Male Sexual Dysfunction and Ankylosing Spondylitis: A Systematic Review and Metaanalysis

Dazhi Fan, Li Liu, Ning Ding, Si Liu, Yanting Hu, Guoqi Cai, Guo Xia, Lihong Xin, Li Wang, Shengqian Xu, Jianhua Xu, Yanfeng Zou, and Faming Pan

ABSTRACT. ***Objective.*** No consensus has been reached on sexual dysfunction in men with ankylosing spondylitis (AS). Our study aimed to derive a more precise estimation of the sexual function and its clinical correlations in men with AS.

Methods. A metaanalysis was performed and the related literature were searched in PubMed, Elsevier Science Direct, China National Knowledge Infrastructure, Chinese Biomedical Literature Database, and in reference lists of articles and systematic reviews. Score of the International Index of Erectile Function (IIEF) was used as the outcome measurement, and standardized mean differences (SMD) with 95% CI were calculated.

Results. Eleven studies were included, including 535 men with AS and 430 male controls. Each domain of the IIEF score (erectile function: SMD –0.52, 95% CI –0.68 – –0.37; orgasmic function: –0.72, –1.03 – –0.42; sexual drive: –0.40, –0.62 – –0.18; intercourse satisfaction: –0.86, –1.15 – –0.56; and overall satisfaction: –0.61, –0.91 – –0.32) were lower in men with AS than in controls. In the subgroup analysis, the results did not change except for the sexual drive in the Asians group (–0.15, –0.42–0.13). At metaregression, no study characteristics were significantly associated with effect size of the IIEF score.

Conclusion. Sexual function is impaired in male patients with AS and further studies are necessary to better understand risk factors for sexual dysfunction in this population. (J Rheumatol First Release Dec 1 2014; doi:10.3899/jrheum.140416)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS SEXUAL DYSFUNCTION MEN METAANALYSIS

Since the early 1980s, original studies[1,2,3,4,5,6,7,8,9,10,11,12,13] and reviews[14] have reported sexual dysfunction in men with ankylosing spondylitis (AS). However, the association between AS and male sexual dysfunction (MSD) had been controversial. Sexual dysfunction is currently established on the basis of the International Index of Erectile Function (IIEF)[15], which explores 5 domains: erectile function (EF), orgasmic function (OF), sexual drive (SD), intercourse satisfaction (IS), and overall satisfaction (OS). Demographic and clinical characteristics have also been described, such as disease duration, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), degree of morning stiffness[3,4,5,8,10,11,12,13], disease activity[3,4,5,8,9,10,11,13], and psychological depression[3,5,12,13].

One potential reason for those heterogeneous findings is that many studies were of small sample sizes, resulting in the need for large casuistics to confirm the idea of AS as a cause/risk factor for sexual dysfunction[7,8,9,10]. Other reasons might be confounding factors such as disease duration and disease activity. Metaanalysis is a systematic approach to identifying, appraising, and synthesizing the results of relevant studies to arrive at conclusions about a body of research, which could enhance the statistical power and draw a more reliable conclusion in comparison to a single study[16].

To have a full picture of sexual dysfunction in men affected by AS, we performed a systematic review and metaanalysis of studies available in the literature to answer the following questions: (1) is the presence of sexual dysfunction, assessed by the IIEF score [standardized mean difference (SMD)], greater in men with AS than in controls; (2) are there any clinical or demographic factors associated with sexual dysfunction; and (3) is there a sample size that allows predicting a significant difference between men with AS and healthy controls?

MATERIALS AND METHODS

Data sources and searches. We searched the related studies from PubMed, Elsevier Science Direct, China National Knowledge Infrastructure, and the

From the Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University; and the Department of Rheumatism and Immunity, the First Affiliated Hospital of Anhui Medical University, Hefei, China.

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D. Fan, MD; L. Liu, MD; N. Ding, MD; S. Liu, MD; Y. Hu, MD; G. Cai, MD; G. Xia, MD; L. Xin, MD; L. Wang, MD; Y. Zou, PhD; F. Pan, PhD, Department of Epidemiology and Biostatistics, School of Public Health; S. Xu, PhD; J. Xu, PhD, Department of Rheumatism and Immunity, the First Affiliated Hospital of Anhui Medical University.

Dr. Fan and Dr. Liu contributed equally to this work.

Address correspondence to Professor F. Pan, Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei, Anhui, 230032, China. E-mail: famingpan@ahmu.edu.cn

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Chinese Biomedical Literature Database (until March 31, 2014) using the terms "ankylosing spondyloarthritis" or "ankylosing" or "spondylitis", and "sexual function" or "sexual dysfunction". A manual search was also performed on reference lists from included articles, reviews, editorials, and proceedings of international congresses.

Inclusion and exclusion criteria. Studies considered in this metaanalysis were required to meet the following criteria: (1) the study was focused on the relationship between the MSD and AS, (2) controls were derived from a population within the same geographic area and ethnic background as study patients with AS, and (3) the publication was in English or Chinese. Studies were rejected if they did not meet the inclusion criteria or if they reported duplicated or useless data.

Study selection and data extraction. When results of 1 study were reported in several publications, only the most recent and complete data were considered. The eligibility of trials was assessed by 2 authors independently (DF and LL; Figure 1). Finally, 11 studies with full text met the inclusion criteria[3,4,5,6,7,8,9,10,11,12,13] (Table 1). Data concerning studies, patient characteristics, and outcomes were extracted by 2 authors (DF and LL). Discrepancies were resolved by agreement, and a third author was consulted if necessary.

Data synthesis and statistical analysis. Difference of the IIEF score in patients with AS and controls were used as study outcomes. Effect size was measured by SMD with 95% CI estimated by a random effects model according to DerSimonian and Laird[17]. Because all of the 5 domains of the IIEF showed different aspects of sexual function, each domain was analyzed in this metaanalysis separately. To assess the influence of heterogeneity on metaanalyses' conclusions, subgroup analysis was conducted on the basis of ethnicity (white vs Asian).

Heterogeneity was assessed through Q and I^2 statistics for each comparison, and potential sources of heterogeneity were discussed where appropriate[18]. A p value < 0.10 was considered statistically significant, and I^2 values of 25%, 50%, and 75% were defined as low, moderate, and high estimates, respectively.

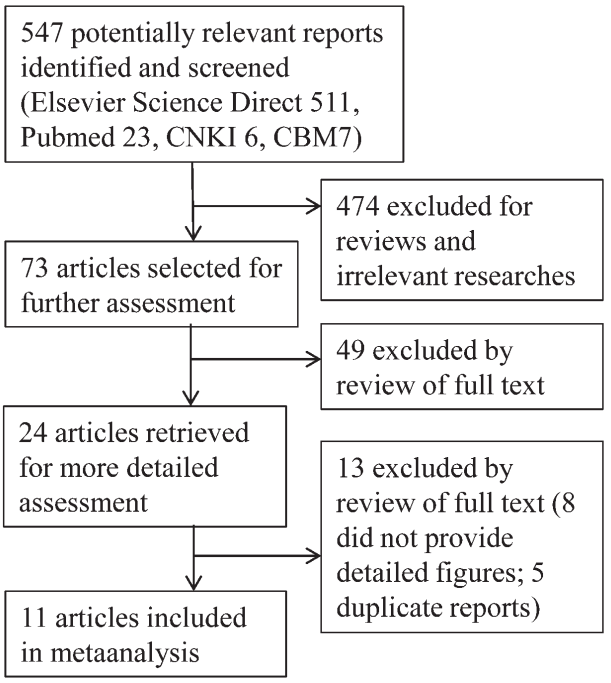

Figure 1. Flow diagram of the study selection process. CNKI: China National Knowledge Infrastructure; CBM: Chinese Biomedical Literature Database.

In forest plots, the vertical line represents no difference in the groups (0 for SMD); squares and horizontal lines represent the point estimates and 95% CI for each comparison; diamonds represent pooled effect size; center represents point estimate and width represents 95% CI. Visual inspection of asymmetry in funnel plots was conducted. Begg rank correlation method and Egger-weighted regression method were also used to statistically assess the publication bias ($p \leq 0.10$ indicated the presence of statistically significant publication bias). Finally, a metaregression analysis was performed based on studies included in the metaanalysis with the following factors as independent variables: age, duration of disease, and size of study. The dependent variable was log-transformed SMD. All statistical analyses were performed using STATA 11.0 (Stata-Corp) and Review Manager Version 5.0 (provided by The Cochrane Collaboration, available from www.cc-ims.net/revman).

RESULTS

Studies included in the metaanalysis. A total of 11 published studies, including 535 men with AS and 430 male controls, were included in our study. Of the 11 published studies, 7 were conducted in Turkey, 2 in China, 1 in Korea, and 1 in Tunisia. Among these studies, 6 used the IIEF, 1 used the Brief Male Sexual Function Inventory, 1 used the Glombok-Rust Sexual Satisfaction Scale, 1 used the self-estimated intravaginal ejaculatory latency times, and 2 used self-administrated questionnaires to measure patients' sexual function. In addition, some studies only reported the frequency of men with sexual dysfunction (FSD), and the others reported mean value of the IIEF score and FSD. The median of mean ages was 36.26 years [interquartile range (IQR) 33.00–38.50], and the median percentage of sexual dysfunction was 33.6% (IQR 15.6–46.1%). The sample size of patients with AS in included studies ranged from 22 to 70. The demographic and clinical characteristics of the patients in each study are summarized in Table 1.

Main results, subgroup, and sensitivity analysis. As shown in Table 2, 6 studies (340 patients with AS, 337 healthy controls) were included in the metaanalysis for EF and AS. Statistical significance was observed (SMD –0.52, 95% CI –0.68 – –0.37) in fixed model ($p = 0.39$, $I^2 = 4\%$; Figure 2). Five, 6, 5, and 6 studies were included in our metaanalysis for OF, SD, IS, and OS, respectively. They were all significantly lower, with an overall SMD of –0.72 for OF (95% CI –1.03 – –0.42), –0.40 for SD (95% CI –0.62 – –0.18), –0.86 for IS (95% CI –1.15 – –0.56), and –0.61 for OS (95% CI –0.91 – –0.32; Figure 3). Because of the significant heterogeneity between studies, they were all determined using the random effect method.

In the subgroup analysis based on ethnicity, subjects were divided into whites and Asians. The results did not change except for SD in the Asian group, where results became insignificant (SMD –0.15, 95% CI –0.42–0.13) in fixed model ($p = 0.80$, $I^2 = 0\%$; Table 2).

Sensitivity analysis was performed in each domain of the IIEF to assess the stability of the metaanalysis. When any single study was deleted, the corresponding pooled SMD were changed slightly (data not shown), with the statistically

Table 1. Studies considered in this metaanalysis (case group).

First Author	Country	Case, n	Age, mean, yrs	Duration, mean, yrs	FSD, n	ED, n	PE, n	ESR, mm/h	CRP, mg/dl	MS, min	VAS, cm	BASFI	BASDAI	BASMI	NSAID	DMARD	TNF
Pirildar, *et al* (2004)[3]	Turkey	65	36.00	12.20	8	8	—	54.0	21.0	220.0	—	52.90	—	—	—	—	—
Xu, *et al* (2007)[4]	China	55	33.00	10.20	9	9	—	63.0	41.0	210.0	—	52.90	—	—	21	49	—
Dincer, *et al* (2007)[5]	Turkey	68	32.90	—	14	—	—	24.1	21.5	54.1	—	4.30	4.90	2.60	51	37	2
Cakar, *et al* (2007)[6]	Turkey	53	32.85	9.09	27	27	—		—	—	—	—	—	—	36	32	—
Oh, *et al* (2009)[7]	Korea	22	37.80	6.30	14	—	14	—	—	—	—	—	7.20	—	—	—	—
Bal, *et al* (2011)[8]	Turkey	37	42.80	10.04	13	13	—	31.5	13.1	4.7	5.30	3.80	3.92	3.90	27	26	—
Ozkorumak, *et al* (2011)[9]	Turkey	43	36.26	7.51	18	2	16	—	—	—	3.30	2.74	2.90	2.67	8	35	—
Younes, *et al* (2010)[10]	Tunisia	27	38.90	11.90	12	12	—	38.6	12.9	—	5.02	4.83	4.61	4.04	—	25	2
Tarhan, *et al* (2012)[11]	Turkey	50	38.50	10.10	16	—	16	50.0	20.0	210.0	—	52.80	—	—	20	40	—
Shi, *et al* (2013)[12]	China	45	33.00	10.00	6	6	—	32.0	17.8	198.0	—	—	4.60	—	—	—	—
Sariyildiz, *et al* (2013)[13]	Turkey	70	36.40	9.90	—	—	—	18.7	4.5	28.2	4.10	3.10	2.30	2.70	58	30	—

FSD: sexual dysfunction including premature ejaculation and erectile dysfunction; ED: erectile dysfunction; PE: premature ejaculation; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MS: morning stiffness; VAS: visual analog scale; BASFI: the Bath Ankylosing Spondylitis Functional Index; BASDAI: the Bath Ankylosing Spondylitis Disease Activity Index; BASMI: the Bath Ankylosing Spondylitis Metrology Index; NSAID: nonsteroidal antiinflammatory drug; DMARD: disease-modifying antirheumatic drugs; TNF: anti-tumor necrosis factor.

Table 2. Metaanalysis of the association between sexual dysfunction and ankylosing spondylitis.

Variables	Eligible Studies	Frequency Case, n	Frequency Control, n	SMD (95% CI)	p	Heterogeneity Test p	Heterogeneity Test I^2, %	Effect Model
EF	6	340	337	–0.52 (–0.68 – –0.37)	< 0.001	0.39	4	Fixed
White	4	240	237	–0.50 (–0.68 – –0.31)	< 0.001	0.18	39	Fixed
Asians	2	100	100	–0.58 (–0.87 – –0.30)	< 0.001	0.93	0	Fixed
OF	5	272	292	–0.72 (–1.03 – –0.42)	< 0.001	0.02	67	Random
White	3	172	192	–0.54 (–0.76 – –0.33)	< 0.001	0.41	0	Fixed
Asians	2	100	100	–1.04 (–1.68 – –0.40)	0.001	0.03	78	Random
SD	6	340	337	–0.40 (–0.62 – –0.18)	< 0.001	0.08	50	Random
White	4	240	237	–0.51 (–0.69 – –0.32)	< 0.001	0.14	45	Fixed
Asians	2	100	100	–0.15 (–0.42–0.13)	0.30	0.80	0	Fixed
IS	5	272	292	–0.86 (–1.15 – –0.56)	< 0.001	0.02	65	Random
White	3	172	192	–0.71 (–0.93 – –0.50)	< 0.001	0.21	35	Fixed
Asians	2	100	100	–1.13 (–0.78 – –0.47)	< 0.001	0.03	79	Random
OS	6	340	337	–0.61 (–0.91 – –0.32)	< 0.001	0.004	71	Random
White	4	240	237	–0.45 (–0.78 – –0.12)	0.007	0.02	68	Random
Asians	2	100	100	–0.96 (–1.25 – –0.67)	< 0.001	0.68	0	Fixed

SMD: standardized mean difference; EF: erectile function; OF: orgasmic function; SD: sexual drive; IS: intercourse satisfaction; OS: overall satisfaction.

similar results indicating a good stability of the metaanalysis.

At metaregression, effect size of the IIEF was analyzed as a function of age, disease duration, ESR, CRP, morning stiffness, and disease activity; however, none of these were significantly associated.

Publication bias. Publication bias of the literature was tested by Begg funnel plot and Egger test. A potential publication bias of the metaanalysis on the sexual function was detected by the funnel plot on EF. The graphical funnel plots of the 6 studies appeared to be symmetrical (Figure 4), and we found no evidence of publication bias in the Egger regression test (t = –1.42, p = 0.23, 95% CI –5.38–1.73).

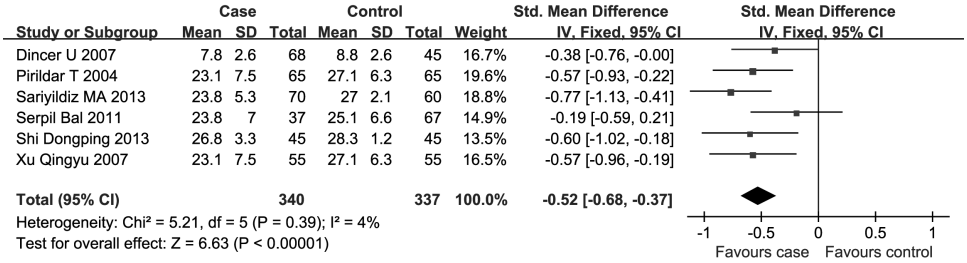

Figure 2. Results of metaanalysis for erectile function domain and its forest plot.

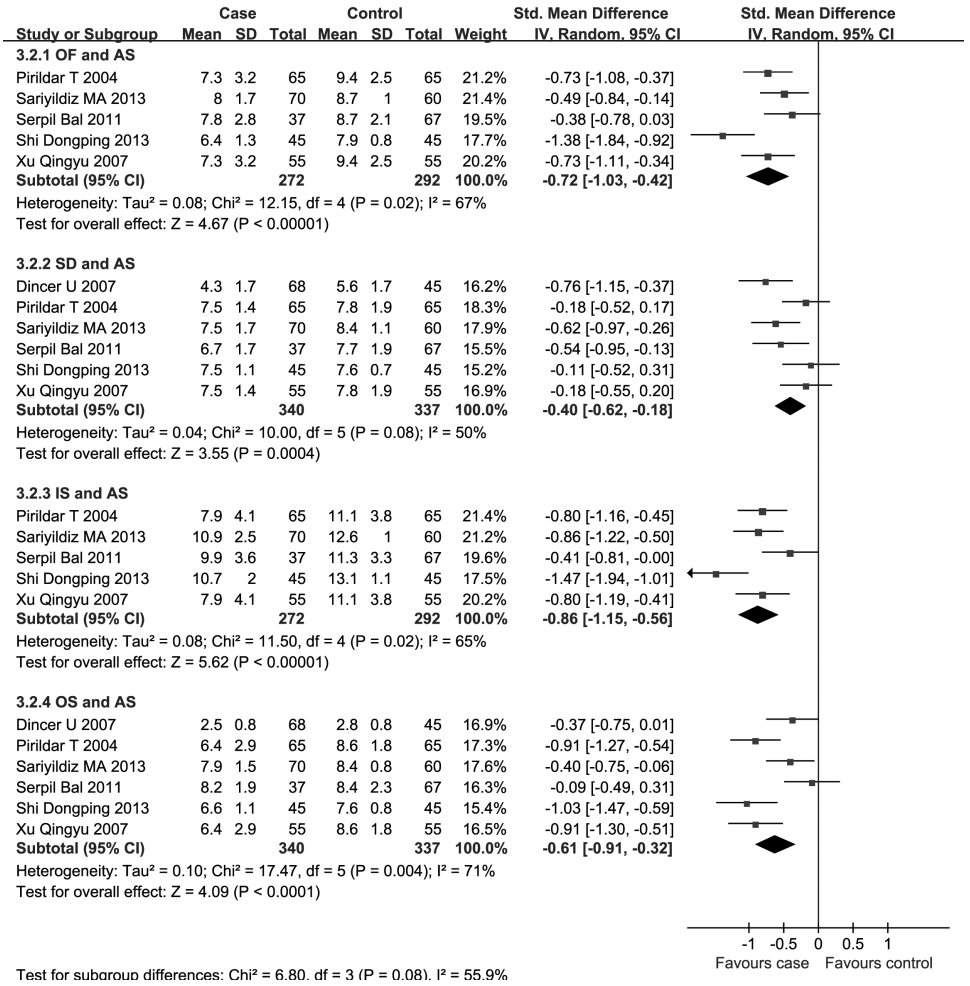

Figure 3. Results of metaanalysis for orgasmic function, sexual drive, intercourse satisfaction, and overall satisfaction domains and their forest plots.

DISCUSSION

AS is a chronic inflammatory joint disease that mainly affects the sacroiliac joints and spinal joints, causing pain and stiffness, and progressive fusion of involved joints[19]. Its common onset age is 20 or 30 years, and it affects men more often than women in a ratio of 2:1[20]. Chronic joint diseases affect millions of people worldwide and have a high burden on society[21,22]. Because of the axial and peripheral joint involvement and the noticeable inflammation, AS in men may have a severe effect on health status, functionality, and quality of life[6,23,24].

Sexuality is an integral part of the personality of human beings. Previous studies have examined sexual problems in patients with AS; the results, however, are controversial

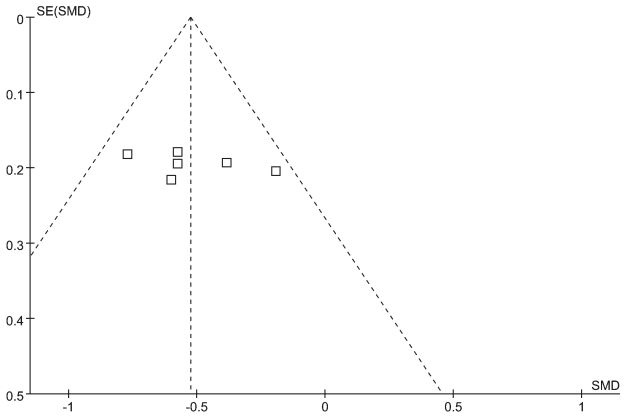

Figure 4. Funnel plot on erectile function to evaluate the publication bias of the literature. SMD: standardized mean difference.

because of relatively small sample sizes. In our study, we demonstrated that patients with AS have significantly lower EF, OF, SD, IS, and OS scores on the IIEF than do healthy controls. All findings, with the exception of EF, were of heterogeneity, which was assessed through metaregression analysis. Surprisingly, the heterogeneity was explained by none of the independent variables (i.e., age, disease duration, ESR, CRP, morning stiffness, and disease activity), suggesting that some other factors may need to be considered in future research.

Sexual function is a prominent component of an individual's quality of life[25]. All domains of sexual activity may be affected by rheumatic diseases[6]. It has been reported that patients with AS have significantly lower EF, OF, IS, and OS scores in the IIEF compared to healthy individuals, although no difference was shown in the SD score[3]. In another study[13], EF, OF, and the IIEF total scores were negatively correlated with CRP levels. Bostan, *et al*[26] suggested that the clinical measures of disease activity and functional disability correlated more with CRP than with other laboratory variables. Another study[27] pointed out that increases in the CRP levels in patients with AS with axial involvement correlated with the clinical severity of the disease. Patients with higher CRP levels may have more pain and limitation that may influence their quality of sexuality.

The most prevalent concerns of patients with AS are pain (especially backaches), stiffness, and physical restrictions. Because of disease activity and comorbid emotional problems, they may be vulnerable to sexual problems. In our present study, the disease activity and functional conditions were evaluated with the Bath Ankylosing Spondylitis Functional Index (BASFI), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and the Bath Ankylosing Spondylitis Metrology Index (BASMI). The effect of the BASFI and BASMI on sexual function has been shown using the linear regression model[13]. Several previous studies[6,24] have also revealed that higher BASFI and BASDAI scores are associated with sexual dysfunction. By limiting the mobility of the axial skeleton, especially in the lower back, AS could lower physical activity during sexual intercourse, and sexual pleasure may be impaired by loss of physical function and by pain. The anticipation that sexual drive or sexual activity will cause back pain could affect psychological status by bringing on depression and anxiety. The sexual health of patients with AS seems to be based on 2 interrelated factors: psychological status and disease activity. Moreover, it is clear that higher disease activity also causes sexual problems and difficulty.

Nonsteroidal antiinflammatory drugs (NSAID) have been demonstrated to increase the risk of erectile dysfunction independent of the indication, and regular use of NSAID was associated with erectile dysfunction[28,29]. In addition, sexual dysfunction was associated with disease-modifying antirheumatic drugs[30]. However, 1 study[7] reported that anti-tumor necrosis factor-α therapy may reduce sexual dysfunction in male patients with AS, in addition to reducing disease activity. In our study, because of limiting data, we could not evaluate whether there was a relationship between drug usage and sexual problems.

Even though the 11 studies included in this metaanalysis were of high quality, there are some limitations, and thus the result should be interpreted with caution. First, only published studies were included in this metaanalysis, and some relevant studies could not be included in our analysis. Therefore, it is possible that publication bias has been introduced as indicated by the funnel plot, which seemed to be asymmetric. Second, we could not perform further subgroup stratifications analysis because of the limited number of published studies. Finally, studies included in our meta-analysis were of retrospective design, which is subject to some methodological deficiencies.

Our metaanalysis demonstrated that each of 5 domains of IIEF was lower in men with AS than in healthy controls. Sexual dysfunction in patients with AS has not been well studied, with only a few publications about this common but underdiagnosed clinical problem. Future well-designed research with large sample sizes may be required.

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