Clinical Rheumatology (2019) 38:555–562
https://doi.org/10.1007/s10067-018-4310-0

ORIGINAL ARTICLE

Increasing incidence and shifting profile of idiopathic inflammatory rheumatic diseases in adults during this millennium

Paula Muilu[1] · Vappu Rantalaiho[2,3] · Hannu Kautiainen[4,5] · Lauri Juhani Virta[6] · Johan Gunnar Eriksson[4,7] · Kari Puolakka[8]

Received: 18 May 2018 / Revised: 12 September 2018 / Accepted: 20 September 2018 / Published online: 26 September 2018

Abstract

To explore the trends in the incidence of idiopathic inflammatory rheumatic diseases (IIRDs) after the turn of the millennium. From a nationwide register maintained by the Social Insurance Institution of Finland, we collected all adult patients with IIRDs granted a new special reimbursement for anti-rheumatic drugs between 2000 and 2014. Temporal trends in the incidences of various IIRDs were estimated in three 5-year intervals. A total of 58,405 adult patients were identified. Between 2000–2004 and 2010–2014, the age-adjusted incidence rate of IIRDs increased from 114 to 116/100000 [incidence rate ratio (IRR) 1.03 (95% CI 1.01 to 1.06)] in women and from 67 to 69/100,000 [IRR 1.10 (95% CI 1.06–1.14)] in men. The incidence of seropositive rheumatoid arthritis (RA) remained stable while that of seronegative RA decreased. For other diagnoses, the incidences either increased (unspecified arthritis, psoriatic arthritis, spondyloarthritis), remained stable (reactive arthritis), or decreased (SLE and the group of diseases with the ICD-10 code M35). The gender difference in spondyloarthritis leveled as the incidence in women increased at a higher rate than in men. Mean age at IIRD diagnosis decreased among women. The total age-adjusted incidence of IIRDs has gradually increased, due to the increase in unspecified arthritis, psoriatic arthritis, and spondyloarthritis. This, in addition to the ascending number of individuals at risk in the population, translates into a growing burden to the health care system.

Keywords Ankylosing spondylitis · Epidemiology · Psoriatic arthritis · Rheumatoid arthritis · Spondyloarthritis · Unspecified arthritis

✉ Paula Muilu
paula.muilu@pshp.fi

[1] Department of Medicine, Tampere University Hospital, PL 2000, 33521 Tampere, Finland

[2] Centre for Rheumatic Diseases, Tampere University Hospital, Arvo Ylponkatu 6, 33520 Tampere, Finland

[3] Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland

[4] Department of General Practice and Primary Health Care, University of Helsinki, PL 20, 00014 Helsinki, Finland

[5] Unit of Primary Health Care, Turku University Hospital, Turku, Finland

[6] Research Department, Social Insurance Institution of Finland, PL 450, 00056 Turku, Finland

[7] Folkhälsan Research Center, Helsinki, Finland

[8] Department of Medicine, South Karelia Central Hospital, Valto Kakelankatu 3, 53130 Lappeenranta, Finland

Introduction

Idiopathic inflammatory rheumatic disease (IIRD) refers to a group of disorders including rheumatoid arthritis (RA) (seropositive and seronegative), juvenile arthritis, spondyloarthritis [SpA, including ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA)], psoriatic arthritis (PsA), reactive arthritis (ReA), inflammatory bowel disease (IBD)-associated arthritis, systemic connective tissue disorders [systemic lupus erythematosus (SLE), Sjögren's syndrome, etc], and unspecified arthritis (UA). The pathogenetic mechanisms underlying these diseases are not fully understood, but both genetic predisposition and unknown environmental triggers are of importance. Studying any trends in the incidences of separate IIRDs is of great interest and can even give rise to new hypotheses on the underlying factors.

Most incidence studies focus on RA, the most common IIRD worldwide. Reports show high RA incidence rates in the northern hemisphere: Canada (54/100,000), USA (41/

100,000), and Sweden (41/100,000) [1–3]; but somewhat lower in the Mediterranean region such as in Spain (20/100,000) and in the southern hemisphere like in Argentina (19/100,000) [4, 5]. Previous studies from Finland have reported varying incidence rates: a study based on a population of 1 million adults, estimated an overall RA incidence of 29/100,000 (37 among women and 21/100,000 among men) in the year 2000 [6]. In another study, the respective numbers were 44/100,000 (59 and 30/100,000) between 2000 and 2007 [7].

The current classification criteria for SpA, including both AS and nr-axSpA, have promoted early diagnosis; however, previous incidence studies mainly encompass only AS. Spondyloarthritis are in general more common in regions with a high frequency of human leucocyte antigen (HLA) B27. In Finland, the incidence of AS has been reported to lie around 7/100,000 [8–10]. Worldwide, the incidences of AS range from 0.5 (Japan) to 15/100,000 (USA) [11–13].

For some reasons, the incidence of PsA has varied even more worldwide, from 0.1 to 41/100,000, in studies from Japan, Norway, Argentina, and Sweden [11, 14–16]. The estimates from Finland have ranged from 6 to 23/100,000 [8, 9, 17]. ReA is mostly self-limiting, and may stay undiagnosed, complicating the estimation of incidence. The reported rates lie between 0.6 and 9/100,000 [8, 9, 18, 19].

UA is an inflammatory arthritis which does not fit into any diagnostic category, but may later evolve into a more specific established disease. Incidence rates around 40/100,000 have been reported from Finland and Sweden [8, 16].

The incidences of SLE (2 to 7/100,000) [20–22] and Sjögren's syndrome (6 to 12/100,000) [22, 23] vary markedly worldwide. The incidence of polymyalgia rheumatica (PMR) is even more difficult to study, since it is often treated by general practitioners. The disease is among the most common IIRDs; in a population-based US study the incidence was 64/100,000 [24].

As the literature demonstrates, comparing the incidences of various IIRDs from epidemiological studies is challenging, since the case definitions may differ between studies. Mostly, patients have been diagnosed on clinical grounds, and the fulfillment of classification criteria varies. Examining the whole population is the gold standard, but seldom possible, since national registers exist only in a few countries [25].

Differential diagnosis between IIRDs is not always straightforward, and classification criteria have changed over time. True biological variation may also occur. In this report we studied all IIRDs side by side to disclose any mutual trends in the occurrence.

Methods

The Finnish social security system is organized by the Social Insurance Institution (SII) and provides all permanent residents in Finland a variety of benefits. The SII refunds (basic refund 35–50%) costs of drugs prescribed by a doctor. Patients with long-term IIRDs can be granted a special reimbursement (65–72%) for disease-modifying anti-rheumatic drugs (DMARDs, conventional, and biologic) and glucocorticoids after filing a medical certificate to SII. This certificate must describe the diagnostic procedures and prescribed medication and be written in a rheumatology clinic. SII maintains a register on the reimbursements including patients' age, sex, ICD10 code of the illness, and date of entitlement. The day of the first reimbursement decision was defined as the index date in this study.

From this national register data, we collected all patients (aged ≥ 18 years) granted the first special reimbursement for medications of various IIRDs from January 1st 2000 to December 31st 2014.

The patients with IIRDs were classified according to the ICD-10 code into eight groups: seropositive RA (M05), seronegative RA (M06), UA (M13), SpA including AS and nr-axSpA (M45–46), PsA (L40.5), ReA (M02), SLE (M32), and a group of diseases under the code of M35 including Sjögren's syndrome, unclassified collagenosis and PMR.

Incidence of inflammatory bowel disease (IBD)-associated arthritis could not be analyzed from the register since the great majority of the incident patients already had special reimbursement for DMARDs on the grounds of their colitis. The number of patients with myositis, scleroderma, or vasculitides was low, and these diagnoses were not included in our analyses.

Statistical methods

The mean annual incidence rates per 100,000 person years in 5-year calendar time intervals (2000–2004, 2005–2009, and 2010–2014) were calculated for both sexes by dividing the number of newly diagnosed IIRD cases by the total number of population (≥ 18 years of age) between 2000 and 2014. Patients and the population at risk were stratified by gender and age (18–24, 25–29…90+), and crude and direct adjusted incidence rates with 95% confidence intervals (CI) were calculated assuming a Poisson distribution. Standardized incidence rate ratios (IRRs) were calculated by using Poisson or negative binomial regression models when appropriate. The patient's age and the calendar year of index date were included in the models as covariates. The assumption of overdispersion in Poisson model was tested using Lagrange multiplier test. Statistical significance for the hypothesis of linearity across categories of calendar years (2000–04, 2005–09 and 2010–14) and patients' age were evaluated by using the analysis of variance with an orthogonal polynomial contrast. Population sizes according gender and age for the calculation of incidence rates were obtained from Statistics Finland. Stata 14.1,

StataCorp LP (College Station, TX, USA) statistical package was used for the analyses.

Ethical considerations

Permission to use databases was obtained from the SII. By the Finnish legislation, no approval of ethical committee nor patient's informed consent is required for register-based studies done without contacting study subjects.

Results

During the 15-year study period, altogether 58,405 patients (63.7% female) contracted a new IIRD requiring the use of DMARDs. Mean age (SD) at the index date was 52 (16) years, range 18 to 96 years. Among women, the age-adjusted mean annual incidence rate of IIRDs increased from 114 [95% confidence interval (CI) 113 to 118] to 116/100,000 (95% CI 115 to 120) from 2000–2004 to 2010–2014 with the incidence rate ratio (IRR) of 1.03 (95% CI 1.01 to 1.06; $p = 0.008$) (Fig. 1). Among men, the respective increase was from 69 (95% CI 67 to 72) to 71/100,000 (95% CI 69 to 74, and the IRR was 1.10 (95% CI 1.06 to 1.14; $p < 0.001$). Due to the increased number of people at risk, the mean yearly number of incident patients with IIRD grew 12%, from 3696 to 4141 between the first and the last 5-year period (Fig. 1). The distribution of different IIRDs at 2014 is shown in Fig. 2. The annual crude incidence rates and mean ages at the index date for each diagnosis are presented in Table 1. Also, the statistical significances of linearity for age- and gender-adjusted incidences and mean ages are shown in this table.

The incidences of seropositive RA and ReA did not change significantly (Table 1, Fig. 3). The increase in the incidence was observed for UA, SpA, and PsA, whereas seronegative RA, group of diseases under the ICD10 code M35, and SLE showed a declining trend. The gender difference in SpA leveled as the incidence in women increased at a higher rate than in men.

The mean age at diagnosis rose significantly in seropositive and seronegative RA and PsA, and decreased in ReA and M35. No significant changes in the mean ages were detected in UA, SpA, or SLE (Table 1).

As seen from Fig. 4a, the mean age of the Finnish population has increased during this millennium (data derived from Statistics Finland), whereas the mean age at diagnosis of IIRDs has slightly decreased, mostly among women. The age distribution of all patients entitled to a special reimbursement for anti-rheumatic medication as well as the age structure of the general population (according to Statistics Finland) in 2014 is presented in Fig. 4b.

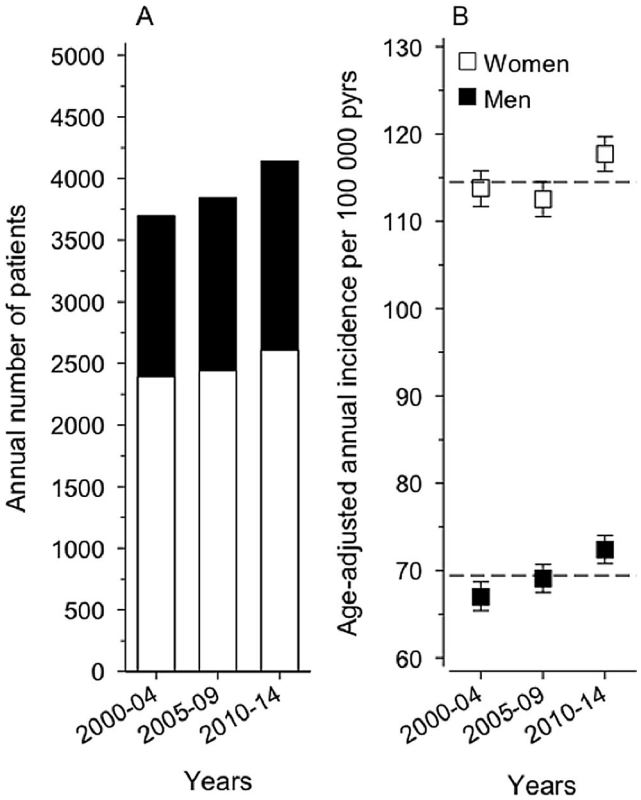

Fig. 1 **a** Mean annual number of incident patients with idiopathic inflammatory rheumatic disease (IIRD) by sex and 5-year intervals during 2000–2014 in Finland. **b** Age-adjusted annual incidence rates of IIRDs by sex and 5-year intervals during 2000–2014 in Finland

Discussion

Our study shows that the age-adjusted incidence of IIRDs has increased by 10% in men and by 3% in women between 2000–2004 and 2010–2014 in Finland. This increase may be attributed to many possible factors. First, the number of new biologic disease cases may have risen. Second, the number of real cases has not grown but more of them may have visited a rheumatologist. Third, the diagnostic threshold may have become lower, or DMARDs have been prescribed for milder cases and consequently more certificates have been filed and more reimbursements granted. In this study, the case identification was based on special reimbursements.

We observed that the mean age at diagnosis declined among women, mostly due to the ascending number of patients in those diagnosis groups that are contracted at a younger age. Taken together, the increasing incidence of IIRDs, younger age at diagnosis in some IIRDs, the need for lifelong monitoring and the lack of cure of IIRDs, as well as longer overall life expectancy, the burden caused by IIRDs on the health care system has increased. Especially rheumatologic clinics that are primarily in charge of diagnosing and treating IIRD patients face the increased burden. A study from Nebraska, USA, based on emergency department visits,

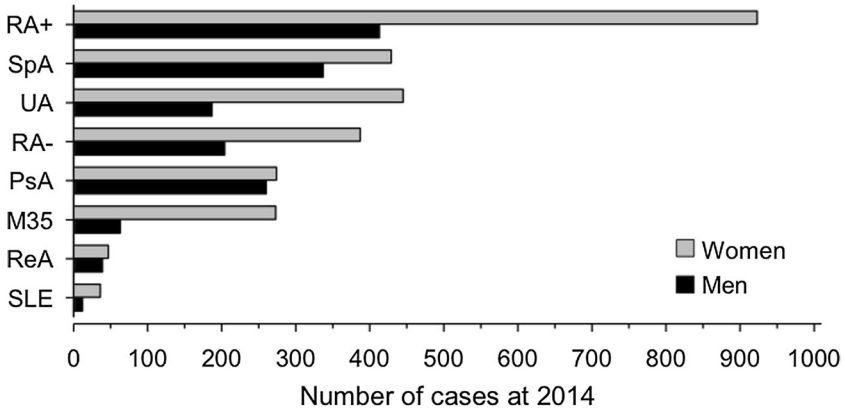

Fig. 2 Number of incident idiopathic inflammatory rheumatic disease cases in Finland in 2014 [seropositive rheumatoid arthritis (RA+), seronegative RA (RA−), unspecified arthritis (UA), spondyloarthritis (SpA), psoriatic arthritis (PsA), reactive arthritis (ReA), systemic lupus erythematosus (SLE), and a group of diseases under the ICD10 code M35]

hospitalizations, and mean charges from visits involving arthritis and other rheumatic conditions also found the total burden of inflammatory arthritis to be increasing [26].

In this study, seven most common phenotypes of IIRD were assessed, and in addition the cases which remained unspecific. Our study included patients with a continuing IIRD requiring anti-rheumatic medication, whereas some early arthritis studies have also enrolled patients with, e.g., viral and crystalline arthritides and are often based on population samples, some of which may be small or biased [8, 9, 16, 26, 27]. Comparing the total incidence of inflammatory arthritis between different studies is thus challenging. There are few

Table 1 Total number of incident cases (*N*), mean annual crude incidence rates per 100,000, and mean ages at diagnosis for various inflammatory rheumatic diseases [seropositive rheumatoid arthritis (RA+), seronegative rheumatoid arthritis (RA−), unspecified arthritis (UA), spondyloarthritis (SpA), psoriatic arthritis (PsA), reactive arthritis (ReA), a group of diseases under the ICD code M35, and systemic lupus erythematosus (SLE)] in Finland during 2000–2014

		Incidence per 100,000				Mean age at diagnosis (SD)			
	N	2000–2004	2005–2009	2010–2014	*P* for linearity	2000–2004	2005–2009	2010–2014	*P* for linearity
RA+	18,163	29	30	29	0.055	57 (14)	57 (14)	58 (15)	< 0.001
Women	12,159	37	38	37		56 (15)	57 (15)	57 (15)	
Men	6004	20	21	20		58 (13)	59 (13)	60 (13)	
RA-	9784	18	15	14	< 0.001	54 (16)	55 (16)	57 (17)	< 0.001
Women	6713	24	20	18		54 (16)	55 (16)	56 (17)	
Men	3071	11	10	9		55 (15)	57 (16)	59 (15)	
UA	7399	9	12	14	< 0.001	48 (15)	49 (16)	49 (17)	0.12
Women	4896	12	16	18		48 (15)	48 (16)	48 (17)	
Men	2503	7	9	9		49 (15)	50 (15)	51 (16)	
SpA	8396	12	14	18	< 0.001	39 (12)	38 (12)	38 (12)	0.74
Women	4047	11	12	19		39 (12)	39 (12)	39 (12)	
Men	4349	13	15	17		38 (12)	37 (12)	38 (12)	
PsA	6702	9	11	13	< 0.001	48 (13)	49 (12)	49 (13)	0.021
Women	3278	8	11	12		48 (13)	49 (13)	49 (13)	
Men	3424	9	12	13		47 (12)	49 (12)	48 (13)	
ReA	1434	3	2	2	0.063	44 (14)	42 (14)	42 (14)	0.028
Women	765	3	3	3		44 (14)	42 (14)	42 (14)	
Men	669	3	2	2		43 (13)	43 (14)	42 (15)	
M35	5535	11	9	8	< 0.001	61 (16)	59 (16)	58 (16)	< 0.001
Women	4504	17	13	12		60 (16)	58 (16)	57 (16)	
Men	1031	4	4	3		64 (15)	62 (14)	63 (14)	
SLE	992	3	2	2	< 0.001	46 (16)	46 (16)	45 (16)	0.26
Women	833	4	2	2		46 (16)	46 (16)	45 (16)	
Men	159	1	1	1		52 (15)	47 (16)	48 (17)	

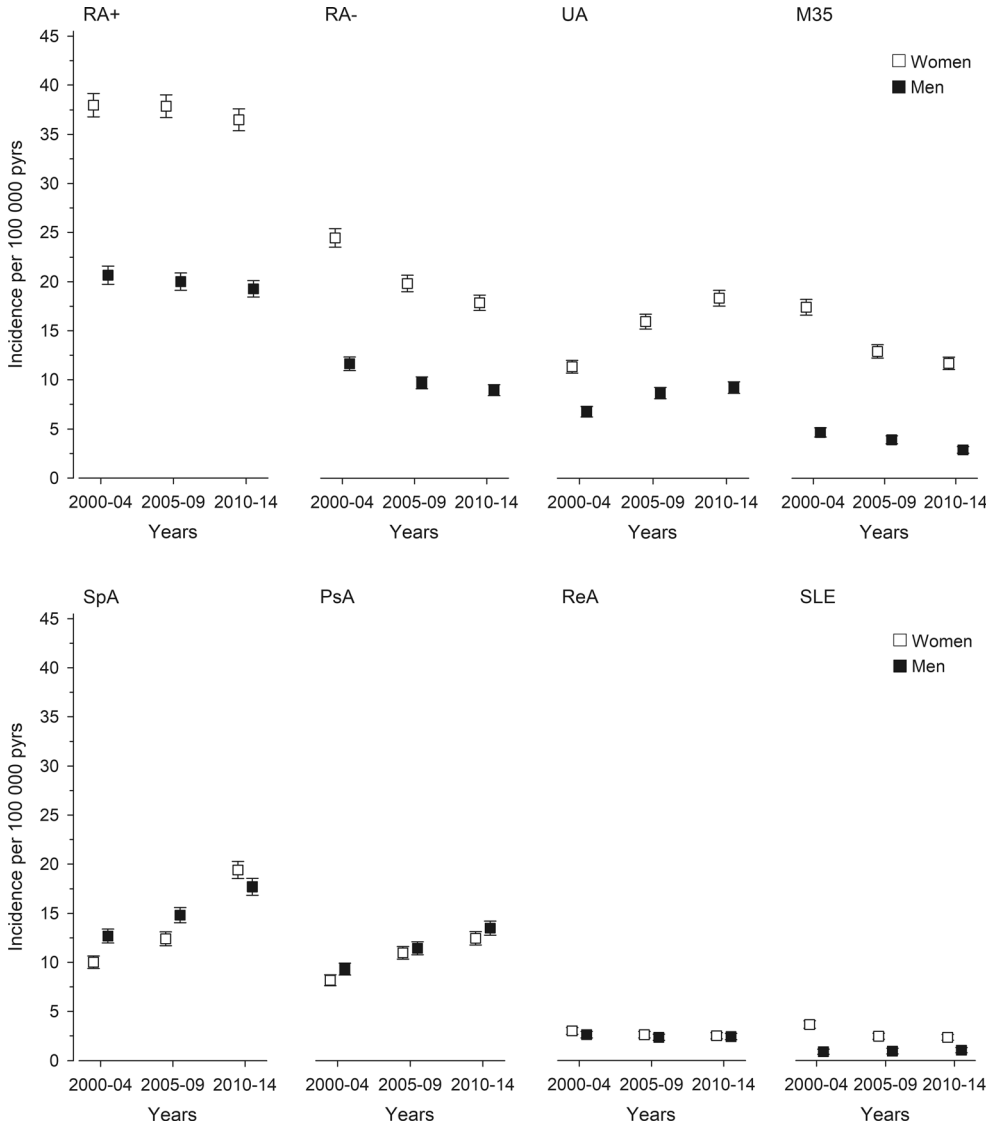

Fig. 3 Age-adjusted annual incidence rates by sex for seropositive rheumatoid arthritis (RA+), seronegative RA (RA−), unspecified arthritis (UA), spondyloarthritis (SpA), psoriatic arthritis (PsA), reactive arthritis (ReA), systemic lupus erythematosus (SLE), and a group of diseases under the ICD10 code M35 presented in 5-year intervals during 2000–2014 in Finland

previous estimates from Finland: A study from the Northern Savo area with the population of 206,441 identified 292 adult arthritis cases and estimated the overall incidence to be 142/100,000 in 2010 [9]. Based upon other earlier estimates from Finland, the Kuopio Arthritis Survey in 2000, and the Heinola Town case-finding study in 1974, the incidence were 271 and 218/100,000, respectively [8, 28]. Our study is the first in Finland to cover the whole population, and we find it to be the most reliable, especially in the case of RA.

Several reports from different countries have informed about declines in RA incidence especially during the late twentieth century [6, 29, 30], but also after the turn of the millennium [31]. However, some studies indicate a rising trend [2, 32]. None of the studies gave clear explanations for these trends reported but environmental factors were speculated to play possible roles. In a Finnish study using the same method as the present study, the incidence of seropositive RA was stable, while that of seronegative RA decreased between 2000 and 2007 [7]; similar trends continued in our study with a longer observation period.

During the past decades, several criteria have been published for classification of RA patients and they also have impact on the diagnostic working. The new ACR/EULAR classification criteria for RA, which are better at identifying early RA than the previous 1987 ACR criteria, were formulated in 2010 [33]. The scoring system in the new RA criteria emphasizes the significance of rheumatoid factor or anti-CCP antibodies. Seronegative arthritis may more often than before be categorized as unspecified (UA) or PsA. In our study, the incidence of seronegative RA decreased whereas that of UA and PsA increased linearly. One explanation for the increasing PsA incidence could be advanced education and knowledge of the rheumatologists, and who are therefore more prone to notice, e.g., family history or nail changes typical to PsA. A study from the USA also showed a rising trend in the incidence of PsA during 1970–1999, and the speculated

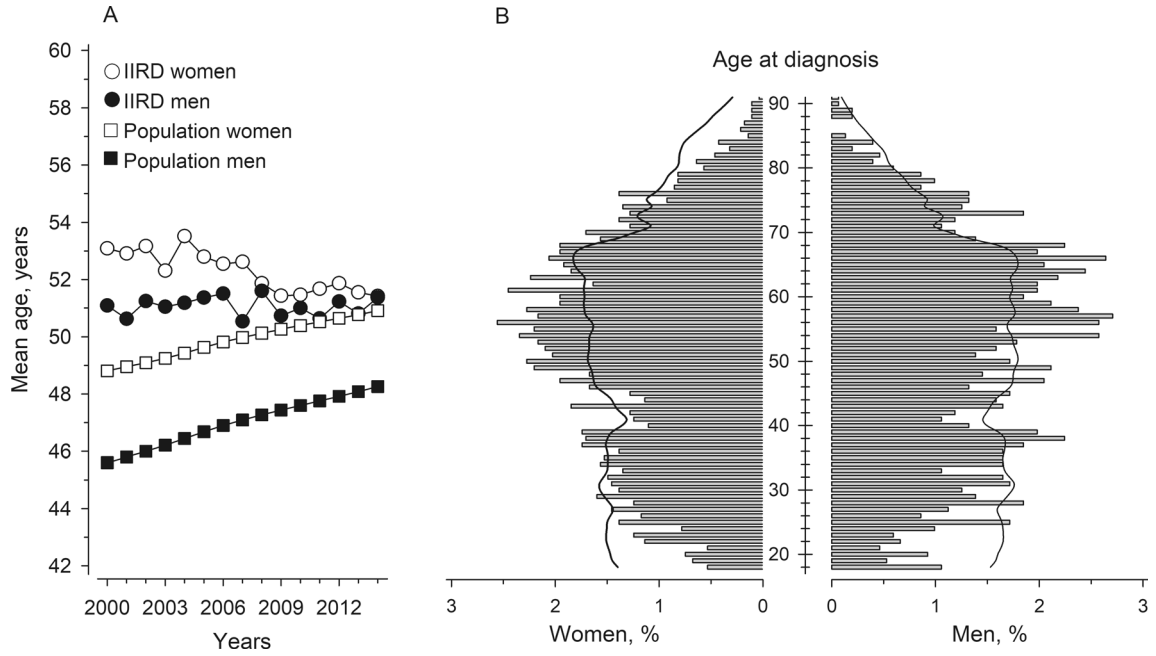

Fig. 4 **a** Age at diagnosis of an idiopathic inflammatory rheumatic disease (IIRD) and the mean age of adult population during 2000–2014 in Finland. White dots refer to the age of women and black dots to the age of men at time of IIRD diagnosis. White squares refer to the mean age of general adult female population and black squares to the mean age of adult male population. **b** Age and gender distribution of incident Finnish patients awarded a special reimbursement for anti-rheumatic medication in 2014. The black lines are indicating the age structure of general population

explanation was either a true change in the incidence, or a better physician's awareness of PsA, or both [34].

The incidence of SpA rose in both sexes. This is probably due to increasingly better diagnostic resources. The diagnosis has earlier depended on the presence of plain radiographic changes (sacroilitis), while nowadays the diagnosis is often supported by abnormalities in MRI, which appear earlier, but their interpretation requires expertise. However, according to the Assessment of SpondyloArthritis International Society (ASAS) classification criteria in 2009, the diagnosis of SpA does not necessarily require any radiographic changes if other findings (HLAB27 and at least two clinical features typical to SpA) are found in a patient with chronic (≥ 3 months) back pain, onset of symptoms before the age of 45. These criteria have raised concern about leading to overdiagnosis [35] but as long as clinicians are aware that classification criteria are not the same as diagnostic criteria, this should not be a problem. Either way, our figure of the incidence of SpA is a severe underestimation since patients with early and mild cases of SpA treated with non-steroidal anti-inflammatory drugs (NSAIDs) were not included, because only patients prescribed a synthetic or biologic anti-rheumatic drug are entitled to special reimbursement and registered by the SII.

AS has been reported to be more common in men, whereas the sex distribution in nr-axSpA is more balanced [36]. Thus, the increasing proportion of women in SpA group noted in our study may be explained by the rising amount of nr-axSpA patients. Somewhat similar results were reported from a retrospective, population-based study in North America including almost 25,000 patients with AS from 1995 to 2010: the incidence and prevalence of AS increased at higher rates in women than in men since the year 2003 [13].

Previous studies have shown both rising [37] or stable [38] trends in the incidence of SLE. We noticed a receding trend. This could be, e.g., due to a decline in real disease cases, due to a decline in prescription of antirheumatic drugs, or due to an increase in the use of intravenously in-hospital administered therapies (e.g., rituximab, belimumab). However, the methods used in our study and the lack of clinical data provide no possibilities to draw conclusions on this.

The group under the ICD-10 code of M35 is somewhat difficult to define. The diagnoses range from Sjögren's syndrome to overlap syndromes, unclassified collagenoses, and PMR, but we have no data about these specific diseases. Further, patients with Sjögren's syndrome not needing anti-rheumatic medication and most PMR patients treated only with inexpensive prednisolone are not found in the special reimbursement register. Regardless of the possible underestimation, the number of patients in M35 group is notable, and all the patients represent those treated by DMARDs thus burdening the health care system, so we decided not to exclude the group from our analysis.

The mean age at diagnosis of an IIRD is related to the diagnosis; in general, patients with SpA are the youngest and RA patients the oldest at the onset of the disease. Previous Finnish studies have reported very similar mean ages

at IIRD diagnosis compared to our results [8, 9]. Between 1975 and 1995, a rise in the mean age at diagnosis of RA from 50 to 59 years was observed in Finland [39].

The main strength of our register-based study is the nationwide scope with a 15-year observation period. The patient identification was based on diagnoses (ICD-10 codes) formulated by qualified specialists or special clinics. Thus, we assume the diagnoses reliable but we have no data on the fulfillment of any classification criteria. Finland belongs to those few countries that are fortunate enough to benefit from high quality public registries that offer opportunities to first class analyses of the incidence of IIRDs.

Some limitations of the present study must be kept in mind. Patients with a mild disease and not requiring DMARD's are not found in the reimbursement register. For example, part of the patients with SpA responds satisfactorily to non-steroidal anti-inflammatory drugs. Further, if the disease course is short and self-limiting, like in most cases of ReA, any DMARDs will not be introduced. In addition, we did not include patients with IBD-associated arthritis and some rare rheumatic diseases. Also, the diagnosis group M35 is heterogeneous and incidences of specific diseases could not be analyzed.

At its best, an epidemiologic register study can help to better understand the factors that contribute to the initiation of rheumatic diseases. However, we lack clinical and health behavior data. Smoking is the only generally accepted environmental risk factor for RA, especially for seropositive RA in men [40], but research data also suggests other factors with either positive or negative association [41]. In Finland, the proportion of 25- to 65-year-old daily smokers has shown a decline both in men and women during this millennium [42]. This may have an impact on the observed incidences. Obesity has been linked to PsA [43] and SpA [44]. Tendency towards increasing obesity had slowed down in the working aged Finnish population between 2007 and 2012 compared to previous decades, but still 65% of men and 46% of women were overweight and 20% were obese [45]. This may partially explain the rising trend in SpA or PsA, although causal relationships cannot be concluded from observational studies.

To summarize, we detected an increasing number of new IIRD cases during this millennium. The focus on early diagnosis and treatment may have had an influence on this trend. The treatment opportunities of most IIRDs have advanced since the year 2000. Also, the outcomes of many IIRDs seem to have improved causing less work disability, hospital stays, joint replacement surgery, as well as overall pain and suffering among these patients. On the other hand, the growing number of new IIRD cases means more patient monitoring in rheumatologic clinics and greater use of costly medicines; thus, translates in an escalated burden impacting both on society and the health care system. Diagnostic modalities have developed and classification criteria have changed, and it is unclear to what extent we are treating milder diseases that we might not have even been diagnosed in the past. Since both the treatments as well as the outcomes of IIRDs have vast economic consequences for the societies, it is important to keep track of the burden caused by these diseases.

Funding information This study was funded by Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital, the Finnish Rheumatology Research Foundation, Tampereen Reumayhdistys, and by the Finnish Cultural Foundation.

Compliance with ethical standards

Disclosure statement Dr. Puolakka, Dr. Virta, Dr. Eriksson, and Mr. Kautiainen have nothing to disclose. Dr. Rantalaiho reports a speaker's honorarium and a congress trip from Pfizer and a congress trip from Celegen outside the submitted work. Dr. Muilu reports a Congress trip from UCB Pharma and a Congress trip from MSD Finland outside the submitted work.

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