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ABSTRACT. ***Objective.*** To identify empirical evidence of diagnostic delay in spondyloarthritis (SpA), determine whether sex-related differences persist, and conduct an analysis from that perspective of the possible causes, including the influence of quality research, in this group of inflammatory rheumatic diseases.

Methods. A systematic review was done of delay in diagnosis of SpA in MEDLINE and EMBASE and other sources. Study quality was determined in line with the Strengthening The Reporting of OBservational studies in Epidemiology (STROBE) statement. A metaanalysis of 13 papers reporting sex-disaggregated data was performed to evaluate sex-related differences in diagnostic delay. The global effect of diagnostic delay by sex was calculated using means difference (D) through a fixed effects model.

Results. The review included 23,883 patients (32.3% women) from 42 papers. No significant differences between the sexes were detected for symptoms at disease onset or during evolution. However, the mean for delay in diagnosis of SpA showed sex-related differences, being 8.8 years (7.4–10.1) for women and 6.5 (5.6–7.4) for men ($p = 0.01$). Only 40% of papers had high quality. A metaanalysis included 12,073 participants (31.2% women). The mean global effect was $D = 0.6$ years (0.31–0.89), indicating that men were diagnosed 0.6 year (7 months) before women.

Conclusion. Delay in diagnosis of SpA persists, and is longer in women than in men. There are no significant sex-related differences in symptoms that could explain sex-related differences in diagnostic delay. Methodological and possible publication bias could result in sex-biased medical practice. (J Rheumatol First Release December 15 2016; doi:10.3899/jrheum.160825)

Key Indexing Terms:
SPONDYLOARTHRITIS SEX DIFFERENCES SEX BIAS DIAGNOSTIC DELAY

Spondyloarthritis (SpA) comprises a heterogeneous group of interrelated inflammatory rheumatic diseases that can affect the synovium, enthesis of axial and peripheral joints, and some extraarticular sites. The SpA group includes reactive arthritis, enteropathic arthritis, juvenile SpA, psoriatic arthritis (PsA), and ankylosing spondylitis (AS), which was the first condition to be characterized and is considered the prototype disease. Initially, the different forms were looked upon as independent diseases, but similarities in their clinical characteristics, and later the association of these diseases with HLA-B27 after its description in 1973, proved that they are similar or closely related conditions now jointly recognized as SpA. In earlier studies, AS had been found to be far more common in men by a ratio of 10:1, but once all the different forms were considered in conjunction, this ratio narrowed to 2–3:1[1,2,3]. The disease commences with spinal or lumbar pain, and enthesitis or peripheral arthritis, most often in the lower limbs. Radiological alterations are slow to appear and hence underrecognition or considerable diagnostic delay has been frequent. As a result of the discovery of the association with HLA-B27, the development of classification criteria for the different clinical forms, and probably, closer attention, delay has been reduced in recent years[4].

Because of the clearly lower frequency of classical AS in women, the disease was considered a male disease, prompting underrecognition in women and resulting in a longer delay to diagnosis than in men, and this delay continues to be reported when all the different clinical forms are considered together[5].

With recent therapeutic advances, early diagnosis and knowledge of sex differences have become indispensable. Several studies have shown that there is a systematic sex bias in healthcare, partially related to biased research hypotheses and/or methods due to insensitivity to sex[6].

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The most widely used definition of sex bias is the differential medical treatment of men and women, the effect of which may be positive, negative, or neutral[7]. However, for research purposes, it is useful to define sex bias as a systematic wrong approach regarding sex insensitivity that incorrectly considers women and men as similar in the natural history of disease[6]. Sex bias in SpA is an interesting area to study[8] because of the longer diagnosis delay in women and the causes of that delay.

The aim of our present study was to identify empirical evidence of diagnostic delay in SpA, determine whether sex-related differences persist, and conduct an analysis from a sex perspective of the possible causes, including the influence of quality research, in this group of inflammatory rheumatic diseases.

MATERIALS AND METHODS

Data sources and literature search. A systematic literature search was conducted in MEDLINE and EMBASE through natural language. The key words were spondyloarthropathies, spondyloarthritis, "reiter arthritis", "reactive arthritis", "juvenile spondyloarthropathy", "ankylosing spondylitis", "enteropathic spondyloarthritis", ("spondyloarthropathy AND inflammatory bowel disease"), ("spondyloarthritis AND inflammatory bowel disease"), and ("ankylosing spondylitis AND inflammatory bowel disease"). Each of these was individually combined with: (delay OR delayed) AND (sex OR gender OR women OR woman) NOT (psoriatic arthritis). Complementary papers potentially eligible were included, a search through snowballing was performed by cross reference, and 16 studies were identified[1,3,8-21]. Ultimately, 379 identified papers were consulted. The search included all material published before April 2016, regardless of date of publication.

Study selection. The inclusion criteria were original articles in which SpA was the main subject, which analyzed delay in diagnosis and included women. We excluded papers with PsA patients because, although this disease also shows diagnosis delay, it is less than that found in AS[4], probably due to the presence of psoriasis in two-thirds of patients prior to arthritis. In addition, papers were excluded if they did not fulfill the study criteria or consisted of editorials, reviews, case studies, questionnaires, or diagnostic/therapeutic techniques. Non-English and non-Spanish papers were excluded.

We obtained 102 papers from MEDLINE and 261 from EMBASE and 16 from other sources. Of these, 226 were eliminated because they were duplicated, and 111 met the exclusion criteria described above. The other 42 were included in the review (Figure 1).

Data extraction and quality assessment. Two observers (JV and BBM) performed a content analysis of the 42 original articles finally selected, for which an information compilation protocol was established and applied, comprising the following variables:

• Patients: total number of patients and number disaggregated by sex, type of SpA (axial, peripheral, or mixed), age at onset of disease, age at diagnosis, duration of disease, HLA-B27 positivity, family history of AS and social/sex-related causes explaining sex differences in delay in diagnosis (family/reproductive and/or productive roles, social factors and/or factors related with medical practice), clinical manifestations at baseline and later (neck and back pain, peripheral arthritis, enthesitis, and uveitis), and delay in diagnosis, which was considered as the time difference between the onset of symptoms and the date of diagnosis by a professional as established by the Assessment of Spondyloarthritis International Society (ASAS).

• Study characteristics: design (cross-sectional, cohort, case control), type of cases (incident, prevalent), data source (hospital, patient group), type of data (medical history, questionnaire, register), classification criteria (Rome, New York, modified New York, European Spondyloarthropathy Study Group, and ASAS).

• The quality of the studies was determined in line with the Strengthening The Reporting of OBservational studies in Epidemiology (STROBE) statement (www.strobe-statement.org), a checklist of items that should be included in reports of observational studies, related to title and abstract, introduction, methods, results, discussion, and other information. Papers were classified as follows: low quality (< 50%), medium (≥ 50% to < 70%), high (≥ 70% to < 90%), and excellent (≥ 90%).

Concordance between the 2 observers was computed for all the variables included in the review. A third observer (RCMT) evaluated cases of disagreement between observers in the classification of some variables.

Data analysis and synthesis. First, a descriptive analysis was carried out of the distribution of the previously mentioned variables. We calculated means and CI 95% to compare age at onset, age at diagnosis, disease duration, and diagnostic delay in women and men. Further, to compare sex-related differences as regards clinical manifestations at onset and during the course of the disease, we calculated means and CI 95% of the percentages of neck and back pain, peripheral arthritis, enthesitis, and uveitis.

Comparisons of the continuous parametric variables were carried out by Student t test and the nonparametric ones by Mann-Whitney U test. A value of $p < 0.05$ was considered significant. Statistical evaluations were performed by SPSS 15.0 package program.

A metaanalysis was performed to evaluate sex-related differences in diagnosis delay, in which women were the case group and men the control one. The main selection criteria were papers that reported information about median and SD of diagnosis delay by sex. Twenty-five papers did not offer diagnostic delay disaggregated by sex, 2 papers were excluded because they did not show SD to calculate the CI, and 1 more was excluded because of low quality. Of the remaining 14 papers, in 2 studies, the SD from the data (no. men and women, means for men and women, and statistical significance) were calculated assuming similar variances for men and women. One of the studies[22] gave data for 4 subgroups that formed 4 different samples and these were included in the metaanalysis (southern China with juvenile AS, southern China with adult AS, northern China with juvenile AS, and northern China with adult AS).

Seventeen samples were included in the metaanalysis (Figure 1). Because delay in diagnosis is a continuous variable, the means difference (D) and its CI (95%) were used to calculate the global effect of diagnostic delay by sex. Heterogeneity between the studies was measured using the chi-squared statistics test; probability value of $p < 0.05$ was considered statistically significant.

The I^2 statistic was used to quantify the degree of heterogeneity of the 17 samples (14 papers), considering a value over 50% high. Because a heterogeneity was obtained not only by chi-squared test ($p < 0.00001$) but also by I^2 statistic = 95% by the randomized effects model, sensitivity analyses were performed to assess the robustness of the results of the metaanalysis. Specifically, the influence of effect sizes was assessed by deletion of each paper to check heterogeneous data that could affect the overall result. Only 1 paper (Bandinelli, *et al*[23]) was identified as the cause of the entire heterogeneity and it was excluded from the metaanalysis. That paper observed less diagnostic delay in women than in men, likely related to higher education, work levels, and peripheral involvement. As Higgins and Green write, if an obvious reason for the outlying result is apparent, the study might be removed with more confidence[24]. This practice is also carried out in a Cochrane review[25].

Then, a second metaanalysis was developed with 16 samples (13 papers). Publication bias was determined by means of a funnel plot. The metaanalysis was performed using Review Manager software (Revman version 5.3; Cochrane Collaboration; http://tech.cochrane.org/revman).

Ethics approval was not required, in accordance with the policy of our institution.

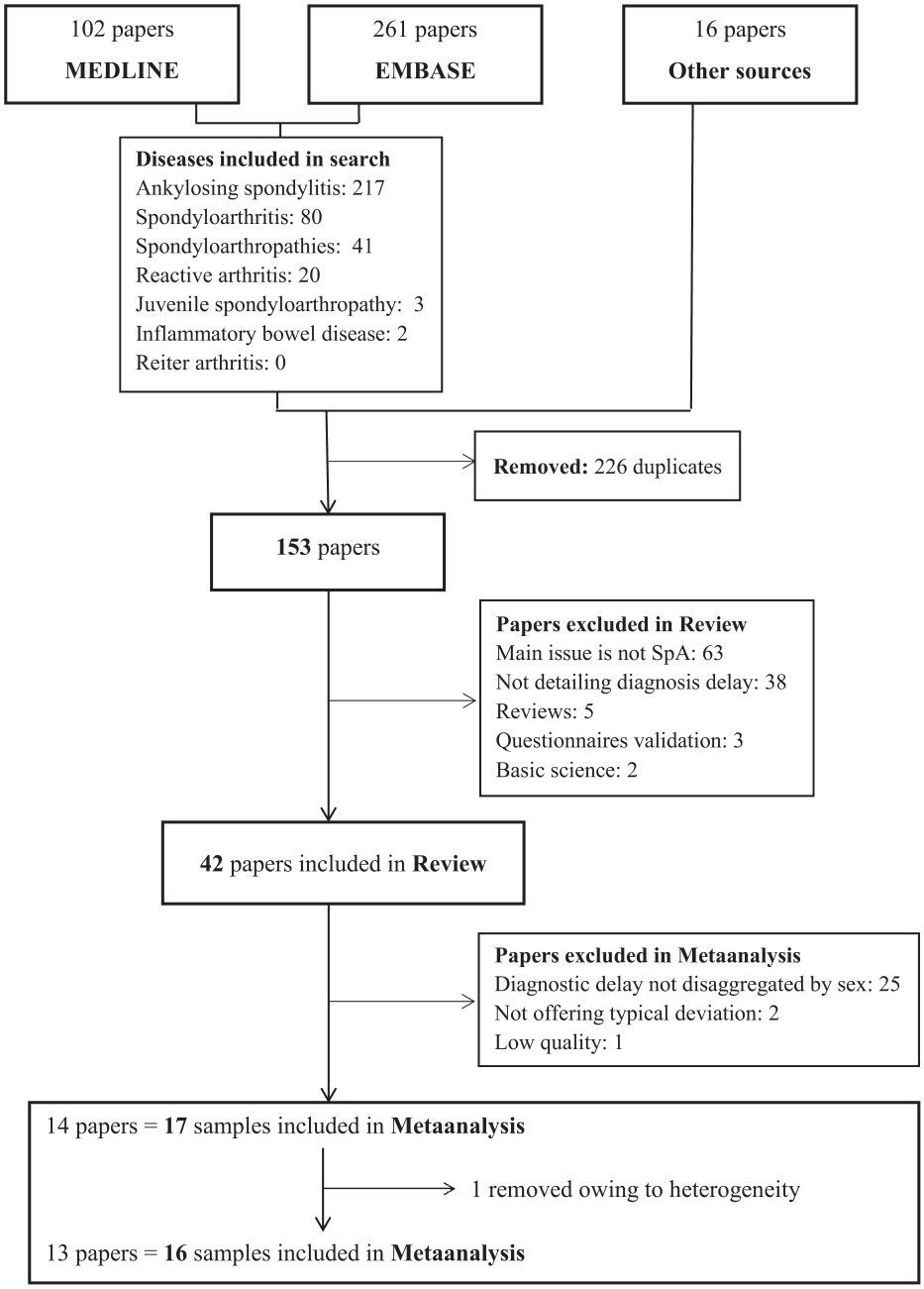


Figure 1. Flowchart of the review process of studies about diagnosis delay of spondyloarthritis (SpA).

RESULTS

Table 1 shows the main characteristics of the 42 studies on diagnostic delay in SpA included in this systematic review[1,2,3,8-18,19,20,21,22,23,26-36,37-47,48]. The review included 23,883 patients (67.6% men, 32.3% women). Prevalent cases accounted for all studies; 97.6% used a cross-sectional design and 1 was a cohort study[48]. Criteria used for patient selection are shown in Table 1.

The mean for delay in diagnosis was given in 3 papers that included women only, and a further 17 studies gave data disaggregated by sex, indicating statistically significant differences between women and men in the mean for delay in diagnosis, with a mean of 8.8 years (7.4–10.1) being obtained for women and 6.5 (5.6–7.4) for men ($p = 0.01$). Thirty papers gave overall data of delay in diagnosis (9 of them also gave data by sex), and the mean was 6.6 years (5.9–7.3).

There were no detected significant sex differences in mean age at onset of disease, age at diagnosis, and mean disease duration.

Table 1. Characteristics of studies of diagnostic delay in spondyloarthritis published between 1976 and 2016.

Author (yr)[ref]	Both Sexes		Women		Men		Study Design	SpA Type	Study Subject Origin	Info Sources	Diagnosis Criteria
	N	Diagnostic Delay, yrs	N	Diagnostic Delay, yrs	N	Diagnostic Delay, yrs					
Conigliaro P (2016)[26]	136	5.2	91	NR	45	NR	CS	A/P	H	MR	ASAS
Bandinelli F (2016)[23]	135	NR	44	6.3 ± 1.1		9.9 ± 0.8	CS	A/P	H	MR	NY, ASAS
Seo M (2015)[27]	105	8 (3–4)	24	NR	81	NR	CS	A/P	H	MR/Q	ASAS
Shahlaee A (2015)[28]	320	NR	67	8.8	253	8	CS	A/P	H	Q	mNY
Zhao J (2015)[29]	256	3.8 ± 2.0	30	NR	226	NR	CS	A/P	H	MR	mNY
Guan M (2014)[30]	J: 50	5.3 ± 5.2	9	NR	41	NR	CS	A/P	H	Q	mNY
	Adult: 89	2.8 ± 3.8	24	NR	65	NR					
Bodur H (2012)[21]	1381	5 ± 6.8	343	5.3	1038	4.9	CS	A/P	H	Q	mNY
Ibn Yacoub Y (2012)[31]	130	NR	43	4.8	87	4.6	CS	A/P	H	MR	mNY
Gerdan V (2012)[32]	393	8.1 ± 8.6	135	NR	258	NR	CS	A/P	H	Q	mNY
Hamilton L (2011)[33]	807	8.57	298	NR	509	NR		NR	H	Q	mNY
Hajialilo M (2014)[34]	60	6.2 ± 3.5	7	8.0 ± 4.7	53	5.9 ± 3.3	CS	A/P	H	Q	mNY
Chung HY (2011)[35]	H+: 435	2.7 ± 4.2	212	NR	223	NR	CS	A/P	H	MR	Amor/ESSG/
	H–: 273	3.7 ± 5.1	171	NR	102	NR					ASAS/mNY
Slobodin G (2011)[36]	151	NR	72	5.7	79	5.9	CS	A/P	H	MR	ASAS/mNY
Roussou E (2011)[37]	516	6	344	6.3	172	5.6	CS	A/P	H	Q	ESSG/
											ASAS/mNY
Ma HJ (2012)[22]	SC: 113	NR	J: 4	10.8	J: 39	8.4	CS	A	H	Q	mNY
			A: 19	6.2	A: 51	6.6					
	NC:121	NR	J: 6	2.1	J: 35	2.2					
			A: 17	4.1	A: 63	4					
Almodóvar R (2011)[14]	F: 263	7.7 ± 9	326	NR	990	NR	CS	A/P	H	R	mNY
	S: 1053	7.8 ± 9									
Bakland G (2011)[38]	677	9	126	NR	551	NR	CS	A/P	H	MR	mNY
Cansu DU (2011)[15]	102	8.6	36	NR	66	NR	CS	A/P	H	MR/Q	mNY
Bakland G (2011)[16]	360	9.4	97	NR	263	NR	CS	A/P	H	Q	mNY
Almodóvar R (2010)[13]	SpA: 443	7 ± 9	120	NR	342	NR	CS	A	H	R	mNY
	SpA + FM: 19	8 ± 7									
Atagunduz P (2010)[19]	235	6.7	96	7.4	139	6.2	CS	A	H	MR/C	mNY
Özgöcmen S (2009)[39]	J: 43	5.0	4	NR	39	NR	CS	A/P	H	MR	mNY
	Adult: 279	9.2	53	NR	226	NR					
Nazarinia MA (2009)[12]	98	3.8 ± 0.8	27	NR	71	NR	CS	A/P	H	MR/C	mNY
Lin YC (2009)[40]	J: 47	5.7 ± 6.3	6	NR	41	NR	CS	A/P	H	Q	mNY
	Adult: 122	4.6 ± 6.8	21	NR	101	NR					
Aggarwal R (2009)[8]	70	6.7	11	8.9	59	6.5	CS	A	H	Q	mNY
Dincer U (2008)[41]	111	6.0 ± 5.0	8	14.4 ± 14.2	103	5.3 ± 5.6	CS	A/P	H	Q	mNY
Reed MD (2008)[42]	126	8.1	35	10.2	91	7.3	CS	A/P	H/PC	MR/C	mNY
Forejtová S (2008)[11]	1001	9.1	379	NR	622	NR	CS	A	SG	Q	mNY
Lin Z (2008)[43]	238	5.9 ± 5.7	38	7.3 ± 7.1	204	5.7 ± 5.4	CS	A/P	H	Q	mNY
Aloush V (2007)[18]	36	NR	18	9.9	18	4.1	CS	A	H	Q	mNY
Uppal SS (2006)[20]	55	7.4 ± 1.9	10	NR	45	NR	CS	A/P	H	MR/Q	ESSG
Stone M (2005)[44]	J: 326	15.3 ± 0.7	929	NR	1418	NR	CS	A	SG	Q	NR
	Adult: 2021	7.6 ± 0.2									
Feldtkeller E (2003)[45]	1080	8.8	389	NR	691	NR	CS	A/P	SG	Q	mNY
Zink A (2000)[17]	8776	NR	2729	6.1	6047	5.5	CS	A/P	H	MR/Q	NR
Koh WH (1993)[46]	38	7.25	9	NR	29	NR	CS	A/P	H	MR	NY
Carbone LD (1992)[3]	158	5.0	37	NR	121	NR	CS	A/P	H	MR	mNY
Ringsdal VS (1989)[47]	179	NR	48	12.6	131	9.5	CS	A/P	SG	Q	NR
Calin A (1988)[2]	J: 129	8.7	32	NR	97	NR	CS	A/P	SG	Q	NR
	E: 129	6.8	36	NR	93	NR					
	L: 129	7.2	38	NR	91	NR					
Riesco M (1985)[9]	22	NR	22	13.2	0	NR	CS	A/P	H	MR	Rome
Marks SH (1983)[48]	50	NR	25	12.8	25	10.3	CC	A/P	H	MR	NR
Goodman C (1980)[10]	12	NR	12	11.5	0	NR	CS	NR	H	Q	NR
Hill H (1976)[1]	39	NR	39	10	0	NR	CS	NR	H	MR	NR

J: juvenile; E: early; L: late; SpA: spondyloarthritis; FM: fibromyalgia; SC: Southern China; NC: Northern China; F: familial; S: sporadic; H+: HLA-B27+; H–: HLA-B27–negative; CS: cross-sectional; CC: case control; A: axial; P: peripheral; H: hospital; PC: primary care; C: community; SG: support groups; MR: medical records; Q: questionnaire; R: register; NY: New York; mNY: modified New York; ESSG: European Spondyloarthropathy Study Group; ASAS: Assessment of Spondyloarthritis International Society; NR: not reported.

HLA-B27 positivity was reported in 26 papers and patients' family history in 22 papers. In both cases, there was no detected statistical significance.

Although 9 papers mention the concepts of social events[21,47], social support[21,42], social system[21], social situation[27,30], effect and consequences[11,21], social status[15,21,23,28], social domain and function[31], and quality of life[21,31], they are not in relation to social/sex-related causes explaining sex differences in delay in diagnosis. Only Aggarwal in 2009 adequately discussed the complex range of sex factors involved in the diagnostic process of SpA according to sex[8].

Table 2 with data of review and metaanalysis shows that no statistically significant differences were detected between the sexes regarding symptoms at onset of disease, nor were statistically significant differences detected in symptoms during evolution of the disease.

As determined according to the different sections of the STROBE Statement, 11 (26.1%) papers were of low quality, 14 (33.3%) were of medium quality, and 17 (40.4%) were high quality; these latter were published after 2005. The low quality of papers was primarily related to the methods section: 41 papers did not describe any attempts to address potential sources of bias, 33 papers did not explain how sample size was calculated, 30 papers did not describe analytical methods that took sampling strategy into account, 35 papers did not explain how missing data were addressed, 21 papers did not describe any methods used to examine subgroups and interactions, and 20 papers did not present key elements of study design early in the paper. In the title or the abstract, 27 papers did not indicate the study design with a commonly used term. Regarding the discussion section, 13 papers did not discuss study limitations in terms of sources of potential bias or inaccuracy (Table 3).

Figure 2 shows the findings of the first metaanalysis of the 17 samples or subgroups (13 papers + 4 samples[22]) concerning delay in diagnosis of SpA disaggregated by sex; this included 12,208 participants (3812 women and 8396 men[8,17,18,19,21,22,23,28,31,34,36,37,41,42]). The mean global effect was D = 0.77 years (–0.58, 2.12); this result was not statistically significant, indicating differences in effects across studies. Therefore, we can say that the average effect reported did not represent the studies adequately because of heterogeneity. Afterward, a sensitivity analysis was performed, and a study[23] with a sample size of 91 men and 44 women identified as the cause of the entire heterogeneity was removed, because the diagnostic delay in men (9.909 ± 0.8453) was significantly higher than in women (6.336 ± 1.104; p = 0.0023). In the second metaanalysis, 16 samples (13 papers) with 12,073 participants (3768 women and 8305 men) were included and the mean global effect obtained was D = 0.6 years (0.31, 0.89), which indicates men were diagnosed 0.6 years (7 months and 6 days) before women, and this result was statistically significant. No heterogeneity was detected in included studies regarding delay in diagnosis of AS by sex: chi-squared test (p = 0.57), and I^2 statistic = 0%, indicate that there was no variability between studies.

A funnel plot (Figure 3) suggests possible publication bias. The slight asymmetry at the lower left indicates that there is a lack of articles with small samples reporting estimations that women have less diagnosis delay than men. In this case,

Table 2. Clinical manifestations of spondyloarthritis at onset and during followup.

Systematic Review — 42 Papers										
At Onset						During Followup				
Women		Men		p	Clinical Manifestations	Women		Men		p
No. Papers	% (CI 95%)	No. Papers	% (CI 95%)			No. Papers	% (CI 95%)	No. Papers	% (CI 95%)	
6	69.7 (48.6–90.7)	5	69.3 (45.2–93.5)	0.9	Back pain: lumbar/dorsal	8	82.9 (64.3–100)	5	78 (48.5–100)	0.6
2	19.8 (0–100)	2	14.4 (0–100)	0.4	Neck pain	9	31.3 (13–49.7)	7	24.6 (7.9–41.3)	0.7
4	37.2 (15.2–59.3)	3	33.1 (0–79.1)	0.9	Peripheral arthritis	11	45 (32.5–57.5)	8	34.7 (22.5–47)	0.2
3	5.9 (2.8–9.1)	2	4.1 (0–21.8)	0.2	Enthesitis	5	37.4 (0–79)	5	27.8 (0–59.6)	0.8
1	11.0	1	12.0	NC	Uveitis	10	25.1 (12.3–37.9)	7	16.3 (6.2–26.4)	0.3
Metaanalysis — 13 Papers (16 samples)										
At Onset						During Followup				
Women		Men		p	Clinical Manifestations	Women		Men		p
No. Papers	% (CI 95%)	No. Papers	% (CI 95%)			No. Papers	% (CI 95%)	No. Papers	% (CI 95%)	
3	69.3 (8.2–100)	3	66.7 (5.6–100)	0.5	Back pain: lumbar/dorsal	3	59.0 (13.4–100)	3	65.0 (10.1–100)	0.8
2	19.8 (0.100)	2	14.4 (0–100)	0.4	Neck pain	3	27.8 (0–75.3)	3	21.6 (0–68.8)	0.5
2	44.2 (0–100)	2	41.5 (0.100)	0.9	Peripheral arthritis	5	34.4 (10.2–58.5)	5	32.1 (9.6–54.7)	0.9
1	6.5	1	2.7	NC	Enthesitis	4	43.8 (0–99.5)	4	30.8 (0–76.2)	0.5
1	11.0	1	12	NC	Uveitis	3	15.5 (0–39.8)	3	13.8 (0–33.6)	0.8

NC: not calculated.

Table 3. Quality of the studies of diagnosis delay in spondyloarthritis evaluated with STROBE.

Author (yr)[ref]	STROBE–positive Items	Score
Conigliaro P (2016)[26]	1a), 1b), 2, 3, 4, 5, 6a), 7, 12a), 12b), 12d), 12e), 13a), 14a), 15, 16a), 17, 18, 20, 21	high
Bandinelli F (2016)[23]	1b), 2, 3, 4, 5, 6a), 7, 8, 10, 11, 12a), 12b), 12e), 13a), 14a), 15, 16a), 16b), 17, 18, 20, 21, 22	high
Seo M (2015)[27]	1a), 1b), 2, 3, 4, 5, 6a), 7, 8, 10, 11, 12a), 12b), 12e), 13a), 14a), 15, 16, 17, 18, 19, 20, 21, 22	high
Shahlaee A (2015)[28]	1b), 2, 3, 4, 5, 6a), 7, 8, 10, 12a), 12e), 13a), 14a), 15, 16a), 18, 19, 20, 21, 22	high
Zhao J (2015)[29]	1a), 1b), 2, 3, 4, 5, 6a), 7, 8, 12a), 12b), 12c), 13a), 14a), 15, 16a), 17, 18, 19, 20, 21	high
Guan M (2014)[30]	1b), 2, 3, 7, 8, 12a), 12b), 12e), 13a), 14a), 15, 16a), 18, 19, 20	low
Bodur H (2012)[21]	1b), 2, 3, 4, 5, 6a), 7, 8, 10, 12a), 12b), 12e), 13a), 14a), 15, 16a), 17, 18, 20, 21, 22.	high
Ibn Yacoub Y (2012)[31]	1b), 2, 3, 4, 6a), 7, 8, 11, 12a), 12b), 13a), 15, 16a), 18, 20, 21, 22	medium
Gerdan V (2012)[32]	1b), 2, 3, 5, 6a), 7, 12a), 12e), 14a), 15, 16a), 17, 18, 19, 20, 21	medium
Hamilton L (2011)[33]	1b), 2, 3, 4, 5, 6a), 7, 8, 12a), 13a), 14a), 15, 16a), 17, 18, 19, 20, 21, 22	medium
Hajialilo M (2014)[34]	1a), 1b), 2, 3, 4, 5, 6a), 8, 12a), 12e), 13a), 14a), 15, 16a), 18, 19, 20, 21, 22	high
Chung HY (2011)[35]	1b), 2, 3, 4, 5, 6a), 7, 8, 11, 12a), 12b), 12e), 13a), 14a), 15, 16a), 17, 18, 19, 20, 21, 22	high
Slobodin G (2011)[36]	1b), 2, 3, 5, 6a), 7, 8, 11, 13a), 14b), 15, 16a), 18, 19, 22	medium
Roussou E (2011)[37]	1b), 2, 3, 5, 6a), 7, 8, 12a), 13a), 15, 16a), 18, 20, 22	medium
Ma HJ (2012)[22]	1b), 2, 3, 5, 6a), 7, 8, 11, 12a), 12b), 13a), 14a), 14b), 15, 16a), 16b), 18, 19, 20, 22	medium
Almodóvar R (2011)[14]	1a), 1b), 2, 3, 4, 5, 6a), 7, 8,12a), 12b), 13a), 14a), 15, 16a), 18, 19, 20	medium
Bakland G (2011)[38]	1b), 2, 3, 4, 5, 6a), 6b), 7, 8, 9, 10, 11, 12a), 12b), 13a), 14a), 15, 16a), 16b), 17, 18, 19, 20, 21, 22	high
Cansu DU (2011)[15]	1b), 2, 3, 5, 6a), 7, 8, 11, 12a), 12b), 13a), 14a), 15, 16a), 18, 19, 20, 21, 22	high
Bakland G (2011)[16]	1a), 1b), 2, 3, 5, 6a), 7, 8, 11, 12a), 12b), 12c), 13a),14a),15, 16a), 17, 18, 19, 20, 21	high
Almodóvar R (2010)[13]	1a), 1b), 2, 3, 4, 5, 6a), 7, 8, 11, 12a), 12b), 13a), 14a),15, 16a), 16b), 17, 18, 20	high
Atagunduz P (2010)[19]	1a), 1b), 2, 3, 5, 6a), 7, 8, 11, 12a), 12b), 13a), 15, 16a), 17, 18, 19, 20, 21	high
Ozgocmen S (2009)[39]	2,3, 4, 5, 6a), 7,8, 12a), 12e), 13a), 14a), 18, 19	low
Nazarinia MA (2009)[12]	1b), 2, 3, 5, 6a), 7, 8, 12a), 13a), 13b), 15, 18, 20, 21, 22	medium
Lin YC (2009)[40]	1b), 2, 3, 4, 5, 6a), 7, 8, 10, 12a), 12e), 13a), 14a), 15, 16a), 17, 18, 19, 20, 21	high
Aggarwal R (2009)[8]	1b), 2, 3, 5, 6a), 7, 8, 11, 13a), 14a),15, 16a), 17, 18, 19, 20, 21, 22	medium
Dincer U (2008)[41]	1a), 1b), 2, 3, 7, 8, 12a), 12b), 12e), 13a), 14a), 15, 16a), 18, 19, 20	medium
Reed MD (2008)[42]	1a), 1b), 2, 3, 4, 5, 6a), 7, 8, 11, 12a), 12b), 13a), 14a), 14b), 15, 16a), 16b), 18, 19, 20, 21	high
Forejtová S (2008)[11]	1b), 2, 3, 4, 5, 6a), 7, 8, 11, 12a), 12b), 13a), 14a), 15, 16a), 16b), 17, 18, 19, 20, 22	high
Lin Z (2008)[43]	1b), 2, 8, 12a), 13, 18	low
Aloush V (2007)[18]	1b), 2, 3, 4, 6a), 7, 8, 13a), 14a), 14b), 15, 18, 20	low
Uppal SS (2006)[20]	1b), 2, 5, 6a), 7, 8, 11, 12b), 13a), 14a), 14b), 15, 16a), 18	medium
Stone M (2005)[44]	1a), 1b), 2, 3, 4, 5, 6a), 7, 8, 10, 11, 12a), 12b), 13a), 14a), 15, 16a), 16b), 17, 18, 19, 20, 21	high
Feldtkeller E (2003)[45]	1b), 4, 6a), 12a), 13a), 13b), 15, 16a), 18, 19, 20	low
Zink A (2000)[17]	1b), 2, 3, 5, 6a), 7, 8, 10, 12a), 12b), 13a), 14a), 15, 16a), 16b), 18, 19, 20, 21	medium
Koh WH (1993)[46]	1b), 5, 6a), 8, 13a), 14b), 15, 16b), 18, 20	low
Carbone LD (1992)[3]	1a), 1b), 2, 3, 5, 6a), 7, 10, 12a), 13a), 14a), 15, 16a), 16b), 18, 19, 20	medium
Ringsdal VS (1989)[47]	1b), 5, 6a), 7, 12c), 13a), 14b), 15, 16a), 18, 19, 20	low
Calin A (1988)[2]	1b), 2, 3, 4, 5, 6a), 6b), 11, 13a), 14a), 15, 18, 19, 20, 21	low
Riesco M (1985)[9]	1b), 7, 8, 14a), 15, 18, 20	low
Marks SH (1983)[48]	1a), 1b), 2, 3, 4, 6a), 6b), 12d), 13a), 14a), 14b), 15, 16a), 18, 19, 20, 21	medium
Goodman CE (1980)[10]	1b), 2, 3, 14a), 15, 18, 20	low
Hill HF (1976)[1]	2, 3, 6a), 14a), 14b), 15, 18, 20, 22	low

STROBE: Strengthening The Reporting of OBservational studies in Epidemiology. Score quality: low quality < 50%; medium: 50% ≥ scoring < 70%; high: 70% ≥ scoring < 90%; excellent ≥ 90%.

metaanalysis would estimate less diagnosis delay in men than in women.

DISCUSSION

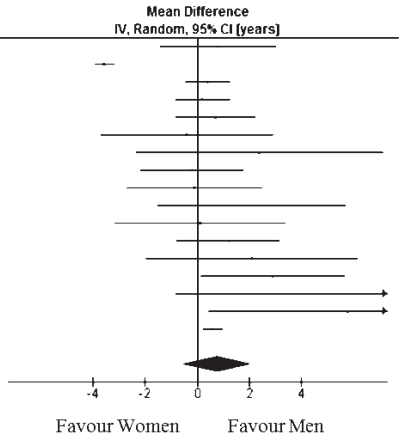
We found that diagnostic delay in SpA was greater in women than in men. One possible explanation for this delay in women could be that they present different clinical symptoms that might delay the diagnosis, as mentioned in the literature; however, none of the studies reviewed in connection to diagnostic delay detected such sex-related differences in symptoms either at the beginning or during the course of SpA.

Delay in diagnosis of SpA has been described in women[5,9,10] and in both sexes[6,7,11-16,20,26,27,29,30,32,33,35,38,39,40,44,45,46], and although Bandinelli[23] observed less diagnostic delay in women than in men, in most of the papers where delay was compared between men and women, it was greater in women[8,17,18,19,21,22,28,31,34,37,41,42,43,47,48]. This implies that patients have had medically unsolved disorders for a long time, have continued searching for a diagnosis and treatment, or are being erroneously diagnosed and managed[49]. One possible explanation is that dorsal/lumbar pain is a frequent symptom occurring in various conditions, and is one of the most common symptoms attributable to

A.

Study or Subgroup	Diagnostic Delay Women Mean [years]	SD [years]	Total	Diagnostic Delay Men Mean [years]	SD [years]	Total	Weight	Mean Difference IV, Random, 95% CI [years]	Year
Shahlaee 2015	8,8	8,51	67	8	7,22	253	6,5%	0,8000 [-1,4234, 3,0234]	2015
Bandinelli 2015	6,336	1,104	44	9,909	0,8453	91	7,9%	-3,5730 [-3,9426, -3,2034]	2015
Bodur 2012	5,3	7	343	4,9	6,9	1038	7,7%	0,4000 [-0,4515, 1,2515]	2012
Yacoub 2012	4,8	2,7	43	4,6	3,1	87	7,6%	0,2000 [-0,8371, 1,2371]	2012
Roussou 2011	6,3	7,2	293	5,6	7,9	150	7,2%	0,7000 [-0,8093, 2,2093]	2011
Ma ASC 2011	6,2	6,4	19	6,6	6	51	5,4%	-0,4000 [-3,7156, 2,9156]	2011
Ma JSC 2011	10,8	4	4	8,4	8,5	39	4,0%	2,4000 [-2,3416, 7,1416]	2011
Slodobin 2011	5,7	6	72	5,9	6,4	79	6,8%	-0,2000 [-2,1780, 1,7780]	2011
Ma JNC 2011	2,1	2,8	6	2,2	4	35	6,1%	-0,1000 [-2,7030, 2,5030]	2011
Hajialilo 2011	8	4,7	7	5,9	3,3	53	5,1%	2,1000 [-1,4933, 5,6933]	2011
Ma ANC 2011	4,1	6,3	17	4	5,2	63	5,4%	0,1000 [-3,1584, 3,3584]	2011
Atangunduz 2010	7,4	7,9	96	6,2	7,1	139	6,8%	1,2000 [-0,7724, 3,1724]	2010
Aggarwal 2009	8,6	6,6	11	6,5	4,7	59	4,6%	2,1000 [-1,9805, 6,1805]	2009
Reed 2008	10,2	7,1	35	7,3	7,1	91	6,0%	2,9000 [0,1322, 5,6678]	2008
Dincer 2008	14,42	14,24	8	5,32	5,65	103	1,5%	9,1000 [-0,8278, 19,0278]	2008
Aloush 2007	9,9	8,2	18	4,1	8,2	18	3,5%	5,8000 [0,4428, 11,1572]	2007
Zink 2000	6,1	8,1	2729	5,5	7,5	6047	7,9%	0,6000 [0,2421, 0,9579]	2000
Total (95% CI)			**3812**			**8396**	**100,0%**	**0,7722 [-0,5756, 2,1199]**	

Heterogeneity: Tau² = 5,95; Chi² = 317,17, df = 16 (P < 0.00001); I² = 95%
Test for overall effect: Z = 1,12 (P = 0,26)

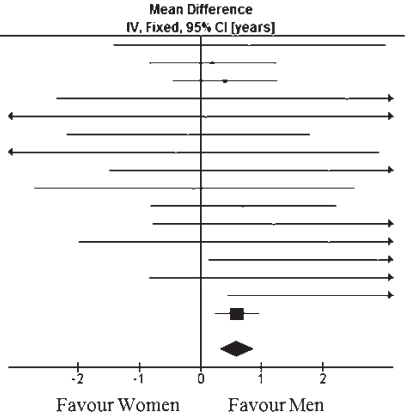


Mean diagnostic delay in women minus mean diagnostic delay in men (years)

B.

Study or Subgroup	Diagnostic Delay Women Mean [years]	SD [years]	Total	Diagnostic Delay Men Mean [years]	SD [years]	Total	Weight	Mean Difference IV, Fixed, 95% CI [years]	Year
Shahlaee 2015	8,8	8,51	67	8	7,22	253	1,7%	0,80 [-1,42, 3,02]	2015
Yacoub 2012	4,8	2,7	43	4,6	3,1	87	7,8%	0,20 [-0,84, 1,24]	2012
Bodur 2012	5,3	7	343	4,9	6,9	1038	11,5%	0,40 [-0,45, 1,25]	2012
Ma JSC 2011	10,8	4	4	8,4	8,5	39	0,4%	2,40 [-2,34, 7,14]	2011
Ma ANC 2011	4,1	6,3	17	4	5,2	63	0,8%	0,10 [-3,16, 3,36]	2011
Slodobin 2011	5,7	6	72	5,9	6,4	79	2,1%	-0,20 [-2,18, 1,78]	2011
Ma ASC 2011	6,2	6,4	19	6,6	6	51	0,8%	-0,40 [-3,72, 2,92]	2011
Hajialilo 2011	8	4,7	7	5,9	3,3	53	0,6%	2,10 [-1,49, 5,69]	2011
Ma JNC 2011	2,1	2,8	6	2,2	4	35	1,2%	-0,10 [-2,70, 2,50]	2011
Roussou 2011	6,3	7,2	293	5,6	7,9	150	3,7%	0,70 [-0,81, 2,21]	2011
Atangunduz 2010	7,4	7,9	96	6,2	7,1	139	2,1%	1,20 [-0,77, 3,17]	2010
Aggarwal 2009	8,6	6,6	11	6,5	4,7	59	0,5%	2,10 [-1,98, 6,18]	2009
Reed 2008	10,2	7,1	35	7,3	7,1	91	1,1%	2,90 [0,13, 5,67]	2008
Dincer 2008	14,42	14,24	8	5,32	5,65	103	0,1%	9,10 [-0,83, 19,03]	2008
Aloush 2007	9,9	8,2	18	4,1	8,2	18	0,3%	5,80 [0,44, 11,16]	2007
Zink 2000	6,1	8,1	2729	5,5	7,5	6047	65,3%	0,60 [0,24, 0,96]	2000
Total (95% CI)			**3768**			**8305**	**100,0%**	**0,60 [0,31, 0,89]**	

Heterogeneity: Chi² = 13,36, df = 15 (P = 0,57); I² = 0%
Test for overall effect: Z = 4,07 (P < 0.0001)



Mean diagnostic delay in women minus mean diagnostic delay in men (years)

Figure 2. Forest plot of the differences between the mean diagnosis delay of spondyloarthritis in women versus men according to published papers. Method performed through inverse-variance by means of random-effect or fixed-effect, according to heterogeneity. A. Including 14 papers and 17 samples before the sensitivity analysis. B. Including 13 papers and 16 samples after the sensitivity analysis.

unsolved disorders that challenge physicians' skills to evaluate patients and give a diagnosis such as SpA as the cause of pain.

This situation is more frequent in women than in men, which is unexpected because the most common clinical manifestations of SpA in both sexes were dorsal and/or lumbar pain followed by peripheral arthritis, with similar prevalence at onset, so diagnostic delay should not have differed.

The longer diagnostic delay in women may be related to a lack of familiarity with the disease in women[47,48], because the prototypic SpA, AS, is predominately a male disease and this has received wide attention. Although the disability rate is worse in women than in men at all ages[17], women are identified as less disabled and with better spinal mobility than men[42]. These differences and the slower progression of radiological changes in women may influence earlier diagnosis in men, because the spine is more severely affected in them[31]. Consequently, the disease is not suspected in women, and a wrong diagnosis or "non-specific symptoms and signs" is given in healthcare records[49].

According to the theory of knowledge, underdiagnosed SpA in women might be due to a biased viewpoint of the physician as observer. Some symptoms of SpA, such as low back pain, morning stiffness, and sleep disorders associated with pain are shared with fibromyalgia (FM)[18] and have traditionally been assigned low status in the cultural hierarchy of medicine. Often, these symptoms in women are not regarded as having the same meaning as similar symptoms in men and they are not usually considered in the differential diagnosis of SpA, in spite of sometimes coexisting with enthesitis and peripheral arthritis[8], sometimes misdiagnosed as FM[36,42]. Further, SpA in women may be confused and patients referred to gynecology, surgery, gastroenterology[36], or psychiatry[10].

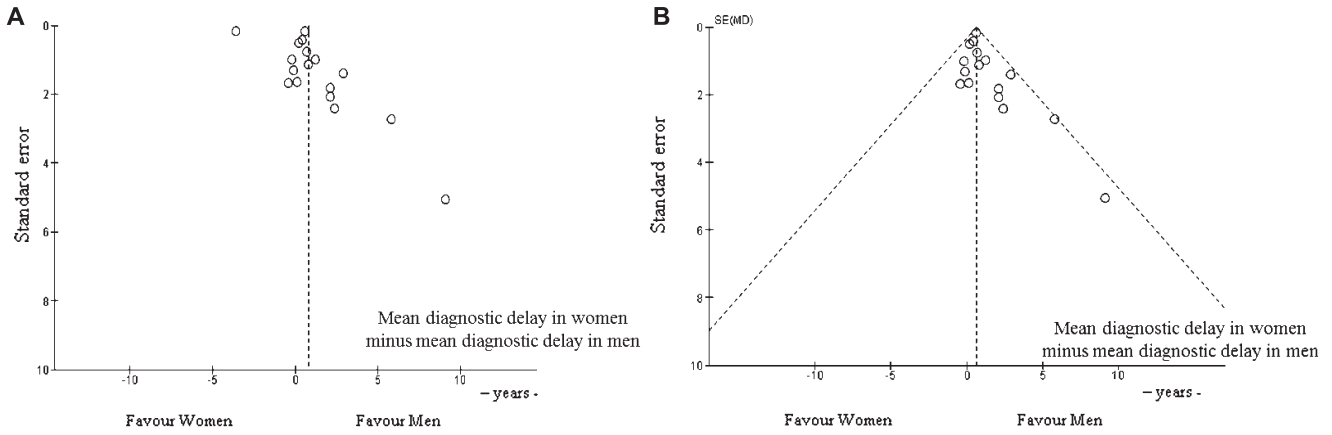


Figure 3. Assessing publication bias of the published papers on diagnosis delay of spondyloarthritis in women versus men (funnel plot). A. Before sensitivity analysis. B. After sensitivity analysis.

The quality of the research on SpA has increased since 2005, and the use of Assessment of SpondyloArthritis International Society criteria has improved the operative definition of this family of diseases, a development that will facilitate comparison between the sexes. However, in the papers reviewed, sex-related differences in delay of diagnosis of SpA may be true or artificial owing to methodological reasons, such as the publication bias observed. Moreover, because the most frequent source of information was the hospital, selection bias is also a possibility, which would affect sex-related differences in diagnostic delay because women patients with SpA would not be recognized at the primary healthcare level and would not be referred to rheumatology clinics, where the research was conducted. In addition, there is a lack of information about how study samples were calculated and how missing data were addressed; only 1 paper described attempts to address potential sources of bias[38]. The low score for quality obtained for the papers was largely related to the methods section. Most of the study designs were descriptive and cross-sectional without strong inferential power. Only 1 paper analyzed a case control study of patients with AS, finding a longer delay in diagnosis in women[48]. Another methodological challenge is related to the lack of sex-stratified results in most studies of diagnostic delay in SpA; influences of sex were rarely discussed. Studies without sex-stratified findings are easier to conduct; even so, some reflection is required on the part of both authors and editors on the reasons for producing and publishing such a large percentage of these studies.

The results of the studies analyzed present some limitations. They provide only a partial picture of worldwide attempts to identify the causes of sex-related differences regarding diagnostic delay in SpA. Few of the articles presented an empirical analysis of the information, and only one-third of them reported a sex analysis or comparison of diagnostic delay in SpA. In the case of studies focusing exclusively on men, which was an exclusion criterion of this review, this proportion would clearly be even lower. The above reflects the near-absence of scientific studies on this issue; it also restricts our ability as researchers to draw meaningful conclusions about the nature of research on the topic.

Another limitation is that, although SpA has more measures of disease than the ones we compared, such as blood tests, radiographic studies, and functional measures, we chose for this review those most frequently described in the papers such as clinical and demographic characteristics. Regarding juvenile arthritis, we offer data together with adult onset; although there are some papers that include juvenile onset, only 6 of them[6,22,30,39,40,44] offer diagnostic delay disaggregated between juvenile and adult onset of disease. About excluding patients with PsA, there is 1 study[37] in this review in which some patients in the sample may have this disease.

From a perspective of sex differences, this review was limited to a number of factors related to family history and HLA-B27, age at onset of symptoms, and at diagnosis, and years of diagnostic delay. No analysis was conducted of information reported by the authors about the influence of social conditions on the delay. This aspect is crucial to understanding whether diagnostic delay is related to the sex context of the female patient (i.e., personal/family history related to productive/reproductive roles on the basis of the delay in the demand for healthcare), or due to unfamiliarity with SpA in women by physicians from primary care or other levels of healthcare. The influence of social conditions was not normally included although it was discussed in a few papers[8,23,27,30,31,32,34]. It is a classic sex bias in which the research approach de-contextualizes women's health risks, blocking new knowledge about the chain of responsibility, in this case related to sex-related differences in diagnostic delay in SpA.

Serious and important consequences of sex bias have been described for women's health in relation to clinical management[50]. It is possible that medical knowledge has been built up over the decades in ways that yield a disease classification more suited to men's complaints and health problems, and signs or symptoms indicative of specific conditions. Patients classified as having nonspecific signs and symptoms may in fact have an identifiable disease, either at an early stage not identified by contemporary (male-based) diagnostic criteria or because they present an atypical (non-male) set of symptoms for the disease. No treatment, or incorrect treatment, at this point can lead to a worsening of the disease, particularly among women[50]. There is probably a lack of knowledge about sex-related aspects of SpA in the medical community, with consequent delays in diagnosis and suitable treatment. More information is required about probably unfounded sex differences in diagnostic delay, such as the number of previous erroneous diagnoses and treatments, and doctors visited, all of which are important factors to achieve the principle of equity in healthcare provision.

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