ORIGINAL ARTICLE

Prevalence of Rheumatoid Arthritis and Spondyloarthritis in Turkey: A Nationwide Study

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ABSTRACT

Objectives: This study aims to estimate the prevalence of rheumatoid arthritis (RA) and spondyloarthritis (SpA) in Turkey using the same telephone questionnaire developed for screening RA and SpA in France and used in Serbia and Lithuania.

Material and methods: The study was performed in two steps. In step I, the French questionnaire was translated into Turkish and validated through a group of 200 patients (80 males, 120 females; mean age 44.0±13.1 years; range, 19 to 75 years) followed up at the rheumatology departments of University Hospitals in Antalya and Ankara. In step II, the validated Turkish questionnaire was administered face-to-face to randomly selected 4,012 subjects (1,670 males, 2,342 females; mean age 41.5±16.8 years; range, 16 to 97 years) by trained general practitioners across the country, in 25 provinces for case detection. The subjects who were suspected of having RA or SpA in accordance with the questionnaire were invited to the nearest university hospital for rheumatologic examination in order to confirm the diagnosis.

Results: In step II, a total of 25 subjects (2 males, 23 females) were diagnosed as RA. The standardized RA prevalence for the general population of Turkey was calculated as 0.56% (95% confidence interval [CI]; 0.33-0.79), 0.10% (95% CI; -0.05-0.25) for males and 0.89% (95% CI; 0.51-1.27) for females. A total of 18 subjects (3 males, 15 females) were diagnosed as SpA. The standardized SpA prevalence for the general population of Turkey was 0.46% (95% CI; 0.25-0.67), 0.17% (95% CI; -0.03-0.37) for males and 0.65% (95% CI; 0.32-0.98) for females. The prevalence of RA was highest in the Northern region (2.00%) and the prevalence of SpA was highest in the Central region (1.49%).

Conclusion: The prevalences of RA and SpA in Turkey are close to each other and there are significant inter-regional variations in prevalences of both RA and SpA.

Keywords: Epidemiology; prevalence; rheumatoid arthritis; spondyloarthritis.

Rheumatoid arthritis (RA) and spondyloarthritis (SpA) are the most common inflammatory arthropathies in adults. RA is a systemic, autoimmune, inflammatory disease primarily affecting the peripheral synovial joints. Owing to progressive joint damage, it may result in functional impairment and disability. SpAs are a group of rheumatic diseases including ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis and enteropathic arthropathies. In developed countries, a large number of publications are available on the prevalence of RA and SpA.[1,2] However, in low- and middle-income countries, studies on RA and SpA are sparse. Likewise, in Turkey, epidemiological studies regarding RA and SpA reported to date are very few and regional, rather than nationwide.[3-5]

After a survey, a telephone questionnaire developed for screening RA and SpA was validated and used for several surveys in France.[6-10] Given the French experience and the support of the European League Against Rheumatism (EULAR), it became possible to carry out similar studies across Europe using the same methodology. In this way, the aforementioned telephone questionnaire was adapted to and validated in Serbian and Lithuanian, and also used in a prevalence survey carried out in Lithuania[11,12] and Serbia.[13] Our study was based on the same questionnaire and endorsed by EULAR and the Turkish League Against Rheumatism. To the best of our knowledge, this is the first nationwide epidemiological study to estimate the prevalence of RA and SpA in Turkey. Therefore, in this article, we aimed to estimate the prevalence of RA and SpA in Turkey using the same telephone questionnaire developed for screening RA and SpA in France and used in Serbia and Lithuania.

MATERIAL AND METHODS

This study was conducted in two steps: in the first step the aforementioned French questionnaire was translated into Turkish and validated through a group of patients followed up at the rheumatology departments of Akdeniz University Hospital (Antalya), and of Ankara University Hospital (Ankara). In step II, the validated Turkish version was used in a nationwide survey to detect the prevalence of RA and SpA in 25 provinces of Turkey. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Step I

The original French questionnaire, which comprised 33 items covering signs, symptoms, self-reported diagnosis and classification criteria for RA (American College of Rheumatology [ACR] 1987)[14] and SpA (The European Spondylarthropathy Study Group [ESSG] 1991),[15] was translated into Turkish using the standard methodology of forward then backward translations and expert committee decision making.[16] 200 patients were included in the study (80 males, 120 females; mean age 44.0±13.1 years; range, 19 to 75 years). The questionnaire's validity was tested by administering it to the subjects, divided into four groups: *(i)* patients with RA, *(ii)* patients with SpA, *(iii)* patients with diagnoses of non-inflammatory musculoskeletal diseases such as osteoarthritis, osteoporosis, fibromyalgia, disc herniation, spondylosis and non-specific mechanical low back pain, and *(iv)* controls. All patients were recruited from the hospital registries of Akdeniz University and of Ankara University, and controls were selected from the general population using randomly sampled telephone numbers. All patients with RA and SpA were also required to fulfill ACR 1987 and ESSG 1991 classification criteria, respectively. Two certified rheumatologists and two physiatrists experienced in rheumatic diseases ascertained the patients' clinical diagnoses and documented their findings on standard forms. All the subjects were interviewed by telephone by a trained layperson who was unaware of the patients' diagnoses. Subjects who did not answer the telephone were reached by subsequent calls.

Step II

Turkey is a country divided into seven geographical regions (the Aegean [the Western], the Marmara [the Northwestern], the Mediterranean [the Southern], the Black Sea [the Northern], the Central, the Eastern, and the Southeastern) and 81 administrative provinces. Its population derived from the national census data was 67.8 million in 2000.[17]

In step II, the validated Turkish questionnaire was administered face-to-face to randomly selected 4,012 subjects

(1,670 males, 2,342 females; mean age 41.5±16.8 years; range, 16 to 97 years) by 20 trained general practitioners across the country for case detection. For randomization process, a two-stage cluster sampling method was used (Table 1). The first stage corresponded to all the seven geographical regions mentioned above and the second stage to 25 provinces: Adana, Afyon(karahisar), Ankara, Antalya, Aydın, Bursa, Denizli, Diyarbakır, Edirne, Elazığ, Erzurum, Gaziantep, Isparta, İstanbul, İzmir, Kayseri, Kırıkkale, Kocaeli, Konya, Malatya, Manisa, Mersin, Samsun, Sivas, and Van (Figure 1). Two levels of either urban or rural settlement type defined the second stage. Urban clusters were selected by the proportional sampling method using zip codes and the rural clusters were sampled from the lists of villages not further than 80 km from the relevant provincial city center. The number of clusters was determined in proportion to the size of the urban and rural population of the relevant province. For intra-cluster sampling, a quota sampling method was used to determine the appropriate number of subjects according to the age and sex. The interviewer chose any street from the sampled zip code by his own will and started the interviews beginning from the first block on the right side of the street in the urban settlements or beginning from the first house on the right side of the reeve's office in the rural settlements until he/she completed the predetermined cluster size. Inclusion criteria for the study were as follows: being 16 years of age or over, giving oral consent to participate in the screening, and being a citizen of Turkey. All the subjects belonging to the household and present on site during the screening were interviewed, but those who were cognitively impaired or unable to understand the questions, or unable to give clear answers were excluded. Any present visitors not belonging to the household but belonging to the same cluster were included; otherwise, they were excluded.

The diagnostic procedure was carried out according to the algorithm suggested by the questionnaire itself. For case confirmation, the subjects who were suspected of having RA or SpA in accordance with the questionnaire were invited to the nearest university hospital to be examined by a rheumatologist or a physiatrist experienced

Table 1. Procedure of sampling and randomization in step II

A. Sampling

1. First stage: Determining of urban and rural sample sizes for all seven geographical regions

Region	Sample size* (n)	
	Urban	Rural
Northwestern	810	220
Northern	240	250
Western	330	210
Central	480	210
Eastern	200	170
Southern	310	200
Southeastern	110	100

2. Second stage: Determining of urban and rural sample sizes for selected 25 provinces

Region	Sample size* (n)	
	Urban	Rural
Adana	120	40
Afyon	30	40
Ankara	270	50
Antalya	80	80
Aydın	30	40
Bursa	110	50
Denizli	30	40
Diyarbakır	110	100
Edirne	20	20
Elazığ	40	30
Erzurum	60	50
Gaziantep	130	50
Isparta	30	20
İstanbul	630	100
İzmir	190	50
Kayseri	60	30
Kırıkkale	20	10
Kocaeli	50	50
Konya	100	90
Malatya	50	40
Manisa	50	40
Mersin	80	60
Samsun	240	250
Sivas	30	30
Van	50	50

B. Randomization

1. Randomizing the urban settlements from the list of zip code and rural settlements from the list of villages not further than 80 km from the provincial center.
2. Performing the interviews beginning from the first block located on the right side of the selected any street by the interviewer belonging to the randomized zip code in the urban settlements and beginning from the first house on the right side of the reeve's house in the rural settlements.
3. Terminating the interviews when the number of performed interviews reached the predetermined cluster size (10-20) for that zip code or village.

* Numbers were rounded to the nearest ten.

in rheumatic diseases and, if needed, to undergo some laboratory and/or X-ray investigations to confirm the diagnosis.
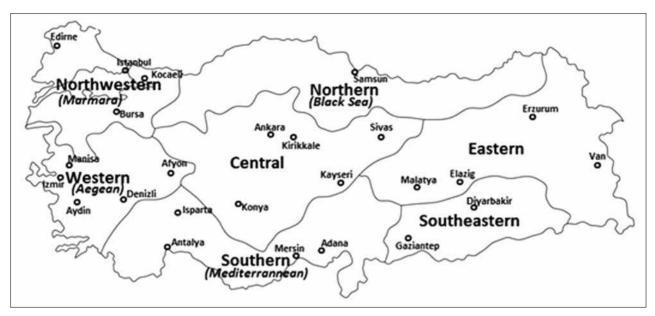
Figure 1. Regions of Turkey and provinces selected for the study.

Statistical analysis

Step I

The sensitivity and specificity were calculated for each item of the questionnaire, separately and in combination, in reference to the clinical diagnosis and the classification criteria. Statistical analysis for step I was performed using SAS® 8.0 statistical software.

Step II

We found that at least 3,984 individuals needed to be included in our study, for an estimated prevalence of 0.03 and precision level of 0.01, corrected by a 1.6-fold increase for the impact of design at an α error level of 0.05. Using the direct standardization method, the prevalence estimates were adjusted for age and sex to Turkey's population based on the data obtained in the 2000 Turkish national census. The 95% confidence intervals (CIs) were calculated as suggested.[18] Odds ratios and 95% CIs for regional variation of standardized prevalence estimates were obtained using MedCalc® statistical software version 17.6 (MedCalc Software bvba, Ostend, Belgium).

RESULTS

Of a total of 200 subjects recruited in step I, 52 (6 males, 46 females) had RA, 49 (42 males, 7 females) had SpA, 49 (11 males, 38 females) had non-inflammatory musculoskeletal diseases, and 50 (21 males, 29 females) were controls. The mean age of patients with RA, SpA, non-inflammatory musculoskeletal diseases, and controls were 52.6±10.0, 39.6±10.8, 49.7±10.0 and 34.2±12.4 years, respectively. All of the subjects were contacted by telephone and they responded to the questionnaire. When the clinical diagnosis was taken as the standard, sensitivity of the items on the questionnaire ranged from 94% to 0% in RA, and from 90% to 2% in SpA (Table 2).

The distribution of the study sample and Turkey's population by age and sex were shown in Table 3. In step II, a total of 25 subjects (2 males, 23 females) were diagnosed as RA (Table 4). The mean age of males and females with RA was 49.0±11.3 years (range, 41-57 years) and 46.5±15.0 years (range, 20-70 years), respectively. The crude prevalence for RA was 0.62% (95% CI; 0.38-0.86) in general, 0.12% (95% CI; -0.05-0.29) for males and 0.98% (95% CI; 0.58-1.38) for females.

The standardized RA prevalence for the general population of Turkey was calculated as 0.56% (95% CI; 0.33-0.79), 0.10% (95% CI; -0.05-0.25) for males and 0.89% (95% CI; 0.51-1.27) for females (Table 5).

Table 2. Diagnostic performance of items of questionnaire using clinical diagnosis and classification criteria

	Rheumatoid arthritis			Spondyloarthritis		
	Clinical diagnosis (n=52)	ACR criteria (n=52)	Control (n=50)	Clinical diagnosis (n=49)	ESSG criteria (n=49)	Control (n=50)
	Sensitivity (%)	Specificity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Specificity (%)
Self-report of diagnosis	77	77	99	89	88	100
Joint pain	94	94	49	71	76	49
Neck, back or low back pain	73	73	43	90	90	43
Joint swelling	71	71	89	27	31	89
Symmetrical joint affected	63	63	92	17	19	92
Hands affected	63	63	94	13	14	94
Lower limbs affected	58	58	91	23	26	91
More than 3 joints affected	48	48	95	10	12	95
More than 6 weeks of pain	38	38	99	15	17	99
Pain on waking	63	63	81	54	57	81
Morning joint stiffness	81	81	78	60	64	78
Nodules	48	48	95	4	5	95
Rheumatoid test performed	23	23	100	8	10	100
Rheumatoid test positive	6	6	100	2	2	100
Hand and wrist X-rays performed	79	79	93	25	29	93
Low back pain started before 45 years of age	38	38	93	29	29	93
Low back pain gradually started	54	54	54	79	81	54
Low back pain increased by effort	60	60	58	69	69	58
Morning back stiffness	50	50	74	67	67	74
More than 3 weeks of low back pain	38	38	78	52	52	78
Family history of:						
Spondylitis	13	13	81	40	45	81
Psoriasis	10	10	93	10	12	93
Uveitis	2	2	94	13	14	94
Reactive arthritis	-	-	98	4	5	98
Crohn's disease	8	8	98	6	7	98
Personal history of:						
Psoriasis	4	4	97	4	5	97
Long-lasting diarrhea	8	8	99	6	7	99
Pain in the heel	44	44	80	23	26	80
Pain in the buttocks	50	50	80	56	64	80
Back or pelvis X-ray performed	69	69	64	96	98	64

ACR: American College of Rheumatology; ESSG: European Spondylarthropathy Study Group.

Table 3. Age and sex distribution of study sample and Turkey's population

Age (year)	Study sample				Turkey's population			
	Female		Male		Female		Male	
	n	%	n	%	n	%	n	%
16-24	419	17.9	302	18.1	6093983	26.5	6382124	27.6
25-34	546	23.3	355	21.3	5376110	23.4	5528800	23.9
35-44	463	19.8	341	20.4	4386033	19.1	4537110	19.6
45-54	374	16.0	273	16.3	3018970	13.1	3067148	13.3
55-64	254	10.8	198	11.9	2007157	8.7	1880553	8.1
65-74	209	8.9	132	7.9	1505409	6.5	1312751	5.7
≥75	77	3.3	69	4.1	603977	2.6	436812	1.9
Total	2342	100.0	1670	100.0	22991639	100.0	23145298	100.0

Table 4. Distribution of cases by age group and sex

Age (year)	Cases with rheumatoid arthritis						Cases with spondyloarthritis						Study sample	
	Female		Male		Total		Female		Male		Total		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
16-24	1	0.14	-	-	1	0.14	2	0.28	-	-	2	0.28	721	100.00
25-34	5	0.55	-	-	5	0.55	6	0.67	1	0.11	7	0.78	901	100.00
35-44	5	0.62	1	0.12	6	0.75	4	0.50	1	0.12	5	0.62	804	100.00
45-54	5	0.77	-	-	5	0.77	2	0.31	1	0.15	3	0.46	647	100.00
55-64	4	0.88	1	0.22	5	1.11	1	0.22	-	-	1	0.22	452	100.00
65-74	3	0.88	-	-	3	0.88	-	-	-	-	-	-	341	100.00
≥75	-	-	-	-	-	-	-	-	-	-	-	-	146	100.00
Total	23	0.57	2	0.05	25	0.62	15	0.37	3	0.07	18	0.45	4012	100.00

The highest prevalence of RA was in the age group of 55-64 years (1.11%) (Table 4). The prevalence of RA was highest in the Northern region (2.00%) indicating a significant regional difference (p=0.003, Table 6).

A total of 18 subjects (3 males, 15 females) were diagnosed as SpA (Table 4). The mean age was 38.0±11.4 years (range, 25-46 years) for males and 36.7±11.2 years (range, 23-62 years) for females. The crude weighted prevalence for

Table 5. Standardized prevalence of rheumatoid arthritis and spondyloarthritis in overall population of Turkey aged 16 or over

	Total (%)	95% CI	Female	95% CI	Male	95% CI
Rheumatoid arthritis	0.56	0.33-0.79	0.89	0.51-1.27	0.10	-0.02-0.38
Spondyloarthritis	0.46	0.25-0.67	0.65	0.32-0.98	0.17	-0.03-0.37

CI: Confidence interval.

Table 6. Crude and standardized prevalence of rheumatoid arthritis in regions of Turkey

Region	Sample	Crude		Standardized				
	n	%	95% CI	%	95% CI	OR	95% CI	p
Northwestern	1,027	0.29	-0.04-0.62	0.25	-0.06-0.56	1.0		
Northern	490	2.04	0.79-3.29	2.00	0.76-3.24	7.1	1.9-26.0	0.003
Western	540	0.56	-0.07-1.19	0.53	-0.08-1.14	1.9	0.4-9.5	0.430
Central	689	0.87	0.18-1.56	0.72	0.09-1.35	2.5	0.6-10.5	0.212
Eastern	368	0.27	-0.26-0.80	0.32	-0.26-0.90	0.9	0.1-9.0	0.950
Southern	509	0.39	-0.15-0.93	0.31	-0.17-0.79	1.3	0.2-8.1	0.745
Southeastern	389	0	0	0	0	0.4	0.0-7.3	0.518

CI: Confidence interval; OR: Odds ratio.

Table 7. Crude and standardized prevalence of spondyloarthritis in regions of Turkey

Region	Sample	Crude		Standardized				
	n	%	95% CI	%	95% CI	OR	95% CI	p
Northwestern	1,027	0.10	-0.09-0.29	0.18	-0.08-0.44	1.0		
Northern	490	0.61	-0.08-1.30	0.78	0.00-1.56	4.2	0.8-23.1	0.097
Western	540	0.37	-0.14-0.88	0.34	-0.15-0.83	1.9	0.3-13.6	0.520
Central	689	1.45	0.56-2.34	1.49	0.59-2.39	7.5	1.6-34.6	0.009
Eastern	368	0.54	-0.21-1.29	0.53	-0.21-1.27	2.8	0.4-20.0	0.304
Southern	509	0	0	0	0	0.4	0.0-8.4	0.557
Southeastern	389	0	0	0	0	1.0	0.8-23.1	0.679

CI: Confidence interval; OR: Odds ratio.

SpA was 0.45% (95% CI; 0.24-0.66) in general, 0.18% (95% CI; -0.02-0.38) for males and 0.64% (95% CI; 0.32-0.96) for females.

The standardized SpA prevalence for the general population of Turkey was calculated as 0.46% (95% CI; 0.25-0.67), 0.17% (95% CI; -0.03-0.37) for males and 0.65% (95% CI; 0.32-0.98) for females (Table 5). The highest prevalence of SpA was in the age group of 25-34 years (0.78%) (Table 4). The prevalence of SpA was highest in the central region (1.49%) pointing to a significant regional difference (p=0.009) (Table 7).

DISCUSSION

To the best of our knowledge, this is the first nationwide survey showing the estimates of prevalence of RA and SpA in Turkey. Previous epidemiological studies on RA and SpA in Turkey were carried out in just one urban metropolitan area, i.e. Antalya[4] or in a few urban quarters not representing the whole metropolitan area, i.e. İzmir[3,5] or in a few regional small urban areas, i.e. the eastern Black Sea region[19] or in an urban and rural area of a small town, i.e. Havsa.[20] All of these studies were performed using face-to-face questionnaires. Of those, three used cluster sampling,[3-5] one intended to reach the entire population living in the study area[20] and one did not mention how the sampling procedure was managed.[19] Four of those studies were held mainly in coastal urban areas,[3-5,19] not taking into consideration the hinterland and rural areas. Therefore, our study had the advantage of covering both urban and rural areas and also inland Turkey.

We used a questionnaire endorsed by EULAR, which was also used in France, Lithuania and Serbia,[9,10,12,13] providing a reliable opportunity to compare the differences between countries. However, we used it in face-to-face interviews unlike the telephone interviews employed in France, Lithuania and Serbia, because neither the landline phones nor the mobile phones were in use in some rural areas of Turkey and landline phones where available in Turkey were largely being replaced by mobile phones at the time the survey was carried out. In doing so, we aimed to capture all the individuals intended to be involved in the study. Thus, despite being less costly than face-to-face surveys, telephone surveys might result in lower response rates.[21]

Our study indicates a prevalence of 0.56% for RA adjusted for the general population aged 16 or over. In previous studies, the prevalence of RA adjusted for the general population aged 20 or over of Turkey was estimated as 0.32%, 0.36%, 0.42% and 1.01% in Havsa, İzmir, Antalya and the eastern Black Sea region, respectively.[3,4,19,20] Those studies indicate that RA prevalence shows regional variations in Turkey. Indeed, our study has also shown that there are regional variations in the prevalence of RA. The prevalence of RA was highest in the Northern region (2.04%) and lowest in the Southeastern region (0%).

Our study showed a prevalence of 0.46% for SpA adjusted for the general population aged 16 or over. As expected, prevalence of SpA was highest in the age group of 25-34 years (1.28%). The prevalence of SpA was also heterogeneous among regions as of RA, being significantly highest in the Central region (1.45%). Interregional variations in prevalence of SpA were also shown in previous studies.[22-24] The prevalence of SpA

shows correlations with the prevalence of human leukocyte antigen B27 (HLA-B27).[24] According to two small non-population based studies, -one from the West and the other from the East of Turkey- the frequency of HLA-B27 varies between 2.8% and 11.1% in Turkey.[25,26] This considerably broad range of HLA-B27 frequency suggests an apparent interregional variation in the prevalence of SpA. However, we are not sure whether the heterogeneity of regional prevalence of SpA in Turkey can be explained by HLA-B27 frequency, as no nationwide data exist on the prevalence of HLA-B27. At present, regarding the paucity of data, we cannot rule out the environmental risk factors for heterogeneity of the prevalence of SpA as well.

On the other hand, we found a higher prevalence of SpA in females compared to males (0.65% vs. 0.17%, respectively). Interestingly, in a previous regional prevalence study performed in Turkey, the prevalence of SpA was also higher in females than in males (1.22% vs. 0.88%, respectively).[5] In that study, it was shown that the overall prevalence of SpA (1.05%) was even higher than of RA. A previous study conducted in Canada revealed that male/female prevalence ratio of AS decreased from 1.70 in 1995 to 1.21 by 2010 and the prevalence of AS tripled over the past two decades.[27] This suggests that both the prevalence of SpA and the proportion of female patients with SpA might be increasing in other parts of the world as well, which may be due to the increasing awareness of SpA in recent years.

We detected no case of RA or SpA in the Southeastern region. This could be partly explained by the region itself, containing one of the smallest populations in the survey. It is hard to establish a conclusion, since no prevalence study conducted in this region exists, which would support this result. Further regional studies using the same methodology related to the prevalence of RA and SpA are required to assist us in understanding the genetic and environmental factors.

Our study has some limitations. Face-to-face interviews might have their own limitations such as encountering more females than males in households, since the labor force is overwhelmingly comprised of males in Turkey, rendering the females mostly homemakers. Accordingly, 58% of the individuals involved in our study were females whereas the national census performed in 2000 showed that females constituted 50% of Turkey's population. The rate of females was even higher (61%) in the Northern region where the prevalence of RA was highest. This could be a bias for the higher prevalence of RA as it is known that RA is mostly seen in females. However, in the Lithuanian study in which the same methodology (by telephone) was used, the authors emphasized the same problem.[12] Another limitation of our study was not studying the HLA-B27.

In conclusion, our study showed that a north-south gradient of RA across Europe might not exist, compared to the prevalence reported from Northern European countries.[12,28] However, a north-south gradient of RA might exist in Turkey. Regarding SpA, the proportion of female patients may be higher than expected while there are interregional differences in the prevalence of SpA.

Declaration of conflicting interests

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