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Review Article

Prevalence of cognitive impairment in chronic kidney disease patients with hypertension or diabetes: a meta-analysis and review

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Abstract: Objective: The goal of this study was to evaluate the incidence of cognitive impairment in chronic kidney disease CKD patients with hypertension or diabetes and to explore its pathological mechanism. Methods: PubMed and Embase were systematically searched to collect literature on cognitive function changes in CKD patients with hypertension or diabetes published on or before Novermber 30th 2016. Heterogeneity test was performed by RevMan 5.3 software. Overall odds ratio and 95% confidence interval was calculated. Results: A total of 8 references were included in this meta-analysis, including 138,943 CKD patients. The incidence of cognitive impairment was calculated for CKD with hypertension or diabetes groups. Meta-analysis showed that the incidence of cognitive impairment in CKD patients with hypertension or diabetes was higher compared with CKD alone (CKD with hypertension vs. CKD alone, $P < 0.0001$, OR = 1.33, 95% CI: 1.26 to 1.53; CKD with diabetes vs. CKD alone, $P < 0.00001$; OR = 1.39, 95% CI, 1.16 to 1.53). The incidence of cognitive impairment in CKD with diabetes was higher compared with CKD with hypertension ($P = 0.02$; OR = 1.16; 95% CI, 1.02 to 1.33). The high incidence rate of cognitive impairment in CKD with the diabetes group might be associated with calcium overload, mitochondrial damage, and long-term hyperglycemia, leading to Aβ deposition and brain tissue damage. The use of angiotensin-converting-enzyme inhibitor to lower the blood pressure in CKD patients with hypertension not only reduced endothelial damage, but also decreased Aβ deposition. Conclusion: The incidence of cognitive impairment in CKD patients with diabetes is higher compared with other CKD patients including those with hypertension. The specific pathogenesis needs further exploration.

Keywords: CKD, cognitive impairment, hypertension, diabetes, meta analysis

Introduction

The kidney has important functions including metabolite clearance, electrolyte and acid-base balance regulation, and especially endocrine secretion. Hormones secreted by kidney can affect erythropoietic growth, maintain bone metabolism, and regulate hemodynamics. Generally, kidney damage lasting more than 3 months or with glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 is defined as chronic kidney disease (CKD). In recent years, the prevalence of CKD has greatly risen, making it one of the 20 leading causes of death according to the Global Burden of Disease Study 2010 [1]. In developed countries, the prevalence of CKD is approaching 5-6% [1]. In the United States, 45% of the patients with chronic kidney disease are over 70 years of age [2]. The prevention and treatment of CKD has become an important worldwide public health issue.

Mental illness and cognitive impairment is common in patients with CKD. Approximately 5% of CKD patients are diagnosed of cognitive impairment [2]. Moreover, as CKD progression from stage 3 to stage 5, the prevalence of cognitive impairment increases from 20-50% to 70% [2]. Patients with end-stage CKD even have delirium, coma, dementia, and other symptoms [1]. Cognitive decline in patients with CKD might be related to nephrotoxins, oxidative stress, cytokines, RAS, hemodynamic changes, asymptomatic cerebral ischemia and other factors. Cardiovascular disease is a common complica-

tion and leading cause of death in CKD patients. Most CKD patients have different degrees of hypertension due to water/sodium retention and increased renin-angiotensin. With the increase in blood pressure and blood flow of brain tissue, the endothelial structure and function are impaired, causing ischemic changes of the brain. When eGFR < 60 ml.min^{-1} per 1.73 m^2, and age > 75 years old, extensive small vessel disease is recognized as an independent risk factor for cognitive impairment [3]. Insulin resistance is also common in CKD patients probably due to reduced ability in renal decomposition of small molecules and other reasons, resulting in diabetes. Chronic hyperglycemia aggravates cerebral ischemic injury, induces Aβ deposition, and aggravates cognitive impairment [4, 5]. Unfortunately, the pathogenesis of cognitive impairment in patients with CKD is not yet fully understood until now. Moreover, the incidence rate of cognitive impairment in CKD patients with hypertension or diabetes and the relevant pathogenesis has not been previously studied, which will be addressed in this meta-analysis.

Methods

Data sources and literature screening

Literature published in English until November 30 2016 was searched mainly through Medline, Pubmed, and Embase, using keywords including CKD, hypertension, diabetes, and cognitive impairment. Included studies were those with randomized, cross-sectional, logical, COX regression, and observational data. According to different purpose of studies, cognitive function was assessed using MMSE, Trails B, modified MMSE, draw-bell experiment, speaking fluency test, Centre for Epidemiological Survey Depression Scale (CES-D) and Montreal Cognitive Assessment, respectively. Studies were excluded based on the following: (1) case reports, meeting reports, reviews, animal experiments, patients aged less than 18 years old and kidney transplant patients; (2) studies not associated with changes in cognitive function in CKD patients with hypertension or diabetes; (3) data cannot be used to calculate odds ratio (OR) value; (4) cognitive function of patients was not assessed.

Data extraction and quality assessment

Two authors (CZ and XP) independently screened the literature for relevant studies based on the title/abstract. In the second round of screening, both authors read the full text of initially selected studies to determine if these studies met the inclusion criteria based on information of patients, outcome (dementia/cognitive impairment/cognitive decline), data, and cognitive assessment scale. The included studies were grouped according to the research purposes, and subjected to quality assessment using the Newcastle-Ottawa Scale (NOS).

Method summary and comprehensive data

The extent of cognitive impairment in similar or identical cognitive domains was assessed using multiple cognitive function assessment scales. Glomerular filtration rate is a sensitive indicator of renal function, and eGFR is commonly used for clinical evaluation, representing the amount of renal interstitial fluid produced per unit time. eGFR < 60 mL/min/1.73 m^2 is defined as moderate kidney injury, and eGFR < 45 mL/min/1.73 m^2 represents moderate to severe renal impairment, i.e. late CKD. When eGFR < 15 mL/min/1.73 m^2, it enters the end-stage of CKD and requires dialysis for maintenance. GFR can be estimated by serum creatinine or Cys-C, whereas most of the eGFRs included in the study were obtained from serum creatinine level. A random-effect model was used in this meta-analysis. The strength of the association between exposure factors and cognitive impairment was expressed as the value of OR. The confidence level of the parameters was expressed as 95% confidence interval, and the heterogeneity was expressed as I^2. Review Manager 5.0 was used to calculate the data.

Results

Characteristics of included studies

The selection procedure is shown in **Figure 1**. A total of 226 articles were initially retrieved, of which 144 did not fit the research objective of this study, including renal transplantation (n = 25), case report/meeting report/review (n = 97), animal study and basic experimental study (n = 18), and subjects under 18 years old (n = 4), and thus were excluded. Of the remaining 82 studies, 66 were excluded due to inability to obtain sufficient raw data to calculate OR value (n = 35), unavailability of cognitive function assessment of study subjects (n = 18), or irrelevance to the purpose of this study (n = 21). Finally, 8 articles were included in this analysis

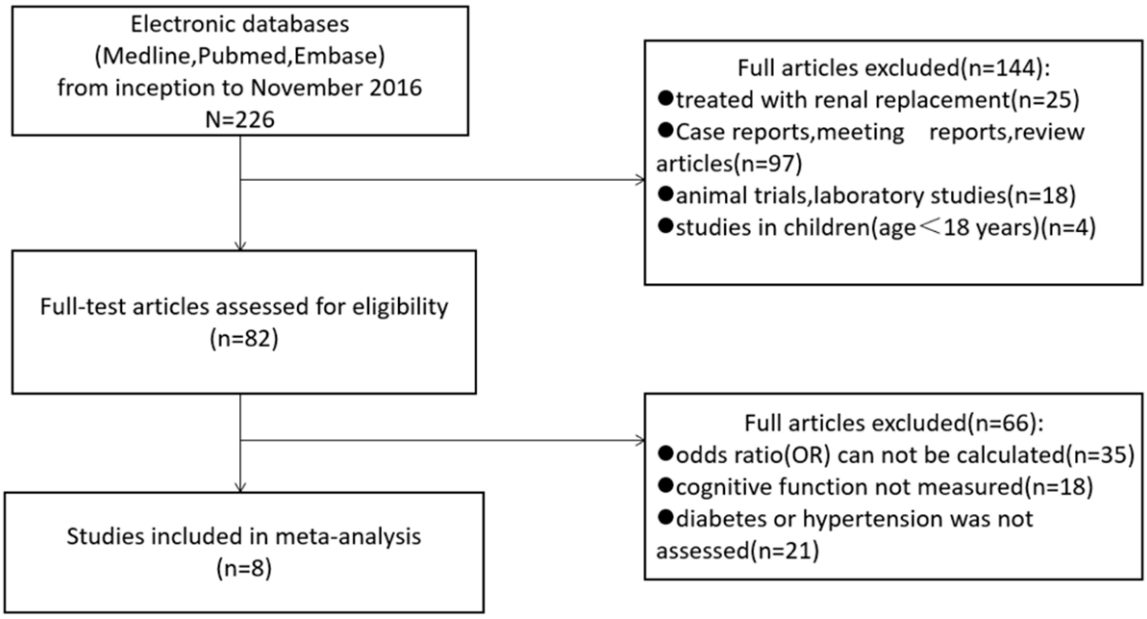

Figure 1. Flow chart of literature review and study selection process.

Table 1. Characteristics of included studies in meta-analysis

Author (year)	Total No.	Male (n)	Age (year)	Type of therapy	The stage of kidney disease	Areas	Follow up time	Cognitive Test/ Diagnostic Criteria
Giovanni et al. [6] (2014)	190	102	77±5.1	/	CKD2-5	Italy	/	MMSE
Fang W et al. [7] (2010)	1243	587	58.8±9.6	/	CKD1-3	China	/	MMSE
Brian T et al. [8] (2010)	241	123	63.8±16.6	HD	CKD5	America	/	CES-D (cognitive impairment score ≥16), MMSE, Trail-Making Test B
Mauizio B et al. [9] (2014)	72	45	62±15	HD	CKD4-5	Italy	/	MMSE
Helmer C et al. [10] (2011)	7839	3038	73.9±5.4	/	CKD3-5	France	7 years	MMSE
Dong J et al. [11] (2015)	458	236	52.1±14.2	PD	CKD5	China	/	3MSE, Trail-Making Test A and B
Kristine Y et al. [12] (2010)	825	416	64.9±5.6	/	CKD2-5	America & UK	/	3MSE, Trail-Making Test A and B, Boston Naming, Verbal Learning
Thorleif E et al. [13] (2009)	3679	1508	73±7.5	/	CKD2-5	America	2 years	6CIT (cognitive impairment score > 7)

Abbreviations: MMSE, Mini-Mental State Examination; 3MSE, modified Mini-Mental Sate Examination; 6CIT, 6-Item Cognitive Impairment Test; ICD-9-CM, International Classification of Diseases 9th Revision and Clinical Modification; TAP, Test of Attention Performance; CKD, chronic kidney disease; PD, peritoneal dialysis; HD, hemodialysis.

including a total of 138,943 patients [6-13]. Detailed information of the literature included in the meta-analysis are listed in **Table 1**. The included studies are all cohort studies and scored on NOS. The quality of the included articles was moderate, with a score of 5.62±0.74 in a 10-star rating system (**Figure 2**).

Evaluation of renal function and cognitive function

The eGFR for renal function in the inclusive population was calculated according to the Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines based on the serum creatinine level. The general cognitive function assessment scale was used to comprehensively evaluate the cognitive status and characteristics of the subjects to facilitate the initial cognitive function screening. The assessments included: (1) Mini-Mental State Examination (MMSE), which defines score under 24 as cognitive dysfunction, valuable for the identification of normal cognitive function or dementia; (2) Modified Mini-Mental State Examination (3MSE), which is used for the assessments in the fields of orientation, attention, language and memory, defining score under 80 as dementia; (3) 6-Item Cognitive Impairment Test (6CIT), which is quick and simple, and suitable for large sample research; (4) clock drawing test (CDT), which defines the score of 30-points-

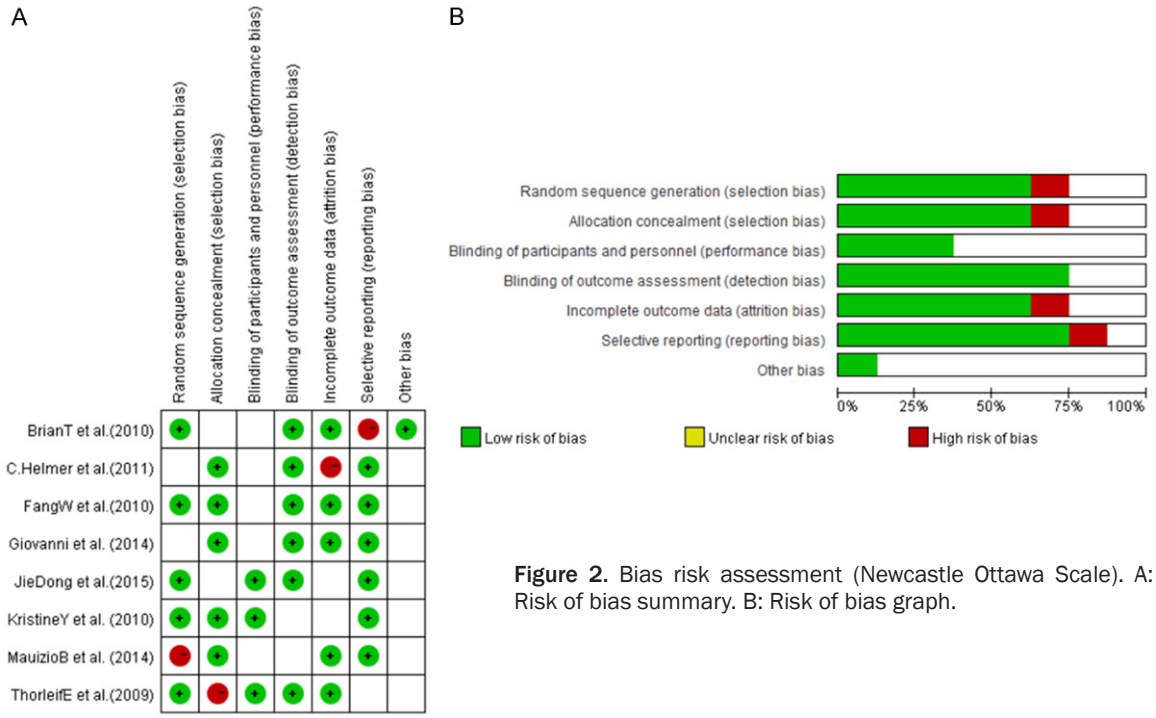

Figure 2. Bias risk assessment (Newcastle Ottawa Scale). A: Risk of bias summary. B: Risk of bias graph.

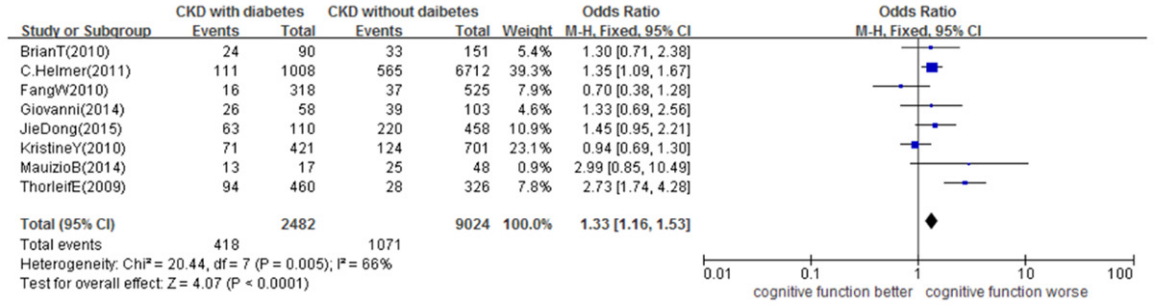

Figure 3. Forest plot assessing the relationship between diabetes and cognitive impairment in CKD patients.

method-A under 2 as mild cognitive impairment, and so as the score of 30-points-method-B under 17. Part of the results were obtained through neuropsychological test, clinical evaluation, diagnosis of related diseases and other methods. A total of 8 articles performed in-depth analysis on the changes in cognitive function in CKD patients with hypertension or diabetes, and 3 studies revealed a significant decline in cognitive function for both patient groups.

Diabetes is a risk factor for cognitive impairment in CKD patients

Eight articles [6-13], and a total of 11,506 subjects were included. CKD patients were divided into experimental group and control group based on whether or not with diabetes, in order to analyze the association between diabetes and the occurrence of cognitive impairment in CKD patients. The OR value of two of those studies was < 1, and the confidence intervals were (0.38, 1.28) and (0.69, 1.30), respectively, while the OR value of the studies as a whole was > 1 and the confidence interval was (1.16, 1.53). The p value was < 0.0001, and I^2 was equal to 66% (**Figure 3**).

Hypertension is a risk factor for cognitive impairment in CKD patients

A total of 8 papers in the related literature were included [6-13], totaling 14,087 subjects.

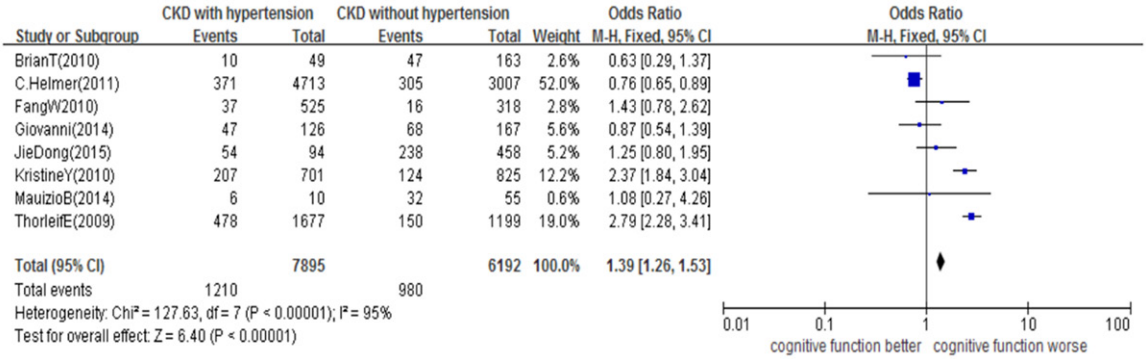

Figure 4. Forest plot assessing the relationship between hypertension and cognitive impairment in CKD patients.

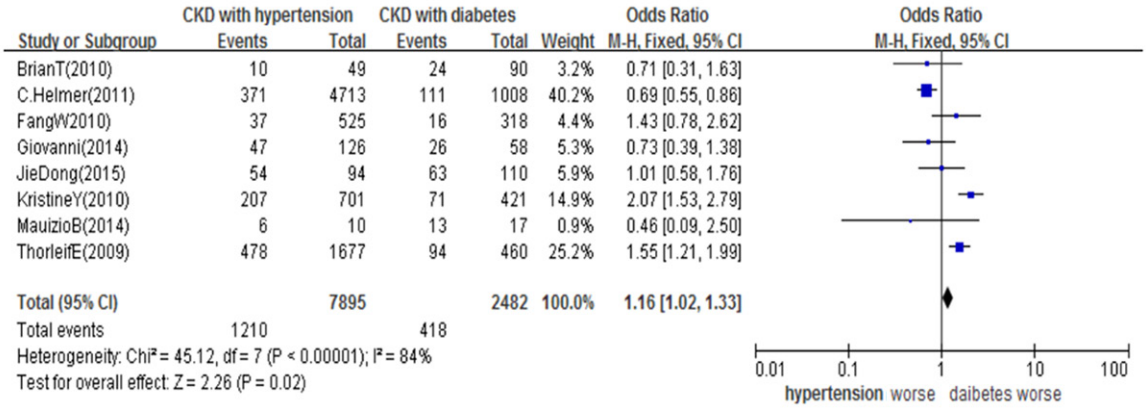

Figure 5. Forest plot comparing the incidence rate of cognitive impairment in CKD patients with diabetes and those with hypertension.

According to whether or not combined with hypertension, the subjects were divided into an experimental group and a control group. A forest diagram was used to show the relationship between hypertension and the incidence of cognitive impairment in the CKD population. Among those, three studies had OR values < 1 (OR = 0.63, 0.76, 0.87) with the confidence intervals of (0.29, 1.37), (0.65, 0.89), and (0.54, 1.39), respectively. However, the results of the whole study indicated that the OR value was > 1 (OR = 1.39), and the confidence interval was (1.26, 1.53) with *p* value < 0.00001 and I^2 = 95% (**Figure 4**).

Diabetes has a stronger association with cognitive impairment in CKD patients compared with hypertension

This meta-analysis explored the relationship of different complications with cognitive impairment or decline in patients with CKD. A total of 10,377 subjects were included in this study. The results indicate that in comparison of hypertension, diabetes was more strongly associated with cognitive decline in patients with CKD. The OR value was 1.16, and confidence interval was (1.02, 1.33) with *p* value = 0.02 and I^2 = 84% (**Figure 5**).

Discussion

This meta-analysis revealed that in CKD patients combined with hypertension or diabetes, the incidence of cognitive impairment was higher than that in patients with CKD only. This conclusion confirmed that diabetes/hypertension as risk factors for cognitive disorder, significantly aggravated the impairment of cognitive function in CKD patients. The relationship of other risk factors, such as infection, anemia, and hyperparathyroidism, with cognitive impairment in CKD patients was still not clear, due to no available relevant data obtained in the literature included in this article. At the same time, regarding the increase of the incidence of cog-

nitive impairment by hypertension or diabetes in patients with CKD, currently the pathogenesis was not yet clear. According to the literature, it may be related to aggravation of cerebral ischemic injury, Aβ deposition and activation of related mechanisms by the complications. First of all, for patients with renal insufficiency, part of the compounds cannot be excreted by the kidney, such as uric acid, indole sulphate sulfate, interleukin 1-β, interleukin 6, TNF-α, and PTH, and accumulate in the body, resulting in increased endothelial dysfunction [14, 15]. When endothelial function is impaired, ischemic changes occur in the corresponding tissues, and further develop into complete or incomplete cerebral infarction, lacunar cerebral infarction as well as demyelination changes [16, 17]. In addition, elevated blood glucose levels in CKD patients cause calcium overload and altered mitochondrial osmotic pressure, leading to further DNA fragmentation and Aβ deposition [4, 5]. Also in CKD patients with elevated blood pressure, endothelial dysfunction causes low perfusion of brain tissue, while RAAS activation increases perfusion. However, brain tissue as a low vascular resistance system is vulnerable to high volume perfusion damage in endothelial function. Furthermore, ACE releases ACE inhibitors to lower blood pressure, but ACE also aggravates Aβ amyloid deposition in frontal cortex. The elevated blood pressure can also increase the expression of RAGE, thereby aggravating Aβ deposition [18]. Whether CKD patients were with hypertension or diabetes mellitus, it can aggravate Aβ deposition, so the cognitive functions in relevant subjects declined significantly.

In CKD patients with diabetes, cognitive function was decreased more significantly and with a higher incidence than that in those with hypertension. This suggests that fluctuations in blood glucose levels have a greater impact on cognitive impairment than blood pressure fluctuations. Additionally, it is already known that acute changes in blood glucose levels will change local cerebral blood flow and neuronal osmotic pressure, and long-term chronic hyperglycemia cause small blood vessel diseases mainly in retina, nerve, and kidney. The EDIC study (Epidemiology of Diabetes Interventions and Complications) revealed that increased HbA1c slowed down patients' movements, while by strict glycemic control cognitive function in patients could be improved. It can be inferred that elevated blood glucose levels will aggravate cognitive impairment. In addition, elevated blood glucose and plasma cortisol levels led to dysfunction of hypothalamus-pituitary-adrenal (HPA) axis, whereas long-term high glucocorticoid levels impaired function of hippocampus, causing cognitive dysfunction [19]. Also in patients with CKD combination of hypertension mainly incurred small blood vessel lesions, such as cerebral white matter lesions, resulting in cognitive dysfunction. Activation of the RAAS system can improve endothelial cell function using ACEI drugs, and reduce Aβ deposition, thereby delaying cognitive decline in patients. Therefore, the degree of cognitive impairment in CKD patients with hypertension is more controllable, and with less pathological changes than that in those with diabetes, so the incidence of cognitive dysfunction is lower.

Due to the limited number of articles included in the present study, the changes of cognitive function of subjects in groups based on eGFR were not discussed. Although the current related research reports that the incidence of cognitive dysfunction in CKD patients gradually increases as the renal function gradually decreases, no relevant study suggests that hypertension or diabetes would change the course of the disease in different stages of CKD, or aggravate the disease in a certain stage of CKD. It was the use of a variety of cognitive function assessment scales, regardless of type, that resulted in the greater subjectivity of the assessment results. This included the subjects' educational level and sometimes did not truly reflect the subjects' disease status, which thus increased the research heterogeneity.

Different countries and different races were included as research population in this article as much as possible, in order to reduce the impact of racial differences on the research results. To avoid heterogeneous sources from the difference in the indicators of renal function, the articles included in this paper were all based on eGFR as assessment index. Although currently there are only a limited number of related studies regarding how cognitive changes in CKD patients with different comorbidities function. Additionally, the pathogenesis is really complex and not yet clear, therefore this paper takes the lead in conducting meta-analysis and systematic review on this issue, and performing comparative studies between the two common comorbidities of hypertension and diabetes. It is anticipated that more pathophysiological studies with large sample sizes will be reported

on the changes of cognitive function in CKD patients with comorbidities.

Disclosure of conflict of interest

None.

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