Declining Trend in the Incidence of Rheumatoid Factor-Positive Rheumatoid Arthritis in Finland 1980-2000

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ABSTRACT. ***Objective.*** To investigate trends in the incidence of rheumatoid arthritis (RA) in Finland.

Methods. We studied all the subjects entitled to receive drug reimbursement for chronic inflammatory joint diseases in 5/21 central hospital districts (population base about 1 million adults) in Finland during 2000. The incidence rates and the mean age at disease onset were compared with those from 1980, 1985, 1990, and 1995.

Results. A total of 714 subjects were entitled to drug reimbursement for chronic inflammatory joint disease that had started at the age of 16 or over. Of them, 321 satisfied the American College of Rheumatology classification criteria for RA, 198 had spondyloarthropathy, and 195 had undifferentiated oligo- or polyarthritis. The incidence of RA was 29.1/100,000 (95% CI 26.0–32.5); the figures for rheumatoid factor (RF)-positive RA and RF-negative RA were 18.2 (95% CI 15.8–21.0) and 10.8 (95% CI 9.0–12.9)/100,000, respectively. The incidence of RA was 36.9 (95% CI 32.1–42.2)/100,000 among women and 20.8 (95% CI 17.2–25.1)/100,000 among men. The age- and sex-adjusted incidence rate ratio declined from 1.00 in the referent year 1980 to 0.55 (95% CI 0.46–0.66) in 2000. A declining trend was evident for the incidence of RF-positive RA ($p < 0.001$).

Conclusion. We verified the declining trend for the incidence of RF-positive RA in both sexes in Finland. Although the etiology of RA remains unknown, public health measures may reduce the risk of RA in the general population. (First Release Oct 1 2006; J Rheumatol 2006;33:2132–8)

Key Indexing Terms:
RHEUMATOID ARTHRITIS INCIDENCE EPIDEMIOLOGY

Epidemiological studies have shown a temporal and geographic variability in the occurrence of rheumatoid arthritis (RA) in diverse populations. The annual incidence lies between 25 and 50/100,000 in most Western populations[1]. A declining incidence of RA has been reported in 2 Caucasian populations, from Rochester, Minnesota, USA, and from Finland[2-4], and in 2 populations of non-Caucasian origin, Pima Indians and Japanese[5,6]. A shift to older age groups in the mean age of disease onset has also been reported from Finland and Japan[7,8].

Rheumatoid factor (RF) has been reported to precede the occurrence of RA[9]. Subjects with RF have a 40-fold risk to develop RA[10]. A decline in production of RF was observed in the UK in the 1970s[11]. It was connected with the improvement of air quality. In the Pima Indian population the prevalence of RF has decreased from 1966–75 to more recent decades both in male and female subjects[12]. Among Pimas, the crude proportion of positive titers increased with increasing age of the subject up to the seventh decade, and a clear birth cohort effect was also shown. The highest likelihood of RF positivity was in those individuals born around the end of the nineteenth century, with continuing decline in RF positivity up to the most recent birth cohort. The birth cohort had a greater effect on the likelihood of being RF-positive than the calendar period during which the samples were collected. Newer marker antibodies like anti-cyclic citrullinated peptide (CCP) antibodies also predate the clinical disease[13]. These findings reflect a long latent incubation period before clinical symptoms.

We continued to investigate trends in the incidence of RA in Finland by using the unified database from the Sickness Insurance Scheme, and compared the recent data from this source with that from the same area published previously[3,4,7].

MATERIALS AND METHODS

Sickness insurance system. 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. An amendment made in 1987 cut the rate to 90%, and a second amendment made in 1994 cut the rate to 75% of the costs. In 2000, the costs of glucocorticoids and disease modifying antirheumatic drugs (DMARD) were specially reimbursed. The Finnish Sickness Insurance Scheme covers the entire population. Eligibility requires a comprehensive medical certificate written by the patient's physician and approved by an expert adviser on behalf of the Sickness Insurance Scheme. All inflammatory rheumatic diseases are grouped under one code in the population register of the Social Insurance Institution. The main diagnostic subsets are RA, juvenile chronic arthritis, ankylosing spondylitis (AS), chronic reactive arthritis, psoriatic arthritis (PsA), and connective tissue diseases.

Study population. Finland is divided into 21 central hospital districts. This study concerned subjects entitled to specially reimbursed medication in 2000 in 5 districts (Jyväskylä, Kotka, Kuopio, Lahti, and Tampere). The study area

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contains about one million adult inhabitants, i.e., one-quarter of the adult population in Finland. Information on the age structure 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).

Inclusion criteria. For our study, patients were considered to have RA if they met at least 4 of the American Rheumatism Association/American College of Rheumatology (ACR) 1987 classification criteria[14]. Symmetry was defined as simultaneous involvement of the same joint areas on both sides and recorded at diagnosis.

Patients. Data concerning the fulfillment of the ACR classification criteria for RA and demographic data on the patients were obtained from the drug reimbursement certificates. Missing information was obtained from hospital records, when information on the reimbursement certificate was insufficient. Information on the certificates proved to be sufficient in three-quarters of the cases. For our purposes, a case was regarded as an incident case if no earlier entitlement to special reimbursement medication had occurred.

A total of 859 patients were entitled to specially reimbursed medication for chronic inflammatory joint diseases that had started at the age of 16 or older. Of these, 134 were not classified as incident cases because their disease was diagnosed earlier and the entitlement was a continuation of the former eligibility. In 7 (0.8%) instances no inflammatory disease could be verified from certificates or files and in 4 (0.4%) instances the information regarding diagnosis remained insufficient, leaving 714 patients eligible for potential inclusion in the study. The date of the certificate was taken as the date of diagnosis.

The mean age at diagnosis was calculated for all incident cases in each study year. When including patients who had had symptoms from disease onset to diagnosis for more than 4 years, the mean age at diagnosis increased by 0.2, 0.2, 0.2, 0.6, and 0.3 years in 1980, 1985, 1990, 1995, and 2000, respectively, compared with patients having symptoms for less than 4 years, which had been used as a criterion in the previous studies[3,4,7].

Statistical analysis. The differences in the mean age at diagnosis between RF-positive and RF-negative RA were tested by the Student t test and between the study years by analysis of variance (ANOVA). The significance between the rate of incident cases and the time period was tested by the Mantel-Haenszel test for linear trend. Ninety-five percent confidence intervals (95% CI) were calculated using the Poisson distribution. The incidence rates were age adjusted by the direct method using the 1990 Finnish population as a reference. A general linear model (Poisson link) was used to evaluate the relationship between the adjusted incidence rates of RF-positive and RF-negative RA.

RESULTS

A total of 714 subjects were entitled to drug reimbursement for chronic inflammatory joint disease that had started at the age of 16 or over. Of these subjects, 198 had a certificate for spondyloarthropathy including AS, PsA, spondyloarthropathy associated with inflammatory bowel disease, chronic reactive arthritis, or undifferentiated spondyloarthropathy. The diagnosis on the certificate was undifferentiated oligo- or polyarthritis for 116 subjects and RA for 400 subjects. Of these 400, 321 patients satisfied the ACR classification criteria for RA, and 79 persons had undifferentiated oligo- or polyarthritis. The crude and age-adjusted annual incidence rates by sex and the presence of RF in the study years are shown in Tables 1-3. In 2000 the incidence of RA was 29.1/100,000 (95% CI 26.0–32.5); the figures for RF-positive and RF-negative RA were 18.2 (95% CI 15.8–21.0) and 10.8 (95% CI 9.0–12.9)/100,000, respectively. For one patient the RF status was unknown. The incidence of RA was 36.9 (95% CI 32.1–42.2)/100,000 among women and 20.8 (95% CI 17.2–25.1)/100,000 among men.

The age-specific incidence rates of RF-positive RA for women and men in 1980, 1990, and 2000 are shown in Figures 1 and 2. The decline in the age- and sex-adjusted incidence rate ratio in RF-positive RA from 1.00 in the referent year 1980 to 0.55 (95% CI 0.46–0.66) in 2000 is shown in Figure 3. A declining trend was evident in the incidence of RF-positive RA ($p < 0.001$), but no similar trend was noted concerning RF-negative RA (p for trend = 0.750; Table 1). The mean age at diagnosis was 59.0 ± 14.8 years; for women 58.2 ± 15.9 and for men 60.4 ± 12.4 years ($p = 0.192$). It was 57.8 ± 14.7 years in RF-positive and 60.9 ± 14.8 years in RF-negative disease ($p = 0.075$). The mean age at diagnosis had increased by 6.4 years from 1980 to 2000 ($p < 0.001$).

DISCUSSION

We observed the declining trend of RA in Finland. The incidence decreased in all age groups up to the age of 65 years and did not increase from 1990 any more in the oldest age groups. The declining trend in the incidence of RF-positive RA was recorded in both sexes. The most remarkable decrease occurred between the birth cohorts born in 1926-35 and 1946-55. In this series the decrease in the incidence of RA was most significant in the young and middle-aged. The incidence decreased by 50% in the middle-aged. It was likely due to disappearance of triggers, changes in their virulence, or increased resistance against them.

Using this type of register data in analyzing trends in the incidence of chronic diseases is possible in Finland, where the coverage of the sickness insurance scheme has been estimated to be about 95%[15]. Those patients who are not treated with DMARD or for whom certificates for health insurance purposes are not written are not included. However, almost all healthcare in Finland is provided within the general healthcare system, and there have not been marked changes in this practice during the last 25 years.

The incidence figures depend on the criteria used for case definition. The 1987 ACR criteria were applied based on findings and symptoms up to when the certificate was written, although the criteria were developed to distinguish established RA from other rheumatic conditions and their use in classifying cases with polyarthritis early in the disease has been criticized[16]. The same criteria were applied in a similar way in all samples[3,4,7], but it is possible that patients with a short duration of symptoms who have been treated at diagnosis as having an unspecified arthritis later develop a disease that will fulfil the classification criteria for RA. In 2000 the numbers of patients with RF-positive and RF-negative polyarthritis not fulfilling the classification criteria did not differ from those in the previous samples[3,4,7]. Only the number of cases with RF-negative oligoarthritis increased in a linear manner during the 20-year period, which may be due to changes in the structure of the population or in the activity to treat less severe cases

Table 1. Annual incidence of total, RF-positive, and RF-negative RA in the study population in 1980, 1985, 1990, 1995, and 2000. Age adjusted to the 1990 Finnish population. Data from references[3,4] and from our study. * For one male patient RF status was unknown in 2000.

	1980	1985	1990	1995	2000	p for trend
Total no. of patients	394	413	349	366	321*	
Crude incidence	38.4	39.1	32.7	33.7	29.1	
(95% CI)	(34.7–42.4)	(35.5–43.1)	(29.4–36.4)	(30.4–37.4)	(26.0–32.5)	
Age-adjusted incidence	40.1	39.1	32.0	31.5	26.7	< 0.001
(95% CI)	(36.3–44.2)	(35.5–43.1)	(28.7–35.6)	(28.3–35.0)	(23.7–29.9)	
RF-positive RA						
No. of patients	302	302	289	264	201	
Crude incidence	29.4	28.6	27.1	24.3	18.2	
(95% CI)	(26.2–32.9)	(25.5–32.0)	(24.1–30.4)	(21.5–27.4)	(15.8–21.0)	
Age-adjusted incidence	30.9	28.7	26.5	22.8	16.9	< 0.001
(95% CI)	(27.6–34.5)	(25.6–32.1)	(23.5–29.7)	(20.0–25.8)	(14.5–19.5)	
RF-negative RA						
No. of patients	92	111	60	102	119	
Crude incidence	9.0	10.5	5.6	9.4	10.8	
(95% CI)	(7.2–11.0)	(8.7–12.7)	(4.3–7.3)	(7.7–11.4)	(9.0–12.9)	
Age-adjusted incidence	9.3	10.4	5.5	8.8	9.7	0.750
(95% CI)	(7.3–11.3)	(8.6–12.6)	(4.2–7.1)	(7.1–10.7)	(8.0–11.7)	

Table 2. Annual incidence of total, RF-positive, and RF-negative RA among women in 1980, 1985, 1990, 1995, and 2000. Age adjusted to the 1990 Finnish population. Data from references[3,4] and from our study.

	1980	1985	1990	1995	2000	p for trend
No.of female patients	265	280	245	240	210	
Crude incidence	49.3	50.8	44.2	42.6	36.9	
(95% CI)	(43.6–55.7)	(45.0–57.1)	(38.8–50.1)	(37.4–48.4)	(32.1–42.2)	
Age-adjusted incidence	50.8	50.5	43.3	40.5	35.0	< 0.001
(95% CI)	(45.0–57.2)	(44.7–56.7)	(38.0–49.1)	(35.4–46.1)	(30.3–40.2)	
RF-positive RA						
No. of patients	194	199	192	171	121	
Crude incidence	36.1	36.1	34.6	30.4	21.3	
(95% CI)	(31.2–41.6)	(31.3–41.5)	(29.9–39.9)	(26.0–35.3)	(17.6–25.4)	
Age-adjusted incidence	37.4	35.9	33.9	29.0	20.4	< 0.001
(95% CI)	(32.4–43.0)	(31.1–41.3)	(29.2–39.1)	(24.7–33.8)	(16.8–24.4)	
RF-negative RA						
No. of patients	71	81	53	69	89	
Crude incidence	13.2	14.7	9.6	12.3	15.6	
(95% CI)	(10.3–16.7)	(11.7–18.3)	(7.2–12.5)	(9.5–15.5)	(12.6–19.2)	
Age-adjusted incidence	13.4	14.3	9.4	11.6	14.4	0.830
(95% CI)	(10.5–16.9)	(11.4–17.9)	(7.0–12.3)	(8.9–14.7)	(11.5–17.9)	

with DMARD. In 2000 the members of the postwar baby boom born in the late 1940s reached the age in which they were most prone to get different types of arthritides.

Early aggressive treatment of RA has been advocated during the last decade. Treating all arthritides whether or not they fulfill any classification criteria may reduce the number of patients who will satisfy the classification criteria for RA later. The number of patients with unspecified arthritis who were under treatment increased in this series from 1990[3,4]. The number of patients with longer than a 4-year delay from symptom onset to diagnosis decreased from 14% in 1980[3] to 3% in 2000. In the Norfolk arthritis series the incidence of RA was 23% higher in women and 42% higher in men if the patients who registered within one year of symptom onset were followed for 5 years and the criteria were applied cumulatively[17]. However, earlier treatment of arthritides does not explain the magnitude of the decrease in the incidence of RA or the birth cohort phenomenon.

In Rochester a more marked decrease in the incidence of RA occurred in women than in men[2]. In that series the RF-positive and RF-negative disease decreased in a similar way. In the earlier years RF testing was done in only 72% of the cases, which might have influenced the results. No increase in the mean age at onset was recorded, but the 1880 and 1890 birth cohorts had the highest incidence rates. Data on changes in the age structure of the background population was not given during the study, but the mean age might have become lower. That would explain why no shift in the mean age at dis-

Table 3. Annual incidence of total, RF-positive, and RF-negative RA among men in 1980, 1985, 1990, 1995, and 2000. Age adjusted to the 1990 Finnish population. Data from references[3,4] and from our study. * For one male patient RF status was unknown in 2000.

	1980	1985	1990	1995	2000	p for trend
No.of male patients	129	133	104	126	111*	
Crude incidence	26.3	26.4	20.3	24.1	20.8	
(95% CI)	22.0–31.3	22.1–31.3	16.6–24.7	20.1–28.7	17.2–25.1	
Age-adjusted incidence	28.0	26.8	19.8	22.0	18.0	< 0.001
(95% CI)	23.5–33.1	22.5–31.7	16.1–24.0	18.2–26.4	14.6–22.0	
RF-positive RA						
No. of patients	108	103	97	93	80	
Crude incidence	22.1	20.3	19.0	17.8	15.0	
(95% CI)	18.1–26.6	16.7–24.8	15.4–23.2	14.4–21.8	11.9–18.7	
Age-adjusted incidence	23.5	20.8	18.4	15.9	13.0	< 0.001
(95% CI)	19.4–28.2	17.0–25.2	14.9–22.5	12.6–19.7	10.1–16.4	
RF-negative RA						
No. of patients	21	30	7	33	30	
Crude incidence	4.3	6.0	1.4	6.3	5.6	
(95% CI)	2.7–6.6	4.0–8.5	0.6–2.8	4.3–8.9	3.8–8.0	
Age-adjusted incidence	4.5	6.0	1.4	5.9	4.9	0.780
(95% CI)	2.8–6.8	4.0–8.5	0.6–2.8	4.0–8.4	3.2–7.2	

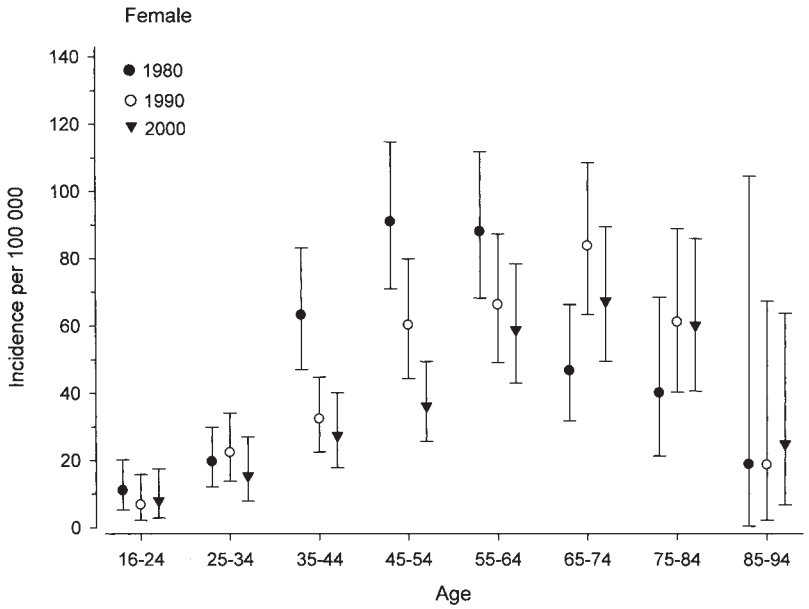

Figure 1. Incidence of RF-positive RA among women in Finland in 1980, 1990, and 2000.

ease onset was recorded. Among women in Rochester, the birth cohort born in the 1940s had only half the incidence of the prior birth cohorts in middle age, as was also the case in our study. In Finland the incidence was highest among those who were born in 1916–45 among women and in 1916–35 among men.

A previous study has suggested that the use of oral contraceptives (OC) reduced the risk of developing RA[19]. In that study, only 11% of the female patients had been exposed to OC. It was estimated that if the entire female population had OC exposure, the number of women who developed RA would have dropped by about 39%. The protective effect was more pronounced against RF-positive than RF-negative disease. Since the 1970s, about 30% of premenopausal women have reported the use of oral contraceptives in the population surveys in Finland[20]. The use of OC may have positively influenced women's health, but in Finland a comparable decrease in the incidence of RA also occurred among men. Prolonged lactation has been reported to protect from RA[21]. However, the number of children has decreased in the families, and the lactation period has also shortened in the younger age groups.

Smoking is the only environmental risk factor that has been firmly verified epidemiologically for RA[22]. In fact, it is

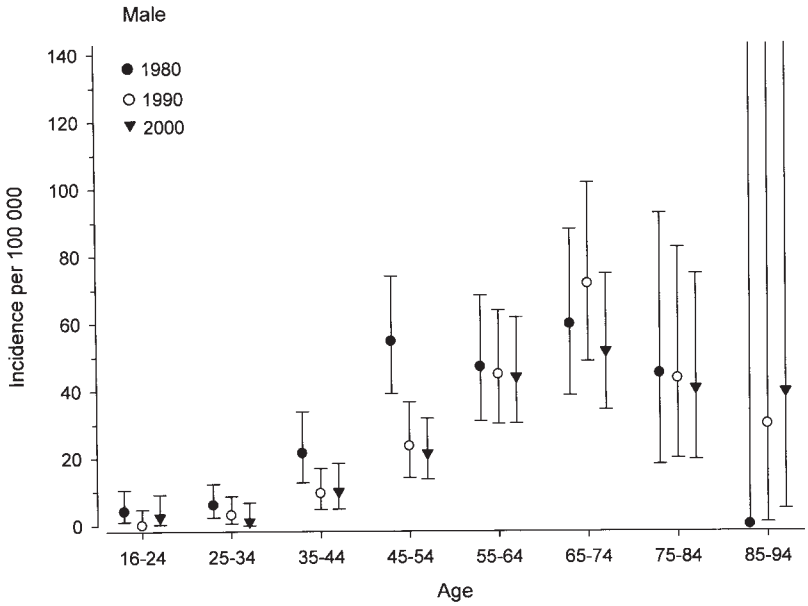

Figure 2. Incidence of RF-positive RA among men in Finland in 1980, 1990, and 2000.

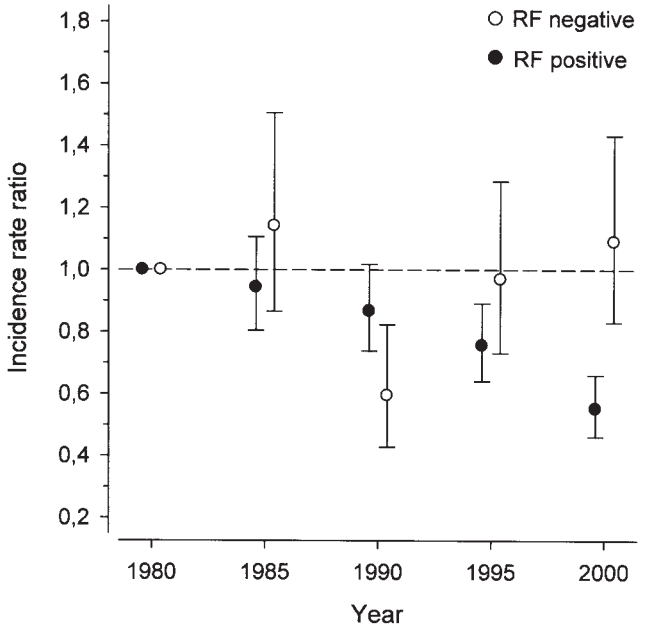

Figure 3. Sex- and age-adjusted incidence rate ratio of RF-positive and RF-negative RA in Finland in 1980, 1985, 1990, 1995, and 2000.

the best known contributing factor for RF-positive RA[23-28]. In Finland smoking habits have changed especially among men. Fifty percent of Finnish men in the 1970s and 30% in 2000 were daily smokers, while during the last 30 years 20% of Finnish women have been regular smokers. In the last 2 decades the prevalence of smoking has increased slightly among young girls. The risk for developing RF-positive RA occurs above a threshold of 5–10 cigarettes each day for 20–30 years[29]. Also, in smokers with a shared epitope the risk for developing RF-positive RA is increased[30]. A decrease in smoking habits might be contributing to the declining incidence of RA, especially among men, in Finland. Concomitantly, decreased passive smoking may have contributed to the declining incidence among women, whereas an increase in smoking among young girls has not yet been reflected as an increase in the incidence of RA. There is no reported data concerning adults, but a potential effect of fetal exposure to tobacco smoke is an increased risk of inflammatory polyarthritis and juvenile RA in girls[31]. Probably most of these children were also exposed to passive smoking.

Changes in environmental factors such as standard of living, diet, and occurrence and treatment of infections may have reduced exposure to factors that promote the development of RA or enhanced protective factors. RA and coronary heart disease (CHD) have joint risk factors[22-28,32]. In Finland, CHD mortality in the middle-aged population has decreased by approximately 70% in 30 years. Mortality from CHD peaked around 1970. During the last 3 decades there has been a shift in coronary mortality toward elderly subjects. In Finland regional differences in the incidence of RA showed a similar geographical trend as in the occurrence of CHD[33].

Sufficient levels of vitamin D may also protect from autoimmune reactions[34]. In a prospective cohort study the higher intake of vitamin D was inversely associated with RA[35]. Although vitamin D levels have been low in the Finnish population, the increasing level of vitamin D as a consequence of better living standards, diet, and use of supplements may have influenced the decreasing incidence figures of RA[36,37].

The same birth cohorts that have the highest incidence of RA also have the highest prevalence of 2 chronic bacterial

infections, tuberculosis and *Helicobacter pylori* infection[38,39]. Since the 1940s children have been vaccinated with BCG and since the 1950s with DTP. Vaccination against measles, mumps, and rubella was launched in 1982. As a consequence, many infectious diseases like diphtheria, tetanus, polio, measles, mumps, and rubella have disappeared from the Finnish population during the last half of the 20th century[40,41]. Reduced load of chronic bacterial and common viral infections might have influenced the decreasing trend of RF-positive RA.

Familial aggregations of RA can be interpreted as evidence for both environmental and genetic factors. In the Finnish and British series the concordance of RA in monozygotic twins was 4-fold that of dizygotic twins[42,43]. Based on these studies it was estimated that the upper limit for the genetic influence on the risk for developing RA was about 60%[44]. However, the rapid changes in the incidence impel one to seek explanations from changes in the environment.

In the Nordic countries lower incidence figures for RA have been reported from Norway and Sweden than from Finland and Denmark[45-47]. These findings might in part be explained by smoking habits[26,48,49]. Denmark has the highest prevalence for smoking in the Nordic countries, which may have influenced the high incidence figures of RA at the turn of the century[47,48]. Seafood in Norway may have protected the population[50,51], and the lower incidence figures in Sweden might reflect protective factors due to a high standard of living and a relatively low prevalence of smoking[49].

Significant changes in the incidence of RA in Finland during the last 2 decades likely reflect changes in environmental factors. The occurrence of marker antibodies, like RF and CCP-antibodies, and increased IgG levels, in the pre-illness specimens[9,13,52] suggest that some key events in the pathogenesis of RA occur many years before the joints become affected. Either the exposure to the triggers leading to autoreactive disease has remained lower or protective factors have increased among persons born after the mid-1940s compared with prior birth cohorts. With Finland as a model, we suggest that it is possible to decrease the burden of RA in society with public health measures including optimizing the diet, decreasing the occurrence of some bacterial and viral diseases, and cigarette smoking control.

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