

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Rheumatoid arthritis and spondyloarthritis prevalence in four European countries – a comparative study

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SUMMARY

Introduction/Objective The objective was to compare rheumatoid arthritis (RA), spondyloarthritis (SpA) and subtypes of SpA prevalence in four European countries.

Methods A 33-items detection questionnaire, containing self-reported diagnosis, classification criteria for RA and SpA, personal and family history, was translated using cross-cultural adaptation and validated in France, Turkey, Lithuania and Serbia, where it was used on a population sample. Suspected cases were evaluated and confirmed by a rheumatologist. Prevalence estimates were age- and sex-standardized to European standard population.

Results In total, 33,454 people older than 18 years were screened and 31,454 interviewed: France 14,671, Lithuania 6,558, Serbia 6,213, Turkey 4,012. Standardized RA prevalence varied from 0.29% (95% CI: 0.17–0.40) in France to 0.57% (0.31–0.84) in Turkey; this inequality was mostly caused by differences in women prevalence (from 0.42% in France to 1.02% in Turkey) SpA prevalence was similar in France (0.30%), Serbia (0.35%) and Turkey (0.37%), but in Lithuania it was 0.89%, which could be caused by geographic and genetic differences, as SpA prevalence was higher in North and East Europe, as well as the human leukocyte antigen B27 presence. SpA prevalence was equally presented by gender for France and Serbia. Regarding SpA subtypes, ankylosing spondylitis prevalence varied from 0.07–0.30% (Serbia–Lithuania), PsA 0.10–0.26% (France–Lithuania), reactive arthritis was 0.09–0.18% (Serbia–Lithuania). Previously non-diagnosed SpA cases were found in 6.9% in France, 25.9% in Lithuania and 31.2% in Serbia.

Conclusion East–West decreasing tendency for the female RA prevalence was noted. SpA was higher in North-Eastern Europe than in its Western and Southern part. One quarter of the SpA patients in Lithuania and one third in Serbia were not previously diagnosed. The SpA population prevalence was higher than expected and similar to RA.

Keywords: prevalence; rheumatoid arthritis; spondyloarthritis; ankylosing spondylitis; psoriatic arthritis; reactive arthritis

INTRODUCTION

In different parts of Europe, rheumatoid arthritis (RA) and spondyloarthritis (SpA) prevalence was estimated variously [1, 2].

In time, prevalence estimates have shown tendency to decrease for RA and to increase for SpA which, in addition to new achievements in imaging, could be attributed to various approaches in studies. For example, the American College of Rheumatology (ACR) 1987 classification criteria for RA do not cover undefined, possible or probable RA cases, like it was before with Rome and American Rheumatism Association (ARA) criteria [1, 3, 4]; in addition, the last ACR 2010 criteria show better sensitivity, though it does not require

radiography [5, 6]. The overtime tendency of the SpA prevalence to increase could be attributed to campaigns for better understanding of the SpA concept and for better identification of the SpA patients [7, 8].

Furthermore, the heterogeneity of the RA and SpA prevalence could be influenced by diverse methodological research methods, including different sampling, various criteria for case detection and case confirmation, different cut-offs for age, incoherent presentation of results (raw or standardized), etc. [1, 2, 7].

The aim of this manuscript was to compare RA, SpA and subtypes of the SpA prevalence in four European countries: France, Turkey, Lithuania, and Serbia. Results were derived by unique study method, comprising random

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sampling, identical cases detection method by using a 33-items detection questionnaire, confirmation of diagnoses by rheumatologist and standardization of results to a common-European population. Separate results by countries have already been presented, standardized to the particular country population.

METHODS

Prevalence estimates for RA, SpA and subtypes of SpA [ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), enteropathic arthritis (EA), and undifferentiated SpA] were achieved by a two-phase study: in a first-detection phase, screening questionnaire was used by trained interviewers or self-help patient groups. In a second-confirmation phase, suspected cases were confirmed by rheumatologist. Study was announced by local press, radio and other means of public advertisement before launching, in order to assure response.

Study was approved by the European League Against Rheumatism (EULAR) Standing Committee of Epidemiology and Health Service Research (SCEHSR). It was also approved by the local Ethical Committee in Lithuania and Serbia, while there was no requirement for an Institutional Review Board authorization for this kind of observational study in Turkey and France at that time. Patients have provided informed consent for participation in a telephone or face-to-face interview, according to the country.

Questionnaire

Screening detection questionnaire was first developed and validated in France [9]. It included self-reported diagnosis, signs and symptoms attributable to RA and SpA according to ACR 1987 classification criteria for RA and the European Spondylarthropathy Study Group 1991 criteria for SpA, personal and family history.

Following guidelines for forward and back translation, the questionnaire was translated and tested separately for Serbia, Lithuania, and Turkey with four groups of patients: RA, SpA, degenerative musculoskeletal disorders and healthy persons, showing acceptable sensitivity and specificity [10, 11, 12].

The questionnaire comprised both past and current symptoms of the investigated disease. In addition to the self-reported diagnosis, if a respondent gave a positive answer to one of the two main questions: "Are you at present experiencing, or have you in the past experienced pain in your joints?" or "Have you or have you had pain in your neck, your back in your buttocks?"; the whole questionnaire was used.

Sample

The questionnaire was applied either by telephone, or face-to-face.

Telephone numbers for dialing were recruited randomly from the local landline telephone list, by dividing a total

number of phones in that area by designed number of participants: in Serbia every 100th telephone number [10], in Lithuania every 50th [11], in France random selection of telephone numbers was combined by the next birthday household member (selection of persons whose birthday is closest to the interview date). Phones owned by business organizations, public offices, social associations or institutions for elderly were excluded before dialing, as well as the second home numbers (for residents living in the place less than one year), to reduce redundancy. Due to low landline telephone coverage in Turkey, random selection of homes in each of the studied areas and provinces was done in order to apply the screening Questionnaire face-to-face [12].

For France, sample has covered seven areas with 20 counties (Bretagne-Ouest, Bretagne-Est, Nord-Picardie, Midi-Pyrénées, Provence-Côte d'Azur, Lorraine, Rhône-Alpes), for Turkey seven geographical regions with 25 administrative provinces (regions: Western (Aegean), Northwestern (Marmaran), Southern (Mediterranean), Northern (Black Sea), Central, Eastern and Southeastern), for Lithuania two largest cities (Vilnius and Kaunas) and for Serbia two geographical regions with four towns (Belgrade in the north region and Čačak, Užice, and Kruševac in the south).

Sampling area was chosen either on the basis of a wide-spread coverage of the population distribution, or by selection of random sample within regions representative of the average population.

Case ascertainment: detection and confirmation

From 30 to 110 volunteer interviewers (patient representatives, trained practitioners, nurses and self-help group members) were engaged in each country in a detection phase. Interviewed persons had to be older than 18 years and resident at the place for at least one year. The survey took place from March to May 2001 in France [13], from September to October 2004 in Lithuania [11] and from April to October 2008 in Serbia [1]. In Turkey, face-to-face interview was done from August 2004 to June 2005 [12]. People who gave answers suggestive for RA or SpA or positive self-reported diagnosis were called again by rheumatologists who asked for additional information about diagnosis and medical history. If diagnosis could not be ruled out, clinical visit was scheduled and diagnoses were approved in a second-confirmation phase.

Statistical analysis

The sample size was calculated on the basis of the expected prevalence of 0.3–0.5%, by using the Poisson distribution assumption [13]. Accordingly, 4000 people contacted by phone would provide a 95% confidence interval (CI) of 0.14–0.54% around a 0.3% estimate, and 0.30–0.77% around a 0.5% estimate.

According to the expected prevalence of RA and SpA in the community of 0.5%, 1% and 2%, the negative predictive value of the Questionnaire: 0.99 for RA and 0.99 for SpA gave us a strong confidence that we would do accurate classification if we declared someone not a case [9].

Age and sex standardization was done by direct method to European standard population, defined as EU-27+European Free Trade Association average populations, based on 2010 estimates [14].

RESULTS

Detection and confirmation

In a detection phase 33,454 persons were screened. After exclusion of second homes, work places and public enterprise numbers, 27,442 people were interviewed by telephone: 14,671 in France, 6,558 in Lithuania and 6,213

in Serbia (response rate 64.7%, 64.7% and 63.3%, respectively) [1, 11, 13]. In Turkey, 4,012 people were interviewed face-to-face (response rate 96,6%) [12] (Figure 1).

RA was confirmed with 32 cases in France (two newly diagnosed), 39 in Lithuania (two newly diagnosed), 23 in Serbia (one newly diagnosed) and 25 in Turkey, comprising females in 84%, 100%, 82.6%, and 92% of cases, respectively [1, 11, 12, 13]. SpA was confirmed with 29 people in France (two newly diagnosed), 27 in Lithuania (seven newly diagnosed), 16 in Serbia (five newly diagnosed) and 18 in Turkey (representing males in 37.9%, 55.6%, 37.5%, and 16.7% of cases, respectively) [8, 11, 12, 15]. The age and sex distribution of samples and cases is given in Table 1.

Standardized RA prevalence estimates in four European countries are shown in Figure 2. RA prevalence for men was similar across countries (0.00–0.19%), but it has differed widely for women: from 1.02% (95% CI: 0.59–1.45) in Turkey and 1.01% (95% CI: 0.68–1.34) in Lithuania to 0.42% (0.26–0.58) in France and 0.52% (0.27–0.76) in Serbia. Considering SpA, higher prevalence was shown in North-Eastern Europe: Lithuania 0.89% (0.78–1) than in its Middle, Western and Southern part: France 0.30% (0.19–0.41), Serbia 0.35% (0.17–0.54) and Turkey 0.37% (0.18–0.56) (Figure 3).

AS prevalence was 0.10% (95% CI: 0.05–0.16) in France 0.12% (0.02–0.22) for males and 0.09% (0.02–0.16) for females; 0.30% (0.27–0.34) in Lithuania, that is 0.29% (0.04–0.60) for males and 0.32% (0.13–0.50) for females, and 0.07% (0.01–0.14) in Serbia, or 0.15% (0–0.36) for males.

PsA prevalence was 0.10% (0.04–0.16) in France, for men 0.09% (0–0.18) and for women 0.11% (0.03–0.19); in Lithuania it was 0.26% (0.2–0.32), for men 0.38% (0.04–0.71) and for women 0.14% (0.01–0.27); in Serbia it was 0.08% (0–0.15), e.g., 0.04% (0–0.11) for men and 0.11% (0.01–0.22) for women.

Prevalence estimates for ReA were 0.18 (0.07–0.29) in Lithuania, 0.15 (0.13–0.17) for males and 0.20 (0.18–0.23) for females and 0.09 (0–0.16) in Serbia, 0.12 (0–0.28) for males and 0.07 (0–0.17) for females.

EA prevalence was 0.02 (0–0.06) in Serbia, e.g., 0.04 (0–0.11) in women.

Undifferentiated SpA population prevalence was 0.04% (0–0.07) in France, e.g., 0.03% (0–0.08) for males and 0.04% (0.01–0.08) for females; it was 0.12% (0.09–0.16)

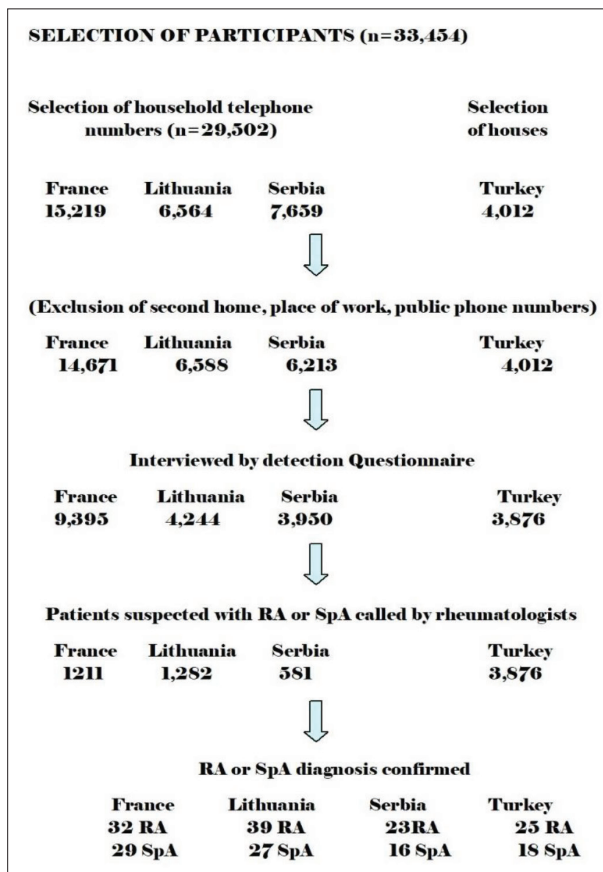


Figure 1. Sampling, case detection and case confirmation

Table 1. Rheumatoid arthritis or spondyloarthritis, sample and cases for France, Lithuania, Serbia and Turkey

Age groups	FRANCE						LITHUANIA						SERBIA						TURKEY					
	Sample		RA cases		SpA cases		Sample		RA cases		SpA cases		Sample		RA cases		SpA cases		Sample		RA cases		SpA cases	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
18–24	330	447	0	0	1	1	144	236	0	1	0	0	76	95	0	0	0	0	238	347	0	1	0	2
25–34	684	960	0	1	2	4	152	356	0	1	1	2	188	281	0	0	2	1	355	546	0	5	1	6
35–44	749	1051	0	1	3	2	190	533	0	2	5	3	195	371	0	2	0	1	341	463	1	5	1	4
45–54	641	935	0	7	2	4	190	542	0	8	3	3	223	373	0	1	0	1	273	374	0	5	1	2
55–64	409	829	2	6	1	2	184	585	0	11	4	3	317	653	1	8	3	6	198	254	1	4	0	1
65–74	488	897	2	12	2	4	152	592	0	15	1	1	226	479	2	7	0	1	132	209	0	3	0	0
75–84	213	560	1	0	0	1	62	291	0	1	1	0	141	264	1	1	1	0	69	77	0	0	0	0
85 +	40	162	0	0	0	0	9	26	0	0	0	0	27	41	0	0	0	0	0	0	0	0	0	0

RA – rheumatoid arthritis; SpA – spondyloarthritis

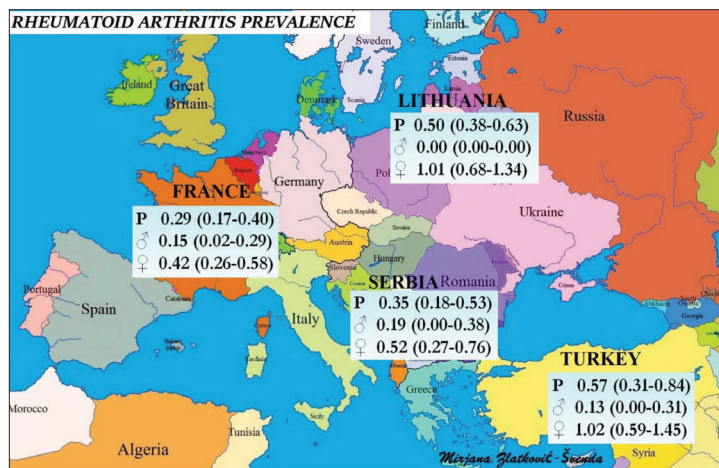


Figure 2. Rheumatoid arthritis prevalence, % (95% confidence interval) for France, Lithuania, Turkey, and Serbia for older than 18 years
P – population; ♂ – male; ♀ – female

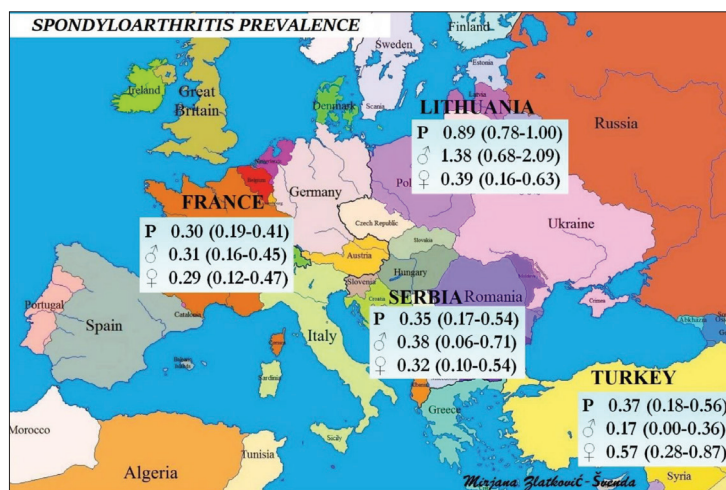


Figure 3. Spondyloarthritis prevalence estimates, % (95% confidence intervals) for France, Lithuania, Turkey, and Serbia for older than 18 years
P – population; ♂ – male; ♀ – female

in Lithuania, 0.22% (0–0.72) for males and 0.03% (0–0.08) for females and 0.02% (0–0.02) in Serbia, 0.13% (0–0.31) for males and 0.04% (0–0.09) for females.

DISCUSSION

The presented joint study effort, endorsed by EULAR, is a first investigation of the RA and SpA prevalence that was conveyed nationwide in countries located in different parts of Europe.

Sample was chosen within representative regions of population by random selection, and therefore the selection bias was considered minimized. The 33-items detection questionnaire comprised self-reported diagnosis, classification criteria for RA and SpA, personal and family history. Owing to main questions that covered both present and past symptoms, the questionnaire was able to include patients with active disease and those in remission, thus, allowing a full prevalence calculation. Diagnoses were confirmed by rheumatologists.

Up to date, RA and SpA prevalence were differently identified: by registry data, face-to-face or sent-by-post questionnaires or by elaborating database of blood donors. Diagnosis was confirmed either by using actual classification criteria or by doctor. Samples were derived from one or more geographic regions, representing the whole population or part of it, by using different age cut-offs, or by exploring one race or ethnicity group only [1, 2].

Since the age and sex mix of the populations is not uniform across countries, standardization of prevalence to a common population was needed; it also allows comparisons and monitoring of the disease progression over time.

Our study RA prevalence varied from 0.29% (95% CI: 0.17–0.40) in France to 0.57% (0.31–0.84) in Turkey (Figure 2). Up to date reported prevalence in Europe goes from 0.18% in Serbia [16] to 0.82% in Spain, 0.90% in Poland, and 0.8–1.1% in the United Kingdom [6, 4, 17].

RA prevalence in the present research decreases when going to the west and the lowest rate was found in far west of the France: Nord (Lille 0.13%) and Bretagne (Brest 0.14%), which is also the lowest rate of the European RA prevalence estimates ever reported [18]. First results of the East Europe RA prevalence were derived in Lithuania – 0.50%, which is in range with North Europe and Turkey [1].

RA mostly affects women and the female/male ratio of our study was 2.7:1 in Serbia, 2.8:1 in France and 7.8:1 in Turkey. High female RA prevalence in Turkey was already published [1, 12], but high Lithuanian RA prevalence in females was not noted before. Virtual absence of men with RA in Lithuania was like due to fluctuation in sample size, i.e., the men prevalence was so small that it could not be caught by the statistically determined sample size, based on the expected overall RA prevalence. This is not an uncommon case in epidemiology, as such lack of men in the RA prevalence was already reported by studies from Africa – Nigeria and Johannesburg, and in Australian Aboriginals, as well as in Thailand and Japan [1, 19].

According to our results, the East–West decreasing tendency of the European female RA prevalence was noted. The last meta-analysis estimation of the global RA prevalence, based on a systematic review, has shown that variations were mostly due to geographical locations and study limitations such as bias assessment and sample size [20]. As we have used identical methodology with the statistically determined sample size, in accordance to this meta-analysis, high women RA prevalence in the East Europe could be attributed to geographic longitude (e.g., less sun exposure due to low insolation in Lithuania, or due to national habits, like covering the face and the body in Turkey), and genetics. The present study SpA prevalence varies from 0.30% (95% CI: 0.19–0.41) in France to 0.89% (0.78–1) in

Lithuania. Published European SpA prevalence ranges from 0.21% in Scottish Highlands [21] to 1.6% in Portugal and 1.9% in Germany [22]. The last one was limited by methodology, as it has evaluated blood donors who were HLA-B27 positive in half of the cases. Stolwijk et al. [23] have given the pooled prevalence of the SpA in Europe of 0.54% (95% CI: 0.36–0.78). Generally speaking, SpA prevalence is lower in northern parts of Europe (0.21% in Scotland [19], 0.45% in Sweden [24] and 0.30% in France [25]) than the southern – 1.06% in Italy [26] and 1.05–1.35% in Turkey [27].

We have found no gender-specific SpA predominance, and our SpA male/female ratio was 1:1.6; 1:5; 1.25:1; and 1:1.7 for France, Turkey, Lithuania, and Serbia, respectively. AS was equally presented for males and females in France and Lithuania, PsA in France, ReA in Lithuania and Serbia, undifferentiated SpA in France.

Khan [28] has hypothesized about the prevalence of SpA, built upon the HLA-B27 prevalence. As HLA-B27 was found to be more prevalent in Ugro-Finnic, Slavic and Northern European populations (Norway, Sweden, Iceland) (7–16%) compared to the Western (6–9%) or Southern Europe (2–6%) and Turkey (2.8–11.1%), SpA would be higher in Northern and Eastern European countries than in its Western and Southern parts, which was confirmed here. The highest SpA prevalence rate in the present study was found in Lithuania (0.89%), followed by France, Serbia, and Turkey (0.29–0.39%). Turkish male SpA prevalence was surprisingly low: 0.17%. A previous regional SpA prevalence study in Izmir has shown female predominance as well (1.22% vs. 0.88% males) with SpA prevalence rate of 1.05% and 1.35% (0.5% for radiographic axial SpA and 0.8% for non-radiographic axial SpA) [27]. Maybe this prevalence difference could be attributed to heterogeneity of HLA-B27 frequency in different parts of Turkey.

Male SpA prevalence in Lithuania of 1.38% is the highest ever recorded, except for Portugal where it was reported to be 2.7%, but calculated only for men older than 50 years [21].

Different environment, living or eating habits, ethnicity or various genetic backgrounds could have the influence.

SpA prevalence derived from registers and hospital records could be underestimated, as we have revealed previously non-identified cases with SpA in 6.9% for France, 25.9% for Lithuania, and 31.2% for Serbia. SpA underestimation could be caused by the lack of familiarity of symptoms by patients or by doctors, wrongly considering patients as having degenerative disease, by inability of the health system to capture SpA patients, inadequate rheumatology coverage of certain areas or simply because of the complicated process of scheduling the examination.

Here, similar estimates of SpA and RA prevalence were found in France (0.30% vs. 0.29%), Serbia (0.35% vs. 0.35%) and Turkey 0.37% (95% CI: 0.18–0.56) vs. 0.57% (95% CI: 0.31–0.84). For Lithuania, SpA prevalence was even higher than the RA (0.89% vs. 0.50%).

The SpA prevalence estimates in the world are constantly growing, and in the current century have even exceeded that for RA in Japan, Germany, Turkey, China, Italy, Australian Aboriginals, and the United States [1, 7].

The strength of our study is the use of a unique survey method. For each of the observed countries study sample was population-based, therefore it is representative. The limitation is a wide study period across countries. However, data were collected in less than a decade (i.e., when there was little chance to observe a significant secular trend), and a systematic literature review has suggested little evidence for a substantial change in the RA frequency over the years [29]. Not exploring the HLA-B27 in SpA could be considered another study limitation, as confirmation of cases in our study was based on the European Spondylarthropathy Study Group criteria, which do not include HLA-B27. However, recent studies have indicated lower prevalence of non-radiographic axial SpA than previously reported [30].

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Преваленција реуматоидног артритиса и спондилоартритиса у четири европске земље – упоредна студија

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САЖЕТАК

Увод/Циљ Циљ је био упоредити преваленцију реуматоидног артритиса (РА), спондилоартритиса (СпА) и подтипова спондилоартритиса у четири европске земље.

Метод Упитник за откривање са укупно 33 питања, укључујући дијагнозу добијену од болесника, класификационе критеријуме за РА и СпА, личну и породичну анамнезу, преведен је уз транскulturну адаптацију и валидиран у Француској, Турској, Литванији и Србији, где је коришћен на случајно одабраном узорку популације. Сумњиви случајеви су евалуирани и потврђени од стране реуматолога. Резултати преваленције су стандардизовани према старости и полу у односу на популацију Европе.

Резултати Скрининговано је укупно 33.454 особа старијих од 18 година, а анкетирано 31.454: Француска 14.671, Литванија 6558, Србија 6213, Турска 4012. Стандардизована преваленција РА креће се од 0,29% (95% CI: 0,17–0,40) у Француској до 0,57% (0,31–0,84) у Турској; неједнакост је углавном узрокована разликама у преваленцији жена (од 0,42% у Француској до 1,02% у Турској). Преваленција СпА је слична у Француској (0,30%), Србији (0,35%) и Турској

(0,37%), али је у Литванији 0,89%, што може бити узроковано географским и генетским разликама, пошто је преваленција СпА виша у северној и источној Европи, као и присуство хуманог леукоцитног антигена В27. Преваленција СпА има подједнак распоред по полу у Француској и Србији. У односу на подтипове СпА, преваленција анкилозирајућег спондилитиса варира од 0,07 до 0,30% (Србија–Литванија), ПсА 0,10–0,26% (Француска–Литванија), реактивни артритис је 0,09–0,18% (Србија–Литванија). Раније недијагностиковани оболели од СпА чине 6,9% у Француској, 25,9% у Литванији и 31,2% у Србији.

Закључак Уочена је тенденција опадања преваленције РА код жена источно–западно. Преваленција СпА је била виша у северноисточној Европи него у њеном западном и јужном делу. Четвртина болесника са СпА у Литванији и трећина у Србији није била претходно дијагностикована. Преваленција СпА у популацији виша је него што је очекивано и у најмању руку је слична као РА.

Кључне речи: преваленција; реуматоидни артритис; спондилоартритис; анкилозирајући спондилитис; псоријазни артритис; реактивни артритис