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Peer Review File

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Reviewer A

Erectile dysfunction is a significant

This manuscript, entitled “Erectile Function after Kidney Transplantation: A Systematic Review and Meta-analysis,” attempts to clarify the relationship between transplantation and ED. The study addresses an important question, and the use of a meta-analysis in this context adds value. I remain concerned about several key points prior to publication:

Reply: Thank you for your positive comments. We feel inspired by your affirmation of this article. By following your comments and suggestions, we have listed our response and corrections to the comments below.

Major comments

*** I am confused by the odds ratios reported in this study. Why are these centered around 0 as opposed to the traditional OR which is centered around 1? Is this a log scale?**

*Reply: Thank you for your advice. After we carefully checked the manuscript, we found we made a writing mistake in the manuscript that SMD was written as OR. In this study, SMD was used as the effect size for continuous variables (IIEF domain scores and endocrine hormone levels), and OR was used as the effect size to evaluate the prevalence of erectile dysfunction. We have revised the mapping errors in the abstract and text. (see Page 2, line11, marked in red: **Compared with the control group, the kidney transplantation group had a lower prevalence of ED (OR 0.49, 95% CI: 0.28-0.86) and higher domain scores for erectile function (SMD 0.53, 95% CI: 0.12-0.94) and sexual desire (SMD 1.19, 95% CI: 0.11-2.27). While there were no significant variations in domain scores for orgasmic function (SMD 0.27, 95% CI: -0.10-0.63), intercourse satisfaction (SMD 0.26, 95% CI: -0.10-0.61), and overall satisfaction (SMD 0.17, 95% CI: -0.21-0.56). Patients in the kidney transplantation group had lower serum testosterone (SMD 1.20, 95% CI: 0.86-1.54) and higher prolactin (SMD -1.46, 95% CI: -2.22--0.69) and luteinizing hormone (SMD -0.97, 95% CI: -1.39--0.55).**)*

*** The three studies comparing age-matched dialysis patients to transplanted patients introduce the potential for bias into this study. Many of the non-transplanted patients likely desired a transplant but were unable to qualify due to comorbidities, which also predispose to ED. I could strongly recommend performing a sub-analysis on the studies with pre- and post-transplanted patients only to validate these results**

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Reply: Thank you for this comment very much. In this study, we included three articles comparing age-matched dialysis patients to kidney transplanted patients^[1-3]. As all three studies were age-matched, this significant difference in ED prevalence among patients could not be attributed to age. Except that, Al Khallaf et al also requested that the enrolled patients be non-diabetic and have an active sexual life^[1]; Park et al requested that the present comorbidities and causes of CKD did not differ significantly between the two groups^[2]; Yavuz et al selected patients without atherosclerosis, diabetes, hypertension, dyslipidemia, or smoking habits who were nearer in age to compare better the two groups^[3]. We considered that the three cross-sectional studies have controlled variables as much as possible and have been published successfully, so the conclusions were reliable. In addition, other reviews also cited these documents to discuss the impact of kidney transplantation on erectile dysfunction^[4].

According to your suggestion, we performed a sub-analysis on the studies with pre- and post-transplanted patients only, as shown in Figure 3. (see Page 9, line 1, marked in red: *To decrease the potential bias introduced by the three studies comparing age-matched dialysis patients to transplanted patients, we performed a sub-analysis on the studies with pre- and post- transplanted patients only. As shown in Figure 3, the prevalence of ED was lower in the pre-transplantation group than in the post-transplantation group (OR 0.45, 95% CI: 0.21-0.98). While no significant difference in the EF domain score was found between pre-transplantation and post-transplantation patients (SMD 0.53, 95% CI: -0.03-1.08).*)

We found that the improvement of erectile function was not significant in a sub-analysis on the studies with pre- and post- transplanted patients, and we analyzed the reasons in the discussion section. (see Page 14, line 3, marked in red: *In addition, we found that the improvement of erectile function was not significant in a sub-analysis on the studies with pre- and post- transplanted patients. In the studies we included, most of the prospective studies were followed up for only 6 months, which may lead to no meaningful benefits detected after kidney transplantation. Even so, it is worth taking note that a large percentage of kidney transplant patients still have not improved their erectile function. This may be related to age, use of immunosuppressants, and other comorbidities(35).*)

Finally, I would like to comment that this study might have raised as many questions as it has answered. Readers should not find that disappointing, as asking the right questions is as important as answering the already asked ones.

[1] Al Khallaf HH. Analysis of sexual functions in male nondiabetic hemodialysis patients and renal transplant recipients. *Transplant international : official journal of the European Society for Organ Transplantation*. 2010;23:176-81.

[2] Park MG, Koo HS, Lee B. Characteristics of testosterone deficiency syndrome in men with chronic kidney disease and male renal transplant recipients: a cross-sectional study. *Transplantation proceedings*. 2013;45:2970-4.

[3] Yavuz D, Acar FN, Yavuz R, Canoz MB, Altunoglu A, Sezer S, et al. Male sexual function in patients receiving different types of renal replacement therapy. *Transplantation proceedings*. 2013;45:3494-7.

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[4] Pertuz W, Castaneda DA, Rincon O, Lozano E. Sexual dysfunction in patients with chronic renal disease: does it improve with renal transplantation? *Transplantation proceedings*. 2014;46:3021-6.

*** The figures uniformly should be improved with larger easier-to-read text and better labeling.**

Reply: Thank you for your positive comments. We are so sorry for the mistake in the performance of figures, which caused inconvenience for the reviewers. By following your comment, we recreated the forest plots using Stata software, increased the size of the text in the pictures, and modified them with Photoshop and Adobe illustrator software to make them meet the requirements of the journal. Besides, we have attached better labels to the pictures at the end of the reference section (see Page 23, line 1-10), and combined pictures more reasonably according to the order in the text. Thank you for your valuable comments.

*** Manuscript would benefit from copy-editing to minimize the numerous grammatical errors**

Reply: Thank you for your advice. I am so sorry for the error in this regard. As you suggested, we have checked the manuscript from beginning to end and corrected the grammatical errors by using the Grammarly plugin. Further, we revised the manuscript by an assisting language checker (WhiteSmoke software) to improve its readability. Finally, we invited a native English-speaking expert in our field to check and revise the manuscript again. (Changes in the manuscript were marked in a red color.)

Minor comments

*** Please number entire manuscript sequentially as opposed to numbering each page separately**

Reply: Thank you for your advice. According to your suggestion, we have re-edited the page number and line number of the manuscript, to facilitate your review.

*** The initial abstract background is misleading - while there have been no reports specifically examining transplant patients alone, the Cochrane review from 2010 by Vecchio et al includes a subset of transplanted patients. I would soften this assertion.**

Reply: Thank you for your positive comments. Based on your opinion, I searched the literature again and found the review you provided. Although Vecchio's study^[1] focused on the efficacy and safety of treatment options for erectile function in chronic kidney disease (CKD) patients, they included a subset of transplanted patients, as you pointed out. So we agree with your suggestion and have deleted this misleading sentence. (see Page 2, line 4, we have deleted the misleading sentence "No review has synthesized the available data.")

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[1] Vecchio M, Navaneethan SD, Johnson DW, Lucisano G, Graziano G, Saglimbene V, et al. Interventions for treating sexual dysfunction in patients with chronic kidney disease. The Cochrane database of systematic reviews. 2010;Cd007747.

*** The systematic review portion of this manuscript is somewhat lacking - I would consider removing this from the title**

Reply: Thank you for your advice. As you suggested, in the revised manuscript, we have changed the title to 'Erectile function after kidney transplantation: a meta-analysis' (the former title was 'Erectile function after kidney transplantation: a systematic review and meta-analysis'). And we now think it is more appropriate for the manuscript. (see Page 1, line 2, we delete “systematic review” from the title)

*** Page 3, line 11 - clarify that “before May 31, 2019” means “published before may 31, 2019”**

*Reply: Thank you very much for your careful review. As you suggested, we have added “published” before this sentence in the revised manuscript. (see Page 5, line 5, marked in red: **published** before May 31, 2019.)*

*** Page 4, line 17 - insufficient is spelled incorrectly**

*Reply: Thank you very much for your careful review. We are very sorry for the spelling error. We have made a correction based on your comment (see Page 6, line 8, marked in red: Studies with **insufficient** data were excluded.). In order to prevent other spelling errors, we used the Grammarly plugin to check and correct the full text. (Changes in the manuscript were marked in red color.)*

*** Given the significant difference in raw scoring, how were the IIEF-5 and IIEF-15 scores combined?**

Reply: Thank you for your advice. In our meta-analysis, we combined IIEF-5 and IIEF-EF to calculate EF domain scores, to quantitatively reflect the erectile function of patients after kidney transplantation. As a simplified version of IIEF-15, IIEF-5 shares the five same questions with IIEF-15^[1]. Besides, we chose the standard mean difference (SMD) as the effect size to decrease the difference caused by raw scoring. Similarly, Lu et al^[2] combined the two scales in the meta-analysis of evaluating the efficacy of low-intensity extracorporeal shock wave treatment for ED. To make the manuscript more complete, we did a subgroup analysis based on different tools, and found that the improvement of erectile function in the kidney transplantation group was more significant when IIEF-5 was used.

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[1] Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *International journal of impotence research*. 1999;11:319-26.

[2] Lu Z, Lin G, Reed-Maldonado A, Wang C, Lee YC, Lue TF. Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis. *European urology*. 2017;71:223-33.

*** Page 6, line 12 - what are non-interesting outcomes? 8/20 (40%) of the available manuscripts were not included for this reason - this should be more specifically explained.**

*Reply: Thank you for your advice. In this study, the main outcomes we are interested in are ED prevalence, IIEF domain scores (including IIEF-EF, IIEF-SD, IIEF-OF, IIEF-IS, and IIEF-OS). All studies that did not include the above outcomes were excluded by a reason of "non-interesting outcome". We explained this issue specifically in the revised manuscript. (see Page 8, line 3, marked in red: **In this study, the main outcomes we were interested in were ED prevalence, IIEF domain scores (including EF, SD, OF, IS, and OS). 8 articles that did not include the above outcomes were excluded by a reason of non-interesting outcome.**)*

*** Consider adding the specific NOS/AHRQ scores for each included manuscript in a supplemental table**

*Reply: Thank you for your advice. As you suggested, in the revised manuscript, we added the specific NOS/AHRQ scores for each included manuscript in supplemental tables 1 and 2. (see Page 8, line 14, marked in red: **The detailed quality scores of each literature were provided in Supplementary Tables 1 and 2.**)*

*** Why are there only 2 studies listed as “cross-sectional” in table 1, when the text refers to 3 studies comparing erectile function in kidney transplant recipients versus age-matched dialysis patients? This type of study by definition is cross-sectional.**

*Reply: Thank you for your advice. After carefully reading the original texts, we considered the 3 studies comparing erectile function in kidney transplant recipients versus age-matched dialysis patients as a cross-sectional study. Based on your suggestion, we made changes in Table 1 and re-scored according to the AHRQ scale. (see Table 1, and Page 8, line 10, marked in red: **The remaining three are cross-sectional studies comparing kidney transplant recipients to age-matched dialysis patients.**)*

*** The heterogeneity between these studies is quite significant (I^2 more than 0.75). Aside from the differences in race and IIEF-5 vs IIEF-15 (which are discussed), can the authors speculate on more physiologic reasons? Perhaps differences in the transplanted cohort in different parts**

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of the world?

Reply: Thank you for your positive comments. In this meta-analysis, we conducted a subgroup analysis based on limited data, to try to find the source of heterogeneity. We agree with you that the characteristics of the kidney transplantation cohort in different regions are different, which may be one of the reasons for heterogeneity. Except that, we consider that the follow-up time after kidney transplantation and the length of dialysis time may be the source of heterogeneity. However, due to the limited data extracted, we did not conduct a subgroup analysis of these factors. This is also a limitation of our meta-analysis.

*** What is the median or mean interval between transplantation and evaluation of IIEF scores in the included studies? This is important information - most parameters are negatively affected immediately around transplant and take months to recover/improve. Knowing this interval is important for interpretation of the data.**

Reply: Thank you for your positive comments. Through this question, I know that you are a well-thought-out clinical expert. This comment is constructive and valuable for modifying and improving our manuscript. In order to respond to this question, we read the included studies again and extracted the time interval between kidney transplantation and evaluation of IIEF scores. We defined it as the follow-up time and put it in the literature characteristic table (Table 1). We found that the included studies all evaluated IIEF scores at least 6 months after kidney transplantation, which was considered an appropriate interval.

*** Why is there a difference between races?**

Reply: Thank you for your question. In our study, a subgroup analysis of Asian studies found that the kidney transplantation group had a lower ED prevalence (OR 0.28, 95% CI: 0.12-0.64, I²=54.8%) and higher EF domain score (SMD 0.83, 95% CI: 0.20-1.47, I²=84.2%) than the control group, as reported in Figure 6B and D. However, no significant difference was found among Caucasians. As we all know, the causes of ED in kidney transplant recipients are multifactorial. We guess that the characteristics of kidney transplantation groups in different regions of the world may be one reason for the racial differences. In addition, the insufficiency of the sample size of these enrolled studies may have led to a certain deviation in racial differences.

*** Page 7 line 7 - why are only 8 studies accounted for when there were 9 studies included?**

Reply: Thank you for your reminder. We checked the enrolled studies, and found we made a mistake in counting studies using IIEF-5. In our meta-analysis, 5 articles used IIEF-15 to evaluate patients' sexual function, and 4 studies used IIEF-5. So we have modified this mistake in the revised manuscript. (see Page 8, line 17, marked in red: In this study, 5 articles used IIEF-15 to evaluate

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patients' sexual function, and 4 studies used IIEF-5.)

*** Figures 7 and 8 are difficult to read and should be re-formatted without the black background**

Reply: Thank you for your advice. To make them easier to read, we changed the black background to white of the two figures. (see Figure 7 Sensitivity analysis of erectile function domain score, Figure 8 Begg's funnel plot and Egger's publication bias plot of erectile function domain score.)

*** Why was the manuscript by Shamsa et al Transplant Proc 2005 not included?**

Reply: Thank you very much for your careful review. We also retrieved this article during the literature search, but it was not included in this meta-analysis after carefully reading the original text. Although this study reported the erectile function of patients before and after kidney transplantation^[1], the results only included the IIEF total score, and there is no score for each section (including IIEF-EF, IIEF-OF, IIEF-SD, IIEF-IS, IIEF-OS). Because there is no outcome of interest, we excluded this study.

[1] Shamsa A, Motavalli SM, Aghdam B. Erectile function in end-stage renal disease before and after renal transplantation. Transplantation proceedings. 2005;37:3087-9.

*** The lack of difference in overall satisfaction is an interesting finding (perhaps even more important than the erectile domains). Even with improved erections, the lack of improvement in satisfaction suggests a complex**

*Reply: Thank you for your positive comments. Firstly, we agree with you that the lack of difference in overall satisfaction is an interesting finding. Then, we analyzed and discussed this issue by consulting the literature in the Discussion section. (see Page 13, line 9, marked in red: **Our study found the IIEF domain score, which reflects the psychological aspects (IIEF-SD) was improved significantly in the kidney transplantation group, except the orgasmic function and patient satisfaction (IIEF-OF, IIEF-IS, and IIEF-OS). There was no improvement in intercourse satisfaction and overall satisfaction, which may suggest that the improvement of erectile function may be limited because a primary outcome of ED for most patients is the inability to attain satisfactory sexual intercourse (33).**)*

*** The authors are to be commended for stating the study is correlative rather than causative, but unfortunately the very next sentence (page 13, line 22) asserts a causal relationship ("kidney transplantation improves erectile function..."). This should be addressed.**

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Reply: We thank you for your suggestion and absolutely agree that the study is correlative rather than causative. This conclusion is a bit arbitrary. We revised the conclusion according to your comments. (see Page 16, line 4, marked in red: In summary, kidney transplantation may be associated with improved erectile function in patients with ESRD.)

*** The quality of evidence throughout the manuscript is consistently rated as “high” despite being small sample sizes and highly heterogeneous, and yet the evidence is subsequently referred to as “poor quality” on page 13 line 20. The authors should rectify this apparent conundrum.**

Reply: Thank you for your reminder. According to your suggestion, we rectified this apparent conundrum in the revised manuscript. (see Page 16, line 1, marked in red: Finally, the sample size of this meta-analysis was not large enough, which suggested that further prospective studies of larger samples were needed.)

Reviewer B

In this manuscript the authors perform a meta-analysis on the relationship between kidney transplantation and erectile function. Their outcomes of interest were ED prevalence and this was measured by the International Index of Erectile Function (IIEF) 5 and 15 questionnaire scores.

The main limitations of the manuscript are the poor quality and heterogeneity of the studies that were analysed for the meta-analysis. By definition, the study is not a meta-analysis as a meta-analysis is not feasible on this topic. Unfortunately, due to these limitations it is difficult to draw any definitive conclusions from the meta-analysis. This means that the manuscript does not contribute to the literature in this field

Reply: Thank you for your comments. The design of our study is a meta-analysis of cohort studies and cross-sectional studies. Our study design strictly followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement^[1,2] to report this meta-analysis, as we have already stated this in the Methods section. Our study aims to assess the impact of kidney transplantation on erectile function in patients with end-stage renal disease (ESRD). We conducted a comprehensive literature search, set strict inclusion and exclusion criteria, and adopted the Newcastle-Ottawa Scale (NOS)^[3] and the Agency for Healthcare Research and Quality (AHRQ) to assess the quality of enrolled studies. The studies we included were of high quality after evaluation. By pooling all enrolled studies and conducting publication bias and sensitivity analysis, our results proved to be stable and reliable. Besides, we also explored possible sources of heterogeneity in the Discussion section. The above-mentioned steps and process in our manuscript made the study design more clear and meet PRISMA Statement requirements. Therefore, we addressed an important

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question about the relationship between kidney transplantation and ED through using meta-analysis, and the conclusions obtained also had certain clinical value.

[1] Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ (Clinical research ed)*. 2015;350:g7647.

[2] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine*. 2009;6:e1000097.

[3] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European journal of epidemiology*. 2010;25:603-5.

Reviewer C

The authors have written a review and meta-analysis looking at the prevalence of ED after kidney transplantation. Overall, there is good data included in this manuscript, but I have some questions and comments

Reply: Thank you for your positive comments. We feel inspired by your affirmation of this article. By following your comments and suggestions, we have listed our response and corrections to the comments below.

I would recommend the authors review the manuscript one more time for grammatical errors.

Reply: Thank you for your advice. I am so sorry for the error in this regard. As you suggested, we have checked the manuscript from beginning to end and corrected the grammatical errors by using the Grammarly plugin. Further, we revised the manuscript by an assisting language checker (WhiteSmoke software) to improve its readability. Finally, we invited a native English-speaking expert in our field to check and revise the manuscript again. (Changes in the manuscript were marked in red color.). Thank you for your careful review.

Abstract

-Background - "No review has synthesized the available data" - please see Payne et al in Sex Med Reviews, 2020.

Reply: Thank you for your positive comments. Based on your opinion, I searched the literature again and found the review you provided. Although Payne's study^[1] focused on ED across all types of solid organ transplant recipients and assess the success of current methods of ED treatment in transplant populations, they included a subset of kidney transplanted patients and reported the prevalence of ED among kidney transplant recipients is 54-66%, higher than that in the general population. So we agree with your suggestion and have deleted this misleading sentence. (see Page

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2, line 4, we have deleted the misleading sentence “*No review has synthesized the available data.*”)

[1] Payne K, Popat S, Lipshultz LI, Thirumavalavan N. The Prevalence and Treatment of Erectile Dysfunction in Male Solid Organ Transplant Recipients. *Sexual medicine reviews*. 2019.

-Results - what was the "control group"? This should be mentioned in the abstract.

Reply: Thank you for your positive comments. According to your suggestion, we defined the control group in the method section in the revised manuscript. (see Page 2, line 8, marked in red: We used age-matched dialysis patients or patients before kidney transplantation as a control group and compared them to kidney transplant recipients.)

-Results - "domain scores of Erectile function..and sexual desire were higher. This sentence is grammatically confusing. Also, how are odds ratios below 0 - I believe the statistics in this manuscript need review.

Reply: Thank you for your advice. Your comment is constructive and helpful. We revised the abstract and corrected the errors you pointed out. (see Page 2, line 11, marked in red: Compared with the control group, the kidney transplantation group had a lower prevalence of ED (OR 0.49, 95% CI: 0.28-0.86) and higher domain scores for erectile function (SMD 0.53, 95% CI: 0.12-0.94) and sexual desire (SMD 1.19, 95% CI: 0.11-2.27). While there were no significant variations in domain scores for orgasmic function (SMD 0.27, 95% CI: -0.10-0.63), intercourse satisfaction (SMD 0.26, 95% CI: -0.10-0.61), and overall satisfaction (SMD 0.17, 95% CI: -0.21-0.56). Patients in the kidney transplantation group had lower serum testosterone (SMD 1.20, 95% CI: 0.86-1.54) and higher prolactin (SMD -1.46, 95% CI: -2.22--0.69) and luteinizing hormone (SMD -0.97, 95% CI: -1.39--0.55).)

Methods - OR with 95% CI was calculated for the incidence rate of patients with ED. - this sentence doesn't make sense.

Reply: Thank you for your comments. We have revised this sentence and made a more standardized description of the statistical methods. (see Page 7, line 11, marked in red: For the prevalence of erectile dysfunction, we chose the Odds ratios (OR) as the effect size and calculated the 95% confidence interval (95% CI). For the IIEF scores and hormone levels, we used the standard mean difference (SMD) as the effect size and calculated the 95% CI.)

Results

-for all IIEF's, was this patients who were not taking PDE5i or intracavernosal injections.

Reply: Thank you for your comment. All enrolled patients did not take PDE5i or intracavernosal

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injections.

-Again, I would have this manuscript considered for statistical review.

Reply: Thank you for your careful review. After we carefully checked the manuscript, we found we made a writing mistake in the manuscript that SMD was written as OR. In this study, SMD was used as the effect size for continuous variables (IIEF domain scores and endocrine hormone levels), and OR was used as the effect size to evaluate the prevalence of erectile dysfunction. We have revised the mapping errors in the abstract and text. (Changes in the text were marked in red.)

Discussion

-Why do the authors suppose that they found a difference between Asian and Caucasian populations?

*Reply: Thank you for your comments. In a subgroup analysis based on ethnicity, we found the benefits of kidney transplantation among Asians, but not among Caucasians. The population characteristics of kidney transplant recipients in different regions are different, which may lead to ethnic differences. In addition, the insufficient sample size of our meta-analysis may also be the reason. (see Page 12, line 15, marked in red: *We guess that the characteristics of kidney transplantation groups in different regions of the world may be one reason for the racial differences. In addition, the insufficiency of the sample size of these enrolled studies may have led to a certain deviation in racial differences.*)*

-The IIEF does not need to be re-explained in the discussion.

Reply: Thank you for your advice. We deleted the repeated explanation about the IIEF in the discussion.

-Overall, the discussion is too much a repetition of the introduction.

Reply: Thank you for your advice. In the revised manuscript, we deleted part of the content that duplicated with the introduction. (see Page 11, line 7, changes in the text were marked in red.)

-Limitations are appropriately discussed and acknowledged.

*Reply: Thank you for your advice and affirmation. we have appropriately modified the limitations of the paper in the revised manuscript. (see Page 16, line 1, marked in red: *Finally, the sample size of this meta-analysis was not large enough, which suggested that further prospective studies of larger samples were needed.*)*