom; NS = not significant.

clusive conditions, since obese persons are also overweight. It is conceivable that genetic factors may be more apparent in those subjects who would fall into the accepted definition of "obesity." We cannot exclude the possibility that shared genetic influences contribute to the BMI-knee OA association in obese subjects. However, our analysis was based on the range of BMI that is representative of the general population in the UK (28).

It has been suggested that bilateral knee OA may be more likely to have a genetic basis. Examination of bilateral patterns of knee OA as well as individual radiographic features of osteophytes and joint space narrowing did not change the cross-trait cross-twin results (data not shown). Patellofemoral joint disease, in contrast to medial compartment disease, has been shown to be much less strongly associated with obesity (29). Another study found that radiographic patellofemoral disease had a strong association with BMI (30). The number of subjects with patellofemoral disease alone in our study was too small to allow any conclusive results for this analysis. The combination pattern of patellofemoral and tibiofemoral joint disease has not been examined, and this requires further evaluation.

A number of points merit discussion. Power considerations mean that we cannot rule out small shared genetic influences between the 2 traits. The study had a 90% power to detect genetic influences that might account for ~10% of the heritable component of knee OA at a nominal significance level of 5%. A higher proportion of MZ twins compared with DZ twins was postmenopausal. The prevalence of knee OA was similar in both groups, with 24% of MZ twins and 20% of DZ twins having radiographic OA. Therefore, the differences in menopausal status were unlikely to influence the result. The classic twin model relies on a number of assumptions, including the specification that shared environmental variance (C) is equal in MZ and DZ twins. Violation of this assumption might overestimate the genetic effect, which is obviously not a concern in this particular study. The reported association between factors in the intrauterine environment and birth weight and the subsequent development of certain adult diseases may also introduce bias (MZ twins, in general, have a lower birth weight than DZ twins). Although it has been shown that birth weight is associated with adult weight, there is no evidence to support the association between birth weight and the development of OA in later life (31). Our twin subjects had no greater prevalence of knee OA than that in the general population (28).

In conclusion, this study demonstrates that the

strong and consistent association between a high BMI and knee OA in women is not likely to be mediated by shared genetic factors. Defining the distinct environmental determinants shared by these 2 traits may provide a better understanding of the factors contributing to the development of knee OA.

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