Papers

Assessment of a genetic contribution to osteoarthritis of the hip: sibling study

Peter Lanyon, Kenneth Muir, Sally Doherty, Michael Doherty

Abstract

Objectives To study the influence of genetics on the development of hip osteoarthritis as determined by structural change on plain radiographs.
Design Sibling study.
Setting Nottinghamshire, England.
Participants 392 index participants with hip osteoarthritis of sufficient severity to warrant total hip replacement, 604 siblings of the index participants, and 1718 participants who had undergone intravenous urography.
Main outcome measure Odds ratios for hip osteoarthritis in siblings.
Results The age adjusted odds ratios in siblings were 4.9 (95% confidence interval, 3.9 to 6.4) for probable hip osteoarthritis and 6.4 (4.5 to 9.1) for definite hip osteoarthritis. These values were not significantly altered by adjusting for other risk factors.
Conclusion Siblings have a high risk of hip osteoarthritis as shown by structural changes on plain radiographs. One explanation is that hip osteoarthritis is under strong genetic influence.

Introduction

Osteoarthritis of the hip is a major cause of pain and disability in the community, resulting in high medical and social costs.[1] For any individual, development of hip osteoarthritis is likely to be multifactorial and depends on individual constitutional and "genetic" susceptibility and local mechanical risk factors. The most studied risk factors associated with hip osteoarthritis are obesity, heavy lifting at work (particularly in farm labourers), and developmental dysplasia, although few cases can be directly attributable to such risk factors in the United Kingdom.[2–7]

Evidence for a genetic predisposition to osteoarthritis is strongest in the subset of patients with generalised nodal osteoarthritis. This was initially reported half a century ago, although robust epidemiological evidence has only recently been forthcoming.[8] In a classic twin study, the heritability was estimated as 39% for osteoarthritis of the knee and 65% for osteoarthritis of the hand.[9] Further evidence of familial aggregation of hand and knee osteoarthritis has come from cohort studies of volunteers in Framingham and Baltimore.[10] [11] Neither study has, however, reported data for hip osteoarthritis, partly because of its lower prevalence compared with hand and knee osteoarthritis. Although there have been two previous attempts to determine whether hip osteoarthritis clusters in families, these studies have been either small or based on questionnaire responses only, with inadequate control groups.[12] [13] We aimed to determine whether there is an important genetic influence on the development of hip osteoarthritis and, if so, whether this relation is independent of other risk factors such as body mass index and nodal status.

Participants and methods

Approval for our study was obtained from the research ethics committees of Nottingham City Hospital and north Nottinghamshire. We compared the prevalence of hip osteoarthritis, as determined by structural changes on plain radiographs, in two groups of participants. These groups differed only in their level of exposure to a genetic risk of hip osteoarthritis. The groups comprised: (*a*) index participants with primary hip osteoarthritis of sufficient severity to warrant a total hip replacement, a surrogate measure of severe symptomatic and structural disease[3] [14]; (*b*) siblings of these index participants, who have a high exposure to genetic risk of hip osteoarthritis; and (*c*) participants who had undergone intravenous urography (urography participants), assumed to represent the average genetic susceptibility of the general population. There is no theoretical reason why these participants should be at any increased or decreased risk of having hip osteoarthritis.

Case ascertainment

Index participants
We identified index participants as patients who had undergone a total hip replacement (primary or revision) at two major orthopaedic centres in Nottinghamshire (Nottingham City and Harlow Wood Hospital) between 1990 and 1996 or who were awaiting this procedure. We only included patients if they had a diagnostic code of primary hip osteoarthritis, and we excluded patients aged over 90 or those who had had surgery at under 40. Index participants were sent a questionnaire designed to examine risk factors for hip osteoarthritis, including height, weight, job title, and self reported finger nodes using a validated diagram ("nodal" was defined as one Heberden's node on at least one finger of each hand).[15]

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Respondents were asked to provide the names and addresses of all living siblings, irrespective of loss of regular contact or whether the sibling had known joint problems. A reminder was sent to non-responders after 4-6 weeks.

Siblings

We identified siblings from the above responses. For practical reasons we elected to study only Nottinghamshire residents. An identical questionnaire was mailed to the siblings, including an invitation to undergo pelvic radiography. We excluded siblings aged under 40 because the low prevalence of change identified by radiography below this age did not justify exposure to radiation.

We emphasised that the invitation was regardless of hip pain or arthritis, and we requested that the questionnaires were returned even if radiography was not wanted. A reminder was sent to non-responders after 4-6 weeks.

Urography participants

We obtained the radiographs of patients aged 40-85 years who had undergone intravenous urography between 1994 and 1996. We also included in the study a "control" urogram that visualised the pelvis, if available. To increase study power, we aimed to recruit about three times as many urography participants of the same sex and similar age (within two years) than siblings. Those alive in 1998 were sent a questionnaire inquiring about risk factors for hip osteoarthritis.

Radiographic assessment

To enable a direct comparison of radiographs, the siblings underwent a modified pelvic radiography with the same radiographic technique used for a "control" urogram (tube to film distance 100 cm, beam centred to allow visualisation of the L1 vertebra to the lesser trochanter). All radiographs were read blind by a single observer. Individual radiographic features of osteoarthritis (narrowing, osteophyte, sclerosis, and cysts) were graded 0-3 according to a standard atlas.[16] An overall qualitative grade of 0-5 was assigned according to a recommended method.[17] Minimum hip joint space at the site of maximum narrowing was measured by a metered dial calliper (RS Components, Switzerland) to within 0.1 mm. Three standard definitions of hip osteoarthritis were utilised according to the minimum hip joint space: 2.5 mm or less (probable hip osteoarthritis), 1.5 mm or less (definite hip osteoarthritis), and an overall qualitative grade of 3-5, about equivalent to Kellgren and Lawrence grades 3-4.[17] All definitions were assumed to have been satisfied if a total hip replacement was present. Reproducibility was assessed in a subset of 40 radiographs, read blind about one month apart.

Statistics

We quantified the levels of agreement with the kappa statistic[18]; reproducibility of continuous variables was assessed by using Bland and Altman's method.[19] We performed unmatched analyses by selecting the "worst hip" per participant—that is, the one showing the greatest severity of the feature under study. We calculated odds ratios by unconditional logistic regression with SPSS.
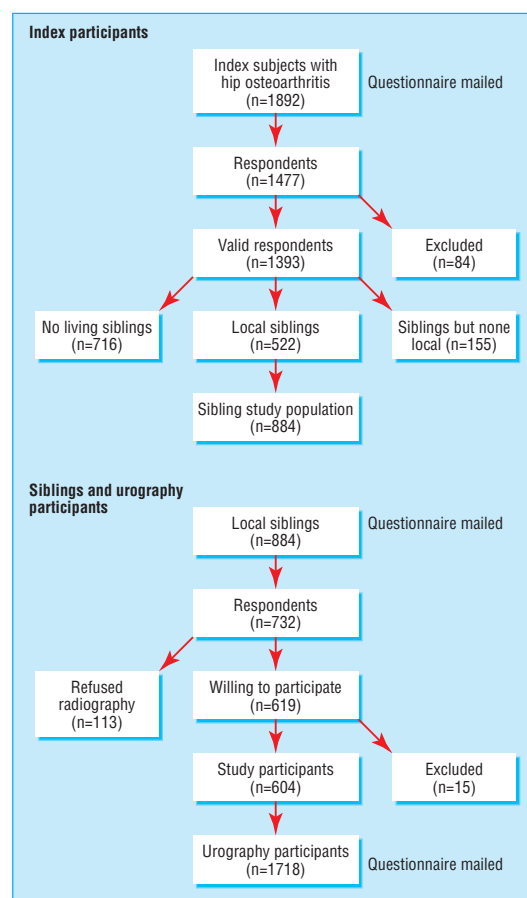

Fig 1 Recruitment of participants

Results

Questionnaires were sent to 1892 index participants, comprising 1134 women and 758 men. Overall, 1477 replies were received, a response rate of 78% (fig 1). Forty five questionnaires were returned uncompleted, and 39 subjects were excluded who indicated alternative diagnoses, the most common being rheumatoid arthritis and hip fracture (11 participants each). Of the 1393 valid respondents, 716 (51%) had no living siblings within the United Kingdom and 155 (11%) had siblings but none of whom resided locally. The remaining 522 index participants (37%) had at least one sibling resident in Nottinghamshire.

Questionnaires were sent to 884 siblings from these 522 families. Overall, 735 replied, a response rate of 83% (fig 1). Of these respondents, 619 (84%) agreed to undergo pelvic radiography or had a pre-existing recent radiograph. Four respondents were excluded because they were under 40, and 11 were excluded because review of the radiographs of their index hip participants showed alternative diagnoses: rheumatoid arthritis (three participants), Paget's disease (one), and hip fracture (one). The remaining 604 sibling participants (354 women, 250 men) comprised 70% of all eligible local siblings and were derived from 392 families (table 1).

Overall, 1718 "control" urograms were analysed, comprising 981 women and 737 men (table 1). A further 21 were not included because the relevant urograms were missing or did not visualise the pelvis. In

Table 1 Age of participants by sex

	Index participants							
	All		With siblings*		Siblings		Controls	
	Women (n=833)	Men (n=560)	Women (n=241)	Men (n=151)	Women (n=354)	Men (n=250)	Women (n=981)	Men (n=737)
Age:								
Mean (95% CI)	73 (72.4 to 73.6)	71 (70.3 to 71.7)	70.7 (69.6 to 71.8)	68.7 (67.5 to 69.9)	65.5 (64.5 to 66.5)	65.2 (64 to 66.4)	65.2 (64.6 to 65.8)	65.1 (64.4 to 65.8)
Range	42-90	46-90	43-87	51-86	42-89	41-88	43-90	43-86

*Who subsequently underwent pelvic radiography.

total, 985 replies were received from the 1442 participants still alive in 1998, a response rate of 68%.

Reproducibility

Reproducibility of the measurement of the width of the joint space was good (mean difference 0.02 mm, 95% limits of agreement 0.5 (SD) mm). Kappa values for narrowing, femoral head osteophyte, cysts, and overall grade were good (greater than 0.7), with lower values for femoral neck and acetabular osteophyte and sclerosis (see table A on website).
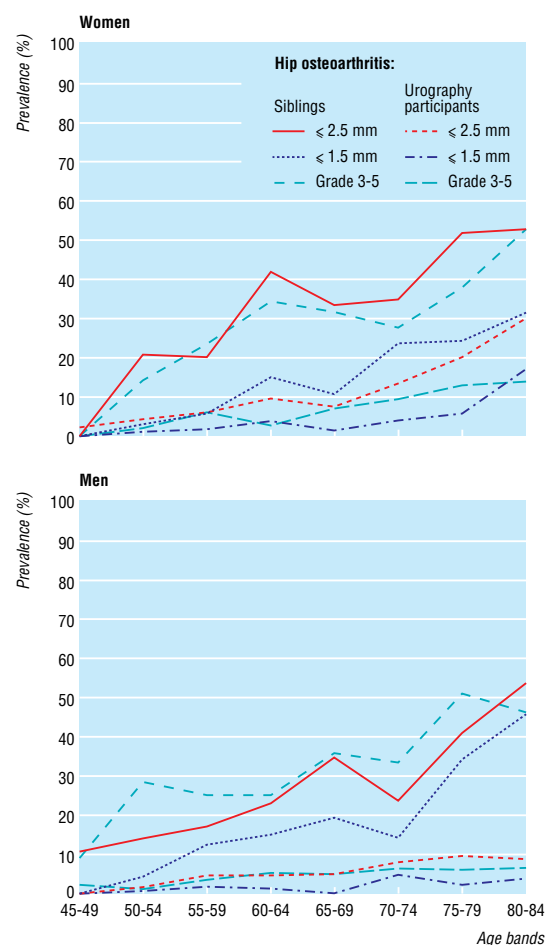
Prevalence of hip osteoarthritis

The overall prevalence of hip osteoarthritis in urography participants varied between 3.8%-11% in women and 2.1%-5.9% in men, according to disease definition (table 2). Prevalence increased with age, with a noticeable increase above 75 years found in women

Fig 2 Prevalence of hip osteoarthritis in siblings and urography participants

Table 2 Prevalence of radiographic change in siblings and controls. Values are numbers (percentages)

	Women		Men	
	Siblings (n=354)	Controls (n=981)	Siblings (n=250)	Controls (n=737)
Joint space narrowing (minimum hip joint space):				
>2.5 mm	235 (66.4)	874 (89.1)	181 (72.4)	693 (94.0)
≤2.5 mm	119 (33.6)	107 (10.9)	69 (27.6)	44 (6.0)
≤1.5 mm	52 (14.7)	40 (4.1)	46 (18.4)	15 (2.0)
Bilateral ≤2.5 mm	47 (13.3)	34 (3.5)	29 (11.6)	8 (1.1)
Osteophyte grade*:				
0	207 (64.5)	924 (89.3)	146 (64.9)	652 (86.7)
1	56 (17.4)	67 (6.5)	31 (13.8)	52 (6.9)
2	48 (15.0)	39 (3.8)	31 (13.8)	41 (5.5)
3	10 (3.1)	5 (0.5)	17 (7.6)	7 (0.9)
Narrowing grade*:				
0	162 (50.5)	840 (81.2)	118 (52.4)	636 (84.6)
1	117 (36.4)	153 (14.8)	77 (34.2)	94 (12.5)
2	29 (9.0)	32 (3.1)	16 (7.1)	14 (1.9)
3	13 (4.0)	10 (1.0)	14 (6.2)	8 (1.1)
Overall grade:				
0	131 (37.0)	738 (75.2)	104 (41.6)	563 (76.4)
1	33 (9.3)	54 (5.5)	16 (6.4)	59 (8.0)
2	86 (24.3)	120 (12.2)	47 (18.8)	78 (10.6)
3	55 (15.5)	39 (4.0)	36 (14.4)	21 (2.8)
4	14 (4.0)	14 (1.4)	18 (7.2)	8 (1.1)
5	2 (0.6)	3 (0.3)	4 (1.6)	2 (0.3)
3-5†	103 (29.1)	69 (7.0)	83 (33.2)	37 (5.3)
Total hip replacement	32 (9.0)	13 (1.3)	25 (10)	6 (0.8)

*Participants with bilateral total hip replacement excluded owing to inability to categorise osteophyte or narrowing.
†Including total hip replacement.

only (fig 2). Among siblings, prevalence was about threefold to eightfold higher (table 2). For individual radiographic features there was an increased frequency of all grades of change (1-3) in siblings.

In male siblings, the odds ratios of hip osteoarthritis were 6.4 for a minimum hip joint space of 2.5 mm or less and 11.8 for one of 1.5 mm or less; the odds were lower in females (4.5 and 4.2 respectively) and did not vary significantly according to the severity of the changes on radiography (table 3).

Selecting for analysis of only one sibling per family (using random number tables) did not alter these results. If the most severe response bias is assumed—that is, that none of the 265 non-participants had osteoarthritis, although the odds are reduced at 2.8 for probable and 4 for definite osteoarthritis, they remain highly significant.

Potential confounding factors—No significant differences were found in mean body mass index or nodal status (28% of women and 8% of men) between siblings and urography participants, and adjusting for these potential confounders did not alter the odds ratios.

Table 3 Odds ratios (95% confidence intervals) of osteoarthritis of hip in siblings. Values are adjusted for age

Definition	Women	Men	Both sexes
Minimum hip joint space:			
≤2.5 mm	4.45 (3.26 to 6.07)	6.41 (4.19 to 9.78)	5.03 (3.93 to 6.46)
≤1.5 mm	4.21 (2.76 to 6.56)	11.85 (6.39 to 21.9)	6.21 (4.36 to 8.84)
Bilateral ≤2.5 mm	4.30 (2.71 to 6.84)	12.5 (5.60 to 27.9)	5.86 (3.95 to 8.68)
Grade 3-5	5.72 (4.06 to 8.07)	9.85 (6.41 to 15.1)	7.12 (6.45 to 9.31)
Total hip replacement	7.73 (4.0 to 14.9)	14.4 (5.77 to 35.8)	9.76 (5.74 to 16.6)

Discussion

Siblings of patients who have undergone a hip replacement are at a substantially increased risk of osteoarthritis of the hip. This increased risk exists across all age groups and is present regardless of which aspects of structural change are used for disease definition. These results robustly support the hypothesis that the development of hip osteoarthritis is under strong genetic influence.

Clearly, familial aggregation of disease might also be explained by non-genetic factors, owing to siblings sharing environmental as well as genetic influences. For example, the effects of minor abnormalities of structural development or skeletal growth patterns reflecting the environment in utero might have influenced these results. This effect could have been inflated by including clusters of related individuals—that is, more than one sibling per family. Attempting to restrict these effects by analysing only one random sibling per family, however, did not alter our results. Moreover, rigorous attempts were made at several stages to exclude atypical families with developmental dysplasia; index participants were excluded if they had undergone premature surgery (more likely to be dysplasia), they had a diagnostic code other than primary hip osteoarthritis, or their questionnaire responses suggested alternative diagnoses. We are therefore confident that the participants are representative of families in the community in which one sibling has hip osteoarthritis.

It is possible that index participants may have preferentially provided details of siblings if they were known to have hip pain or arthritis. We attempted to limit this potential bias by emphasising a wish to know about all living siblings, regardless of hip pain. Only 70% of the eligible siblings participated, and it is likely that non-participants had a much lower prevalence of hip osteoarthritis. Even assuming the most severe possible bias, however, siblings remain at a significantly increased risk. For practical reasons we only studied siblings who were resident in Nottinghamshire. Although this could have introduced bias (owing to local siblings possibly sharing similar environmental or occupational influences), the main advantage of this approach was that siblings and urography participants were derived from the same geographical population.

Utilising "control" urograms is a well recognised methodology and avoids the need to radiograph a de novo population, thus limiting both exposure to radiation and costs.[17 20] The main indications are to identify calculi and assess structure in the presence of urine abnormalities or suspected malignancy. None of these conditions are known to have any positive or negative association with hip osteoarthritis. In view of these important indications, it is unlikely that hip osteoarthritis or pain would reduce the eligibility for this examination. Thus, the urography participants can be regarded as representative of the background population in terms of risk factors for hip osteoarthritis. Moreover, the prevalence of osteoarthritis in the urography participants broadly agrees with other studies.[21–25]

Our reported genetic influence is greater than in other studies. This is largely explained by methodological differences in study power and design. Lindberg reported a relative risk of 1.86 among siblings of patients who had undergone hip replacement, but utilised only an unspecified number of pre-existing pelvic radiographs rather than attempting to radiograph all siblings.[12] A UK study reported a relative risk for hip replacement of 1.78[13]; this was determined from questionnaire responses only, and spouses (who share environmental risk factors and might themselves be biased towards surgery) were the urography participant group. These differences might explain the lower risks reported.

What is already known on this topic

Osteoarthritis of the hip is a major cause of pain and disability in the community

The risk of developing hip osteoarthritis is likely to be multifactorial, depending on individual genetic susceptibility and local mechanical risk factors

Several studies have provided evidence for familial aggregation of osteoarthritis of the hand and knee

What this study adds

Siblings of patients who have undergone a hip replacement for osteoarthritis are at a substantially increased risk of hip osteoarthritis

This finding supports the hypothesis that the development of hip osteoarthritis is under strong genetic influence

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Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis

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Abstract

Objectives To assess the incidence of gastrointestinal haemorrhage associated with long term aspirin therapy and to determine the effect of dose reduction and formulation on the incidence of such haemorrhage.

Design Meta-analysis of 24 randomised controlled trials (almost 66 000 participants).

Intervention Aspirin compared with placebo or no treatment, for a minimum of one year.

Main outcome measures Incidence of gastrointestinal haemorrhage.

Results Gastrointestinal haemorrhage occurred in 2.47% of patients taking aspirin compared with 1.42% taking placebo (odds ratio 1.68; 95% confidence interval 1.51 to 1.88); the number needed to harm was 106 (82 to 140) based on an average of 28 months' therapy. At doses below 163 mg/day, gastrointestinal haemorrhage occurred in 2.30% of patients taking aspirin compared with 1.45% taking placebo (1.59; 1.40 to 1.81). Meta-regression showed no relation between gastrointestinal haemorrhage and dose. For modified release formulations of aspirin the odds ratio was 1.93 (1.15 to 3.23).

Conclusions Long term therapy with aspirin is associated with a significant increase in the incidence of gastrointestinal haemorrhage. No evidence exists that reducing the dose or using modified release formulations would reduce the incidence of gastrointestinal haemorrhage.

Introduction

The use of aspirin in the prevention of cardiovascular disease is now well established; an estimated 50 million Americans have started taking aspirin over the past two decades.[1] However, aspirin causes haemorrhagic complications. A systematic review in 1993 showed that the risk of gastrointestinal haemorrhage was significantly increased by long term aspirin.[2] Only four of the 21 trials included in that review, however, used doses below 300 mg a day. Since then, new data have become available from eight studies involving 24 964 patients taking aspirin doses of 50-162.5 mg a day.

Recent trends towards the use of lower doses have been driven by the belief that these offer a better safety profile while retaining equivalent therapeutic efficacy. Is there evidence that the risk of gastrointestinal haemorrhage is substantially reduced at lower doses, and if so, by how much? Expensive "modified release" formulations have been developed in an attempt to reduce the likelihood of adverse gastrointestinal effects. What is the evidence that they do so?

We reviewed the safety of aspirin, studying the effect of dose and formulation and incorporating the new data from the eight studies mentioned above.

Methods

The review was conducted using a defined protocol.

Inclusion criteria

Studies—We included reports if they were full journal publications of randomised controlled trials of aspirin used as an antiplatelet agent. Trials were excluded if the term "randomised" was not specifically mentioned in the report or if the investigators clearly used non-random allocation, such as by date of birth. Abstracts, review articles, case reports, clinical observations, and unpublished data were not included. Trials with fewer than 50 patients in each arm were not included in the analysis because they were unlikely to be able to detect uncommon or rare adverse effects.[3]