# PREVALENCE OF ERECTILE DYSFUNCTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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**ABSTRACT**

Growing evidence reports that chronic kidney diseases (CKD) might play a role in erectile dysfunction (ED), but limited knowledge is available. Therefore, we performed a systematic review up to 21/08/2019 to investigate the associations between CKD and ED.The main analysis reported the prevalence of ED as absolute estimates (in %) with their 95% confidence intervals (CIs) and across CKD stages (when specified), hemodialysis and transplant, calculating the p for interaction across strata.

Among 291 studies, we included 34 articles with 5986 men. We found an overall prevalence of 76% (95%CI: 72-79) with a high degree of heterogeneity ($I^2$=84.2%; p<0.0001). Analyzing the data by CKD stage, we found a significant higher prevalence of ED in CKD (78%; 95%CI: 75-81%; $I^2$=not possible) compared to hemodialysis stage (prevalence=77%; 95%CI: 73-80%; $I^2$=84.5) or to patients undergoing transplant (prevalence=64%; 95%CI: 54-74%; $I^2$=54%) (p across strata=0.036)

Considering the high prevalence of ED in men with CKD, health care practitioners should focus on issues of sexual health in men with CKD. Given the advancements in dialysis and therapy and the associated advancements in survival and life expectancy, maintaining the patients' sexual function is important for their well-being and quality of life.

## INTRODUCTION

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for at least 3 months with implications for health and represents a major public health issue worldwide (1). CKD typically has a slow evolvement with a long latency period being clinically silent, presents symptoms only in the late stage, and thus, precise calculation of the prevalence and the burden is difficult. The global prevalence is estimated at about 13.4% (11.7–15.1%), and the number of people with end-stage kidney disease between 4.902 and 7.083 million worldwide (1). The etiology of CKD is mainly due to diabetes and hypertension in developed countries and glomerulonephritis and unknown causes in developing countries (2). This difference reflects the higher chronic lifestyle-related diseases and increased life expectancy in developed countries and the higher prevalence of infectious diseases, such as HIV, schistosomiasis, and leishmaniasis, which also contribute to CKD in low- and middle-income countries (3). The burden of CKD is not restricted to the demand for renal replacement therapy, but includes other important health issues including, primarily, cardiovascular events and mortality (4). Male patients with CKD frequently experience infertility, loss of libido and impotence, often resulting in a decreased quality of life (5, 6). In particular, increasing attention is focusing on dysfunction (ED) that is considered the most prevalent manifestation of sexual dysfunction in men with CKD. ED is defined as the inability to achieve and/or maintain an erection sufficient to permit satisfactory sexual intercourse and might result from psychological, neurologic, hormonal, arterial or cavernosal impairment or the combination of these factors (7). Although it is considered an age-related disease, affecting 20% of men aged > 40 years, it can be present across all the life-span from adolescence, especially when risk factors such as diabetes, metabolic syndrome or cardiovascular diseases coexist (7, 8). Several studies of men with CKD demonstrated a wide variability of ED prevalence, ranging from 41% to 93% (9-11). This high variability has been explained by different study methodologies, difficulties in quantifying the kidney disease duration and different diagnostic criteria for ED. Interestingly, in 2010, Navaneethan and colleagues published a meta-analysis of observational studies that showed an

estimate of ED in men with CKD was 70% (9). Given this, the aim of this study was to conduct a systematic review of existing data to estimate prevalence of ED in men with CKD.

## METHODS

This systematic review and meta-analysis is adherent to the PRISMA (12) and MOOSE (13) statements, following a predetermined, but unpublished protocol.

### *Data sources and literature search strategy*

Two investigators (NV and DP) independently conducted a literature search using PubMed, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials and Clinicaltrials.gov without any language restriction, until 21st August 2019 for any study investigating the association between CKD and presence of ED. Any inconsistencies were resolved by consensus with a third author (LS). In PubMed, the following search strategy was used: ("erectile dysfunction" OR "erectile function" OR "sexual dysfunction" OR "sexual function" OR "impotence") AND ("Renal failure" OR "hemodialysis" OR "renal transplant" OR "dialysis" OR "CKD" OR "chronic kidney disease" OR "nephropathy"). Reference lists of included articles were hand-searched to identify and potential additional relevant articles, whilst conference abstracts were excluded.

### *Study selection*

Inclusion criteria for this meta-analysis were: i) observational studies (case-control, cross-sectional, prospective) reporting the prevalence of ED in CKD; ii) using a validated tool for the detection of ED (e.g. the International Index of Erectile Function, IIEF-5) (14).

### *Data extraction*

Two independent investigators (NV and DP) extracted key data from the included articles in a standardized Excel sheet. A third independent investigator (LS) checked the extracted data, if there was any disagreement during the extraction. For all articles, we extracted data about authors, year of publication, country, number of participants, demographics (mean age and standard deviation), methods of assessment of ED; stage of CKD (when specified), hemodialysis

(HD) receiving patients, transplant; the HD mean duration (in months); the prevalence of diabetes, hypertension, cardiovascular disease and the presence of active smokers prevalence.

***Outcomes***

The primary outcome was the prevalence of ED across CKD stages (when specified), HD and transplant.

***Assessment of study quality***

Study quality was assessed by two investigators (DP, LS) using the Newcastle-Ottawa Scale (NOS) (17, 18). The agreement between DP and LS was overall good being the Spearman's rho =0.74 and the intraclass correlation–coefficient (ICC) of 0.80. A third reviewer was available for mediation (NV). The NOS assigns a maximum of 9 points based on three quality parameters: selection, comparability, and outcome.

***Data synthesis and statistical analysis***

All analyses were performed using R (version 3.6.1).

The main analysis reported the prevalence of ED as absolute estimates (in %) with their 95% confidence intervals (CIs) and across CKD stages (not specified; transplant; hemodialysis), calculating the p for interaction across strata.

Heterogeneity across studies was assessed by the $I^2$ metric and taking as measure of high heterogeneity an $I^2 \geq 50\%$ and/or $p<0.05$ (19). In case of high heterogeneity and having at least 10 studies for the outcome, we used, as possible moderators, the mean age of the population, the HD mean duration (in months), the prevalence of diabetes, hypertension, cardiovascular disease, the active smokers' prevalence. We applied the logit transformation to the observed prevalences across primary studies to make the transformed prevalences follow a normal distribution, and the meta-regression analysis was based on the transformed scale. Univariate meta-regression analysis for each moderator was used due to very limited sample size introduced by sparse data.

Publication bias was assessed by visual inspections of funnel plots and carrying out the Egger's bias test (20). In case of publication bias ($p<0.10$), we planned to apply the trim and fill-analysis (21) to account for and evaluate the impact of this bias.

For all analyses except the Egger's bias test, a p-value < 0.05 was considered as statistically significant.

## RESULTS

### *Search results*

As shown in **Figure 1**, the search produced 291 independent articles. After excluding 242 articles based on title/abstract review, 49 articles were retrieved for full text review and 34 articles were included in the qualitative/quantitative synthesis (full references are reported in **Supplementary Table 1**).

### *Study and patient characteristics*

As shown in **Table 1**, the 34 studies included a total of 5,986 participants. The largest proportion of studies were conducted in Middle-East Asia (n=9) and in America (n=9), six in Europe, five in Asia and the last five in Africa. Thirty studies had a cross-sectional design and, 4 were case-controls. All the studies were performed among outpatients and used the IIEF-5 for the diagnosis of ED. The mean age was 53.9 years (SD=12.3).

The median quality of the studies was 4.9 (range: 4-6), indicating an overall good quality of the studies, according to the NOS (**Table 1**).

### *Prevalence of ED in CKD*

**Figure 2** shows the prevalence of ED in CKD. Pooling the data of the 34 studies, we found an overall prevalence of 76% (95%CI: 72-79) with a high degree of heterogeneity ($I^2$=84.2%; $p<0.0001$). This result was not affected by any publication bias and the trim and fill analysis did not modify our results.

When analyzing the data by CKD stage, we found a significant higher prevalence of ED in III and IV CKD in two studies (the only 2 studies considering CKD stages) (78%; 95%CI: 75-81%; $I^2$=not possible) compared to HDR patients (n=28 studies; prevalence=77%; 95%CI: 73-80%; $I^2$=84.5) or to patients undergoing transplant (n=4 studies; prevalence=64%; 95%CI: 54-74%; $I^2$=54%) (p across strata=0.036) (**Figure 1**).

***Meta-regression analysis***

Results of meta-regression analyses on studies of HD stage set and studies of all three CKD stages set are given top and bottom panels respectively in Table 2. As we can see, only the factor of prevalence of cardiovascular disease account for a small proportion (8.49% and 3.76% respectively) of heterogeneity among primary studies in the two sets.

***Publication bias assessment***

The predicted overall ED prevalence across all stages of CKD by the trim and fill analysis is 0.73 with 95% C.I. (0.70, 0.77) **(Supplementary Figure 1)**, which is not much different from the observed estimate which is 0.76 with 95% C.I. (0.72, 0.79) (**Supplementary Figure 2**). In addition, p-value of Eager's test is 0.1812. Based on the assessment results above, there is no publication bias in reporting the overall ED prevalence for studies across all CKD stages.

The predicted ED prevalence in HDR patients by the trim and fill analysis is 0.76 with 95% C.I. (0.72, 0.80) (**Supplementary Figure 3**), which is not much different from the observed estimate which is 0.77 with 95% C.I. (0.73, 0.80) (**Supplementary Figure 4**). In addition, p-value of Eager's test is 0.1294. Based on the assessment results above, there is no publication bias in reporting the overall ED prevalence for studies in HDR patients.

Because the number of parameters to be estimated is larger than the number of observations in both trim and fill analysis and Eager's test for studies in CKD stage, these analyses are not executable for the only two studies in CKD stage (**Supplementary Figure 5**).

## DISCUSSION

In this meta-analysis including 34 studies and almost 6,000 participants, we found that the prevalence of ED in CKD is extremely high, effecting 3/4 of the population included. This is in line with a previous meta-analysis of observational studies indicating a prevalence of ED in CKD patients of 70% (9). When separating by stage, the prevalence of ED was significantly higher in CKD compared to HD receiving patients or in patients undergoing transplant.

ED in patients with CKD has a multifactorial etiology including endocrine, vascular and neurologic systems. First of all, even just a moderate reduction of glomeruli filtration rate is able to result in a disturbance of the pituitary-gonadal axis that rarely normalize with dialysis which could, however, generally be restored by a well-functioning kidney transplant (22). Regarding the effect of renal transplantation on ED some authors reported improvement of erectile function after renal transplantation, while others reported erectile function deterioration after transplantation (23). Interestingly, Mirone and colleagues demonstrated that renal transplant is not always a restorative treatment in terms of sexual function and in younger patients ED worsens after transplant (24).

The consequent testicular damage manifests both with infertility and sexual dysfunction. In fact, on the one hand there is sperm impairment with decreased volume of ejculate, either low or complete azoospermia, and a low percentage of motility (25). On the other hand, athe defect in hormonal regulation of the Leydig and Sertoli cells results in gonadotropin deficiency or resistance (26). In particular, total and free testosterone levels are reduced, while sex hormone-binding globulin is normal (27). Consequently, the main clinical outcomes related to this are the loss of libido and ED, some regression of secondary sexual characteristics, fatigue, decrease of bone mineral density, and loss of muscle mass and strength (10). This condition is further exacerbated by the hyperprolactinemia that is a common finding in CKD patients and is associated with infertility, loss of libido, low circulating testosterone levels, and inappropriately low LH levels (28).

Vascular system plays a key role in penile erection, thus, all vascular diseases may result in ED. Patients with CKD are commonly associated with vascular ED due to occlusive disease of the

cavernosal artery or the more proximal ileac and pudendal arteries in what is referred to as the pelvic arterial steal syndrome (29). Moreover, veno-occlusive dysfunction may occur, leading to venous leakage and consequent inability to achieve or maintain an erection. Finally, atherosclerosis and endothelial dysfunction, also in other vascular districts, contribute to effect a normal erection (30). Furthermore, it is well known that sympathetic and parasympathetic systems play a key role in erection mechanism and, thus, the abnormalities of the neurologic system associated with CKD, especially in presence of diabetes and uremic toxicity, are easily included in the pathogenesis of ED in these patients (31). Indeed, renal anemia may partially participate in the pathogenesis of sexual dysfunction while erythropoietin therapy has been shown to improve sexual function in male dialysis patients, with a direct effect upon endocrine function, as well as anemia (32).

Finally, contrasting data are present regarding the role of depression in ED in CKD patients and, while some authors showed no association between the presence or absence of depression in chronic kidney failure patients and outcomes about sexual function (10), other authors found a lower assessment of their overall quality of life (10).

Although there is consistent literature on the topic of ED in CKD patients, unfortunately, the majority of studies assessed the sexual function in a non-standardized way. In order to be rigorous, we only included studies with validated questionnaires to asses ED and, thus, we included only 34 studies and this represent a strength but, at the same time, the main limitation of our review. Another limitation is lack of available data assessing renal function, such information may be excluded from primary studies as the majority included patients at the final stage of CKD and undergoing dialysis.

In conclusion, our systematic review and meta-analysis confirmed the previous literature highlighting a very high prevalence of ED in patients with CKD both where the patients are undergoing dialysis or have received kidney transplants. Thus, it is mandatory to include screening and management of ED in men with CKD as a part of the assessment of their cardiovascular risk. This is particular important in order to achieve quality of life improvements especially considering the significant advances obtained by dialysis therapy in terms of survival and expectancy of life in patients

225 with CKD. Further studies are needed to characterize others risk factors such as duration of disease
226 or other pathological conditions which are involving in the development of ED.

227 **Conflict of Interest:** all authors declare no conflict of interest

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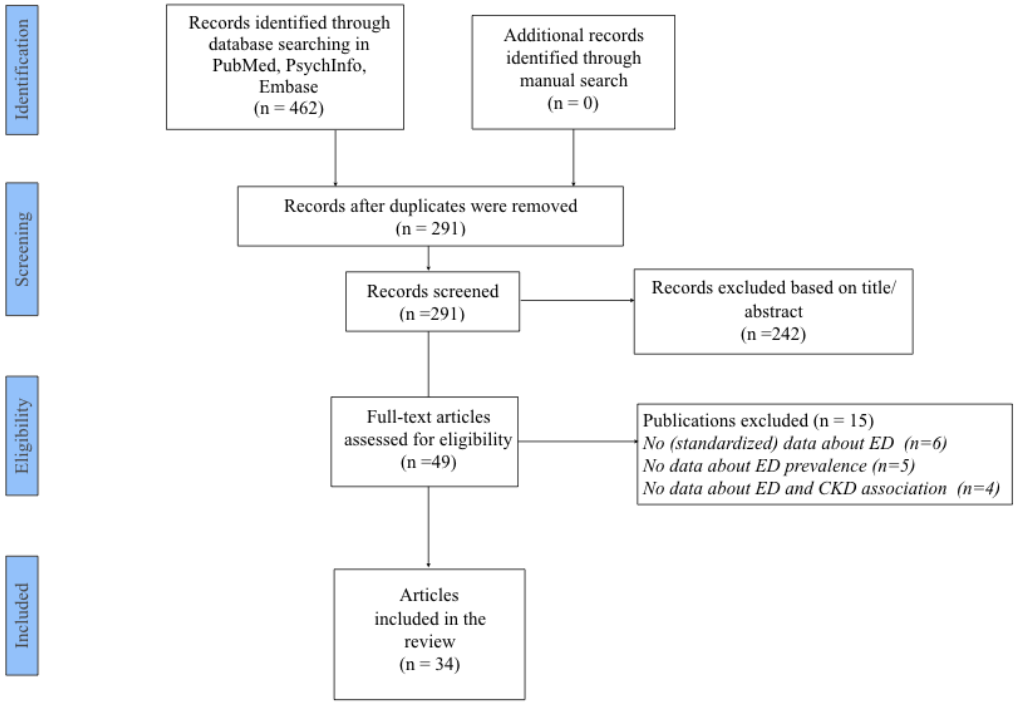
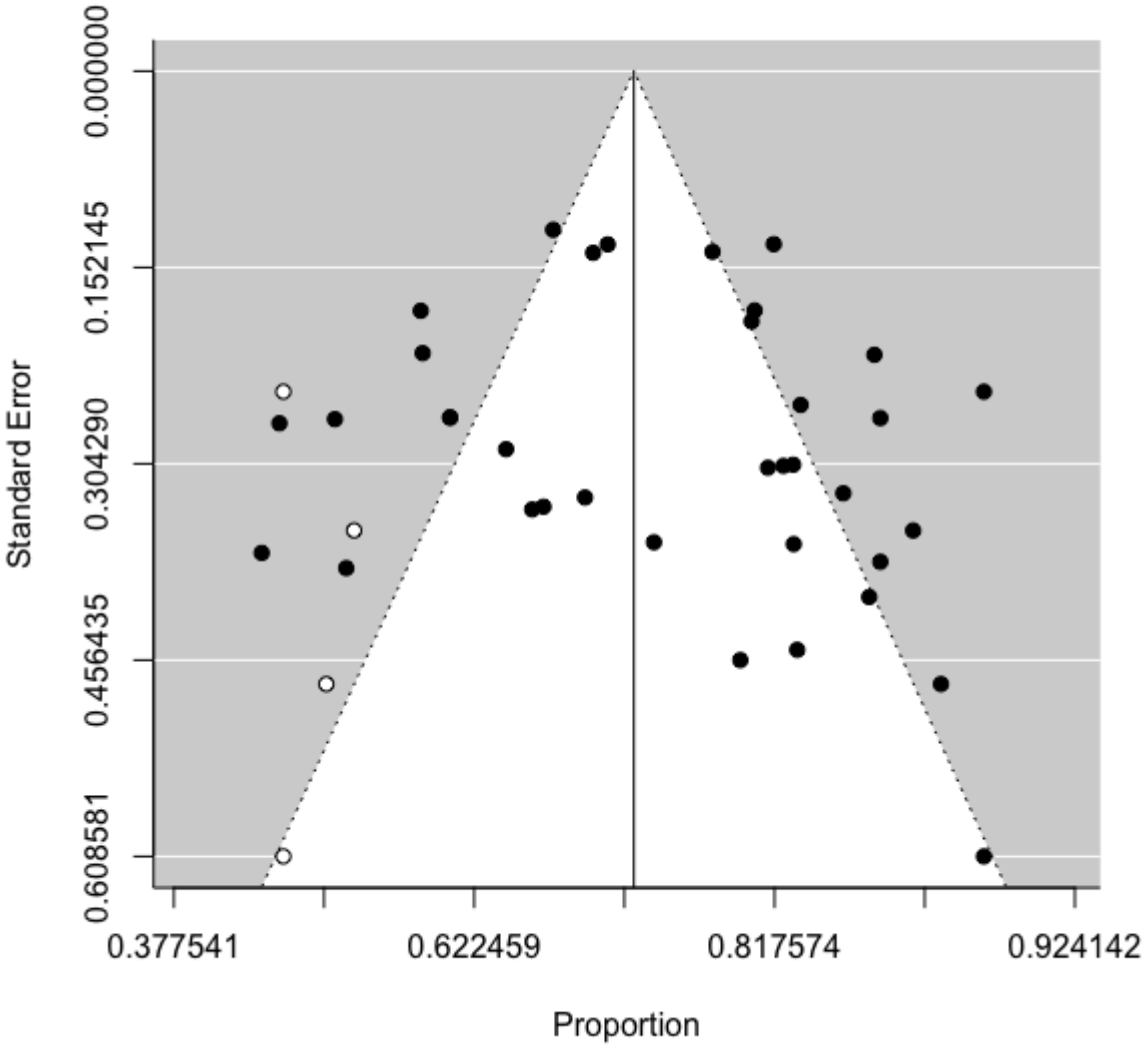
## Tables and Figures

**Figure 1. PRISMA flow chart.**



322 **Figure 2. Forest plot of prevalence of erectile dysfunction by CKD category.**

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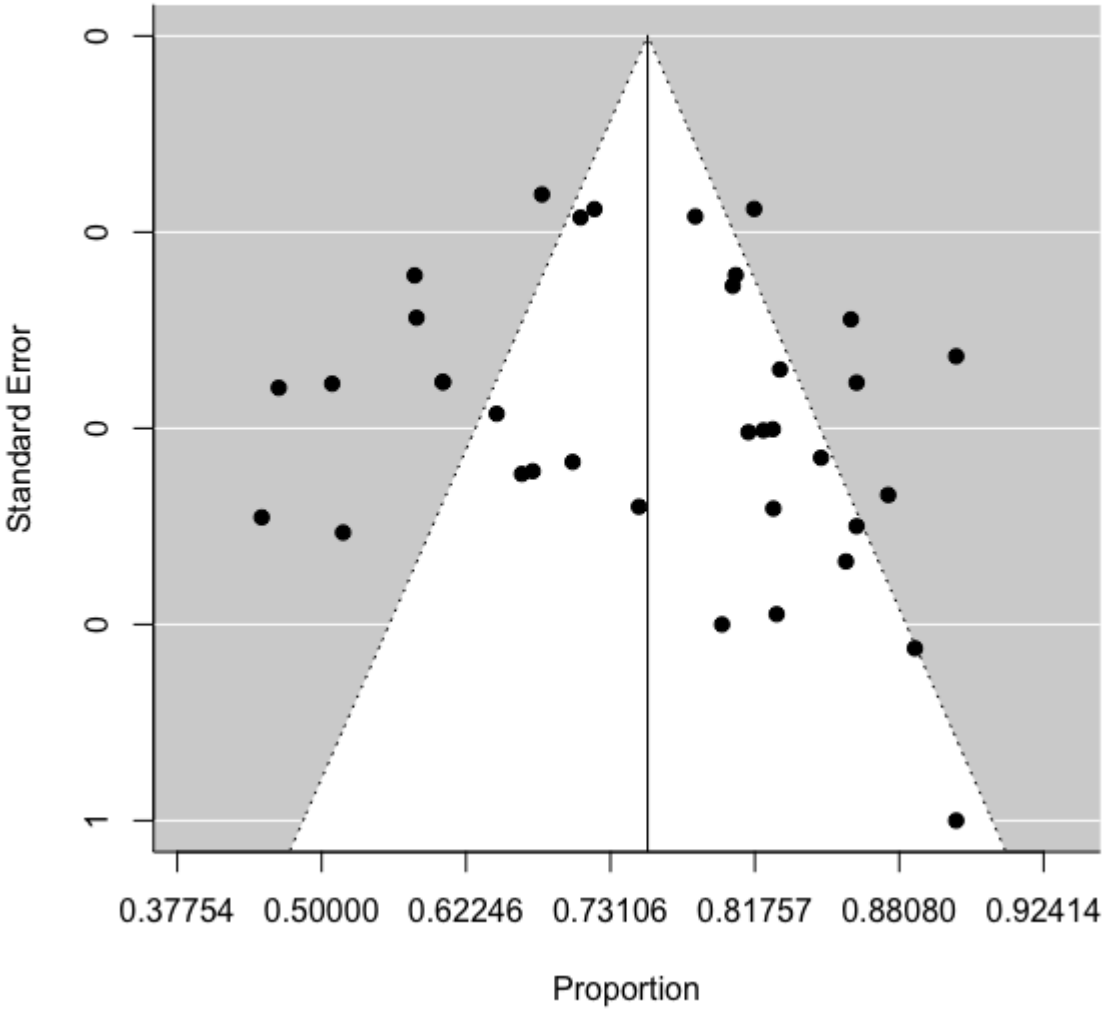
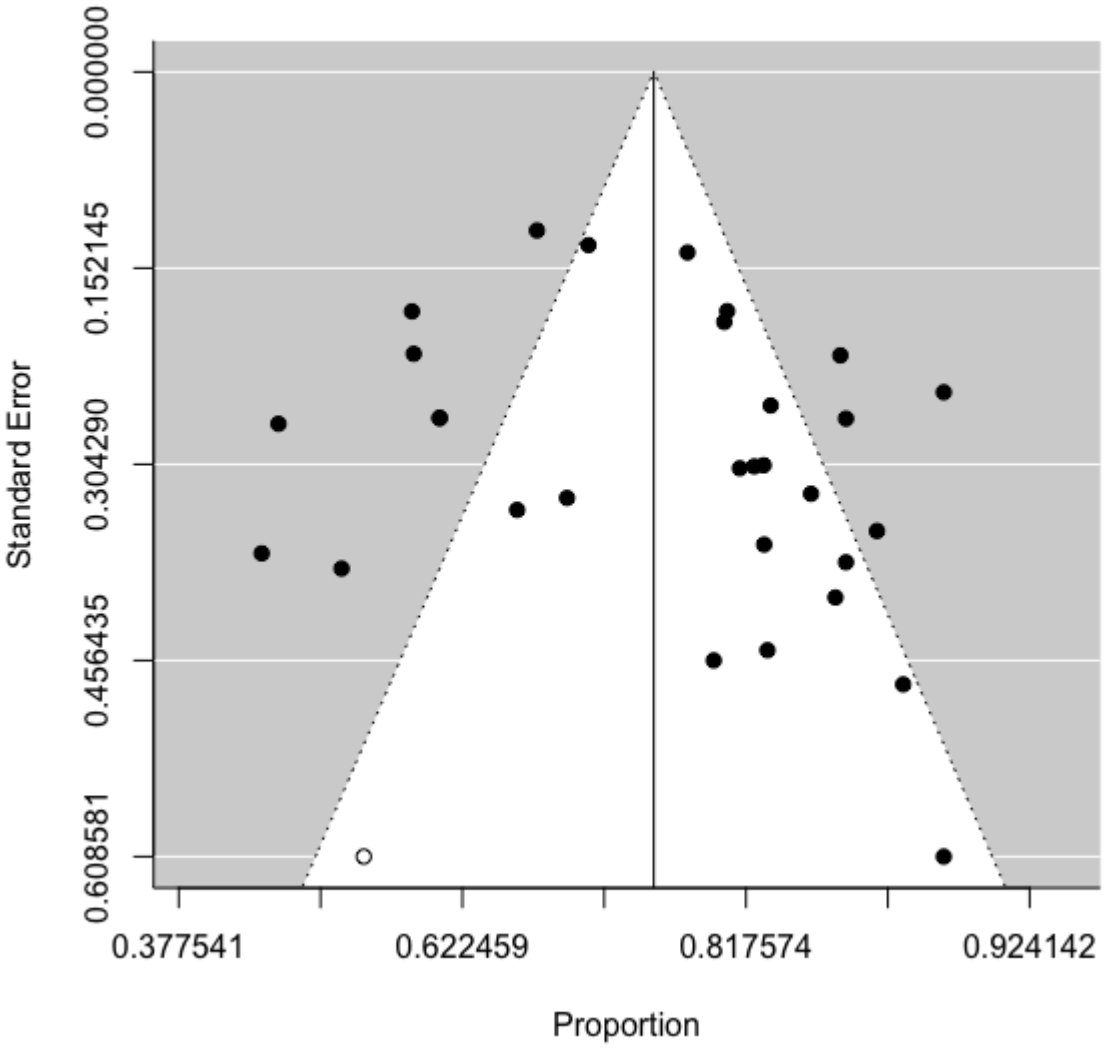
324 **Abbreviations: CI, confidence interval; CKD, chronic kidney diseases.**

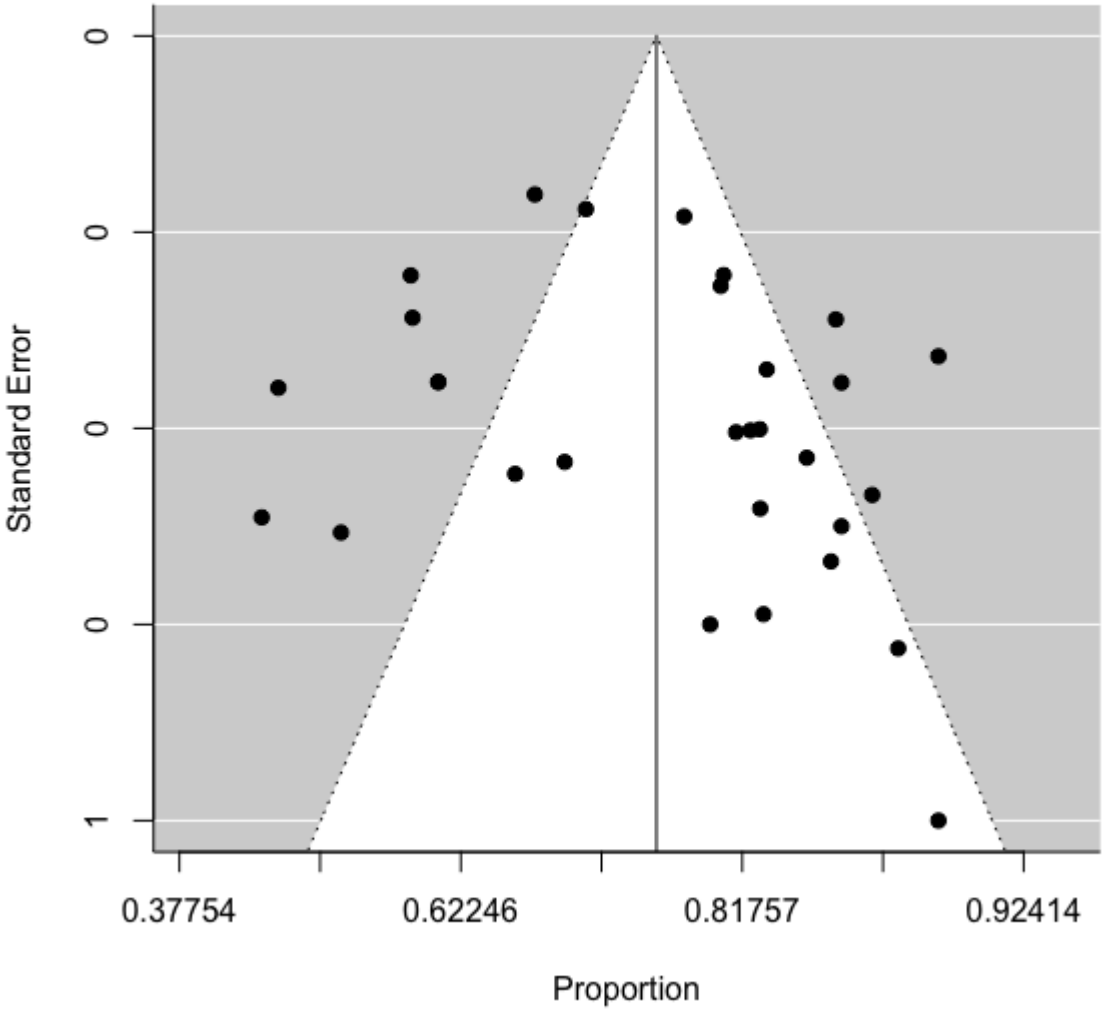
**Supplementary Figure 1. Funnel plot of the trim and fill analysis on overall ED prevalence across all stages of CKD.**



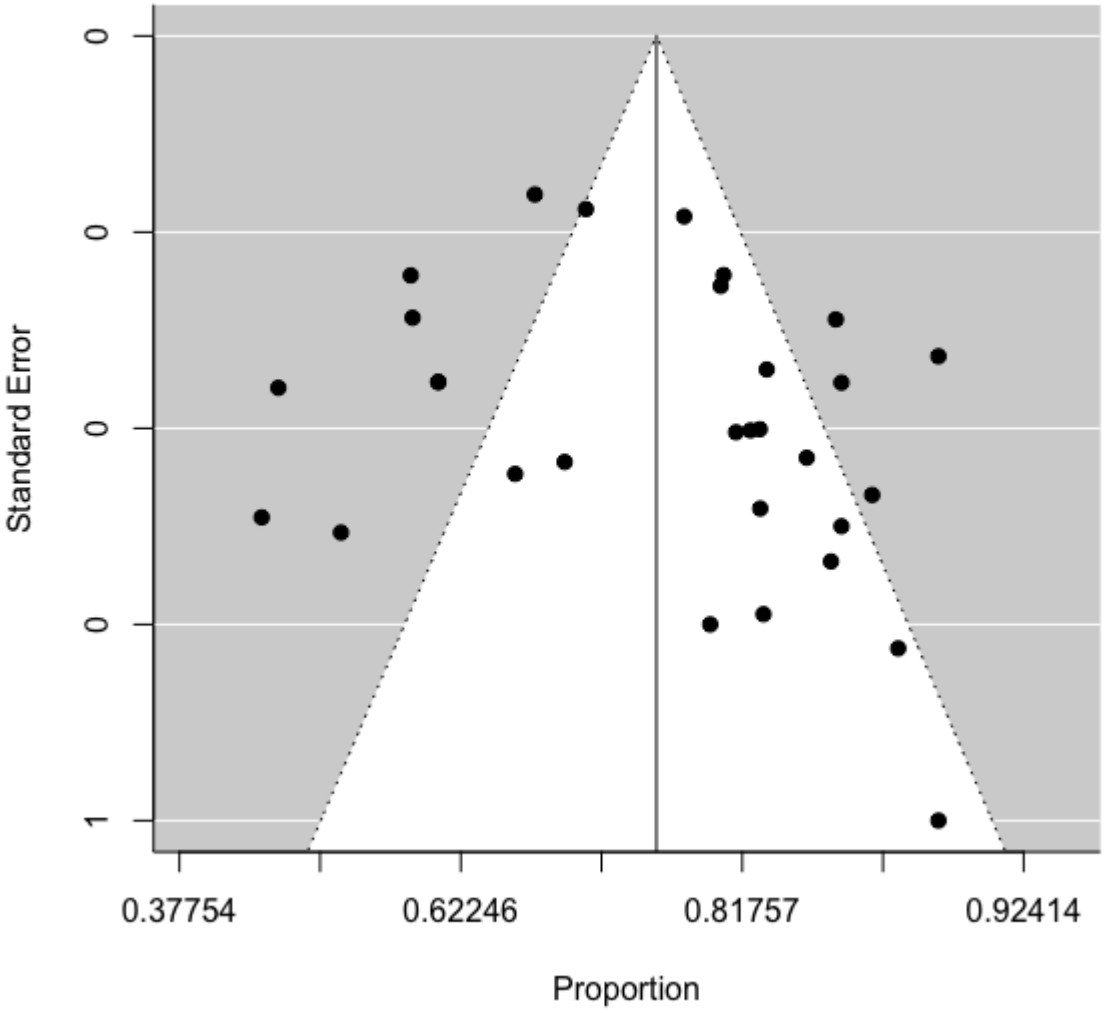
**Supplementary Figure 2. Funnel plot of overall ED prevalence across all stages of CKD.**



**Supplementary Figure 3. The funnel plot of the trim and fill analysis on ED prevalence in Hemodialysis stage.**



333 **Supplementary Figure 4. The funnel plot of ED prevalence in Hemodialysis stage.**

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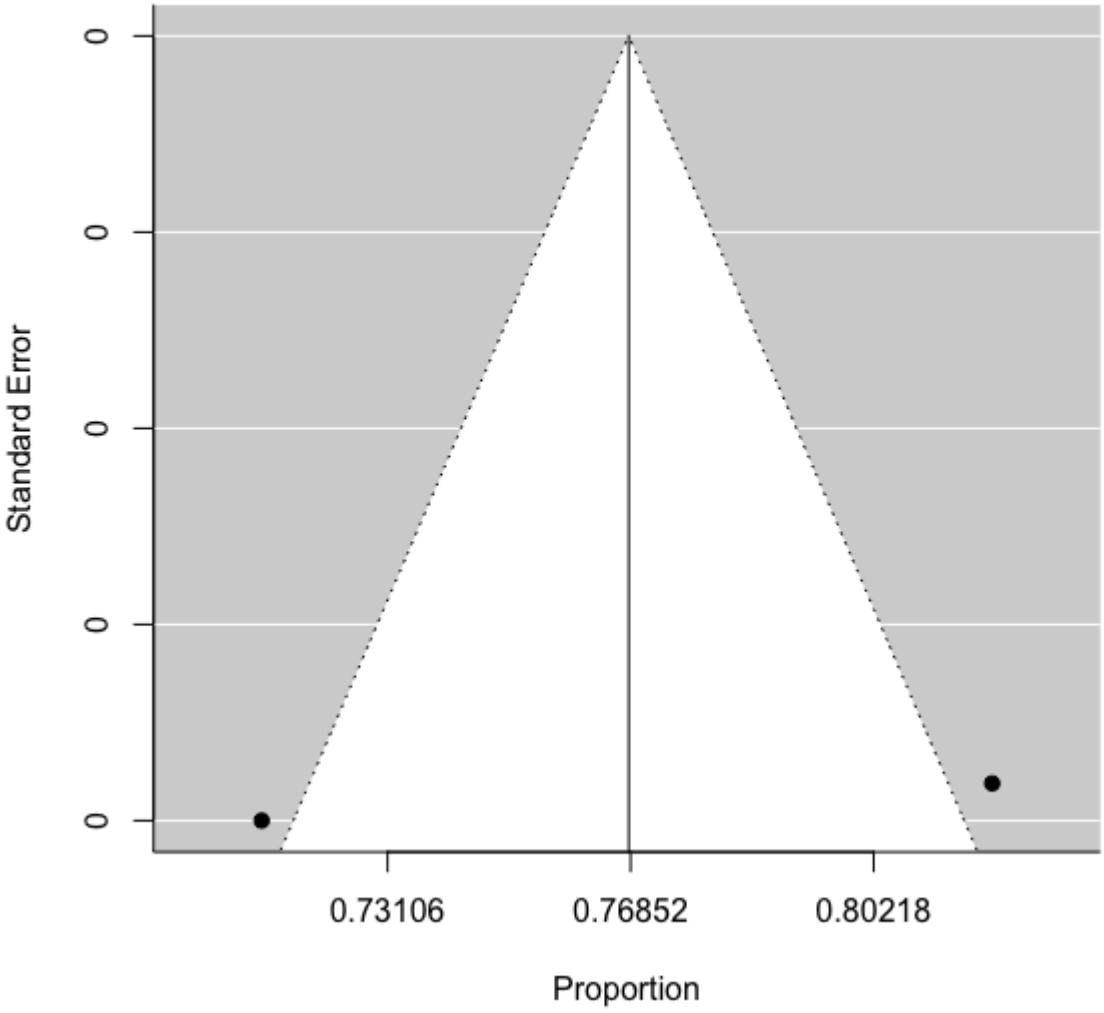
335 **Supplementary Figure 5. The funnel plot of ED prevalence in CKD.**

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337 **Table 1. Descriptive characteristics of the studies included**
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| Author, year | Country | Setting | Type of study | Sample size | Mean age (SD) | Method of assess-ment of ED | NOS |
|---|---|---|---|---|---|---|---|
| Ali, 2005 | Egypt | Outpatient | Case-control | 1023 | NA | IIEF-5 | 6 |
| Antonucci, 2015 | Italy | Outpatient | Case-control | 95 | | IIEF-5 | 5 |
| Mekki, 2013 | Sudan | Outpatient | Case-control | 146 | | IIEF-5 | 4 |
| Naya, 2002 | Japan | Outpatient | Case-control | 1307 | | IIEF-5 | 4 |
| Miyata, 2004 | Japan | Outpatient | Cross-sectional | 180 | | IIEF-5 | 5 |
| Nassir, 2009 | Saudi Arabia | Outpatient | Cross-sectional | 52 | 58.5 (14.3) | IIEF-5 | 4 |
| Premužić, 2017 | Croatia | Outpatient | Cross-sectional | 92 | | IIEF-5 | 6 |
| Rosas, 2001 | USA | Outpatient | Cross-sectional | 302 | 59.5 (15.5) | IIEF-5 | 5 |
| Stolic, 2010 | Serbia | Outpatient | Cross-sectional | 73 | 54.5 (6.9) | IIEF-5 | 5 |
| Sudarević, 2017 | Croatia | Outpatient | Cross-sectional | 40 | | IIEF-5 | 5 |
| Anees, 2009 | Pakistan | Outpatient | Cross-sectional | 50 | | IIEF-5 | 5 |
| Arslan, 2002 | Turkey | Outpatient | Cross-sectional | 187 | 49.3 (13.2) | IIEF-5 | 4 |
| Azevedo, 2014 | Portugal | Outpatient | Cross-sectional | 57 | | IIEF-5 | 5 |
| Cerqueira, 2002 | Brazil | Outpatient | Cross-sectional | 119 | 47.3 (15.9) | IIEF-5 | 5 |
| Costa, 2014 | Brazil | Outpatient | Cross-sectional | 305 | 54.1 (13.2) | IIEF-5 | 5 |
| Costa, 2017 | Brazil | Outpatient | Cross-sectional | 245 | 65.1 (14.0) | IIEF-5 | 5 |
| Fernandes, 2010 | Brazil | Outpatient | Cross-sectional | 275 | 48.6 (12.8) | IIEF-5 | 4 |
| Gorsane, 2016 | Tunisia | Outpatient | Cross-sectional | 30 | 49.1 (NA) | IIEF-5 | 5 |
| Hassan, 2018 | Israel | Outpatient | Cross-sectional | 39 | 62.7 (12.2) | IIEF-5 | 5 |
| Hassan, 2018 A | Israel | Outpatient | Cross-sectional | 27 | 59 (7.1) | IIEF-5 | 4 |

| Author, year | Country | Setting | Type of study | Sample size | Mean age (SD) | Method of assessment of ED | NOS |
|---|---|---|---|---|---|---|---|
| Inci, 2008 | Turkey | Outpatient | Cross-sectional | 35 | 51.6 (NA) | IIEF-5 | 5 |
| Ka, 2014 | Senegal | Outpatient | Cross-sectional | 73 | 53.8 (12.5) | IIEF-5 | 5 |
| Krishnan, 2003 | Canada | Outpatient | Cross-sectional | 44 | 61.8 (13.9) | IIEF-5 | 5 |
| Lai, 2007 | Taiwan | Outpatient | Cross-sectional | 99 | NA | IIEF-5 | 5 |
| Makarem, 2011 | Iran | Outpatient | Cross-sectional | 59 | 54.7 (14.1) | IIEF-5 | 6 |
| Malekmakan, 2011 | Netherlands | Outpatient | Cross-sectional | 73 | 55.4 (16.1) | IIEF-5 | 4 |
| Messina, 2007 | Brazil | Outpatient | Cross-sectional | 58 | 50.2 (14.6) | IIEF-5 | 5 |
| Neto, 2002 | Brazil | Outpatient | Cross-sectional | 118 | 48 (13) | IIEF-5 | 5 |
| Savadi, 2016 | Iran | Outpatient | Cross-sectional | 30 | 40.2 (8.2) | IIEF-5 | 5 |
| Seck, 2011 | Senegal | Outpatient | Cross-sectional | 70 | 52 (11.3) | IIEF-5 | 4 |
| Toprak, 2017 | Turkey | Outpatient | Cross-sectional | 372 | 72.5 (4.4) | IIEF-5 | 5 |
| Wong, 2007 | Canada | Outpatient | Cross-sectional | 55 | 50 (NA) | IIEF-5 | 5 |
| Ye, 2015 | China | Outpatient | Cross-sectional | 170 | 43.2 (9.6) | IIEF-5 | 6 |
| Zamd, 2005 | Morocco | Outpatient | Cross-sectional | 86 | 46.3 (15.7) | IIEF-5 | 5 |
| **Total** | | **34 studies: outpatients** | **30 studies: cross-sectional; 4 studies: case-control** | **5986** | **53.9 (12.3)** | **34 studies: IIEF-5** | **5** |

Abbreviations: ED, erectile dysfunction; SD, standard deviation; IIEF, International Index of Erectile Function ; NOS, Newcastle-Ottawa Scale.

342 Table 2. Meta regression of moderators of erectile dysfunction presence by CKD stage

| Moderator* | Number of comparisons | β | 95% CI | P-value | $R^2$ |
|---|---|---|---|---|---|
| | | ***Hemodialysis*** | | | |
| *Mean age of the population* | 1 | 0.0064 | (-0.0352 0.0479) | 0.7643 | 0.00% |
| *Mean duration of HD* | 1 | 0.0018 | (-0.0033 0.0070) | 0.4859 | 0.00% |
| *Prevalence of diabetes* | 1 | 0.6080 | (-1.3604 2.5763) | 0.5449 | 0.00% |
| *Prevalence of hypertension* | 1 | -0.1638 | (-1.3120 0.9844) | 0.7798 | 0.00% |
| *Prevalence of cardiovascular disease* | 1 | 0.8614 | (-1.5732 3.2960) | 0.4880 | 8.49% |
| *Prevalence of active smokers* | 1 | 0.7864 | (-2.0262 3.5989) | 0.5837 | 0.00% |
| | | ***All studies*** | | | |
| *Mean age of the population* | 1 | 0.0100 | (-0.0185, 0.0386) | 0.4912 | 0.00% |
| *Mean duration of HD* | 1 | 0.0014 | (-0.0036, 0.0064) | 0.5937 | 0.00% |
| *Prevalence of diabetes* | 1 | 0.3892 | (-1.4905, 2.2689) | 0.6848 | 0.00% |
| *Prevalence of hypertension* | 1 | -0.5238 | (-1.5205, 0.4729) | 0.3030 | 0.00% |
| *Prevalence of cardiovascular disease* | 1 | 0.9763 | (-1.4083, 3.3610) | 0.4223 | 3.76% |
| *Prevalence of active smokers* | 1 | 1.1571 | (-0.6038, 2.9180) | 0.1978 | 0.00% |

343 **Abbreviations:** CI, confidence intervals; HD hemodialysi

**Supplementary Table 1: list of eligible studies**


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