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Review

Erectile dysfunction in ankylosing spondylitis: a systematic review and meta-analysis

Yuyang Zhang, MB[1,2,3], Xu Wu, MB[1,2,3], Wei Zhang, MB[1,2,3], Guodong Liu, MB[1,2,3], Xingliang Feng, MM[4,5,*], Hui Jiang, MD, PhD[6,*], Xiansheng Zhang, MD, PhD[1,2,3,*]

[1]Department of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, 230031, China
[2]Institute of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, 230031, China
[3]Anhui Province Key Laboratory of Genitourinary Diseases, Anhui Medical University, Hefei, Anhui, 230031, China
[4]Department of Urology, The Third Affiliated Hospital of Soochow University, Changzhou, Jiangsu, 213000, China
[5]Department of Urology, The First People's Hospital of Changzhou, Changzhou, Jiangsu, 213000, China
[6]Department of Urology, Peking University First Hospital Institute of Urology, Peking University Andrology Center, Beijing, 100000, China

*Corresponding author: Department of Urology, The Third Affiliated Hospital of Soochow University, Changzhou, Jiangsu, China. Email: drf120@126.com; Department of Urology, Peking University First Hospital; Institute of Urology, Peking University Andrology Center, Beijing, China. Email: jianghui@bjmu.edu.cn; The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui Province, China. Email: zhangxiansheng@ahmu.edu.cn

Y.Z., X.W., and W.Z. contributed equally.

Abstract

Background: The prevalence of erectile dysfunction (ED) in ankylosing spondylitis (AS) patients was reported rarely and with small sample.
Aim: The study sought to explore the prevalence of ED in men with AS and to determine whether AS is a risk factor for ED.
Methods: A systematic search was conducted in the China National Knowledge Infrastructure, Wanfang, VIP Database, CBM, PubMed, Web of Science, and Cochrane Library. The search was restricted to the articles published up to October 2022. Assessment tools adapted for prevalence studies were used to evaluate the quality of cross-sectional studies, and the quality of case-control studies was assessed by Newcastle–Ottawa scale. The relative risk (RR) and the standard mean difference (SMD) were used to evaluate the association between AS and ED. The subgroup analyses were conducted to identify the resources of heterogeneity. The sensitivity analysis was performed to assess the stability of the pooled estimates. Data were analyzed and graphed using STATA 16.0.
Outcomes: The pooled prevalence of ED in AS patients was calculated and the RR and the SMD were used to evaluate the association between AS and ED.
Results: A total of 393 AS patients, enrolled in the 8 included studies, were assessed for the prevalence of ED. The pooled ED prevalence estimate was 44% (95% confidence interval [CI], 25% to 63%, $P < .001$) with the statistical heterogeneity ($I^2 = 95.1\%$, $P < .001$). After pooling the data for RR, the results showed that men with AS were at a significantly higher risk for ED when compared with the general population without AS (RR, 2.04; 95% CI, 1.28 to 3.25, $P = .003$; heterogeneity: $I^2 = 72.6\%$, $P = .003$). The pooled results of 5 studies, which provided the International Index of Erectile Function (IIEF) score, demonstrated that patients with AS had significantly lower values in the IIEF erectile function domain as compared with the healthy control subjects (SMD, −0.60; 95% CI, −0.80 to −0.41; $P < .001$; heterogeneity: $I^2 = 34.4\%$, $P = .192$). Additionally, the other domain of the IIEF also showed lower values when compared with the general population without AS ($P < .05$).
Clinical Implications: The present meta-analysis provides evidence of the management of ED in men with AS.
Strengths and Limitations: This is the first meta-analysis to provide the prevalence of ED in AS patients and to demonstrate that AS is a risk factor for ED. However, the results after pooling the included studies showed significant heterogeneity.
Conclusion: Our meta-analysis demonstrated the high prevalence of ED in men with AS and that AS is a potential risk factor for ED.

Keywords: erectile dysfunction; ankylosing spondylitis; prevalence; meta-analysis.

Introduction

Ankylosing spondylitis (AS), defined as an inflammatory rheumatic disease involving the spine and sacroiliac joint, mainly affects young male subjects, with the ratio of men to women approximately 2 to 3:1.[1,2] According to an epidemiological survey, the prevalence of AS is between 0.1% and 1.4%, with a difference among geographic area, and about 80% of patients first develop symptoms at an age younger than 30 years.[3] Importantly, the age when AS occurred and progressed coincided with the age when men were in their most sexually active period. The typical clinical symptoms of AS included sacroiliac joint pain and backaches, and the patients developed dorsal kyphosis with the progress of disease.[4] The inflammation and pain resulted in a spinal stiffness, a loss of spinal motility, sleep disturbance, and secondary anxiety and depression.[5] Inevitably, the sexual function of AS patients was impaired, as the previously mentioned physical and psychological adverse effects were the risk factors of sexual dysfunction.[6] However, the physical and anatomic impairments of AS surely claim most attention, while easily overlooking sexual function.[7,8]

Sexual function is an essential component of men's quality of life.[9] Erectile dysfunction (ED), defined as the persistent or recurrent inability to achieve and/or maintain an erection

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sufficient for sexual intercourse,[10] is one of the most prevalent sexual dysfunction diseases in adult men. It negatively affects self-esteem and a harmonious sexual relationship.[11,12] Ultimately, the primary or secondary ED of AS and AS creates a vicious cycle, which destroys the therapy and life confidence of patients. The researches of sexual function in patients with AS have greatly expanded in the last decade.[13–15] Pirildar et al[16] conducted a case-control study to compare erectile function between AS patients and healthy control subjects and demonstrated that all the domains of the International Index of Erectile Function (IIEF) were lower than those in healthy control subjects. Another case-control study was consistent, showing that AS patients complained of more severe erectile function than generally healthy subjects.[17] Also, the authors found that sexual function was correlated moderately with disease activity and psychological status. However, no validated instruments to assess erectile function were used, limiting credibility. Another study based on a population-based database elucidated the tight association between ED and AS, enrolling a larger sample size and homogeneous population.[18] Actually, a meta-analysis was conducted to explore the relationship between ED and AS.[19] However, the enrolled studies were heterogeneous and rife with conflicting results. Nonvalidated or standard instruments in the original studies should contribute to the heterogeneity, and the authors failed to exclude some replicated studies.[20] Furthermore, there was also no direct calculation for the prevalence of ED in patients with AS.

Therefore, there is an urgent need to enroll more well-designed studies with validated instruments, to investigate the association between ED and AS, and the pooled prevalence of ED, which could remind doctors to attach more importance to the sexuality of their AS patient and also to provide AS patients with a holistic evaluation and high-quality healthcare services. Consequently, the present systematic review and meta-analysis was performed to elaborate the association between ED and AS, and included the following 3 aspects: (1) assessing the prevalence of ED in AS patients, (2) assessing the relative risk (RR) of ED in AS patients; and (3) assessing the difference in male sexual function between AS patients and generally healthy subjects. To our knowledge, this is the first comprehensive meta-analysis to evaluate the association between ED and AS using different evidence.

Methods

The present meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) protocols.[21] The study protocol was registered in the PROSPERO (International Prospective Register of Systematic Reviews; CRD42022369246). There was no need for the related ethic statement, as no ethics issues were involved.

Data sources and search strategy

Two types of databases were included in the systematic search, including the China National Knowledge Infrastructure, Wanfang, and VIP Database mainly for Chinese-language articles and the CBM, PubMed, Web of Science, and Cochrane Library mainly for English-language articles. The search was restricted to the articles published up to December 2022 without any language restriction.

For the search strategy, the following free and vocabulary terms were used in various combinations using the Boolean functions AND/OR, as "ankylosing spondylitis," "erectile dysfunction," "sexual dysfunction," and "impotence." Also, we screened the reference lists of the eligible studies to identify additionally pertinent studies for the meta-analysis. If there was uncertainty regarding the articles from the abstract, the full text would be retrieved to assess the eligibility.

Inclusion and exclusion criteria

The present study not only evaluated the prevalence of ED in patients with documented diagnosis of AS, but also assessed the association between ED and AS through calculation the standard mean difference (SMD) and RR. Studies were identified for quantitative analysis when they met the following inclusion criteria: (1) all subjects were adult men older than 18 years of age; (2) the diagnosis of ED was based on IIEF or IIEF-5; (3) the studies were cross-sectional, reporting the prevalence of ED; a case-control study reporting the difference of IIEF and IIEF-5 between AS and healthy control subjects; or other study designs reporting sufficient data to calculate the relative outcomes of interest; and (4) the AS patients were recruited from the general population or the cohort of patients.

On the contrary, the studies were excluded from analysis when they met any of the following exclusion criteria: (1) the diagnosis of ED was based on other tools, or even a self-designed tool with a dichotomous yes-no response option; (2) the studies used the same data for analysis; (3) the studies were case series, case reports, or other secondary research studies (meta-analysis, letters to editor, etc.); (4) the studies were performed on animals; and 5) the study contained no data for analysis. The eligibility of included studies was evaluated independently by 2 authors YY Z and X W., and the consensus would be hold to resolve any disagreements or discrepancies between them.

Data extraction and quality assessment

After the final decisions of included studies, the related data were extracted from the original studies by 2 independent researchers YY Z and W Z. The extracted data included the first author's name, publication year, location, study designs, mean age of cases, mean disease duration, and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) evaluating the disease activity. For calculations, the extracted data included the total number of cases with AS and the number of ED patients. Additionally, the numbers of ED patients in the AS and healthy control groups were also obtained. For studies reporting the mean and SD of the IIEF or IIEF-5, the related values in the AS and healthy control groups were also extracted for calculation.

For the quality assessment of included studies, different tools were used based on the study design. When the study was cross-sectional, the adapted Assessment Tool for Prevalence Studies was used,[22] which included 10 different items for evaluating the selection process, the representativeness of the study population, the possibility of nonresponse bias, the data collection process, the acceptable case definitions, and the measurement of parameters. When the study was a case-control study, the Newcastle–Ottawa scale was used,[23] which included 9 domains for evaluating the selection process, comparability of cohorts, and outcomes ascertainment. For the former, the risk of bias was judged based on the overall

judgement of 10 items, as following overall low risk of bias (low risk for 7-10 items), overall moderate risk of bias (low risk for 4-6 items), and overall high risk of bias (low risk for 0-3 items). For the latter, the bias was defined based on the total scores of the Newcastle–Ottawa scale, as following low quality (total score 0-3), moderate quality (total score 4-6), and high quality (total score 7-9).

Outcomes assessment and statistical analysis

The outcomes assessment included the pooled prevalence of ED in AS patients, the pooled RR with 95% confidence interval (CI) evaluating the strength of the association between AS and the risk of ED, and the SMD with 95% CI evaluating the difference of the IIEF between AS and healthy control subjects. Different models were used based on the calculated heterogeneity. If statistical heterogeneity exists, the random-effects model was used for calculation, and the fixed-effect model was used when no statistical heterogeneity exists. The I^2 statistic and Cochrane Q statistic were calculated to assess the heterogeneity among included studies. There would be substantial heterogeneity among studies when I^2 was >50% and/or *P* was <.05. Subgroup analyses were further conducted to evaluate the effect played by related factors and also identify the resources of heterogeneity.

Sensitivity analysis was performed to assess the stability of the pooled estimates, by eliminating each study consecutively at a time. Begg's rank correlation test and Egger's regression asymmetry test were conducted simultaneously to evaluate the publication bias, and significant publication bias was identified when *P* was <.05. For all statistical analyses, significance was accepted when the 2-sided *P* was <.05. All analyses were performed using STATA software (version 16.0; StataCorp).

Results

Literature search

Figure 1 shows the flowchart for selecting eligible studies; we initially retrieved a total of 351 studies, of which 343 were from electronic searches and 8 studies were from the reference lists of eligible studies. All the titles and abstracts were screened to eliminate duplicate studies and unrelated studies, of which 184 were duplicates and 148 studies were irrelevant. Afterward, the full texts of the remaining studies were obtained to assess the eligibility for final meta-analysis, and 10 studies were excluded owing to various reasons such as being review articles,[2] containing wrong measurements,[4] being letters to editor,[1] and containing insufficient data.[3] Eventually, a total of 9 studies were included in the meta-analysis.[7,8,16,24–29] Among them, 8 studies provided data for calculating the prevalence with 95% CI; 6 studies provided data for calculating RR with 95% CI, and 5 studies provided data for calculating the SMD with 95% CI.

Study characteristics and quality assessment

The characteristics of included studies and relevant data for calculation are summarized in Tables 1, 2, and 3. For the study designs, only one study was a cross-sectional study, and with the remainder being case-control studies. The publication years of these studies ranged from 2004 to 2021. AS was diagnosed mainly based on the modified New York criteria, while ED was diagnosed mainly based on the IIEF-5 or IIEF. Of note, the IIEF is a short, reliable, multidimensional, self-applied index, which assesses 5 domains of sexual function as the following: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction.

The study quality was evaluated independently by 2 reviewers YY Z and W Z. For the cross-sectional study, the result was low risk for Q (Question)2, Q3, Q4, Q6, Q7, Q9, and Q10 and high risk for Q1, Q5, and Q8. It showed an overall low risk of bias (Table 4). As shown in Table 5, of the case-control studies, 6 were evaluated to be of high quality and the remaining 2 studies were evaluated to be of moderate quality. Generally, all included studies were evaluated to be high quality for meta-analysis, which guaranteed the authenticity of the pooled results.

Quantitative synthesis

Prevalence of ED in AS patients

The prevalence of ED was assessed in a total of 393 AS patients, enrolled in the 8 included studies. As shown in Figure 2, the pooled ED prevalence estimate was 44% (95% CI, 25% to 63%; $P < .001$) with statistical heterogeneity ($I^2 = 95.1\%$, $P < .001$).

Relative risk of ED between men with and without AS

After pooling the data for RR, the results showed that men with AS were at a significantly higher risk for ED when compared with the general population without AS (RR, 2.04; 95% CI, 1.28 to 3.25; $P = .003$; heterogeneity: $I^2 = 72.6\%$, $P = .003$). The results are shown in Figure 3.

SMD of IIEF between men with and without AS

In agreement with the previously mentioned findings, the pooled results of 5 studies, which provided the IIEF score, demonstrated that patients with AS had significantly lower values in the IIEF erectile function domain as compared with healthy control subjects (SMD, −0.60; 95% CI, −0.80 to −0.41; $P < .001$; heterogeneity: $I^2 = 34.4\%$, $P = .192$). Additionally, the other domains of the IIEF also showed lower values when compared with general population without AS. All the results (shown in Figure 4) suggested that men with AS more frequently experienced ED than men without AS.

Subgroup analyses on prevalence

To further reveal the source of heterogeneity of the pooled results, subgroup analyses were conducted on the pooled prevalence, based on location (undeveloped country vs developed country), sample size ($N < 50$ vs $N \geq 50$), publication year (before 2010 vs after 2010), patients' age (<40 years of age vs ≥40 years of age), disease duration (duration <10 years vs duration ≥10 years), and BASDAI score (<3 vs ≥3).

Subgroup analyses of pooled prevalence of ED are shown in Figure 5. Concerning the study location, sample size, and publication year, no statistical decreases of heterogeneity were found. With regard to the patients' age, the pooled prevalence estimates of ED were 53% (95% CI, 18% to 88%; $I^2 = 90.2$, $P = .001$) in men older than 40 years of age and 41% (95% CI, 19% to 63%; $I^2 = 95.9$, $P < .001$) in men younger than 40 years of age. When the disease duration was restricted to longer than 10 years, the prevalence estimate of ED was 42% (95% CI, 17% to 66%; $I^2 = 96.2$, $P < .001$). And the prevalence estimate of ED was 51% (95% CI, 30% to

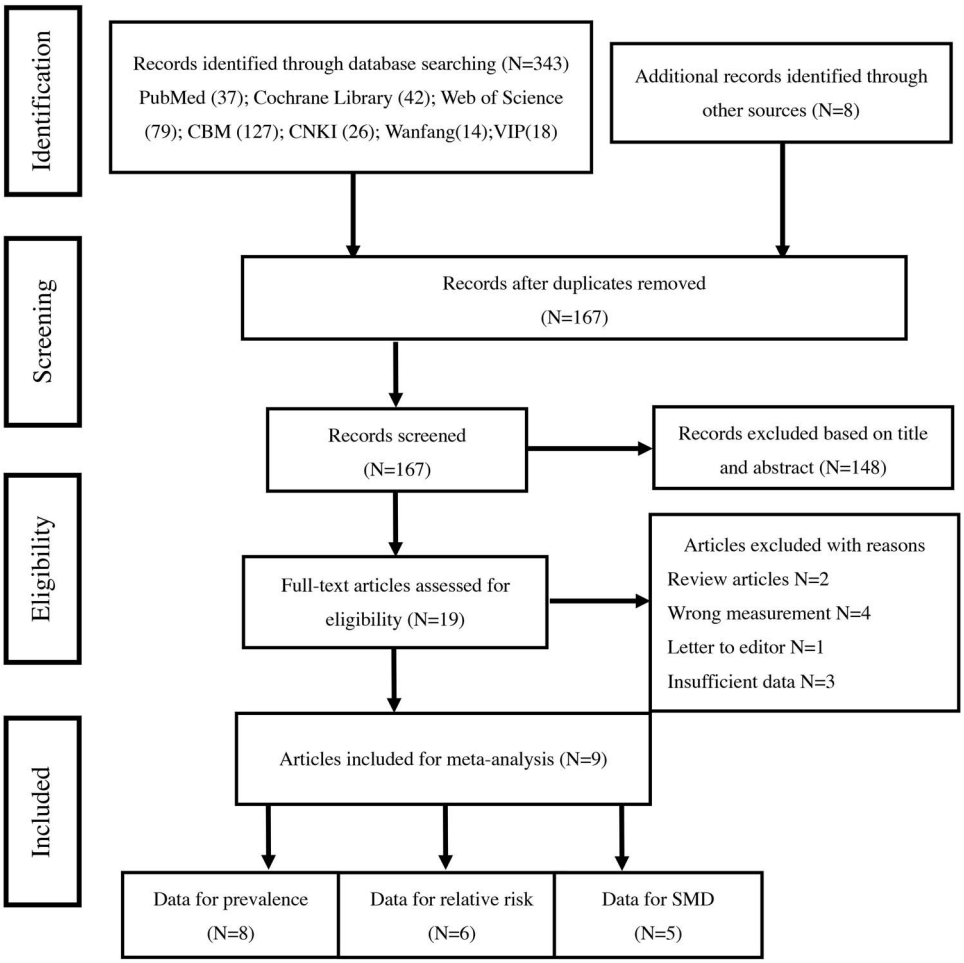

Figure 1. Flow diagram of the study selection process.

Table 1. Baseline characteristics of the eligible studies for the prevalence.

Study	Location	Study design	Age of cases (y)	Disease duration (y)	BASDAI	AS (T)	AS with ED (N)	Diagnosis of ED
Pirildar et al (2004)[16]	Turkey	Case-control	36 ± 8.1	12.2 ± 6.4	NA	65	8	IIEF
Oh et al (2009)[7]	Korea	Cross-sectional	37.8 ± 5.8	6.3 ± 4.1	7.2 ± 1.5	22	14	IIEF
Bal et al (2011)[24]	Turkey	Case-control	42.8 ± 10.8	10.04 ± 8.98	3.92 (0-10)	37	13	IIEF
Shi et al (2013)[26]	China	Case-control	33.0 ± 4.0	10.0 ± 3.0	4.6 ± 1.8	45	6	IIEF
Dhakad et al (2015)[8]	India	Case-control	34.4 ± 9.8	6.3 ± 0.8	0.96 ± 1.68	100	42	IIEF
Santana et al (2017)[27]	Brazil	Case-control	45.8 ± 11.4	18.0(8.2-20.0)	2.4 (1.4-4.0)	40	33	IIEF
Erdem et al (2020)[28]	Turkey	Case-control	37.7 ± 7.6	10.8 ± 9.3	2.9 ± 2.4	50	19	IIEF-5
Nisihara et al (2021)[29]	Brazil	Case-control	52.8 ± 7.1	10.0(6.0-12.0)	2.5 (0.8-3.6)	34	24	IIEF-5

Values are mean ± SD, mean (range), or n. Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ED, erectile dysfunction; IIEF, International Index of Erectile Function; T, total patients; N, number of ED patients.

Table 2. Additional characteristics of the eligible studies for the relative risk.

Study	Location	Age of cases (y)	Disease duration (y)	BASDAI	AS (T1)	AS with ED (N1)	HC (T2)	HC with ED (N2)	Diagnosis of ED
Bal et al (2011)[24]	Turkey	42.8 ± 10.8	10.04 ± 8.98	3.92(0-10)	37	13	67	18	IIEF
Shi et al (2013)[26]	China	33.0 ± 4.0	10.0 ± 3.0	4.6 ± 1.8	45	6	45	0	IIEF
Dhakad et al (2015)[8]	India	34.4 ± 9.8	6.3 ± 0.8	0.96 ± 1.68	100	42	100	18	IIEF
Santana et al (2017)[27]	Brazil	45.8 ± 11.4	18.0 (8.2-20.0)	2.4 (1.4-4.0)	40	33	40	5	IIEF
Erdem et al (2020)[28]	Turkey	37.7 ± 7.6	10.8 ± 9.3	2.9 ± 2.4	50	19	50	15	IIEF-5
Nisihara et al (2021)[29]	Brazil	52.8 ± 7.1	10.0 (6.0-12.0)	2.5 (0.8-3.6)	34	24	104	48	IIEF-5

Values are mean ± SD, mean (range), or n. Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ED, erectile dysfunction; HC, healthy control; IIEF, International Index of Erectile Function; T, total number; N, number of patients.

Table 3. Additional characteristics of the eligible studies for the standardized mean difference.

Study	Location	Age of cases (y)	Disease duration (y)	BASDAI	Patients (T)	IIEF-EF	IIEF-OF	IIEF-SD	IIEF-IS	IIEF-OS
Pirildar et al (2004)[16]	Turkey	36 ± 8.1	12.2 ± 6.4	NA	AS (65)	23.1 ± 7.5	7.3 ± 3.2	7.5 ± 4.1	7.9 ± 4.1	6.4 ± 2.9
					HC (65)	27.1 ± 6.3	9.4 ± 2.5	7.8 ± 1.9	11.1 ± 3.8	8.6 ± 1.8
Bal et al (2011)[24]	Turkey	42.8 ± 10.8	10.04 ± 8.98	3.92 (0-10)	AS (35)	23.8 ± 7.0	7.8 ± 2.8	6.7 ± 1.7	9.9 ± 3.6	8.2 ± 1.9
					HC (35)	25.1 ± 6.6	8.7 ± 2.1	7.7 ± 1.9	11.3 ± 3.3	8.4 ± 2.3
Sariyildiz et al (2013)[25]	Turkey	36.4 ± 7.4	9.9 ± 6.9	2.3 ± 1.9	AS (70)	23.8 ± 5.3	8.0 ± 1.7	7.5 ± 1.7	10.9 ± 2.5	7.9 ± 1.5
					HC (60)	27.0 ± 2.1	8.7 ± 1.0	8.4 ± 1.1	12.6 ± 1.0	8.4 ± 0.8
Shi et al (2013)[26]	China	33.0 ± 4.0	10.0 ± 3.0	4.6 ± 1.8	AS (45)	26.8 ± 3.3	6.4 ± 1.3	7.5 ± 1.1	10.7 ± 2.0	6.6 ± 1.1
					HC (45)	28.3 ± 1.2	7.9 ± 0.8	7.6 ± 0.7	13.1 ± 1.1	7.6 ± 0.8
Dhakad et al (2015)[8]	India	34.4 ± 9.8	6.3 ± 0.8	0.96 ± 1.68	AS (100)	20.48 ± 7.14	6.98 ± 2.55	6.76 ± 1.69	9.05 ± 3.52	7.27 ± 2.01
					HC (100)	24.87 ± 3.8	8.92 ± 1.36	6.6 ± 1.15	11.39 ± 2.23	7.94 ± 1.57

Values are mean ± SD, mean (range), or n. Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ED, erectile dysfunction; EF, erectile function; HC, healthy control; IIEF, International Index of Erectile Function; IS, intercourse satisfaction; NA, not applicable; OF, orgasmic function; OS, overall satisfaction; SD, sexual desire; T, total number.

Table 4. Quality assessment of studies included in the meta-analysis.

Study	Study design	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Overall
Oh et al (2009)[7]	Cross-sectional	H	H	H	L	L	H	L	H	L	H	High risk of bias

Q1. Was the study's target population a close representation of the national population in relation to relevant variables? Q2. Was the sampling frame a true or close representation of the target population? Q3. Was some form of random selection used to select the sample, OR was a census undertaken? Q4. Was the likelihood of nonresponse bias minimal? Q5. Were data collected directly from the subjects (as opposed to a proxy)? Q6. Was an acceptable case definition used in the study? Q7. Was the study instrument that measured the parameter of interest (prevalence of erectile dysfunction) shown to have reliability and validity? Q8. Was the same mode of data collection used for all subjects? Q9. Was the length of the shortest prevalence period for the parameter of interest appropriate? Q10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? OVERALL. Summary item on the overall risk of study bias: 7-10 items with "low risk" judgment = overall low risk of bias; 4-6 items with "low risk" judgment = overall moderate risk of bias; 0-3 items with "low risk" judgment = overall high risk of bias. Abbreviations: H, high risk; L, low risk; Q, Question.

Table 5. Quality assessment for all the included studies.

Study (year)	Selection				Comparability		Outcome			Score
	Case definition adequate	Representativeness of the cases	Selection of control subjects	Definition of control subjects	Main factor	Additional factor	Ascertainment of exposure	Same method of ascertainment for cases and control subjects	Nonresponse rate	
Pirildar et al (2004)[16]	*	*	*	*	*	*	—	*	—	7/9
Bal et al (2011)[24]	*	*	*	—	*	*	*	*	—	7/9
Sariyildiz et al (2013)[25]	*	*	*	*	*	—	*	*	—	7/9
Shi et al (2013)[26]	*	*	*	*	*	—	—	*	—	6/9
Dhakad et al (2015)[8]	*	*	—	*	*	*	*	*	—	7/9
Santana et al (2017)[27]	*	*	*	*	*	*	*	*	—	8/9
Erdem et al (2020)[28]	*	*	*	*	*	—	*	*	—	7/9
Nisihara et al (2021)[29]	*	—	*	*	*	—	*	*	—	6/9

*Indicates "fulfilled" or "yes."

72%; I^2 = 72.3%, P = .057) when the disease duration was shorter than 10 years. There were 3 and 4 studies reporting the BASDAI, and the prevalence estimates of ED in patients with BASDAI ≥3 and patients with BASDAI <3 were 36% (95% CI, 9% to 64%; I^2 = 90.5%, $P < .001$) and 58% (95% CI, 36% to 80%; I^2 = 92.1%, $P < .001$), respectively.

However, these results only partially accounted for the resource of heterogeneity. Consequently, further meta-regression analysis was performed based on the previously mentioned variables. No statistical significance was found ($P > .05$).

Sensitivity analysis and publication bias

Sensitivity analyses were performed to further assess the influence of a single study on the pooled prevalence estimates and RR by omitting 1 study in turn. As shown in Figure 6, there were no substantial changes in the pooled results after removing any of the included studies, which indicated that no single study dominated the pooled results and the heterogeneity in the included studies.

For publication bias, analyses were conducted not only on the prevalence estimates of ED in the enrolled 8 studies, but also on the RR of the enrolled 6 studies. The publication

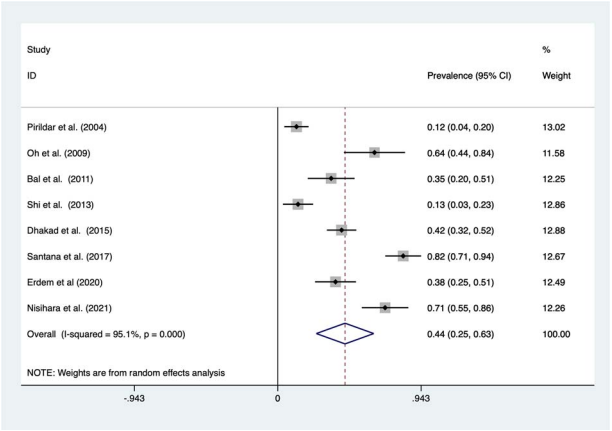

Figure 2. Forest plot indicating the pooled prevalence estimate for erectile dysfunction (ED) in men with ankylosing spondylitis (AS).

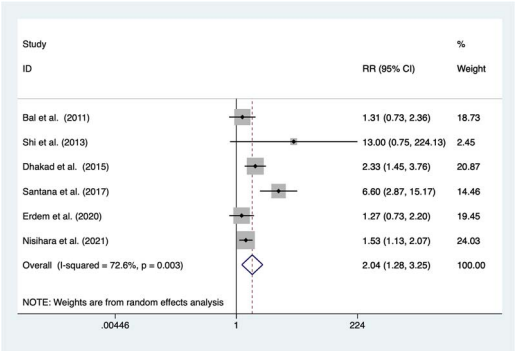

Figure 3. Forest plot depicting the association between erectile dysfunction (ED) and ankylosing spondylitis (AS).

bias was detected by Begg's rank correlation test or Egger's regression asymmetry test when appropriate. For the pooled prevalence, no significant publication bias among the 8 studies was found (Egger's, $P > |t| = 0.109$). For the pooled RR from 6 studies, there was also no significant publication bias (Egger's, $P > |t| = 0.083$).

Discussion

The relationship between AS and sexual dysfunction was investigated in several case studies, which showed a higher prevalence of sexual dysfunction in AS patients than in normal men.[30] However, the higher prevalence of ED in the AS population is difficult to demonstrate in some studies.[19,24] Therefore, we conducted this study to assess the relationship between AS and ED and to further determine whether AS is a risk factor for ED. In articles included in the present study, the prevalence of ED among adult male patients with AS ranged from 12% to 71%. Based on the available clinical data from these enrolled studies, our meta-analysis showed that the pooled prevalence of ED was 44% (95% CI, 25% to 63%) in adult men with AS. The high prevalence (44%) of ED may suggest a tight association between AS and ED. It is controversial whether there is a direct causal relationship between AS and ED, as erectile function is impaired in both the active and chronic phases of AS.[19] Moreover, another study demonstrated that the mean IIEF-EF domain score was significantly lower in the AS group than in the control group.[28]

We also calculated the RR of ED between men with and without AS, to further evaluate the relationship between AS and ED, and the results showed that men with AS were at a significantly higher risk for ED when compared with the general population without AS (RR, 2.04; 95% CI, 1.28-3.25; P = .003), indicating a 2.04-fold increased risk of ED in men with AS. Moreover, we analyzed the available data for inclusion in the studies to demonstrate that patients with AS had significantly lower values on the IIEF erectile function domain as compared with healthy control subjects ($P < .001$).

ED is a multifactorial disease, such as hypertension, diabetes, and cardiovascular disease, which are the most common organic causes, and may also occur secondary to psychological disorders triggered by chronic diseases.[31] The specific assessment of erectile function in male patients with AS is currently a relatively neglected topic.[30] However, according to previous studies, disease activity, duration, patient age, and mental status may be risk factors for ED in patients with AS.[8,32] Disease activity may be the main reason for impaired erectile function in patients with AS. A study demonstrated that AS inflammatory disease activity measured by BASDAI is strongly associated with ED.[27] The BASDAI assesses disease activity in AS by indicators of pain in the spine, peripheral joints, and enthesis; fatigue; and the degree and duration of morning stiffness.[33] Pirildar et al[16] conducted the first study on the frequency of ED in men with AS and reported that the only clinical feature associated with ED in AS patients was the duration of morning stiffness. Another study used a linear regression model to demonstrate a negative association between the BASDAI scores and erectile function.[25] In addition, several previous studies have shown that higher BASDAI scores are strongly associated with sexual dysfunction.[7,15] Inflammatory activity is associated with pain, morning stiffness, and fatigue and is well known to impair sexual function in rheumatic diseases.[34] An important cause of ED due to disease activity in AS may be inflammation, which is also a major factor in the development of AS and plays an essential role in the development of atherosclerosis.[15] Inflammatory mediators, especially C-reactive protein (CRP), are independent risk factors for cardiovascular disease, with mean CRP values reflecting average levels of inflammation.[35] In contrast, erythrocyte sedimentation rate and CRP have been considered as markers of AS activity.[33] On the other hand, the most common concerns of patients with AS are pain (especially back pain), stiffness, and physical limitations, and when in the active phase of the disease, the exacerbation of these manifestations may lead to reduced physical activity during sexual intercourse.[19]

The relationship between the disease duration of AS and ED is controversial. Gallinaro et al[34] reported that sexual dysfunction in AS patients may be associated with a longer duration of the disease. Consistent with this, Dhakad et al[8] found a mean duration of 76 months for patients with ED compared with 45 months for those without ED, further concluding that the duration of the initial years of the disease may be related to ED. In contrast, several articles found no association between AS disease duration and ED.[16,25] A recent study also demonstrated that there was no significant association between disease duration and ED in patients with AS.[28] In addition, ED in men with AS may also be related to higher age and mental disorders (anxiety, depression). Several studies demonstrated that higher age, anxiety, and depression in AS patients are risk factors for ED.[8,28] However,

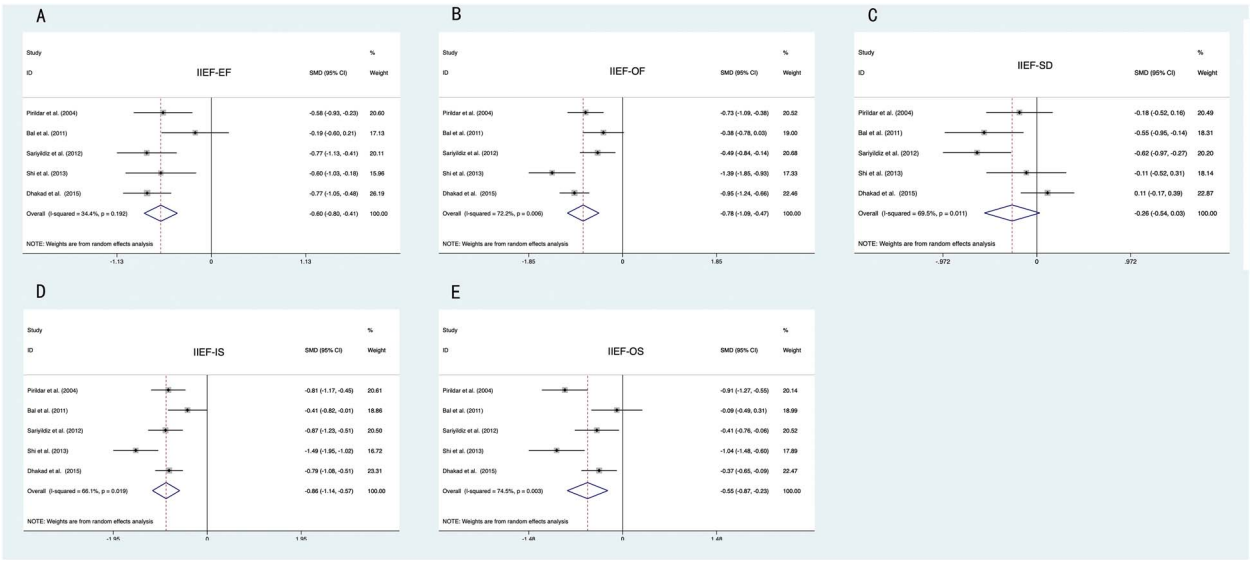

Figure 4. Forest plot of the difference in the International Index of Erectile Function score for men with or without ankylosing spondylitis (AS): (A) erectile function, (B): orgasmic function; (C) sexual desire; (D) intercourse satisfaction; (E) overall satisfaction.

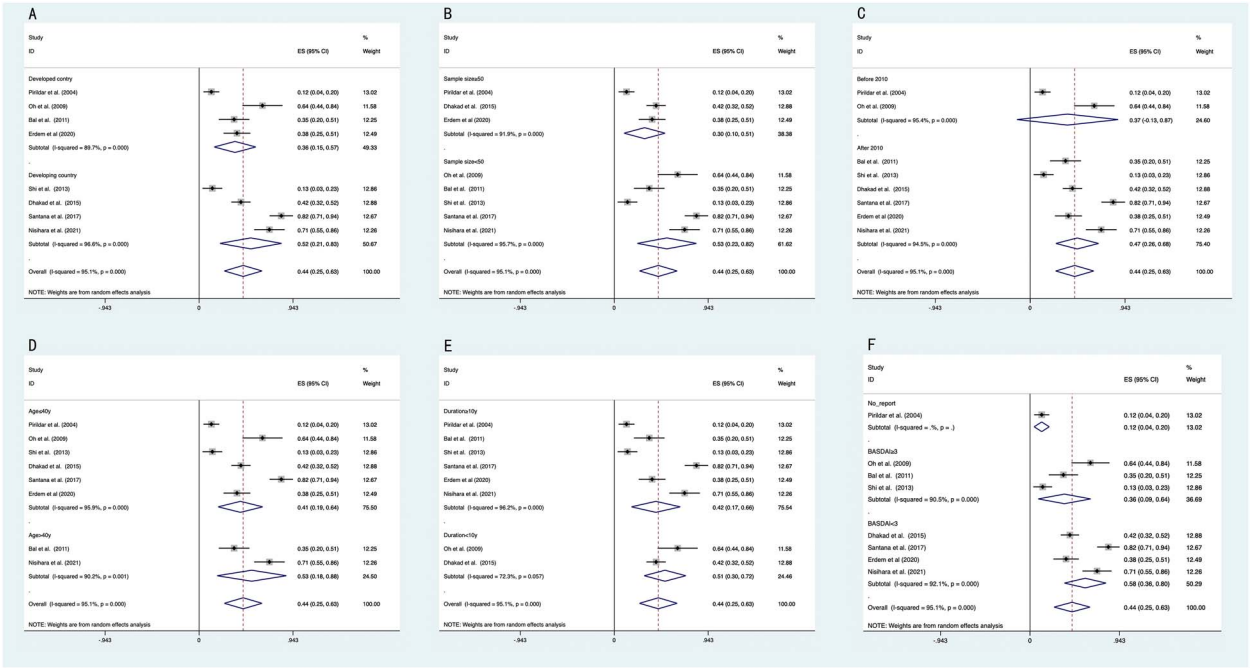

Figure 5. Subgroup analysis of the erectile dysfunction (ED) prevalence in men with ankylosing spondylitis (AS) for (A) location, (B) sample size, (C) publication year, (D) patients' age, (E) disease duration, and (F) Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

the opposite result of no association between age and ED in AS patients appears in other studies,[27,34] explaining that the association may be blurred by low erectile function in younger AS patients due to disease activity.

When AS patients experience acute disease activity, they experience severe psychological disorder as depression and anxiety, resulting from pain, morning stiffness, and physical restrictions. Additionally, restricted physical activity during sexual intercourse could decrease sexual behavior and satisfaction, which also affects psychological status by bringing on depression and anxiety. Erdem et al[28] elucidated that the AS patients with ED showed higher Beck Anxiety Inventory and Beck Depression Inventory scores when compared with AS patients without ED. Ozkorumak et al[17] and Sariyildiz et al[25] reported a significant correlation between IIEF and Hospital Anxiety and Depression Scale scores[36] in AS patients, respectively. A Chinese study suggested a link between depression-induced social dysfunction and sexual dysfunction.[14] Mental disorders are a risk factor for ED not only in patients with rheumatoid diseases, but also in all cases.[28] These psychological burdens could seriously affect erectile function of AS patients by several mechanisms including negative thinking, decreased sexual desire, and emotional problems. Owing to the limited data, our meta-analysis failed to compare the psychological effect on ED in AS patients, and more clinical study is needed to clarify.

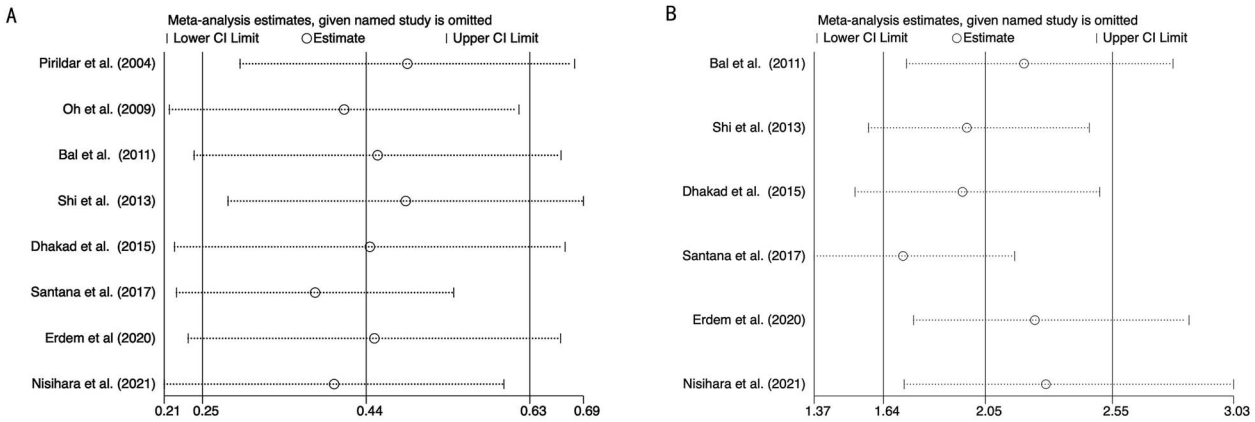

Figure 6. Sensitivity analysis of the enrolled studies for the prevalence of erectile dysfunction (ED) in patients with ankylosing spondylitis (AS).

There are several limitations in our study. First, after pooling the included studies, there was significant heterogeneity in the results of our meta-analysis. Even though we performed subgroup analysis and meta-regression analysis, it could only partially explain the heterogeneity. However, sensitivity analysis further verified the high stability of the results in our study. Second, the studies included in our meta-analysis were of observational design, which may reduce the reliability of this evidence. Finally, due to data limitations, the number of studies we have included is on the low side and will be explored further in the future when opportunities arise.

To our knowledge, this is the first meta-analysis to explore the prevalence of ED in men with AS and to demonstrate that AS is a risk factor for ED. More high-quality studies are needed in the future to elicit the underlying mechanisms of ED in AS patients.

Conclusion

Overall, our meta-analysis demonstrated the high prevalence of ED in men with AS and that AS is a potential risk factor for ED by including 8 studies. ED in patients with AS has rarely been explored and studied and is easily neglected. Therefore, our study provides evidence of the management of ED in men with AS. Future studies with large samples and well-designed studies are needed to continue to explore this issue.

Author contributions

Conceptualization: Y.Z., X.W., W.Z., G.L.; Data curation: Y.Z., X.W., W.Z.; Formal analysis: Y.Z., X.W., W.Z.; Funding acquisition: X.F., H.J., X.Z.; Investigation: Y.Z., X.W., W.Z., G.L.; Methodology: Y.Z., X.W.; Project administration: X.F., H.J., X.Z.; Resources: X.F., H.J., X.Z.; Software: X.W., W.Z., G.L.; Supervision: X.F., H.J., X.Z.; Validation: X.F., H.J., X.Z.; Visualization: X.F., H.J., X.Z.; Writing – original draft: Y.Z., X.W.; Writing – review & editing: Y.Z., X.W.

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