

Regional differences in the incidence of rheumatoid arthritis in Finland in 1995

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Abstract

Objective—To investigate regional differences in the incidence of rheumatoid arthritis (RA).

Methods—Those subjects entitled to receive drug reimbursement for chronic inflammatory joint diseases in 11/21 central hospital districts (population base about 1.8 million adults) in Finland during 1995 were studied. The incidence rates from these central hospital districts were compared.

Results—A total of 1213 subjects were entitled to drug reimbursement for chronic inflammatory joint disease which had started at the age of 16 or over. Of these, 598 subjects satisfied the American Rheumatism Association 1987 criteria for RA. The age adjusted incidence of RA was 31.7/100 000 (95% CI 29.2 to 34.4) and varied significantly ($p < 0.001$) among the central hospital districts, ranging from 16.3 to 44.8/100 000.

Conclusion—There are regional differences in the incidence of RA. The reasons for these are probably environmental rather than genetic.

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Patients and methods

SICKNESS INSURANCE SYSTEM

Data on the incidence of chronic arthritis were obtained from the Finnish Sickness Insurance Scheme, which covers the entire population. Since 1966, the Sickness Insurance Act has provided for the prescription of drugs free of charge for certain chronic diseases, including chronic inflammatory rheumatic diseases. After an amendment in 1987, 90% of the costs were reimbursed and a second amendment in 1994 cut the rate to 75% of the costs. In 1995 glucocorticoids and disease modifying anti-rheumatic drugs were specially reimbursed. All inflammatory rheumatic diseases are grouped under one code in the population register of the Social Insurance Institution. The main diagnostic subsets are RA, ankylosing spondylitis, psoriatic arthritis, chronic reactive arthritis, juvenile chronic arthritis, and systemic connective tissue diseases. Finnish rheumatologists tend to begin early treatment of patients with prolonged arthritis with disease modifying antirheumatic drugs. Drug entitlement is usually for life, but can be for a fixed period. Eligibility requires a comprehensive medical certificate written by the attending doctor and approved by an expert adviser on behalf of the sickness insurance scheme.

STUDY POPULATION

Finland is divided into 21 central hospital districts. The study embraced subjects entitled to specially reimbursed drugs in 1995 in 11 districts (Hämeenlinna, Joensuu, Jyväskylä, Kotka, Kuopio, Lahti, Mikkeli, Savonlinna, Seinäjoki, Tampere, and Vaasa). The study area covered about 1.8 million inhabitants aged 16 years or over—that is, almost half the adult population in Finland. The population varied from 57 136 to 354 126 adults in different central hospital districts. The study area was easy to reach to obtain supplementary information from patient records, and the central part of the area was also included in our earlier studies. Information on the age distribution of the central hospital districts included in the study was obtained from the Finn Region Database maintained by Statistics Finland at VTTK Group Ltd (formerly the State Computer Centre).

PATIENTS

Basic information on history, symptoms, and signs as well as on radiographic and laboratory findings was obtained from drug reimbursement certificates. If this proved insufficient for classification purposes, additional information was obtained from hospital records. This was needed in 204/1418 cases (14%). A case was

The prevalence of rheumatoid arthritis (RA) is reported to be 0.5–1.0% in most Western countries for which reliable information is available. The annual incidence lies between 25 and 50/100 000 in most white populations.¹ Lower figures than this have been reported in France.² Pima Indians, on the other hand, have a much higher incidence than in white populations.^{3,4} Little is yet known of regional differences within countries about the incidence and prevalence of RA. Some regional differences in the prevalence of RA have been seen in Scotland,⁵ and modest evidence of spatial clustering of new RA cases was noted in the Norfolk Arthritis Study.⁶ The reasons for these differences remain unknown.

It is generally accepted that a combination of genetic and environmental factors plays a part in the cause of RA. Regional differences in its occurrence may provide clues on the environmental factors. Regional differences in the incidence and prevalence of many chronic diseases—for example, coronary heart disease (CHD), goitre, type I diabetes, and multiple sclerosis, have been reported from Finland.⁷⁻¹⁰ The nationwide register on sickness insurance benefits provides a unique opportunity to obtain information on the occurrence of chronic inflammatory rheumatic diseases in Finland.¹¹ We now report regional differences in the occurrence of RA in Finland.

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Table 1 Classification of subjects entitled to special reimbursement for drugs in the study area in 1995

Rheumatoid arthritis as diagnosis on certificate		743
Rheumatoid arthritis, disease duration <4 years*	564	
Rheumatoid arthritis, disease duration >4 years*	34	
Oligo- or polyarthritis not satisfying ACR criteria	145	
Other oligo- or polyarthritis		146
Spondyloarthropathy		312
Renewed entitlements		205
Insufficient information		12
All		1418

*Incident cases.

regarded as an incident case if entitled for the first time to specially reimbursed medication, either for life or for a fixed period, regardless of the duration of symptoms. The date of entitlement to antirheumatic drugs was taken as the date of diagnosis.

In 1995, a total of 1418 subjects were granted entitlement to specially reimbursed drugs for chronic inflammatory joint diseases which had started at 16 years of age or older. Of these, 205 were not classified as incident cases because of an earlier entitlement for a fixed period; these subjects had only a renewal of their eligibility. In 12 instances (0.8%) the available information about diagnosis was insufficient. In 889 cases the diagnosis on the reimbursement certificate was RA (n=743) or a related condition (oligo/polyarthritis, n=146), while 312 patients had spondyloarthropathies. In Finland the treatment of most patients with chronic inflammatory rheumatic and connective tissue diseases is supervised by specialists in rheumatology or internal medicine. In every central hospital district of the study area there was at least one doctor experienced in rheumatology. Certificates were provided by general practitioners in fewer than 10% of the cases.

INCLUSION CRITERIA

For this study a patient was considered to have RA if he/she met at least four of the American Rheumatism Association 1987 classification criteria.¹² Symmetry was defined as simultaneous involvement of the same joint areas on both sides and recorded at diagnosis. There were altogether 598 cases of RA. Table 1 shows the classification of incident cases.

STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS/PC+ program (SPSS Inc, Chicago, IL, USA). The incidence rates were age adjusted

by the direct method using the 1990 Finnish population as a reference. Confidence intervals (CI) were calculated using Poisson distribution. Differences in the incidence rates between different regions were tested by the χ^2 test, and the significance of the relation between incident cases and the time period in five districts was tested by the Mantel-Haenszel test for linear association. The difference in mean age at diagnosis between central hospital districts was tested with analysis of variance. Pearson's correlation coefficient between RA and cases of undifferentiated arthritis in the study area was calculated.¹³

Results

The age adjusted incidence of RA in the adult population was 31.7/100 000 (95% CI 29.2 to 34.4). The incidence among women was 40.0/100 000 (95% CI 36.0 to 44.2) and among men 23.2/100 000 (95% CI 20.2 to 26.7). The incidence rates varied significantly among the study areas ($\chi^2=32.3$, $df=10$; $p<0.001$), ranging from 16.3 to 44.8/100 000; among women from 23.2 to 56.1/100 000 and among men from 9.4 to 32.5/100 000. Table 2 and fig 1 show regional incidence rates. The highest incidence occurred in the eastern part of the study area near the Russian border (North Karelia) and the incidence was lowest in the Vaasa district on the coast of the Gulf of Bothnia.

The mean (SD) age at diagnosis for those patients (564/598) who had had symptoms of the disease for fewer than four years was 58.2 (14.3) years (range 16.7–87.6); 57.7 years for women and 59.3 for men. The rheumatoid factor (RF) status was known for all cases; positive results were recorded in 72.4% of the cases. The mean age at diagnosis was 57.9 years among RF positive and 59.1 years among RF negative cases.

Of the patients, 88–100% were receiving treatment within four years from symptom onset in all central hospital districts except the smallest district, Savonlinna, in which only 13/18 patients with RA were receiving drugs within this period. The shortest periods from symptom onset to diagnosis were recorded in the areas of the highest and lowest incidence. A correlation was seen between the RA and undifferentiated arthritis cases (that is, cases diagnosed as RA but not satisfying the American College of Rheumatology criteria or cases

Table 2 Regional incidence rates and total incidence of rheumatoid arthritis in the study area in Finland in 1995. The figures are age adjusted to the Finnish adult population in 1990

Area	All incidence (95% CI)	No of cases	Men incidence (95% CI)	No of cases	Women incidence (95% CI)	No of cases
Vaasa	16.3 (9.8 to 24.3)	21	9.4 (3.4 to 20.3)	6	23.2 (13.5 to 38.2)	15
Seinäjoki	28.9 (21.3 to 38.9)	47	20.0 (10.9 to 32.2)	15	38.7 (26.0 to 54.3)	32
Tampere	26.6 (21.5 to 32.5)	97	25.1 (17.9 to 33.6)	37	30.6 (23.3 to 39.9)	60
Hämeenlinna	34.3 (24.8 to 45.4)	48	21.3 (12.1 to 37.1)	13	46.0 (31.7 to 65.4)	35
Jyväskylä	43.1 (34.4 to 52.9)	91	30.0 (20.3 to 42.9)	29	54.5 (41.9 to 70.3)	62
Lahti	27.9 (20.6 to 37.3)	48	12.5 (6.0 to 23.1)	10	41.7 (29.7 to 58.2)	38
Kuopio	36.3 (28.7 to 45.7)	79	25.1 (16.2 to 36.9)	28	44.2 (32.6 to 59.0)	51
Mikkeli	29.9 (19.9 to 44.0)	30	28.2 (14.4 to 48.6)	14	31.7 (18.2 to 53.6)	16
Kotka	31.1 (23.1 to 41.5)	51	24.3 (14.3 to 38.2)	19	35.9 (23.6 to 51.3)	32
Joensuu	44.8 (34.6 to 57.3)	68	32.5 (20.8 to 49.3)	23	56.1 (40.5 to 76.7)	45
Savonlinna	28.6 (16.0 to 45.5)	18	15.4 (3.9 to 36.8)	5	39.8 (21.1 to 71.4)	13
Total	31.7 (29.2 to 34.4)	598	23.2 (20.2 to 26.7)	199	40.0 (36.0 to 44.2)	399

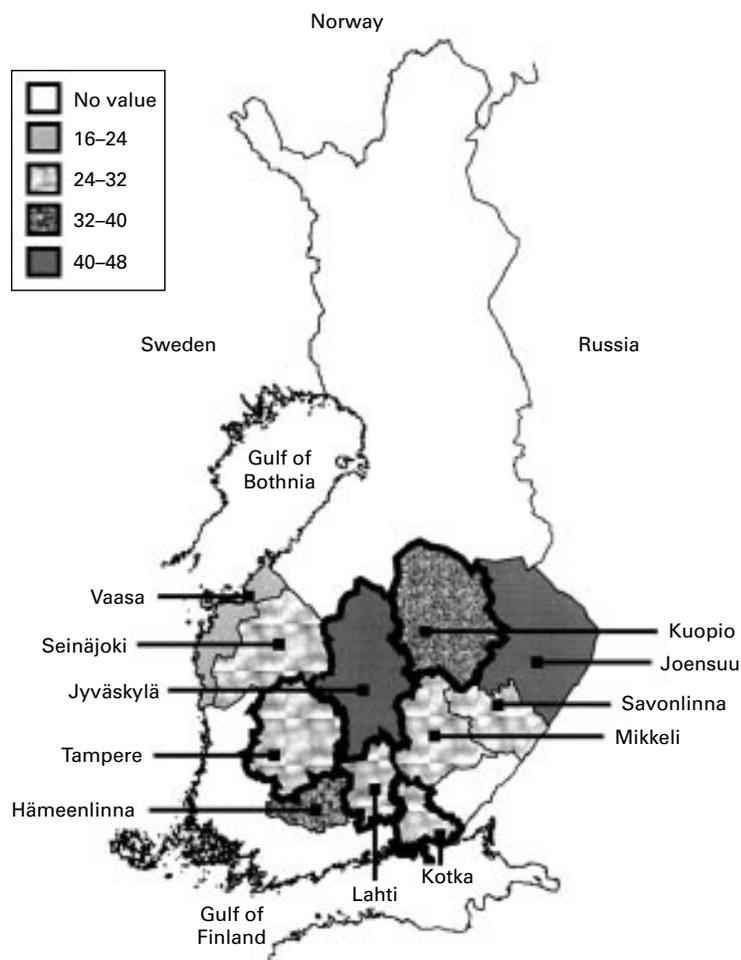


Figure 1 Age adjusted incidence rates of rheumatoid arthritis in 11 central hospital districts in Finland in 1995. The area of our previous study is outlined with a thicker line on the map.

diagnosed as oligoarthritis or polyarthritis; see table 1) in the study area, $r=0.71$ (95% CI 0.19 to 0.92).

Table 3 shows the incidence rates of RA in central hospital districts in the area included in our previous study in 1980, 1985, and 1990.¹⁴ Throughout the whole period the incidence was highest in the Jyväskylä region. The combined four year incidence in the Jyväskylä region was significantly ($p=0.002$) higher than in the Tampere region, where it was the second highest. A statistically significant decline was noted in the Tampere region.

Discussion

The main finding of this study was the highly significant regional differences in the incidence of RA in Finland that are equally wide among

both sexes. A significant positive correlation was shown between the incidence rates of RA and undifferentiated arthritis in the study area, supporting the contention that these differences are real. In the absence of any prior hypothesis, the possibility of chance variation, however, cannot be wholly excluded. These differences cannot be explained by inequalities in health services or in diagnostic practice. In every central hospital district, patients with rheumatological problems are referred in most instances to experienced consultants and the treatment of patients is uniform throughout the whole country. In the Lahti area, where the Rheumatism Foundation Hospital is located and where many consultant services are available, the incidence of RA was average. The period from symptom onset to diagnosis did not differ significantly between the different districts. The sensitivity of specially reimbursed drugs as an inclusion criterion is about 95%,¹⁵ which argues against marked differences in registration patterns.

It has to be noted that the boundaries between central hospital districts are somewhat artificial. The population density in the study area is about 12/km². About half of the population lives in urban and the other half in sparsely populated rural areas. The number of cases was too small for a more detailed spatial analysis.

The Finnish gene pool has evolved under the influence of a founder effect maintained by isolation. Genetic differences are present among language groups owing to the history of human settlement in Finland. The population of the Finnish western coast is influenced by Swedish heritage; the degree of Finnish admixture with the Swedish-speaking population is estimated to be about 60%.¹⁶ Frequencies of HLA antigens have been studied among healthy voluntary donors ($n=10\ 000$) registered with the Finnish Bone Marrow Donor Registry.¹⁷ Wide regional variations were found in the frequencies of some antigens, yet no differences were detected in HLA-B27 or DR4; their prevalences were 14% and 23%, respectively. In the western coastal area half of the population is Swedish speaking, and the incidence of RA was only one third of that in North Karelia (Joensuu district). No appreciable differences were seen in the prevalence of RA between Finland and Sweden.¹¹ Thus the low incidence of RA in the western coastal area cannot be explained by genetic factors known to be associated with RA.

Regional differences and changes over time have been seen in many diseases in Finland. In this regard, CHD is of special interest, because CHD and RA appear to have certain risk

Table 3 Regional incidence rates (95% confidence intervals) of rheumatoid arthritis in five central hospital districts in the central part of the study area included in our previous study in 1980, 1985, 1990, and 1995. The figures are age adjusted to the Finnish adult population in 1990

Area	1980	1985	1990	1995	p Value*
Kotka	38.6 (29.6 to 50.0)	34.6 (26.0 to 45.1)	24.4 (17.5 to 33.9)	31.1 (23.1 to 41.5)	0.113
Lahti	30.5 (22.5 to 40.4)	34.0 (25.5 to 44.1)	32.4 (24.1 to 42.1)	27.9 (20.6 to 37.3)	0.637
Tampere	44.8 (38.0 to 52.8)	41.3 (34.8 to 48.9)	30.3 (24.9 to 36.8)	26.6 (21.5 to 32.5)	<0.001
Jyväskylä	48.6 (39.0 to 59.4)	44.2 (35.6 to 54.8)	41.4 (32.7 to 51.1)	43.1 (34.4 to 52.9)	0.361
Kuopio	33.5 (25.9 to 42.6)	38.8 (30.8 to 48.6)	31.1 (23.9 to 39.7)	36.3 (28.7 to 45.7)	0.958

*Mantel-Haenszel test for linear association.

factors, particularly smoking, in common.^{18–19} The prevalence of CHD in the western part of the country is only half of that in eastern part in North Karelia (Joensuu district).²⁰ Mortality from CHD peaked around 1970. During the past three decades there has been a shift in coronary mortality towards elderly subjects. CHD mortality in the middle-aged population of Finland has decreased by approximately 65%. Most of this rapid decline in CHD mortality can be explained by decreasing prevalence in the three main coronary risk factors: smoking, hypertension, and hypercholesterolaemia.²¹ On the other hand, these risk factors appear to be only minor causes of geographical differences in CHD.²²

In Finland, CHD mortality of migrants seems to be determined strongly by their region of origin and to a much lesser extent by their region of destination.²⁰ This finding suggests that the reason for regional differences may be an environmental factor that in childhood or youth exerts its effect on the adult risk of the disease. So far, no conclusive evidence is available to demonstrate that an inflammatory agent or some other early life experiences can explain the differences in CHD morbidity.^{20–23} For RA it has been suggested that some as yet unknown key events in its pathogenesis may occur many years before the joints become affected. Perhaps the primary trigger may be traced from childhood or adolescence.²⁴

A decreasing incidence of RA was shown when the rates from the years 1990 and 1995 were compared with those from 1980 and 1985.^{14–19} In the 35–54 year age group the incidence decreased by 50% among both women and men.^{15–19} On the other hand, the mean age of disease onset and the peak incidence shifted towards the older age groups. These changes were seen in the central part of this study area (Jyväskylä, Kotka, Kuopio, Lahti, and Tampere districts), whereas the most western and eastern parts in the present study area were not included in former studies. Of note is that of the area of our earlier study the incidence was highest throughout the whole period in the Jyväskylä district. If the regional morbidity differences in RA and CHD are mainly due to poor childhood conditions, the rapid improvement of living standards since the beginning of last century will have reduced some of the differences between regions, because the relative variation in the standard of living between eastern and western regions has been decreasing during the latter half of the 20th century.²⁵ Thus studies of the incidence of RA and its age of onset in migrant populations are warranted.

Differences in the geochemical environment have been suggested as a possible source of geographical differentials in CHD,²⁶ and this hypothesis cannot be ruled out because the eastern, central, and western parts of Finland differ from each other geologically and geochemically.^{27–29} There is, however, little evidence to connect differences in specific geochemical risk factors with variations in heart disease.^{20–23} The effect of geological factors on inhabitants is complicated and often masked

by other factors. Currently, foods are produced and marketed throughout the country, and only a small proportion of the populace consumes locally self grown cereals and vegetables. However, drinking water reflects geological factors and its content of trace elements differs in the eastern, central, and western parts of the country.²⁷ In eastern Finland the characteristic geochemical features of the soil in the area of high coronary mortality include higher barium, cobalt, chromium, copper, nickel, and titanium concentrations than in the area of low coronary mortality. Characteristic geochemical features of groundwater include low fluoride concentrations and low hardness values²⁶; the main source of fluoride for humans is drinking water.

In the central hospital district of Jyväskylä, which has a high incidence of RA, the bedrock is composed mostly of granitoids. The contents of most nutrients in granitoids are low, and soil is characterised by the presence of moraine and sand, which are enriched with silica.²⁸ The trace element content in groundwater is low. The broad coastal belt of western Finland was covered by the post-glacial Litorina sea and thus fine-grained mineral soils—for example, clay and silt, prevail.²⁹ Marine factors—that is, relict sea salts in overburden and bedrock, increase the concentrations of dissolved components in groundwater. Thus well water concentrations of fluoride, magnesium, sodium, calcium, boron, iron, sulphate, and bicarbonate are higher in the Vaasa district than in the other central hospital districts. The water hardness value is also higher in this coastal area than inland. Whether characteristics of drinking water have any association with regional differences in the incidence of RA remains unknown.

In conclusion, there are regional differences in the incidence of RA in Finland, the reasons for which are unknown. Sharpening the focus of epidemiological research in other countries might reveal similar differences that ultimately could lead to unravelling a common denominator.

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