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Meta-analyses

Association between fibre intake and indoxyl sulphate/P-cresyl sulphate in patients with chronic kidney disease: Meta-analysis and systematic review of experimental studies

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SUMMARY

Background and objective: Indoxyl sulphate (IS) and p-cresyl sulphate (PCS), which are difficult to excrete adequately out of the body, are closely related to the progression of chronic kidney disease (CKD) and various deuteropathy. Better than peritoneal dialysis (PD) and haemodialysis (HD), dietary fibre has been considered to reduce IS and PCS levels. In view of the absence of formal recommendations on fibre intake in CKD nutritional guidelines, we conducted this meta-analysis to assess the effects of dietary fibre on IS and PCS for CKD patients.

Methods: The effects were pooled and expressed in terms of weighted mean difference (WMD) with 95% confidence interval (95% CI). Q test and I^2 statistics were used to assess the heterogeneity.

Results: A total of 12 relevant estimates from 7 reports, including 203 CKD patients, showed that dietary fibre significantly reduced their PCS level (WMD = −16.160, 95% CI: −23.824, −8.495).

Conclusions: The meta-analysis produced a strong corroboration that dietary fibre intake does have a good therapeutic effect on patients with CKD. The conclusions need to be validated by randomised controlled experiments (RCT) with better design, larger samples, longer course of treatment and higher quality.

1. Introduction

Accumulating studies have shown that uremic toxins make a difference in chronic kidney disease (CKD), and they could trigger a series of secondary diseases and complications such as cardiorenal syndrome, bone and mineral disease (MBD), even cognitive impairment and so on; almost all body organs and systems would be affected by uremic toxins retained during renal dysfunction [1–8]. Despite treatment with peritoneal dialysis (PD) and haemodialysis (HD), the plasma uremic toxin level in a CKD patient's body is still difficult to reduce because some uraemia toxins could be produced by the patient's own metabolism or colonic microbial metabolism and combined with plasma albumins [9]. Because conventional dialysis therapy cannot adequately remove these uremic toxins, researchers have turned to other ways to treat CKD. A growing number of studies over recent years have suggested that intestinal microflora tissue alteration and disruption may lead to the production of uremic toxins and affect the progression of CKD [10]. Therefore, gut-derived uremic toxins, especially indoxyl sulphate (IS) and p-cresyl sulphate (PCS), aroused wide attention from researchers because of their extremely high protein-binding rates, nephrotoxicity and cardiovascular toxicity [11–15].

Since the early 1980s, accumulating studies have already confirmed through constant trials that dietary fibre could alleviate the clinical symptoms of CKD by regulating the growth of intestinal bacteria [16–18]. Yatzidis et al. and Rampton et al. found that dietary fibre could make a significant contribution to reducing serum

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urea and creatinine levels in CKD patients [19,20]. Furthermore, a cross-sectional study in Australia and a cohort study in China suggested that the gut-derived uremic toxin levels in patients with CKD may also be associated with fibre intake [21,22]. Because there is no formal recommendation on fibre intake in the CKD nutritional guidelines and no sufficient experimental study to demonstrate that dietary fibre could actually reduce the level of gut-derived uremic toxins, we conducted this meta-analysis and systematic review of experimental studies to assess the impact of dietary fibre on IS and PCS in CKD patients.

2. Materials and methods

2.1. Search strategy

The relevant reports were collected according to the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for meta-analysis [23,24].

We searched PubMed, Web of Science and Cochrane Library for publications through 1 September 2017, using the search terms 'CKD or chronic kidney disease or HD or haemodialysis or PD or peritoneal dialysis' AND 'fiber' AND 'IS or indoxyl sulfate or PCS or p-cresyl sulfate'. Each identified report was carefully scanned by two of the authors.

2.2. Selection criteria

Reports needed to satisfy the following criteria for inclusion: (1) controlled trials; (2) involved with intervention in CKD patients; (3) at least 2 weeks for course of treatment; (4) have clear dosage design for fibre intake. Reports as follow were excluded: (1) animal or cell trials; (2) observational studies; (3) case reports, reviews, letters or comments; (4) not involved in the association between fibre and IS/PCS in CKD patients.

2.3. Data extraction and quality assessment

Each collected report was reviewed by two reviewers independently and carefully (MY Wu, XL Cai). The data were extracted through a standardised data extraction form. If there was any disagreement among three reviewers, the report was discussed and excluded unless the three reviewers reached a consensus. We used the Heyland Methodological Quality Score to assess the report quality, based on nine quality criteria: randomisation, analysis, blinding, participant selection, comparability of groups at baseline, course of treatment, treatment protocol, co-interventions applied equally across groups and results; studies receiving scores $\geq$8 were considered of high methodological quality (high MQS). The extracted information of included reports consisted of first author's name, publication year, participants, sample size, country, average age, study design, type of fibre, dose design, course of treatment (days) and the intervention results of two groups.

If a report collected treatment data at two or more time points, the treatment results were analysed separately as independent trials. Therefore, a report provided two sets of experimental data with the same group of patients [25]. To perform meta-analysis of measurement data, mean value and standard deviation (SD) were used to express and analyse the effect of dietary fibre for IS/PCS on CKD patients. It is of note that two of the included reports used p-cresol as their microbial metabolites. In fact, these levels are the reflection of two conjugates, PCS and p-cresyl glucuronide (PCG), because p-cresol cannot be measured at present. The majority of p-cresol is metabolised into PCS. Only a very small part will be metabolised into PCG; therefore, we use the levels of p-cresol to estimate the levels of PCS through conversion [26]. The meta-analyst converted some trial data from median and interquartile range (IQR) to mean value and SD through a standard formula mentioned by Hozo et al. [27].

2.4. Statistical analysis

All statistical analysis was performed with STATA 12.0 (StataCorp LP, College Station, TX) software. Meta-regression analysis was conducted to verify whether some covariates (study design, stable dosage of dietary fibre intake, average age and course of treatment) would influence the association between dietary fibre intake and IS/PCS, and we could confirm the influence factor with a positive coefficient ($P \leq 0.05$).

The pooled effects of included trials were expressed in terms of weighted mean difference (WMD) with 95% confidence interval (CI). Q test and I^2 statistics were used to assess the heterogeneity among the effect results, and the pooled effect sizes of dietary fibre for IS/PCS on CKD patients were computed using a fixed-effects model or random-effects model. If the χ^2 and I^2 statistics showed no heterogeneity ($P > 0.05$ and $I^2 \leq 50\%$), we used a fixed-effects model; otherwise, we used a random-effects model. Forest plots were produced to show each trial's result and estimate the pooled effect sizes. Publication bias was tested by funnel plots, using Begg's [28] and Egger's [29] tests. Sensitivity analysis was used to measure the impact of each individual trial on the combined effects and the robustness of results.

3. Results

3.1. Search results and trial characteristics

The literature screening process is presented in Fig. 1; 5327 reports were retrieved after the databases were searched, and 27 reports were retained after reviewing the title and summary according to the exclusion criteria. Then 20 reports were excluded after full text review. A total of 12 trials provided by 7 reports satisfied the criteria for inclusion and entered the meta-analysis, 5 trials for plasma IS and 7 trials for plasma PCS.

Details of the trial characteristics are given in Table 1, and the extraction data for the effect of fibre on IS and PCS are given in Table 2. A total of 203 participants with CKD or chronic renal failure completed the trials; both males and females were recruited. The participants tended to be middle-aged men and their average age was 61.5 years. Most of the participants (70.0%) came from North America or Europe, a few came from Australia or Saudi Arabia. Six trials were of RCT (randomised controlled trial) design and 6 trials were of pre–post (PP) design. Nine trials were randomised and 75% of trials used the blind method (double-blinded for 6 and single-blinded for 3). All the trials set up control groups, with a group for supplementary dietary fibre and the other group for placebo. The trials tended to be of short duration with an average course of treatment of five weeks. Each trial identified the type of dietary fibre used and described the dosage design in detail; resistant starch and inulin were the main source of dietary fibre. Most trials allowed patients to take a half dose of dietary fibre before reaching a stable dosage to prevent gastrointestinal discomfort. Seventy-five percent of trials were of higher quality, assessed by the Heyland Methodological Quality Score ($\geq$8).

3.2. Fibre intake and IS

A total of 5 trials for plasma IS were included in this meta-analysis [30–34]. The average plasma IS level of the placebo group was 45.120 μM (range: 5.628–145.399 μM), whereas the

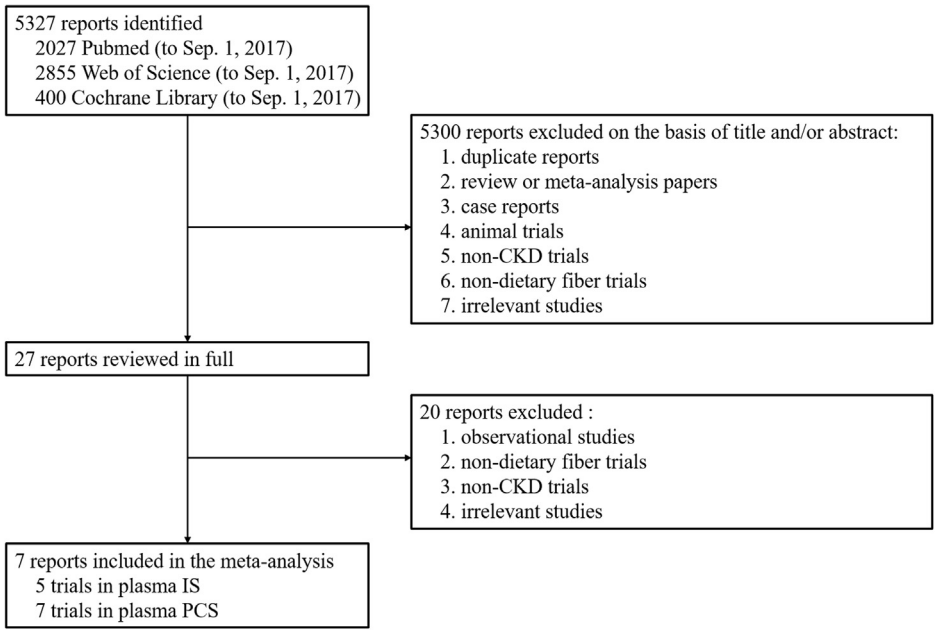

Fig. 1. Flowchart of search strategy.

Table 1
Characteristics of included trials in the meta-analysis.

Study, Year	Study design	Randomisation	Blinding	Course of treatment (days)	Stage of CKD	Type of fibre	Dose design	MQS
Meijers, 2010	PP	N	Not blinded	28	NA	Oligofructose-enriched inulin	10 g/d for the first week, 20 g/d for following weeks	7
Sirich, 2014	RCT	Y	Single-blinded	42	NA	Resistant starch	9 g/d for the first week, 18 g/d for following weeks	10
Guida (1), 2014	RCT	Y	Double-blinded	15	stage 3–4 CKD	Inulin & resistant starch	10.5 g/d	11
Guida (2), 2014	RCT	Y	Double-blinded	30	stage 3–4 CKD	Inulin & resistant starch	10.5 g/d	11
Salmean, 2015	PP	N	Single-blinded	70	stage 3–5 CKD	Pea hull & inulin	10 g/d for the first four weeks, 25 g/d for following weeks	7
Rossi, 2016	RCT	Y	Double-blinded	42	stage 4–5 CKD	Synbiotics	7.5 g/d for the first three weeks, 15 g/d for following weeks	10
Poesen, 2016	PP	Y	Double-blinded	28	stage 3–4 CKD	Arabinoxylan oligosaccharides	20 g/d	13
Elamin, 2017	PP	Y	Not blinded	28	stage 3B–4 CKD	Gum arabic	25 g/d	10

Notes: HD, hemodialysis; CKD, chronic kidney disease; PP, pre–post; RCT, randomised controlled trials; N, no; Y, yes; MQS, Methodological Quality Score.

supplementary dietary fibre group's plasma IS level was 42.682 μM (range: 5.628–136.018 μM). Meta-regression analysis was conducted to verify the possible influential factors, and the result showed that study design (pre–post trials or randomised controlled trials), stable dosage of dietary fibre intake (<20 g/d or ≥20 g/d), average age (≤60 or >60) and course of treatment (≤28d or >28d) were not influential factors (study design: $P = 0.746$; stable dosage of dietary fibre intake: $P = 0.746$; average age: $P = 0.981$; course of treatment: $P = 0.746$). Therefore, all 5 estimates were incorporated into the meta-analysis.

There is no statistical evidence that fibre could reduce the plasma IS in the overall analysis (WMD = −0.212, 95% CI: −2.350,

Table 2
Extraction data for the effect of fibre on IS and PCS.

Study		Average age, years	Country	Fibre total	$\bar{x}\pm s$(μm)	Control total	$\bar{x}\pm s$(μm)
IS	Meijers	62.2 ± 12.8	Belgium	22	105.20 ± 66.57	22	111.1 ± 74.72
	Sirich	56 (>18)	America	20	136.02 ± 65.66	20	145.40 ± 56.28
	Rossi	69 ± 10	Australia	31	15.00 ± 11.86	31	16.00 ± 11.11
	Poesen	70 ± 6	Belgium	40	10.86 ± 5.63	40	10.90 ± 5.71
	Elamin	49.8 (>18)	Saudi Arabia	30	5.63 ± 11.26	30	5.63 ± 13.60
PCS	Meijers	62.2 ± 12.8	Belgium	22	170.00 ± 114.234	22	204.60 ± 130.47
	Sirich	56 (>18)	America	20	154.09 ± 85.02	20	164.72 ± 74.39
	Guida (1)	59.5 ± 13.1	Italy	18	21.27 ± 21.92	12	34.22 ± 28.11
	Guida (2)	59.5 ± 13.1	Italy	18	7.40 ± 23.30	12	36.06 ± 17.85
	Salmean	65 ± 3	America	10	53.82 ± 15.91	10	67.04 ± 16.09
	Poesen	70 ± 6	Belgium	40	50.16 ± 50.82	40	52.00 ± 37.81
	Rossi	69 ± 10	Australia	31	75.00 ± 48.19	31	93.00 ± 60.79

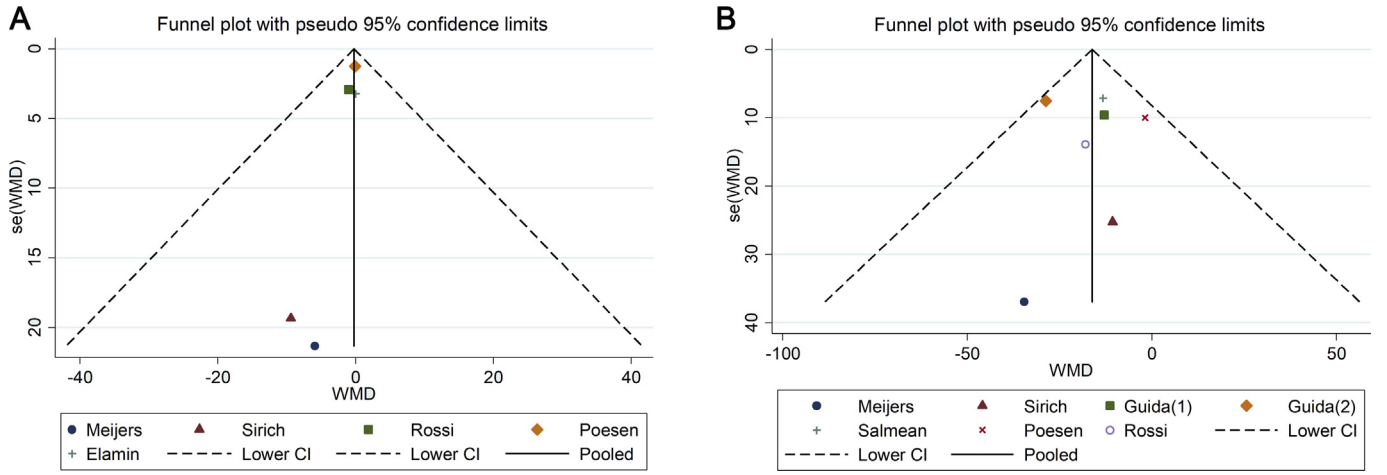

Fig. 2. Funnel plots with pseudo 95% confidence intervals. (A) Funnel plots for IS. (B) Funnel plots for PCS.

1.926). The funnel plot, as shown in Fig. 2, suggested we could rule out the publication bias (Begg's test $z_C = 0.73$, $P = 0.462$; Egger's test $t = -3.09$, $P = 0.054$). The results of subgroup analysis also supported the general conclusion from overall analysis and we still did not find any obvious effects of dietary fibre on plasma IS. The meta-analysis result was robust according to the sensitivity analysis as shown in Fig. 3 and the result is given in Table 3.

Generally, it seemed that dietary fibre had no significant pooled effect on plasma IS for CKD patients.

3.3. Fibre intake and PCS

A total of 7 trials for plasma PCS were included in this meta-analysis [25,30–33,35]. The average plasma PCS level of the placebo group was 92.722 μM (range: 19.660–204.626 μM), whereas the supplementary dietary fibre group's plasma PCS level was 75.931 μM (range: 7.386–169.981 μM). Meta-regression analysis was conducted to verify the possible influential factors, and the result showed that study design (pre–post trials or randomised controlled trials), stable dosage of dietary fibre intake (<20 g/d or ≥20 g/d), average age (≤60 or >60) and course of treatment (≤28d or >28d) were not influential factors (study design: $P = 0.212$; stable dosage of dietary fibre intake: $P = 0.212$; average age: $P = 0.260$; course of treatment: $P = 0.233$). Therefore, all seven estimates were incorporated into the meta-analysis.

The result of pooled analysis is shown in Fig. 4. Compared with the placebo group, the plasma PCS level of the supplementary dietary fibre group was significantly reduced (WMD = −16.160, 95% CI: −23.824, −8.495). The funnel plot showed no obvious asymmetry among these trials, and we could rule out the publication bias (Begg's test $z_C = 0.60$, $P = 0.548$; Egger's test $t = 0.09$, $P = 0.933$) (Fig. 3). The meta-analysis result was robust according to the sensitivity analysis as shown in Fig. 4 and the result is given in Table 3.

4. Discussion

Uraemia toxins are difficult to excrete adequately out of the body through urine for patients with renal dysfunction, and they will keep accumulating in the body. They are closely related to the progression of CKD and various deuteropathy such as cardiovascular disease (CVD), mineral and bone disorder (MBD) and central nervous system disorder (CNSD). Almost every organ and system would be negatively affected by uremic toxins. Indoxyl sulphate (IS) and p-cresyl sulphate (PCS) have attracted the most attention from researchers for their toxicity among all the uraemia toxins. Patients with CKD are at obviously higher risk of CVD than the general population [36]. A series of studies have shown that IS and PCS play a prominent role in the occurrence and progression of CVD [37–39]. They aggravate CVD by promoting pro-oxidant and

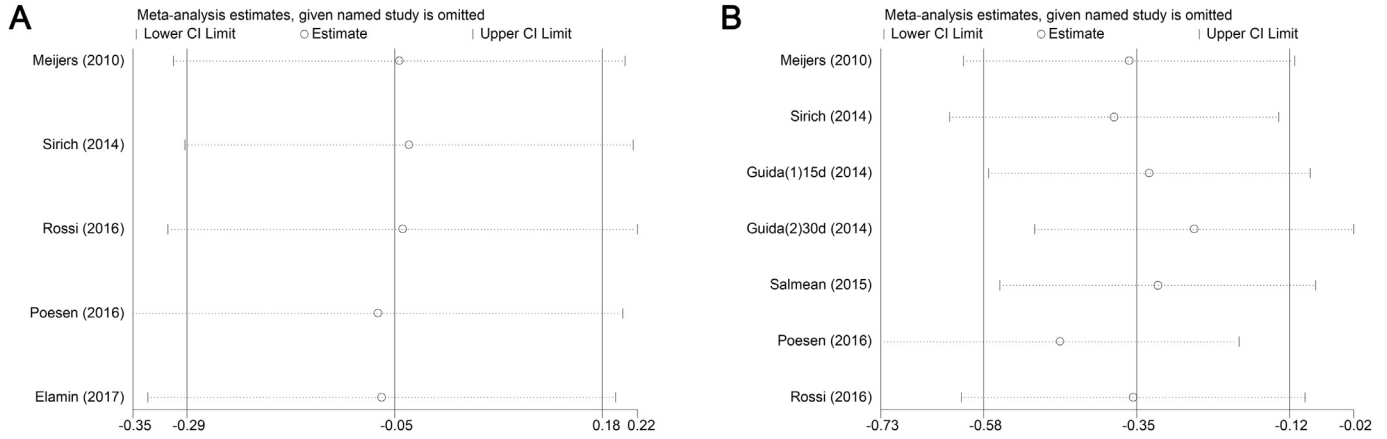

Fig. 3. Results of sensitivity analysis. (A) Sensitivity analysis for IS. (B) Sensitivity analysis for PCS.

Table 3
Sensitivity analysis result of IS and PCS.

Study omitted		Estimate (μm)	95% CI
IS	Meijers, 2010	−0.050	−0.302–0.202
	Sirich, 2014	−0.039	−0.289–0.211
	Rossi, 2016	−0.046	−0.308–0.216
	Poesen, 2016	−0.074	−0.347–0.200
	Elamin, 2017	−0.070	−0.330–0.191
	Combined	−0.055	−0.287–0.177
PCS	Meijers, 2010	−0.359	−0.606–0.111
	Sirich, 2014	−0.381	−0.627–0.135
	Guida (1), 2014	−0.329	−0.569–0.088
	Guida (2), 2014	−0.261	−0.500–0.023
	Salmean, 2015	−0.315	−0.552–0.080
	Poesen, 2016	−0.462	−0.730–0.194
	Rossi, 2016	−0.352	−0.609–0.100
	Combined	−0.347	−0.576–0.119

pro-inflammatory response; the toxins on the endothelium could inhibit endothelial repair and participate in accelerating atherosclerosis (AS). It has a greatly negative effect on the prognosis for CKD and will tremendously reduce the quality of life of patients. Some studies concluded that the increases of IS and PCS levels are associated with rising mortality in patients with CKD, and PCS may also be associated with higher risk of CVD [40–42]. Both IS and PCS are primarily produced in the gut and are difficult to get rid of completely by PD or HD because they have extremely high protein-binding capacity. The metabolism of intestinal microflora could generate many uremic retention solutes, which play an important role in the production of uraemia toxins [43,44]. Since 2001, it has been thought that IS and PCS levels could be reduced by modifying the intestinal flora generation or absorption instead of merely relying on PD or HD [17,43].

Dietary fibre is widely noticed by researchers because it may affect the composition of gastrointestinal microbial communities or change their activity [45–47]. They could stimulate beneficial gut bacteria and confer benefits on the host. As a kind of polysaccharide that could neither be absorbed by the gastrointestinal tract nor produce energy, dietary fibre was once considered a non-nutritive substance and thus did not attract enough attention for a long time. However, with the further development of nutrition and science, researchers have gradually discovered that dietary fibre has a very important physiological function. According to whether it is dissolved in water, dietary fibre can be divided into two categories, soluble dietary fibre and insoluble dietary fibre. Soluble dietary fibre can hardly provide energy but its water absorption is strong. It could be combined with carbohydrates and starch in the gastrointestinal tract and delay the absorption of the latter. Soluble dietary fibre plays a significant role in reducing postprandial blood sugar [48,49]. Insoluble dietary fibre mainly comes from cereal grains. Its role in the human body is to promote gastrointestinal peristalsis, accelerate food through the gastrointestinal tract and reduce absorption. Some insoluble fibre could absorb water, softening the stool in the large intestine, and it plays an important role in preventing and treating constipation [50]. In addition, some studies have shown that dietary fibre also plays an important role in CKD. A trial on rats with CKD showed that dietary fibre intake significantly retards CKD progression; it could attenuates oxidative stress and inflammation [51]. An observational study suggested that a healthy diet, including dietary fibre intake, could reduce the mortality of patients with CKD [52].

Our meta-analysis is another strong corroboration that dietary fibre intake does have a good therapeutic effect on patients with CKD. We used meta-regression to determine that different study designs did not have an impact on the results. Although we did not get effective evidence that dietary fibre could reduce plasma IS levels, the pooled effects from 7 relevant trials showed that dietary fibre could significantly reduce plasma PCS in the patients with CKD. This outcome has positive implications for clinical treatment. Compared with PD and HD, dietary fibre is less burdensome for patients. Both PD and HD have relative contraindications, and it seems that they may cause more complications and infections. Once the treatment regimen is identified, the patients may take dietary fibre at home to control the level of uremic toxins without going to the hospital frequently. Because we were restricted to the number of included reports, we did not conduct subgroup analysis. Therefore, we could not assess the effect of dietary fibre for different age groups or different course of treatment groups. However, as with other medications, dietary fibre may have different effects on people of various age levels, which is closely related to the physiological condition of the patients themselves, and researchers should develop different dietary fibre–taking programs for them. Stable dietary fibre intake may have a more consistent and significant effect on reducing the PCS level for CKD patients. Considering the pathway and half-life of dietary fibre in vivo, the optimal course of treatment should be carefully determined, especially when further relevant trials are done in the future.

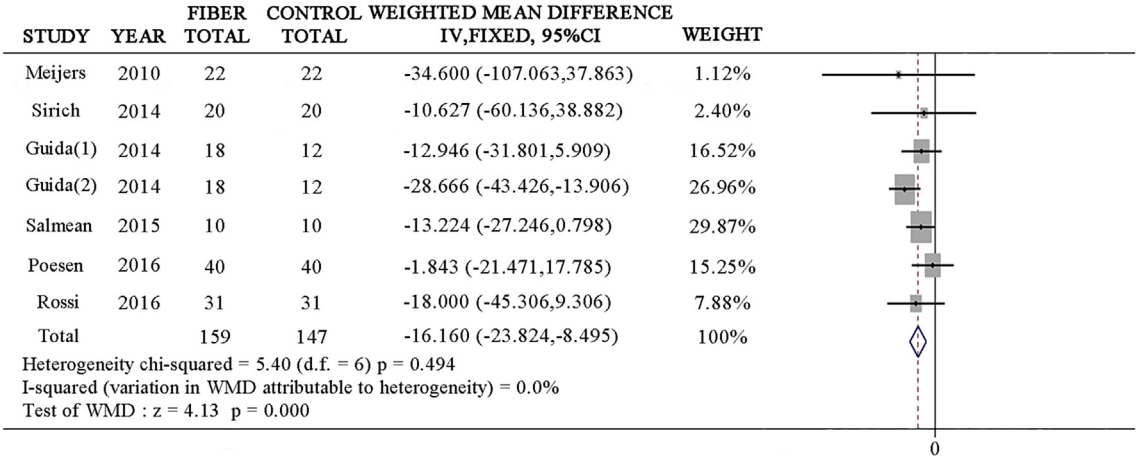

Fig. 4. Forest plot for the effect of fibre on plasma PCS (mg/dl). The pooled effects of included trials were expressed in terms of weighted mean difference (WMD) with 95 percent confidence interval (CI), using a fixed-effects model. Q test and I^2 statistics were used to assess heterogeneity among the effect results at a significance level of $P \leq 0.10$. If $I^2 \geq 50\%$, it was considered to be significantly heterogeneity.

Our meta-analysis has some limitations. Only seven reports satisfied our screening criteria, only five trials on IS. We do not have enough samples for subgroup analysis. In Poesen's report, we extracted the data of indoxyl sulphate and p-cresyl sulphate during treatment with fibre intake through figures. Although this may cause some errors, we do not want to lose this valuable research data due to the current sparse research on fibre and uremic toxins. The variety of dietary fibre is very broad, and its working mechanism in the body is not completely clear. Currently, there are no detailed criteria or guidelines for dietary fibre intake for patients with CKD. We note that almost all the enrolled patients are at stage 3–5 of CKD so that we cannot conduct further subgroup analysis of this information. Compared to other treatments, the role of fibre in CKD patients is easily overlooked, so choosing the patients who are at stage 3–5 of CKD for these experimental studies may be a better way to study the association between fibre intake and indoxyl sulphate/p-cresyl sulphate. But we also think it necessary to obtain corresponding data from patients at other stage of CKD to demonstrate our conclusions in further research. Our meta-analysis lacks discussion on different kinds of dietary fibres. Besides, we did not have a good enough judgment on the dosage groups; all of the studies included set only a dietary fibre supplementary group and a placebo group as control, without high–low dose comparisons, which leads to our conclusion being affected rather than perfect. Not all trials were conducted long enough, and we were not able to compare the long-term effect and relative short-term effect. The sources of the included reports were limited, lacking trials from underdeveloped or developing countries. In addition, we just discussed the relationship between dietary fibre and IS/PCS; the role of dietary fibre on other uremic toxins remains to be further studied.

Our research also has some advantages. Ours is the first meta-analysis to evaluate the impact of dietary fibre intake on uraemia toxins systematically for patients with CKD. There is no obvious heterogeneity among the reports included through meta-regression analysis and sensitivity analysis. Furthermore, according to the Begg's test, Egger's test and the funnel plots, there is no evidence of major publication bias.

To sum up, our conclusions need to be validated by a randomised controlled experiment with better design, larger samples, longer course of treatment and higher quality.

5. Conclusions

The meta-analysis results of pooled data suggest that dietary fibre supplementation in patients with CKD can significantly reduce the level of plasma PCS, which is one of the main gut-derived uraemia toxins and closely associated with the progress of CKD. However, there is no obvious evidence to show that dietary fibre intake can also reduce the level of plasma IS in CKD patients.

Statement of authorship

XY Li, MY Wu and XL Cai conceived and designed the meta-analysis; MY Wu, JJ Lin and XH Zhang searched the literature; MY Wu, JJ Lin and XH Zhang analysed the data; XL Cai contributed analysis tools; MY Wu wrote the paper; XY Li and E.M.Scott revised the manuscript.

Conflicts of interest and statement of funding sources

The authors declare no conflicts of interest.

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