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Risk factors in familial osteoarthritis The GARP sibling study

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Abstract

Purpose

To investigate the association between systemic and local risk factors and familial osteoarthritis (OA) at multiple sites.

Methods

Patients and their siblings had primary OA at multiple sites at middle age. OA diagnosis followed the American College of Rheumatology criteria. We recruited 345 controls (mean age 57 years (range 40-76), 64% women) by random sampling from the population by telephone and collected all data by questionnaires. Odds ratios (OR) were adjusted for sex, age and body mass index (BMI) kg/m², 95% confidence intervals were computed using robust standard errors with the intra-family effect taken into account.

Results

382 patients (mean age 60 years (range 43-79), 82% women) had OA in the spine (80%), hands (72%), knees (34%) and hips (24%). In women an association of familial OA with a young age at natural menopause (<45 years), OR=2.6 (CI95 1.5-4.5) was found. Physically demanding jobs led to an increased risk of familial OA in men: OR=2.6 (CI95 1.3-5.3). Familial OA was more prevalent in individuals with a BMI >30, OR=2.0 (CI95 1.3-3.2) compared to a BMI of <25. Taller persons had a lower risk of familial OA, OR=0.33 (0.1-0.8) in the height category >180 cm relative to a height of < 160 cm. A history of meniscectomy, increased the risk of familial OA at multiple sites with knee involvement, OR=6.2 (CI95 3.0-12.7).

Conclusions

Systemic and local risk factors play a role in the etiology of familial OA at multiple sites.

Key words

osteoarthritis, etiology, generalised, BMI, hormonal

Introduction

Osteoarthritis (OA) is a debilitating joint disorder with a multicausal etiology involving systemic and local risk factors. In this etiological model systemic risk factors, as age, sex, hormonal status, smoking, etc., which also include genetic factors, determine an individual's susceptibility to the impact of local risk factors, as obesity and occupations entailing high physical labor, with OA as a result in a certain joint [1]. Recently, genetic risk factors have been shown to be associated with OA, such as cytokine genes [2, 3], matrillin gene [4], and frizzled-related protein gene [5, 6]. Few data are available on the hypothesis whether, in patients with identified genetic risk factors, other systemic and local risk factors, contribute to OA development.

In the Ulm OA study, the investigators observed a positive association between knee OA and obesity, but this association was not found in the subset of patients with knee OA with concomitant polyarticular hand OA [7], a subset of OA with a strong familial predisposition, suggesting that in the presence of genetic risk factors, local factors have no additional contribution. A recent study however, by Englund et al, provided data suggesting interaction between genetic and local risk factors by demonstrating concomitant hand OA to increase the risk of knee OA after a meniscectomy [8]. Coggon et al showed that the presence of concomitant Heberden nodes increased the risk of knee OA associated with obesity, but this was not so clear for hip OA [9].

In the present study we investigated whether systemic and local risk factors are associated with osteoarthritis in an OA phenotype, where genetic risk factors have been shown to be important. In earlier publications we demonstrated that familial OA at multiple sites is associated with frizzled-related protein gene [6] and higher innate *ex-vivo* production of IL-1 β [2]. A positive association with other systemic and local factors with familial OA at multiple sites, would underscore the concept of a multicausal etiology of OA.

Material and Methods

The present study is part of the ongoing GARP study (Genetics, Arthrosis and Progression), which is described earlier [10]. The GARP study is primarily aimed at the identification of genetic determinants of OA susceptibility and progression, so Caucasian sib pairs of Dutch ancestry with predominantly symptomatic OA at multiple sites were included. This well-characterised patient population enables us to investigate the role of systemic and local risk factors in familial OA at multiple sites.

Recruitment and clinical evaluation of patients

1874 index patients (probands) aged between 40 to 70 with symptomatic OA in the hands, knees or hips, diagnosed by rheumatologists, orthopaedic surgeons and general practitioners in Leiden, The Hague, Delft, Haarlem and Amsterdam were informed of the ongoing study by mail. Of these 833 interested probands were screened by a mailed questionnaire for symptoms and signs of OA,

medical history and a family history of OA. Subsequently, eligible probands with a positive family history in first-degree relatives (n=521) were requested to introduce a sibling "with joint complaints", who was also addressed by a mailed questionnaire. Of these probands, 353 had at least one sibling with joint complaints. One hundred and thirty-nine of these siblings were either unwilling to participate (n=92) or they did not meet the GARP criteria (n=47), resulting in 214 eligible siblings. After obtaining informed consent, all siblings underwent a physical examination by a medical doctor (NR) at the outpatient clinic.

Patients with secondary OA and familial syndromes with a Mendelian inheritance pattern were excluded. Considered as secondary OA were: 1) major congenital or developmental diseases and bone dysplasias, 2) major local factors such as severe scoliosis and hypermobility, 3) certain metabolic diseases associated with joint disease such as hemochromatosis and Wilson's disease, 4) inflammatory joint diseases such as rheumatoid arthritis, 5) other bone diseases such as morbus Paget and osteochondritis and 6) intra-articular fractures. Patients with a shortened life expectancy were also excluded. Crystal deposition arthropathies (unless in the case of severe polyarticular gout), and diabetes mellitus or thyroid conditions were not considered as exclusion criteria.

OA diagnosis

Probands and siblings were included in the GARP study with OA at multiple joint sites in the hands or with OA in two or more of the following joint sites: hand, spine (cervical or lumbar), knee, or hip. Both subjects were required to have symptomatic OA (as defined below) in at least one joint site. Subjects with symptomatic OA in just one joint site were required to have structural abnormalities in at least one other joint site defined by the presence of radiographic OA or the presence of two or more Heberden nodes, Bouchard nodes or squaring of at least one carpometacarpal (CMC) 1 joint on physical examination.

Symptomatic OA in the knee and hip was defined following the American College of Rheumatology (ACR) recommendations for knee and hip OA [11, 12]. Knee OA was defined as pain or stiffness for most days of the prior month and osteophytes at joint margins of the tibiofemoral joint (x-ray spurs). Hip OA was defined as pain or stiffness in the groin and hip region on most days of the prior month in addition to femoral or acetabular osteophytes or axial joint space narrowing on radiograph. Joint prosthesis in the hips or the knees as a result of end-stage OA was included as OA in that particular joint. Spine OA (cervical and lumbar) was defined as pain or stiffness on most days of the prior month in the spine in addition to a Kellgren-Lawrence score of two in at least one disc or one apophyseal joint. OA in hand joints was defined according to the ACR criteria [13] as pain or stiffness on most days of the prior month in addition to three of the following four criteria: bony swelling of 2 or more of the 10 selected joints (bilateral DIP joints 2 + 3, bilateral PIP joints 2 + 3 and CMC 1 joints), bony swelling of 2 or more DIP joints, less than 3 swollen MCP joints and deformity of at least 1 of the 10 selected joints.

Radiographs

Conventional radiographs of the hands (dorso-volar), knees (Posterior-Anterior (PA) in weight bearing / semi flexed and lateral supine), hips (PA, weight bearing), lumbar (PA and lateral, supine) and cervical spine (Anterior-Posterior, lateral and transbuccal) were obtained from all participants. Conventional radiographs were scored by a single experienced musculoskeletal radiologist (HK) for osteophytes in the knees and hips and joint space narrowing in the hips. In addition to the hands (DIPs, PIPs and CMC1), the discs and apophyseal joints of the cervical and lumbar spine, the hips and tibiofemoral joints of the knees were also scored according to the Kellgren-Lawrence scale with the help of the original atlas [14]. This is a five point scale, scoring system with ascending severity, based on the presence of osteophytes, joint space narrowing, sclerosis and degenerative cysts. A Kellgren-Lawrence score of ≥ 2 depicts OA in a particular joint.

The intra-reader variability for the different joint sites, scored by the Kellgren-Lawrence method, depicted by the intra-class correlation-coefficient (ICC) (95% confidence interval) was for the hands 0.95 (0.92-0.96), for the knees (tibio-femoral) 0.92 (0.86-0.96), for the hips 0.95 (0.92-0.98), for the cervical spine (apophyseal and disc) 0.71 (0.52-0.84) and for the lumbar spine (apophyseal and disc) 0.67 (0.46-0.81). The intra-reader variability was based on the examination of radiographs of 40 subjects, that were selected randomly throughout the duration of the study period and were blinded for any patient characteristics.

Controls

Controls in the present study were frequency-matched to the probands for age (± 5 years) and geographic region. As the probands consisted of 162 women and 29 men, we aimed to recruit a minimal of 170 women and 100 men as controls. The controls were recruited by random sampling of the population by telephone using the Mitofsky-Waksberg method for random-digit-dialing [15], where random telephone numbers are generated and called. If a residence is contacted during the first attempt, the last two digits of that number are randomly varied and called, the Primary Sampling Unit (PSU). Within each PSU, a predetermined number of residential telephones K , is sampled. In the present study K was 10 and a telephone number was abandoned after seven failed attempts made at different times to obtain a response. Callers were given detailed instructions for the telephoning procedure and were requested to enquire for a specific person in the household on the basis of the sex and age category of the required control. The controls who were willing to participate were sent questionnaires similar to the questionnaires used in the GARP study.

Data assessment in GARP

Demographic characteristics, height, weight, hormonal status, job titles and the presence of OA symptoms were collected by standardized questionnaires and verified at the outpatient clinic.

Job title classification of physically demanding work was based on a revised classification scheme constructed according to a comprehensive occupational classification scheme by Schellart, of physical and mental work demands into different categories according to an expert judgement of job titles used in the Netherlands [16]. The category of physically demanding work is characterized by

Table 1. The characteristics of the 382 patients with familial osteoarthritis (OA) at multiple sites included in the GARP (Genetics, Arthrosis and Progression) study.

Patient characteristics	
Women, no. (%)	312 (82)
Age (years), mean (range)	60 (43-79)
BMI ¹ (kg/m ²), median (range)	26 (19-47)
Height (cm), median (range)	168 (150-196)
Weight (kg), median (range)	74 (48-125)
Affected sites with symptomatic OA, no. (%)	
Hand	276 (72)
Spine	304 (80)
Hip	93 (24)
Knee	130 (34)
Combination of sites with symptomatic OA, no. (%)	
Hand-spine	217 (57)
Hand-knee	82 (21)
Hand-hip	51 (13)
Knee-spine	104 (27)
hip-spine	78 (20)
hip-knee	29 (8)

¹body mass index**Table 2.** The odds ratio (OR) of having osteoarthritis (OA) in relation to marital status, years of formal education and smoking in 382 patients with familial OA at multiple sites included in the GARP (Genetics, Arthrosis and Progression) study and 345 controls representative of the Dutch population.

Variables	GARP	Controls	OR (CI95)*
Marital status			
Unmarried	39	68	1
Married	274	205	2.0 (1.3-3.3)
Divorced/widowed	69	70	1.2 (0.7-2.0)
Years of formal education			
0-6	159	115	1
6-12	145	134	1.0 (0.7-1.5)
>12	74	93	0.95 (0.6-1.5)
Smoking			
Never	177	133	1
Ever	138	121	1.0 (0.7-1.4)
Current	67	90	0.68 (0.4-1.0)

*adjusted for age, sex and BMI. CI95 are based on robust standard errors

lifting of heavy objects, handling of heavy tools, stooping, frequently in combination with standing or walking. Examples of occupations in this category are jobs in construction work, the agricultural sector and industry. Job title classification was done simultaneously and blinded for patients and controls.

Natural menopause was defined as the age of natural cessation of menses; all women who were premenopausal at the time of either hysterectomy or ovariectomy were not included in these analyses. Women with a unilateral ovariectomy in the history were also not eligible, because this is known to be associated with an earlier age at menopause. Further, not included in these analyses were all women whose age at menopause could not be determined with certainty due to hormone supplements. In line with other studies on this subject, early menopause was defined as natural menopause before the age of 45 [17].

Statistical analysis

OA at each site was dichotomised according to the presence or absence of OA. Odds ratios (OR) were calculated, using logistic regression, to adjust for age and sex and BMI. OR are presented with a 95% confidence interval (CI95). To take into account the intra-family effect, robust standard errors were computed using the statistical programme STATA 7.0. Continuous data were analysed using Student's t-test.

Results

Study population

After a clinical and radiographic evaluation, 382 patients (191 sib pairs) were included in the GARP study. The controls were recruited from 527 potential candidates from 1202 household contacts of the 3360 telephone numbers that were called. Of the 527 candidates, 376 (71%) were willing to participate and 345 returned a completed questionnaire.

The characteristics of the 382 patients with familial OA are shown in Table 1. The mean age of the patients was 60 years (43-79). There was a small difference between the mean age of the patients and that of the controls who were 57 years (40-76), mean difference=3.3 (CI95 2.1-4.6). The patients consisted for 82% of women in comparison to 64% women in the controls. All patients had structural abnormalities at multiple sites and nearly all patients (97%) had pain or stiffness at multiple sites. The majority of patients, n=344 (90%), had symptomatic OA at multiple sites in the hands or at two or more joint sites. The predominant form of OA in this patient population were, spine n=304 (80%) and hand OA, n=276 (72%). The combination of Hand- spine, (57%) and knee-spine, (27%) were the most common concurring forms of OA in this population.

Systemic risk factors of familial OA at multiple sites

OA was associated with married status, OR=2.0 (CI95 1.2-3.3), was unrelated to years of formal education and OA tended to be negatively associated with smoking, OR=0.68 (0.4-1.0) (Table 2).

Table 3. The odds ratio (OR) of having osteoarthritis (OA) in relation to hormonal status in 312 women with OA at multiple sites included in the GARP (Genetics, Arthrosis and Progression) study and 221 women controls representative of the Dutch population.

Hormonal status	GARP	Controls	OR (CI95)*
Hysterectomy	81	41	1.5 (0.9-2.4)
Ovariectomy	40	15	1.8 (0.9-3.4)
Age at natural menopause ¹			
< 45	52	15	2.6 (1.5-4.5)
45-52	113	88	1
>52	41	23	1.3 (0.7-2.4)
Having children (≥1 vs 0)	241	183	0.66 (0.4-1.1)
Current use of hormone supplements	21	28	0.72 (0.4-1.3)

*adjusted for age and BMI. CI95 are based on robust standard errors

¹GARP (n=206), controls (n=126)

Table 4. The odds ratio (OR) of having osteoarthritis (OA) in relation to body mass index (BMI) and anthropometrics in 382 patients with OA at multiple sites included in the GARP (Genetics, Arthrosis and Progression) study and 345 controls representative of the Dutch population

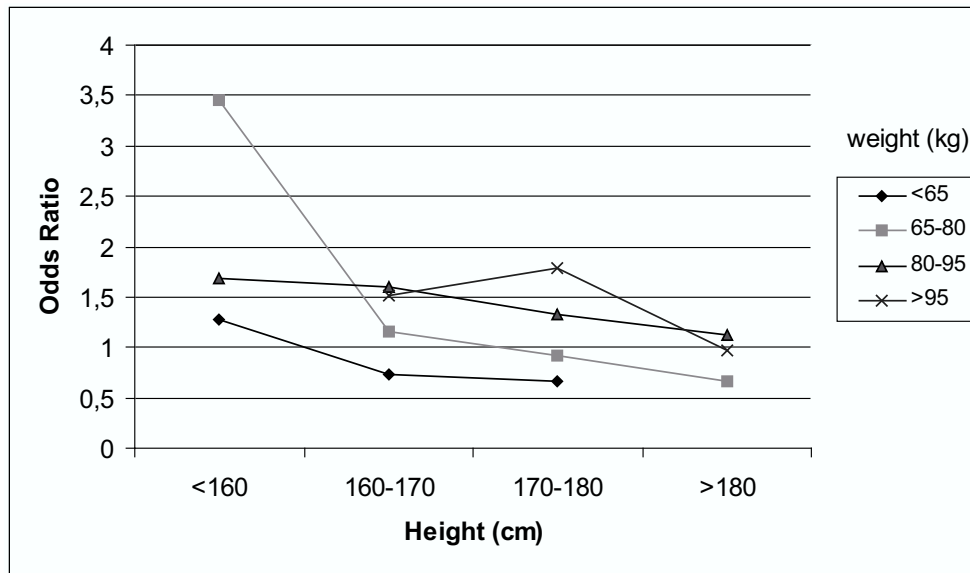
Variables	GARP	Controls	OR (CI95)*
BMI (kg/m ²)			
<25	142	183	1
25-30	156	108	1.9 (1.3-2.7)
>30	81	48	2.1 (1.3-3.3)
Height (m) ¹			
<1.60	70	32	1
1.60-1.70	191	149	0.51 (0.3-0.9)
1.70-1.80	96	110	0.47 (0.2-0.9)
>1.80	25	54	0.33 (0.1-0.8)
Weight (kg) ²			
<65	102	94	1
65-80	156	140	1.4 (1.0-2.2)
80-95	87	79	2.1 (1.2-3.5)
>95	36	32	2.0 (1.0-3.8)

*adjusted for age and sex. CI95 are based on robust standard errors

¹ additional adjustments for weight

² additional adjustments for height

Figure 1. The risk of osteoarthritis (OA) expressed in age and sex adjusted odds ratios (OR) in relation to height (cm) stratified for weight as assessed in 382 patients with familial OA at multiple sites and 345 controls representative of the Dutch population



Hormonal status in women

Of 466 women who reported to be postmenopausal, 110 did not have a natural menopause and in 24 the time of menopause could not be determined with certainty, hence 332 were included in the following analyses. An early menopause, before the age of 45 years, was associated with a three-fold risk of familial OA in relation to the reference category 45-52 years (Table 3). Further an association was seen between a history of ovariectomy and hysterectomy, and the risk of familial OA, although with wide confidence limits. Risk estimates were not different for users and non-users of hormonal supplements.

Local biomechanical risk factors of familial OA at multiple sites

Profession. Physically demanding jobs were associated with an increased risk of familial OA, OR=1.9 (95CI 1.1-3.3). Of the men who had participated in GARP, 37% had been exposed to a high workload in their lifetime in contrast to 6% of the women. When men and women were analyzed separately, the risk of OA in men with physically demanding work was OR=2.5 (1.2-5.3), while no such association was observed in women OR=1.3 (0.6-2.8).

Obesity

Familial OA was more prevalent in individuals with a high BMI: a BMI of 25-30 kg/m², OR=1.9 (1.3-2.7) and a BMI of >30 kg/m², OR= 2.1 (CI95 1.3-3.3) relative to a BMI of <25 kg/m² (Table 4). In a separate analysis of height and weight, familial OA was less prevalent in individuals taller than 180 cm relative to a height of <160 cm (Figure 1).

Risk factors of familial OA with regard to specific joint sites

The risk of familial OA at multiple sites with knee involvement ($n=130$) was increased in subjects with a history of meniscectomy, a high BMI or weight and in men, with physically demanding work; a history of meniscectomy, was associated with an $OR=6.2$ (CI95 3.0-12.7). Relative to a BMI of $<25 \text{ kg/m}^2$, a BMI of $25\text{-}30 \text{ kg/m}^2$ was associated with an $OR=2.9$ (CI95 1.8-4.9) and a BMI $>30 \text{ kg/m}^2$ was associated with an $OR=4.1$ (CI95 2.3-7.3). Relative to a weight of $<65 \text{ kg}$, the risk of familial OA with knee involvement increased in subjects of $65\text{-}80 \text{ kg}$, from $OR=1.6$ (CI95 0.9-2.9) to $OR=3.0$ (CI95 1.7-6.6) in subjects of $80\text{-}95 \text{ kg}$ to $OR=3.6$ (CI95 1.8-9.0) in weight category $>95 \text{ kg}$. Further, in men with physically demanding work the risk of familial OA involving the knee increased, $OR=4.3$ (CI95 1.7-11.4).

A separate analyses in subjects with familial OA involving the hip ($n=93$), physically demanding work was also associated with an increased risk of familial OA, $OR=3.3$ (CI95 1.3-8.2) in these subjects, but no clear association was found with a high BMI or weight.

Discussion

In the present study, we found that several risk factors, notably a married status, a high BMI, a shorter stature, in men, occupations entailing heavy physical labor and in women an early age at menopause increase the risk of familial OA at multiple sites associated with genetic risk factors. Further, a history of meniscectomy was strongly associated with familial OA at multiple sites involving the knees. This study underscores the multicausal etiology of OA.

In the present study we found an early age at menopause to be associated with familial OA at multiple sites. Variation in menopausal age has been shown to be largely heritable. Heritability estimates of up to 0.63 have been provided by two independent twin studies [17]. It has been suggested that estrogens may have a role in triggering the initial changes in proteoglycans in cartilage, either directly or indirectly via cytokines. The efficacy of this trigger may be modulated by the state of the articular cartilage and the individual's genetic make-up [18]. In humans, menopause has been associated with an increased production of interleukin-1 (IL-1) by peripheral blood mononuclear cells, a condition that may be reversed by estrogen replacement [19]. IL-1 is an important cytokine in OA. In an earlier study in the GARP sib pairs, we found that a high innate *ex vivo* production of IL-1 was associated with the risk of familial OA [2]. Given the genetic variation of age at menopause, it is conceivable that genes involved in the regulation of hormonal status in women such as the estrogen receptor alpha gene may also predispose to the susceptibility of OA. This gene was also recently shown to play a role in determining adult stature in women [20].

An important risk factor in OA, is obesity. The risk of OA in relation to BMI has been reported in several studies, investigating single joint sites [21-24]. However, to our knowledge, only one study has investigated the risk of OA at multiple sites in relation to this factor. In the Ulm OA study [25], the risk of OA at multiple sites in relation to BMI was studied. Multiple site involvement was defined as the concomitant presence of radiological OA in a number of hand joints and advanced OA in

the hip or knee joint in need of prosthesis. Interestingly, the authors found a strong association between a high BMI and knee OA but this association was absent in the 34% of these patients with generalized OA. No association was found with hip OA or with the 19% of these patients with OA at multiple sites. These findings suggest that, in presence of a systemic susceptibility for OA, BMI does not have an additional contribution to the susceptibility of knee OA. The discrepancy between findings in the present study and the Ulm study may be due to a different selection of control and case definition. In the Ulm study, rather than comparing individuals with OA to those without OA, different patterns of OA were assessed. Furthermore, although hand involvement may suggest a systemic predisposition to OA, not all patients with hand OA have a positive family history. In the present study all patients had multiple site involvement and a first degree relative with OA. Therefore, the findings in our study may be a more realistic reflection of interaction between an endogenous susceptibility to OA and BMI.

In a separate analysis of determinants of BMI, we observed that familial OA at multiple sites was less prevalent in individuals with a tall stature, after adjusting for weight, sex and age. In an earlier study by Cerhan et al, on the progression of OA in a cohort of older women, the authors found increasing height to be inversely associated with OA progression [26]. Whether a tall stature is protective for familial OA or OA in general, is unknown. Systemic disorders of the skeleton often have an endogenous, mostly heritable cause like osteochondroplasias. The pathogenetic effect on the skeleton may become manifested as a disturbance of growth and as an epiphyseal deformity and structural change [27]. In addition, aspects of skeletal size have been implicated in the risk of several diseases such as cancer and cardiovascular disease [20]. In more extreme OA phenotypes, a short stature resulting from osseous deformities is part of familial syndromes associated with severe premature OA [28]. Although these syndromes have a different genetic background than the familial OA in GARP, skeletal development may well be related to the susceptibility for OA development. One can hypothesize that increased biomechanical forces on joints in relative more compact individuals, by inducing endogenous alterations in articular cartilage biochemistry, may contribute to OA development.

Physical labor has been found in several studies to be associated with knee and hip OA [29, 30]. Knee OA has been associated with occupations such as carpenters and floor layers and activities such as stair climbing and knee bending. Farming has been shown to increase the risk of hip OA [29]. In the present study, self-reported occupations entailing physical labor relative to low or medium occupational exposure to physical labor and housekeeping, was more prevalent in individuals with familial OA at multiple sites. This association was found in men only. The lack of association in women is possibly a result of the small number of women in the GARP study and the controls that had been exposed to jobs entailing heavy physical work. This finding is also reflected in the literature, as most of these studies have assessed the risk of occupational exposure in men only [29]. A history of meniscectomy was found, in the present study, to be strongly associated with knee involvement in familial OA at multiple sites. Several studies have shown a clear relationship between prior meniscectomy and OA. In a prior study by Englund et al, patients with a hereditary risk factor of OA were shown to have an increased frequency of radiographic knee OA after meniscectomy [8].

The strong association found in the present study supports the notion that interaction between hereditary and environmental risk factors influences the development to OA.

The observation that heritable characteristics such as stature and early menopause are associated with the risk of familial OA suggests a possible shared genetic background. In this regard the finding that the FRZB locus, which plays a critical role in skeletal and joint patterning in embryogenesis [5], is associated to Hip OA in women in a UK study [31] and to the presence of OA at multiple joint sites in GARP [6] is highly relevant.

The patient population included in the GARP study represents a population with symptomatic familial OA at multiple sites with a relatively early onset between the ages 40 to 70 years. To our knowledge the prevalence of this OA phenotype in the population, has not been established. In a population based study by Mannoni et al, the prevalence of symptomatic hand, hip and knee OA was assessed in an older rural population. OA at multiple sites was found to be present in 9% of the screened individuals [32]. This is comparable to the prevalence of OA in the Rotterdam population-based study [33], where generalized radiological OA has been reported to occur in 23% of the population aged 55-70 [6]. The controls in the present study were not screened for the presence of familial OA, since the controls should represent the source population for the cases, not the entire nondiseased population [34]. Further, inclusion of patients with familial OA at multiple sites in the controls and hence, misclassification, would lead to an underestimation of the presented OR in the present study.

In the present study, we sought to investigate the effect of systemic and local risk factors on the risk of OA in a subset of patients with a clear genetic predisposition for OA. Patients with this phenotype are believed to have a faster disease progression [35] and consequent disability, constituting a patient population with an important social and economic impact as a result of OA. Insight in the etiological determinants in this phenotype, will not only lead to a better understanding of the pathophysiology of this disorder, but may also provide us with management options. Preventive measures, such as weight reduction, shown to reduce the risk of knee OA [36], may be of particular importance in these patients. The result of the present study underscores the multicausal etiology of this disease. In patients with familial OA, mechanical factors were particularly important in the occurrence of knee OA.

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