

## THE GENETIC CONTRIBUTION TO RADIOGRAPHIC HIP OSTEOARTHRITIS IN WOMEN

### Results of a Classic Twin Study

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**Objective.** To assess the genetic contribution to radiographic hip osteoarthritis (OA) by measuring the distribution of disease features in monozygotic (MZ) and dizygotic (DZ) twins.

**Methods.** A population-based, cross-sectional study was conducted of 135 MZ and 277 DZ healthy female twin pairs, 50 years of age and older, who were recruited into the St. Thomas' UK Adult Twin Registry. Pelvic radiographs were read by a single observer who was blinded to the pairing and zygosity of the twins. The films were assessed for overall OA grade using a modification of the Kellgren and Lawrence scheme, and assessed for individual radiographic features.

**Results.** There was evidence of significant familial clustering for grade I and grade II OA changes, with an excess concordance in MZ twins compared with DZ twins, suggesting a genetic effect. The MZ versus DZ excess was also apparent for those classified as having more severe disease, although the number of pairs with these disease features was small. Familial clustering attributable to genetic factors was evident for joint space narrowing of <2.5 mm. Familial, but not genetic, clustering was seen for subchondral sclerosis. The number of pairs concordant for definite osteophytes in the sample was too low to assess this feature alone. These results translate into a significant heritability of 58%

for OA overall and 64% for joint space narrowing. The heritability estimates decreased a little when the potential confounding influences of age, body mass index, and hip bone density were taken into account.

**Conclusion.** Genetic factors have a significant contribution to OA at the hip in women and account for ~60% of the variation in population liability to the disease.

The familial aggregation of clinical and radiographic features of osteoarthritis (OA) was first convincingly demonstrated by Stecher (1) in the 1940s in studies of Heberden's nodes, and has since been confirmed for hand and knee OA in several community-based studies (2–5). Identifying familial aggregation for radiographic OA at the hip, where changes are relatively rare compared with other sites, has proved more problematic. Recently published community family studies either have not included data on radiographic hip OA (4,5) or have been unable to accrue sufficient cases to allow inference about familial aggregation of OA at the hip joint alone (6). Studies that have examined the frequency of disease among the siblings of probands who have undergone total hip or total knee replacement have suggested a familial effect (7–9). However, interpretation of their results is limited by several potential biases.

Studying twins provides a classic approach to separating genetic influences from the shared family environment as a cause of familial aggregation (10). Twin studies also allow the genetic contribution to disease and disease-related traits in the population to be quantified. In 1996, we and other investigators published results of an analysis of radiographic OA of the knee and hand conducted among twins recruited from the healthy population, which demonstrated that genetic factors accounted for between 39% and 65% of the variation in

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liability to disease at these sites (11). Herein we report on the familial aggregation and genetic influences on the occurrence of radiographic hip OA in an extended group of twins with a comparable age distribution from this same sample.

## SUBJECTS AND METHODS

**Study subjects.** The study subjects comprised female–female twin pairs recruited from the St. Thomas’ UK Adult Twin Registry (12). This is a volunteer-based group of adult twins drawn from the healthy UK population and assembled through successive media campaigns. The twins eligible for inclusion in the present study had no history of chronic bone or joint disease other than OA. All twins completed a nurse-administered questionnaire documenting details of their lifestyle and occupational history. Their zygosity was determined by a standard questionnaire and confirmed by DNA fingerprinting.

**Radiologic assessment.** Pelvic radiographs with the subject in the supine anteroposterior position, with a standard tube-to-film distance of 100 cm and the feet positioned in 15 degrees of internal rotation were obtained.

All films were assessed by a single observer and scored for the following radiographic features: minimum joint space (MJS), the presence of osteophytes, maximum thickness of subchondral sclerosis, and cyst formation. Both MJS and sclerosis were measured visually, along a radius from the center of the femoral head (determined using a plastic overlay of concentric circles), using a plastic ruler with 1-mm gradations. Osteophytes were graded on a 4-point scale of 0–3, using an atlas of individual features (13); definite osteophytes were considered to be those graded as 2 or higher.

An overall OA grade was defined as follows: grade 0 = no change; grade I = definite osteophytes only; grade II = joint space narrowing (JSN) only (defined as an MJS of <2.5 mm); grade III = presence of 2 of the following: JSN, osteophytosis, subchondral sclerosis (of  $\geq 5$  mm), and cyst formation; grade IV = presence of 3 of the following: JSN, osteophytosis, subchondral sclerosis (of  $\geq 5$  mm), and cyst formation; and grade V = same as grade IV, but with deformity of the femoral head. Cases of total hip replacement due to OA (verified by record review) were classified as grade V and allocated a 0-mm joint space. This classification follows Croft’s scheme (14), which has been used widely in contemporary population studies of hip OA and is a modification of the Kellgren and Lawrence classification (15,16). In the Croft scheme, grade I OA is roughly equivalent to Kellgren and Lawrence grade II.

The films were read by a single observer (LA) who was blinded to the pairing and the zygosity of the twins. Films were read individually and in random order. If an abnormality was seen, the radiographs were read independently by a second observer (MM). If there was a discrepancy, the opinion of a third specialist was asked. In a sample of 350 films selected to show a range of disease features, the intrarater agreement (assessed by the kappa statistic) was 0.81 for overall OA grade, 0.84 for JSN, 0.73 for subchondral sclerosis  $>5$  mm, and 0.83 for osteophyte grade.

**Statistical analysis.** To permit valid comparison with existing population data and with previously published results on hand and knee OA in these twins, our analysis was confined to subjects over the age of 50 years. All analyses were conducted using the statistical software package Stata (17). The genetic contribution to hip OA was estimated for the overall presence of disease by grade and separately for 3 individual radiographic features: 1) JSN, 2) sclerosis of  $\geq 5$  mm, and 3) definite osteophytes. Data from the worst affected hip in each individual were used in the analysis.

The similarity in the twins’ OA characteristics was measured by estimating casewise concordance ( $P_c$ ) (Appendix A) (18). This is a measure of the risk to a twin if her cotwin is classified as a case (for DZ twins, the  $P_c$  provides a measure that is analogous to the sibling recurrence risk [19]). Familial aggregation is suggested to be evident if the  $P_c$  among either the MZ or DZ twins exceeds the prevalence of the trait or disease in the population. An excess in the  $P_c$  estimate in MZ twins compared with DZ twins suggests the presence of a genetic contribution.

For variables in which familial aggregation was suggested, the relative size of the contribution of genetic and environmental factors was estimated using a variance components approach (20). This method considers phenotypic variation for a disease or trait in a population of twins to have a potential contribution from additive (A) and dominance (D) genetic variance components, and from shared (C) and unique (E) environmental variance components. The proportion of population-level phenotypic variance in a trait or disease that can be attributed to genetic variation is termed “heritability” (21).

The interpretation of raw concordance data is limited by the fact that both the absolute levels of concordance and the size of the difference between MZ and DZ concordance are influenced by the prevalence of the trait under consideration (22,23). Variance components analysis provides more readily interpretable measures of the relative size of genetic and environmental influences underlying a trait or disease. The method involves the assumption that a trait is expressed when an underlying and continuously distributed liability exceeds a certain threshold. This is accepted to be an appropriate model for complex diseases (24). Unlike concordance estimates, variance components analysis provides measures of underlying genetic influence that can be compared between traits or diseases with different prevalence (23).

The variance components were estimated by constructing logistic regression equations in which a twin’s phenotype was modeled as a function of her cotwin’s phenotype and their zygosity (25). The size of each variance component was estimated from the parameters of the model that provided the most parsimonious explanation of the data selected by standard backward elimination rules using a threshold of  $P = 0.05$  for retaining variables. Further details of the method are provided in Appendix B.

Data relating to the influence of potential confounding variables were also examined. These included age, body mass index, menopause status, the use of hormone replacement therapy, and weight-bearing physical activity status according to current activity and according to that in the subject’s third decade of life (measured by a modification of the Allied Dunbar Physical Activity Grading Score [26]). A modest

**Table 1.** Characteristics of the twins\*

	MZ (n = 270)		DZ (n = 554)	
	Value	R/ $P_c$	Value	R/ $P_c$
Mean age in years (range)	57.8 (50–72)	1.00	57.2 (50–72)	1.00
Mean height in cm (SD)	160.1 (6.0)	0.90	162.2 (5.1)	0.54
Mean weight in kg (SD)	64.4 (10.0)	0.74	66.1 (9.5)	0.34
Mean body mass index in kg/m <sup>2</sup> (SD)	24.9 (3.7)	0.69	25.1 (3.6)	0.39
Mean femoral neck BMD in gm/cm <sup>2</sup> (SD)	0.76 (0.12)	0.79	0.76 (0.12)	0.42
Smoking ever, %	49	0.74	47	0.59
Alcohol use ever, %	59	0.84	55	0.73
ERT use ever, %	45	0.72	48	0.57
Postmenopausal, %	91	0.99	93	0.96
Current weight-bearing activity, %	7	0.35	8	0.23
Past weight-bearing activity, %	23	0.76	21	0.36

\* Standard deviations (SD) represent the between-pair SD. MZ = monozygotic; DZ = dizygotic; R = intraclass correlation;  $P_c$  = casewise concordance; BMD = bone mineral density; ERT = estrogen replacement therapy.

association between bone mineral density at the femoral neck and OA has been reported within twin pairs from this population (27). To account for potential confounding from shared genetic and environmental influences between bone density and OA, data on bone mineral density at the left femoral neck, assessed by dual x-ray absorptiometry, were also included as confounding variables. The similarity in the distribution of confounding variables among twins was measured by comparing concordance for discontinuous characteristics (such as smoking) and the intraclass correlation coefficient for continuous characteristics such as height and weight.

## RESULTS

A total of 135 MZ and 277 DZ female twin pairs was studied. Their characteristics are shown in Table 1. The MZ and DZ twins were well matched for age and other individual characteristics. However, as expected, MZ twins showed greater similarity in anthropometric variables (such as height and weight) and lifestyle variables (such as smoking and current weight-bearing physical activity) than did DZ twins. Although a slight excess was observed in the prevalence of variables related to hip OA in DZ twins when compared with MZ twins, none of these differences was significant (Table 2).

The extent of similarity in disease features in the twins is shown in Table 3. For grade I and grade II changes, the casewise concordance among the MZ and DZ groups was higher than would have been expected from the prevalence in the group as a whole (Table 2) and suggests significant familial clustering. Concordance for OA among MZ twins also exceeded the concordance in DZ twins, suggesting that this familial clustering has a

genetic basis. These differences were apparent for all OA grades, although the small numbers of pairs concordant for severe disease produced wide confidence intervals for those classified as having grade III or higher disease.

Among individual disease features, a genetic contribution to JSN was suggested by the greater concordance in MZ twins when compared with DZ twins. For sclerosis of  $\geq 5$  mm, both MZ and DZ concordances were approximately twice those expected from their prevalence in the sample, suggesting familial aggregation. However, there was no clear evidence of an excess in the MZ twins. Osteophytes could not be assessed in 21 hips that had undergone total joint replacement surgery. The number of pairs that were concordant for definite osteophytes was too low to allow comment on possible familial aggregation for this feature individually.

**Table 2.** Radiologic features of OA in the MZ (n = 270) and DZ (n = 554) twins\*

	MZ	DZ
Overall OA grade		
Grade I or higher	33 (12)	101 (18)
Grade II or higher	24 (9)	72 (13)
Grade III or higher	13 (5)	47 (8)
Grade IV or higher	4 (1)	22 (4)
Individual radiographic features		
JSN	23 (9)	67 (12)
Sclerosis >5 mm	47 (17)	96 (17)
Definite osteophytes†	17 (6)	48 (9)

\* Values are the no. (%) of subjects. OA = osteoarthritis; JSN = joint space narrowing (see Table 1 for other definitions).

† Osteophytes were not coded in 21 hips that had undergone total joint replacement.

**Table 3.** Concordance for disease features in MZ and DZ pairs\*

	MZ				DZ			
	N <sub>c</sub>	N <sub>d</sub>	P <sub>c</sub>	95% CI	N <sub>c</sub>	N <sub>d</sub>	P <sub>c</sub>	95% CI
Overall OA grade								
Grade I or higher	7	19	0.42	0.21–0.64	14	73	0.28	0.16–0.39
Grade II or higher	5	14	0.42	0.17–0.67	7	58	0.20	0.07–0.32
Grade III or higher	2	9	0.31	0.00–0.64	3	41	0.12	0.00–0.26
Grade IV or higher	1	2	0.50	0.00–1.00	2	18	0.18	0.00–0.40
Individual radiographic features								
JSN	5	13	0.43	0.18–0.69	7	53	0.21	0.08–0.34
Sclerosis >5 mm	9	29	0.39	0.20–0.56	18	59	0.38	0.25–0.50
Definite osteophytes	1	15	0.12	0.00–0.33	1	45	0.04	0.00–0.12

\* N<sub>c</sub> = number of concordant pairs; N<sub>d</sub> = number of discordant pairs; 95% CI = 95% confidence interval (see Tables 1 and 2 for other definitions).

The results of biometric modeling for the variables for which there was definite evidence of familial aggregation are shown in Table 4. For disease classified as grade I or higher and grade II or higher, the most appropriate model included contributions from additive genetic factors and the unique twin environment (AE model). There was no significant evidence of a contribution from the common twin environment (C) or from the dominance (D) genetic variation. Additive genetic variance contributed to 58% of the variation in liability to disease for both of these lower grades of OA. For individual disease features, an AE model provided the most appropriate description of JSN, with genetic factors contributing 64%. In contrast, for sclerosis, the familial aggregation was best explained by factors in the shared family environment of the twins (CE model) and there was no suggestion of a contribution from genetic factors.

Analysis of the effect of potential confounding variables showed only age and body mass index as

factors contributing to the risk of hip OA. A site-specific association between OA and bone mineral density at the femoral neck was also present in these twins (27). When these variables were retained in the regression models, the size of the OA heritability estimated to be independent of the genetic and environmental factors shared with these variables was a little reduced, but remained significant (Table 4). Including data from confounders also had no important effect on the size of the contribution of the shared environment to subchondral sclerosis.

**DISCUSSION**

This is the first twin study to examine the genetic contribution to the occurrence of radiographic OA at the hip in an unselected population. Our data show the heritability of radiographic hip OA among women to be ~60%. This is of a similar magnitude to that found for OA at the knee and hand in a smaller group of the same twins with a comparable age range (11). We have also

**Table 4.** Variance components analysis\*

	Model	A	95% CI	C	95% CI
Overall OA grade					
Grade I or higher	AE	0.58	0.29–0.87	–	–
	AE†	0.42	0.10–0.75	–	–
Grade II or higher	AE	0.58	0.26–0.89	–	–
	AE†	0.41	0.05–0.77	–	–
Individual radiographic features					
JSN	AE	0.64	0.32–0.96	–	–
	AE†	0.47	0.10–0.83	–	–
Sclerosis >5 mm	CE	–	–	0.45	0.27–0.63
	CE†	–	–	0.45	0.26–0.64

\* Values are the parameter estimates and their 95% confidence intervals (95% CI) for additive genetic variance (A) and common environmental variance (C) estimated from the biometric model selected as the best reflection of the distribution of concordance in the data for each variable. All models contained a term representing environmental variation unique to each twin (E). No model selected included the dominance genetic variance. See Table 2 for other definitions.  
 † Model includes the covariates age, body mass index, and bone density at the left hip.

shown that genetic factors specifically influence JSN, which is the most reliable predictor of pain from the disease in populations (15). The genetic influence observed in this study cannot be attributed to confounding resulting from age differences between the 2 groups, anatomic differences between the twins in terms of height or build, differences in bone mineral density at the hip, or differences in lifestyle variables such as smoking or exercise.

A genetic contribution to OA at the hip has been suggested in studies of relatives of patients undergoing total joint replacement surgery. Lindberg (7) showed that the frequency of radiologic OA among the siblings of 184 probands was more than 2-fold that in age- and sex-matched controls from the general population. Chitnavis et al (8) also reported a similar magnitude of increase in the risk of hip OA among relatives of 402 probands undergoing total joint replacement, compared with spouse controls. Recently, Lanyon et al (9) in a preliminary report using a similar design involving 398 families of probands with total hip replacement, showed a 4-fold risk for JSN of  $<2.5$  mm among siblings compared with population-based controls. All of these studies used highly selected groups of individuals with severe disease. Interpretation of their results in isolation is limited by possible biases in recruitment, and by the potential for misclassification of disease among the probands, relatives, and controls.

Population-based studies published to date have been severely limited by the inclusion of insufficient numbers of cases to allow an assessment of the joint-specific heritability of hip OA. No data on hip OA were available in the recent studies of familial aggregation of radiographic OA conducted in the Baltimore and Framingham cohorts (4,5). Bijkerk et al (6), in a random sample of 1,583 individuals and their siblings drawn from the Rotterdam study, identified insufficient numbers of siblings with disease at the hip to permit an estimate of heritability at that site. A joint-specific heritability estimate for hip OA is also precluded in recent data from a Finnish twin cohort (28), in which a questionnaire-based survey of 266 twin pairs identified only 4 MZ pairs and no DZ pair concordant for physician-diagnosed hip OA.

Our approach addresses a number of the limitations of earlier studies. Our twins were ascertained from the healthy population. They were not selected for study on the basis of disease and had no knowledge of the aim of the study when recruited. The disease status in all subjects was classified by radiographic criteria. By studying twins, our concordance estimates in the MZ and DZ groups are naturally matched for

age. In estimating heritability, we have been able to separate genetic effects and the influence of the shared family environment—these 2 components are confounded in standard, nontwin study designs. We have also taken into account biases that result from potential confounders.

Two common criticisms of the twin cohort design, however, need to be addressed in interpreting our findings. First, the representativeness of twins themselves is often questioned. For example, concerns are frequently raised that twins may be unusually susceptible to disease in later life through their adverse fetal environment (29). Potential developmental differences in hip morphology in twins compared with singletons might have biased our results. Second, concerns are often expressed that greater environmental sharing in MZ twins than in DZ twins has the potential to inflate measures of heritability if there is an association between the shared risk factor and disease (30).

Our data showed no significant difference in the prevalence of OA changes when MZ twins and DZ twins were compared. The slight excess in disease features documented in the DZ twins would have tended to bias our heritability estimates downward. The prevalence of radiologic changes at the hip recorded in this study was similar to that found in other population samples in the UK in which the same classification methods were used. Among the Chingford study cohort, which involved a population-based study of unrelated women who were ascertained from a general practice register, the prevalence of radiographic narrowing among subjects between 50 and 65 years of age was 9% (31). The mean joint space determined from absolute measures of width in our twin pairs (MZ mean 3.27 mm [SD 0.71], DZ mean 3.11 [SD 0.73]) was comparable with that reported by Smith et al (32) in a population-based study of older UK women between 60 and 75 years of age (mean joint space width 3.02 mm [SD 0.7]). The prevalence of definite osteophytes in our sample, however, was higher than the 3.6% reported by those investigators (32). Hip morphology was not assessed specifically in all twins in this study. However, measurements of center-edge angle and acetabular depth were made using published methods (14) in a sample of 462 twins. No differences were found between the MZ twins and DZ twins, and the mean measurements were also similar to those reported in the survey by Smith et al (32).

Thus, there is no evidence that this group was unduly susceptible to developmental abnormalities. Although our results clearly cannot be extrapolated to men, for whom the genetic contribution may differ (28),

it is likely that our findings can be extended to the general population.

Our findings confirm a greater degree of environmental sharing in MZ twin pairs compared with DZ twin pairs for a number of variables, including smoking and alcohol consumption and lifetime exposure to physical exercise (Table 1). However, none of the measured environmental variables was significantly associated with OA in this data set. It is highly improbable that an unmeasured risk factor in the shared environment could exert an influence of sufficient magnitude to affect these results (33). Our analysis also suggests that there are genes influencing hip OA that are independent of the genetic factors that determine body mass index or bone mineral density.

As would be expected in an unselected population-based sample, although all grades of disease severity were represented, our principal findings relate to a definition of disease that encompasses mild changes of OA. The study was not designed specifically to examine more severe grades individually, nor to examine specific features of the disease or particular disease patterns, such as bilateral versus unilateral disease. To address these questions in this study design would have required a prohibitively large sample size. Our definition of hip OA also did not include symptoms of hip pain. However, our approach focused on a widely accepted epidemiologic definition of the disease that relates to the biologic status of the joint (34). Our data also indicate that the genetic effect was consistent across all grades of OA and, taken together with the results of studies using probands that have been selected on the basis of severe disease (7,8), suggest a genetic influence across the spectrum of clinical disease.

Whereas analysis of individual disease features showed a clear genetic contribution to JSN, subchondral sclerosis showed evidence of familial clustering that was attributable to the shared family environment. This contrast was not the result of the arbitrary placement of the cutoff point for definition of these variables: more stringent cutoff points produced similar results. It also could not be explained by measurement error. It is likely, therefore, that different etiologic factors are responsible for the development of JSN and sclerosis in OA. Our results underline that the genetic basis of the disease is likely to be complex (10). Radiologic JSN is a surrogate for cartilage loss, and it is of interest that preliminary genetic linkage data in OA have implicated chromosomal regions encoding cartilage matrix components including fibronectin and the  $\alpha 2$  chain of type V collagen (35,36). Subchondral sclerosis is distinct from carti-

lage change in the pathologic development of OA (37) and may reflect mechanical environmental stimuli (38).

There is currently considerable work in progress with regard to isolation of the specific genes involved in OA. Our data confirm that, as with disease at the hand and knee, the occurrence of hip OA in the population has an important genetic basis. Our heritability estimates indicate that ~60% of the variance in liability to disease is explained by genetic factors in the female population and point to the likely success of linkage and association studies in identifying the genetic basis of the disease.

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#### APPENDIX A: CASEWISE CONCORDANCE ANALYSIS OF TWIN DATA

Casewise concordance can be defined as the probability that one twin is classified as a case given that her cotwin is classified as a case (18). In a random sample of twins, the maximum likelihood estimate of  $P_c$  and of its variance,  $\text{var}(P_c)$ , are given by the following equations:

$$P_c = \frac{2N_c}{2N_c + N_d} \text{ and}$$

$$\text{var}(P_c) = P_c^2(1 - P_c)^2 \left( \frac{1}{N_c} + \frac{1}{N_d} \right)$$

where  $N_c$  and  $N_d$  are the number of concordant and discordant pairs in the sample, respectively.

#### APPENDIX B: VARIANCE COMPONENTS ANALYSIS FOR BINARY DATA ON TWINS

For a binary trait, the association between the phenotype status of a proband twin and his or her cotwin was assessed using a modification of the DeFries-Fulker regression equation (25,39). The probability ( $p$ ) of the cotwin expressing the disease or trait (coded as a binary [0,1] variable according to the cotwin's status below or above a threshold liability) was modeled as the logit function ( $g$ ) of their proband twin's status, such that:

$$g(p) = \ln \left( \frac{p}{1-p} \right) = \beta_0 + \beta_1 R + \beta_2 P + \beta_3 PR + \beta_4 PD + E$$

where  $\ln$  is the natural logarithm,  $P$  is the binary state of the proband twin rescaled (0,k), with  $k$  estimated from the difference of the mean liability above and below the threshold for the trait,  $R$  is the coefficient of relationship (coded 1 for MZ twins and 0.5 for DZ twins),  $D$  represents dominance, coded 1 for MZ twins and 0.25 for DZ twins, and  $E$  represents random error. In this parameterization, the regression coefficient  $\beta_2$  is the proportion of variance due to shared environmental factors ( $C$ ),  $\beta_3$  is the additive genetic variance ( $A$ ), and  $\beta_4$  is the dominance genetic variance ( $D$ ). Because of collinearity, only 1 of the 2 terms,  $PR$  or  $PD$ , can be included in a single regression analysis in conjunction with  $P$ . The model was extended to include confounding variables by using double-entered data to account for the covariates of both members of the pair. Model standard errors were corrected by a factor of  $\sqrt{2}$ . An implementation of this method programmed for the statistical software package Stata (17) is available from the authors and can be downloaded from our Web site, <http://www.twin-research.ac.uk>.