EXTENDED REPORT

Relative risk of knee chondrocalcinosis in siblings of index cases with pyrophosphate arthropathy

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Objectives: To examine the genetic contribution to common, apparently sporadic, radiographic knee chondrocalcinosis (CC) and pyrophosphate arthropathy (PA).
Method: (1) Design: radiographic sibling study. Comparison of the prevalences of knee CC and PA in siblings of index cases with PA with those in the community. (2) Subjects: 80 index cases with PA listed for total knee replacement; 122 of their siblings aged ≥40 years; and 1729 participants from community knee pain surveys who had undergone knee radiographs. (3) Main outcome measure: odds ratios of knee CC and PA in siblings versus community participants.
Results: The prevalence of knee CC was 13% (15/116) in the siblings and 6.9% (119/1727) in the community participants. The adjusted odds ratio (aOR) was 1.2, 95% confidence interval (CI) 0.6 to 2.3. The main risk factors for knee CC were age, knee pain, and knee OA. The prevalence of knee PA was 7% (9/122) in the siblings and 3.4% (59/1729) among the community participants (aOR = 1.1, 95% CI 0.4 to 2.7). The main risk factors for PA were age and knee pain. The age, sex, and knee pain standardised prevalence of PA in the Nottingham community aged ≥40 was 2.40%.
Conclusion: The risk of knee CC and PA in siblings of index cases with PA is no higher than that in the general population. Although rare familial CC is recognised, this study suggests that no major genetic predisposition to CC occurs in common symptomatic knee OA.

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C hondrocalcinosis (CC), refers to calcification within cartilage, and is usually due to deposition of calcium pyrophosphate dihydrate (CPPD) crystals. The sites most commonly affected are the knee, wrist, and symphysis pubis. CC is readily visualised on plain radiographs.[1] It may be asymptomatic or associated with acute and chronic pain syndromes and structural changes of osteoarthritis (OA).[2–4] In Europe the term "pyrophosphate arthropathy" (PA) is often used for the combination of CC and structural OA.[2–4] We recently reported a standardised prevalence of radiographic CC of 4.5% in Nottingham, UK, in those aged 40–79 years, rising from 4% in those aged 55–59 to 18% in those aged 80–84.[5] Similar prevalence estimates for CC have been obtained in the US Framingham cohort.[6] However, the community prevalence of PA has not been reported.

A number of risk factors for CC are recognised. Aging is a major risk factor in all studies. Joint damage and OA are also considered common predisposing factors,[2 4 7] though the association with OA may largely reflect a more direct association with osteophytes.[5] Risk factors that are considered less common or rare are familial predisposition[8] and metabolic diseases that affect inorganic pyrophosphate metabolism.[9] Most reports of familial CC are of monogenic disorders with phenotypes ranging from isolated CC to mild or severe PA, often with florid early onset polyarticular CC.[4 8] However, less florid familial forms with later onset oligoarticular CC or PA are also reported.[4 10 11]

The role of genetic factors in predisposition to common, apparently sporadic CC and PA remains unknown. Although McCarty *et al* initially found a 25% prevalence of familial CC in their case series,[12] there have been just three systematic studies, all undertaken in Spain, to determine the prevalence of CC in first degree relatives of patients with apparently sporadic CC or PA. All concur in reporting high prevalence rates of 11%,[13] 26%,[14] and 28%.[15] However, caveats to these studies include focused selection of index cases from

rheumatology units; small numbers of index cases; high non-participation rates in index cases and relatives; and, importantly, absence of a community control population. We therefore undertook the present controlled study to determine the relative risk of CC and PA in siblings of index cases with PA awaiting knee surgery. The Nottingham Total Joint Replacement Register provides a convenient cohort of index cases with clinically significant PA referred from the whole county of Nottinghamshire. We compared the prevalence of knee CC and PA in siblings of these index cases with the prevalence in a large sample of the Nottingham community, adjusting for the potential risk factors age, sex, body mass index (BMI), and presence of knee pain. A secondary objective was to determine the first ever standardised community prevalence estimate of PA.

METHODS
Approval for this study was obtained from the local research ethics committee.

Participants
Three stages were followed to identify participants: (*a*) identification of index cases aged ≥40 years awaiting total knee replacement, with both radiographic OA and CC (that is, PA); (*b*) prospective recruitment of siblings of the index cases with PA aged ≥40 years, irrespective of whether or not they had knee symptoms or known OA or CC; and (*c*) control participants in the existing databases derived from two Nottingham community knee pain studies.[16 17]

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Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CC, chondrocalcinosis; CI, confidence interval; CPPD, calcium pyrophosphate dihydrate; OA, osteoarthritis; PA, pyrophosphate arthropathy; PFJ, patellofemoral joint; TFJ, tibiofemoral joint
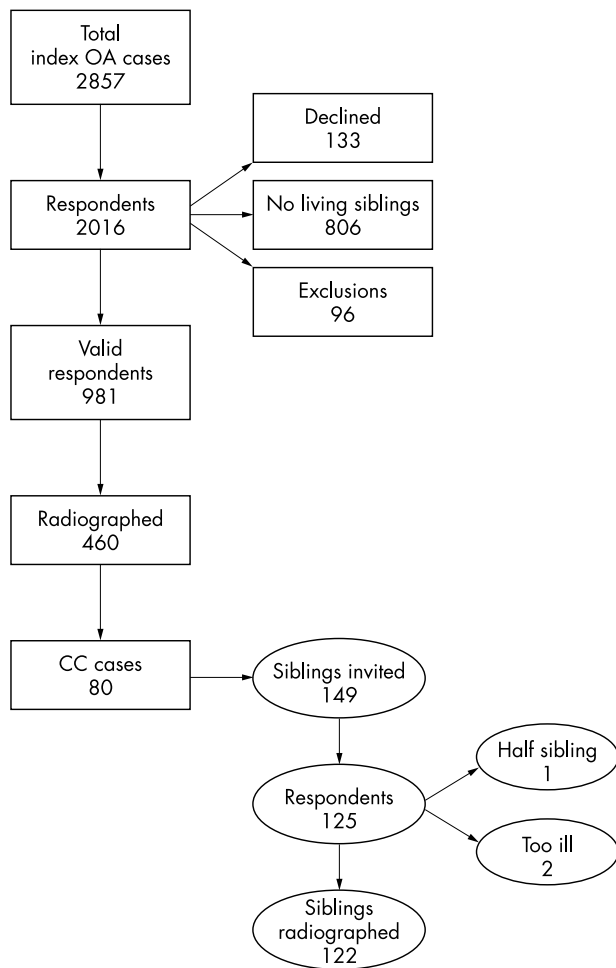
Figure 1 Recruitment of index cases and siblings.

Table 1 Characteristics of participants

Characteristics	Siblings	Community	p Value
Number	122	1729	
Age, mean (SD)	70.3 (8.3)	63.7 (9.4)	0.00
Sex, No (%)			
Male	48 (39)	644 (37.2)	0.70
Female	74 (61)	1085 (62.8)	
BMI, mean (SD)	26.6 (4.9)	26.8 (4.3)	0.52
Knee pain, No (%)	57/97 (59)	1000/1729 (57.8)	0.92

BMI, body mass index (kg/m^2); SD, standard deviation.

radiographs and metrologist examination. Exclusion criteria included total knee replacement, terminal illness, and incapacity to give informed consent.[5] [16] [17]

Data collection
Data collected from all postal questionnaires included age, sex, and presence or absence of knee pain (defined as ever having knee pain on most days for at least a month, and having pain within the past year). Metrologists measured the BMI in kg/m^2 in those who underwent radiographic examination.

Radiographic assessment
All radiographs were taken under the same standardised conditions, and were weightbearing, fully extended, antero-posterior views (55 kV, 8 mA/s, full scale deflection 100 cm), and skyline 30° flexion views (60 kV, 10 mA/s, full scale deflection 100 cm) using standard Fuji film.

A single observer (RN) read all radiographs. Sibling and community radiographs were mixed and read blind. Films were read first for OA and then for CC. An independent researcher selected 40 sets of films, representing a wide range of radiographic changes, which were re-read by the study observer to test reproducibility.

Tibiofemoral joint (TFJ) views were assigned a global Kellgren and Lawrence grade for OA.[18] An adaptation of a previously validated line drawing atlas was used to score osteophyte (0–5) at eight sites (medial and lateral femur, medial and lateral tibia, medial and lateral patella, and medial and lateral femoral trochlea).[19] Joint space narrowing was assessed for each compartment (medial TFJ, lateral TFJ, medial patellofemoral (PFJ) and lateral PFJ).

OA was defined as a Kellgren and Lawrence grade ≥2 at the TFJ, or definite joint space narrowing and definite osteophyte at the PFJ. CC was recorded as present or absent, and the site of CC (TFJ or PFJ, medial or lateral, hyaline or fibrocartilage or capsular) was recorded.

Statistical analysis
For both groups the prevalence of each of the following conditions was estimated:

- All CC (CC whether or not OA was present)
- Isolated CC (CC in the absence of OA)
- All OA (OA whether or not CC was present)
- Isolated OA (OA in the absence of CC)
- PA (CC with OA).

As the number of siblings contributed from each family was different, the risk might vary from family to family if it was not independent and hence influence the overall risk estimation for the sibling group. We therefore undertook a correlation analysis using Pearson's χ^2 test to examine whether the number of siblings contributed would influence the risk for the above conditions.

Case ascertainment
Index cases
Index cases with PA were identified from consecutive patients aged ≥40 years with knee OA who were awaiting total knee replacement at any of the three principal Nottinghamshire orthopaedic centres between 1997 and 2000. Preoperative knee radiographs were reviewed. Subjects with CC in any knee compartment were included. Index cases were sent a questionnaire asking for the contact details of all of their siblings, irrespective of whether they were thought to have arthritis. Non-responders were mailed again once after 4 weeks.

Siblings of index cases with PA
Siblings were identified from the questionnaire responses of index cases. Siblings aged <40 and half-siblings were excluded. Siblings were sent a postal questionnaire and were invited to undergo knee radiographs and metrologist examination, irrespective of whether or not they had knee symptoms or were thought to have arthritis. Those who did not reply were mailed again once after 4 weeks.

Community sample
Data and radiographs from two Nottingham community knee pain studies performed at our centre between 1995 and 1999 were used. In these studies[16] [17] random samples of people aged ≥40 years registered at general practices in Nottingham had been mailed questionnaires about knee pain, and a selection of respondents were invited to undergo knee

Table 2 Prevalence and odds ratios of knee chondrocalcinosis, osteoarthritis, and pyrophosphate arthropathy

	Prevalence (%)			
	Siblings	Community	OR (95% CI)	aOR (95% CI)
All CC	15/116 (13)	119/1727 (6.9)	2.01 (1.13 to 3.56)*	1.16 (0.58 to 2.29)
Isolated CC	6/122 (5)	60/1729 (3.5)	1.44 (0.61 to 3.40)	1.07 (0.41 to 2.78)
All OA	62/120 (52)	466/1725 (27.0)	2.89 (1.99 to 4.20)**	2.17 (1.35 to 3.48)**
Isolated OA	48/122 (39)	405/1729 (23.4)	2.12 (1.45 to 3.10)**	1.74 (1.10 to 2.76)*
PA (CC+OA)	9/122 (7)	59/1729 (3.4)	2.25 (1.09 to 4.66)*	1.09 (0.44 to 2.68)

CC, chondrocalcinosis; OA, osteoarthritis; PA, pyrophosphate arthropathy; OR, odds ratio; CI, confidence interval; aOR, adjusted OA by age, sex, BMI, knee pain, CC (for all OA only) and OA (for all CC only).
*$p \leqslant 0.05$; **$p \leqslant 0.01$.

Crude odds ratios of each condition in siblings versus community participants were calculated and adjustment made for age, sex, BMI, and knee pain using logistic regression. All analyses were undertaken using SPSS, version 11.

The age, sex, and knee pain adjusted estimate for the prevalence of PA was calculated by standardisation using data from the 1991 census[20] and the knee pain survey data.[21]

RESULTS

Response rate: index cases
Questionnaires were mailed to 2857 index cases. After the second mailing 2016 replies were received, a response rate of 70.6% (fig 1). From these, the following were excluded: 133 who did not want to participate, 806 with no living siblings, 32 who did not supply siblings' contact details, 7 with half-siblings, 30 who had died, and 27 with diagnoses other than OA. Of the remaining 981 index cases, 460 underwent knee radiographs and 80 of these had both radiographic OA and CC.

Response rate: siblings
Invitations were mailed to 149 siblings of the 80 index cases, including 15 who were not local; 125 replies were received, giving a response rate of 83.9% (fig 1). From these, one half-sibling and two siblings who subsequently were too ill to come for x ray examination were excluded.

Response rate: community sample
The overall response rate to the two community postal questionnaires was 70.1% after the second mailing; 1729 participants with radiographs were available for the analysis. Further details of this sample have been reported previously.[5]

Participant characteristics
Siblings were older than community participants, but the two groups did not differ for sex distribution, BMI, or prevalence of knee pain (table 1).

Reproducibility
Intraobserver reproducibility for Kellgren and Lawrence grade was good ($\kappa = 0.74$ for the right knee, 0.84 for the left knee). Good agreement was also seen using the line atlas. The value of κ for joint space narrowing scores ranged from 0.69 (left medial PFJ) to 0.85 (left medial TFJ). The κ value for osteophyte scores ranged from 0.70 (right lateral femur) to 0.90 (left medial trochlea). Reproducibility for the presence of CC was very good ($\kappa = 0.9$).

Prevalence of CC, OA, and PA
The crude prevalence of all CC or PA was higher among the siblings than among the community controls, but there was no difference in the prevalence of isolated CC once OA cases were excluded (table 2). By contrast, the prevalence of OA in siblings was significantly higher than in the community controls, irrespective of the presence of CC.

Adjusted odds ratios of CC, OA, and PA
Although the crude odds ratios (ORs) showed that the risk of all CC was higher in the siblings than in the community (OR = 2.01, 95% confidence interval (CI) 1.13 to 3.56), after adjusting for age, sex, BMI, knee pain, and knee OA the difference was not statistically significant (aOR = 1.16, 95% CI 0.58 to 2.29; table 2). The risk factors for all CC were age, knee pain, and knee OA (table 3). Siblings were not at increased risk. Isolated CC was associated with age only. By contrast, the risk of OA was higher in siblings. OA was also associated with age, BMI, and knee pain. However, the risk of PA was not higher in siblings after adjusting for age, sex, BMI, and knee pain. The risk factors for PA were age and knee pain only (table 3).

To examine whether the risk in the sibling group increased with the number of siblings contributed from different families, a correlation analysis was undertaken. The results showed that the risk did not increase with the number of

Table 3 Risk factors and adjusted odds ratios for knee chondrocalcinosis, osteoarthritis, and pyrophosphate arthropathy

	Sibling of PA (present/absent)	Age (per 10 year increase)	Sex (Female/male)	BMI (kg/m^2) (WHO criterion†)	Knee pain (present/absent)	CC (present/absent)	OA (present/absent)
All CC	1.16 (0.58 to 2.29)	2.25 (1.79 to 2.82)**	0.76 (0.52 to 1.10)	0.90 (0.70 to 1.14)	1.76 (1.15 to 2.69)**	N/A	1.71 (1.15 to 2.55)**
Isolated CC	1.07 (0.41 to 2.78)	1.87 (1.41 to 2.48)**	0.92 (0.55 to 1.52)	0.87 (0.63 to 1.20)	1.35 (0.80 to 2.30)	N/A	N/A
All OA	2.17 (1.35 to 3.48)**	2.15 (1.83 to 2.45)**	0.96 (0.76 to 1.21)	1.48 (1.27 to 1.71)**	3.74 (2.89 to 4.83)**	1.70 (1.14 to 2.53)**	N/A
Isolated OA	1.74 (1.10 to 2.76)*	1.85 (1.63 to 2.10)**	1.02 (0.81 to 1.29)	1.48 (1.28 to 1.72)**	3.27 (2.52 to 4.24)**	N/A	N/A
PA	1.09 (0.44 to 2.68)	2.88 (2.10 to 3.93)**	0.64 (0.38 to 1.06)	1.01 (0.72 to 1.41)	2.97 (1.68 to 5.43)	N/A	N/A

CC, chondrocalcinosis; OA, osteoarthritis; PA, pyrophosphate arthropathy; N/A, not appropriate.
*$p \leqslant 0.05$; **$p \leqslant 0.01$.
†WHO criteria for BMI: normal (<25 kg/m^2), overweight (25–29.99 kg/m^2), and obese ($\geqslant 30$ kg/m^2).
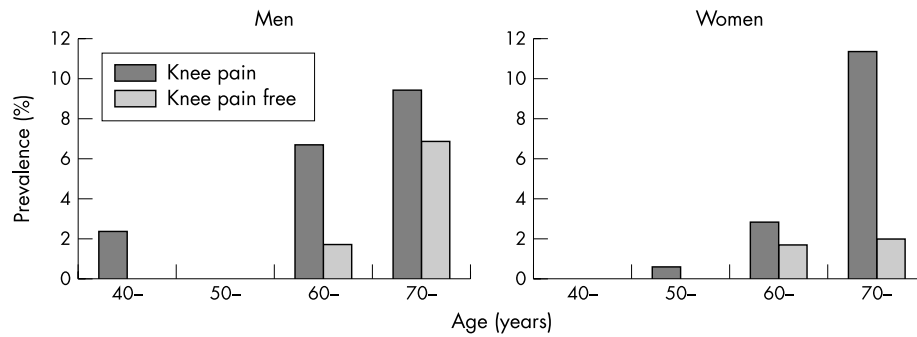
Figure 2 Prevalence of pyrophosphate arthropathy in the Nottingham community.

siblings contributed (p = 0.41, 0.37, 0.36, 0.14, and 0.66 for all CC, isolated CC, all OA, isolated OA, and PA, respectively).

Standardised prevalence of PA

Figure 2 shows the rising prevalence of PA in both men and women with age. Adjustment for age, sex, and presence of knee pain gave a standardised prevalence of 2.40% for PA in adults aged >40 in Nottingham.

DISCUSSION

This study did not show evidence of genetic predisposition to CC or PA in siblings of index subjects with symptomatic PA sufficient to warrant joint replacement. The crude prevalence of CC that we found in siblings (13%) was within the range that has been reported previously (11–28%), and is very similar to the 11% prevalence in the study by Rodriguez-Valverde et al.[13] Several factors may have led to the prevalence in our study being at the lower end of the estimates that have been reported. Firstly, we restricted the study to siblings rather than to all available relatives.[13–15] Secondly, we undertook radiographic screening of knees only, rather than knees, pelvis, and hands.[13–15] Thirdly, we selected consecutive index cases from a surgical register rather than patients from rheumatology clinics. Another factor is that we had a higher participation rate than in the other three studies and therefore possibly less selection bias towards relatives with symptomatic disease.

Importantly, our study is the only one that includes comparison of the prevalence of CC in first degree relatives with that observed in community subjects after adjustment for potential risk factors such as age and sex. Our standardised community prevalence of CC[5] is very similar to that reported in the Framingham population.[6] Direct age-sex standardisation applying our estimates to the Framingham population sample gives an expected prevalence of 10.4%, and the prevalence observed in that population was 8.1%.[6] It therefore seems unlikely that either a significant underestimation of sibling prevalence or an overestimation of community prevalence of CC explains the lack of genetic risk that we found.

We investigated risk factors for five possible situations: all CC (CC whether or not OA was present), isolated CC (CC in the absence of OA), all OA (OA whether or not CC was present), isolated OA (OA in the absence of CC), and PA (CC with OA). The risk factors examined were family aggregation, age, sex, BMI, and knee pain. Although the crude prevalence of all CC in siblings was higher than in the community (OR = 2.01, 95% CI 1.13 to 3.56), after adjusting for OA the risk of all CC in siblings did not differ significantly from that in the community. In addition to OA, risk factors for all CC were age and knee pain. However, isolated CC was associated only with advancing age. This suggests that sporadic isolated CC is predominantly an age related condition. Investigation

of the association of CC with knee pain was limited by our definition of knee pain, which predominantly relates to chronic pain. Short, self limiting episodes of pseudogout therefore might have been missed. However, the observation that knee pain was associated with each scenario except for isolated CC, suggests that it is structural change rather than CC itself that is associated with chronic pain. Unlike hospital studies, where female predominance is almost universally reported,[2 13–15 22] there was no association of CC or PA with sex. This concurs with the findings for CC among the community participants.[5] We found no association of CC with BMI. This has been examined only infrequently, the theoretical basis for such an association being that excessive mechanical loading of joints can stimulate chondrocytes to release more ATP, a potent source of extracellular pyrophosphate.[23]

None of the three scenarios of CC demonstrated statistically significant sibling aggregation. As expected, and in contrast, there was a strong genetic contribution to OA. It is noteworthy that although both familial aggregation and obesity were associated both with all OA and isolated OA, these associations were lost when OA was examined in association with PA. This might suggest that the structural changes of PA represent a distinct entity separate from OA. Previous reports have highlighted features that may distinguish PA from OA, such as marked cyst formation, a "hypertrophic" bone response with florid osteophyte formation, and an atypical distribution within and between joints.[4 24] The differences in risk factors seen in our study lend epidemiological support to the concept that PA is a discrete subset within the broad spectrum of "OA".

Absence of familial predisposition to CC and PA is consistent with recent studies of the genetics of familial CC. Mutations of the ANKH gene on chromosome 5 p have been identified as the cause of familial CC in separate kindreds from the UK, France, and the USA.[25–27] The ANKH gene encodes the ank protein that functions as an ion channel for transport of pyrophosphate across the cell membrane to the extracellular space.[25 28] A search for ANKH mutations in 95 consecutive patients referred to hospital with CC in Nottingham found a prevalence of <1%,[25] suggesting that this major cause of reported familial CC is a rare cause in community subjects with apparently sporadic CC.

There are a number of caveats to this study. Firstly, the index cases all had symptomatic PA and different results might have been obtained if index cases with asymptomatic PA or isolated CC had been included. Secondly, although the largest study of its kind, the size of the index and sibling groups remains small. Therefore, possibly, there were insufficient numbers to demonstrate a more modest genetic influence. Thirdly, the radiograph is relatively insensitive for detection of crystals, and although CPPD is the commonest

cause of radiographic CC, specific crystal identification was not attempted. Studies based on synovial fluid analysis might be more sensitive and specific for crystal detection, but such an approach is impractical for investigation of community controls. Another caveat is that we did not exclude underlying metabolic disease in participants. This is unlikely to have influenced our findings, however, because other studies that have undertaken systematic screening of family members have identified no cases of metabolic predisposition.[13 15]

This is the first study to report the community prevalence of PA (2.40%) in community subjects aged >40, standardised for age, sex, and presence of knee pain. As with CC[5] there was no difference in the prevalence of PA between women and men. This is contrary to the often marked female preponderance reported in hospital series and presumably reflects the marked confounding by age and the higher proportion of women in the older population. From these data it appears that just over half of all cases of CC in the community (standardised prevalence 4.5%) are associated with structural changes of PA.

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