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A population-based study on early arthritis in southern Sweden. Incidence, preceding infections, diagnostic markers and economic burden.

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Abbreviations

ACR	American College of Rheumatology
AFA	antifilaggrin antibodies
AIMS	Arthritis Impact Measurement Scales
AKA	antikeratin antibodies
ANCA	antineutrophil cytoplasmic antibodies
ССР	Cyclic citrullinated peptide
APF	antiperinuclear factor
ARA	American Rheumatism Association
AS	ankylosing spondylitis
COMP	cartilage oligomeric matrix protein
CRP	C-reactive protein
CTX-I	type I collagen carboxyterminal telopeptide
CTX-II	type II collagen carboxyterminal telopeptide
DAS	Disease Activity Score
DMARD	disease-modifying anti-rheumatic drug
ESR	erythrocyte sedimentation rate
HAQ	Health Assessment Questionnaire
HLA	human leukocyte antigen
ICTP	type I collagen carboxyterminal telopeptide
MCTD	mixed connective tissue disease
MMP	matrix metalloproteinase
PICP	type I collagen carboxyterminal propeptide
PIIINP	type III procollagen N-propeptide
PsoA	psoriatic arthritis
RA	rheumatoid arthritis
ReA	reactive arthritis
SE	shared epitope

- SLE systemic lupus erythematosus
- TNF tumour necrosis factor
- VAS visual analogue scale

List of original publications

This thesis is based on the following papers, referred to in the text by their Roman numerals. In addition, some unpublished results are presented. The publishers of the original comunications have kindly granted their permission to reproduce these publications in this doctoral thesis.

I Söderlin MK, Börjesson O, Kautiainen H, Skogh T, Leirisalo-Repo M. Annual incidence of inflammatory joint diseases in a population based study in southern Sweden. Ann Rheum Dis 2002;61:911-915.

II Söderlin MK, Kautiainen H, Puolakkainen M, Hedman K, Söderlund-Venermo M, Skogh T, Leirisalo-Repo M. Infections preceding early arthritis in southern Sweden: a prospective population-based study. J Rheumatol 2003;30:459-64.

III Söderlin MK, Kastbom A, Kautiainen H, Leirisalo-Repo M, Strandberg G, Skogh T. Antibodies against cyclic citrullinated peptide (CCP) and levels of cartilage oligomeric matrix protein (COMP) in very early arthritis: relation to diagnosis and disease activity. Submitted.

IV Söderlin MK, Kautianen H, Jonsson D, Skogh T, Leirisalo-Repo M. The costs of early inflammatory joint disease: a population-based study in southern Sweden. Scand J Rheumatol 2003;32:216-224.

1. Abstract

A population-based study on early arthritis in southern Sweden. Incidence, preceding infections, diagnostic markers and economic burden.

The total annual incidence of arthritis in this prospective cross-sectional study on adults was 115/100 000. The annual incidence of rheumatoid arthritis (RA) was 24/100 000, 29/100 000 for women, and 18/100 000 for men. For reactive arthritis (ReA) the annual incidence was slightly higher, 28/100 000, and for undifferentiated arthritis 41/100 000. The annual incidence of Lyme disease and sarcoid arthritis was low. The annual incidence of arthritis in this study compares well with findings in earlier reports from both registers and case review studies. Almost 50% of the patients in the series of 71 patients with arthritis of less than 3 months' duration had a preceding infection. Campylobacter jejuni ReA dominated the enteric ReA group. We found only a few patients with preceding Chl. trachomatis, Chl. pneumoniae, Borrelia burgdorferi or parvovirus B19 infections. The arthritis patients with a preceding infection went into remission more often than the patients without a preceding infection. The disease specificity of anti-CCP antibodies for RA was high, 96%, confirming earlier results. Anti-CCP antibodies differentiated RA from other arthritides. Several patients in the different diagnosis groups had raised serum COMP levels, indicating cartilage involvement very early in the disease, even in mild and self-limiting disease with good prognosis. The economic burden of early joint inflammation was found to be considerable already during the first few months of the arthritis irrespective of diagnosis. Surprisingly, patients with ReA generated almost as high costs as patients with RA during the

first few months of the disease, even though most of the ReA patients had a relatively mild disease. Sick leave accounted for about 50% of the costs. The distribution of costs in the different patient groups was skewed. The median cost per patient for the group of patients with RA was US\$4385, for ReA US\$4085, for other types of specified arthritis US\$3361, and for undifferentiated arthritis US\$1482. This underlines the necessity of quick referral and therapy, not only to decrease the inflammation and prevent functional impairment, but also to decrease the costs of early arthritis.

2. Introduction

Different epidemiological methods have been used in studies on the incidence of rheumatic diseases. The results depend on the methods and criteria used and also on the local and national settings of health care.

The annual number of new cases of inflammatory joint diseases in a defined population has major implications for the planning of rheumatology health care. However, it is often very difficult to establish the true incidence of these diseases due to difficulties in diagnosing the diseases reliably, and due to differences in the local and national health care systems. Patients often seek both outpatient and inpatient care. Depending on the local conditions and the patients' clinical picture, patients may be treated by physicians with different specialities. Local and national treatment practices vary, for example concerning referral policy, i.e. which patients are referred to specialists, or whether the patients should be treated as inpatients.

There are four approaches in measuring incidence: 1. A single population survey. 2. Duplicate population surveys identifying incident cases between the surveys. 3. A retrospective review of diagnosed cases. 4. A prospective registration system.

Several biases and problems in epidemiological studies of joint inflammation can be identified. A typical problem in hospital-based studies of arthritis is that usually only severe cases of joint inflammation are seen at the secondary or tertiary centre, i.e. referral bias. Case verification is also a problem, particularly in retrospective studies, where medical records are examined. The records often lack information regarding diagnostic criteria. The fact that many incidence studies rely on medical record data, interviews and postal questionnaires, instead of an investigation and examination of the patients by a qualified professional, may also lead to a bias. Patients in a certain recruitment area may also seek treatment in other areas and thus be missed, i.e. left censorship. Diagnostic consistency over time and among physicians is a problem, i.e. case ascertainment. Since the disease may start insidiously, in particular rheumatoid arthritis (RA), the time of symptom onset may be unclear, i.e. recall bias.

Although inflammatory joint disease is probably common in the population, only few studies have focused on this. A population-based Finnish study from the Heinola Rheumatism Foundation Hospital area, using combined patient series, reported a total rate of inflammatory joint disease of 218/100 000 (1). This study also included gout and osteoarthritis.

The diagnosis of RA is based on a combination of clinical and laboratory measures, and the diagnostic criteria have been revised several times. Earlier studies have reported incidence figures based on the 1958 American Rheumatism Association (ARA) criteria, where both the low sensitivity and low specificity have been a problem (2). Later studies use the 1987 American College of Rheumatology (ACR) criteria (3). However, the 1987 ACR criteria do not seem to be very reliable in diagnosing early RA (4-7). Additionally, there is the bias of late presentation, as RA may start insidiously, and several months, even years, may elapse before the patient sees a doctor and is diagnosed as having RA. Not all of the RA patients fulfil the 1987 ACR criteria for RA at first. This means that a "cumulative" incidence for patients fulfilling the ACR criteria over time should be reported (8). Additionally, the incidence of RA is heavily age-dependent, most studies reporting highest RA incidence in age groups over 60 (9-12), and incidence studies should thus include older patients as well. For men, the age at which the RA incidence peaks is about 10 years later than in women (13).

The definition of incidence date for RA also varies between different studies. Some studies use the start of the symptoms as the incidence date, whereas others use the date when study personnel were contacted by the referring unit, or the time when the patient fulfilled the ACR criteria, or the time when the physician diagnosed the patient as having RA. Therefore, the results may vary depending on the criteria used.

3. Incidence of rheumatoid arthritis (RA)

Table 1 shows a summary of the RA incidence studies using the 1987ACR criteria for RA. These studies give the incidence of 13-66/100 000for women and 5-28/100 000 for men.

Registers can be useful in incidence studies. A Finnish study using the national data base of the Finnish National Sickness Insurance Scheme for drug reimbursement for chronic joint inflammation reported a total rate of inflammatory joint disease of 65/100 000 in 1995 (14). The coverage of the national data-base is good, and it has been shown that at least 95% of the subjects with chronic inflammatory rheumatic disease have gained the entitlement for drug reimbursement (15). A previous Finnish study using the same drug reimbursement data-base reported an annual incidence of

The Kuopio 2000 Arthritis Survey reported the total incidence and distribution of inflammatory joint diseases in a population of 87 000 inhabitants in eastern Finland in the year 2000. This study included also children and crystal arthropaties. The total incidence of arthritides for adults was 271/100 000, and for RA 36/100 000 in adults. The mean age at diagnosis for RA was 60 years. For psoriatic arthritis, the incidence for adults was 23/100 000, and for reactive arthritis, 10/100 000. For viral arthritis for adults, the incidence was 7/100 000, and for crystal arthropathy, 19/100 000. For undifferentiated arthritis, the incidence for adults was 149/100 000. In this study, the incidence was defined as the patients' first referral for inflammatory arthritis to either primary care or secondary care during the year 2000. At least one joint with peripheral synovitis, or signs of an inflammatory disorder in sacroiliac, glenohumeral, or hip joints had to be registered at the first visit. There was no time limit for the symptom duration. Patients with an established diagosis of reactive arthritis, who had a new attack in 2000, were included. Patients with trauma, only tenosynovitis or bursitis, and osteoarthritis were excluded (17).

A prospective population-based register, using a standardised diagnostic assessment by specially trained nurses, i.e. metrologists, in Norfolk, UK, reported an annual incidence of RA of 36/100 000 for women and 14/100 000 for men (18). In this British study patients were registered as RA if they fulfilled the 1987 ACR criteria at presentation, and were given at least one year to present from the onset of symptoms. However, if the RA patients were given up to five years to fulfil the ACR criteria cumulatively, the incidence figures went up to 54/100 000 for women and 25/100 000 for men (8). A retrospective RA register study in Oslo, Norway, reported an annual overall incidence of RA of 26/100 000, 37/100 000 for women, and 14/100 000 for men (10). In this study the authors estimated an 85% capture rate.

A prospective notification of referrals of new female patients with RA in a health maintenance organisation in Seattle, Washington, US, reported an annual age-adjusted incidence figure of 24/100 000 for RA for women (11). These patients were 18-64 years old and were seen by a rheumatologist who verified the diagnosis. There are several retrospective studies using hospital and outpatient medical records, i.e. case review, reporting annual incidence figures of 13-66/100 000 for women, 5-28/100 000 for men, and total annual incidence for RA 9-49/100 000 (9, 12, 19-21). The study by Linos and coworkers from Rochester, Minnesota, US, used only the 1958 ARA criteria (19), whereas the others used the 1987 ACR criteria. A high incidence of RA of 42 cases per 10 000 personyears has been reported from a Pima Indian reservation (22).

The incidence of RA is probably declining (11, 16, 19, 23), although this observation has been contradicted in other studies (9, 12). One study from Rochester, Minnesota, US, found a definite and progressive decline in the incidence and also a difference in the age distribution between men and women, and a cyclical variation in the disease incidence over time (13).

using 1987 ACR	criteria.					
Author	Country	Total annual incidence /100 000	Annual incidence for women /100 000	Annual incidence for men /100 000	Comment	
Kaipiainen- Seppänen et al. 1996 (16)	Finland	39	NA	NA	National register for dr reimbursemer	
		NIA	26	1 /	Due an a stirre	

Table 1. Summary of the studies on the incidence of RA in literature

		incidence /100 000	for women /100 000	for men /100 000	
Kaipiainen- Seppänen et al. 1996 (16)	Finland	39	NA	NA	National register for drug reimbursement
Symmons et al. 1994 (18)	UK	NA	36	14	Prospective population- based register
Wiles et al. 1999 (8)	UK	NA	54	25	Same register as Symmons et al. Five years from symptom onset
Uhlig et al. 1998 (10)	Norway	26	37	14	RA register
Dugowson et al. 1991 (11)	US	NA	24	NA	Health Maintenance Organisation. Women aged 18-64
Drosos et al. 1997 (21)	Greece	24	36	12	Medical records
Guillemin et al. 1994 (20)	France	9	13	5	Medical records
Chan et al. 1993 (9)	US	42	60	22	Health Maintenance Organisation. Medical records
Riise et al. 2000 (12)	Norway	29	36	21	Medical records
Doran et al. 2002 (13)	US	45	58	30	Medical records. 40- year time period
Savolainen et al. 2003 (17)	Finland	36	46	25	Kuopio 2000 Arthritis Survey

4. Incidence of ankylosing spondylitis and psoriatic arthritis

The incidence of ankylosing spondylitis (AS) has been reported to be 6.6- $7.3/100\ 000$ in three studies, two studies from the US using medical records in Rochester, Minnesota, and a Finnish study using a national data-base for drug reimbursement (24-26). The Kuopio 2000 Arthritis Survey reported an incidence of $6/100\ 000\ (17)$. The studies on the incidence of psoriatic arthritis (PsoA) are difficult to interpret because of the lack of defined criteria, but incidence rates of 6-7/100 000 have been reported (27, 28). The Kuopio 2000 Arthritis Survey reported an incidence of 23/100 000 for psoriatic arthritis (17). Moll and Wright defined psoriatic arthropathy as inflammatory rheumatoid factor negative arthritis associated with psoriasis, where other causes for arthritis have been excluded (29). The European Spondylarthropathy Study Group (ESSG) proposed the following criteria for spondylarthropathy: inflammatory spinal pain or synovitis together with at least one of the following: positive family history, psoriasis, inflammatory bowel disease, urethritis or acute diarrhoea, alternating buttock pain, enthesopathy, or sacroiliitis as determined from the radiography of the pelvic region (30). A Swedish study reporting disease manifestations and HLA associations in psoriatic arthropathy used the criteria of peripheral arthritis of more than 6 weeks' duration, enthesitis and/or radiologically assessed axial involvement as diagnostic criteria for psoriatic arthropathy (31). In the Kuopio 2000 Arthritis Survey, the authors used the criteria of peripheral arthritis with psoriasis, excluding rheumatoid factor positive polyarthritis or spondylitis with psoriasis (17).

5. Incidence of reactive arthritis (ReA)

The lack of universally accepted criteria for reactive arthritis (ReA) hampers the comparison between studies. ReA is included in the spondylarthropathy disease group, which also includes PsoA, AS, arthritis associated with inflammatory bowel disease, sacroiliitis and oligoarthritis. Several criteria have been proposed for ReA and other spondylarthropaties (30, 32-39). Some differences exist between these criteria, but they all include arthritis and/or enthesopathy in the presence of a previous infection. Most studies describing the incidence, infectious aetiology and clinical presentation of ReA have been based on selected cohorts of patients with a known previous infection. There have been only a few previous studies trying to establish the incidence of ReA in the general population. A Norwegian study from Oslo reported an annual incidence of C. trachomatis ReA of 5/100 000 and postenteric ReA 5/100 000 (40). In the study, 36% of the patients with C. trachomatis ReA and 26% of the patients with postenteric ReA were asymptomatic for the triggering infection. The incidence of ReA in Finland has been estimated to be $14/100\ 000\ (1)$. A Finnish study using a national data-base reported an incidence of 2/100 000 for chronic ReA requiring reimbursed medication (14). The Kuopio 2000 Arthritis Survey reported an incidence of 10/100 000 for ReA, and 7/100 000 for viral arthritis (17). Table 2 shows the frequency of reported enteric infections and Chlamydia trachomatis infections in Kronoberg county and in Sweden during the time of the study (1999 and 2000) and in 2002.

Table 2. Number of reported cases /100 000 inhabitants/year. Data fromthe Swedish Institute for Infectious Disease Control(Smittskyddsinstitutet).

Bacteria	Kronoberg	Kronoberg	Kronoberg	Sweden	Sweden	Sweden
	county 1999	county 2000	county 2002	1999	2000	2002
Campylobacter	71.6	83.2	83.2	86.5	94.7	80.2
Y ersinia	8.4	9.6	9.0	6.1	/.1	6.8
Salmonella	63.2	48.6	35	58.0	54 5	43.7
Chl. trachomatis	143.9	209.4	219	188.5	217.0	277.5

6. Early arthritis

"Early arthritis" is currently not a very well-defined concept, as the symptom duration from onset of symptoms to diagnosis may vary in different studies from months to years. Sixty-six per cent of rheumatologists used the term "early" for a disease duration that was shorter than three months in a survey (41). Additionally, there is no consensus as to which laboratory tests or radiological tests should be performed routinely for patients with early arthritis. Out of 210 French rheumatologists, 25% recommended radiographs of hands, feet, knees, chest x-ray, blood cell counts, rheumatoid factor (RF), antinuclear antibodies (ANA), antikeratin antibodies (AKA), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), creatinine, alanine aminotransferase (ALT), urinalysis for proteinuria, and joint aspiration, for patients with recent-onset polyarthritis without extra-articular manifestations. There was a wide variance, indicating a need for standardisation (42).

The diagnosis of early arthritis is challenging. It would be very important to diagnose and treat patients who will develop erosive aggressive chronic joint inflammation early, since it has been shown that early referral and treatment of RA improves prognosis (43, 44). However, there are several practical difficulties. RA may initially be indistinguishable from other arthritic conditions, the symptoms may vary from patient to patient, the disease may start insidiously, and there is often a considerable delay in referral and initiation of treatment. Erosions usually develop later on in the disease and seldom aid in the diagnosis early in the disease. Only 13% of RA patients had erosions already at the first visit to a rheumatologist in an early arthritis clinic (5). The established criteria for RA seem to perform less well in early RA (4, 5), and problems arise from the low sensitivity and specificity, the fact that synovitis has to be present for 6 weeks, and that the criteria are not valid if the synovitis disappears due to treatment.

Visser and co-workers have proposed a model to predict early erosive arthritis that consists of seven variables (symtom duration, morning stiffness, arthritis in \geq 3 joints, bilateral compression pain in the metatarsophalangeal joints, rheumatoid factor positivity, anti-cyclic citrullinated peptide antibody positivity, and the presence of erosions in the hands and feet) (45). This model could predict reliably self-limiting arthritis, persistent nonerosive arthritis and persistent erosive arthritis.

6.1. Early arthritis clinics

Early arthritis clinics have been established to enable a quick referral to rheumatologists to enable early diagnosis and treatment. The patients presenting at early arthritis clinics usually have various diagnoses. Of the patients presenting in early arthritis clinics, RA constituted 13-19% of the patients, ReA 11-17% of the patients, and 20-56% of the patients have a diagnosis of undifferentiated arthritis, and the rest other diagnoses (46-48). A study from Austria reported that RA constituted 60% of the patients with arthritis of less than 3 months' duration. In this study, 30% of the diagnoses changed during the first year. However, for 90% of the RA patients, the diagnosis was established within 6 months after the onset of symptoms (5). In this Austrian study, patients with RA were referred later than patients with other diagnoses, possibly mirroring the more insidious onset of RA as compared with other arthritides.

6.2. Undifferentiated arthritis

It is usually thought that the patients with undifferentiated arthritis have a benign disease. In a French study of patients with incipient undifferentiated arthritis with a follow-up of 3 years, 55% of the patients developed a specific rheumatologic disease, 75% of them developing mostly mild RA. Twenty-eight per cent of the patients went into remission during a three-year follow-up. Sixteen per cent of the patients still had undifferentiated arthritis in the follow-up (49). A Finnish study on 64 seronegative oligoarthritis patients showed a good prognosis in an 8-year follow-up (50). In a Norwegian study of patients with oligoarthritis, a combination of elevated CRP, genitourinary symptoms, metatarsophalangeal joint involvement, and HLA-B27 positivity could predict ReA with 70% sensitivity and 94% specificity (51).

However, a Dutch study showed that 42% of undifferentiated arthritis patients had progressive disease (52). A progressive outcome was associated with older age, higher disease activity and arthritis in the hands. Patients with a diagnosis of undifferentiated arthritis seemed to be suboptimally treated as compared to RA patients, and the authors recommended treatment based on the severity of the disease rather than on the diagnosis (52). In a study from UK, 78% percent of patients with a mild, early joint inflammation had persistent inflammatory arthritis, with over 50% of the patients having RA, and >50% requiring a disease-modifying anti-rheumatic drug (DMARD) by 6 months (53). Duration of arthritis of >12 weeks, RF positivity and shared epitope (SE) positivity were risk factors for a persistent disease. The mean disease duration at presentation was shorter for those patients who went into remission.

6.3. Markers for the diagnosis and prognosis of early arthritis

Many efforts have been made to identify reliable diagnostic markers to enable early diagnosis and referral of arthritis patients. Several studies have been published to evaluate whether markers examined during the first months of the arthritis can be used to predict the outcome, i.e. development into a chronic erosive disease, such as RA, as compared to an often self-limiting disease, for example ReA. Several studies have also evaluated whether markers at the very beginning of the disease can be used to distinguish those patients with a chronic joint inflammation who develop an aggressive disease from those patients with a chronic disease but with a better prognosis. This is important since new therapies are now available that efficiently reduce joint inflammation and influence the progression of the disease.

6.3.1. Rheumatoid factor (RF)

To date, the only laboratory marker for RA used routinely as a diagnostic criterion for RA is the rheumatoid factor (RF), i.e. an autoantibody binding to the Fc portion of IgG. RF is highly associated with RA, but often occurs also in infectious diseases, primary Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis and cryoglobulinaemia (54). The frequency of a positive serum test for agglutinating RF in a healthy population ranges from 1.3-4% in Caucasians (55) compared to about 70% of RA patients (56). RF predates RA, and individuals with high RF titres are at an increased risk of developing RA (57-59). RF also predicts disease severity, such as erosions (60-64). RF levels decrease in patients responding to conventional DMARD therapy or anti-TNF-alpha therapy (65-67). In an early RA cohort of 266 patients from Sweden (TIRA), 65% of the patients were RF-positive as measured by the latex agglutination. IgM-RF and IgA-RF correlated significantly. In this cohort, no correlation between RF levels and disease activity as measured by the Disease Activity Score 28 (DAS-28) was found. RF did not correlate with a marker of cartilage breakdown, cartilage oligomeric matrix protein (COMP) either (Lindroos Anette, unpublished observation, TIRA material, Linköping University Hospital, Sweden).

6.3.2. Antifilaggrin antibodies (AFA)

Other markers used for diagnosis of early RA and to predict outcome in RA are antikeratin antibodies (AKA) and the antiperinuclear factor (APF). It was reported in 1995 that these autoantibodies recognise human epidermal filaggrin and profilaggrin-related proteins, and that these are largely the same autoantibodies, and the name antifilaggrin antibodies (AFA) was proposed (68). IgG AFA recognise citrulline-bearing epitopes present on various molecular forms of profilaggrin and filaggrin in epithelial tissue. Intracellular citrullinated proteins not recognised by AFA monoclonal antibody were present in the synovium of 50% of RA patients, but in none of the controls (69).

AKA, APF and AFA seem to be highly specific for RA, 95-99%, with a sensitivity of 52-76%, depending on the test used (70-75). None of the three tests (AKA, APF or AFA) bear all the epitopes recognized by AFA, and using the different tests together can improve sensitivity (71). AKA have been shown to be detectable in early RA, and they have prognostic significance in RA, patients having AKA showing a more active disease course than the patients who were negative for AKA (76). AKA were also more common in RA than in ReA or normal controls, about a third of the RA patients being positive for AKA (76, 77). Paimela and coworkers reported that the level of AKA paralleled disease activity (76), but this has not been found in other studies (77, 78). AFA supplements RF, but controversial results have been reported as to the ability of AFA to predict erosiveness; some studies have shown a positive result (77-81), whereas others have not (82). The pre-illness serum AFA level was found to be in direct proportion to the risk of development of RF-positive RA (83). AKA have been shown to be a useful marker in differentiating

patients with RA from those with arthritis associated with hepatitis C infection, the patients having HCV infection being significantly less often AKA-positive (84).

Recently, a synthetic cyclic citrullinated peptide (CCP) has been shown to function as a target for autoantibodies with a very high specificity for RA (85, 86). With the most recent modifications of an enzyme-immuno assay (EIA) for anti-CCP antibody analysis, the sensitivity is about 50-70% and the specificity >90% for RA (85-90). In several studies, anti-CCP antibody positive patients also developed more radiological damage than anti-CCP antibody negative cases (86, 88, 91, 92). Using anti-CCP antibodies in combination with IgM-RF enhanced the value of RF alone in predicting the development of RA in an early arthritis clinic, and in predicting erosiveness (93, 94), and a similar result for IgA-RF was obtained in patient cohorts of established RA and recent-onset RA (95). In a recently published study on patients with early arthritis, including RA and patients with undifferentiated arthritis, anti-CCP positivity combined with radiographic damage at baseline was the best predictor for radiographic progressive disease at 2 years. The prognostic value of anti-CCP lied mainly in its ability to predict mild disease. This effect was accentuated in IgM-RF negative patients (96). Seven criteria, one of which was anti-CCP antibody positivity, discriminated well between selflimiting, persistent nonerosive, and persistent erosive arthritis in a Dutch early arthritis cohort (45). Anti-CCP antibodies predicted the development of RA in a normal population (97). In this study, the new CCP2 test was used. A recent study reported a high prevalence of a positive anti-CCP test in palindromic rheumatism, but the predictive value of anti-CCP as a marker of progression in palindromic rheumatism is still uncertain (98). In this study, similar proportions of anti-CCP

antibodies were observed in palindromic rheumatism and RA.

As anti-CCP antibodies can be present years before disease onset (97), it has been hypothesised that the immune response to CCP results from loss of tolerance to normally occurring citrullinated peptides at sites of tissue injury. Also, in an animal model, defects in the regulation of B cell survival were crucial for the production of anti-CCP antibodies (99). These findings present some very interesting options, such as identifying early polyarthritis patients, who have not yet developed full-blown RA, identifying patients with early RA, and eventually developing treatment against the loss of tolerability and defects in the regulation of apoptosis (100).

6.3.3. Markers of bone and cartilage degradation in RA

Degradation products of articular connective tissue are released into the circulation and excreted with the urine, and can be measured. Several attempts have been made to measure bone and cartilage destruction in arthritis to help with the decision whether or not to begin aggressive therapy with DMARDs in early RA. Because there is often an imbalance between the synthesis and degradation, it is often necessary to look at both the synthesis and degradation of cartilage molecules. However, none of these markers are as yet routinely used in clinical practice.

Type I and II collagen

Immunoassays measuring the carboxyterminal telopeptide of type I

collagen (ICTP, CTX-I, CrossLaps) enable the analysis of type I collagen breakdown products in blood. A study of 99 patients with RA with a disease duration <1 year showed that the serum concentration of ICTP was higher in RA patients than in the normal population, and the concentration correlated with the extent of joint inflammation (101). The correlation between the serum ICTP and joint destruction indices was also significant, but weaker. Another study of RA patients with a longer disease duration showed that ICTP correlated with determinants of impairment and with markers of inflammatory activity (102). A study on RA patients with a disease duration of <1 year showed that patients with elevated serum ICTP levels combined with positive RF and elevated CRP had more joint destruction than patients without these findings (62). Synovial fluid ICTP levels correlated with future joint destruction in RA patients with a mean disease duration of 10 years (103). In a cohort of patients with a duration of RA ≤ 1 year, serum levels of ICTP correlated with the radiological progression (104). Another study showed that serum ICTP discriminated between RA patients with destructive joint disease and milder disease (105).

Carboxyterminal crosslinking telopeptide fragments of type II collagen (CTX-II) in urine can be used as a specific marker of cartilage degradation (106). High baseline levels of urinary CTX-I and CTX-II independently predicted an increased risk of radiologic progression over 4 years in patients with early RA (mean disease duration 5 months) in a Dutch study (106). Increased baseline urinary levels of CTX-I and CTX-II were the most important predictors of new joint damage for patients without radiographic destruction, whereas disease activity and ESR were not predictive. This study showed that bone and cartilage are degraded very early in RA.

Other markers

Low-dose prednisolone treatment in early RA (disease duration <2 years) had no significant effect on cartilage turnover as measured by glycosaminoglycan and keratan sulphate epitope 5D4, but there was a reduction of synovium-derived markers, hyaluronate and N-propeptide of type III procollagen (PIIINP), and serum osteocalcin, a proposed marker of bone formation. The authors concluded that early erosions do not involve cartilage surfaces, and that low-dose prednisolone (7.5 mg/day) reduces synovitis and suppresses bone turnover, suppressing osteoblast function without reducing bone resorption (107).

Measurement of the urinary excretion of the collagen crosslinks pyridinoline, the major crosslinking compound in the bone, and deoxypyridinoline, a bone-specific marker, may give an indication of patients with early RA who are losing bone mass quickly (108).

Patients with RA with a disease duration of <2 years with elevated procollagen type III N-propeptide (PIIINP) levels, a marker for collagen III synthesis, had a higher rate of radiographic progression than patients with normal mean levels on PIIIINP (109).

Levels of carboxyterminal propeptide of type I procollagen (PICP), a marker of collagen synthesis, were reduced in patients with recent onset RA, suggesting decreased bone formation (110).

Matrix metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) are a family of proteases thought to

play a central role in the degradation on the extracellular matrix of articular bone and cartilage. MMPs are divided into four different groups of enzymes: 1.) Collagenases (MMP-1, MMP-8 and MMP-13), 2.) Gelatinases (MMP-2, MMP-9) 3.) Stromelysins (MMP-3, MMP-10) and 4.) Others. In RA, the MMPs play a major role in the destruction of cartilage and other components of connective tissue in the joints. MMP-3 is considered to be the main MMP involved in cartilage degradation (111).

Patients with radiographic erosions had higher levels of MMP-2 in the synovial fluid than patients without erosions in an RA patient population with a disease duration of <1 year (112). Serum MMP-3 levels were related to CRP, ESR and clinical variables, and the levels decreased in patients with early RA (disease duration <1 year), who responded to DMARD treatment (113). High serum MMP-3 levels were associated with the development of radiological damage in patients with early RA (114, 115). Baseline serum MMP-1 and MMP-3 levels correlated with disease activity and predicted functional and radiographic outcome in early (disease duration <1 year) untreated RA (116).

The MMP-3 genotype in combination with the shared epitope had prognostic significance for the development of erosions (111). The radiographic damage or its progression over 4 years did not differ across MMP-1 genotypes. A combination of cartilage markers has also been studied. High baseline levels of glucosyl-galactosyl-pyridinoline, a marker of joint destruction, CTX-II and MMP-3 were associated with increased risk of progression of joint destruction in early RA (117).

Cartilage oligomeric matrix protein (COMP)

Cartilage oligomeric matrix protein (COMP) is a non-collagenous, cartilage-specific protein with five identical disulphide-linked subunits (pentameric) with a total molecular mass of 434 kDa (118). COMP was first described in cartilage but is also found in non-cartilage tissue such as tendons, synovial membrane, meniscus and ligaments. The precise function of COMP is not known, but raised levels in synovial fluid and serum may reflect both degradation and repair of the cartilage, and possibly also synovitis (119, 120). Serum levels of COMP can be used to monitor the progress of cartilage destruction and repair in RA and osteoarthritis before radiographic changes appear (118).

Conflicting results have been reported concerning the predictive value of serum COMP levels in joint destruction (121-123). COMP does not correlate with inflammatory markers (122, 124-126). Studies on ReA have reported conflicting results concerning the levels of serum and synovial fluid COMP (118, 124).

7. Prognostic factors of RA

There are several retrospective and prospective studies using univariate and multivariate analysis to establish initial individual factors associated with a worse prognosis in RA. The best approach to study prognostic markers in RA seems to be to include patients with early-onset RA (<1 year) with regular examinations, including standardised evaluations of clinical, laboratory and radiographic measurements (127). Radiologic damage mirroring disease progression is usually considered the "gold standard". The studies usually employ radiographic damage as an end point and report a combination of clinical factors, such as age and sex, number of tender or swollen joints or the Ritchie index for swollen joints, and patients' and physicians' subjective perceptions, such as pain or general assessment of the disease activity. Laboratory variables, such as ESR, CRP and RF, and results of functional assessment of disease activity, such as the Health Assessment Questionnaire (HAQ), composite scores such as the Disease Activity Score (DAS), and different genetic and immunologic markers such as HLA analysis, shared epitope, tumour necrosis factor alpha (TNF- α) microsatellite analysis and autoantibodies are often included in the predictive factors.

A Finnish study on 200 patients with a recent-onset arthritis found that symmetrical polyarthritis in peripheral joints, serum rheumatoid factor, X-ray changes, morning stiffness, high ESR and old age correlated best with a destructive joint disease (128). A French study on 191 RA patients with a disease duration of <1 year in 1993-1994 reported that baseline radiologic scores, RF, ESR, HLA-DRB1*04, duration of morning stiffness, pain and CRP correlated significantly with radiologic outcome (127). Genetic information (HLA DRB1 shared epitope) was useful in predicting radiographic damage in RA patients with mean disease duration of 10 years (129). Another study of 86 RA patients with a mean disease duration of eight years reported that subcutaneous nodules, HLA DRB1*04 or DRB1*01, AKA, ESR and CRP were risk factors for radiographic damage (79).

A study from the UK reported that the combination of polyarticular disease, positive RF and low serum sulphydryl levels were very specific for predicting persistent disabling disease in an early arthritis cohort, but this combination lacked sensitivity (130). Positive RF latex test was the most prominent risk factor for the development of persistent synovitis in another early arthritis cohort from the UK (131). Female sex, longer disease duration, large joint involvement, and a high baseline HAQ were the strongest predictors of future disability in the Norfolk Arthritis Register, a primary care based inception cohort of patients with polyarthritis (132). Rheumatoid factor, HLA DRB1* 04 allele, and a tentative diagnosis of RA were the factors predicting progression to RA in a French study of patients with an inflammatory arthritis of a disease duration of < 1 year (49). A Canadian study on 127 patients with palindromic rheumatism reported positive RF, early involvement of the wrist and proximal interphalangeal (PIP) joints, female sex and older age onset as prognostic factors for development of palindromic rheumatism into RA or another connective tissue disease (133).

8. Reactive arthritis

Reactive arthritis is a joint inflammation developing after certain enteric, urogenital tract, or respiratory tract infections (e.g. *Salmonella, Yersinia, Shigella, Campylobacter, Chlamydia trachomatis* and *Chlamydia pneumoniae*). These bacteria are intracellular pathogens and, since they are all Gram negative, they contain lipopolysaccharide (LPS). The list of bacteria reported to cause reactive arthritis is growing (134). Bacterial DNA and RNA or live intra-articular bacteria have only occasionally been detected in ReA triggered by enterobacteria (135). Contrary to that, chlamydial DNA and RNA have been frequently detected in the affected joints of patients suffering from *C. trachomatis*-triggered ReA, suggesting that the bacteria are viable and metabolically active in synovium, but persisting in a non-cultivable form (136).

It is not known why certain patients develop ReA after infection. Different stages of the infection may be important, i.e. invasion of the microbes into the cells, intracellular survival, and antigen presentation and recognition. Higher antibody concentrations in patients with ReA as compared to infected patients without ReA have been interpreted to indicate bacterial persistence in patients with *Salmonella*- and *Yersinia*triggered ReA (137). The arthritogenicity of the microbes seems to differ between different bacteria, and even between different serotypes (138).

The role of human leukocyte antigen-B27 (HLA-B27) in the development of ReA seems to be complex. Studies suggest that HLA-B27 decreases the invasion of reactive arthritis-triggering bacteria, alters the intracellular survival of these bacteria, and modulates different signalling pathways. Misfolding of the HLA-B27 heavy chain is associated with overload of the endoplasmic reticulum (135, 139). Most hospital-based studies have shown a high association of HLA-B27 and arthritis (140-142). However, studies on *Salmonella* arthritis after outbreaks of *Salmonella* have reported lower frequencies of HLA-B27 positivity (143-145). In a recent population-based study of *Campylobacter* ReA, the arthritis was not associated with HLA-B27 (146).

A study from the US on patients with oligoarthritis of undetermined origin, studying *Chl. trachomatis*, *Mycoplasma* and *Borrelia* reported that 69% of the patients with oligoarthritis and 20% of the controls were carriers of clinically silent infections. Thirty-six per cent of the patients but no controls had evidence of prior or persistent chlamydial infection. The HLA-B27 haplotype represented a risk factor for the development of oligoarthritis. In a 1-year follow-up, the outcome and course of oligoarthritis did not correlate with a specific infectious organism and were not affected by antibiotic treatment (147).

Lately, there have been reports on some new agents causing arthritis. In three previous studies, *C. pneumoniae* was a triggering factor in 2.2%-10% of cases with acute ReA (148-150). In an early arthritis register, 2.7% of the patients had parvovirus B19 arthritis (151). Other studies have reported figures of 3-6% for parvovirus B19 infection in early RA (152-154), and of 11-18% in unspecified inflammatory arthritis (152, 153, 155, 156).

9. Costs of early arthritis

The burden of RA has been shown to be enormous for both the patient and the health services. In Sweden, the annual total cost of RA in 1994 was estimated to be 2.9 billion SEK, 292 million US\$ (157). There are only a few studies assessing the costs of RA with a disease duration of less than one year (158-163). The studies are difficult to compare, partly due to different patient settings, but also because different methods are used to assess the costs, and because treatment traditions vary locally and nationally. The studies are summarised in **Table 3**. To our knowledge, there is no data on the costs of early ReA or undifferentiated arthritis.

A burden-of-illness study of arthritis patients enrolled prospectively in 1990-1991 in the Norfolk Arthritis Register in the UK reports the costs for inpatient stays, outpatient visits and second-line drugs (160). The costs for sick leave, health professionals and radiographs were excluded. The annual cost per patient for a RA patient was US\$709, a conservative estimate according to the authors. A Health Assessment Questionnaire value (HAQ) of \geq 1 (164) and positive rheumatoid factor were associated with higher costs.

In two previous studies from Sweden, the Markov model was used to assess the costs of RA (159, 163). In the Markov model, the annual costs for a Swedish RA patient with a HAQ score <0.6 and HAQ scores between 0.6 and 1.1, with low Larsen scores (165), were US\$693-723 and US\$5952-7290, respectively. The annual cost for an RA patient with a HAQ score <0.6 in the UK was US\$1376 and for a patient with a HAQ score 0.6-1.1 in the UK US\$5676. In a Dutch study, the mean annual direct costs for a patient with early RA were US\$7372, with a wide range. Functional disability and lower age were related to higher costs (158). The Dutch study also included non-medical direct costs, such as aids in the home, but excluded indirect costs. A US study on patients with severe early RA (mean HAQ 1.24, mean tender and swollen joint count 25 and 21, respectively) reported an annual cost of US\$5760 per patient, and shorter disease duration and comorbid conditions were associated with higher cost (161). Hospitalisation costs in this study were low, only 3.5% of the total direct costs. A German study assessing indirect costs in early RA in 1995 reported indirect annual costs of US\$11 750 using the human capital approach (162).

A study of the costs incurred by patients with inflammatory polyarthritis of a mean disease duration of 47 months from the Norfolk Arthritis Register reported a mean cost of US\$4530 per person during a 6-month follow-up (166). Fifty percent of the patients had RA. This study included outpatient visits and inpatient stays, out-of-pocket expenses, time lost from usual activities and household help. The study excluded sick leave, radiographs, laboratory tests, and visits to health professionals. Fourteen per cent of the costs were incurred by the health care services, and the remaining 86% of the total costs was non-health costs. The distribution of the costs was heavily skewed. A positive rheumatoid factor, HAQ score and age were significantly associated with cost (166).

Tab	le 3.	Literature	review	of the	articles	published	on	costs	ofe	early	RA	٩.
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Author, year	Country	Ν	Disease duration, mean	Age, mean	Included	Excluded	Costs/year/ patient	Comment
Cooper et al., 2000 (160)	UK	344	5 months	56	Inpatient, outpatient visits, second- line drugs	Health professionals, radiographs, indirect costs	US\$ 709	50% of cohort had RA
Merkesdal et al., 2001 (162)	Germany	133	7 months	47	Indirect costs for work loss	Direct costs	US\$ 11 750 per person- year	Human capital approach
Newhall- Perry et al., 2000 (161)	US	150	6 months	51	Inpatient, outpatient visits, medication, radiographs, laboratory tests, indirect costs	-	US\$ 5760	Severe disease Questionnaire

Van Jaarsveld et al., 1998 (158)	The Netherlands	363	0-6 years	60	Outpatient, inpatient visits, medication, laboratory tests, radiographs, alternative medicine, health care workers,	Indirect costs	US\$ 5891	Questionnaire
					devices and adaptations at			
					home			
Kobelt et al., 1999 (159)	Sweden	116	<2 years	52	Outpatient costs, inpatient costs, medication, drug safety monitorig, work capacity, lost market production	Short-term sick leave, radiographs, health professionals	HAQ<0.5 and Larsen 0-7: US\$ 693 HAQ>2.6 and Larsen 100- 200: US\$ 19 900	Markov model based on HAQ and Larsen scores
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Kobelt et al., 2002 (163)	Sweden and the UK	Tot. 1099	8-11 months	52-54	Outpatient costs, inpatient costs, medication, drug safety monitoring, work capacity, lost market production	Short-term sick leave, radiographs, health professionals, non-medical direct costs, costs of informal care	Swedish patients: HAQ<0.6: US\$ 723 HAQ 0.6-1.1 : US\$ 7290 UK patients: HAQ<0.6: US\$ 1376 HAQ 0.6- 1.1: US\$	Markov model based on HAQ
							5676	

HAQ= Health Assessment Questionnaire

Aims of the study

The aims of this study were as follows:

I To estimate the annual incidence of inflammatory joint diseases in a prospective population-based referral study in Kronoberg County in southern Sweden.

II To detect evidence of infections preceding early arthritis and to compare the clinical outcome of remission during a 6-month follow-up for patients with and without signs of prior infection.

III To study whether a new serological marker, antibody test for cyclic citrullinated peptides (anti-CCP), and a marker for cartilage destruction, cartilage oligomeric matrix protein (COMP), discriminate between patients with early joint inflammation.

IV To study health care consumption and costs of health care in a population-based cohort of very early arthritis.

11. Study setting

11.1. Background

At the time of the study, the county of Kronoberg in Southern Sweden (Småland) had a population of 177 000, and the number of inhabitants over 16 years of age was 140 000. This county has two hospitals, the Central Hospital in Växjö and the local District Hospital in Ljungby. In this county, the care of patients with active rheumatological diseases who need specialist treatment is concentrated either in the Rheumatology Department in Växjö Central Hospital or at the one private practitioner participating in the study. The county has 25 primary health care centres. **Figure 1.**



Figure 1. Map of Scandinavia showing Kronoberg county.

11.2. Patients and methods

11.2.1. Incidence of early arthritis (I)

The flow of the patients in the study is shown in **Figure 2**. The incoming patients were included as incident cases in the study if they had a new joint inflammation with swelling of at least one joint, if they were over the age of 16, and provided the onset of the joint inflammation occurred between May 1, 1999 and May 1, 2000. Children aged 16 or less, and patients with osteoarthritis, septic arthritis and crystal deposition diseases were excluded from the study. Patients with a previous history of joint swelling before May 1999 were excluded. The general practitioners in the participating primary health care centres referred the patients either to the outpatient clinic at the Rheumatology Department in Växjö Central Hospital or to the private rheumatologist in Växjö (Olof Börjesson), where the patients were recruited into the study. Only patients resident in this county were included in the study. As some of the patients might present several months after the onset of the joint symptoms, the incoming referrals to the rheumatology unit and the private practitioner were systematically screened until January 31, 2001. Altogether, 21 primary health care centres, the one private outpatient rheumatology unit, and all specialised units at Växjö Central Hospital and at Ljungby District Hospital where patients with inflammatory joint diseases might present (e.g. departments of internal medicine, orthopaedics, dermatology and infectious diseases) participated in the study. The coverage area encompassed an adult population (>16 years) of 132 000 people.

After inclusion in the study, the diagnosis of the aetiology of the arthritis was conducted as follows. All of the patients defined as having RA

fulfilled the 1987 ACR (American College of Rheumatology) criteria during the inclusion time, i.e. from May 1, 1999 to January 31, 2001 (3). Radiographs of the inflamed joints, usually hands and feet, were taken of all the patients with suspected RA at presentation. Psoriatic arthritis was defined as psoriasis in association with arthritis, with a negative test for rheumatoid factor (29). The criteria for Lyme arthritis were a medical history of mono- or oligoarthritis with no alternative explanation and a positive serology for *Borrelia burgdorferi* as analysed by the enzymeimmunoassay at the local microbiology laboratory (167). Reactive arthritis was defined as an inflammatory joint disease either preceded by an infection and verified by cultures and/or positive serology, or, in the absence of a history of infection, by cultures and/or serology alone. The patients with joint inflammation not meeting the above-mentioned criteria were classified as cases of undifferentiated arthritis. The Larsen method was used for the evaluation of joint erosion (165).

The patients were treated according to the current treatment principles for rheumatic diseases, and no specific treatment protocol was used. The patients were initially started on non-steroidal anti-inflammatory drugs (NSAIDs), and DMARDs were initiated in ongoing joint inflammation. Intra-articular corticosteroid injections were given when needed and were the primary alternative for corticosteroid treatment. Oral corticosteroid treatment was initiated when needed, usually in polyarthritis causing functional incapacity.



Figure 2. The flow chart of the study.

11.2.2. Infections preceding arthritis (II)

The patients presenting less than three months from the start of the symptoms were included in a patient cohort. A total of 71 patients were included in this cohort. The patients underwent the same clinical and laboratory examinations at presentation and after 1 month, 3 months and 6 months, or, if they recovered during the first 6 months, up to recovery. A chest radiograph and radiographs of the joints involved were obtained at presentation. All the patients were interviewed as to infections preceding the onset of arthritis. The patients were screened with routine laboratory tests (ESR, CRP, blood cell counts, urinalysis, alanine transferase, serum creatinine) and also screened extensively for preceding infections. The Swedish version of the Health Assessment Questionnaire (HAQ) (168), the patients' and physicians' global assessment by the visual analogue scale (VAS), and the patients' assessment of pain by the VAS scale were analysed at each clinical assessment. The number of swollen and tender joints were analysed by the 44-joint count and the 53-joint count, respectively, and the Ritchie index for tender joints was analysed at each visit. Table 4 shows the microbiological and serological tests used and the time intervals of the tests. The patients were initially followed up for 6 months. The patients included in the cohort of 71 patients were also invited to a 2-year follow-up.

Table 4. A schematic presentation of the microbiological and serological tests used in the study for infections preceding arthritis also showing the time intervals for the tests (II).

Test	Timing 0 month (inclusio n)	Timing 1 month	Timing 3 months
Yersinia serology (169)	Х	Х	
<i>Campylobacter jejuni</i> serology (170)	Х	Х	
Salmonella typhimurium and enteritidis serology (171)	Х	Х	
Borrelia burgdorferi serology (167)	х		х
<i>Chlamydia trachomatis</i> serology (172, 173)	х		X
Chlamydia pneumoniae serology	Х		Х
<i>Chlamydia trachomatis</i> DNA, first- void urine (174)	х		x
Parvovirus B19 serology (175)	х		х
Faecal culture	x		
Throat swab	х		

11.2.3. Anti-CCP antibodies and COMP in early arthritis (III)

Anti-CCP antibodies and serum COMP were analysed in the cohort of 69 patients with very early arthritis. Serum levels of anti-CCP antibodies were analysed by enzyme-immunoassay (EIA) (Immunoscan RA, Euro-Diagnostica, Arnhem, The Netherlands), using the second generation CCP2 test. Serum COMP was measured by EIA (AnaMar Medical, Lund, Sweden).

11.2.4. Costs of early arthritis (IV)

To establish the health care consumption and costs of health care services in the cohort of 71 patients with very early arthritis, a burden-of-illness study was conducted. Fifty-six patients agreed to participate in this part of the study.

Inpatient stays and outpatient visits at Växjö Central Hospital at the departments of medicine, orthopaedic surgery, general surgery, infectious diseases and dermatology, as well as visits to the emergency department, were recorded from the onset of the symptoms to the last control in the study. Visits to general practitioners, physiotherapists and occupational therapists were also recorded. Costs of laboratory tests for monitoring the safety of the DMARDs according to a standard schedule were recorded. As to the medication, only the use of corticosteroids and DMARDs were recorded. The costs of radiographs were included.

For indirect costs, i.e. costs for sick leave, the National Health Insurance Institution provided the time period and reimbursement for patients in the study with sick leave for over 2 weeks. For patients with less than 2 weeks' sick leave, the days of sick leave were obtained from the patient records.

Results

12.1. Incidence of early arthritis

The total annual incidence for joint inflammation was 115/100 000. **Table 5** summarises the total annual incidences in the different diagnosis groups. We also calculated the incidence for RA including the patients with clinical RA, who did not fulfil the 1987 ACR criteria, but had the clinical diagnosis of RA. By this calculation, the total incidence for RA was 30/100 000, for women 39/100 000, and for men 21/100 000. The total incidence for ReA was 28/100 000, and for postenteric ReA 18/100 000. The mean age for patients with RA was 60 years, and for the patients with psoriatic arthropathy was 52 years. The incidence of Lyme arthritis and sarcoid arthritis was low. **Table 5**. The absolute numbers and annual incidences (/100 000) ofinflammatory joint diseases in Kronoberg county in SouthernSweden (I).

Diagnosis	Women		Men		Tota	l
	N	Incidence (95% CI)	Ν	Incidence (95% CI)	N	Incidence (95% CI)
Rheumatoid	19	29	12	18	31	24
arthritis		(17-45)		(9-32)		(16-33)
Reactive	23	35	14	21	37	28
arthritis		(22-52)		(12-36)		(20-39)
Undifferentiat	27	41	27	41	54	41
ed arthritis		(27-59)		(27-60)		(31-54)
Psoriatic	8	12	3	5	11	8
arthritis		(5-24)		(1-13)		(4-15)
Lyme arthritis	1	2	2	3	3	2
		(0-8)		(0-11)		(0-7)
Sarcoid	0	0	3	5	3	2
arthritis		(0-6)		(1-13)		(0-7)
Other	10	15	2	3	12	9
		(2-32)		(0-11)		(5-16)
Total	88	132	63	96	151	115
		(106-163)		(74-123)		(97-134)

12.2. Infections preceding arthritis

Seventy-one patients were included in the study. The diagnoses are shown in **Table 6**. The demographics of the patients are shown in **Table 7**. In these two tables, the diagnoses at two years are used. In the original article, the diagnoses and data at 6 months were reported. Altogether, 32 (45%) patients had an infection shortly before onset of arthritis, as verified by positive serology and/or history of infection (< 2 months from the onset of arthritis symptoms). All of the faecal cultures were negative, as were the throat swabs. Seventeen (63%) of 27 ReA patients had had a recent *C. jejuni*-infection. Three patients each had evidence of two recent prior infections as determined by serology. **Table 8**.

Table 6. Diagnosis and number of patients in the study of 69 patients of infections preceding arthritis. The diagnoses at 2 years are used in this table.

Diagnosis	Men	Women	Total (%)
Rheumatoid	6	10	16 (23%)
arthritis			
Reactive	10	18	28 (41%)
arthritis			
Undifferentiated	4	6	10 (14%)
arthritis			
Other	5	10	15 (22%)
Total	25 (36%)	44 (64%)	69 (100%)
	1		

Table 7. The demographics and clinical characteristics of the early arthritis cohort of 69 patients at inclusion. The diagnoses at 2 years are used in this table.

Demographics	RA	ReA	Undifferentiated	Other
	N=16	N=28	N=10	N=15
Mean age (SD)	58 (13)	45 (18)	53 (18)	47 (17)
Number of	10 (63)	18 (64)	6 (60)	10 (67)
female patients				
(%)				
Mean symptom	7.6 (1-12)	6.6 (0-12)	8.2 (1-12)	7.5 (1-12)
duration				
weeks, range				
Mean ESR,	37 (2-90)	30 (2-100)	19 (4-78)	31 (4-100)
range				
Median Ritchie	4.5 (0-15)	1 (0-8)	0.5 (0-6)	1 (0-9)
score, range				
Median joint	10 (2-50)	2.5 (0-34)	1.5 (0-6)	3 (1-12)
score, range*				
HAQ, median	0.8	0.5	0.4	0.5
Education,%				
-manual skilled	13	22	30	7
-university	13	11	10	53

ESR= erythrocyte sedimentation rate, HAQ=Health Assessment

Questionnaire

* Joint score for 44 joints scored for the extent of swelling in a scale of 0-

3, 0 not swollen joint, 3 very swollen joint.

Serology	Recent infection	Past infection
Campylobacter jejuni serology	17 (24%)	NA
Salmonella serology	1 (1%)	NA
Yersinia serology	1 (1%)	NA
Parvovirus B19 serology	2 (3%)	49 (69%)
Chl. pneumoniae serology	2 (3%)	48 (68%)
Chl. trachomatis serology	1 (1%)	12 (17%)

Table 8. The infections for the 71 patients as determined by serology.

NA= not available

Two patients had IgM antibodies against *C. pneumoniae*, and two patients had a serologically verified recent parvovirus B19 infection. Seventeen per cent of the patients had past *C. trachomatis* immunity. Sixty-eight and sixty-nine per cent had past immunity for *C. pneumoniae* and parvovirus B19, respectively.

Altogether 17 patients had a *Campylobacter jejuni* ReA, 63% of all ReA in the study. A total of 19 patients were classified as postenteric ReA. Of the *Campylobacter* ReA patients 82% were women. The mean age was 45 years. Sixty-five per cent had no comorbidities. Only one patient had preceding gastrointestinal symptoms. Eighty-eight per cent were RF negative. One patient had psoriasis and one had tendinitis and daktylitis. None of the patients had carditis or eye involvement. The median number of tender joints was 2, swollen joints was 2, median ESR 24 mm, and the median HAQ value was 0.75. Thus, the patients were relatively young, had few preceding symptoms and had relatively mild disease (unpublished data).

Follow-up data at six months were available for 64 patients (90%). In all, 37 (58%) patients were in remission within the first 6 months. Among the 32 patients with a recent infection, 22 (69%) were in remission. Among the 39 patients without a recent infection, the frequency of remission was lower, 15 (38%), p=0.011. Thirty-three per cent of the patients with RA were in remission. Forty-seven per cent of the patients with undifferentiated arthritis were in remission, as compared to 71% of the *C. jejuni* ReA patients. NB. Erratum in the original article in The Journal of Rheumatology.

Fifty-three patients agreed to participate in a 2-year control. Of these, 24 (45%) were in remission. Eight (11%) patients changed diagnosis during the two-year follow-up. One patient was originally classified as "other" and seven were classified as "undifferentiated". Two patients were later found to have gluten enteropathy with arthritis, one patient developed systemic lupus erythematosus, two were found to have erosive osteoarthritis, and one had ReA. One patient developed seropositive RA. One patient had arthritis and pustulosis palmoplantaris and was classified as psoriatic arthropathy. **Figure 3**. Of the patients with RA, 13 patients agreed to participate in the 2-year follow-up. Four RA patients (31%) were in remission at two years. Of the ReA patients, 22 came to the 2-year follow-up. Of these, 12 (55%) were in remission (unpublished data).



At 2 years 69 patients

Two patients were excluded from the analysis at two years because of erosive osteoarthritis at re-evaluation.

Figure 3. Flow chart of the study during the 2-year follow-up showing the diagnostic groups and the patients who changed diagnosis.

12.3. Anti-CCP antibodies and COMP in early arthritis

Altogether, 69 (97%) of the original cohort of 71 patients participated in the study. Two patients were excluded because the diagnosis of erosive osteoarthritis at two years. The diagnoses at 2 years were used in this part of the study. The group "Other" included five patients with psoriatic arthropathy, two patients with gluten enteropathy, two patients with systemic lupus erythematosus, two patients with sarcoid arthritis, and one patient each with Lyme arthritis, mixed connective tissue disease, ankylosing spondylitis and polymyalgia rheumatica.

Anti-CCP antibodies

The results of the anti-CCP antibody analysis are shown in **Figure 4.** The seropositive patients are shown with black dots. There was a significant difference between the four groups in the positivity of the anti-CCP antibody test (p<0.001). The sensitivity of the anti-CCP antibody test for RA of 44% (95% confidence interval [CI] 20% to 70%), and the specificity 96% for RA (95% CI 87% to 100%). There was a statistically significant difference between the seronegative and seropositive RA patient groups in the presence of the anti-CCP antibodies (p=0.005). There was also a statistical difference between the RA group and the ReA group in the presence of the anti-CCP antibodies (p=0.007). There was no correlation between the anti-CCP antibody level and clinical variables (data not shown).



Figure 4. The distribution of anti-CCP in the different patient groups.

COMP

The baseline serum levels of COMP in the different patient groups are shown in **Figure 5.** Fourteen (18%) of the 80 patients in the control group

had elevated serum COMP levels. There were no statistical differences between the different diagnosis groups concerning a positive serum COMP test (p=0.48). Serum COMP correlated with age (r=0.46 [95% CI 0.25 to 0.63], p=0.0001), with the number of swollen joints (r=0.3 [95% CI 0.06 to 0.51], p=0.02) and with CRP (r=0.28 [95% CI 0.04 to 0.49], p=0.02), but not with other clinical variables.





12.4. Costs of early arthritis

Out of 71 patients fulfilling the inclusion criteria, 56 (79%) agreed to

participate in this economic analysis. The diagnoses and number of patients in each diagnosis group are shown in **Table 9**. **Tables 10** and **11** show the demographics and clinical characteristics of the patients. The diagnoses at 6 months were used in this study. The excluded patients did not differ demographically from the included patients. For the whole patient group, direct and indirect costs caused 56% and 44% of the total costs, respectively. Visits to physicians and health professionals accounted for 22% and 3% of all the costs respectively. Radiographs and laboratory tests for DMARD safety monitoring caused 7% and 2% of the total costs respectively. Medication, i.e. DMARD and corticosteroid treatment, accounted for 2% of all costs.

Table 9. The distribution of the 56 patients in the cost analysis in eachdiagnosis group. The diagnoses at six months were used.

Diagnosis	Men	Women	Total
			(%)
Rheumatoid arthritis	6	7	13 (23%)
Reactive arthritis	6	15	21 (38%)
Undifferentiated	6	8	14 (25%)
arthritis			
Other	2	6	8 (14%)
Total	20	36	56
	(36%)	(64%)	(100%)

Table 10. Demographics of the study population of 56 patients in the costs analysis at inclusion. The diagnoses at six months were used.

Demographics	RA N=13	ReA N=21	Undifferentiated arthritis N=14	Other N=8
Mean age (SD)	58 (15)	48 (18)	52 (16)	62 (12)
Number of female (%)	7 (54)	15 (71)	8 (57)	6 (75)
Number of married (%)	8 (62)	15 (71)	12 (86)	7 (88)
Number of retired (%)	5 (39)	4 (19)	3 (21)	4 (50)
Education:				
manual skilled, n (%)	2 (15)	2 (14)	2 (14)	1(12)
university, n (%)	2 (15)	2 (10)	4 (29)	3 (38)
Number of pat. with comorbidities (%)	5 (39)	12 (57)	7 (50)*	3 (38)
Rheumatoid factor present (%)	4 (31)	1 (5)	3 (21)	2 (25)
Mean follow-up time, months (range)	7.5 (5.5- 9.0)	5.5 (1.1- 9.0)	5.6 (0.3-8.7)	7.8 (6.0- 9.0)
Mean duration of symptoms, weeks (range)	7.2 (1-12)	7.5 (0-12)	7.2 (1-12)	9.9 (5-12)

* For one patient the data were missing

Table 11. Clinical characteristics of the 56 patients in the cost analysis study population at inclusion. The diagnoses at six months were used.

Clinical characteristics	RA N=13	ReA N=21	Undifferentiated arthritis	Other N=8
			N=14	
Median number (44 joint index) of swollen joints (range)	14 (2-50)	4 (0-34)	2 (0-4)	4 (1-12)
Median Ritchie score (range)	5 (0-15)	1 (0-6)	1 (0-9)	1 (0-4)
Median CRP, mg/l, (range)	34 (3-241)	31 (3-275)	3 (3-197)	10 (3-74)
Median HAQ (range)	0.8 (0.13-1.88)	0.6 (0-1.75)	0.3 (0-2.0)	0.5 (0-3.0)
Patients' global assessment, VAS, median	56	31	50	17
Number of patients with DMARD (%) *	8 (62)	5 (24)	2 (14)	3 (38)
Number of patients with corticosteroids, (%) *	10 (77)	12 (57)	5 (36)	4 (50)
Number of patients in remission (%)**	5 (38)	16 (76)	7 (50)	3 (38)

*The patients had this medication at the clinical assessment at six months.

** At six months.

DMARD=disease modifying anti-rheumatic drug, CRP=C-reactive protein, HAQ=Health Assessment Questionnaire,

VAS=visual analogue scale

Figure 6 shows the percentages of the direct costs in the different patient groups. For undifferentiated arthritis, the costs of inpatient stays and medications were negligible. The 17 patients (30%) who were hospitalised caused approximately as much costs as the outpatients in all the groups except undifferentiated arthritis, where there was only one inpatient.



Figure 6. The distribution of the direct costs in the different diagnosis groups.

All patients generated costs. The distributions of the total costs per patient were skewed. **Figure 7.** The median cost per patient in the entire group was US\$ 3362. The median cost for a patient with RA was US\$ 4385. For a ReA patient, the median cost per patient was US\$ 4085. For a patient with undifferentiated arthritis and other arthritis, the median cost per patient was US\$ 1482 and US\$ 3361, respectively. There was no statistical difference in the median cost per patient in the different patient groups (p=0.34). The patient with the highest cost in the ReA group had a diagnosis of *Campylobacter* ReA, and she was treated as an inpatient at two departments, which partially explains the costs. The patient with the highest cost in the group of undifferentiated arthritis later developed SLE. High costs generated by sick leave partially explained her costs (unpublished results).





Total costs (\$)

13. Discussion

The local setting, whereby patients with rheumatological diseases in Kronoberg county are concentrated in the care of rheumatologists at Växjö Central Hospital and at the one privately practising rheumatologist, enabled us to calculate reliably the incidence of inflammatory joint diseases in this population. Also, the widely accepted clinical practice in Sweden, whereby patients with recent-onset joint inflammation are quickly referred to a rheumatologist for diagnosis and treatment, minimised the bias that only severe cases are usually seen at the secondary or tertiary centre. Thanks to the very good cooperation with the general practitioners and with other specialist physicians, the selection and referral biases were minimised. We calculated the referral bias to be 5%, based on the seven patients identified only through hospital records for joint aspirates. However, we probably missed several subacute patients, as well as patients with short-lived joint inflammation, due to referral bias, particularly Chl. trachomatis ReA and Salmonella ReA. In previous studies on outbreaks of Salmonella infection (143, 176), as well as in a study of joint symptoms during *Campylobacter* infection at a population level, a considerable proportion of the patients did not visit a physician for joint complaints (177). Also, a cross-sectional study setting underestimates the true incidence particularly of RA, as patients need time to present, and as RA patients should be given time to cumulatively fulfil the ACR criteria (8). However, the relatively short inclusion time enabled us to gather comprehensive information about the patients.

Our study included the whole spectrum of ReA, with both mild and

severe cases, some of which developed into chronic cases, and the total annual incidence was 28/100 000. We used quite a broad definition of ReA, including also arthritis preceded by upper respiratory tract infections and soft tissue infections. This partly explains the high incidence of ReA in this study. The annual incidence of postenteric ReA was 18/100 000, with *Campylobacter jejuni* being the predominant aetiological agent. Most epidemiological studies of ReA are conducted during known outbreaks of gastroenterological infections, where the incidence rates for ReA are calculated from the arthritis patients with a known infection. In this study of 71 patients with very early arthritis, we tested all patients for the same pathogens regardless of symptoms or history of infections. To minimise referral bias it would have been interesting to examine all the patients with positive cultures for enteric pathogens and *Chl. trachomatis* in this county during the inclusion period for joint symptoms, but unfortunately this was not possible. The incidence of positive faecal cultures for enteric pathogens and positive Chl. trachomatis urinanalysis findings in Kronoberg county during the study period 1999-2000 mirrors well the situation i Sweden (The Swedish Institute for Infectious Disease Control (Smittskyddsinstitutet)). Table 2. The low incidence of *Chl. trachomatis* ReA in this study was surprising, and is difficult to explain.

The fact that there are no universally accepted criteria for ReA or psoriatic arthropathy hampers the diagnosis of these illnesses and comparison of different epidemiological studies. Hopefully, a consensus on the diagnostic criteria will be reached in the near future.

In all, 45% of the patients in this study of 71 patients with very early arthritis had an infection preceding the arthritis, indicating the importance

of systematic surveillance for infections in patients presenting with early arthritis. However, only a few patients had signs of recent infection with Chl. trachomatis, Chl. pneumoniae, Borrelia burgdorferi and parvovirus B19. Campylobacter jejuni dominated the postenteric ReA group. The practical implication of this finding is that more extensive routine microbiological testing in recent-onset joint inflammation is not warranted, and more extensive testing should be guided by the clinical picture. Arthritis preceded by infection seems to have a good prognosis, as most of the patients with a recent infection were in remission at 6 months. Also, almost 60% of the patients with undifferentiated arthritis and a third of the RA patients went into remission. However, even patients with inflammatory polyarthritis, even if they do not initially fulfil the 1987 ACR criteria for RA, need follow-up and active treatment, as 30% of the patients in a population-based patient cohort with inflammatory polyarthritis from the UK were shown to have a HAQ score of at least 1 at one year (132).

To date, the only serological test used in the diagnosis of RA is RF. A new serological marker, antibodies against cyclic citrullinated protein (anti-CCP antibodies), has performed well in clinical trials in RA patient populations and early arthritis clinics, and will most probably be used in routine clinical practice to diagnose RA (85, 86). The mechanism whereby antibodies against CCP are formed is not known, but may be due to the loss of tolerance to physiologically occuring citrullinated proteins, or defects in apoptosis. Testing for anti-CCP antibodies presents interesting possibilities in the future, such as screening patients with early polyarthritis, differentiating between chronic nonerosive polyarthritis and polyarthritis patients with a more aggressive erosive disease, and eventually developing medications against the possible loss of tolerance and defects in apoptosis, and using the test as a means to support the choice of anti-rheumatic pharmacotherapy. Anti-CCP antibodies have also been included in a proposed set of new diagnostic criteria for early polyarthritis (45). Our study confirmed the excellent specificity of anti-CCP antibodies for RA, 96%, early in the disease. Our study also confirmed the recent observation that anti-CCP antibodies differentiate RA from undifferentiated arthritis during the first months of disease (93).

Intensive research into the role of other markers, for example markers for cartilage metabolism, such as COMP, or collagen metabolism, such as ICTP, is ongoing, but the benefit of measuring cartilage and collagen markers in the diagnosis and follow-up of RA in clinical practice is as yet unclear. Used as a sole marker for cartilage metabolism in a crosssectional setting in patients with early polyarthritis with different diagnoses, serum COMP levels did not differentiate between the different patient groups in our study. Several of our patients had raised serum COMP levels, indicating cartilage involvement very early in the disease even in mild and self-limiting disease with good prognosis. The fact that serum COMP levels are age-dependent, and that COMP is also produced in the synovial tissue, further complicates the interpretation of the results. The structure and metabolism och cartilage and collagen is complex, and to gather reliable information about the cartilage or collagen breakdown or repair process in arthritis necessitates most probably several markers used together in serial measurements over time.

The study shows that inflammatory joint disease has substantial economic impact for the patient and for society from the onset of symptoms irrespective of the diagnosis. Despite the fact that most ReA patients had relatively mild disease, the median cost per patient in the ReA group was

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almost as high as for the RA group (US\$ 4085 and US\$ 4385, respectively). Sick leave accounts for about 50% of the total costs in all the groups already at an early stage of the disease. The annual total cost for the 151 patients with a recent-onset joint inflammation in this county in 1999-2000 was considerable, approximately US\$ 500 000 (4.3 million SEK) in 1999-2000, as judged from extrapolation from the patient cohort of 56 patients, using the figure US\$ 3300/patient/year. It can be concluded that all inflammatory joint diseases are relatively expensive initially because of the high indirect costs. However, most of the ReA patients go into remission, and the lifetime costs for these patients are probably not high. However, since most of the RA patients have lifelong disease, the lifetime costs of RA are enormous.

This study underlines the importance of early referral and treatment. Early referral and early start of therapy have been found to be the optimal treatment principle, as early therapy has been shown to influence the prognosis and costs of RA (43, 178). In this study, 33% of the RA patients were in remission at six months, and 31% at two years, figures considerably higher than in a Swedish patient cohort (7% of the patients in remission) (179), and figures comparable to the remission rate for a patient cohort treated with the sawthooth principle in Finland, 32% (180). Both the early referral and treatment, and the population-based setting, might explain the high remission rate in our cohort. New medications that enable better inflammatory control are now available, and early induction of therapy has been shown to influence the prognosis and costs of RA (178). The role of the new biological treatment options in ReA, particularly anti-TNF- α treatment, has not yet been established.
14. Conclusions

- The incidence of RA, ReA, psoriatic arthropathy, sarcoid arthritis and undifferentiated arthritis in this population-based study compared well with figures published earlier. Cases of Lyme disease were rare. The referral bias was estimated to be small.
- Forty-five per cent of the patients with early arthritis had evidence of a recent infection preceding the arthritis, as indicated by laboratory tests and/or disease history. *Campylobacter jejuni* ReA dominated the ReA group.
- 3. Anti-CCP antibodies had high specificity for RA in this patient cohort of early arthritis. Serum COMP was elevated in all the diagnosis groups, indicating cartilage involvement even in early mild selflimiting disease.
- 4. The health care costs per patient with RA and ReA during the first months of follow-up were quite similar, roughly US\$4000. Costs were lower for the patients with undifferentiated arthritis and other arthritides. Indirect costs caused about 50% of the total costs already at the beginning of the disease.

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16. Svensk sammanfattning

I denna prospektiva populationsbaserade tvärsnittsstudie från Landstinget Kronoberg, presenteras data på vuxna patienter med nydebuterade inflammatoriska ledsjukdomar under ett år (1999-2000). Den totala årliga incidensen av artrit i var 115/100 000. För reumatoid artrit (RA) var incidensen 24/100 000 (29/100 000 för kvinnor och 18/100 000 för män), för reaktiva artriter (ReA) 28/100 000 och för ospecificerade artriter 41/100 000. Incidensen av sarkoidosartrit och Borrelia-utlöst artrit var låg. I en kohort utgjord av 71 patienter med mycket tidig artrit (artritsymptom högst 3 månader), undersöktes sambandet till föregående infektioner mindre än 3 månader från sjukdomsdebut. Hos närmare hälften fanns indikationer på föregående infektion, oftast gastrointestinalt och särskilt Campylobacter jejuni. Två patienter hade haft en föregående infektion med Chlamydia pneumoniae och två hade en föregående infektion med parvovirus B19. Artriten gick i remission hos flertalet patienter med föregående infektion – signifikant oftare än när föregående infektionstecken saknades. Vi undersökte två serummarkörer, anti-CCP antikroppar och COMP (en broskmolekyl), hos 69 patienter. Anti-CCP antikroppar hade hög diagnostisk specificitet för RA och kunde skilja RA-patienterna från andra diagnosgrupper. COMP-nivåerna var förhöjda i serum hos flera patienter i alla diagnosgrupper, vilket tyder på broskengagemang redan mycket tidigt i sjukdomsförloppet. Kostnaderna för vård och sjukskrivningar under de första månaderna av sjukdomen analyserades i en patientgrupp bestående av 56 fall med mycket tidig artrit. Redan tidigt i sjukdomsförloppet var kostnaderna höga. Något oväntat var kostnaderna för gruppen av patienter med reaktiva ledinflammationer nästan lika höga som för patienterna med RA.

Sjukskrivning svarade för nästan 50% av de totala kostnaderna. Stora kostnadsvariationer sågs inom grupperna av patienter med samma diagnos. Mediankostnaden för RA-patienter var 37 400 SEK (US\$4385), vilket kan jämföras med 34 800 SEK (US\$4085) för ReA. För patienterna med ospecificerad artrit var mediankostnaden 12 600 SEK (US\$1482) och för patienterna med övriga diagnoser 28 700 SEK (US\$3361). För samtliga 151 patienter med tidig artrit i Landstinget Kronoberg 1999-2000 var den totala årliga kostnaden ca. 4,3 miljoner SEK (US\$500 000). Vid nydebuterad artrit är tidig remittering till reumatolog viktigt för ställningstagande till medicinsk behandling för att effektivt hämma inflammationen och motverka funktionsnedsättning, men också för att minska sjukdomsrelaterade kostnader, särskilt sjukskrivning.

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