Systematic review and meta-analysis of diagnostic delay in axial spondyloarthritis

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Abstract

Background . Delay to diagnosis in axial spondyloarthritis (axSpA) is longer than many other rheumatic diseases. Prolonged delay has been shown to associate with poorer outcomes including functional impairment and quality of life. Our aims were to describe 1) global variation in delay to diagnosis, 2) factors associated with delay, and 3) differences in diagnostic delay between axSpA and psoriatic arthritis (PsA).

Methods . We searched Medline, PubMed, EMBASE and Web of Science using a predefined protocol in accordance with PRISMA guidelines. Delay to diagnosis was defined as years between age at symptom onset and age at diagnosis. We pooled mean diagnostic delay using random-effects inverse variance meta-analysis. We examined variations in pooled estimates using pre-specified subgroup analyses and sources of heterogeneity using meta-regression.

Results. A total of 54 studies reported mean diagnostic delay in axSpA patients. The pooled mean delay was 6.8 years (95% confidence interval 6.2 to 7.3) with high levels of heterogeneity. Delay to diagnosis did not improve over time when stratifying results by year of publication. Studies from high-income countries (defined by the World Bank) reported longer delay than those from middle-income countries. Factors consistently reported to be associated with longer delay were: lower education levels, younger age at symptom onset and absence of extra-articular manifestations. Pooled estimate for diagnostic delay from 8 PsA studies was significantly shorter, at 2.6 years (95%CI 1.6 to 3.6).

Conclusion. For axSpA patients, delay to diagnosis remains unacceptably prolonged in many parts of the world, although some countries have reported remarkable improvements. Patient factors (education) and disease presentation (age at onset and extra-articular manifestations) should inform awareness campaigns to improve delay. Targets for improvement should aim to resemble delays in other spondyloarthritis patients.

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease characterised by significant inflammatory pain, stiffness and functional impairment [1]. Symptoms typically begin in early adulthood, which is a critical time for education, career, social networks and development of personal

identity in general. Consequently, axSpA can significantly impact on mental health, quality of life and work productivity over the life course, at costs to the individual and the economy [2,3].

The disease impact is often compounded by a prolonged diagnostic delay, that is, time from onset of symptoms to getting a diagnosis. This is may partly be explained by the insidious symptom onset, but may also be due to lack of awareness of axSpA, the higher prevalence of other causes of back pain, a perception that musculoskeletal symptoms are self-limiting in young adults, or referral delays to rheumatology. Duration of delay is reported to range from 8 to 10 years – longer than many other rheumatic diseases - although estimates can vary considerably from study to study. Some studies have also found no improvement in diagnostic delay over recent decades [4], despite improved understanding of the disease and access to imaging.

There is abundant evidence that diagnostic delay is associated with worse functional impairment, greater radiographic progression, poorer quality of life and reduced response to treatment [5,6]. Those with longer delays to diagnosis also report greater work disability, unemployment and healthcare costs [5]. Although the impact of delay is well described, potential causes of delay (i.e., how delay can be improved) are not. Examining how delay durations vary across parts of the world and factors associated with delay will help inform targets for improvement.

The aim of this systematic review was to 1) describe global variation in diagnostic delay and 2) describe patient and disease factors that have been reportedly associated with delay to diagnosis. We also sought to 3) formally compare delay duration in axSpA with other SpA (e.g., psoriatic arthritis) to highlight the need and target for improvement.

Methods

We performed a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. The protocol for this review was pre-registered in advance (PROSPERO: CRD42020161887). We searched Medline, PubMed, EMBASE and Web of Science for relevant literature in September 2019 using the following search terms: (ankylosing OR spondyloarthritis OR psoriatic) AND ((delay AND diagnosis) OR (symptom AND (onset OR duration))). Studies were included if they reported mean delay to diagnosis (i.e., the mean difference between

age at symptom onset and diagnosis) or if they reported both mean age at onset *and* at diagnosis. We excluded studies using the same (or very similar) cohort to studies already included. We also excluded studies reporting medians only. Letters and published conference abstracts were considered, as some prevalence studies may not be published as full articles but may have sufficiently detailed methodology and results. Reviews, comments and editorials were excluded.

Two independent reviewers screened titles and abstracts, assessed full-texts for eligibility and extracted data from qualifying studies (BP, NH). Any discrepancy at each stage was resolved through discussion moderated by a third reviewer. Information from included studies was extracted into predefined tabulated summaries (Supplementary Table S1). Studies were assessed for risk of bias using adapted versions of the Newcastle Ottowa Scale (Supplementary Table S2).

Analysis

We pooled mean diagnostic delay using inverse variance weighted random-effects models (DerSimonian-Laird method). This was performed for studies of axSpA (including AS), then separately for psoriatic arthritis (PsA) and spondyloarthritis (SpA, which includes axSpA, PsA and other members of the SpA family). Where mean delay to diagnosis was not reported, it was imputed as the difference in mean age at symptom onset and mean age at diagnosis. Where the standard deviation of diagnostic delay was missing, we imputed it using methods recommended by Cochrane (in essence, based on standard deviations of age at onset, age at diagnosis and their correlation in all studies [7]) or the standard deviation of a study reporting the most similar mean delay duration. We performed sensitivity analyses without imputed values. Heterogeneity of meta-analysis estimates was presented using the I^2 statistic. Funnel plots were used to assess risk of publication bias.

We used random-effects meta-regression to examine whether heterogeneity in axSpA diagnostic delay could be explained by study characteristics, i.e., year of publication (pre-2010, 2010-2015, post 2015), geography (regions defined by the World Health Organisation [8]), economic status of the country (World Bank economic class [9]), sample sources (e.g., single centre, multicentre etc), age at symptom onset (tertile) and proportion of males (tertile). Meta-regression was not performed for PsA and SpA due the limited number of studies. Analyses were performed using R version 3.6.2 and the

“meta” and “metafor” packages.

Results

A total of 3286 publications were found from the literature search. After excluding duplicates, irrelevant and ineligible studies, 86 studies remained. 15 studies using the same cohorts (or subsets thereof) were excluded. The study by Rojas-Vargas et al was excluded as it only included patients with ≤2 years of symptoms. The selection flowchart is shown in Supplementary Figure S1. The 66 included studies are summarised in Supplementary Table S1. 55 studies reported delays among axSpA patients, 8 PsA and 5 SpA. Feld et al [10] and Sørensen et al [11] reported delay in both axSpA and PsA. Bias scores were mostly 2 to 4 out of 6 stars (Supplementary Table S2 and Figure S2) indicating moderate bias.

Diagnostic delay in axSpA

Sample size for axSpA studies ranged from 5 to 2,887 patients. 38 studies were of AS (including 25 using modified New York criteria) and 18 of axSpA (including 11 using the ASAS criteria). Delay ranged from 2.8 years in a small Albanian study (of 54 cases over 6 years), to 11.1 years in a single UK centre [12,13]. The mean delay to diagnosis was 6.8 years overall (95% confidence interval 6.2 to 7.3, I^2=99%).

Results of stratified meta-analysis are shown in Table 2. 38 axSpA studies were from countries in the European region, 7 West Pacific, 7 Eastern Mediterranean, 4 Americas and 3 South East Asia. Across these WHO regions, the mean delay and heterogeneity were not significantly different. When these studies were stratified according to World Bank economic class, the High-income group had longer mean delays than the upper- and lower-middle income countries. When mean delays were pooled according to country (with ≥3 studies), the average diagnostic delay was significantly shorter in Turkey than in the UK. Mean delay duration did not differ according to year of publication or disease definition. Studies with older mean age of symptom onset showed trends for shorter delay durations. When the above study characteristics were entered into a multivariable meta-regression model, only economic status was significantly associated with mean delay duration (Supplementary Table S2). Countries in the upper- and lower-middle income category had shorter mean delay by 2.8 and 4.1

years, respectively.

Sensitivity analyses (for mean delay and meta-regression) excluding studies with imputed mean and/or standard deviation of delay produced similar results (data not shown).

Table 1. Meta-analysis of delay duration stratified by study characteristics.

	n	mean delay	95% CI	I^2
World Health Organisation regions				
European	34	7.02	6.31, 7.73	98.2%
West Pacific	7	6.43	4.49, 8.37	96.8%
Eastern Mediterranean	7	6.62	5.37, 7.88	90.4%
Americas	4	5.76	2.63, 8.89	98.7%
South East Asia	3	6.38	-1.40, 14.15	96.7%
World Bank economic class				
High	34	7.61	7.03, 8.18	97.4%
Upper middle	16	5.38	4.46, 6.30	96.8%
Lower middle	5	5.59	3.21, 7.96	95.7%
Countries with ≥3 studies				
UK	8	8.69	7.14, 10.23	94.9%
Turkey	8	5.54	4.39, 6.68	90.4%
Italy	3	7.68	2.67, 12.69	99.6%
Iran	3	7.35	4.83, 9.87	79.5%
China	3	4.61	1.47, 7.75	85.6%
Recruiting methods				
Single centre	32	6.60	5.84, 7.36	98.5%
>1 centre	23	7.02	6.23, 7.83	98.8%
Year of publication				
<2010	8	7.08	5.87, 8.30	95.4%
2010-15	25	6.82	5.93, 7.70	97.3%
>2015	22	6.61	5.70, 7.53	99.3%
Disease definition				
Ankylosing spondylitis	38	6.54	5.90, 7.19	97.9%
Axial spondyloarthritis	17	7.26	6.22, 8.30	98.5%
Age at symptom onset (tertiles)				
22.7 - 24.2 years	10	7.37	6.11, 8.64	98.0%
24.4 - 27.1 years	11	7.70	6.59, 8.81	94.5%

27.3 - 35 years	11	6.33	4.50, 8.16	99.1%
Proportion of males (tertiles)				
39-68%	17	7.05	6.09, 8.01	98.7%
68-80%	17	7.52	6.55, 8.48	95.0%
80-100%	18	5.70	4.91, 6.48	94.8%

Factors associated with delay to diagnosis

Most results were from unadjusted comparisons (table 2). Delay was reportedly longer in males in studies by Bandinelli (10 v 6.3 years, p=0.002) and Sykes (9.4 v 8.3, p=0.097) [4,14], but longer in females in studies by Fallahi (8.7 v 7.7, p=0.68), Dincer (14 v 5.3, p=0.06), Hajialilo (8.0 v 5.9, p=0.14), Jones (8.5 v 5.6) and Redeker (by 1.9yrs, p<0.05) [15–19], albeit mostly not statistically significant. Similarly, 2 studies reported longer delay in those with peripheral arthritis [15,17], while 5 reported longer delays in those without [4,6,14,20,21]. There was also inconsistency in whether studies found HLA-B27 status to be associated with diagnostic delay: 4 studies reported significantly longer delays in HLA-B27 negative patients [15,16,19,22], while 5 other studies did not [14,20,21,23,24].

There was better consensus among the studies that longer delay was associated with: the absence of EAMs [4,17,23], lower education [15,16,20,25], and younger age of onset [19,20,24,25].

Table 2 Factors associated with longer delay to diagnosis in axial spondyloarthritis (results reported as mean duration in years).

Aggarwal 2009 [23]	Absence EAMs v presence (8.7 vs 5.9, p=0.03) Onset <16 v >16 yrs (9.1 v 6.1, p=0.03)
Bandinelli 2016 [14]	Male v females (10 vs 6.3, p=0.002) Manual v non-manual workers (11 vs 8.3, p=0.047) Axial presentations compared to arthritis or enthesitis (8.5 vs 4.3, p=0.002) Lower education (<high school v high school v universit v 8.6 v 7.3, p=0.076)
Dincer 2008 [16]	HLA-B27 negative v positive (9.2 vs 5.3, p=0.037) Family history v none (10 vs 4.6 p=0.003) Onset ≤16 v >16 yrs (8.9 v 5.5, p=0.027) Lower education (<9yrs v 9-11 v 12-13 v 14-15: 12 v 6. 5.0 v 4.6, p=0.018) Females v males (14 v 5.3, p=0.061)
Fallahi 2016 [15]	Enthesitis v no enthesitis (8.8 vs 6.0, p=0.007) HLA-B27 negative v positive (10 vs 7.1, p=0.013) Lower education (correlation r=0.24 p=0.002) Presence of peripheral arthritis v absence (8.9 v 6.8, p=0.086)

Feldtkeller 2003 [22]	HLA-B27 negative v positive (11 v 8.5, p<0.01)
Gerdan 2012 [25]	With v without prior diagnosis of lumbar disc herniation vs 6.2, p=0.002) First contact being rheumatology v non-rheumatology (2.9, p<0.001) Younger age at onset (b=-0.18, p=0.003) Lower education (b=-0.252, p=0.018)
Hajialilo 2014 [17]	Presence of peripheral arthritis v absence (11 vs 5.1 p<0.001) Absence of uveitis v presence (6.4 v 2.4 p=0.02) Presence of heal pain v absence (13 v 5.9 p=0.004) Females v males (8.0 v 5.9, p=0.14)
Jones 2014 [18]	Females v males (8.5 vs 5.6)
Masson Behar 2017 [20]	Univariable regression showed longer delay with Older age at diagnosis (b=0.15 p<0.001) Lower education (b=-1.7 p=0.03) Later calendar year of diagnosis (0.1 p=0.005) Multivariable regression showed longer delay with Older age at diagnosis (b=0.1, p<0.001) Entheseal pain v none (b=1.5 p=0.015) Absence of peripheral arthritis/dactylitis v presence (b= p=0.005)
Nakashima 2016 [21]	Absence articular involvement vs presence (8.9 v 5.2, p=0.03) Disease onset pre-2000 v post (7.5 v 3.5 p=0.02)
Reed 2008 [26]	Delay longer with later calendar year and younger age onset (p<0.05)
Seo 2015 [6]	Long-delay (v short delay <=8 years) category associat with: Absence of peripheral symptoms (OR 2.2, p=0.06) Prior diagnosis of mechanical back pain (OR 2.8, p=0.0 In univariate analysis, mechanical back pain remained significant in multivariable model
Sykes 2015 [4]	Absence of peripheral arthritis vs presence (9.4 v 7.6, p=0.045) Absence of IBD v presence (9.2 v 6.5, p=0.012) Presence of uveitis vs absence (10 v 8.4, p=0.033) Females v males (9.4 v 8.3, p=0.097)
Redeker 2018 (abstract) [19]	Multivariable regression showed longer delay in Female v males (b=1.9, 95%CI 1.1 2.7) Younger age of symptom onset, per 10yrs (-1.9, 95%CI -1.5) HLA-B27 negative v positive (-3.6, 95%CI -5.1, -2.1) Psoriasis v no psoriasis (1.4, 95%CI 0.1, 2.7)
Resende 2018 (abstract) [24]	Presence of EAMs v absence (8.7 v 5.0, p<0.001) Younger age onset (r=-0.28, p<0.001)
EAM, extra-articular manifestations (anterior uveitis, psoriasis, inflammatory bowel disease)	

PsA and SpA

Sample size for PsA studies ranged from 69 to 1970 patients. Diagnostic delay ranged from 1.0 years in the Dutch South-West Psoriatic Arthritis to 4.6 in a Swedish population-based cohort [27,28]. The

mean delay to PsA diagnosis was 2.6 years (95%CI 1.6 to 3.6, I^2=99%) (Figure 2). SpA studies ranged from 16 to 275 participants in size and 1.6 to 7.6 years in diagnostic delay. The mean delay to SpA diagnosis was 4.2 years (95%CI 2.1 to 8.1, I^2=96%) (Figure 2).

Discussion

The mean delay to diagnosis was 6.8 years across 54 axSpA studies worldwide. Interestingly, countries classed as high-income by the World Bank had significantly longer delays to diagnosis than medium-income countries. Factors associated with delay to diagnosis varied and were often contradictory across studies; the most consistently reported factors were lower education, absence of extra-articular manifestations and younger age of onset. Diagnostic delay in axSpA was significantly longer than in PsA (2.6 years) and when SpA were combined (4.2 years).

Mean duration of delay varied significantly within (e.g., from 5.7 to 11 years in the UK and 3.7 to 8.1 years in Turkey) and between countries. This may reflect multiple factors that could not be assessed in this review, such as local healthcare infrastructure and awareness of the disease. Our finding that delay was longer in high-income countries was unexpected. It may be that research centres in these countries received referrals for the most diagnostically challenging cases or served comparably deprived areas. Conversely, it may be that only centres with good referral infrastructure are publishing research in middle-income countries.

Our meta-analysis showed no meaningful change in diagnostic delay over time. This is consistent with results from the UK [4,29], France [20] and Germany [19]. In stark contrast, delay to diagnosis improved dramatically in Japan (pre- v post-2000: 7.5 v 3.6 years [21]), Italy (1990s v 2000s: 7.4 v 2.1 years [30]), Denmark (2000 v 2011: 5.5 v 0.3 years [11]), Egypt (pre- v post-2010: 11 v 4.6 years [31]) and Australia [26]. We could not examine the cause of this variation in detail, but diagnostic approaches likely varied from country to country. For example, the extent to which HLA-B27 and gender were associated with delay differed between countries, suggesting that these factors may have differential importance in their respective diagnostic process.

Inflammatory back pain in axSpA typically has an insidious onset, with subtle signs on clinical

examination. There is also a plethora of highly prevalent differential diagnoses that may be incorrectly used to explain symptoms; for example, lumbar disc disease can co-exist with axSpA and prolong delay to diagnosis [6,25]. Peripheral joint involvement is relatively more acute in presentation, with clearer signs such as swelling and erythema. This may explain the much shorter diagnostic delay in PsA than in axSpA. Among axSpA studies, the presence of peripheral joint involvement was associated with shorter delay to diagnosis in Italian [14], UK [4], French [20] and Japanese [21] studies, while these patients had longer delays in Iran [15,17]. It may be the case that these Iranian patients were given other diagnoses prior to the correct axSpA label.

To reduce delay to diagnosis, intuitive targets would be to improve awareness of axSpA as a cause of back pain; general education was inversely associated with delay. Younger age of onset was also consistently associated with prolonged delay. (Although this may be an artefact of “delay” being derived from, and being dependent on, age at onset.) Education is needed among non-rheumatologists that axSpA is a cause of back pain in young people. However, there will be cases that remain more diagnostically challenging, such as patients with few SpA features.

A key strength of this review is the large and globally representative number of studies. There were however limitations. Diagnostic delay is known to be right-skewed in distribution, meaning that the mean is inflated above the median by a high proportion of people with disproportionately long delays. In other words, the mean may be sensitivity to these outliers (e.g., atypical clinical features or individuals with poor access to healthcare) and remain unchanged, even if diagnostic delay generally improved for many patients. We chose mean firstly because it permits meta-analysis, but also because median would take emphasis away from those with unusually long delays - precisely the individuals needing improvement to diagnosis. Some meta-analysis estimates for delay had negative lower-bounds in the confidence interval, which is not possible by definition. This is an artefact of the random-effects methodology; in each case, there is one study with a much shorter delay than others in the category, resulting in wide intervals required to cover the pooled estimate for this subgroup. This artefact disappears in fixed-effects models, which were not used in this study due to high heterogeneity between the studies. We did not review the impact of delay to diagnosis as this was

recently reviewed by Yi et al [5].

Conclusion

The diagnostic delay across the world is 6.8 years on average in axSpA, which is significantly longer than 2.6 years for PsA. Although delay has improved over time in some parts of the world, many countries such as the UK need additional efforts to improve delay to diagnosis. Lower education levels, absence of EAMs and younger age of onset were associated with longer delays; therefore, improved education for physicians and patients with back pain may help reduce diagnostic delay.

Abbreviations

axSpA

axial spondyloarthritis

AS

ankylosing spondylitis

SpA

spondyloarthritis

PsA

psoriatic arthritis

EAM

extra-articular manifestation

Declarations

Ethics approval and consent to participate: not applicable

Consent for publication: not applicable

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Authors' contributions: SZ wrote the manuscript with significant contribution from all co-authors. BP, NLH, KN performed the literature search, data extraction and quality assessment. SZ and DMH performed all statistical analysis and conceived of the project. All authors read and approved the final manuscript.

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Figures

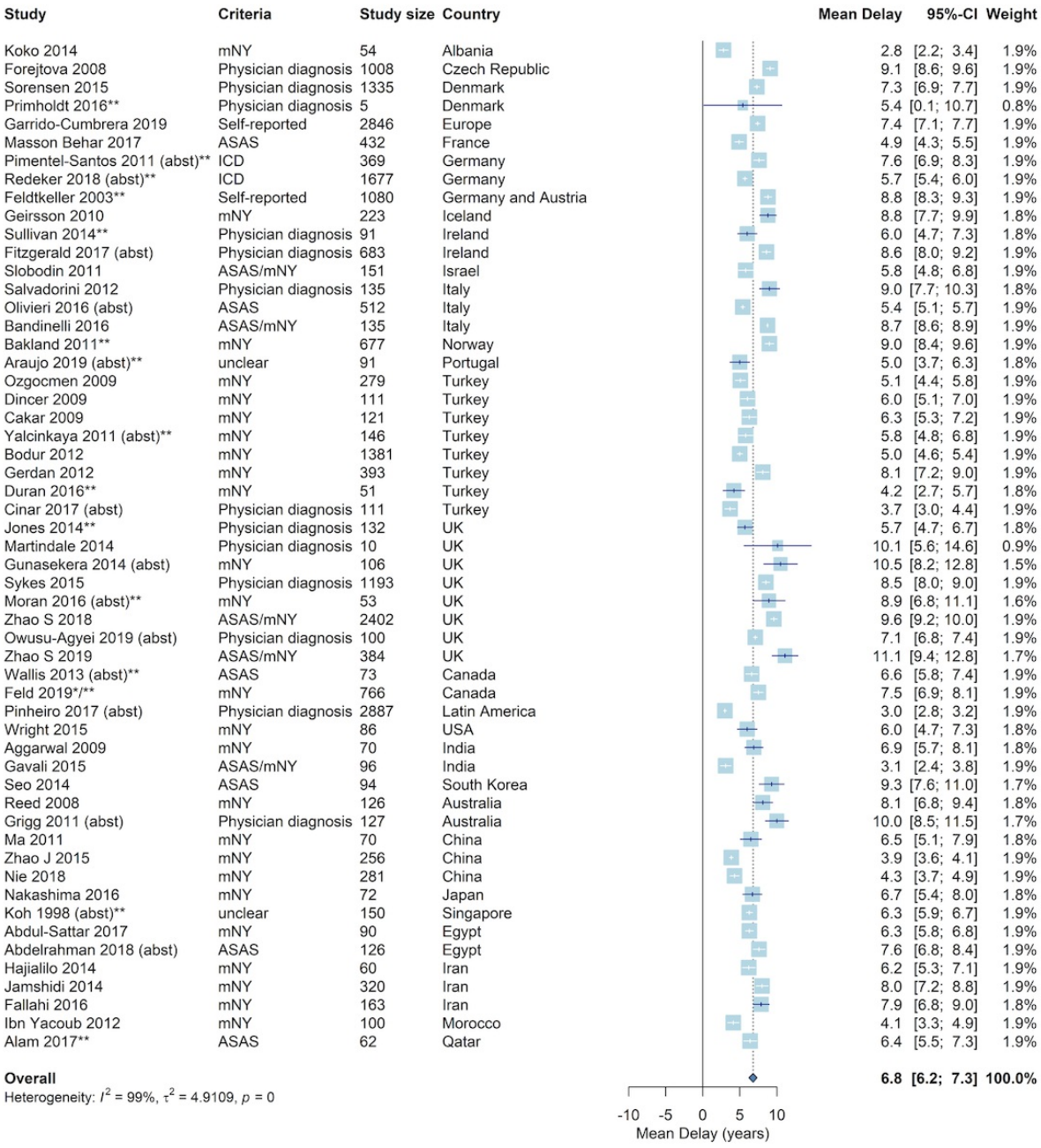

Figure 1

Pooled estimate of diagnostic delay in axial spondyloarthritis (including ankylosing spondylitis). Results ordered according to geography and year of publication.

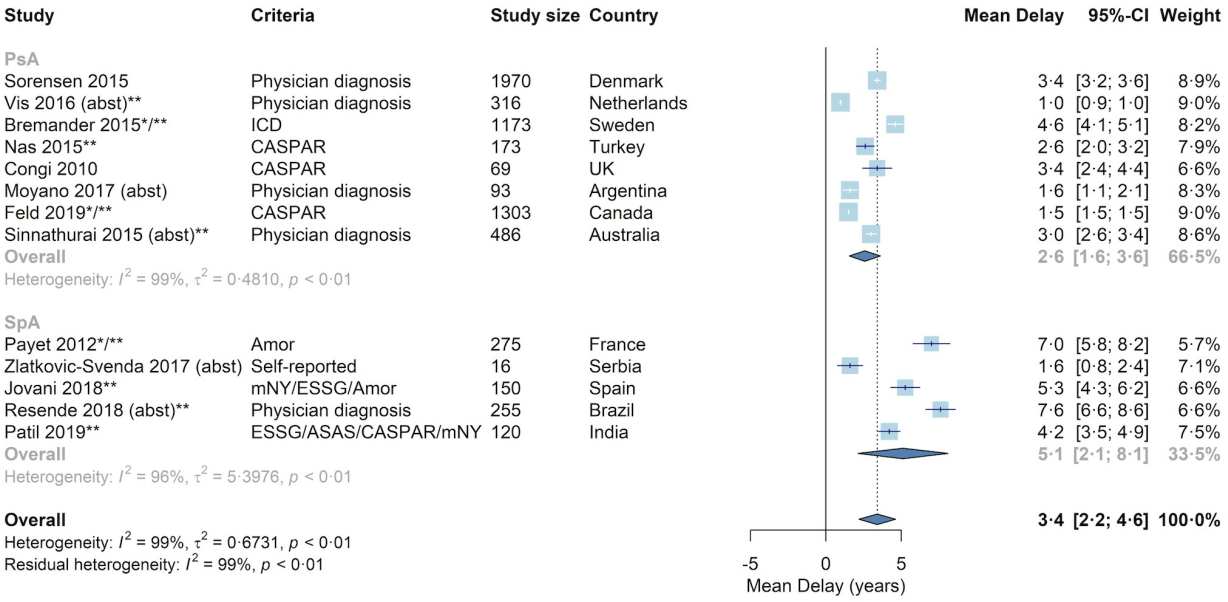

Figure 2

Pooled estimate of diagnostic delay in psoriatic arthritis and spondyloarthritis.

Supplementary Files

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