Inflammatory bowel disease is associated with worse sexual function: a systematic review and meta-analysis

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Background: Several studies report that sexuality is often affected by inflammatory bowel diseases (IBD). The aim of this meta-analysis was to investigate the association between IBD and sexual function.

Methods: A literature search was conducted in PubMed, Web of Science, and EMBASE databases (up to September 1, 2020). Scores of sexual functions with a standard deviation and odds ratio (OR) or relative risk (RR) with a 95% CI were used to analysis the association between IBD and sexual function.

Results: Eleven studies with 7,018 male IBD cases and 1,803 female IBD cases were included in the meta-analysis. In male individuals, the pooled results revealed that IBD was significantly associated with impaired erectile function and poor sexual satisfaction (RR for erectile function =1.50, 95% CI: 1.22 to 1.84, P<0.0001; standard mean difference for sexual satisfaction =−0.24, 95% CI: −0.33 to −0.15, P<0.0001). And among female individuals, IBD had impact on most sub-domains of sexual function, except pains.

Conclusions: IBD is associated with worse sexual function. It has significant impact on erectile function and satisfaction for male individuals and has impact on most sub-domains of sexual function for female individuals.

Keywords: Inflammatory bowel disease (IBD); sexual function; erectile function; satisfaction in sexual; systematic review and meta-analysis

Introduction

Inflammatory bowel diseases (IBD) are a group of idiopathic chronic inflammatory intestinal ailments that are divided into two primary types: ulcerative colitis (UC) and Crohn's disease (CD) (1). IBD is usually diagnosed in young individuals between the age of 15 and 30 (2). Commonly, it is more frequent in Western countries than in other areas of the world, with a prevalence of over 0.3% and affecting over 3.5 million individuals, according to the most recent statistics available (3,4). As a lifelong chronic disorder, IBD may impact health in several ways such as abdominal pain,

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diarrhea, and fatigue during the active phase of IBD. Also, many studies showed that IBD can cause severe depression and declines in health-related quality of life (5-7). Sexual quality is an important determinant of quality of life and depression is known as an important risk factor of sexual dysfunction. Thus, an association between IBD and sexual dysfunction may exist.

In fact, Gazzard *et al.* had reported decreased sexual activities in IBD patients 42 years ago (8). And several studies in recent years report that sexual problems are more common among IBD patients compared to the general population of similar age (9). The proportion of sexual dysfunction (reported by Knowles *et al.* and Mahmood *et al.*) (10,11) ranges between 44% to 53.9% and 40% to 66% in male patients and female patients, respectively. Besides, there are evidences indicating that IBD do not affect every specific aspect of sexual function (12). The number of relevant studies is still limited without a systematic review focused on specific sub-domains of sexual function. Therefore, the aim of current meta-analysis was to investigate the impact of IBD on overall and specific sub-domains of sexual function. We present the following article in accordance with the MOOSE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-22-190/rc).

Methods

Literature search

A literature search was performed using the PubMed, Web of Science, and EMBASE databases with restrictions to the English language and publication time between January 1, 1990 and September 1, 2020. It was also registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42020204951) before screening studies for inclusion. The main search terms were sexual function, sexual dysfunction, sexual desire disorders, sexual arousal disorders, erectile dysfunction, premature ejaculation, orgasm disorders, sexual pain disorders, IBD, Ulcerative colon, and Crohn's disease. The literature search was performed independently by 2 authors and discrepancies were resolved by consultation with a third author.

Study selection criteria

Any available epidemiologic evidence reporting the association between IBD and risk of sexual dysfunction in

individuals was included in the present study. According to the patient, intervention, comparison, outcome, and study design (PICOS), the question that guided this meta-analysis was "Does IBD lead to a worse sexual function?". The PICOS evidence was comprised of the following combinations: adult IBD patients (P); a history of sexual dysfunction or decreased sexual function consciously (I); compared with the general or non-IBD population (C); the assessment of sexual function (O); all study designs were accepted (S). Moreover, we also include studies that provided adequate data to calculate relative risk (RR) or odds ratios (OR) with 95% CI. The excluded criteria were as follows: (I) missing population data literatures; (II) review articles, comments, editorials, or case reports, etc.; (III) animal experiments; (IV) duplicated data; (V) IBD patients with relevant surgery history.

Measurement of IBD and sexual function

IBD and sexual function were defined according to the international classification of diseases codes (13). IBD were diagnosed according to the clinical criteria. Sexual function was measured by any existing and validated scales, such as the International Index of Erectile Function (IIEF), Female Sexual Function Index (FSFI), Brief Index of Sexual Functioning in Women (BISF-W), Arizona Sexual Experience Scale (ASEX), and Sexual Quality of Life Questionnaire (SQoL).

The BISF-W is a validated self-reported, 22-item inventory of sexual desire, activity, arousal, orgasm, and satisfaction (14). This scale is initially developed in response to the lack of a brief, standardized self-reported assessment of women's overall sexual function that could assess both the qualitative and quantitative domains. It's considered a useful and established instrument by several studies, although its scoring algorithm is still confronted with questions (15-17).

The ASEX is one of the most commonly used scales to measure sexual function. Its five items quantify sexual impulse, arousal, vaginal lubrication or penis hardening, orgasm reaching capacity, and orgasmic endurance satisfaction (18). This scale has been utilized in a variety of cross-sectional prevalence studies and randomized controlled trials of pharmacological treatment. It has been proven reliable and valid in the assessment of sexual function, as well as being easy-to-use in various clinical settings (19-21). Low scores indicate that the sexual response is strong, easy, and satisfactory, whereas high scores indicate the presence of sexual dysfunction. To obtain
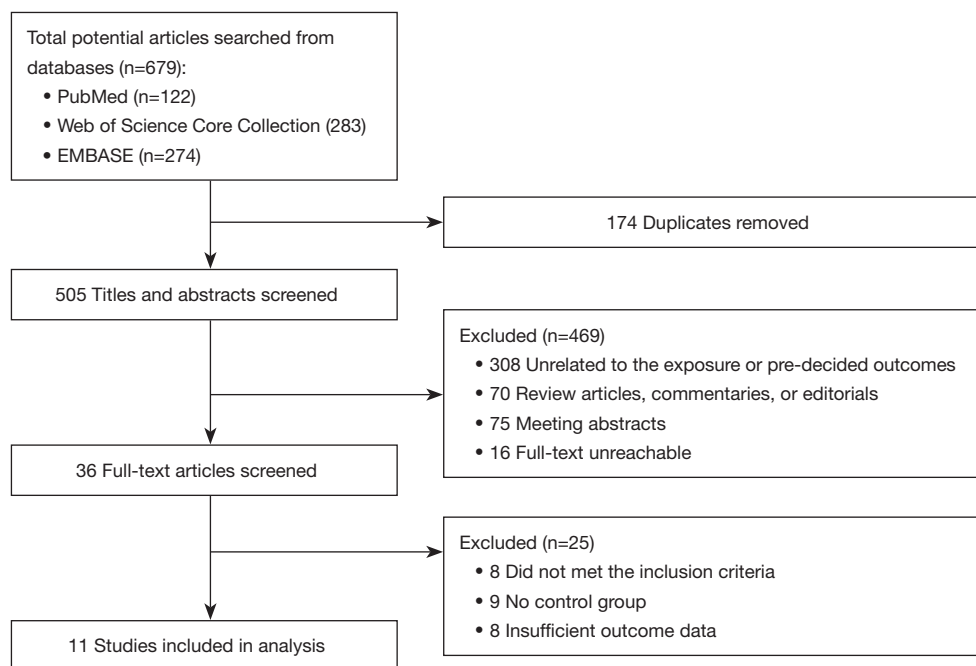
Figure 1 Flow chart of studies selection.

a more efficient correlation between IBD and worse sexual function, we picked a negative value of ASEX scores, since the outcome of the ASEX is different from all the other instruments.

Data extraction

Electronic extraction forms were used to extract the data. The extracted data included the authors, study titles, publication year, country, study design, age, number of participants, assessment of sexual function, scores, and OR/RRs for each sub-domain of sexual dysfunction. Discrepancies were resolved by consensus or by consultation with a third reviewer. Data extraction was performed independently by 2 authors and discrepancies were resolved by consultation with a third author.

Quality assessment

The Newcastle–Ottawa Quality Assessment Scale (NOS) was used for quality assessment of the case-control/cohort studies (22). Cross-sectional studies were assessed by using the Agency for Healthcare Research and Quality (AHRQ) checklist, which is an eleven-score system (23). The detail of quality assessment is provided in the supplementary.

Statistical analyses

The impact of IBD on specific sub-domains of sexual function was assessed by using the scores of various sexual function scales and standard deviation (SD). The association between IBD and sexual dysfunction was assessed by using OR/RR and its 95% CI. A random-effects model was used if significant heterogeneity existed (P<0.10, or P>0.10 but I^2>50%), otherwise a fixed-effects model was used (P>0.10, or P<0.10 but I^2<50%).

Heterogeneity among the studies was assessed using the Cochrane Q test (P<0.10) and I^2 statistic. I^2 values above 50% were considered high degrees of heterogeneity. Subgroup analyses and sensitivity analyses were conducted to further investigate the potential source of heterogeneity. Publication bias analyses were not conducted because of the limited number of studies in each analysis. Data analyses were performed using RevMan (Version5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Literature search

Eleven studies (24-34) with 8,821 IBD patients (7,018 males and 1,803 females) were included in this meta-analysis.

Figure 1 shows a flow chart of the study selection process.

Study characteristics

Among these 11 studies, five studies are cohort studies, two are case-control studies, and three are cross-sectional studies. The mean age of male individuals and female individuals ranged from 31.3 to 52.4 years and 33.6 to 43.8 years, respectively. The detailed characteristics of the 11 included studies are presented in *Table 1*.

Study quality

The results of the quality assessment of the included studies were presented in Tables S1-S3. Two studies (24,26) were considered high quality, eight (25,28-34) were considered moderate quality, and one (27) were considered low quality due to the lack of information about potential confounders and follow-up years.

Main meta-analysis results

The main results are shown in *Figures 2-5*. Other results (For male: orgasm, desire, and overall satisfaction; For female: pains) are shown in Figures S1,S2. Tables S4-S11 show the results of sensitivity analyses in males. Tables S12-S19 show the results of sensitivity analyses in females.

Association between IBD and sexual function in male
Overall sexual function
Seven studies (24,25,28,30,31,33,34) evaluated the impact of IBD on overall sexual function. *Figure 2* indicates that IBD patients had worse overall sexual function than individuals without IBD (OR =1.61, 95% CI: 1.17 to 2.23, P=0.004). Also, *Figure 2* shows that there was a statistically significant association between IBD and low overall sexual function scores (SMD =−0.15, 95% CI: −0.29 to −0.01, P=0.03). Subgroup analyses regarding age showed that (*Figure 2*), IBD patients under 45 years old exhibited a significantly increased risk of sexual dysfunction compared to those without IBD, while no significant association was found in the group older than 45 years old (OR for <45 years =1.88, 95% CI: 1.25 to 2.82, P=0.002; OR for ≥45 years =1.23, 95% CI: 0.72 to 2.11, P=0.44).

The sensitivity analysis for the overall scores (Table S11) indicated that substantial changes took place on the pooled SMD of analysis for total sexual function when the Ateş Bulut 2019 (25) (SMD =−0.13, 95% CI: −0.27 to 0.02), the

Table 1 Characteristics of 11 included studies in this meta-analysis

Study	Design	Specific diseases	Gender	Study Group Mean age	Study Group No.	Control Group Mean age	Control Group No.	Diagnosis of IBD	Assessment of sexual dysfunction	Adjustments for potential confounders	Score*
Bel 2015 (24), The Netherlands	Retrospective cohort	IBD	M/F	M: 51.1±12.8; F: 42.9±12.9	M: 119; F: 168	M: 52.4±12.7; F: 43.8±12.8	M: 91; F: 106	Registered of Gastroenterology departments of a tertiary referral center and a general hospital	M: IIEF; F: FSFI	Age, depression, diseases activity	7
Ateş Bulut 2019 (25), Turkey	Cross-sectional	IBD	M/F	41±13	M: 69; F: 53	43±13	M: 20; F: 22	Diagnosed by the gastroenterology outpatient or inpatient clinics with UC or CD	ASEX	Age, depression and anxiety, diseases activity	5
Kao 2016 (26), China	Prospective cohort	IBD	M	50.1±16.6	1,845	49.7±16.8	7,380	The Longitudinal Health Insurance Database 2000 (LHID2000) of the NHIRD, provided by the NHRI of Taiwan	IIEF-5	Age, sex, and comorbidities of CAD, PAD, stroke, CKD, hypertension, diabetes, hyperlipidemia, depression, and anxiety, and medications of steroids, opiates, antidepressants, and anxiolytics	9

Table 1 (*continued*)

Table 1 (*continued*)

Study	Design	Gender	Specific diseases	Study Group		Control Group		Diagnosis of IBD	Assessment of sexual dysfunction	Adjustments for potential confounders	Score*
				Mean age	No.	Mean age	No.				
Marín 2013 (28), Spain	Case-Control	M/F	IBD	M: 46.5±10.2; F: 42.7±9.4	M: 153; F: 201	M: 46.1±10.6; F: 41.1±8.9	M: 73; F: 127	Identified from the IBD databases of Hospital Universitari Germans Trias i Pujol (Badalona) and Hospital de la Santa Creu i Sant Pau (Barcelona)	M: IIEF; F: FSFI	Age, corticosteroids, biological agents, perianal disease, depression, arterial hypertension, diabetes	6
Moody 1992 (29), UK	Retrospective cohort	F	CD	34.7±6.1	50	33.6±6.0	50	Identified from the epidemiological data bases in Cardiff and Leicestershire	The modified structured questionnaire developed during actinological studies of risk factors in cervical adenocarcinoma	Age	5
Moody 1993 (30), UK	Retrospective cohort	M	UC	40.2±7.9	40	38.6±9.4	38	The community data base for IBD in Leicestershire	A modified version of a previously validated questionnaire on sexual problems	NA	5
Rivière 2017 (31), France	Cross-sectional	M/F	IBD	M: 39; F: 38	M: 166; F: 192	M: 39; F: 36	M: 56; F: 53	IBD units of two French tertiary care university hospitals [Bordeaux and Nancy]	M: IIEF; F: FSFI	Age	7
Roseira 2020 (32), Portugal	Cross-sectional	M/F	IBD	NA	M: 389; F:458	NA	M: 206; F: 192	Confirmed diagnoses of CD or UC in 6 centers in Portugal	SQoL	Age, diagnosis, marital status, depression disorders, and perianal disease	5
Timmer 2007 (33), German	Retrospective cohort	M/F	IBD	M: 40; F: 38	M: 153; F: 181	M:40.5; F: 39	M: 153; F: 181	The national patients organization and the German Crohn's and Colitis Association (Deutsche Morbus Crohn/Colitis ulcerosa Vereinigung, DCCV e.V)	M: IIEF; F: FSFI	Age, SES, comorbidity, diabetes, hypertensive therapy, confession of faith, type of residency, depression, anxiety	6
Valer 2017 (34), Spain	Cross-sectional	M	IBD	32.0±38.8	52	31.3±5.1	22	Patients attending outpatient IBD clinics of the 4 participating university hospitals	IIEF	Age, smoking, PRL	7

*, scores of quality assessment. IBD, inflammatory bowel disease; IIEF, International Index of Erectile Function; FSFI, Female Sexual Function Index; UC, ulcerative colitis; CD, Crohn's Disease; ASEX, Arizona Sexual Experience Scale; NHRI, National Health Research Institute; CAD, coronary artery disease; PAD, peripheral arterial disease; CKD, chronic kidney disease; NA, not available; SQoL, Sexual Quality of Life Questionnaire; SES, socioeconomic status; PRL, prolactin.
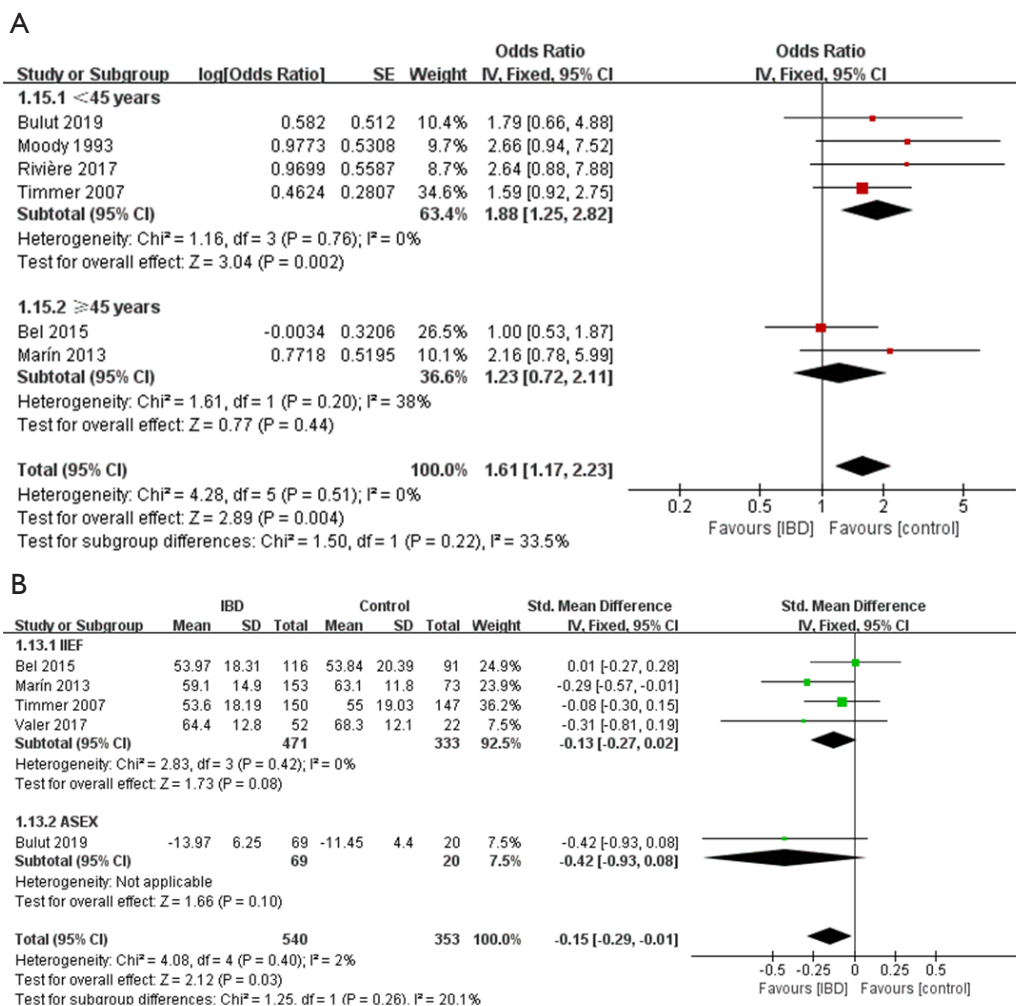
A

B

Figure 2 Forest plot showing subgroup analysis results of the prevalence of sexual dysfunction (A) and the total sexual function scores (B) for males. Controls represent male individuals without inflammatory Bowel diseases. SD, standard deviation; IIEF, International Index of Erectile Function; ASEX, Arizona Sexual Experience Scale.

Marín 2013 (28) (SMD =–0.11, 95% CI: –0.26 to 0.05) or the Valer 2017 (34) (SMD =–0.14, 95% CI: –0.28 to 0.01) was omitted respectively.

Sub-domains of sexual function

(I) Erectile function

Seven studies (24-28,33,34) evaluated the impact of IBD on erectile dysfunction (ED). As shown in *Figure 3*, the presence of IBD was significantly associated with an increased risk of ED (RR =1.50, 95% CI: 1.22 to 1.84, P<0.0001). However, no statistical difference in the erectile function scores was found between individuals with or without IBD (SMD =–0.21, 95% CI: –0.43 to 0.02, P=0.07; *Figure 3*).

As subgroup analyses showed, when using the scale ASEX, IBD was significantly associated with the decreased erectile function scores, while using the scale IIEF did not (SMD for ASEX =–0.69, 95% CI: –1.20 to –0.19, P=0.007; SMD for IIEF =–0.12, 95% CI: –0.30 to 0.06, P=0.18; *Figure 3*). Interestingly, IBD patients under 45 years old exhibited a significantly increased risk of ED compared to those without IBD (*Figure 3*) (RR =1.51, 95% CI: 1.20 to 1.91, P=0.0005), while no significant association was found in the group older than 45 years old (RR =1.38, 95% CI: 0.81 to 2.36, P=0.24).

In sensitivity analysis (Tables S5), a substantial change

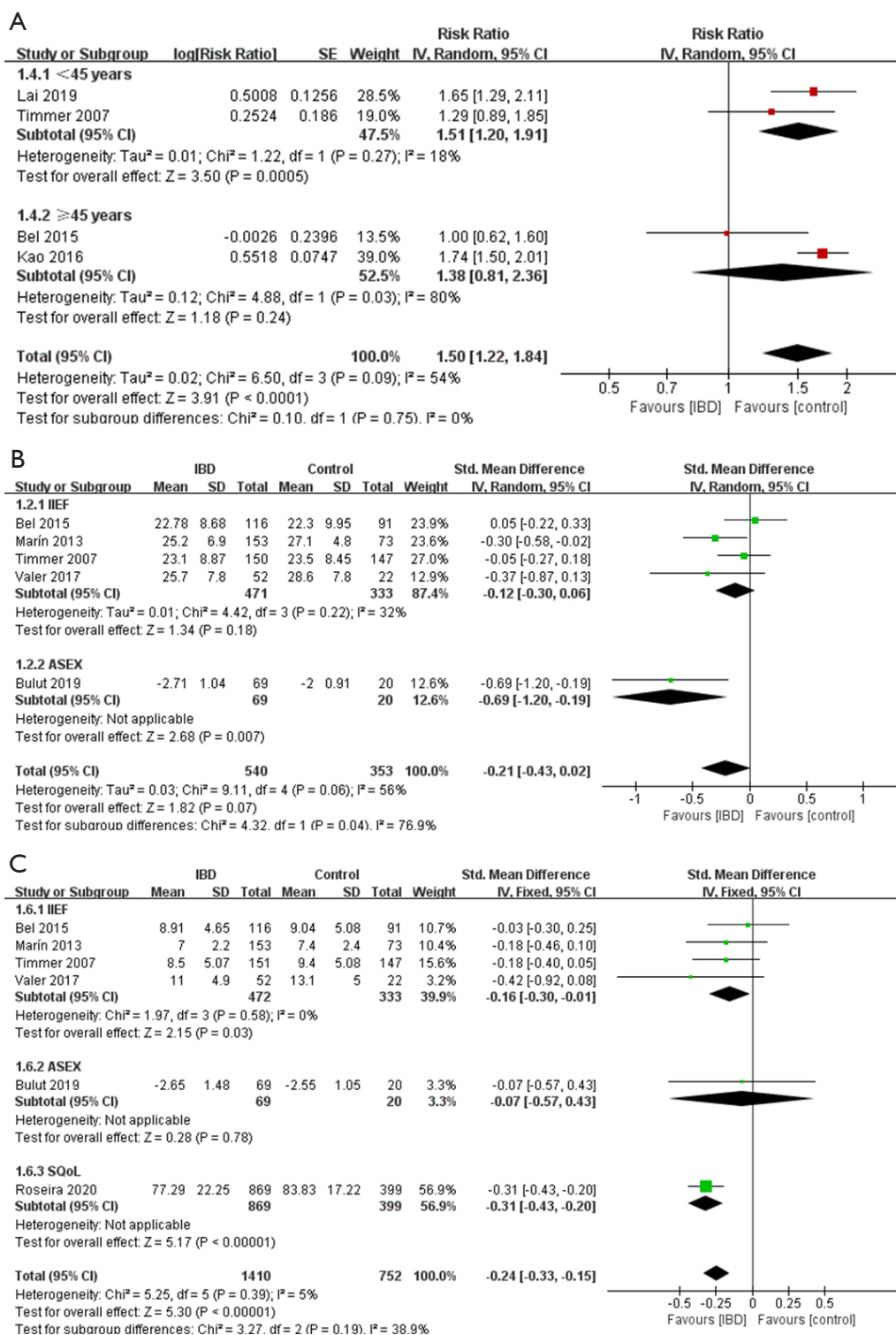**Figure 3** Forest plot showing subgroup analysis results of the prevalence of ED (A), the erectile function scores (B), and the "satisfaction and quality" scores (C) for male. Controls represent male individuals without inflammatory bowel diseases. SD, standard deviation; IIEF, International Index of Erectile Function; ASEX, Arizona Sexual Experience Scale; SQoL, Sexual Quality of Life Questionnaire; ED, erectile dysfunction.
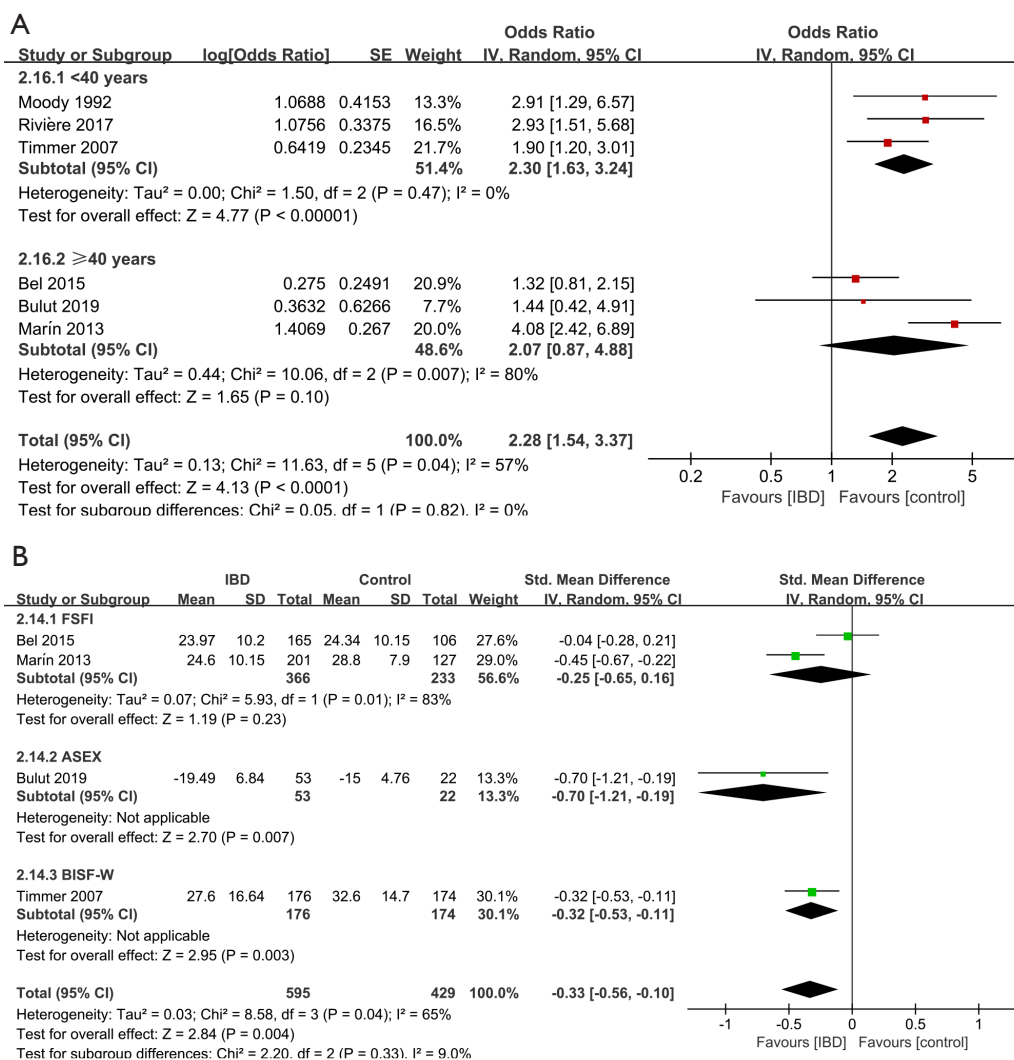
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Figure 4 Forest plot showing subgroup analysis results of the prevalence of sexual dysfunction (A) and the total sexual function scores (B) for female. Controls represent female individuals without inflammatory bowel diseases. SD, standard deviation; FSFI, Female Sexual Function Index; ASEX, Arizona Sexual Experience Scale; BISF-W, Brief Index of Sexual Functioning in Women.

was detected on the new pooled SMD, after omitting the Bel 2015 (24) in the analysis of erectile function scores (SMD =−0.29, 95% CI: −0.54 to −0.03), which meant that the synthetic results of this analysis might be influenced by Bel 2015. As shown in Tables S4, in the sensitivity analysis for the ED prevalence, heterogeneity changed significantly after eliminating the Bel 2015 (24) (I^2=11%, P=0.33), which indicated that this study might be the potential sources of the heterogeneity.

(II) Satisfaction & quality

Six studies (24,25,28,32-34) evaluated the satisfaction & quality scores in sexual activities. A significant association

between IBD and low sexual satisfaction was found (SMD =−0.24, 95% CI: −0.33 to −0.15, P<0.00001; *Figure 3*).

Subgroup analyses showed (*Figure 3*) no significant difference was found between individuals with or without IBD when using the scale ASEX, while significant difference was found using other scales (SMD for ASEX =−0.07, 95% CI: −0.57 to 0.43, P=0.78; SMD for SQoL =−0.31, 95% CI: −0.43 to −0.20, P<0.0001; SMD for IIEF =−0.16, 95% CI: −0.30 to −0.01, P=0.03). The result of sensitivity was shown in Tables S6.

(III) Other sub-domains of sexual function

Five studies (24,25,28,33,34) evaluated the impact of IBD

A

Study or Subgroup	IBD Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
2.2.1 FSFI									
Bel 2015	3.07	1.17	165	3.19	1.24	106	27.1%	-0.10 [-0.34, 0.14]	
Marín 2013	3.2	1.4	201	4	1.2	127	27.6%	-0.60 [-0.83, -0.37]	
Subtotal (95% CI)			366			233	54.7%	-0.35 [-0.84, 0.14]	

Heterogeneity: Tau² = 0.11; Chi² = 8.71, df = 1 (P = 0.003); I² = 89%
Test for overall effect: Z = 1.41 (P = 0.16)

2.2.2 ASEX									
Bulut 2019	-4.25	1.39	53	-3.14	0.94	22	17.9%	-0.86 [-1.38, -0.34]	
Subtotal (95% CI)			53			22	17.9%	-0.86 [-1.38, -0.34]	

Heterogeneity: Not applicable
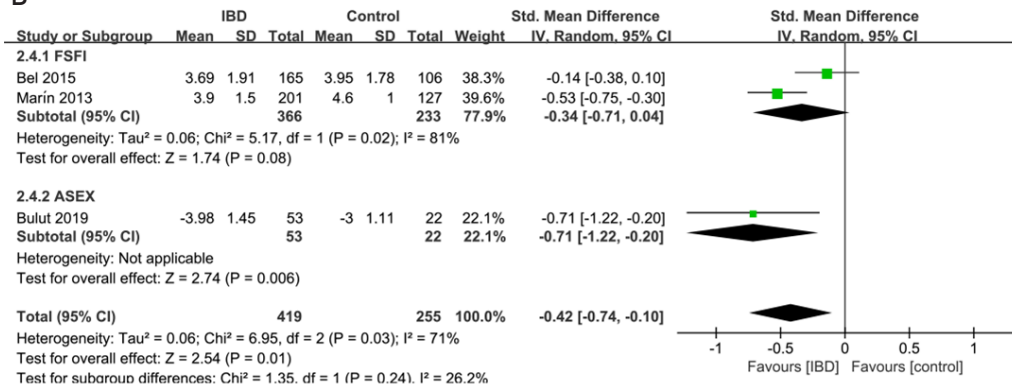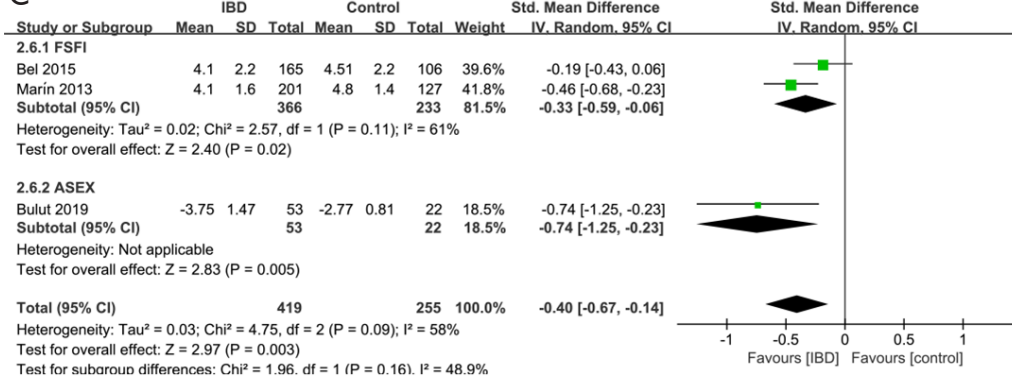Test for overall effect: Z = 3.26 (P = 0.001)

2.2.3 BISF-W									
Timmer 2007	4.3	2.44	180	4.5	2.36	117	27.4%	-0.08 [-0.32, 0.15]	
Subtotal (95% CI)			180			117	27.4%	-0.08 [-0.32, 0.15]	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.49)

| **Total (95% CI)** | | | 599 | | | 372 | 100.0% | -0.37 [-0.70, -0.04] | |

Heterogeneity: Tau² = 0.09; Chi² = 17.21, df = 3 (P = 0.0006); I² = 83%
Test for overall effect: Z = 2.19 (P = 0.03)
Test for subgroup differences: Chi² = 7.49, df = 2 (P = 0.02), I² = 73.3%

B

Study or Subgroup	IBD Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
2.4.1 FSFI									
Bel 2015	3.69	1.91	165	3.95	1.78	106	38.3%	-0.14 [-0.38, 0.10]	
Marín 2013	3.9	1.5	201	4.6	1	127	39.6%	-0.53 [-0.75, -0.30]	
Subtotal (95% CI)			366			233	77.9%	-0.34 [-0.71, 0.04]	

Heterogeneity: Tau² = 0.06; Chi² = 5.17, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 1.74 (P = 0.08)

2.4.2 ASEX									
Bulut 2019	-3.98	1.45	53	-3	1.11	22	22.1%	-0.71 [-1.22, -0.20]	
Subtotal (95% CI)			53			22	22.1%	-0.71 [-1.22, -0.20]	

Heterogeneity: Not applicable
Test for overall effect: Z = 2.74 (P = 0.006)

| **Total (95% CI)** | | | 419 | | | 255 | 100.0% | -0.42 [-0.74, -0.10] | |

Heterogeneity: Tau² = 0.06; Chi² = 6.95, df = 2 (P = 0.03); I² = 71%
Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Chi² = 1.35, df = 1 (P = 0.24), I² = 26.2%

C

Study or Subgroup	IBD Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
2.6.1 FSFI									
Bel 2015	4.1	2.2	165	4.51	2.2	106	39.6%	-0.19 [-0.43, 0.06]	
Marín 2013	4.1	1.6	201	4.8	1.4	127	41.8%	-0.46 [-0.68, -0.23]	
Subtotal (95% CI)			366			233	81.5%	-0.33 [-0.59, -0.06]	

Heterogeneity: Tau² = 0.02; Chi² = 2.57, df = 1 (P = 0.11); I² = 61%
Test for overall effect: Z = 2.40 (P = 0.02)

2.6.2 ASEX									
Bulut 2019	-3.75	1.47	53	-2.77	0.81	22	18.5%	-0.74 [-1.25, -0.23]	
Subtotal (95% CI)			53			22	18.5%	-0.74 [-1.25, -0.23]	

Heterogeneity: Not applicable
Test for overall effect: Z = 2.83 (P = 0.005)

| **Total (95% CI)** | | | 419 | | | 255 | 100.0% | -0.40 [-0.67, -0.14] | |

Heterogeneity: Tau² = 0.03; Chi² = 4.75, df = 2 (P = 0.09); I² = 58%
Test for overall effect: Z = 2.97 (P = 0.003)
Test for subgroup differences: Chi² = 1.96, df = 1 (P = 0.16), I² = 48.9%
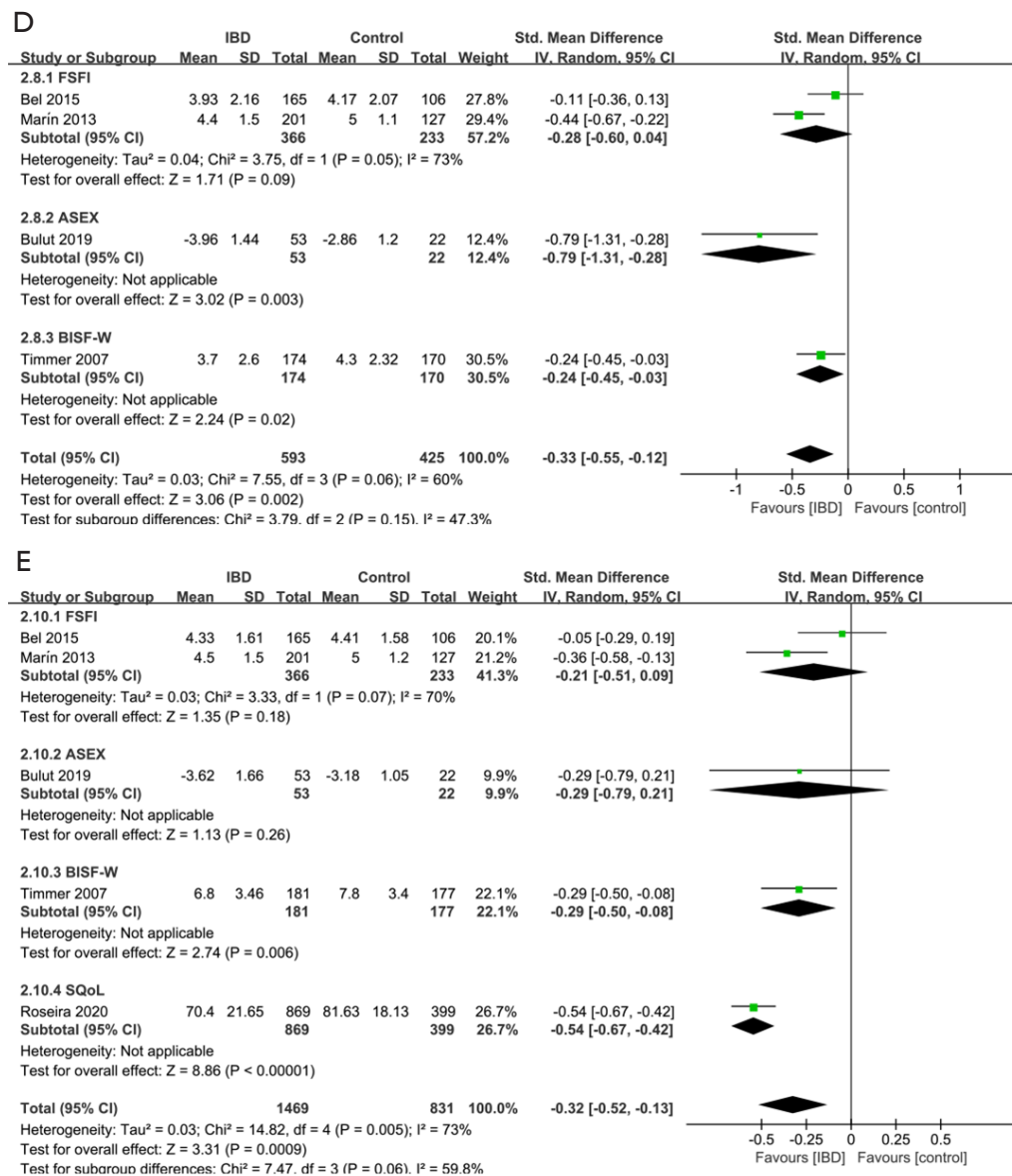
Figure 5 Forest plots showing subgroup analysis results of the specific domains scores for females according to different sexual function assessment scales. (A) Desire, (B) Arousal, (C) Lubrication, (D) Orgasm, (E) Satisfaction and quality. Controls represent male individuals without Inflammatory Bowel Diseases. CI, Confidence interval; SD, Standard deviation; FSFI, Female Sexual Function Index; ASEX, Arizona Sexual Experience Scale; BISF-W, Brief Index of Sexual Functioning in Women. SQoL, Sexual Quality of Life Questionnaire.

on other sub-domains of sexual function in male. Poor performance on orgasm (SMD =–0.07, 95% CI: –0.20 to 0.07, P=0.28), desire (SMD =0.03, 95% CI: –0.11 to 0.16, P=0.70), and overall satisfaction (SMD =–0.32, 95% CI: –0.65 to 0.02, P=0.06) were not significant associated with IBD (Figure S1). The results of sensitivity analysis were shown in Tables S7-S9.

Association between IBD and sexual function in female
Total sexual function

Six studies (24,25,28,29,31,33) evaluated the impact on total sexual function. *Figure 4* shows the pooled OR result, which revealed that IBD was significantly associated with an increased risk of sexual dysfunction (OR =2.28, 95% CI: 1.54 to 3.37, P<0.0001), with high heterogeneity (I²=57%, P=0.04).

There was also a significant statistical difference in the total sexual function scores between individuals with or without IBD (SMD =–3.44, 95% CI: –5.52 to –1.37, P=0.001**).**

Subgroup analyses regarding age showed that (*Figure 4*) female IBD patients younger than 40 years old exhibited a significantly increased risk of sexual dysfunction compared to those without IBD, while no significant association was found in the group older than 40 years old. (OR for <40 years =2.30, 95% CI: 1.63 to 3.24, P<0.00001; OR for ≥40 years =2.07, 95% CI: 0.87 to 4.88, P=0.10). As regarding the scale used to score sexual function, shown in *Figure 4*, no significant difference in total sexual function was found between individuals with or without IBD when using the scale FSFI (SMD =–0.25, 95% CI: –0.65 to 0.16, P=0.23). And when using the scale ASEX and the scale BISF-W, the difference between individuals with or without IBD was significant (SMD for ASEX =–0.70, 95% CI: –1.21 to –0.19, P=0.007; SMD for BISF-W =–0.32, 95% CI: –0.53 to –0.11, P=0.003; *Figure 4*).

Sensitivity analysis (Tables S18) of the prevalence of sexual dysfunction showed that the heterogeneity changed significantly after eliminating the Bel 2015 (24) (I^2=30%, P=0.22) and Marín 2013 (28) (I^2=21%, P=0.28), which indicated that the two studies might be the potential sources of the heterogeneity. Tables S19 also showed that, in the analysis of total scores, a substantial change was detected on the new pooled SMD, after omitting the Bel 2015 (24) (I^2=5.7%, P=0.35) and Ateş Bulut 2019 (25) (I^2=0%, P=0.76), which indicated that the two studies might be the potential sources of the heterogeneity.

Sub-domains of sexual function

Five studies (24,25,28,32,33) evaluated the impact of IBD on Sub-domains of sexual function in female. IBD patients seemed to have significant worse performance on desire (SMD =–0.37, 95% CI: –0.70 to –0.04, P=0.03), arousal (SMD =–0.42, 95% CI: –0.74 to –0.10, P=0.01), lubrication (SMD =–0.40, 95% CI: –0.67 to –0.14, P=0.003), orgasm (SMD =–0.33, 95% CI: –0.55 to –0.12, P=0.002), and satisfaction & quality (SMD =–0.32, 95% CI: –0.52 to –0.13, P=0.0009) (*Figure 5*). Surprisingly, the poor performance on pain (SMD =–0.16, 95% CI: –0.65 to 0.33, P=0.52) of IBD patients was not significantly associated with IBD (Figure S2).

Subgroup analysis showed that, when using the ASEX scale to measure the sub-domains of sexual function, it's usually easier to find a significant difference between the general population and female IBD patients (*Figure 5A-5E*). While using the FSFI scale, the association

was not significant between poor performance on sub-domains (except lubrication) of sexual function and IBD (*Figure 5A-5E*). The results of sensitivity analysis were shown in Tables S12-S17.

Discussion

Sexual health is defined as a condition of physical, emotional, mental, and social well-being associated with sexuality that is not merely the absence of disease, malfunction, or infirmity (35). Just like body image, it is a critical part of psychosocial functioning that has a major impact on overall Quality of Life (10). Thus, sexual health is a vital issue in IBD since IBD usually strikes adolescent or younger individuals who are at the stage of self-development and reproducing (36). Assessing sexual function is a very valuable approach toward sexual health.

Almost two decades ago, Giese and Terrell (37) had recognized that sexual health issues in IBD patients (include growth and development, body image, intimacy, sexual functioning, fertility, and pregnancy) may be influenced by the disease itself or by the medical and surgical interventions used for treatment. However, the correlation between IBD and sexual function is still controversial because of the significant heterogeneity in study aims, the definition of sexual dysfunction, design, and samples between the studies. Within this context, we conducted this meta-analysis aiming to examine the correlation between IBD and each sub-domain of sexual dysfunction. 36 studies were identified after systematically searching and 11 studies (24-34) were included in the end. The results of this meta-analysis indicated that IBD was significantly associated with worse sexual function in both sexes. The prevalence of sexual dysfunction in males and females was higher compared to the individuals without IBD. And IBD patients had worse performance on specific sub-domains of sexual function compared with individuals without IBD.

Specifically, there were significant decreases in the satisfaction & quality and total sexual function, indicating that male individuals' sexual function in these two sub-domains may be impacted by IBD. It is worth noting that, even the scores for several sub-domains of sexual function had no difference between patients with or without IBD, it did not absolutely mean that sexual function in these sub-domains did not get worse, for example, erectile function. A significant association between IBD and erectile dysfunction was found in the analysis of RRs of ED. However, as for the erectile function scores, there was no statistical difference

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between individuals with or without IBD. It might be because the cut-off for ED was different in included studies. Additionally, the impact on sexual function of female patients caused by IBD was much greater than that of male patients (almost all sub-domains scores decreased). These results were consistent with several studies (10-12,38). Additionally, the subgroup analysis was conducted regarding age and scales for sexual function, which indicated that IBD patients at older age seemed to have less impact on sexual function compared to patients at a younger age. One possible explanation for this result is that IBD mainly occurs in adolescence or early aged adults. Elderly patients usually have a longer disease duration. And sexual function is relatively less impacted by IBD with a longer disease duration and is not affected by the long-term severity of the disease (39).

Individuals suffering from IBD may develop hypogonadism as a result of chronic inflammation. Proinflammatory cytokines are known in pediatric studies to disrupt sex steroid synthesis at the testes and ovaries, thereby affecting normal growth. Tumor necrosis factor-α (TNF-α) and interleukins 1 (IL-1) and 6 (IL-6) have been shown to inhibit testosterone generation in Leydig cells and steroidogenesis production in ovarian cells, respectively (40,41). Furthermore, evidence suggests that serum TNF-α levels have a negative correlation with erectile function (42). Additionally, zinc absorption occurs throughout the small intestine, both in the proximal tract (duodenum and jejunum) and the distal tract (ileum). Certain symptoms of inflammatory bowel injury, such as zinc deficiency, have been linked to hypogonadism, which impairs sexual function (43).

Depression is commonly reported to be associated with decreased quality of life and considered as an independent or inter-related factor for chronic conditions (44,45). It is reported as frequent psychological comorbidity in IBD and the major factor for sexual dysfunction (24,28,31,46). The rate of depression is found up to 20–30% in IBD patients in remission disease activity (6). Therefore, comprehensive management of the quality of life and psychological factors is important in IBD patients. And it is essential to assess psychological state when IBD patients report a poor performance on sexual function.

Furthermore, medical treatment and lifestyle (such as alcohol intake) are considered as the factors affecting sexual function. Marín et al. (28) reported that corticosteroids are independently associated with sexual dysfunction, which may be because they could affect body image and then

sexual function. Importantly, evidence has shown that immunosuppressive drugs can affect male sexual function and reproduction through multiple mechanisms, such as altering reproductive hormone secretion and/or action, which results in sexual dysfunction, including libido decreases, erectile dysfunction, more difficulty achieving an orgasm or poor performance on orgasm, and sexual satisfaction decreases (47). Also, alcohol intake in IBD patients could cause relapse or deterioration by an inactive state (48), which leads to sexual dysfunction.

Previous meta-analysis conducted by Zhao et al. (49) has investigated the association between IBD and sexual dysfunction. However, only overall sexual dysfunction and subgroup analyses based on age were evaluated. Nevertheless, our meta-analysis is more up-to-date, incorporating 11 studies, and is the first report of the association between IBD and sexual function in specific sub-domains, including the analyses of erectile function, satisfaction and quality, orgasm and desire performance in male, and pain, desire, arousal, lubrication, orgasm and satisfaction and quality in female. Evidence provided by this study enables more precise therapy planning for IBD patients with sexual dysfunctions based on sub-domain analyses.

And several limitations of the current study should also be acknowledged. First, the number of included studies was limited. Compared to other medical diseases, IBD has received less attention in sexual medication and few studies on this topic were conducted. And the information in those studies provided was also limited. Thus, it's difficult for us to conduct a stratification analysis based on the activity, severity, duration of IBD or specific comorbidities since limited studies provided this information. Zhang's study (50), which conducted an analysis between medical comorbidities and sexual dysfunction in IBD patients, also raised the same concern about limited data on pertinent risk factors. Second, the majority of the included studies were retrospective cohort studies, which were considered moderate quality with insufficient strength of evidence. Third, even though we tried to minimize heterogeneity by clearly defining the exclusion and inclusion criteria, substantial heterogeneity still existed between those studies for IBD individuals, in spite of the fact that confounding factors were partially adjusted in most of the included studies. The differences in sample size, age, geographical area, comorbidities, medication usage, and varied characteristics of subjects may be responsible for the heterogeneity. Fourth, the subgroup analysis revealed that

there was no obvious association between IBD and sexual dysfunction in the elderly population. It's well-known that gonadal function would decline gradually with age, which might lead to worse sexual function. However, it does not mean that elderly IBD patients must show significantly worse sexual function than those without IBD. The impact of IBD on sexual function was weakened by age, and it might be one reason for the formation of heterogeneity, especially in studies whose participants were in older age. Moreover, the scales used for sexual function assessment vary among different studies. IIEF and FSFI were used to assess sexual function in most studies, while ASEX, SQoL, BISF-W, and the modified structured questionnaire were used in the other studies. O'Toole *et al.* (51) and de Silva *et al.* (52), have established and validated a new IBD-specific psychometric tool to assess sexual function for IBD patients for both sexes. Further studies should be conducted basing on these two scales.

Conclusions

IBD is associated with worse sexual function. It has significant impact on erectile function and satisfaction for male individuals and has impact on most sub-domains of sexual function for female individuals. Physicians should assess these specific sub-domains in the sexual functions of IBD patients, and give precision treatment for these areas.

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-22-190/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-22-190/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1 Quality assessment of cohort studies by Newcastle–Ottawa Scale

Study	Selection				Comparability		Outcome			Total Scores
	A	B	C	D	A1	B1	A2	B2	C2	
Bel 2015 (24)	1	1	1	0	1	1	0	1	1	7
Kao 2016 (26)	1	1	1	1	1	1	1	1	1	9
Lai 2019 (27)	1	1	1	0	0	0	1	0	0	4
Moody 1992 (29)	1	1	1	0	1	0	0	0	1	5
Moody 1993 (30)	1	1	1	0	1	0	0	0	1	5

A: Representativeness of exposed cohort. B: Representativeness of unexposed cohort. C: Ascertainment of exposure (If the exposure data was obtained from prescription database or medical record). D: Outcome was not present at start. A1: Important factor (If adjusted for the age, a point was assigned.) B1: Additional factor (If adjusted for any other additional factors.) A2: Assessment of outcome. B2: Exposure Follow-up for outcomes. C2: Rate of follow-up.

Table S2 Quality assessment of case-control studies by Newcastle–Ottawa Scale

Study	Selection				Comparability		Outcome			Total Scores
	A	B	C	D	A1	B1	A2	B2	C2	
Marín 2013 (28)	1	1	1	1	1	0	0	1	0	6
Timmer 2007 (33)	1	1	1	1	1	0	0	1	0	6

A: Adequacy of case definition. B: Representativeness of the cases. C: Selection of controls. D: Definition of controls. A1: Important factor (If adjusted for the age, a point was assigned.) B1: Additional factor (If adjusted for any other additional factors.) A2: Ascertainment of exposure. B2: Same method of ascertainment for cases and controls. C2: Non-response rate.

Table S3 Quality assessment of cross-sectional studies by AHRQ

Study	A	B	C	D	E	F	G	H	I	J	K	Total Scores
Roseira 2020 (32)	1	1	0	1	0	0	0	1	0	1	0	5
Ateş Bulut 2019 (25)	1	1	1	1	0	0	0	1	0	0	0	5
Valer 2017 (34)	1	1	1	1	0	0	1	1	0	1	0	7
Rivière 2017 (31)	1	1	1	1	0	0	1	1	0	1	0	7

A: Define the source of information. B: List inclusion and exclusion criteria. C: Indicate time period used for identifying patients. D: Consecutiveness of subjects if not population-based. E: if evaluators of subjective components of study were masked to other aspects of the status of the participants. F: any assessments undertaken for quality assurance purposes. G: Explain any patient exclusions. H: Description of confounding assessment and control. I: Explain how missing data were handled. J: Summarize patient response rates and completeness of data collection. K: Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained.
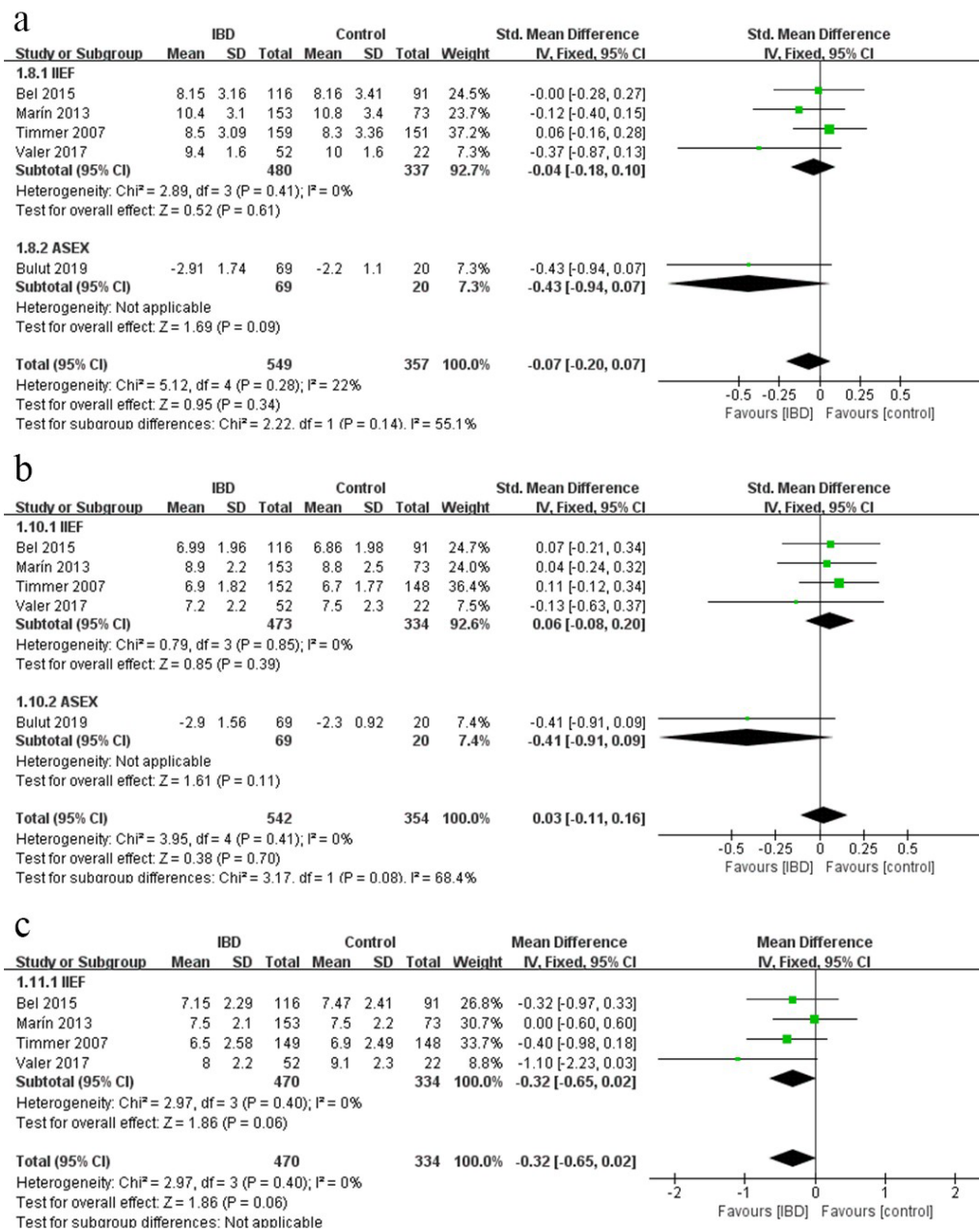
Figure S1 Forest plots showing subgroup analysis results of the specific domains scores for male according to different sexual function assessment scales. (A) Orgasm, (B) Desire, (C) Overall satisfaction. Controls represents male individuals without Inflammatory Bowel Diseases.
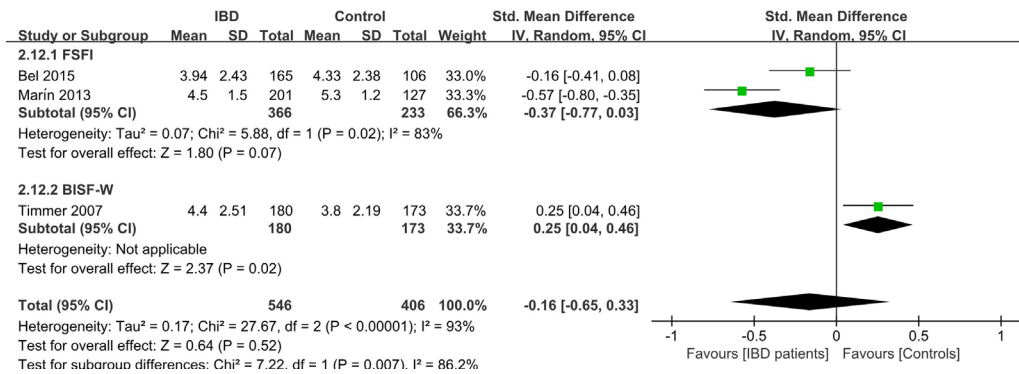
Figure S2 orest plot showing subgroup analysis results of the pains scores for female according to different sexual function assessment scales. Controls represents female individuals without inflammatory bowel diseases.

Table S4 Sensitivity analysis of erectile function-RRs

Study omitted	RR (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	1.65 [1.45, 1.88]	11%	0.33
Kao 2016 (26)	1.36 [1.02, 1.79]	48%	0.14
Lai 2019 (27)	1.38 [1.00, 1.92]	69%	0.04
Timmer 2007 (33)	1.55 [1.23, 1.96]	59%	0.09

Table S5 Sensitivity analysis for erectile function-scores

Study omitted	Std. Mean difference (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	−0.29 [−0.54, −0.03]	52%	0.10
Ateş Bulut 2019 (25)	−0.12 [−0.30, 0.06]	32%	0.22
Marín 2013 (28)	−0.19 [−0.47, 0.09]	61%	0.05
Timmer 2007 (33)	−0.28 [−0.58, 0.02]	61%	0.05
Valer 2017 (34)	−0.19 [−0.44, 0.06]	64%	0.04

Table S6 Sensitivity analysis for satisfaction and quality-scores

Study omitted	Std. Mean difference (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	−0.27 [−0.36, −0.17]	0%	0.63
Ateş Bulut 2019 (25)	−0.25 [−0.34, −0.16]	16%	0.31
Marín 2013 (28)	−0.25 [−0.35, −0.16]	20%	0.29
Roseira 2020 (32)	−0.15 [−0.29, −0.01]	0%	0.72
Timmer 2007 (33)	−0.26 [−0.35, −0.16]	18%	0.30
Valer 2017 (34)	−0.24 [−0.33, −0.15]	16%	0.31

Table S7 Sensitivity analysis for orgasm-scores

Study omitted	Std. Mean difference (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	−0.09 [−0.24, 0.07]	38%	0.18
Ateş Bulut 2019 (25)	−0.04 [−0.18, 0.10]	0%	0.41
Marín 2013 (28)	−0.05 [−0.20, 0.11]	39%	0.18
Timmer 2007 (33)	−0.14 [−0.31, 0.03]	3%	0.38
Valer 2017 (34)	−0.04 [−0.18, 0.10]	16%	0.31

Table S8 Sensitivity analysis for desire-scores

Study omitted	Std. Mean difference (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	0.01 [−0.14, 0.17]	22%	0.28
Ateş Bulut 2019 (25)	0.06 [−0.08, 0.20]	0%	0.85
Marín 2013 (28)	0.02 [−0.14, 0.18]	24%	0.27
Timmer 2007 (33)	−0.02 [−0.19, 0.15]	4%	0.37
Valer 2017 (34)	0.04 [−0.10, 0.18]	15%	0.32

Table S9 Sensitivity analysis for overall satisfaction-scores

Study omitted	Std. Mean difference (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	−0.32 [−0.71, 0.08]	33%	0.23
Marín 2013 (28)	−0.46 [−0.86, −0.06]	0%	0.48
Timmer 2007 (33)	−0.27 [−0.69, 0.14]	30%	0.24
Valer 2017 (34)	−0.24 [−0.59, 0.11]	0%	0.62

Table S10 Sensitivity analysis for total sexual function-ORs

Study omitted	OR (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	1.92 [1.31, 2.79]	0%	0.87
Ateş Bulut 2019 (25)	1.59 [1.13, 2.24]	5%	0.38
Marín 2013 (28)	1.56 [1.11, 2.19]	0%	0.42
Moody 1993 (30)	1.53 [1.09, 2.15]	0%	0.51
Rivière 2017 (31)	1.54 [1.10, 2.16]	0%	0.49
Timmer 2007 (33)	1.62 [1.09, 2.42]	6%	0.37

Table S11 Sensitivity analysis for total sexual function-scores

Study omitted	Std. Mean difference (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	−0.20 [−0.36, −0.04]	0%	0.48
Ateş Bulut 2019 (25)	−0.13 [−0.27, 0.02]	0%	0.42
Marín 2013 (28)	−0.11 [−0.26, 0.05]	0%	0.41
Timmer 2007 (33)	−0.19 [−0.36, −0.02]	13%	0.33
Valer 2017 (34)	−0.14 [−0.28, 0.01]	18%	0.30

Table S12 Sensitivity analysis for desire-scores

Study omitted	Std. Mean difference (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	−0.48 [−0.92, −0.04]	85%	0.001
Ateş Bulut 2019 (25)	−0.26 [−0.60, 0.08]	84%	0.002
Marín 2013 (28)	−0.27 [−0.61, 0.08]	74%	0.02
Timmer 2007 (33)	−0.48 [−0.91, −0.06]	83%	0.003

Table S13 Sensitivity analysis for arousal-scores

Study omitted	Std. Mean difference (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	−0.56 [−0.76, −0.35]	0%	0.51
Ateş Bulut 2019 (25)	−0.34 [−0.71, 0.04]	81%	0.02
Marín 2013 (28)	−0.38 [−0.94, 0.17]	75%	0.05

Table S14 Sensitivity analysis for lubrication-scores

Study omitted	Std. Mean difference (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	−0.50 [−0.71, −0.30]	0%	0.33
Ateş Bulut 2019 (25)	−0.33 [−0.59, −0.06]	61%	0.11
Marín 2013 (28)	−0.41 [−0.95, 0.12]	73%	0.06

Table S15 Sensitivity analysis for orgasm-scores

Study omitted	Std. Mean difference (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	−0.41 [−0.65, −0.17]	54%	0.11
Ateş Bulut 2019 (25)	−0.27 [−0.45, −0.09]	48%	0.14
Marín 2013 (28)	−0.30 [−0.58, −0.02]	63%	0.06
Timmer 2007 (33)	−0.39 [−0.72, −0.07]	72%	0.03

Table S16 Sensitivity analysis for satisfaction and quality-scores

Study omitted	Std. Mean difference (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	−0.41 [−0.56, −0.26]	47%	0.13
Ateş Bulut 2019 (25)	−0.33 [−0.54, −0.11]	79%	0.002
Marín 2013 (28)	−0.31 [−0.56, −0.06]	80%	0.002
Roseira 2020 (32)	−0.25 [−0.39, −0.10]	18%	0.30
Timmer 2007 (33)	−0.33 [−0.58, −0.08]	78%	0.004

Table S17 Sensitivity analysis for pain and problems-scores

Study omitted	Std. Mean difference (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	−0.16 [−0.97, 0.65]	96%	<0.0001
Marín 2013 (28)	0.05 [−0.36, 0.46]	84%	0.01
Timmer 2007 (33)	−0.37 [−0.77, 0.03]	83%	0.02

Table S18 Sensitivity analysis for total sexual function-OR

Study omitted	OR (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	2.66 [1.87, 3.77]	30%	0.22
Ateş Bulut 2019 (25)	2.37 [1.55, 3.63]	64%	0.03
Marín 2013 (28)	1.92 [1.40, 2.65]	21%	0.28
Moody 1992 (29)	2.20 [1.40, 3.44]	64%	0.02
Rivière 2017 (31)	2.17 [1.37, 3.44]	63%	0.03
Timmer 2007 (33)	2.39 [1.45, 3.96]	64%	0.03

Table 19 Sensitivity analysis of total sexual function-scores

Study Omitted	Std. mean difference (95% CI) for remainders	Heterogeneity	
		I²	P
Bel 2015 (24)	−0.41 [−0.56, −0.25]	5.7%	0.35
Ateş Bulut 2019 (25)	−0.27 [−0.50, −0.04]	0%	0.76
Marín 2013 (28)	−0.29 [−0.59, 0.01]	68.6%	0.04
Timmer 2007 (33)	−0.35 [−0.71, −0.00]	47.6%	0.17