

## Review

# What epidemiology has told us about risk factors and aetiopathogenesis in rheumatic diseases

Jacqueline E Oliver and Alan J Silman

Arthritis Research Campaign, Copeman House, St Mary's Court, St Mary's Gate, Chesterfield, Derbyshire, S41 7TD, UK

Corresponding author: Alan J Silman, [a.silman@arc.org.uk](mailto:a.silman@arc.org.uk)

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## Abstract

This article will review how epidemiological studies have advanced our knowledge of both genetic and environmental risk factors for rheumatic diseases over the past decade. The major rheumatic diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, scleroderma, osteoarthritis, gout, and fibromyalgia, and chronic widespread pain, will be covered. Advances discussed will include how a number of large prospective studies have improved our knowledge of risk factors, including diet, obesity, hormones, and smoking. The change from small-scale association studies to genome-wide association studies using gene chips to reveal new genetic risk factors will also be reviewed.

valuable and robust information. Unfortunately, epidemiological data often are obtained from retrospective studies and underpowered case-control studies, resulting in contradictory findings (for example, studies on the role of caffeine in RA). Although some of the studies have found significant associations with novel risk factors, these studies often suffer from poor design. Meta-analyses have also been performed in an attempt to form conclusions from the available epidemiological data and these are also discussed.

## Introduction

This article will review epidemiological studies that have advanced the knowledge of both genetic and environmental risk factors for the rheumatic diseases, outlining the major advances that have been achieved over the past decade (Table 1). It will focus on the following diseases: rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), scleroderma (Scl), osteoarthritis (OA), gout, and fibromyalgia (FM) and chronic widespread pain (CWP).

Over the past decade, genetic research has moved from the approach of small-scale association studies, to test for candidate genes in case-control studies, to whole-genome scans of linkage based on sibling pairs which proved to be limited in the small numbers of both pairs and markers (both in the hundreds). The more recent and exciting approach has been genome-wide association studies using gene chips which have allowed hundreds of thousands of single-nucleotide polymorphisms (SNPs) to be investigated as exemplified by the Wellcome Trust Case-Control Consortium (WTCCC) study of common diseases (including RA) [7]. The advantage to this approach is clearly the opportunity to identify novel genes for the diseases; however, the disadvantage is that it results in large numbers of hints that require verification in further studies to validate the results.

A number of large prospective studies have improved our knowledge of risk factors: the Framingham Study [1] and the Chingford 1000 Women Study [2] for OA, the Nurses' Health Study cohort for RA [3] and SLE [4], the European Prospective Investigation of Cancer in Norfolk (EPIC-Norfolk) for inflammatory polyarthritis [5], and the Health Professionals Follow-up Study for gout [6]. These types of studies provide

In general, the studies discussed in this review identify risk factors in whole populations of patients with the disease but it is more likely that each of the individual disease phenotypes results from a number of different combinations of genetic and environmental risk factors. Thus, some risk factors may

*ADAM12* = a disintegrin and metalloproteinase domain 12; AS = ankylosing spondylitis; BMI = body mass index; CARD15 = caspase recruitment domain 15; CMC = carpometacarpal; CWP = chronic widespread pain; CYP2D6 = cytochrome P450 2D6; DIP = distal interphalangeal; FM = fibromyalgia; FRZB = frizzled-related protein-3; HPA = hypothalamic-pituitary-adrenal; IL = interleukin; JIA = juvenile idiopathic arthritis; LOD = logarithm of the odds; MCP = metacarpophalangeal; MHC = major histocompatibility complex; MICA = class I major histocompatibility complex chain-related gene A; MIF = migration inhibitory factor; NARAC = North American Rheumatoid Arthritis Consortium; OA = osteoarthritis; OR = odds ratio; PADI4 = peptidyl arginine; PsA = psoriatic arthritis; PTPN22 = protein tyrosine phosphatase; RA = rheumatoid arthritis; RF = rheumatoid factor; RR = relative risk; Scl = scleroderma; SE = shared epitope; SLE = systemic lupus erythematosus; SNP = single-nucleotide polymorphism; TGF = transforming growth factor; TNF = tumour necrosis factor; VDR = vitamin D receptor; WTCCC = Wellcome Trust Case-Control Consortium.

**Table 1****Risk factors for the major rheumatic diseases over the past 10 years**

Disease	Host/Environmental risk factor	Gene
Rheumatoid arthritis	Diet (caffeine and Mediterranean diet) Smoking Hormones	<i>PTPN22</i> <i>PADI4</i> <i>CTLA4</i> <i>FCRL3</i> <i>MHC2A</i> <i>HLA DRB1</i>
Juvenile idiopathic arthritis		Macrophage inhibitory factor ( <i>MIF</i> ) <i>PTPN22</i> <i>NRAMP1</i> <i>IL-6</i>
Psoriatic arthritis	Rubella vaccination Injury requiring medical consultation Recurrent oral ulcers Moving house Corticosteroids Pregnancy	<i>CARD15</i> <i>MICA</i> <i>TNF</i> <i>IL</i>
Ankylosing spondylitis		<i>ARTS1</i> <i>IL-23R</i> <i>IL-1</i> gene cluster Cytochrome P450 2D6 ( <i>CYP2D6</i> ) gene
Systemic lupus erythematosus	Breast-feeding Early natural menopause Lipstick	<i>MHC</i> <i>ITGAM</i> <i>IRF5</i> <i>BLK</i> <i>STAT4</i> <i>PTPN22</i> <i>FCGR2A</i>
Scleroderma	Exposure to silica or organic solvents	Familial risk <i>HLA-DQA1</i> Fibrillin-1 SNP haplotypes <i>TGF-β</i> <i>CTGF</i> Foetal microchimerism
Osteoarthritis	Obesity/Body mass index Physical activity Grip strength Previous injury	<i>IL-1</i> gene cluster Frizzled-related protein-3 ( <i>FRZB</i> ) gene Matrilin-3 gene <i>IL-4</i> receptor Metalloproteinase gene <i>ADAM12</i> Asporin ( <i>ASP</i> ) gene Estrogen receptor
Gout	High purine diet Dairy products Hypertension Pharmacologic agents	<i>TNF-α</i> promoter
Fibromyalgia and chronic widespread pain	Physical trauma Somatisation Health-seeking behaviour Poor sleep	Serotonin transporter gene Familial risk <i>COMT</i>

*ADAM12*, a disintegrin and metalloproteinase domain 12; *ARTS1*, type 1 tumor necrosis factor receptor shedding aminopeptidase regulator; *BLK*, B lymphoid tyrosine kinase; *CARD15*, caspase recruitment domain 15; *COMT*, catechol-O-methyltransferase; *CTGF*, connective tissue growth factor; *CTLA4*, cytotoxic T lymphocyte-associated antigen-4; *FCGR2A*, Fc fragment of IgG, low-affinity IIA, receptor (CD32); *FCRL3*, Fc-receptor like-3; *IL*, interleukin; *IRF5*, interferon regulatory factor 5; *ITGAM*, integrin, alpha M; *MHC*, major histocompatibility complex; *MHC2A*, major histocompatibility complex 2A; *MICA*, class I major histocompatibility complex chain-related gene A; *NRAMP1*, natural-resistance-associated macrophage protein 1; *PADI4*, peptidyl arginine; *PTPN22*, protein tyrosine phosphatase; *SNP*, single-nucleotide polymorphism; *STAT4*, signal transducer and activator of transcription 4; *TGF-β*, transforming growth factor-beta; *TNF*, tumour necrosis factor.

have a strong effect but only in a small proportion of patients, whereas others will have weak effects and be present in a greater number of individuals but require the involvement of other risk factors. Thus, the size of any increased risk is not a reflection of the level of its attribution to disease causation. However, the sense of strength of risk in this review has been split arbitrarily into three groups based on the typically reported strength of association: 'small' (odds ratio [OR] or relative risk [RR] of less than 2), 'moderate' (OR or RR of between 2 and 5), or 'substantial' (OR or RR of greater than 5).

## Rheumatoid arthritis

### Environmental risk factors

Studies of environmental risk factors in RA have focused on diet, smoking, and hormones [8]. Several studies have investigated consumption of coffee/tea/caffeine as a risk factor but with mixed conclusions. Caffeine has been reported to moderately increase the risk of rheumatoid factor (RF)-positive RA, but no increased risk for RF-negative RA was found [9]. Decaffeinated coffee has been associated with a moderately increased risk of RA, whereas tea has been shown to have a protective effect [10]. The authors suggest that the decaffeination process (use of industrial solvents) and small traces of solvents may play a role in the disease whereas tea may have both anti-inflammatory and antioxidative properties [10]. However, other studies have found no association of caffeine/coffee consumption with RA [3]. Clearly, studies that are more robust are needed to verify these results.

The so-called 'Mediterranean diet' has been linked with health benefits for a number of diseases and this is also true for RA [11,12]. High consumption of olive oil, oil-rich fish, fruit and vegetables [13], or vitamin D [14] has been shown to have a protective role in the development of RA. High consumption of red meat and meat products [5] has been associated with a moderately increased risk of inflammatory polyarthritis, but no risk was found in a more recent study [15].

Data on the link between smoking and RA are more compelling and include recent studies implicating a gene-environment interaction (see below). The duration and intensity of smoking have been linked to the development of RA in postmenopausal women [16]. Current smokers and those who had quit for 10 years or less were found to have a small increased risk of RA, whereas those who had quit for more than 10 years had no increased risk. Heavy cigarette smoking has been linked with a substantial increased risk of RA [17] (over 13-fold) and there was an increasing association between increasing pack-years of smoking and RA. Current smoking has been found to be a risk factor for RA, with the risk moderately increased in men and more so in men with seropositive RA [18]. Other studies have also shown a small increased risk due to smoking for seropositive RA in both women and men but have not shown an increased risk for

seronegative RA [19]. This risk was evident in subjects who had long-term smoking habits (>20 years) and was evident even if daily smoking intensity was only moderate. Duration of smoking rather than intensity has also been found to be a risk factor in a study of female health professionals [20]. Smoking has also been linked with an increase in both the severity of RA and disease activity [21,22], supporting a role for smoking in the development of RA. Other host factors that have been associated with RA include blood transfusion and obesity [23] and (high) birth weight [24], which have been linked with a moderate increased risk, and breast-feeding [25] and alcohol [26], which have been linked with a decreased risk/protective role. Stress has also been reported to have a role in the development of RA [27].

### Genetic risk factors

Genetic factors implicated in RA have been widely studied using both candidate genes and whole-genome screens [28]. Whereas the strongest genetic risk factor for RA remains the *HLA DRB1* shared epitope (SE), other candidate genes have been consistently implicated. In particular, an SNP (R620W) in the protein tyrosine phosphatase (*PTPN22*) gene, which has regulatory activities for both T and B cells, has been associated with RA [29]; furthermore, this has been replicated in well-powered studies in different populations [30-33]. This polymorphism has been associated with other autoimmune diseases, including JIA and SLE [28]. Studies on peptidyl arginine (*PADI4*) have shown a significant association [34] but so far this has been replicated in one other Japanese study [35] only and not in populations from the UK [36], France [37], or Spain [38]. A recent meta-analysis of three Asian and six European studies has shown that *PADI4* polymorphisms were associated with Asian populations; in European populations, only *PADI4\_94* had a significant association [39]. Genes such as *CTLA4*, *FCRL3*, and major histocompatibility complex 2A (*MHC2A*) have also been the focus of recent research [28].

The search for novel genes has been advanced by the powerful approach of genome-wide association studies as typified by the UK WTCCC. This has identified three genes with independent associations for RA: two that have been reported to have strong associations (*HLA-DRB1* and *PTPN22*) and a further one on chromosome 7 that had different genetic effects between genders with a strong and apparently additive effect on disease status in females [7]. Further susceptibility loci are likely to be discovered using this approach. Similarly, alleles from 14 genes from over 2,300 cases and 1,700 controls from the North American Rheumatoid Arthritis Consortium (NARAC) (the US version of the WTCCC) and the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) collections have supported evidence for association of RA with *PTPN22*, *CTLA4*, and *PADI4* (NARAC cohort only) [40]. There is also evidence that there is a genetic overlap with other autoimmune diseases (SLE, AS, multiple sclerosis, and inflammatory bowel disease)

[41]. One of the newer and possibly more exciting areas of research focuses on evidence that certain polymorphisms can predict the response of a patient to treatment [42] and this is likely to be the focus of a number of future studies.

### Gene-environment interactions

One of the most interesting studies has shown evidence of an important gene-environment interaction between the SE and smoking [43]. This Swedish population-based case-control study showed that the risk of developing RF-positive RA substantially increased in smokers carrying double copies of SE genes (RR = 15.7) compared with smokers with no copies of SE genes (RR = 2.4). Recent research has also shown additive and multiplicative interactions between *PTPN22* and heavy cigarette smoking [44]. It has also been proposed that risk factors such as smoking, alcohol and coffee consumption, obesity, and oral contraceptive use may depend on the presence or absence of autoantibodies to cyclic citrullinated peptides [45,46].

### Juvenile idiopathic arthritis

Epidemiological studies of JIA have been hampered by a lack of standardised criteria and case ascertainment, resulting in wide-ranging results: reported prevalence ranges from 0.07 to 4.01 per 1,000 children, and annual incidence varies from 0.008 to 0.226 per 1,000 children [47]. Hopefully, the development of new diagnostic criteria will aid future studies in having results that are more consistent. Ethnicity has been studied and European descent has been associated with a moderately increased risk of JIA; additionally, JIA subtypes differed significantly between ethnic groups [48]. There have been few developments in terms of environmental risk factors, although infection remains the most favoured hypothesis.

### Genetic risk factors

Major advances in epidemiological studies of JIA have focused mainly on genetic aspects. A genome-wide scan in 121 families (247 affected children) confirmed linkage of juvenile RA to the HLA region [49]. In addition, early-onset polyarticular disease has been linked to chromosome 7q11 and pauciarticular disease has been linked to chromosome 19p13, suggesting that multiple genes are involved in the susceptibility to juvenile RA. Other candidate genes, including polymorphisms in the migration inhibitory factor (*MIF*) gene, have been associated with JIA. A study of UK JIA patients showed that patients with an MIF-173\*C allele had a small increased risk of JIA [50], and serum *MIF* levels were also higher in patients with this allele. An SNP in the *PTPN22* gene (a gene associated with both RA and SLE) has also been shown to have a novel association with JIA [30]. A recent meta-analysis has confirmed that the T allele and the T/T genotype of *PTPN22* C1858T are associated with JIA [51]. Polymorphisms in the *NRAMP1* gene may also play a role in the pathogenesis of JIA [52]. There is some evidence that a potentially protective CC genotype of the interleukin-6 (*IL-6*) gene is reduced in young patients [53].

### Psoriatic arthritis

Epidemiologically, PsA is a complex disease to study as it is not simple to disentangle whether the risk factors revealed are for the complete disease phenotype of PsA or for one of its two components. Studies that compare PsA with healthy controls are not able to address this.

### Environmental risk factors

Studies of environmental risk factors for PsA have focused on infection-related triggers and hormones. In a recent case-control study, exposure to rubella vaccination substantially increased the risk of PsA whereas injury requiring medical consultation, recurrent oral ulcers, and moving house all moderately increased the risk of PsA [54]. The strongest associations were with trauma, adding support to the hypothesis of a 'deep Koebner phenomenon' in PsA. These data suggest that infection-related triggers may be relevant and further studies are required to verify these results. In a nested case-control study, corticosteroid use (moderate increased risk) and pregnancy (decreased risk) were both associated with PsA, suggesting that changes to the immune system may play a role in this disease [55].

### Genetic risk factors

Developments in the pathogenesis of PsA again have been mainly in the genetic field. There is evidence that caspase recruitment domain 15 (*CARD15*), a susceptibility gene for Crohn's disease, has a role in PsA, and this is supported by the fact that patients with Crohn's disease have an increased incidence of psoriasis. Initial reports suggested that over 38% of probands with PsA had at least one variant of the *CARD15* gene compared with 12% of controls [56]. This pleiotropic autoimmune gene was proposed as the first non-MHC gene to be associated with PsA. Unfortunately, this has not been replicated in German [57] and Italian [58] cohorts; in these cohorts, no such association was found. A novel model that suggests that PsA susceptibility is determined by the balance of activating and inhibitory composite killer Ig-like receptor-HLA genotypes has been proposed [59]. Class I MHC chain-related gene A (*MICA*) may confer additional susceptibility to PsA. The MICA-A9 triplet repeat polymorphisms were present at a substantially higher frequency in PsA patients [60]. A linkage scan reported evidence that suggests that a locus on chromosome 16q is implicated in PsA; furthermore, the logarithm of the odds (LOD) score is much higher for paternal transmission than maternal transmission (4.19 and 1.03) [61]. Functional cytokine gene polymorphisms have also been associated with PsA [62], with tumour necrosis factor-alpha (TNF- $\alpha$ ) -308 and TNF- $\beta$  +252 polymorphisms being significantly associated with age at psoriasis onset, presence of joint erosions in PsA, and progression of joint erosions in early PsA. A genome-wide association study recently replicated associations of PsA with IL-23 receptor and IL-12B polymorphisms and also identified a novel locus on chromosome 4q27 [63]. A case-control study found evidence that HLA-Cw\*06 and

HLA-DRB1\*07 are associated with the occurrence of type I psoriasis in patients with PsA, suggesting that the primary association is with age of onset of psoriasis [64].

## Ankylosing spondylitis

Most of the epidemiological advances in AS have come from the ascertainment of novel genetic associations. Few environmental risk factors have been studied.

### Genetic risk factors

Epidemiological studies have focused on the genetics behind AS. Twin studies have estimated the influence of genetics on the aetiopathogenesis of AS, indicating that additive genetic effects account for 94% of the variance in the causation of AS [65]. Genome-wide scans have confirmed the strong linkage of the MHC with AS, which is not surprising given the overwhelming relationship between HLA B27 and AS. However, this study suggested that only 31% of the susceptibility to AS is from genes in the MHC [66]. Thus, the search for non-MHC genes has gained much interest [67]. One of the most exciting developments has been the identification of two new loci for AS from a major genetic association scan: *ARTS1* and *IL-23R* [68]. It was calculated from these studies that these genes are responsible for 26% (*ARTS1*) and 9% (*IL-23R*) of the population-attributable risk of AS. Another strong non-MHC linkage lies on chromosome 16q (overall LOD score of 4.7) [69]. Other scans have identified regions on chromosomes 6q and 11q [70]. Combined analysis of three whole-genome scans by the International Genetics of Ankylosing Spondylitis Consortium showed that regions on chromosomes 10q and 16q had evidence suggestive of linkage. Other regions showing nominal linkage (in two or more scans) were 1q, 3q, 5q, 6q, 9q, 17q, and 19q. Evidence was also confirmed for regions previously associated with AS on chromosomes 2q (the *IL-1* gene cluster) and 22q (cytochrome P450 2D6 [*CYP2D6*]) [71].

A linkage study of chromosome 22 in families with AS-affected sibling pairs found that homozygosity for poor-metaboliser alleles in the *CYP2D6* (debrisoquine hydroxylase) gene was associated with AS. The authors of that study postulated that altered metabolism of a natural toxin or antigen by this gene may increase the susceptibility to AS [72]. AS has also been linked to the IL-1RN\*2 allele [73] as have other inflammatory diseases such as ulcerative colitis and Crohn's disease.

## Systemic lupus erythematosus

### Environmental risk factors

The majority of research into environmental risk factors for SLE has focused on the role of hormones due to the higher prevalence of this disease in women. In a recent population case-control study, breast-feeding was found to be associated with a reduced risk of SLE, with a trend for the number of babies fed and total weeks of breast-feeding [74]. Women who developed SLE had an earlier natural

menopause whereas there was little association with current use or duration of use of hormonal replacement therapy or oral contraceptive pill and no association with the use of fertility drugs. The authors of that study proposed that early natural menopause may be a marker for susceptibility to SLE. However, another study has shown that risk of SLE or discoid lupus was moderately increased among current users of estrogens who had exposure of at least 2 years [75]. A prospective cohort study of women found no relationship between oral contraceptive use, either with duration or time since first use [4].

There has been a long-standing interest in the role of chemical exposures causing SLE. An interesting association has been found with lipstick use and SLE [76]. Researchers found that using lipstick 3 days per week was significantly associated with a small increased risk of SLE and this may be worth replicating in future studies on environmental risk factors. The authors suggest that chemicals (these include eosin, 2-octynoic acid [a xenobiotic], and phthalate isomers) present in lipsticks may be absorbed across the buccal mucosa and have a biological effect on disease development. Other risk factors associated with an increased risk of SLE include history of hypertension, drug allergy, type I/II sun-reactive skin type, and blood transfusions (all moderately increasing the risk) and family history substantially increasing the risk of SLE [77]. Consumption of alcohol has been inversely associated with the risk of SLE [77]. A small increased risk was found with smoking, but exposure to estrogen or hair-colouring dyes, both of which previously have been proposed as risk factors, was not associated.

### Genetic risk factors

There has been a major increase in the understanding of the genetics behind SLE, particularly over the last year, and this topic is concisely summarised in a recent review [78]. Two high-density case-control genome-wide association analyses have been published [79,80]. From these studies, overwhelming evidence for the association of various genes with SLE (*MHC*, *ITGAM*, *IRF5*, *BLK*, and *STAT4* [79,80]) and strong evidence for a role for *PTPN22* and *FCGR2A* [51,79,81] have emerged. Other genes for which there is evidence of an association, including the TNF superfamily gene [82], in which the upstream region of TNFSF4 contains a single risk haplotype for SLE, have also emerged. Gene copy number variation may lead to variation in disease susceptibility as highlighted in studies on the complement component C4 in which patients with SLE had a lower gene copy number of total C4 and C4A [83]. Zero copies or one copy of the C4A gene increased the risk of disease susceptibility, whereas three or more copies appeared to have a protective role. The risk of SLE was substantially greater in subjects with only two copies of total C4, but those with five or more copies of C4 had a reduced risk of disease. Another area of research focus has been on the role of sex chromosomes in the development of SLE, especially given

the high incidence in females. An interesting observation was the increased incidence of Klinefelter's syndrome (47, XXY) in male patients with SLE, in whom the frequency was substantially increased (14-fold) compared with men without SLE, suggesting that the susceptibility to SLE could be due to an X-chromosome gene-dose effect [84].

## Scleroderma

### Environmental risk factors

Epidemiological studies of Scl have focused on the role for toxic environmental exposures. Specifically, studies have carefully investigated silica and organic solvents as both are thought to stimulate the immune system and cause inflammation and increase antibody production. Recent reports show that occupational silica exposure moderately increases the risk of Scl, with medium exposure increasing the risk twofold and high exposure increasing the risk fourfold [85]. There is still interest in the relationship of silicone breast implants and Scl. However, a recent meta-analysis of nine cohorts, nine case-control studies, and two cross-sectional studies found no association with Scl or other connective tissue diseases [86]. Exposure to organic solvents remains a moderate risk factor and the presence of anti-Scl-70 autoantibodies may be an effect modifier as the association was stronger in patients with these antibodies [87]. However, such studies are difficult to undertake as exposure to other chemicals cannot be controlled.

### Genetic risk factors

There is increasing evidence for a genetic role in Scl development [88]. The familial risk of Scl has been investigated in three large US cohorts with a significant increase in risk observed: 2.6% in families with Scl compared with 0.026% in the general public [89]. Studies of HLA alleles suggest that the DQA1\*0501 allele is significantly increased in men with Scl compared with healthy men. This allele was found to be moderately associated with diffuse Scl in men but not with limited Scl [90]. HLA associations have also been studied in mutually exclusive autoantibody subgroups, lending support to the theory that Scl in subgroups are actually separate diseases [91]. Transforming growth factor-beta (TGF- $\beta$ ) and connective tissue growth factor may have roles in Scl but further studies are required [92,93]. Increased expression of TGF receptors may account for the increased production of collagen type I by Scl fibroblasts [94]. Fibrillin-1 SNPs haplotypes have been strongly associated with Scl in Choctaw and Japanese populations [95]. Long-term foetal microchimerism is also still being investigated as a potential risk factor [96,97].

## Osteoarthritis

### Environmental risk factors

Studies on environmental risk factors for OA have focused on obesity, physical activity, and prior joint injury, all of which may increase stress on the joints. There have been several major cohort studies of OA, including the Framingham Study

[1], the Chingford 1000 Women Study [2], Bristol OA 500 [98], and the North Staffordshire Osteoarthritis Project (NorSTOP) [99]. From these and other studies, a number of risk factors, including high body mass index (BMI), previous injury, and regular sports participation, have been found [100,101]. The main preventable risk factor, and hence the subject of many reports, is obesity, which has been shown to substantially increase the risk of knee OA [100,102]. A moderate influence of obesity has also been found with hip OA [103]. Data from adult twins (St. Thomas' Hospital Adult Twin Registry) have shown a moderate association between high BMI and knee OA (OR = 3.9) [104]. Manek and colleagues, who gathered those data, also concluded that this association was not influenced by shared genetic factors. Other influences have been the effect of physical activity on OA [105]. One study found a moderate association between heavy physical workload and hip OA [106]. High levels of physical activity were found to be a moderate risk factor for OA of the knee/hip joints in men younger than 50 years [107].

Men with maximal grip strength have been found to have a moderately increased risk of OA in the proximal interphalangeal, metacarpophalangeal (MCP), and thumb base joints, and women with maximal grip strength have been found to have a moderately increased risk of OA in the MCP joints [108]. There is some evidence that occupation can increase the risk of hand OA. A recent case-control study showed that occupations involving repetitive thumb use and jobs in which there were perceived to be insufficient breaks were associated with OA of the carpometacarpal (CMC) joints [109]. However, not all studies agree and a cross-sectional study found no association with occupation, physical activity, or sports participation but found a moderate increase in risk for hand OA for self-reported digital fracture [110].

### Genetic risk factors

Genetic studies in female twins have estimated that the genetic contribution to radiographic hip OA is 58% for OA overall and 64% for joint space narrowing [111]. Studies have revealed that disease risk differs for males and females at different sites and thus there may be specific genes rather than a single OA phenotype [112]. The *IL-1* gene cluster is a key regulator in a number of chronic disease processes, and within this cluster, haplotypes such as IL1A-IL1B-IL1RN, which confers a moderate increase in the risk of OA, and IL1B-IL1RN, which confers a fivefold reduced risk, have been identified [113]. This cluster has also been proposed to confer susceptibility for knee OA but not hip OA [114]. Functional polymorphisms in the frizzled motif associated with bone development (*FRZB*) genes have been found to confer susceptibility to hip OA in females [115]. Radiographic OA is also associated with genotypes of the insulin-like growth factor I gene [116].

Data from the Rotterdam study showed that polymorphisms in the estrogen receptor-alpha (*ESR1*) gene are associated

with radiographic knee OA in elderly men and women [117]. In a case-control study, several candidate genes were investigated: the strongest associations with clinical knee OA were found with a haplotype in *ADAM12* (a disintegrin and metalloproteinase domain 12) and *ESR1* in women [118] and again with *ADAM12* in men along with the CILP (cartilage intermediate layer protein) haplotype. There is also evidence that the cyclooxygenase-2 enzyme encoded by *PTGS2* has a role in the pathogenesis of knee OA [119]. The iodothyronine-deiodinase enzyme type 2 (*DIO2*) gene has been identified as a new susceptibility locus for OA, using a genome-wide linkage scan [120]. A meta-analysis of more than 11,000 individuals provided evidence for an SNP in *GDF5* having a positive association with knee OA in both European and Asian cohorts [121]. Other genes so far implicated include the *IL-1* gene cluster, matrilin-3 gene, IL-4 receptor, frizzled-related protein-3 (*FRZB*) gene, metalloproteinase gene *ADAM12*, and the asporin (*ASPM*) gene [122]. An ambitious study that will screen over 8,000 people with hip or knee OA and 6,000 healthy controls – arcOGEN (Arthritis Research Campaign Osteoarthritis GENetics) [123] – has been recently announced and is likely to lead to the identification of further genes associated with OA.

The Dutch GARP (Genetics, Arthrosis, and Progression) study has shown that there is a moderate increased risk for familial aggregation of both hand and hip OA whereas there was no increased risk for knee OA [124]. That there should be greater genetic effects on OA of the hand compared with other sites is not surprising given the relatively weaker role for environmental (including mechanical) factors. The familial risk of hand OA has shown a moderate increase in risk in sisters of women affected with hand OA and this risk was substantially increased with the severity of the disease, with sisters of those with severe first CMC OA having an RR of 6.9 [125]. Whole-genome linkage scans on female twins have shown significant linkage of distal interphalangeal (DIP) OA on chromosome 2 and Tot-KL (Kellgren-Lawrence score for both hands) on chromosome 19 [126]. Polymorphisms in the vitamin D receptor (*VDR*) gene have also been associated with symmetrical hand OA, with a novel finding of a joint effect of low calcium intake and *VDR* polymorphisms (aT haplotype) having a moderate increased risk of symmetrical hand OA [127]. Data from the Framingham Study have shown that several chromosomes (DIP joint on chromosome 7, first CMC joint on chromosome 15, and two sites in the female DIP joint on chromosome 1 and first CMC joint on chromosome 20) contain susceptibility genes for hand OA and that a joint-specific approach rather than a global approach to hand OA may be more useful in further investigations of these regions [128]. Genome-wide scans have also revealed linkage peaks on chromosomes 4q, 3p, and the short arm of chromosome 2 for idiopathic hand OA [129]. Genome-wide significance was reached for a locus on chromosome 2 for first CMC and DIP joints coinciding with the *MATN3* gene, which encodes the extracellular matrix protein, matrilin-3.

## Gout

### Environmental risk factors

Studies on environmental risk factors for gout have focused mainly on the long-established risk factors of high purine diet and diuretic use. The incidence of gout is increasing [130] and high alcohol consumption is no longer the only risk factor for the disease [131]. Other risk factors that have been proposed include longevity, metabolic syndromes [132], and use of certain pharmacologic agents [133]. The high incidence in some ethnic groups has no obvious host factor, and genetic factors may be implicated in these groups.

Dietary factors have a strong association with gout. Much of the research in this area has been conducted by Choi and colleagues [6,134-137]. As part of a large prospective study in men (the Health Professionals Follow-up Study), a number of factors were associated with an increased risk of gout. Higher adiposity, hypertension, and diuretic use were all moderate risk factors, whereas weight loss had a protective role [136]. High intake of sugar-sweetened drinks and high fructose intake from fruit juice and fruit have been associated with a small increased risk of gout [137]. High meat intake and seafood intake (purine intake) have also been positively associated with gout with a small increase in risk [6]. In the same study, long-term coffee consumption was inversely associated with gout [138]. Consumption of low-fat dairy products has been shown to decrease the risk of gout [6]; milk proteins (casein and lactalbumin) can reduce serum uric acid levels in healthy individuals.

### Genetic risk factors

Advances in the genetic factors behind gout have included a variation in the *SLC2A* gene, which appears to make it more difficult for uric acid to be removed from the blood [139]. A polymorphism in the TNF- $\alpha$  promoter gene has been shown to be significantly associated with gout [140]. Genetic studies have included families with purine metabolism defects and case-control studies of isolated aboriginal cohorts with primary gout [133].

### Fibromyalgia and chronic widespread pain

These poorly defined conditions are nonetheless the target of many investigations seeking to unravel risk factors for their causation or severity.

### Environmental risk factors

Studies on environmental risk factors for FM and CWP have focused on physical trauma and psychosocial factors. Physical trauma in the months prior to disease onset has been significantly associated with FM [141]. FM was found to be 13 times more likely in patients who had a prior injury to the cervical spine compared with those with injuries to the lower extremities [142]. In a population-based prospective study, three psychosocial factors independently predicted a moderate increased risk of the development of CWP: somatisation, health-seeking behaviour, and poor sleep [143].

Subjects with all three factors had a substantial increased risk of developing CWP.

There may be biologically based risk factors. Thus, abnormalities in the hypothalamic-pituitary-adrenal (HPA) stress-response system may predict the onset of CWP. In a recent study, high levels of cortisol after dexamethasone and high levels in evening saliva moderately increased the risk of CWP [144]. Low levels in morning saliva were also associated with a small increase in risk. These factors were both independent and additive predictors of CWP, with over 90% of new-onset cases of CWP being identified by one or more of these HPA factors.

### Genetic risk factors

Perhaps surprisingly, there have been some interesting suggestions of a genetic basis to FM. FM has been shown to aggregate strongly in families: the odds of FM in a relative of a proband with FM versus the odds of FM in a relative of a proband with RA was 8.5 [145]. Genotypes in the promoter region of the serotonin transporter gene (5-HTT) were analysed in FM patients. A higher frequency of the S/S genotype was found in patients compared with controls [146], supporting the hypothesis of altered serotonin metabolism in FM patients. Family studies have also shown significant genetic linkage of the HLA region to FM [147]. Polymorphisms in the gene encoding the COMT (catechol-O-methyltransferase) enzyme may also have a role in FM as certain genotypes combined are higher in patients than controls and a third genotype was significantly lower in control groups [148].

### Conclusions

Over the last 10 years, there have been some major epidemiological advances, particularly in the field of genetic risk factors, in which new candidate genes have been identified and useful gene-environment interactions have been studied. Studying lone environmental factors has been less fruitful. The problem epidemiologically is that these factors often explain only a small number of cases, and on

their own, they are not sufficient to cause the disease; both of these issues present considerable epidemiological challenges. The hope is that, as we begin to understand more about the genetics behind the diseases and genetic studies become more technically practical, it will enable stratification by genetic subgroups to identify environmental triggers (such as smoking). However, in other disease areas, progress has been very slow and we still understand very little.

### Competing interests

The authors declare that they have no competing interests.

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### The Scientific Basis of Rheumatology: A Decade of Progress

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