

## Female Sexual Dysfunction after Kidney Transplantation: A Meta-Analysis

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### Abstract

**Background:** In patients with end-stage renal disease (ESRD), sexual dysfunction (SD) is very common. There is some clear evidence that kidney transplantation improves female sexual dysfunction in end-stage renal disease. However, there are also some studies that suggest that sexual function deteriorates after kidney transplantation. So, we conducted a meta-analysis on the relationship between female sexual dysfunction and kidney transplantation.

**Methods:** A literature search was conducted on PubMed and Web of Science until November 30, 2022. Primary outcomes were FSD prevalence and each domain score of the Female Sexual Function Index (FSFI) questionnaire. We used two methods including compared before and after the kidney transplantation surgery and compared age-matched dialysis patients and after the kidney transplantation surgery.

**Results:** Finally, a total of 7 articles were finally enrolled in the study. The prevalence of sexual dysfunction in the kidney transplant group was lower than in the control group (OR 1.47, 95% CI: 1.05, 2.06) and the FSFI score of the kidney transplant group was higher than that of the control group (SMD -0.90, 95% CI: -1.35, -0.44). There was a significant difference in FSFI scores before and after transplantation (SMD -1.15, 95% CI: -1.66, -0.65) and the FSFI score of the kidney transplant group was significantly higher than that of the hemodialysis group (SMD -0.69, 95% CI: -1.36, -0.03). The scores of desire (SMD -1.15, 95% CI: -1.89, -0.41), arousal (SMD -0.92, 95% CI: -1.40, -0.43), lubrication (SMD -0.66, 95% CI: -1.02, -0.30), orgasm (SMD -0.65, 95% CI: -1.09, -0.21), satisfaction (SMD -0.80, 95% CI: -1.26, -0.35) and pain (SMD -0.77, 95% CI: -1.46, -0.09)

were higher than those in the control group. Follicle-stimulating hormone (SMD1.09, 95% CI:0.01, 2.18) and luteinizing hormone (SMD0.83, 95% CI: 0.25, 1.42) transplant hormone levels were lower than in the control group, while prolactin (SMD1.05, 95% CI:-0.34, 2.45) were not statistically significant.

**Conclusions:** Kidney transplantation may be associated with improved sexual function in patients with ESRD. This may be due to correction of endocrine hormone disorders in patients after kidney transplantation.

**Keywords:** Female sexual dysfunction (FSD); End-stage renal disease (ESRD); Kidney transplantation; Meta-analysis

## Introduction

Female sexual dysfunction is defined as: lack of sexual desire, difficulty in arousal, inability to achieve orgasm, pain during intercourse and failure to feel pleasure from sex [1-6], which may have an impact on physical and psychosocial health, as well as the Quality of Life (QoL) of patients and their partners [7]. FSD is a serious complication of end-stage renal disease that the problem has not been fully recognized in female with end-stage renal disease [8]. There are three treatments for end-stage renal disease: hemodialysis, peritoneal dialysis and kidney transplantation. All three treatments can cause sexual dysfunction [9]. In one study, it was shown that sexual dysfunction in women with end-stage renal disease was up to 92%, which is greater than the average for the population [10]. Kidney transplantation is generally considered to be the most effective treatment for end-stage renal disease. With the continuous development and maturity of technology, more and more patients receive kidney transplantation every year [11]. Some studies have shown that the symptoms of female sexual dysfunction improve after kidney transplantation [12], and some scholars believe that sexual function will worsen after kidney transplantation [13]. Therefore, the quality of life, psychological condition especially sexual function of kidney transplant recipients is increasingly concerned by doctors and recipients. Whether kidney transplantation improves female sexual dysfunction is controversial, so we conducted a meta-analysis of the available literature to assess the effect of kidney transplantation on sexual function.

## Methods

### Search strategy

The study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. Two authors (YUN JING, XUECHUN GUAN) independently searched relevant literature on PubMed and Web of Science, published before November 30, 2022. The retrieval strategy we used for PubMed is as follows: (renal transplantation OR kidney grafting OR kidney transplantation OR renal replacement therapy OR uremia OR end stage kidney disease OR chronic kidney failure OR chronic renal failure) AND (female sexual dysfunction OR sexual dysfunction OR female sexual pain disorder OR hypoactive

sexual desire disorder in women OR female sexual arousal disorder OR female sexual behavior disorder OR sexual behavior).

### Select criteria

**Inclusion criteria:** (1) the study evaluated the relationship between kidney transplantation and female sexual function; (2) the study is either prospective or cross-sectional; (3) sexual function is assessed by the Female Sexual Function Index; (4) control groups were patients before kidney transplantation or age-matched dialysis patients.

**Exclusion criteria:** (1) use unverified questionnaires; (2) studies with insufficient data; (3) the publication was in a language other than English; (4) full text was not available.

### Date extraction

The data from the included studies were extracted independently by the two authors (YUN JING and XUECHUN GUAN) using a standardized form. A third author (JUNPENG CHEN) would participate in the discussion to make a decision when the two authors disagreed. The data we extracted includes: first author, publication year, country, study design, sample size, and the major outcomes, like female sexual function index total score and subdomain gets divide and hormone levels. FSFI includes 19 questions covering 6 dimensions of FSD, including low desire disorder, arousal disorder, lubrication disorder, orgasmic disorder, satisfaction disorder, and pain disorder. The overall score is 36 points, and it is now commonly accepted that the total score below 26 is sexual dysfunction.

### Quality evaluation

We assessed the quality of the included cross-sectional studies using 11 scales recommended by the Agency for Healthcare Research and Quality (AHRQ). If the answer is “Not Clear” or “No”, the project will get "0"; Conversely, if you answer “Yes”, the item has a score of "1". Article quality is estimated as follows: a total score of 0-3 is low quality, 4-7 is medium quality, and 8-11 is high quality. The quality of the included prospective studies was also assessed using the 9-point Newcastle-Ottawa Scale (NOS) in three terms [13], including selection, comparability, and outcomes. A total score of 1-3 is low quality, 4-6 is medium quality and 7-9 is high quality.

### Statistical analysis

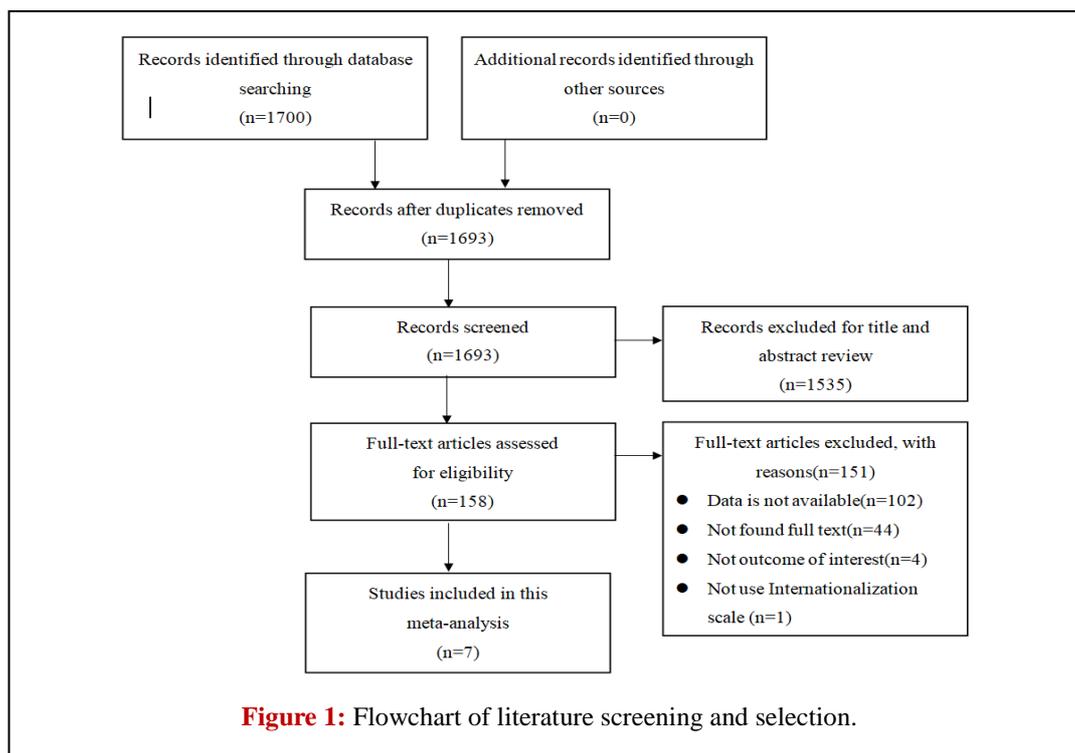
For the prevalence of female sexual dysfunction, we choose the Odds ratios (OR) as the effect size and calculated the 95% confidence interval (95% CI). For the FSFI scores and hormone levels, we used the Standard Mean Difference (SMD) as the effect size and calculated the 95% CI. Heterogeneity between these studies was tested by  $I^2$ . When the value of  $I^2$  was greater than 50%, we performed a subgroup analysis. We assessed publication bias using the Begg test and the Egger test, with significant publication bias when  $p < 0.05$ . To assess the robustness and reliability of the included findings, we performed sensitivity analysis. All data from

meta-analysis was provided by state software, MacBook Air version 17.0.

## Results

### Study characteristics

We searched for 1700 relevant articles, 7 of which were duplicates, and after heading and abstract reading, we excluded 1535 because they were not relevant. We read the remaining 158 in full text and excluded 151 for reasons of unavailability of data, failure to obtain full text, absence of outcome measures of interest, and non-use of internationalization scales. Ultimately, 7 studies with 738 participants from 5 countries were included in the meta-analysis (Figure 1). This is shown in Figure 1. Of these 7 studies, 3 were prospective studies that compared female sexual function before and after kidney transplantation in people with ESRD; 4 were cross-sectional studies comparing kidney transplant recipients with age-matched dialysis patients. Table 1 shows the basic characteristics of the seven included studies. 7 studies were assessed as of quality using AHRQ and NOS scales, 1 study was classified as moderate-quality, and the remaining 6 studies were of high quality. Detailed literature quality scores are shown in Table 2a and b.



**Table 1:** Characteristics of included studies.

Study	Country	Study design	Sample size	FED evaluation tool	Follow-up period (mo)
E. K. Basok (2009)	Turkey	Cross-sections study	20/106	FSFI	≥6
E.Kettaş (2010)	Turkey	Prospective study	21/26	FSFI	27.5 ±20.4
L. Yu (2013)	Guangzhou	Prospective study	42/42	FSFI	≥6
A. Altunoglu (2014)	Turkey	Cross-sections study	47/157	FSFI	≥6
I. M. Vranješ (2022)	Croatia	Cross-sections study	39/123	FSFI	Not mentioned
N. Yilmaz, (2018)	Turkey	Cross-sections study	62/192	FSFI	Not mentioned
M. Laguerre, N (2021)	France	Prospective study	26/92	FSFI	≥6

**Table 2a:** The Newcastle-Ottawa Scale scores for prospective studies.

Study	Selection					Outcomes			
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcomes of Interest was not	Comparability	Assessment of outcome	Follow-up long enough	Adequacy of follow-up	Total scores

				present at start of study					
E. Kettaş (2010)	1	1	1	1	2	0	1	1	8
L. Yu (2013)	1	1	1	1	2	0	1	1	8
M. Laguer re, N (2021)	1	1	1	1	2	0	1	1	8

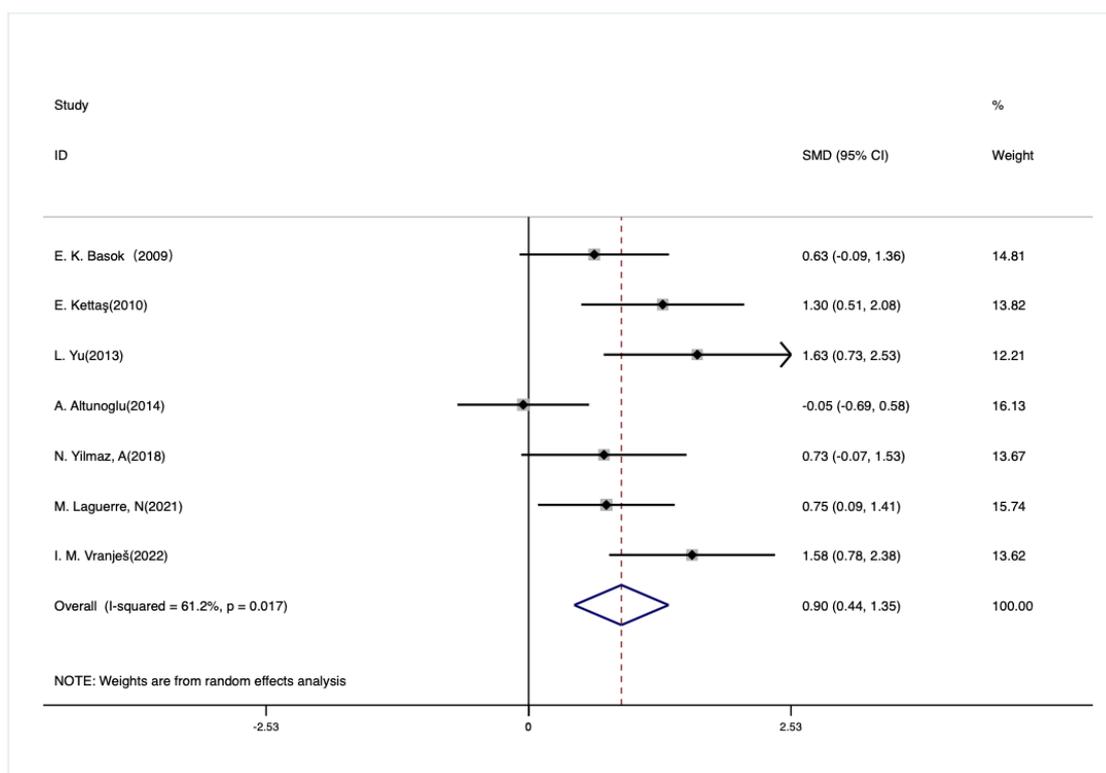
**Table 2b:** The Agency for Healthcare Research and Quality (AHRQ) for cross-sectional studies.

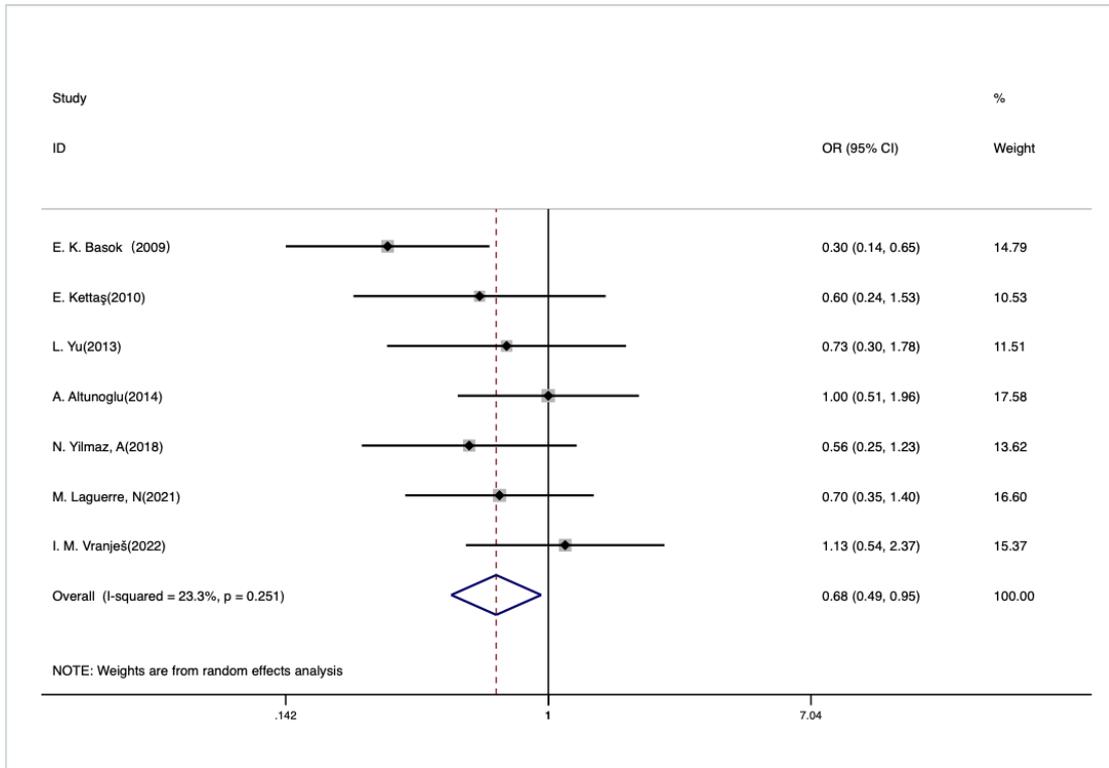
Item		Study		
	E. K. Basok (2009)	A. Altunoglu (2014)	I. M. Vranješ (2022)	N. Yilmaz, A (2018)
1) Define the source of information (survey, record review)	Yes	Yes	Yes	Yes
2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	Yes	Yes	Yes	No
3) Indicate time period used for identifying patients	Unclear	Unclear	Unclear	Unclear
4) Indicate whether or not subjects were consecutive if not population-based	Yes	Yes	Yes	Yes
5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	Unclear	Unclear	Unclear	Unclear
6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)	Yes	Yes	Yes	Yes
7) Explain any patient exclusions from analysis	Yes	Yes	Yes	Yes
8) Describe how confounding was assessed and/or controlled.	Yes	Yes	Yes	Yes
9) If applicable, explain how missing data were handled in the analysis	Yes	Yes	Yes	Yes
10) Summarize patient response rates and completeness of data collection	Yes	Yes	Yes	Yes
11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	Yes	Yes	Yes	Yes
Total scores	8	8	8	5

### **FSD prevalence and female sexual function domain score**

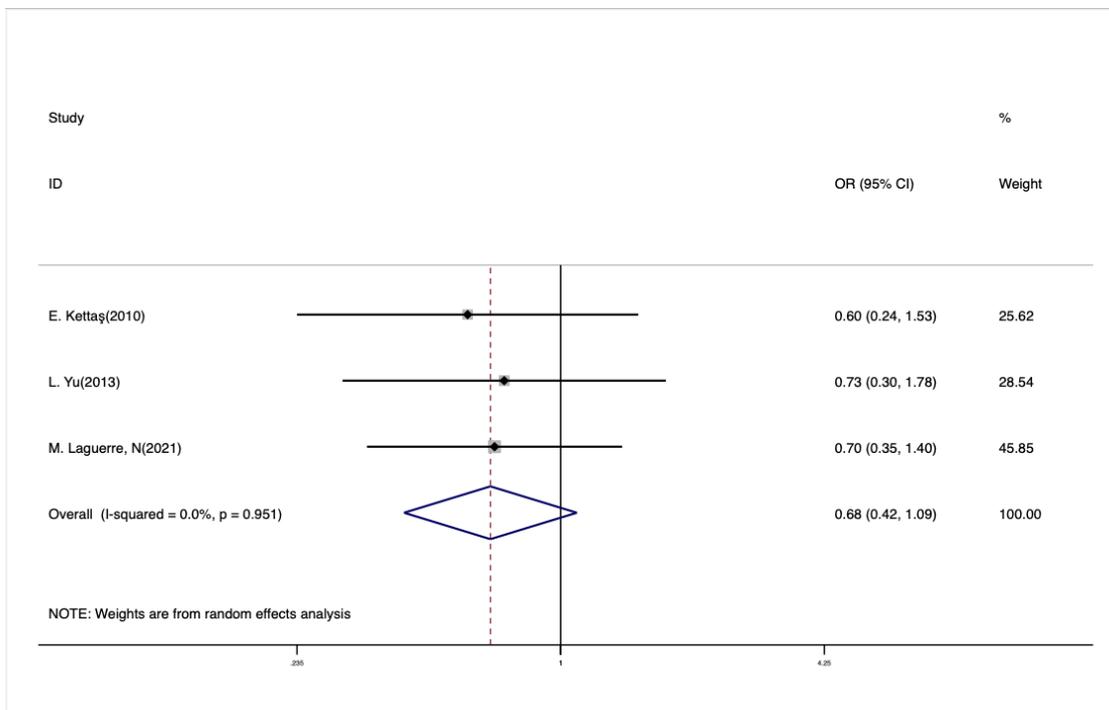
In this meta-analysis, we all assessed sexual function using the validated international scale, the Female Sexual Function Index<sup>[14]</sup>. As shown in **Figure 2a**, the prevalence of sexual dysfunction in the kidney transplant group was lower than in the control group (OR1.47, 95% CI: 1.05, 2.06), and, as shown in **Figure 2b**, the FSFI score of the kidney transplant group was significantly higher than that of the

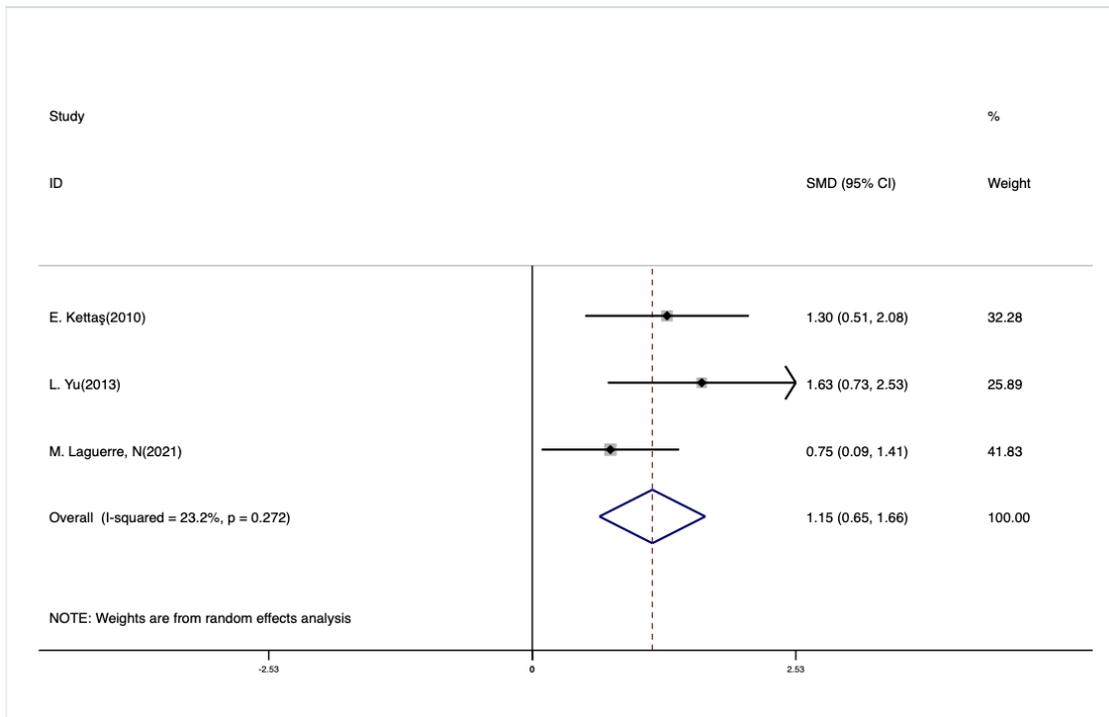
control group, which was statistically significant (SMD-0.90, 95% CI: -1.35, -0.44). In addition, we only performed subgroup analysis of studies in patients before and after kidney transplantation. As shown in **Figure 3a and 3b**, there was no significant difference in prevalence before and after transplantation (OR1.47, 95% CI: 0.92, 2.36), but there was a significant difference in FSFI scores before and after transplantation and FSFI score (SMD-1.15, 95% CI: -1.66, -0.65). Afterwards we also compared 4 cross-sectionsstudy of age-matched dialysis patients. As shown in Figures 3c and 3d, there was no significant difference in prevalence between kidney transplantation and age-matched dialysis patients (OR1.49, 95% CI: 0.82, 2.70), but FSFI scores did (SMD-0.69, 95% CI: -1.36, -0.03).



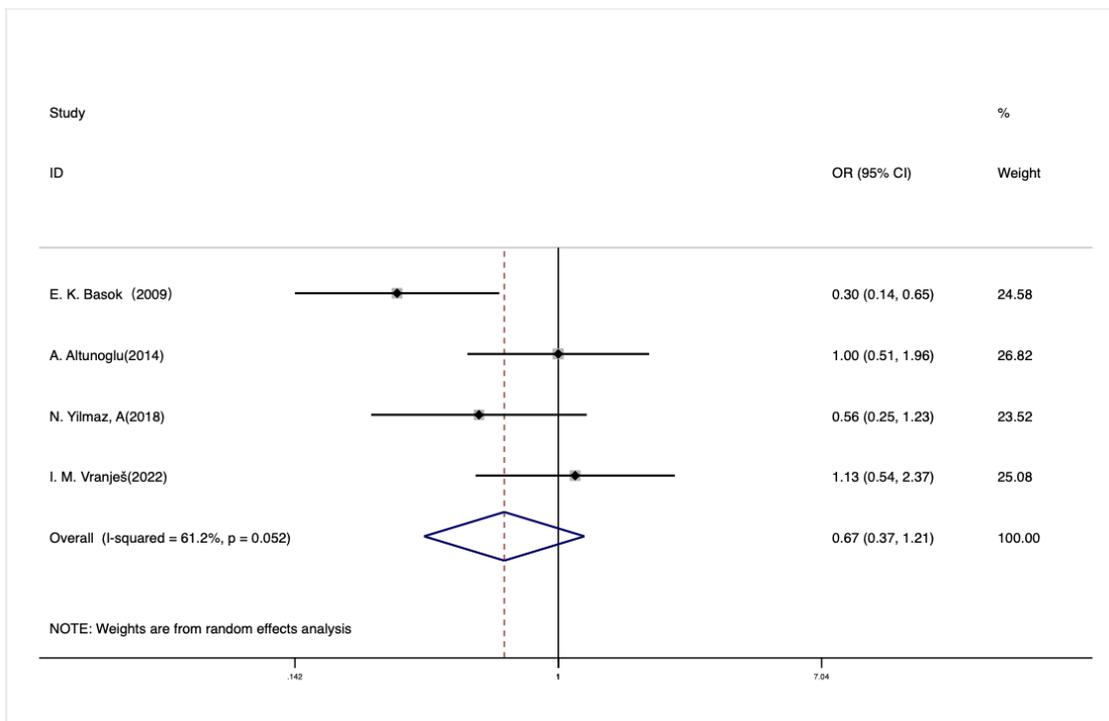


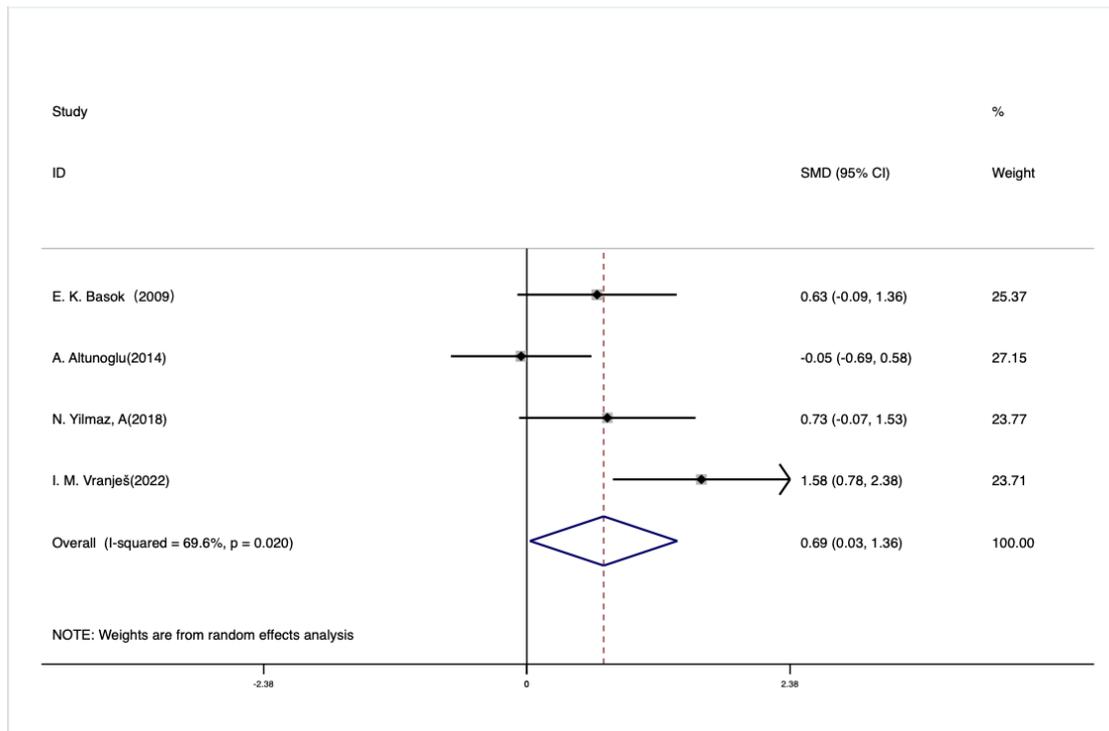
**Figure 2:** Forest plot of FSD prevalence (2a), and FSFI domain score (2b).





**Figure 3:** Forest plot of FSD prevalence (3a), and FSFI domain score (3b) performed on the 3 studies comparing pre- and post-transplanted patients only.

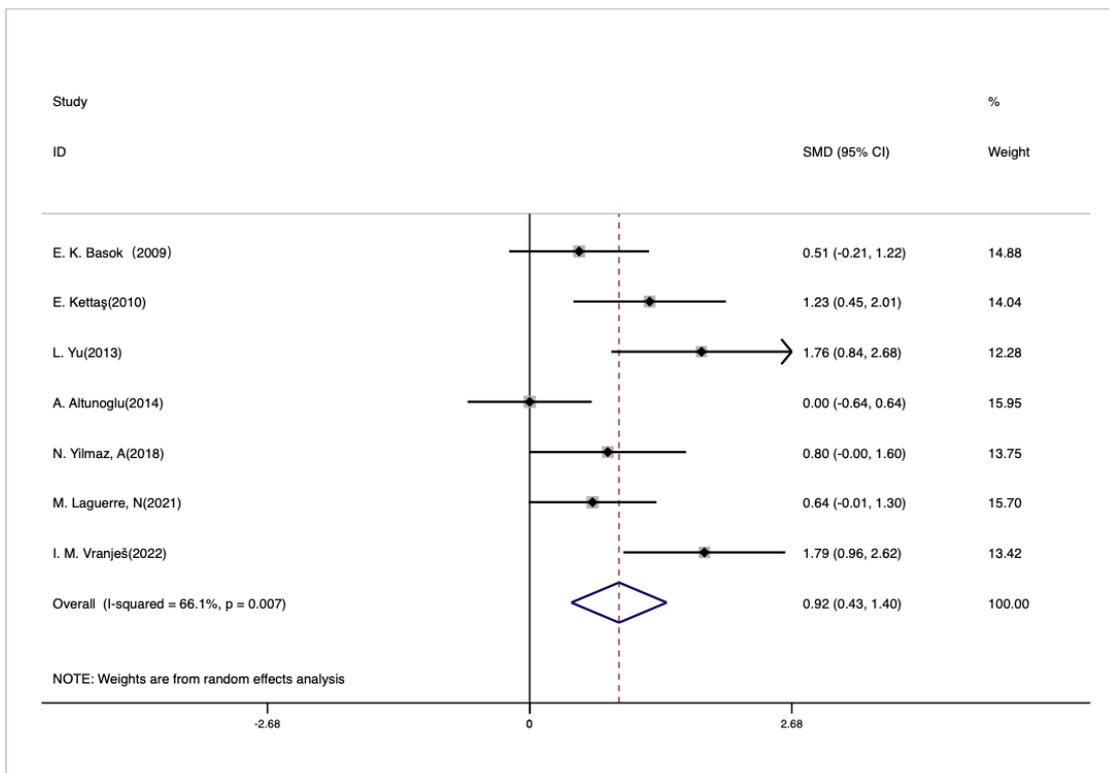
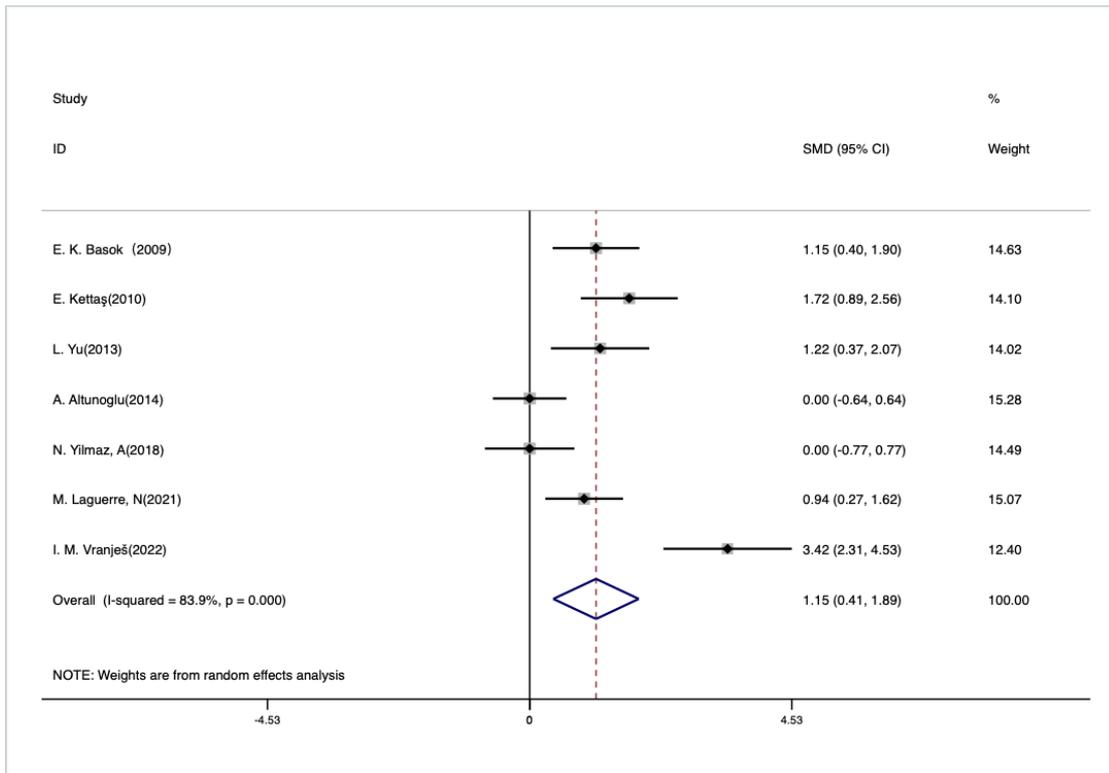


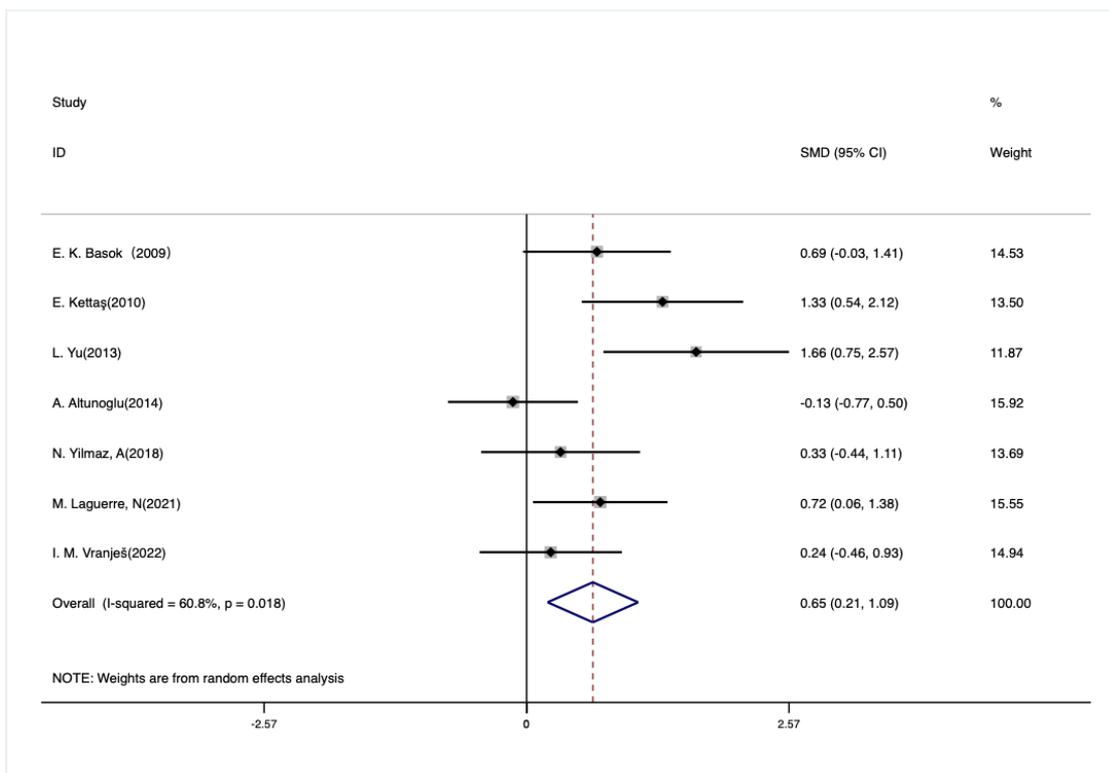
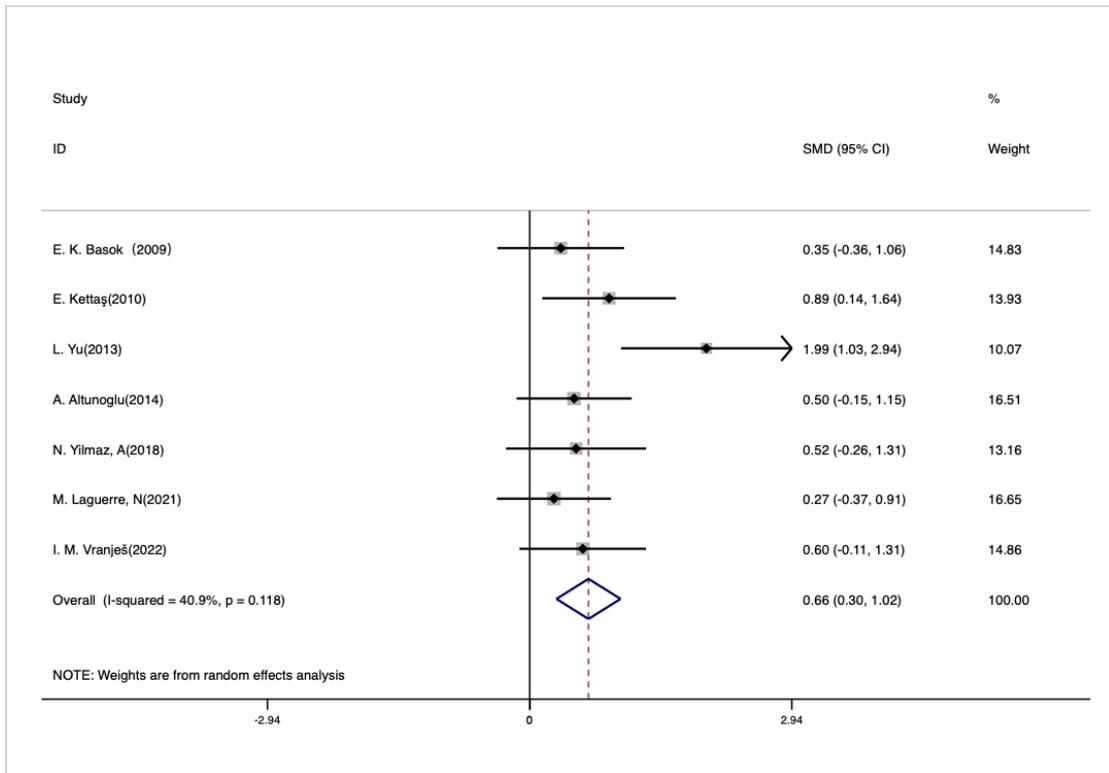


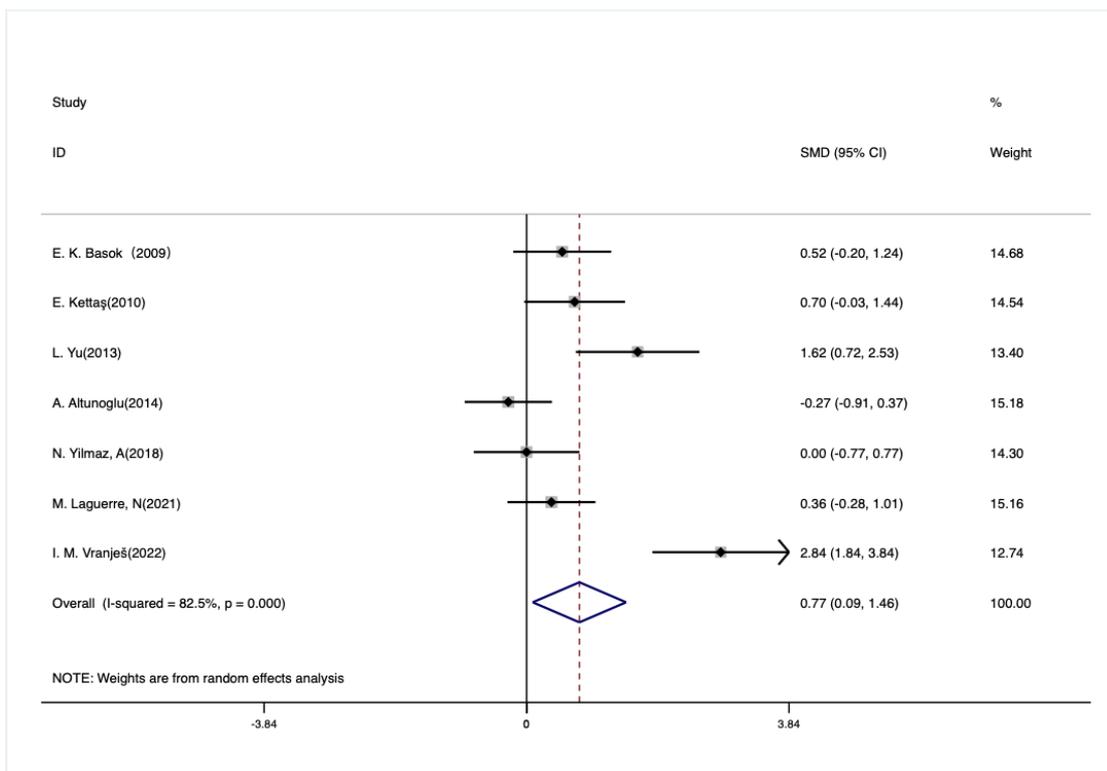
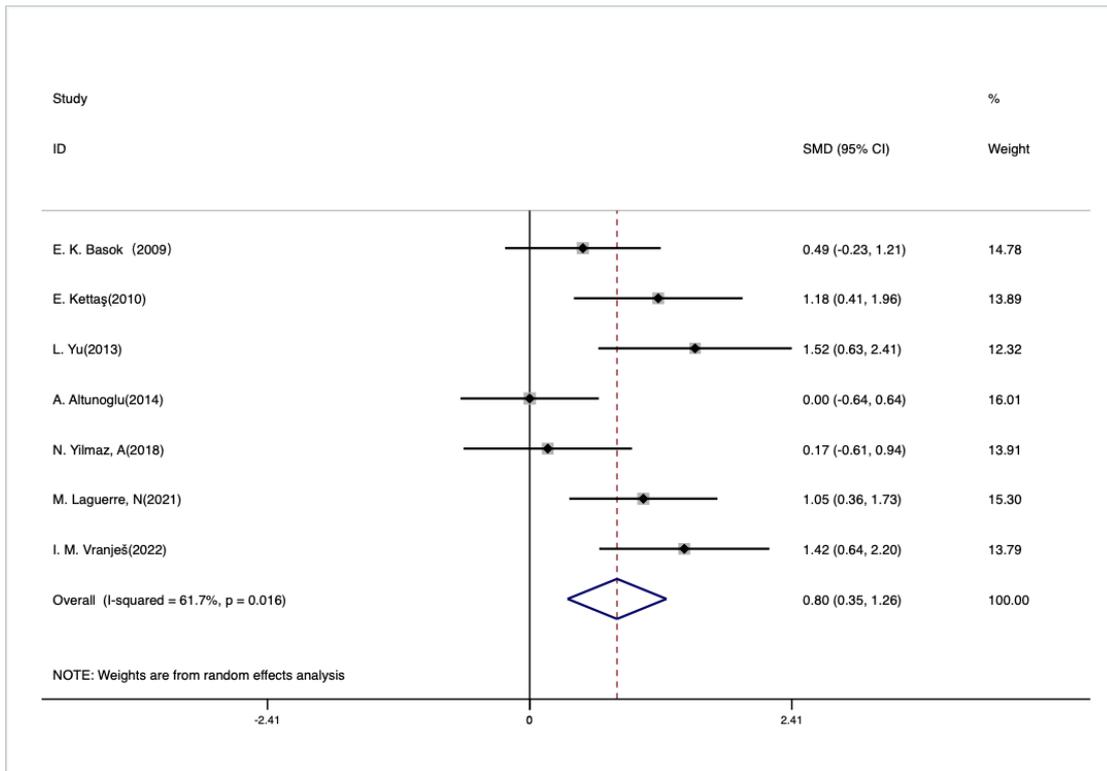
**Figure 3:** Forest plot of FSD prevalence (3c), and FSFI domain score (3d) performed on the 4 studies age-matched dialysis patients and post-transplanted patients.

### The other domain scores of FSFI

The FSFI scale was divided into 6 domains, and we conducted meta-analysis for each of the six domains to understand the effect of kidney transplantation on all aspects of sexual function. As shown in **Figure 4a** (SMD-1.15, 95% CI: -1.89, -0.41), 4b SMD-0.92, 95% CI: -1.40, -0.43), 4c (SMD-0.66, 95% CI: -1.02, -0.30), 4d (SMD-0.65, 95% CI: -1.09, -0.21), 4e (SMD-0.80, 95% CI: -1.26, -0.35), 4f (SMD-0.77, 95% CI: -1.46, -0.09), the scores of desire, arousal, lubrication, orgasm, satisfaction and pain were higher than those in the control group. Among them, there are significant differences in the field of arousal and lubrication.





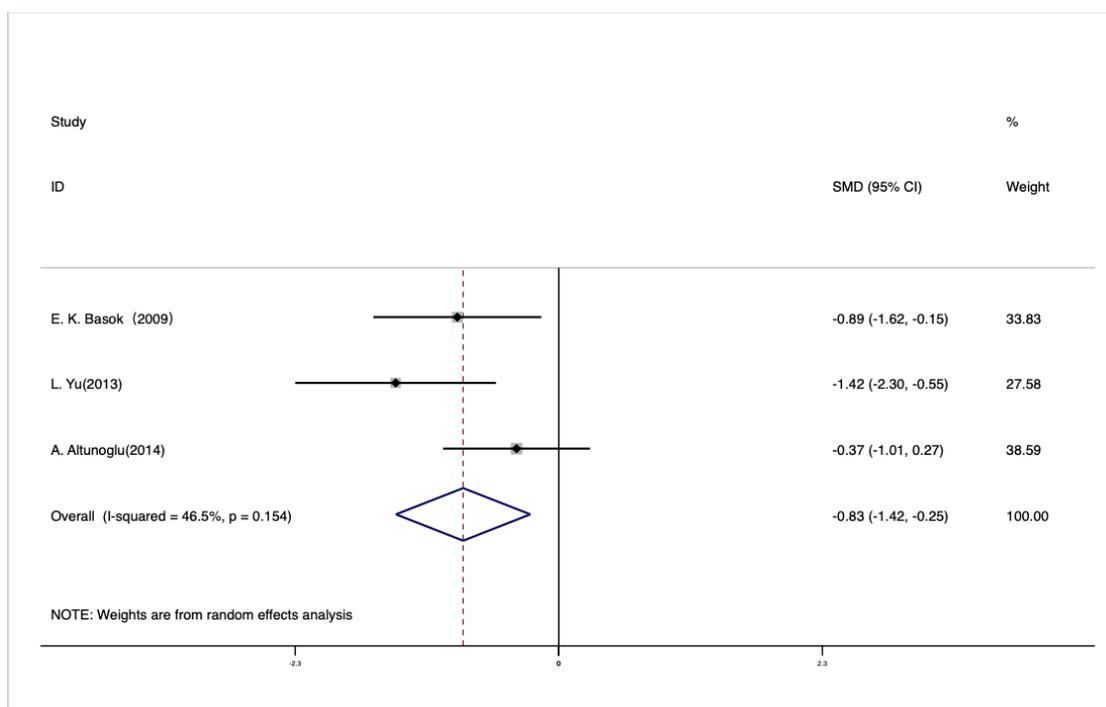
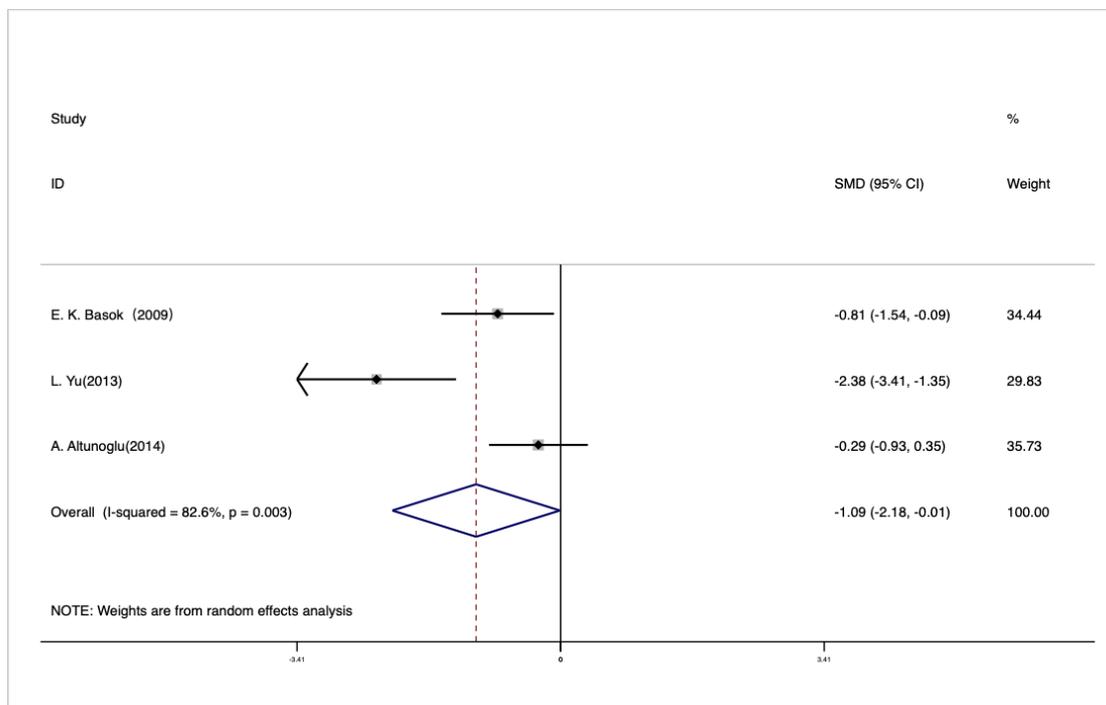


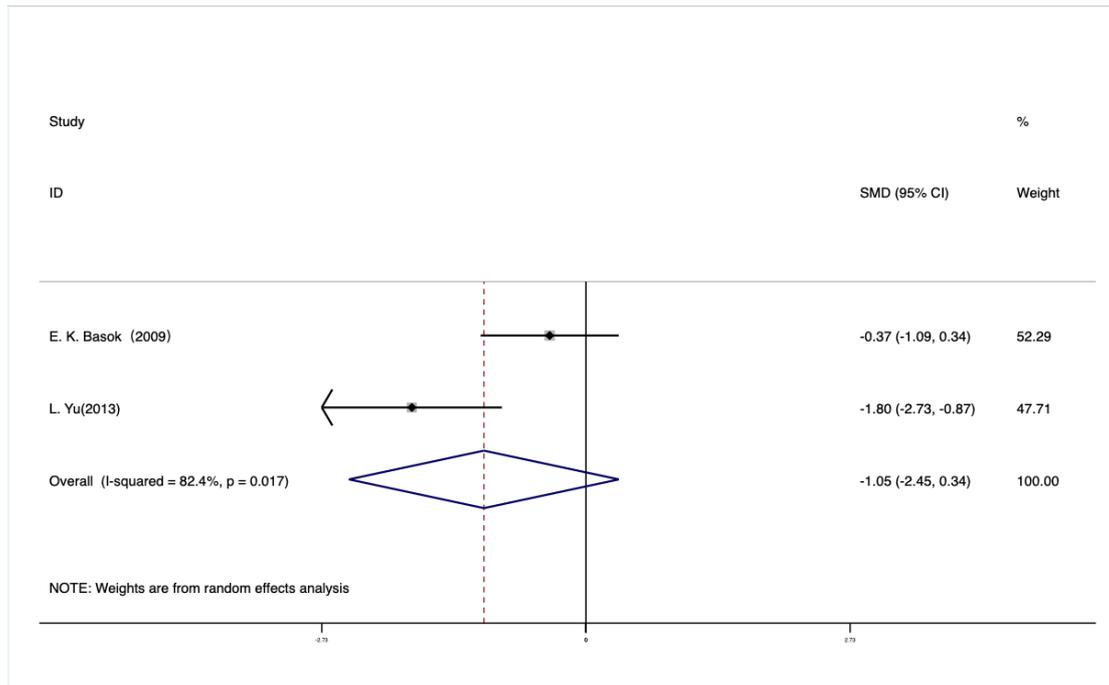
**Figure 4:** Forest plot of Desire (4a), Arousal (4b), Lubrication (4c), Orgasm (4d), Satisfaction (4e) and Pain (4f).

### Endocrine hormone levels

Of the 7 included studies, 3 reported Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH), and 2 reported prolactin (PRL). As shown in **Figure 5a and b**, follicle-stimulating hormone

(SMD1.09, 95% CI: 0.01, 2.18) and luteinizing hormone (SMD0.83, 95% CI: 0.25, 1.42) transplant hormone levels were lower than in the control group, while prolactin (SMD1.05, 95% CI: -0.34, 2.45) were not statistically significant, as shown in **Figure 5c**.

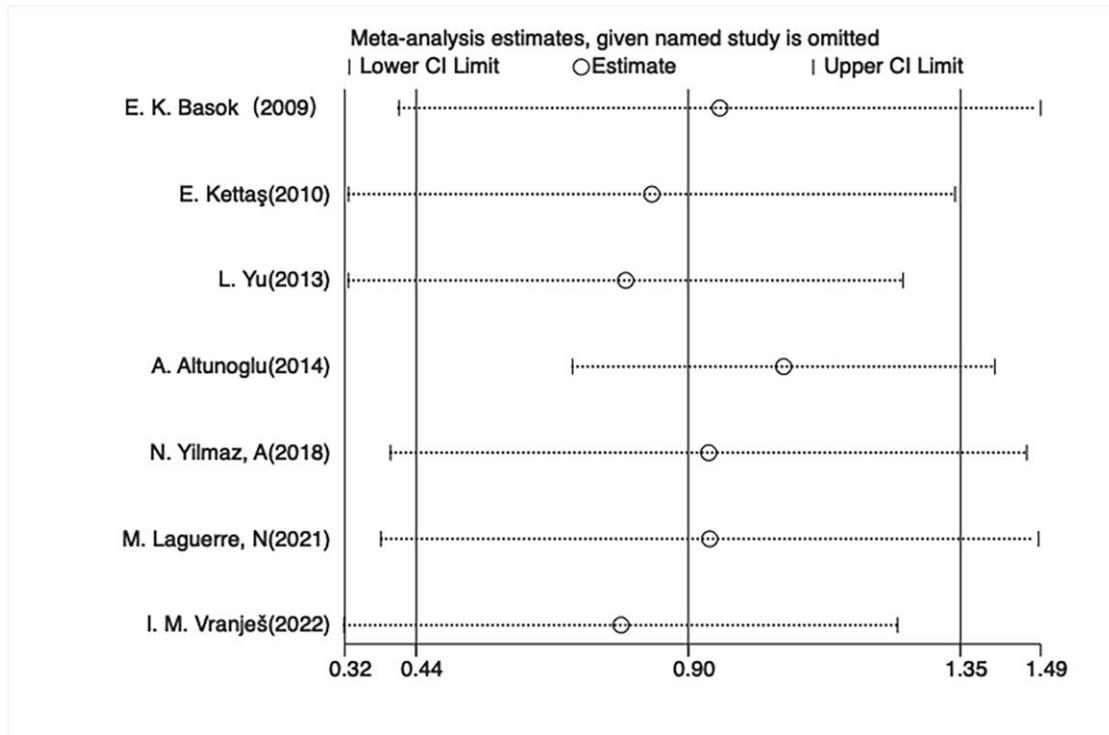




**Figure 5:** Forest plot of endocrine hormone levels: FSH (5a) LH (5b) PRL (5c).

### Sensitivity analysis

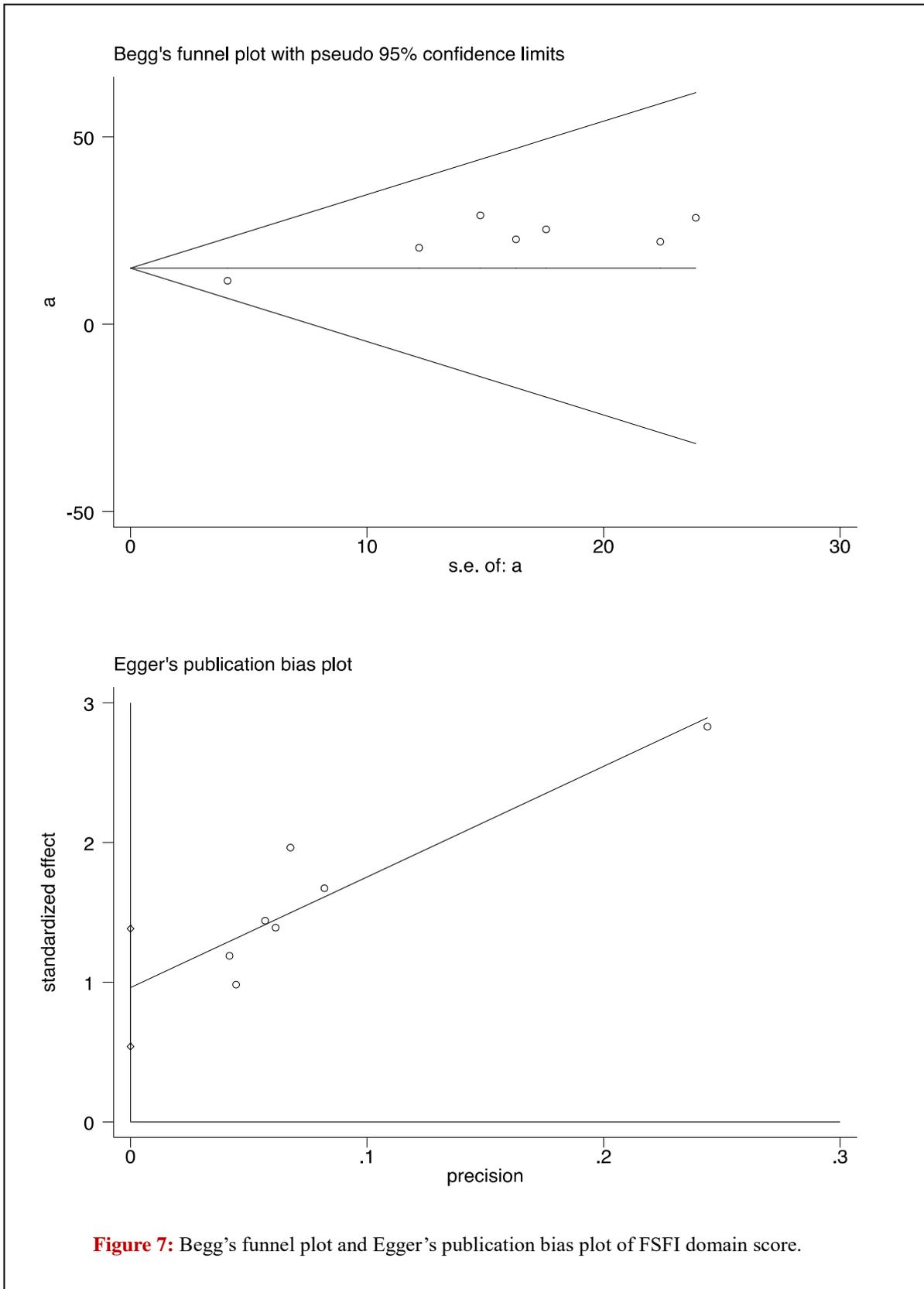
To determine the impact of a single study on the pooled results, we ran a sensitivity analysis by deleting each enrolled single study one at a time. **Figure 6** illustrates how trustworthy our findings were and how no single study significantly changed the pooled SMD comparison of the Female Sexual Function Index domain score.



**Figure 6:** Sensitivity analysis of FSFI domain score.

### Publication bias

Begg's and Egger's tests were used to assess the meta-analysis's publication bias. **Figure 7** shows that there was no obvious publication bias in the Female Sexual Function Index domain score, with a P value of 0.548.



**Figure 7:** Begg's funnel plot and Egger's publication bias plot of FSFI domain score.

## Discussion

This review included 7 studies involving a total of 257 women who underwent kidney transplantation to investigate the effects of kidney transplantation on sexual dysfunction. Sexual dysfunction is a common issue in patients with end-stage renal disease [15]. In a meta-analysis analysis [16], the prevalence of sexual dysfunction in women with all end-stage renal disease was 74%, with sexual dysfunction occurring in 63% in kidney transplant recipients, 80% in hemodialysis patients, and 67% in peritoneal dialysis patients. In end-stage renal disease, sexual dysfunction may be associated with age, high blood pressure, antihypertensive drugs, hormone levels and psychological factors [6,17,18]. Studies have also shown that sexual function is related to biochemistry and neuropathy in patients with end-stage renal disease [19]. Women with end-stage renal disease experience hormonal decline, dysmenorrhea, and ovarian dysfunction, which can lead to infertility [20]. Women's sexual dysfunctions have gotten comparatively little attention and are frequently not adequately addressed. This should be of great concern to us [21]. The prospective study [22] suggests that while dialysis treatment can relieve most symptoms of end-stage renal disease, sexual dysfunction does not. So, the majority of patients with end-stage renal disease now choose kidney transplantation as their preferred CRRT [23-25]. In the United States, about 440,000 people have received kidney transplants since 1960 [26]. Questions about sexual function are now particularly important as part of the health-related quality of life in women with kidney transplantation [2,18,27]. After kidney transplantation, sexual dysfunction improves, providing women of childbearing age with the possibility of a successful pregnancy, but preterm birth and intrauterine growth retardation are common, so this requires us to explore a larger sample size of pregnant women with kidney transplantation [28]. In one age-matching analysis, FSFI scores increased significantly after kidney transplantation [29]. In a prospective study, 15 of the 19 sexually active patients before transplantation were diagnosed with female sexual dysfunction compared with 11 of the 36 sexually active patients after transplantation, a statistically significant difference ( $P < 0.005$ ) [30]. In another prospective study of 21 sexually active women, 20 (95.2%) women had sexual dysfunction prior to kidney transplantation. After kidney transplantation, 8 cases had normal sexual function, and 12 cases still had sexual dysfunction [31]. Some scholars have shown that after undergoing kidney transplantation, their sexual function deteriorates their desire for sexual activity, and the frequency of sexual activity decreases significantly lower than before kidney transplantation [3]. However, because this study did not use internationalized scales, it was not included, and the authors themselves consider that it may be related to comorbid diseases and some drugs. Although a successful kidney transplant may improve sexual function, in many women, some

degree of sexual dysfunction may persist. Whether kidney transplantation improves female sexual function in patients with end-stage renal disease remains controversial and we need a larger sample size for further validation. In a prospective study by E. Kettaş [31] of showed that over a 5-year period, 21 sexually active women underwent kidney transplantation and FSFI scores, and the mean total sexual function score increased from  $17.57 \pm 7.07$  to  $25.3 \pm 3.28$ , showing a significant difference ( $P = 0.001$ ), suggesting that successful kidney transplantation may improve sexual function. In a cross-sectional study, the FSFI score in the hemodialysis group was significantly lower than ( $p < 0.05$ ) in the kidney transplant group and the control group, and this preliminary study suggests that successful kidney transplantation may positively affect female sexual function [32]. In a prospective study that assessed the prevalence of female sexual dysfunction based on FSFI cut-off points, sex hormone status, and menstrual status during dialysis and 12 months after kidney transplantation, 16 out of 39 patients (41%) admitted to having an active sex life during dialysis. 34 of the 39 transplant patients (88%) admitted to having an active sex life (Fischer precise test  $P = 0.000039$ ). Hormone levels and FSFI outcomes improved significantly after transplantation [2]. In a cross-sectional study [33], the sexual function of 72 transplanted and 40 hemodialysis patients was compared. Sexual relationship, sexual function, sexual frequency, and sexual fear are significantly better in kidney transplant patients than in HD patients. Sexual intercourse satisfaction appeared to be greater in kidney recipients than in HD patients. In another cross-sectional study [32], patients in the hemodialysis group had significantly lower FSFI scores than those in the kidney transplant group and the control group, with a statistically significant difference. These studies were consistent with the results of our meta-analysis. The Female Sexual Function Index (FSFI), as confirmed by the study, has been considered the gold standard for measuring female sexual function for the past 20 years, with over 1,000 published manuscripts citing the article [14,34,35]. Patients with end-stage renal disease often receive dialysis before receiving kidney transplantation, resulting in low sexual function [36]. In this prospective study, areas of sexual function included desire ( $P = 0.001$ ), arousal ( $P = 0.001$ ), lubrication ( $P = 0.003$ ), orgasm ( $P = 0.001$ ), Satisfaction ( $P = 0.001$ ) and pain ( $P = 0.02$ ) improved significantly after kidney transplantation [31]. In a prospective study, patients in the hemodialysis group scored significantly lower on each FSFI variable and overall score compared to patients in the kidney transplant group ( $P < 0.01$ ) [1]. This is consistent with the results of our meta-analysis that the scores of desire, arousal, lubrication, orgasm, satisfaction and pain were higher than those in the control group. Women with end-stage renal disease face changes in hormone levels in addition to sexual dysfunction [28]. Studies have shown that estrogen has a protective effect on the kidneys and is particularly important in calcium and phosphorus metabolism, so decreased estrogen and abnormalities of the hypothalamic pituitary gonadal axis also

affect kidney and sexual function [37,38]. Some studies say that during dialysis, FSH and PRL levels will increase, and E<sup>2</sup> levels will decrease. But, the levels of sex hormones in patients after successful kidney transplantation will improve, including significantly lower PRL, FSH, and LH than before kidney transplantation, E<sup>2</sup> and P were elevated compared with preoperative [30]. One study of hormone levels receiving different renal replacement therapy said Dehydroepiandrosterone Sulfate (DHEAS) (P<0.01), prolactin (P<0.01), and free testosterone (P<0.01) were all significantly different between the RT and HD and CAPD groups [39]. A study of changes in hormone levels in young women after successful kidney transplantation showed a significant reduction in serum concentrations of FSH and LH after successful kidney transplantation. This is consistent with the results of our meta-analysis. In multiple comparative analyses, the reduction in serum PRL concentration after kidney transplantation did not reach statistical significance, and renal transplantation was observed in healthy controls with no significant effect on serum estradiol concentration [40]. Several of the studies we included reported hormonal changes. Our meta-analysis showed a significant difference in FSH and LH between the kidney transplant group and the control group, while PRL was not statistically significant. However, in a study with a transplant cycle of 1~5 years, 72.7% of women also observed a regular menstrual cycle, and similar serum FSH, LH and PRL concentrations and estrogen levels were observed in kidney transplant recipients compared with healthy non-recipients. Increased estrogen levels put this group of patients at risk for gynecologic lesions [41]. Researchers have increasingly suggested that sexual dysfunction in ESRD has an endocrinological foundation, and that kidney transplantation can enhance sexual function by addressing the anomalies of the hypothalamus-pituitary-gonadal axis [42]. Therefore, we still need studies with large samples and long follow-up periods to prove whether sexual function will improve, and hormone levels can return to normal after kidney transplantation.

### **Limitations**

Although we have searched databases as much and comprehensively as possible and obtained relatively optimistic results, our study had some limitations. The reasons for the heterogeneity we observed in the outcomes were complex, possibly due to the observational studies we included, which caused bias and uncertainty about the duration of dialysis patients and the duration of follow-up for kidney transplant patients. Although we have performed subgroup analysis and sensitivity analysis to explore potential causes of observed heterogeneity. However, it is undeniable that the sample size is too small, and the data are limited to perform all subgroup analysis. In conclusion, we need larger sample sizes for further prospective studies.

## Conclusion

The results of our meta-analysis showed that patients in the kidney transplant group a lower prevalence and a higher FSFI score than those in the control group, and patients received higher FSFI scores after kidney transplantation than before kidney transplantation. Also, patients in the kidney transplant group had higher FSFI scores than patients with hemodialysis group, indicating better sexual function. Whether hormone levels can return to normal after kidney transplantation needs to be further verified by prospective studies with larger sample sizes.

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