The Validity and Heritability of Self-Report Osteoarthritis in an Australian Older Twin Sample

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In order to investigate the genetic and environmental antecedents of osteoarthritis (OA), self-report measures of joint pain, stiffness and swelling were obtained from a population-based sample of 1242 twin pairs over 50 years of age. In order to provide validation for these self-report measures, a subsample of 118 twin pairs were examined according to the American College of Rheumatology clinical and radiographic criteria for the classification of osteoarthritis. A variety of statistical methods were employed to identify the model derived from self-report variables which would provide optimal prediction of these standardised assessments, and structural equation modelling was used to determine the relative influences of genetic and environmental influences on the development of osteoarthritis. Significant genetic effects were found to contribute to osteoarthritis of the hands, hips and knees in women, with heritability estimates ranging from 30–46% depending on the site. In addition, the additive genetic effects contributing to osteoarthritis in various parts of the body were confirmed to be the same. Statistically significant familial aggregation of osteoarthritis in men was also observed, but it was not possible to determine whether this was due to genetic or shared environmental effects.

Osteoarthritis (OA) is globally the most common form of chronic arthritis, and has attracted attention as a target condition for the Bone and Joint Decade (BJD), inaugurated in 2000 by the World Health Organisation (WHO) (Brooks, 2001). Despite the fact that prevalence of OA increases with advancing age, there are several reasons for believing that OA is not simply a manifestation of ageing but rather a condition that finds expression generally in mid to late life. In particular the prevalence curve plateaus at the extreme of age (van Sasse et al., 1989) and OA cartilage and healthy elderly cartilage differ both histologically and histochemically (Heinegard et al., 1998).

Several twin studies have previously investigated aspects of the heritability of osteoarthritis (MacGregor & Spector, 1999). The first of these (Spector et al., 1996) used radiological screening of 250 female twin pairs to diagnose osteoarthritis of the hand and knee, and found genetic influences ranging from 39–65% for different sites. In a study of recalled physician-diagnosed osteoarthritis, Kujala et al. (1999) found evidence for differences in the aetiology of OA between men and women, with additive genetic effects explaining 44% of variance in women, but non-genetic familial effects explaining 37% of total variance in liability to OA in men. Bijkerk et al. (1999) have also investigated significant evidence of heritability in radiologically determined osteoarthritis of the hand, but failed to find evidence of a genetic effect in the development of OA of the hip or knee. MacGregor et al. (2000) have examined the genetic contribution to radiographic hip OA in women and concluded that the genetic contribution is significant, and accounts for approximately 60% of the variation in population liability to the disease.

The American College of Rheumatology (ACR) Classification Criteria for Osteoarthritis (OA) permit the categorization of individuals for OA of the hand, knee and hip according to uniform criteria. This method of classification is of known sensitivity and specificity (Altman, 1991), and may use clinical or clinical and radiographic diagnostic techniques. In this study, we have investigated the extent to which self reported symptoms suggestive of OA are predictive of patients fulfilling the ACR Classification Criteria for OA when applied in a community-based sample. Statistical methods were used to identify the model of self-report variables which provides optimal prediction of the clinical and radiological assessments of OA, and this information was then used to investigate the genetic and environmental influences on the development of OA in a large sample of Australian twins.

Method

Sample

A study designed to cover a wide range of health issues affecting older people was undertaken as a multi-wave

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mail-out between 1993 and 1995. 2281 pairs of twins aged over 50 and listed with the Australian Twin Registry were invited to participate, by completion of a 16-page questionnaire. Included in the questionnaire were a range of psychological scales, lifestyle measures assessing smoking, alcohol consumption and physical activity, items on bones and joints, vitamins and sun exposure and a detailed disease checklist. Questionnaire responses were received from 3116 individuals (1279 complete pairs and 558 singles), with a response rate for individuals (excluding deaths and non-contacts) of 71%, and a complete pairs response rate of 61%. The group of respondents consisted of 2197 females (response rate 75%) and 919 males (63%). The mean age of respondents was 61.5 ± 8.7 years, with an age range for males of 50 to 89 years, and for females of 50 to 94 years.

Zygosity Diagnosis

Upon receipt of self-report questionnaires from pairs of twins, zygosity was decided on the basis of their responses to standard questions about similarity and the degree to which others confused them. Pairs giving inconsistent responses were recontacted for clarification. Such procedures have been shown to give at least 95% agreement with diagnosis based on extensive blood-typing (Martin & Martin, 1975; Ooki et al., 1990).

Self-report Data

In the bones and joints section of the Over 50s study, subjects were questioned about ever having experienced pain, swelling or stiffness in any joints; prior diagnosis of osteoarthritis or degenerative arthritis, rheumatoid arthritis, and other forms of arthritis or rheumatism; prior bone fracture or joint injury; radiographs taken of hands, hips or knees in the last 5 years. They were also asked to indicate on a homunculus any joints currently affected by pain or swelling. Registrants were asked to respond to these questions first considering themselves and then provide information regarding their co-twin.

Self report of pain and/or swelling in the joints of the hands, hips and knees were used as indicators of potential OA, excluding those joints indicated to have sustained prior injury. Data for the left and right sides of the body were combined. For the hands, pain or swelling in any of the DIP, PIP, MCP or CMC joints (excluding prior injury) was used as the indicator for potential osteoarthritis. Subjects indicating a history of rheumatoid arthritis were excluded from the study.

Validation Sample

From a combination of self-reported OA and involvement of target joints for OA without prior history of joint trauma, twins potentially affected by OA were identified. In contrast, those twins not identifying joint problems were categorized as being unaffected by osteoarthritis. This phase of the study required the examination of study subjects, along with taking radiographs and obtaining blood samples. Given age and condition, it was reasoned that participants would be unlikely to travel more than 50 kilometers from home. Consequently, 118 twin pairs residing in the vicinity of Brisbane or Melbourne were invited to participate: 63 pairs with at least one member potentially affected by OA (41 discordant and 22 concordant pairs) and an additional 55 unaffected pairs.

Clinical examination — Validation Sample

On the day of study, subjects were examined independently by two consultant rheumatologists, blood was taken by venepuncture, a skin mold was made and radiographs taken of hands, knees and hips. Not all twins attended in pairs although many did. They were not examined in any set order and clinical examinations were carried out in separate rooms. No discussion was allowed regarding individual examinations.

Rheumatologist Assessment — Standard Homunculus: A standard homunculus was completed by the rheumatologist for each subject to indicate whether there was evidence of OA in each of 68 peripheral joints. In order to make that decision, the rheumatologists were permitted to perform any clinical assessment, or combination of assessments, that they normally used in routine clinical practice, without reference to radiographs or laboratory test results.

Rheumatologist Assessment — ACR Clinical Criteria: Each rheumotologist also determined the presence or absence of osteoarthritis in the hands, hips and knees of each subject according to the clinical criteria developed by The American College of Rheumatology (Altman et al., 1986; 1990; 1991). Pain, morning stiffness, crepitus and bony enlargement were elicited using standard clinical techniques. Range of movement was measured using a Baseline long-arm goniometer, applied in a standard fashion. No radiographic or laboratory data were available at the time of these clinical assessments.

Rheumatologist Assessment — ACR Clinical, Radiographic and Laboratory Criteria: Following completion of the clinical portion of the study for each subject, radiographic and erythrocyte sedimentation rate (ESR) data were made available to the rheumatologists for assessment of the subject's joints according to the ACR Clinical, Radiographic and Laboratory criteria (Altman, 1991).

Radiographs

Radiographs were sent to Royal Brisbane Hospital for central reading by two consultant radiologists (PT and DW). The Burnett et al. (1994) atlas was used to compare study films against photographic standards. The radiographs were read independently by the two radiologists, blind to the original self-reported diagnosis and without reference to their pairing. The features depicted in the atlas which were used in the study were as follows: DIP-Joint Space Narrowing (JSN), Osteophytes (OP); PIP - JSN, OP; MCP - JSN, OP; 1st CMC - JSN, OP; Wrist - JSN, OP; Knee JSN, OP, Sclerosis (SCL), Tibial Spiking (SPK); Hip - JSN, OP, SCL, Cyst(CYS). The gradations permitted by the atlas were as follows: JSN 0-3, OP 0-3, SCL 0/1, SPK 0/1 and CYS 0/1. In addition, a global judgement was made by the radiologist for each joint as to whether there was evidence of OA. The left and right joints were rated separately. Following the initial reading by PT, films were selected for repeat reading by both radiologists. Those films were selected because they represented a cross-section of films from normal through mild or moderate to severe OA

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in the three areas of anatomic interest. Rereading was performed over a period of several months following the initial reading. The films from 70 subjects were assessed four times (i.e. twice by PT and twice by DW); the films from 30 subjects were assessed twice (i.e. once by PT and once by DW); and the films from 59 subjects were read once only by PT.

Statistical Methods

Osteoarthritis modelling using self-report data: Logistic regression, CART (Classification and Regression Trees; Breiman et al., 1984), MARS (Multivariate Adaptive Regression Splines; Friedman, 1991) and RDA (Regularised Discriminant Analysis; Friedman, 1989) methods were used to construct a variety of models for osteoarthritis based on ACR clinical and radiographic classification rules. The aim of these analyses was to identify the model derived from variables from the self-report questionnaire that would provide optimal prediction of the clinical and radiological assessments of OA.

Structural Equation Modelling: Correlations between variables are calculated on the assumption that underlying each variable is a continuum of liability that is normally distributed in the population. In the case of the osteoarthritis variables considered here, there are two categories: OA present and OA absent. Polychoric correlations for monozygotic and dizygotic twin pairs were calculated separately for males and females using PRELIS 2.12, along with correlations between members of opposite-sex twin pairs.

Significant twin correlations establish the fact that there is familial aggregation for the measures of interest. Our task, however, is to distinguish between the possible mechanisms by which this familial likeness may arise. The accepted method is via structural equation modelling as implemented in LISREL, Mx, or similar packages (Neale & Cardon, 1992). One can conceive of several causes of variation, three of which (additive genetic influences 'A', non-additive genetic effects 'D' and shared environment 'C') make family members more alike than random pairs of individuals, and one of which (unique environmental experiences 'E') makes siblings different. With the limitation that shared environment and non-additive genetic effects are confounded in a study of twins reared together, the task then is to decide which combination of these parameters provides the most parsimonious explanation for the observed pattern of MZ and DZ twin correlations. Where information is available from males and females in MZ twin pairs and DZ same-sex and opposite-sex twin pairs, modelling techniques can be extended to include considerations of whether there are sex differences in the aetiology of the phenotype. The methods of structural equation modelling are readily expanded to the more complex

Table 1

Sensitivity and Specificity Values for the Hand, DIP Joints, PIP Joints, CMC Joints, Hip and Knee Using the Self-report as a Predictor of OA Diagnosed by Rheumatologist and Radiologist Assessment and ACR Criteria (Clinical; Clinical, Radiographic and Laboratory).

	NB (n = 159)		AK (n = 87)		KM (n = 30)	
Joint	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
			Rheumatologist assessment (homunculus)			
Hand	28.19	85.21	27.50	82.98	25.93	89.66
DIP	14.71	93.96	11.76	94.34	11.76	94.87
PIP	30.51	88.80	14.75	85.84	0.00	87.50
CMC	0.00	98.26	0.00	98.72	22.22	97.87
Hip	41.67	95.42	50.00	94.05	50.00	94.34
Knee	53.33	85.76	50.00	88.36	50.00	82.05
			ACR Criteria (clinical)			
Hand	65.00	79.86	85.71	80.00	0.00	75.00
Hip	44.44	95.15	NA	92.53	50.00	94.74
Knee	66.67	88.30	53.25	89.24	100.00	80.36
			ACR Criteria (clinical, radiographic and laboratory)			
Hip	41.67	95.42	57.14	94.55	33.33	94.55
Knee	67.57	88.61	55.00	90.26	100.00	80.39

	Radiologist assessment							
	PT				DW			
	Reading 1 (n = 159)		Reading 2 (n = 30)		Reading 1 (n = 100)		Reading 2 (n = 30)	
Joint	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Hand	24.68	88.37	24.37	80.00	23.74	88.52	25.71	82.86
DIP	12.37	94.31	10.00	94.87	10.48	97.37	13.16	96.88
PIP	22.46	91.06	17.98	86.00	21.69	91.45	21.13	88.41
CMC	3.85	99.16	0.00	97.65	0.00	98.73	0.00	98.04
Hip	13.51	96.09	10.53	93.91	6.25	95.00	9.09	93.91
Knee	30.13	94.67	33.33	92.19	43.14	91.28	44.00	91.11

Note: NA indicates that there were no cases rated as having OA for that joint by the ACR criterion

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questions of multivariate causation, in which one is trying to discover not only the sources of covariation (A, C or D, E), but the pattern or structure in which these differentially influence the covarying measures. The same principles of parsimony apply in arriving at the preferred model (Neale & Cardon, 1992).

Results

Validation sample

A total of 159 subjects (74 complete pairs, 11 incomplete pairs) were examined using the protocol described above. Detailed results of investigations into replication of OA diagnoses by rheumatologists and radiographers in this sample are reported elsewhere (Bellamy et al., 1999a–c). Results of sensitivity and specificity calculations comparing self-reported joint pain and/or swelling with rheumatologist and radiologist diagnoses of OA for hand (including DIP, PIP, MCP and CMC), hip and knee joints are summarised in Table 1 (sensitivity in this case is defined as the probability that self report of pain/swelling will occur if the rheumatologist/radiologist diagnoses OA at that joint, whereas specificity is the probability that pain/swelling will not be self-reported in the absence of an OA diagnosis). Also included in Table 1 are the results obtained in comparing self-reported pain and/or swelling with the ACR clinical criteria for OA of the hand, hip and knee joints and the ACR clinical, radiographic and laboratory criteria for diagnosis of osteoarthritis of the hip and knee joints only.

Using self-report of joint pain or swelling as a predictor of OA diagnosis provides a consistently high specificity (≥ 80%) across all primary joints for all radiologists and rheumatologists. However, the general level of sensitivity is quite poor (0–53%). Self report of hip and knee joint pain and swelling has substantially higher sensitivity (≥ 40%) than the joints of the hand when compared with the assessments given by all rheumatologists, but this effect is not observed for radiologists' reports. The sensitivity of self report of OA of the hand is generally improved when the self report data is compared with the results obtained from rheumatologists using the ACR clinical criterion, while the sensitivity for the hip and knee joints remained at approximately the same values for diagnoses based on both ACR clinical and ACR clinical, radiographic and laboratory criteria.

Osteoarthritis modelling using self-report data: A substantial number of variables from the self-report questionnaire were available for use in the OA models, including age, sex, height, weight, BMI (body mass index),

Table 2

Modelling of Osteoarthritis (ACR Clinical Criteria and ACR Clinical and Radiographic Criteria) Using Self-report Data. Parameters such as "Cost", "Loss" and "Weight" Represent the Cost to the Model Fit of Misclassifying an Affected Case as Unaffected. The First Three RDA Models Were Derived Using Self-reported OA, Number of Joints Affected by Pain or Swelling, and BMI, while the Second Set Were Built Using Information on Age, Sex, Height, Weight, BMI, Pain, Swelling or Stiffness in any Joint, and Pain or Swelling in Hand, Hip or Knee Joints.

Criteria					ACR Clinical Criteria			ACR Clinical and Radiographic		
Model	Procedure	Model Size	Parameters	Performance	Validation Sample False Positives	Validation Sample False Negatives	Performance	Validation Sample False Positives	Validation Sample False Negatives
1	CART	2 nodes	Cost = 5, SERULE = 1	CV_{rel} = 0.58 ± 0.125	26	7	CV_{rel} = 0.90 ± 0.128	15	13
2	CART	4 nodes	Cost = 10, SERULE = 0.1	CV_{rel} = 0.97 ± 0.225	39	2	CV_{rel} = 0.87 ± 0.166	25	9
3	CART	3 nodes	Cost = 8; SERULE = 0.1	CV_{rel} = 0.81 ± 0.195	32	4	CV_{rel} = 0.74 ± 0.143	30	5
4	MARS	1 basis fn	Weight = (2–10), mi = 1, nk = (10–30)	gcv = 0.144	26	7	gcv = 0.179	25	9
5	MARS	2 basis fns	Weight = (5–10), mi = 5, nk = (10–30)	gcv = 0.132	32	4	gcv = 0.162	30	5
6	Logistic	2 variables	Stepwise/Forward, Weight = 1	Deviance = 122.91	15	16	Deviance = 131.73	22	9
7	Logistic	6 variables	Stepwise, Weight = 10	Deviance = 351.08	31	4	Deviance = 376.46	28	5
8	RDA	3 variables	Loss = 5, Weight = 1	CV_{rel} = 0.49	49	4	CV_{rel} = 0.53	50	5
9	RDA	3 variables	Loss = 10, Weight = 1	CV_{rel} = 0.63	71	2	—	—	—
10	RDA	3 variables	Loss = 5, Weight = 10	CV_{rel} = 0.51	64	2	CV_{rel} = 0.54	62	3
11	RDA	11 variables	Loss = 5, Weight = 1	CV_{rel} = 0.49	43	4	CV_{rel} = 0.52	38	5
12	RDA	11 variables	Loss = 10, Weight = 1	CV_{rel} = 0.68	96	0	CV_{rel} = 0.53	46	4
13	RDA	11 variables	Loss = 5, Weight = 10	CV_{rel} = 0.53	37	5	CV_{rel} = 0.52	54	3

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Table 3

Prevalence Estimates and Twin Pair Correlations (with 95% Confidence Intervals) for Self-report of Osteoarthritis of the Hands, Hips and Knees.

	Site			
	Hands	Hips	Knees	Any
Prevalence Estimates				
Females	21.8%(19.8–23.9%)	10.6%(9.1–12.1%)	17.3%(15.5–19.2	45.6%(43.0–48.1%)
Males	10.5%(8.3–13.1%)	5.5%(4.0–7.3%)	12.6%(10.2–15.3%)	34.8%(31.2–38.6%)
Twin Correlations				
MZF (496 pairs)	0.469 (0.322 – 0.599)	0.334 (0.110 – 0.533)	0.365 (0.191 – 0.521)	0.410 (0.283 – 0.526)
MZM (155 pairs)	0.513 (0.190 – 0.755)	–1.000* (–1.000 – 0.318)	0.142 (–0.264 – 0.513)	0.261 (0.005 – 0.491)
DZF (270 pairs)	0.087 (–0.143 – 0.312)	0.217 (–0.103 – 0.510)	0.025 (–0.224 – 0.274)	0.221 (0.035 – 0.396)
DZM (77 pairs)	0.305 (–0.232 – 0.728)	–0.007* (–1.000 – 0.875)	0.385 (–0.111 – 0.753)	0.129 (–0.263 – 0.487)
DZFM (134 pairs)	0.026 (–0.369 – 0.420)	0.174 (–0.416 – 0.665)	0.170 (–0.186 – 0.500)	0.190 (–0.089 – 0.445)
DZMF (110 pairs)	0.497 (0.044 – 0.796)	0.314 (–0.094 – 0.681)	–0.243 (–0.658 – 0.254)	0.071 (–0.218 – 0.175)

Note:* no MZM or DZM twin pairs were found with both males meeting OA self-report criteria for the hip joint.

self-reported pain / stiffness / swelling in any joints (3 separate variables), self-reported osteoarthritis, number of joints currently affected by pain or swelling (excluding joints which had sustained prior injury), and composite measures from the homunculus indicating current pain or swelling of the hands, hips and knees. Results of a range of models fitted to the data appear in Table 2.

In most cases, little difference was observed between the models created using the ACR clinical criteria as the outcome measure and those using the ACR clinical and radiological criteria. CART models seemed to focus on self-reported OA and number of joints affected by pain or swelling, with weight or BMI (body mass index) sometimes appearing in the models. Models produced using the MARS technique were similar, also using self-reported OA and number of joints affected by pain or swelling as variables. Logistic regression models were of questionable accuracy, with the variables selected by the modelling procedure varying according to the weight and outcome measure used, while regularised discriminant analysis produced models with good false negative rates but extremely poor false positive rates.

Models 1, 3, and 5 from Table 2 appear to give the most consistently reliable results, with models 3 and 5 in particular yielding low false negative rates and reasonable false positive rates. These models can be summarised as follows:

- Model 1 (CART): At least one joint currently affected by pain or swelling versus no joints affected
- Model 3 (CART): Self-report of OA plus at least one joint reported to be currently affected by pain or swelling *vs* no self-report or no affected joints
- Model 5: (MARS):

$$\log\left(\frac{p}{1-p}\right) = -2.363 - 2.9784 \times (\mathrm{OA}_{\mathrm{SR}} - 1)_{+} \times (1 - j)_{+},$$

where $\mathrm{OA}_{\mathrm{SR}}$ is self-reported osteoarthritis (1 = yes, 2 = no) and j is the number of joints reported to be affected by pain or swelling. According to this model, subjects who have self-reported OA have a constant risk of OA diagnosis regardless of the number of affected joints marked on the homunculus, while those who class themselves as unaffected have a low base risk of OA diagnosis which rises with increasing number of joints marked on the homunculus.

Since both the CART and MARS models give very similar results, and make use of the same variables, self-report osteoarthritis (including the subcategories of OA of the hands, hips and knees) in the full questionnaire sample will be determined according to the criteria of Model 3: Self-report of OA plus at least one (hand / hip / knee) joint reported to be currently affected by pain or swelling.

Questionnaire Sample

Univariate analysis: Prevalence estimates and polychoric correlations appear in Table 3 for osteoarthritis of the hands, hips and knees, along with 95% confidence intervals. These results are from all available complete twin pairs in the questionnaire sample (496 MZ female pairs, 155 MZ male pairs, 270 DZ female pairs, 77 DZ male pairs, and 244 DZ opposite-sex pairs) and use the self-report OA criteria derived above. No significant difference in OA prevalence was found between monozygotic and dizygotic twins at any site. Self-reported OA is significantly more common in women than in men overall, as well as specifically in the hand, hip and knee joints. Correlations between members of MZ female pairs are generally higher than those observed for DZ female pairs for all three

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Table 4

Proportions of Variance of Self-reported OA due to Additive Genetic (A), Shared Environment (C), Non-additive Genetic (D) and Unique (E) Influences, with 95% Confidence Intervals. Models Allow for Separate Estimates to be Made for Women (Subscript f) and Men (Subscript m).

	Proportions of Variance — Females				Proportions of Variance — Males				Model Fit
OA Site	A_f	C_f	D_f	E_f	A_m	C_m	D_m	E_m	χ^2_{12}
Hands	0.18(0.00 – 0.56)	—	0.28(0.00 – 0.57)	0.54(0.41 – 0.69)	0.53(0.00 – 0.76)	0.00(0.00 – 0.62)	—	0.47(0.24 – 0.77)	12.41
Hips	0.12(0.00 – 0.52)	0.21(0.00 – 0.47)	—	0.67(0.48 – 0.87)	0.11(0.00 – 0.45)	0.08(0.00 – 0.45)	—	0.91(0.54 – 1.00)	19.17
Knees	0.00(0.00 – 0.47)	—	0.36(0.00 – 0.51)	0.64(0.49 – 0.81)	0.00(0.00 – 0.53)	0.24(0.00 – 0.52	—	0.76(0.46 – 1.00)	10.63
All	0.36(0.00 – 0.52)	0.05(0.00 – 0.40)	—	0.59(0.48 – 0.72)	0.25(0.00 – 0.47)	0.00(0.00 – 0.41)	—	0.75(0.54 – 0.97)	8.727

specific sites plus OA in any joint, indicating the possibility of genetic control of familial aggregation. However, this is only observed in men for self-reported OA of the hands and for OA in any joint.

Table 4 demonstrates the results of univariate structural equation modelling of self-reported OA of the hands, hips and knees, plus OA at any site. Note that for all 4 variables for females there are statistically significant familial effects, distinguishable by the confidence intervals rejecting models in which unique environment (E) accounts for 100% of the variance. In addition, these significant familial effects are demonstrated to be of genetic origin (additive genetic effects 'A' plus non-additive genetic effects 'D') for OA of the hands and knees in women. For males, statistically significant familial effects are observed for OA of the hands and OA in any joint, but it is not possible to determine whether these shared influences are genetic or environmental in origin.

In structural equation modelling, it is also possible to fit reduced models by equating or dropping various parameters from the models without significant loss of fit to the data. For OA of the hands, the most parsimonious model providing the best fit (by chi-square and Akaike Information Criteria) is an AE model consisting of the same additive genetic (46% of variance) and unique environment effects (54% of variance) for men and women (χ^2_{15} = 13.44). A similar model also provides the best fit to data for OA of the knees, with 30% of the variance in men and women attributable to additive genetic effects, and the remainder to unique environment (χ^2_{15} = 13.41). The model for OA of the hips that provides the best fit (χ^2_{15} = 20.65) is one consisting of shared environment (25% of variance for men and women) and unique environment (75% of variance). However, a model consisting of additive genetic and unique environment effects (30% and 70% of variance respectively) also provides a reasonable fit to the data (χ^2_{15} = 21.31). The most parsimonious model for OA occurring at any site is one consisting of additive genetic (37% of variance) and unique environmental effects (χ^2_{15} = 10.38), although a model consisting only of shared and unique environmental influences could not be rejected (χ^2_{15} = 15.94).

Multivariate analysis: Cross-twin cross-trait polychoric correlations were estimated using PRELIS 2.20 for each sex-zygosity group, and are shown in Table 5. The twin1-twin2 correlations for the three key variables are highlighted in bold. The benefit of multivariate analysis is that additional information about the genetic and/or environmental influences on each variable lies in all the other cross-twin cross-trait correlations involving that variable, providing additional statistical power.

Multivariate structural equation modelling based on the cross-twin cross-trait correlations in Table 5 could only be performed on the data from female twin pairs, due to numerical difficulties arising from the small numbers of affected males at each of the OA sites of interest. Figure 1 illustrates a Cholesky decomposition model, which dissects the relative contributions of genes and environment to the covariation between the three OA self-report measures. All non-zero paths of the full model are shown. This model fits

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Table 5

Polychoric Correlations for MZ and DZ Twin Pairs for Self-reported OA of the Hands, Hips and Knees for Twin 1 and Twin 2 (Twin Designated by Subscript). Correlations for MZ and DZ Pairs are Shown Above and Below the Main Diagonal Respectively for Same-sex Pairs. Results for Opposite-sex Pairs are Divided into Pairs where Twin 1 is Female (Above the Main Diagonal) and where Twin 1 is Male (Below the Diagonal). Co-twin Correlations for each Measure are Shown in Bold.

	$HANDS_1$	$HIPS_1$	$KNEES_1$	$HANDS_2$	$HIPS_2$	$KNEES_2$
			MZ Female Pairs (496 pairs)			
$HANDS_1$	—	0.242	0.306	**0.477**	0.270	0.170
$HIPS_1$	0.410	—	0.377	0.105	**0.349**	0.253
$KNEES_1$	0.463	0.595	—	0.172	0.320	**0.366**
$HANDS_2$	**0.089**	0.058	0.041	—	0.286	0.345
$HIPS_2$	0.366	**0.241**	0.188	0.466	—	0.430
$KNEES_2$	0.145	0.135	**0.026**	0.540	0.531	—
			DZ Female Pairs (270 pairs)			
			MZ Male Pairs (155 pairs)			
$HANDS_1$	—	0.661	0.467	**0.562**	0.230	0.358
$HIPS_1$	–0.788	—	0.585	0.223	**0.115**	0.206
$KNEES_1$	0.393	0.511	—	0.092	0.484	**0.274**
$HANDS_2$	**0.350**	–0.716	–0.846	—	0.553	0.473
$HIPS_2$	0.299	–0.667	0.701	0.476	—	0.115
$KNEES_2$	–0.166	–0.788	**0.393**	0.050	0.299	—
			DZ Male Pairs (77 pairs)			
			DZ Opposite-sex pairs (Female — Male) (134 pairs)			
$HANDS_1$	—	0.617	0.380	**0.191**	0.625	0.201
$HIPS_1$	0.132	—	0.680	0.400	**0.472**	0.376
$KNEES_1$	0.203	0.186	—	0.147	0.254	**0.284**
$HANDS_2$	**0.461**	–0.178	0.161	—	0.309	0.686
$HIPS_2$	0.186	**0.328**	–0.057	0.224	—	0.766
$KNEES_2$	0.028	–0.066	**–0.231**	0.161	0.112	—
			DZ Opposite-sex pairs (Male — Female) (110 pairs)			

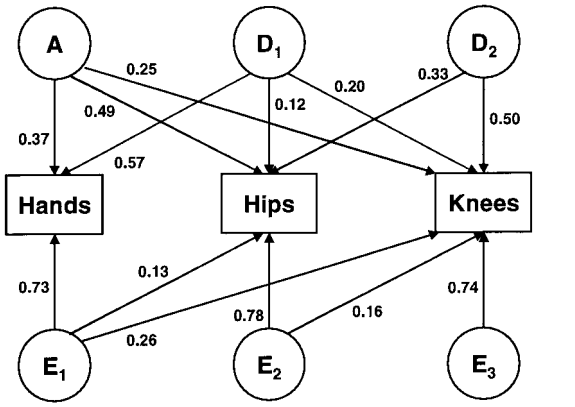

Figure 1

Cholesky decomposition model of osteoarthritis of the hands, hips and knees. Latent genetic environmental influences (in circles) on the measured phenotypes of OA of the hands, hips and knees (shown in rectangles). 'A' represents an additive genetic factor, 'D_1' and 'D_2'' are non-additive genetic factors and 'E1', 'E2' and 'E3' are unique environmental factors. All non-zero paths of the model are shown, with numbers by paths representing path coefficients which must be squared to obtain proportions of variance of the measured variable accounted for by the latent variable.

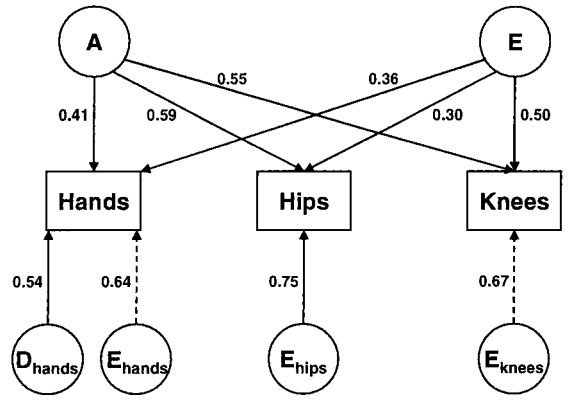

Figure 2

Independent pathway model of osteoarthritis of the hands, hips and knees, and a submodel of that shown in Figure 1. Notation is identical to that of Figure 1, except that statistically non-significant paths are denoted by a dotted path vector.

the available data very well (χ^2_{16} = 18.08, p = 0.319), and provides a superior fit to the data than one including shared environment instead of non-additive genetic effects (χ^2_{16} = 21.77, p = 0.150).

As with the univariate modelling, it is possible to fit reduced Cholesky models by equating or dropping various parameters from the models without significant loss of fit to the data. Figure 2 illustrates an independent pathway model (Kendler et al., 1987) of the data, so-called because the model includes common factors each with their own pathways to the individual variables. In this model, the same additive genetic effects explain approximately 17%,

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35% and 30% of the variation between individuals in OA of the hands, hips and knees respectively in women. Statistically significant non-additive genetic effects are only seen in OA of the hands, accounting for a further 29% of variance. The remainder of the variance is attributable to unique environment effects, of which a substantial percentage (14% to 35%) is common to OA at all three sites. Inclusion in the model of shared environmental effects for any variable resulted in no improvement on the fit of the model.

Discussion

The exact prevalence of OA in Australia has not been clearly defined. Self-reported OA in the Dubbo study occurred in 25% of subjects aged over 60 years (Jones et al., 1995). In a Swedish twin study of self-reported joint pain, involving subjects in the age range for OA (45–89 years), 22% of the women and 19% of the men reported having joint pain (Charles et al., 1999). Recent US-based studies have reported the estimated prevalence of hand OA at 19–26% (Sowers et al., 2000; Hirsch et al., 2000), knee OA at 9–23% (Sowers et al., 2000) and hip OA at 3–6% (Hoaglund et al., 2001) in various population subgroups.

Results from this study are based on self-report variables that were found to provide optimal prediction of ACR clinical and radiographic classification criteria for OA. This provides some of the benefits of using a standard classification method (Altman, 1999), combined with the statistical power and logistical advantages of a larger study sample in which individual clinical and radiographic examination of each subject is not required. In addition, many of the potential problems of case ascertainment bias were avoided by using a population-based cohort of twins. Although the use of different diagnostic criteria for OA would obviously provide different individual diagnoses and prevalence rates in a given sample, it should be noted that a previous twin study of the aetiology of osteoarthritis (Spector et al., 1986) found that estimates of the genetic and environmental influences on OA remained consistent regardless of whether radiographic diagnosis or joint pain was used as the clinical criteria.

This study found that significant genetic effects contribute to osteoarthritis in women, with broad heritability estimates (additive + non-additive genetic effects) of approximately 46% (32–59%) for OA of the hands, 35% (19–52%) for OA of the hips and 30% (17–45%) for OA of the knees. These estimates are somewhat lower than, but still consistent with, the results of the study by Spector et al. (1996), which found estimates ranging from 39 to 65% for OA of the hands and knees. In addition, the present study has demonstrated that the same additive genetic effects (and, to a certain extent, the same unique environmental effects) contribute to osteoarthritis in various parts of the body. However, the current study was unable to determine whether the familial aggregation of osteoarthritis in men is due to genetic or shared environmental effects, in contrast to the study of Finnish twins by Kujala et al. (1999), which found significant shared environmental effects contributing to OA in men.

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References

Altman, R. D. (1991). Criteria for classification of clinical osteoarthritis. *Journal of Rheumatism, 18,* 10–11.

Altman, R., Alarcon, G., Appelrouth, D., Bloch, D., Borenstein, D., Brandt, K., Brown, C., Cooke, T. D., Daniel, W., Feldman, D., et al. (1991). The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis and Rheumatism, 34,* 505–514.

Altman, R., Alarcon, G., Appelrouth, D., Bloch, D., Borenstein, D., Brandt, K., Brown, C., Cooke, T. D., Daniel, W., Gray, R., et al. (1990). The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis and Rheumatism, 33,* 1601–1610.

Altman, R., Asch, E., Bloch, D., Bole, G., Borenstein, D., Brandt, K., Christy, W., Cooke, T. D., Greenwald, R., Hochberg, M., et al. (1986). Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis and Rheumatism, 29,* 1039–1049.

Bellamy, N., Klestov, A., Muirden, K., Kuhnert, P., Do, K-A., O'Gorman, L., & Martin, N. G. (1999a). Perceptual variation in categorising individual peripheral joints for the presence or absence of osteoarthritis using a standard homunculus: Observations based on an Australian Twin Registry study of osteoarthritis. *Inflammopharmacology, 7,* 37–46.

Bellamy, N., Klestov, A., Muirden, K., Kuhnert, P., Do, KA., O'Gorman, L. & Martin, N. G. (1999b). Perceptual variation in categorising individuals according to American College of Rheumatology classification criteria for hand, knee and hip osteoarthritis (OA): Oservations based on an Australian Twin Registry study of OA. *Journal of Rheumatology, 26,* 2654–2658.

Bellamy, N., Tesar, P., Walker, D., Klestov, A., Muirden, K., Kuhnert, P., Do, K-A., O'Gorman, L., & Martin, N. G. (1999c). Perceptual variation in grading hand, hip and knee radiographs: Observations based on an Australian Twin Registry study of osteoarthritis. *Annals of Rheumatic Diseases, 58,* 766–769.

Bijkerk, C., Houwing-Duistermaat, J. J., Valkenburg, H. A., Meulenbelt, I., Hofman, A., Breedveld, F. C., Pols, H. A., van Duijn, C. M., & Slagboom, P. E. (1999). Heritabilities of radiologic osteoarthritis in peripheral joints and of disc degeneration of the spine. *Arthritis and Rheumatism, 42*, 1729–1729.

Breiman, L., Friedman, J. H., Olshen, R. A., & Stone C. J. (1984). *Classification and regression trees.* Monterey, CA: Wadsworth & Brooks/Cole.

Brooks, P. M., & Hart, J. A. L. (2000). The bone and joint decade 2000–2010. *Medical Journal of Australia, 172,* 307–308.

Burnett, S., Hart, D. J., Cooper, C., & Spector, T. D. (1994). *A radiogrraphic atlas of osteoarthritis.* London: Springer-Verlag.

Charles, S. T., Gatts, M., Pedersen, M. L., & Dahlberg, L. (1999). Genetic and behavioural risk factors for self-reported joint

https://doi.org/10.1375/twin.5.2.98 Published online by Cambridge University Press

pain among a population-base sample of Swedish twins. *Health Psychology, 18*(6), 644–654.

Friedman, J. H. (1991). Multivariate Adaptive Regression Splines. *Annals of Statistics, 19,* 1–141.

Friedman, J. H. (1989). Regularized discriminant analysis. *Journal of the American Statistical Association, 84,* 165.

Heinegar, D., Bayliss, M., & Lorenzo, P. (1998). Biochemistry and metabolism of normal and osteoarthritic cartilage. In K. D. Brandt, M. Doherty, & L. S. Lohmander (Eds.), *Osteoarthritis* (pp. 74–84). Oxford: Oxford University Press.

Hirsch, R., Guralnik, J. M., Ling, S. M., Fried, L. P., & Hochberg, M. C. (2000). The patterns and prevalence of hand osteoarthritis in a population of disabled older women: The Women's Health and Aging Study. *Osteoarthritis Cart, 8*(Supp. lA), S16–21.

Hoaglund, F. T., & Steinbach, L. S. (2001). Primary osteoarthritis of the hip: Etiology and epidemiology. *The Journal of the American Academy of Orthopaedic Surgeons, 9*(5), 320–327.

Jones, G., Nguyen, T., Sambrook, P. N., Lord, S. R., Kelly, P. J., & Eisman, J. A. (1995). Osteoarthritis bone density, postural stability and osteoporotic fractures — a population based study. *Journal of Rheumatology, 22*(5), 921–925.

Kujala, U. M., Leppavuori, J., Kaprio, J., Kinnunen, J., Peltonen, L., & Koskenvuo, M. (1999). Joint-specific twin and familial aggregation of recalled physician diagnosed osteoarthritis. *Twin Research, 2,* 196–202.

MacGregor, A. J., & Spector, T. D. (1999). Twins and the genetic architectural osteoarthritis. *Rheumatology, 38,* 583–590.

Martin, N. G., & Martin, P. G. (1975). The inheritance of scholastic abilities in a sample of twins. I. Ascertainments of the sample and diagnosis of zygosity. *Annals of Human Genetics, 39,* 213–218.

Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families.* Dordrecht: Kluwer Academic Publishers.

Ooki, S., Yamada, K., Asaka, A., & Hayakawa, K. (1990). Zygosity diagnosis of twins by questionnaire. *Acta Geneticae Medicae et Gemellologiae, 39,* 109–115.

Macgregor, A. J., Antoniades, L., Matson, M., Andrew, T., & Spector, T. D. (2000). The genetic contribution to radiographic hip osteoarthritis in women. *Arthritis and Rheumatism, 43*(11), 2410–2416.

Spector, T. D., Cicuttini, F., Baker, J., Loughlin, J., & Hart, D. (1996). Genetic influences on osteoarthritis in women: A twin study. *British Medical Journal, 13,* 940–943.

Sowers, M., Lachance, L., Hochberg, M., & Jamadar, D. (2000). Radiographically defined osteoarthritis of the hand and knee in young and middle-aged African American and Caucasian women. *Osteoarthritis Cart, 8*(2), 69–77.

Van Saase, J. L., van Romunde, L. K., Catts, A., Vandenbroucke, J. P., & Valkenburg, H. A. (1989). Epidemiology of osteoarthritis. Zoetermeer survey: Comparisons of radiological osteoarthritis in a Dutch population with that in ten other populations. *Annals of Rheumatic Diseases, 48*(4), 271–280.

https://doi.org/10.1375/twin.5.2.98 Published online by Cambridge University Press