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SYSTEMATIC REVIEW

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Kidney function and cognitive impairment: a systematic review and meta-analysis

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ABSTRACT

Background: A worldwide evaluation exploring the link between a broad-spectrum kidney function and cognitive impairment (CI) prevalence, and related risk factors has yet to be conducted.
Methods: Studies published before November 2024 were retrieved from PubMed and Web of Science. R software (R Foundation for Statistical Computing, Vienna, Austria) and Review Manager (Cochrane Collaboration, London, UK) were used to analyze the relationship of CI with various estimated glomerular filtration rate (eGFR) level and the associated risk factors. A random model effect was adopted for a heterogeneity (I^2) of more than 50%.
Results: Seventeen (involving 32,141 participants) out of 5892 studies were included. The MMSE and MoCA were the most commonly used tests to assess cognitive function. The prevalence of CI raised significantly with declining kidney function: 10% for eGFR ≥60 mL/min/1.73 m^2, 47.3% for 60–30 mL/min/1.73 m^2, and 60.6% for <30 mL/min/1.73 m^2, totaling 16.7% overall. Thirteen potential risk factors were ascertained and analyzed. In the forest-plot analysis, T2DM, cardiovascular diseases, cerebrovascular diseases, and lower education emerged as strong predictors of risk, with odds ratios of 1.55, 1.63, 1.95, and 2.59, respectively. A mean meta-analysis of the continuous variable indicators revealed that advanced age and elevated parathyroid hormone (PTH) levels were statistically significant in the occurrence of CI.
Conclusions: The poorer the renal function, the higher the prevalence rate of CI. Patients with chronic kidney disease (CKD) have multiple risk factors that lead to CI.

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Introduction

Chronic kidney disease (CKD) is a pervasive and progressively deteriorating condition that impacts over 10% of the global population, translating to an astonishing figure of over 800 million individuals worldwide [1]. By 2040, CKD is projected to ascend to the fifth leading cause of mortality globally [2]. Coupled with the aging demographic, CKD patients face a significantly heightened vulnerability to cognitive impairment (CI), which has detrimental consequences on their quality of life [3]. CI is often linked with poor health outcomes in CKD patients and mortality, particularly due to cardiovascular and cerebrovascular diseases [4,5].

CI is a significant public health concern characterized by hidden and gradually worsening cognitive function, including memory, learning, reasoning, and decision-making, which can interfere with daily life and independence [6,7]. Distinct from cognitive decline, which refers to a gradual deterioration of cognitive function that can occur with aging or various neurological conditions, CI is a broader term that represents a specific state where an individual exhibits reduced cognitive performance that are more severe than expected for a person's physical age [8,9]. While CI can significantly impact the daily lives of affected individuals, its implications extend beyond cognitive function. In CKD patients, CI is associated with worsened adherence to medical treatments, further exacerbating health outcome, contributing to higher rates of hospitalization and increasing mortality risk [6].

The risk of CI is notably elevated in CKD patients, particularly as renal function declines [10]. Emerging studies suggests that the pathophysiology of CI in CKD is liked to

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various mechanisms, including accumulation of uremic toxins, altered electrolyte balance, and increased cardiovascular risk, all of which can further jeopardize cognitive health [11,12]. Given the complex relationship between renal function and CI, it is crucial to explore how different stages of kidney dysfunction affect cognitive health, with a particular focus on non-dialysis dependent CKD (ND-CKD) patients.

While the connection between end stage renal disease and CI has been well documented, much of the existing literature focuses on patients undergoing maintenance hemodialysis (MHD), where dialysis itself is known to worsen CI through mechanisms such as blood pressure fluctuations, oxidative stress, and inflammation [13]. However, studies examining the relationship between kidney function and CI in ND-CKD patients remain limited. A meta-analysis by Etgen et al. highlighted the impact of CKD on CI but did not provide specific prevalence rates of CI across different levels of kidney function [14]. A deeper understanding of the relationship between renal function and CI in this population could help distinguish the effects of CKD itself from those caused by dialysis, offering a clearer understanding of when CI begins to manifest in CKD progression.

Previous meta-analyses have primarily focused on MHD patients, often overlooking earlier stages of CKD and the potential for cognitive changes in ND-CKD individuals [15,16]. As a result, the prevalence of CI in ND-CKD patients and the risk factors contributing to CI in these individuals remain poorly understood. Therefore, this meta-analysis was designed to elucidate the association between the kidney function and CI by quantifying the prevalence of CI at different levels of estimated glomerular filtration rate (eGFR) and to assess the potential related risk factors contributing to CI among ND-CKD.

Method

Data sources and search strategy

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17], a comprehensive search was conducted on PubMed and Web of Science, spanning from their inception up until November 2024. The keywords used in the search are indexed in the Medical Subject Headings (MeSH), which are 'cognition,' 'dementia,' 'neurocognitive disorder,' 'cognitive decline,' and 'cognitive disorder,' alongside 'chronic kidney disease,' 'non-dialysis kidney disease,' 'pre-dialysis,' 'renal failure,' and 'kidney failure.' The following combinations were used 'cognition' OR 'dementia' AND 'chronic kidney disease' OR 'non-dialysis CKD'; 'neurocognitive disorder' OR 'cognitive decline' AND 'non-dialysis kidney disease' OR 'pre-dialysis'; 'cognitive disorder' OR 'dementia' AND 'non-dialysis kidney disease,' OR 'renal failure'; 'cognitive impairment' AND 'kidney failure.' Two investigators (X.H.P. and N.B.B.) independently extracted information from each study using a standardized collection form. The initial search encompassed various permutations of keywords, focusing solely on titles. Subsequently, an exhaustive search was conducted in both databases and via a secondary method, where the reference lists of the included studies were reviewed to identify other relevant studies, furthermore, exploring additional terms and comprehensive combinations of them. Following this, duplicates were meticulously eliminated. Subsequently, the abstracts of potentially relevant studies underwent scrutiny, and finally, the complete texts of these studies were comprehensively analyzed.

Literature screening and eligibility assessment

The inclusion criteria for this study were meticulously crafted to encompass the following characteristics: (1) observational studies; (2) participants with varying levels of eGFR but not undergoing dialysis; (3) studies that reported sufficient data to facilitate an accurate assessment of prevalence and risk factors; (4) a clear and precise evaluation of CI utilizing appropriate and validated scales; (5) an examination of risk factors specifically in patients with an eGFR of less than 60 mL/min/1.73 m^2; (6) individuals aged 18 years and older; and (7) studies published in the English language. The exclusion criteria were as follows: (1) duplicate published studies; (2) intervention studies; (3) incomplete data reporting or studies with severely missing data; and (4) reviews, conference abstracts or letters.

Literature screening: An extensive search was conducted across PubMed, Web of Science to identify studies relevant to the research question. Subsequently, studies were screened based on predefined inclusion and exclusion criteria, eliminating those irrelevant or of poor quality.

Eligibility assessment: A rigorous assessment of the eligibility of the screened studies was performed, focusing on scientific rigor, methodological reliability, and completeness of results. Potential publication bias was assessed using funnel plot tests and Egger's test. If the funnel plot is symmetrical and the *p* value from Egger's test is greater than .05, it indicates that there is no publication bias in the outcome indicators; otherwise, it indicates that there is publication bias.

If any disagreement existed, two investigators would recheck and discuss referring to the full text.

Data extraction and quality assessment

Extraction content: Key information was extracted from each included study, including study design, sample size, CI assessment measures, the level of risk factors, kidney function, scores of cognitive, and any variability factors (e.g., region, population characteristics, eGFR evaluation equations).

Standardized forms: A uniform data extraction form was developed, specifying the data items to be extracted, such as year, location, sample size, CI assessment details, eGFR levels, and measurement scales. This ensures consistency and traceability of data sources.

Double-checking: Data extraction was performed independently by at least two researchers, with results cross-checked to minimize subjectivity and enhance accuracy. A kappa score of 0.82 was achieved during the data selection

and extraction process, indicating a high level of agreement and consistency. Disputes were resolved by consensus or the third researcher (W.H.Z.).

Homogeneity assessment

Inter-study heterogeneity tests: Statistical tests (I^2 statistic) were used to assess the degree of consistency among study results. If $I^2 \leq 50\%$, the heterogeneity between the included studies can be ignored, and the fixed-effect model combined with the effect size was selected, otherwise the random effect model was selected.

Subgroup or sensitivity analysis: In cases of significant heterogeneity, subgroup or sensitivity analyses are conducted to identify potential sources of heterogeneity and evaluate their impact on the overall analysis.

Data cleaning and preparation

Data cleaning: Anomalies, missing values, and other issues in the extracted data were identified and addressed to ensure data completeness and consistency.

Data compilation: Cleaned data were compiled and prepared for subsequent statistical analysis, adhering to the analysis requirements.

Documentation and record keeping

Detailed record: Every step of the data extraction process, including encountered issues and their resolutions, was meticulously documented for future review and reproducibility.

Archive management: All extracted data, forms, statistical outputs, and related documents were securely archived to ensure accessibility and reproducibility of the meta-analysis.

Quality assessment

The quality of the studies was assessed using the JBI (The Joanna Briggs Institute) critical appraisal tools [18]. Based on the number of 'YES' responses, a percentage score was calculated to determine the quality of each study. A score of 80% or higher was classified as high quality, 60–79% as medium quality, and below 60% as low quality.

Statistical analysis

Initially, the aggregated prevalence rate of CI was computed encompassing all participants, subsequently exploring the correlation between kidney function and CI across varying levels of kidney level. Within stratified analyses by renal function status, pertinent risk factors were identified, leveraging the odds ratio (OR), mean difference (MD), and 95% confidence interval (CI) as metrics to quantify the impact of these factors on CI risk among individuals with ND-CKD.

The comprehensive analysis framework was executed utilizing the 'meta' package within R software, version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), in conjunction with Review Manager 5.3 (Cochrane Collaboration, London, UK). The threshold for statistical significance was established at $p < .05$. For continuous variables, appropriate statistical methods were employed (specified as R software, R Foundation for Statistical Computing, Vienna, Austria), while categorical variables were evaluated using forest plots for a clear and concise comparison.

Results

The primary database search generated 3188 studies sourced from PubMed and an additional 2704 from Web of Science. Upon rigorous deduplication, a consolidated list of 3996 studies underwent initial screening based on their titles and abstracts. This meticulous process led to the detailed evaluation of 335 full-text studies, ultimately culminating in the inclusion of 17 studies for the comprehensive meta-analysis [19–35]. The search process was clearly outlined and depicted in Figure 1 and the included studies are presented in Table 1.

Features and quality appraisal of included studies

Out of the 17 included studies that were meticulously analyzed, 12 were cross-sectional, while the remaining five comprised longitudinal cohort studies. These studies hailed from diverse geographical locations, with five originating from the USA, three from China, two from the UK, and individual contributions from Thailand, Colombia, Brazil, France, Ethiopia, Russia, and Canada.

The 17 studies were published between the year 2008 and 2024. The age of participants reported was between 50 and 80 years. While the majority of studies reported age using mean ± SD, there were exceptions such as Nikitina et al. [27] and Yang et al. [35] that only provided the age range utilized in their research and An et al. [30] who presented age solely as the mean. In terms of cognitive assessment, the MMSE and MoCA stood out as the most prevalent tests. Notably, a Russian study deviated from this trend by employing the SAGE scale, while four American studies administered a battery of tests. For the MoCA, a score falling below 26 served as an indicator of CI. The MMSE utilized a threshold of less than 24, and a SAGE score under 20 was also deemed indicative of impairment. For the Lawton test, a score exceeding 7 was considered, and for Battery tests, a score more than 1.0 standard deviations below the published mean were applied as the criterion. The quality appraisal disclosed that 11 of the 17 studies were of high quality, while the remaining six were deemed to be of moderate quality. More detailed characteristics of the included studies are presented in Table 1.

Prevalence of CI in ND-CKD

All the 17 studies were analyzed to observe the relationship between various kidney function and CI, encompassed 32,141

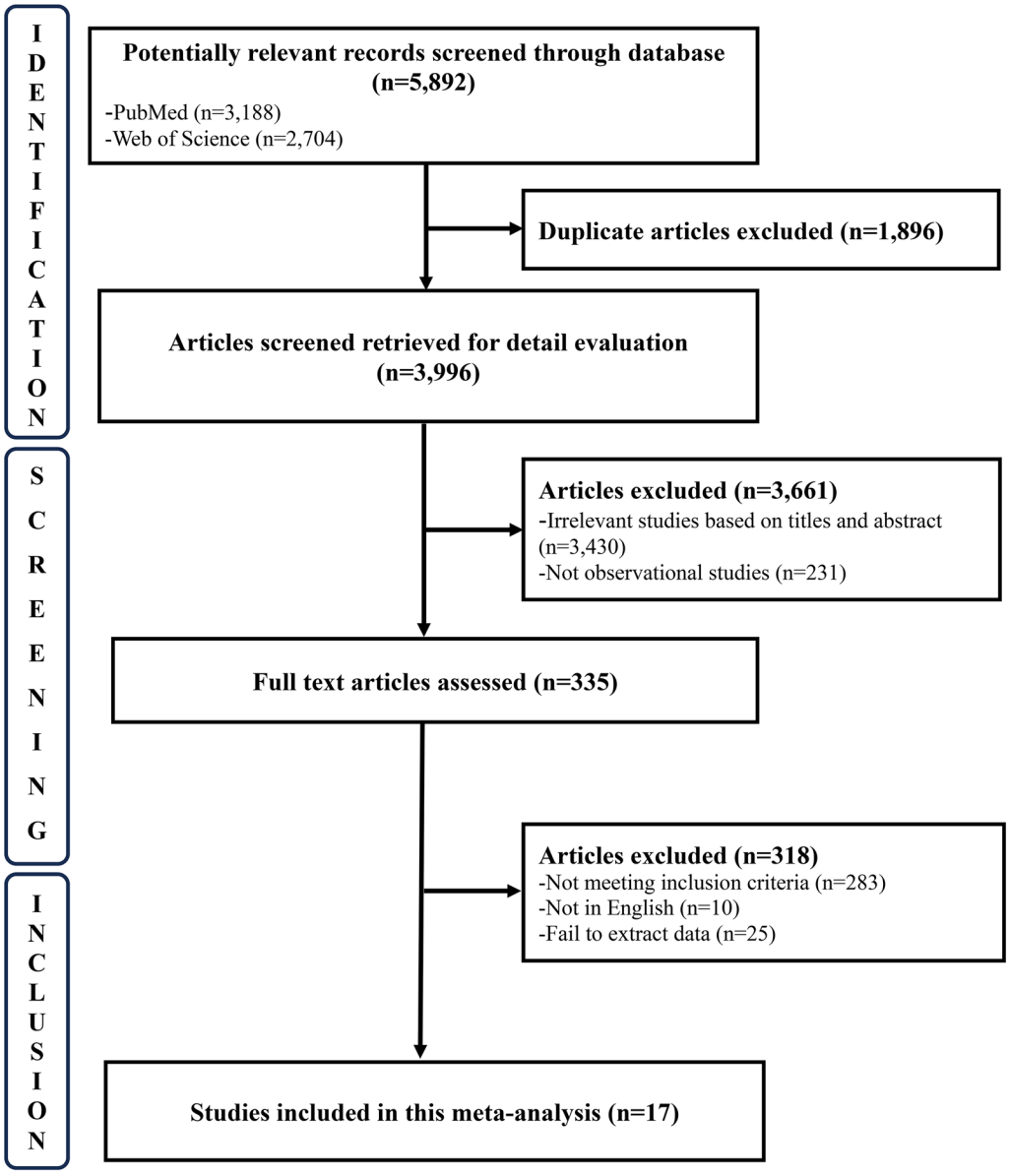


Figure 1. Flowchart diagram of the included studies for the meta-analysis.

participants. The prevalence of CI exhibited considerable variability, with rates ranging from as low as 8% to as high as 73%. The combined data from these studies indicated an overall pooled prevalence of CI at 16.7% for the total participants.

While only six studies reported on the prevalence of CI in individuals with an eGFR exceeding 60 mL/min/1.73 m^2, this encompassed a significant sample size of 21,946 participants, yet the overall CI prevalence within this cohort remained modest at 10%. In stark contrast, the 10,225 subjects with an eGFR below 60 mL/min/1.73 m^2 exhibited a substantially higher CI prevalence, reaching 31%, which was three times that of the group with better kidney function. This clearly demonstrates the decline in cognitive function as eGFR drops below 60 mL/min/1.73 m^2. Additionally, a subgroup analysis revealed that among the 1504 patients with an eGFR ranging from 60 to 30 mL/min/1.73 m^2 (extracted from six studies), the prevalence of CI escalated to 47.3%. Furthermore, the most severely affected group, consisting of 940 patients with an eGFR below 30 mL/min/1.73 m^2 (extracted from seven studies), demonstrated an alarmingly high CI prevalence of 60.6%.

The detailed data for the above results are presented in Table 1, and a visual comparison could be found in Figure 2.

Risk factors

To assess their influence on CI among ND-CKD patients, 13 potential risk factors were analyzed. These factors encompassed demographic characteristics such as age and gender, lifestyle habits like smoking, educational background, and medical conditions like hypertension, type 2 diabetes mellitus (T2DM), cardiovascular disorders, and cerebrovascular disorders. Additionally, laboratory results, including hemoglobin, albumin, phosphate, and PTH levels, were also evaluated.

Table 1. Features and quality appraisal of included studies.

Study	Year	Country	Study design	eGFR range	Age	Total	Events	Prevalence (%)	Assessment of eGFR	Assessment of CI	Quality rating
Kurella et al. [19]	2008	USA	Cross-sectional	≥60 and <60	64.9 (SD 9.6)	23,405	1967	8.4	MDRD	MMSE	Medium
Foster et al. [20]	2016	Canada	Cross-sectional	<60	68.0 (56.0–78.0)	385	237	61	NR	MoCA	High
Paraizo et al. [21]	2016	Brazil	Cross-sectional	<60 (<30)	56.74 (SD 7.63)	23	17	73.9	NR	MoCA	Medium
Rodríguez-Angarita et al. [22]	2016	Columbia	Cross-sectional	<60	76.3 (SD 7.9)	251	128	51	MDRD	Lawton test	High
Bai et al. [23]	2018	China	Longitudinal study	<60	82.8 (81.3–85.1)	163	109	66.9	MDRD	MMSE	High
Burns et al. [24]	2018	USA	Cross-sectional	≥60 and <60 (60–30, <30)	69.2 (SD 9.8)	574	266	46.3	CKD-EPI	Battery	High
Thancharoen et al. [25]	2020	Thailand	Cross-sectional	<60	65.7 (SD 12.2)	379	60	15.8	NR	MMSE	High
Gela et al. [26]	2021	Ethiopia	Cross-sectional	≥60 and <60	54.1 (SD 17)	163	66	40.5	Cockcroft–Gault	MMSE	Medium
Nikitina et al. [27]	2021	Russia	Cross-sectional	≥60 and <60 (60–30, <30)	32.75–64.25	98	56	57.1	CKD-EPI	SAGE	Medium
Paterson et al. [28]	2021	UK	Longitudinal cohort	<60 (60–30, <30)	64 (SD 9)	928	508	54.7	CKD-EPI	MoCA MMSE	High
Tollitt et al. [29]	2021	UK	Longitudinal cohort	<60	66 (53–74)	250	123	49	NR	MoCA	High
An et al. [30]	2022	China	Cross-sectional	<60 (60–30, <30)	53.08	120	59	49	CKD-EPI	MoCA	Medium
Grasing et al. [31]	2022	USA	Longitudinal cohort	≥60 and <60	74 (SD 7)	1127	761	67.5	CKD-EPI	Battery	High
Murray et al. [32]	2022	USA	Cross-sectional	<60 (60–30, <30)	69.8 (SD 9.9)	436	212	48.6	CKD-EPI	Battery	Medium
Sheets et al. [33]	2022	USA	Cross-sectional	<60	69.7 (SD 9.7)	420	202	48.1	CKD-EPI	Battery	High
Pépin et al. [34]	2023	France	Longitudinal cohort	<60	66.82 (SD 12.87)	3003	387	13	CKD-EPI	MMSE	High
Yang et al. [35]	2024	China	Cross-sectional	≥60 and <60 (60–30, <30)	<65 >65	416	210	50.4	NR	MoCA MMSE	High

eGFR: estimated glomerular filtration rate (mL/min/1.73 m^2); eGFR range: referring to the GFR interval reported in the selected literature, suggesting the level of kidney function in the subjects; total: number of the all participants in each study; events: participants with cognitive impairment; prevalence: events/total × 100%; CI: cognitive impairment; MDRD: modification of diet in renal disease equation; CKD-EPI: chronic kidney disease-epidemiology collaboration equation; MoCA: Montreal Cognitive Assessment Scale; MMSE: Mini-Mental State Examination Scale; SAGE: Self-Administered Gerocognitive Examination Scale; NR: not reported.
Quality appraisal was carried out by Joanna Briggs Institute, 2016.

For the seven non-continuous variables under investigation, T2DM, cardiovascular disease, and cerebrovascular disease exhibited significant impacts on CI, with OR of 1.55 (95% CI: 1.33–1.81), 1.63 (95% CI: 1.20–2.22), and 1.95 (95% CI: 1.55–2.45), respectively. Furthermore, lower education level was strongly associated with CI, with an OR of 2.59 (95% CI: 1.32–5.09), albeit displaying a high heterogeneity of 90%. Notably, female gender, smoking status, and hypertension did not show significant effects on CI, with respective OR of 1.33 (95% CI: 0.92–1.90), 0.78 (95% CI: 0.61–1.01), and 1.26 (95% CI: 0.78–2.05).

The remaining six risk factors were continuous variables, which were evaluated using MDs and 95% CIs. Notably, older age emerged as a significant predictor of CI, with a MD of 4.20 (95% CI: 1.70–6.70). In contrast, body mass index (BMI), hemoglobin, serum albumin, and serum phosphate did not demonstrate any significant effect on CI, exhibiting MD of 0.06 (95% CI: −0.41 to 0.53), −0.32 (95% CI: −0.45 to −0.18), −0.67 (95% CI: −1.10 to −0.18), and 0.02 (95% CI: −0.01 to 0.04), respectively. However, elevated serum PTH levels were found to have a significant impact on CI, with a MD of 2.43 (95% CI: 1.27–3.59). The detailed findings of these analyses are comprehensively presented in Tables 2 and 3 and visually illustrated in forest plots in Figure 3.

Publication bias

Risk factors which were analyzed in more than five studies and showed high heterogeneity (I^2 > 50%) were assessed by funnel plots and Egger's test. No publication bias and high symmetry of the included studies were proved by Deeks' funnel plot asymmetry test (Supplement Figure).

Discussion

To the best of our knowledge, this represents the inaugural meta-analysis dedicated to assessing the prevalence of CI among individuals with ND-CKD, spanning various stages of renal function. Prior extensive researches have established those complications of CKD, such as renal anemia and secondary hyperparathyroidism (SHPT), begin to manifest progressively as GFR declines below 60 mL/min/1.73 m^2 [36]. However, the relationship between CI and CKD, particularly the precise stage of renal insufficiency when the incidence of CI escalates, has been unclear or overlooked due to the insidious nature of both conditions, which often lack distinctive early symptoms.

Fortunately, amidst the global demographic shift toward an aging population, Alzheimer's disease and other forms of dementia have garnered heightened attention, fostering a surge in research focusing on comorbidity [37]. It is within this context that our meta-analysis emerges, synthesizing data from 17 relevant reports published over the past years, sourced from 10 diverse countries or regions worldwide. This endeavor aims to shed light on the previously underexplored intersection of CKD and CI.

Among the 17 studies reviewed, most focused on CI in ND-CKD patients with a GFR below 60 mL/min/1.73 m^2, while a few examined CI across the GFR range around this

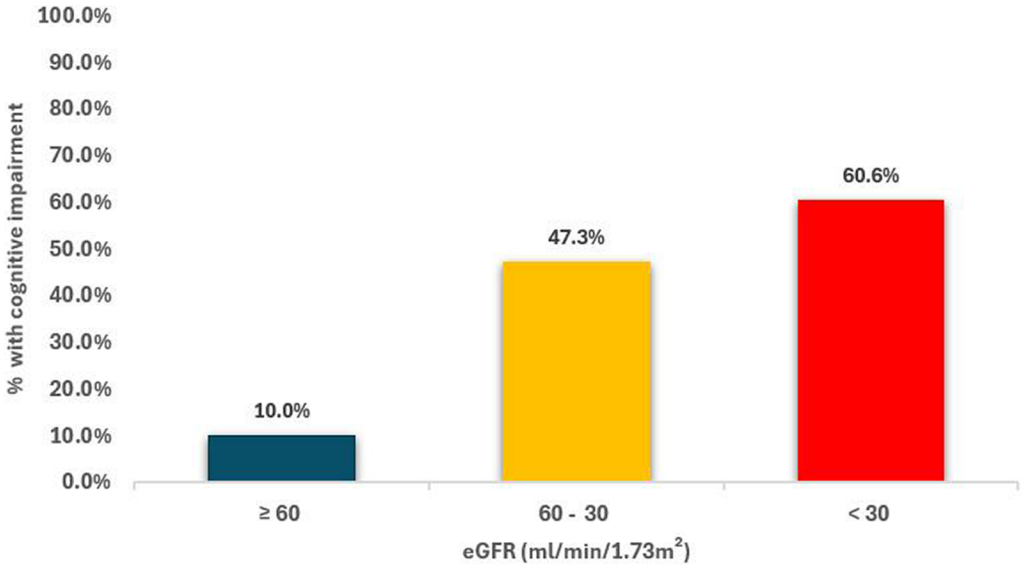


Figure 2. Prevalence of CI in various kidney function.

Table 2. Evaluation of non-continuous variables impacting on cognitive impairment among non-dialysis CKD patients by odd ratios.

Risk factor	No. of studies included	Effect estimate (OR)	95% CI	*p* Value	Heterogeneity tau², I^2
Female	7	1.33	0.92–1.90	<.01	0.1726, 78%
Lower education	5	2.59	1.32–5.09	<.01	0.5101, 90%
Smoking	5	0.78	0.61–1.01	.13	0.0906, 44%
Hypertension	6	1.26	0.78–2.05	<.01	0.2305, 69%
Type 2 diabetes mellitus	6	1.55	1.33–1.81	.11	0.0359, 44%
Cardiovascular disease	6	1.63	1.20–2.22	.05	0.0724, 55%
Cerebrovascular disease	5	1.95	1.55–2.45	.12	0.0657, 45%

OR: odds ratio.

The data were obtained by statistical analysis using R software (R Foundation for Statistical Computing, Vienna, Austria). I^2 was used to assess the degree of consistency among study results. If I^2 < 50%, the heterogeneity between the included studies can be ignored, and the fixed-effect model combined with the effect size was selected, or the random effect model was selected.

Table 3. Evaluation of continuous variables impacting on cognitive impairment among non-dialysis CKD patients by mean difference.

Risk factor	No. of studies included	Mean difference	95% CI	*p* Value	Heterogeneity tau², I^2
Age	7	4.20	1.70, 6.70	.001	9.95, 93%
BMI	4	0.06	−0.41, 0.53	.8	0.00, 0%
Hemoglobin	4	−0.32	−0.45, −0.18	<.00001	0.00, 0%
Serum albumin	3	−0.67	−1.10, −0.23	.003	0.04, 27%
Serum phosphate	2	0.02	−0.01, 0.04	.14	0.33, 0%
Serum parathyroid hormone	2	2.43	1.27, 3.59	<.0001	1.91, 48%

BMI: body mass index; CI: confidence interval.

These data were obtained from statistical analysis using Review Manager (Cochrane Collaboration, London, UK). I^2 was used to assess the degree of consistency among study results. If I^2 <50%, the heterogeneity between the included studies can be ignored, and the fixed-effect model combined with the effect size was selected, otherwise the random effect model was selected.

threshold. We extracted CI prevalence rates and risk factors at various renal function levels from these studies, finding an overall CI prevalence of 16.7%. Zhang et al.'s recent meta-analysis, which included CKD patients regardless of dialysis or transplantation status, reported a 40% CI prevalence [16]. CI was more prevalent in hemodialysis (53%) and peritoneal dialysis patients (39%) compared to those without dialysis (32%) and post-kidney transplant (26%). These findings, combined with ours, support the hypothesis that decreased renal function significantly increases CI incidence.

To further validate this hypothesis, we meticulously categorized the participants from all studies into groups based on varying levels of renal function to extract data. Although the inherent heterogeneity in renal function assessment across studies, this endeavor necessitates dedicated time and effort.

A striking observation from our meta-analysis was the pronounced increase in CI as CKD progresses from earlier to more advanced stages. For patients with an eGFR above 60 mL/min/1.73 m^2, CI prevalence was 10%, consistent with Kurella Tamura et al.'s observation of lower CI in early CKD stages [19].

In contrast, patients with an eGFR below 60 mL/min/1.73 m^2 had a significantly higher CI prevalence of 31%, with those having an eGFR between 30 and 60 mL/min/1.73 m^2 showing a prevalence of 47.3%. These results align with Kurella et al.'s findings of increased CI severity with advancing CKD stages [38].

The significant rise in CI prevalence with eGFR below 60 mL/min/1.73 m^2 highlights a critical shift in CI risk as renal function deteriorates. Hailpern et al. found higher CI prevalence in moderate CKD patients [39], and CI prevalence escalated to 60.6% in those with eGFR below 30 mL/min/1.73 m^2, indicating severe worsening.

This increase aligns with recent studies, including Burns' research, which observed a marked rise in CI in advanced CKD [24]. The progressive nature of CI with advancing CKD stages is further supported by Otobe et al. who noted increasing CI prevalence in later CKD stages [40]. This emphasizes the need for vigilant management to address cognitive decline in CKD progression.

As the kidney function declines, multiple factors, including anemia, albuminuria, hypertension, parathyroid hormone (PTH) levels, phosphate levels, cardiovascular diseases, and cerebrovascular diseases may emerge as critical issues

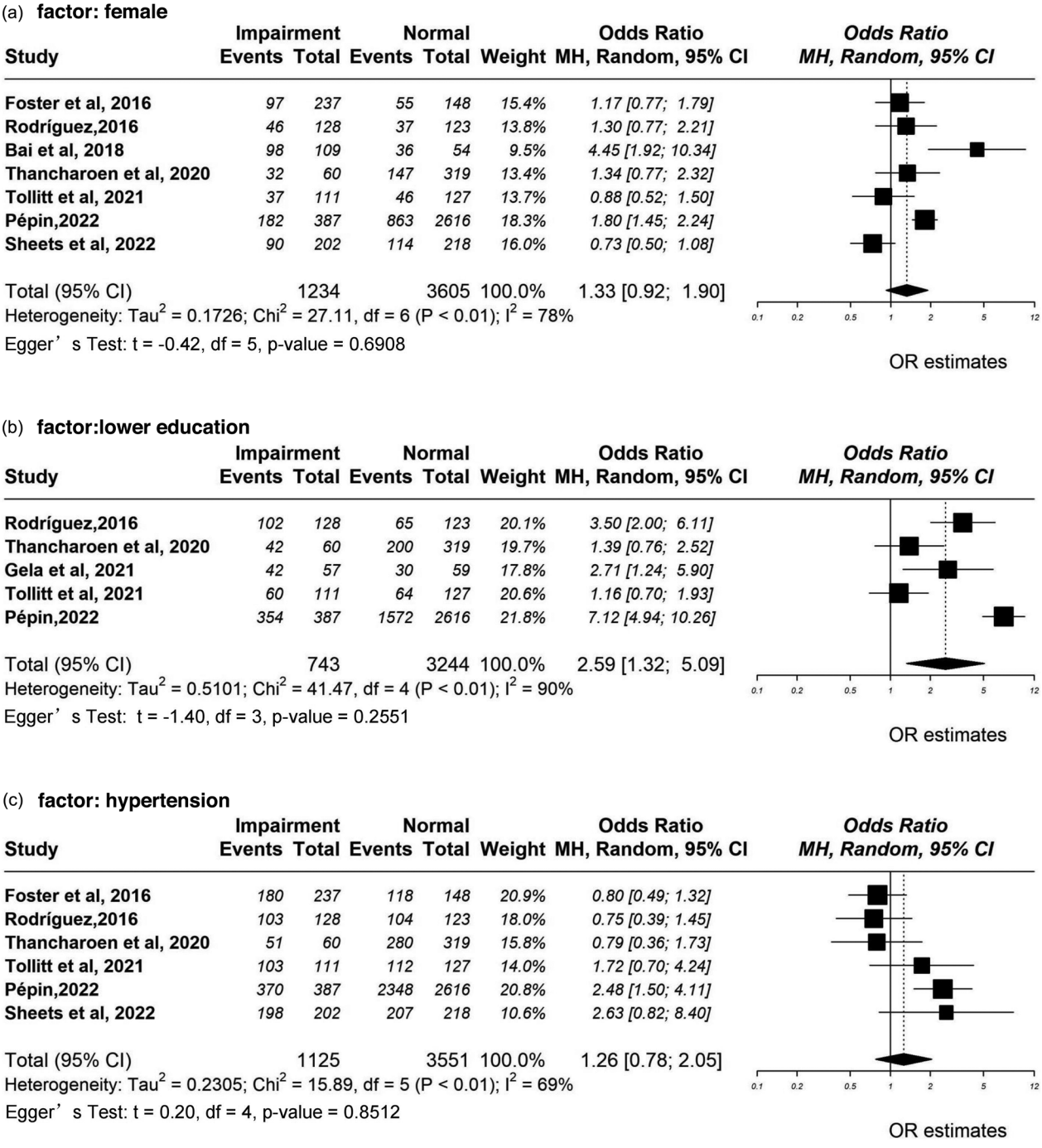
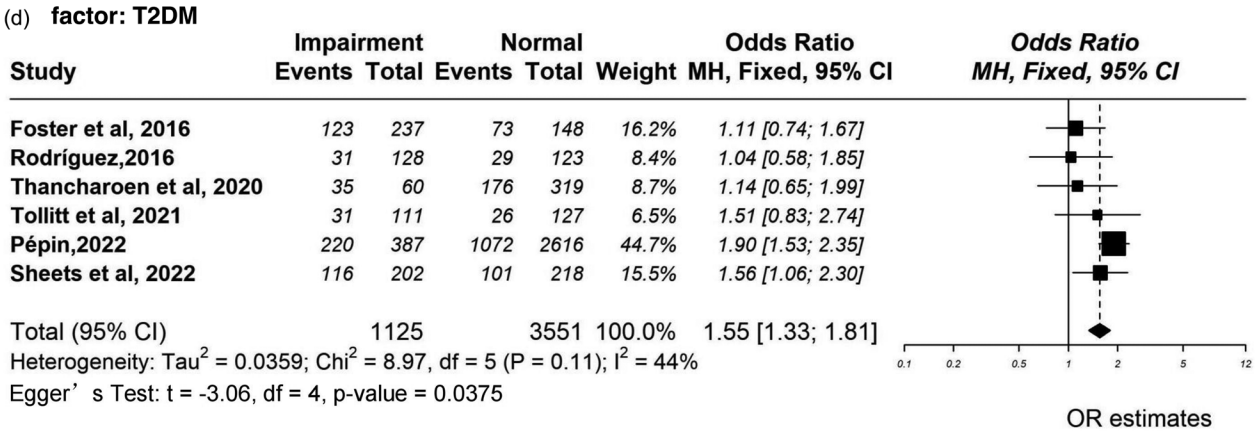
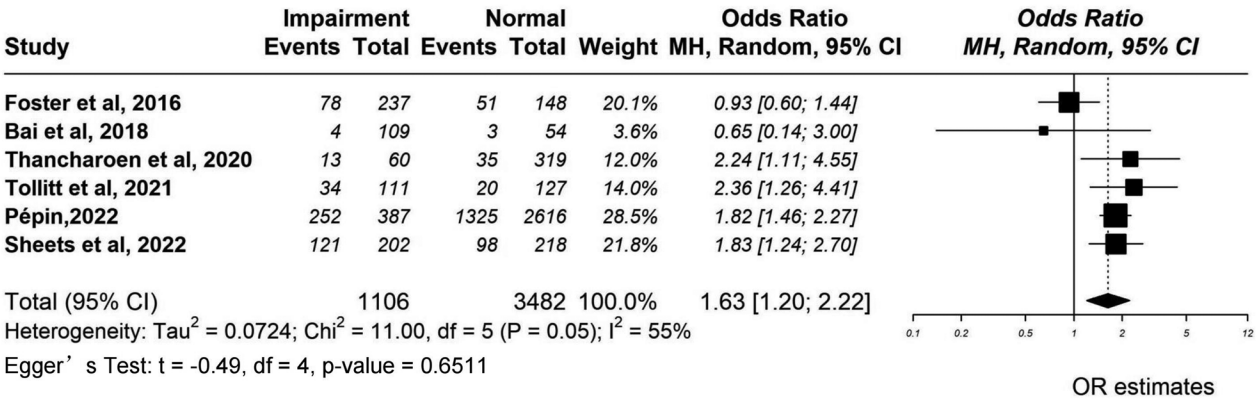


Figure 3.Forest plots of pooled risk factors affecting CI in ND-CKD assessed by OR.





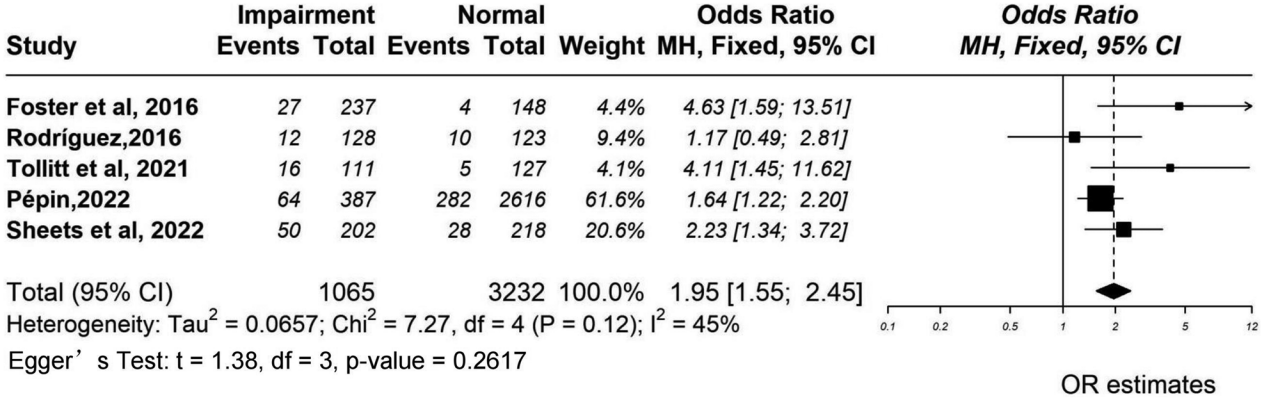


Figure 3. Continued.

[41–47]. Diabetes mellitus is also a significant cause of renal failure that can exacerbate these issues [48]. Additionally, the impact of aging, gender and lower education must be considered as they have been also associated with declining renal function [49–51]. In this context, our study aimed to analyze the potential risk factors that may influence cognitive function as renal function deteriorates.

Older age and lower educational attainment emerged as the most significant, similarly affecting the general population [52]. Previous research links cognitive decline, a natural aging process, to brain changes such as amyloid-β plaque accumulation and hippocampal damage [53,54]. Our meta-analysis highlights limited education as the strongest risk factor for CI in CKD patients, with an OR of 2.59. The cognitive reserve hypothesis suggests that higher education enhances brain flexibility and resilience, potentially delaying neurocognitive disorders [55–57].

Although female gender is commonly associated with cognitive decline in the general population, our findings show no significant link between female gender and CI in CKD patients, consistent with earlier research [52].

Our meta-analysis identified vascular risk factors affecting CI in ND-CKD patients. We found no significant links between hypertension, smoking, or BMI and CI. However, T2DM emerged as a significant risk factor. The connection between T2DM and CI may involve insulin resistance, which leads to chronic hyperinsulinemia, vasoconstriction, elevated blood pressure, and reduced cerebral perfusion. This impaired blood flow could contribute to vascular CI and cognitive decline [58,59].

Additionally, we found cardiovascular and cerebrovascular diseases significantly contribute to CI in CKD patients. Cardiovascular disease-related hypoperfusion and inflammation adversely affect brain function, leading to CI [60].

Our analysis found that cerebrovascular disease, with an OR of 1.95, is a significant risk factor for CI in CKD patients. This increased risk is largely due to cerebral small vessel disease, which causes reduced cerebral blood flow and impaired autoregulation [61,62]. These issues disrupt cerebral perfusion and lead to cognitive decline, highlighting the need for interventions to protect cerebrovascular health.

Regarding laboratory parameters, hemoglobin, serum albumin, and serum phosphate levels showed no significant impact on CI. However, elevated serum PTH levels, with a MD of 2.43, were notably associated with CI in CKD patients. Elevated PTH, often seen in early CKD stages due to decreased 1,25-hydroxyvitamin D production [63,64], can cross the blood–brain barrier and negatively affect cognitive function [65]. Fortunately, SPTH can be managed with treatments like phosphate binders, vitamin D analogs, calcimimetics, and, in some cases, parathyroidectomy [66,67]. Addressing elevated PTH levels may improve cognitive outcomes in ND-CKD patients, underscoring the need for early diagnosis and intervention.

In summary, our findings underscore a pronounced escalation in the prevalence of CI as kidney function progresses from benign to loss. Protecting GFR from falling below 60 mL/min/1.73 m^2, delaying the progression of cardiovascular and cerebrovascular diseases, and effectively preventing and treating complications could reduce the occurrence of CI in CKD patients. This pivotal observation underscores the paramount importance of incorporating regular cognitive assessments into the routine management of CKD patients. Given the inexorable rise in CI incidence with advancing CKD severity, clinicians must maintain a heightened vigilance for signs of declining cognitive function, particularly among those with moderate to severe disease stages. By proactively addressing modifiable risk factors at an early juncture, we can effectively manage CI and enhance patient outcomes. This proactive approach necessitates a holistic understanding of the interplay between CKD and cognitive function, fostering a collaborative effort among healthcare professionals to optimize care for this vulnerable patient population.

Strengths and limitations of the current study

This meta-analysis incorporated studies from 10 different countries providing a more global perspective on the prevalence of CI among the ND-CKD and reducing racial disparities. We meticulously screened the two primary database, applying specific inclusion and exclusion criteria to ensure the studies were relevant to various kidney function. The analysis involved calculating pooled prevalence and assessing risk factors using appropriate software. However, in the concluding section of this meta-analysis, we must acknowledge its inherent limitations. First, despite our efforts to include all high-quality and homogeneous studies, we often face challenges in achieving a completely unbiased sample due to the diversity of study designs, the heterogeneity of patient populations, methods for evaluating CI and eGFR, and limitations in data access. This heterogeneity is manifested not only in the clinical characteristics of patients, such as age, gender, and disease stage, but also in differences in research methodologies, including the specific implementation of interventions, the duration of follow-up, and the definition of outcome measures. Second, publication bias represents another inescapable issue in meta-analysis. Positive findings with statistical significance are more likely to be published and reported, while studies that fail to show significant results may be overlooked or omitted, potentially affecting the comprehensiveness and accuracy of the meta-analysis results. Another key limitation of this review is that it was not registered with systematic review registry prior to its initiation. Even though we have adhered to established best practices in systematic review methodology, we acknowledge that formal registration could enhance the credibility and transparency of the review and hence is an area for improvement in future reviews.

Furthermore, as a secondary research method, the reliability of the conclusions drawn from meta-analysis is contingent upon the quality of the primary studies included. Any methodological flaws or incomplete data reporting in the original studies may be propagated into the meta-analysis, compromising the robustness of its conclusions. Finally, we only analyzed studies published in English language; it is possible that other potentially relevant studies may have not been included. Therefore, when interpreting the results of a meta-analysis, we must maintain a cautious attitude, considering its limitations and synthesizing them with other evidence.

Conclusions

This meta-analysis clearly demonstrates a high prevalence of CI among ND-CKD patients, beginning in the early stages of the disease and increasing significantly in the later stages of renal failure. Maintaining a GFR above 60 mL/min/1.73 m^2, would significantly reduce the prevalence of CI. These findings highlight the importance of incorporating cognitive assessment from the onset of CKD to reduce the adverse outcomes associated with CI. Identifying and managing multiple modifiable risk factors early on could help mitigate the impact of cognitive dysfunction in ND-CKD patients.

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Author contributions

Conceptualization: Weihong Zhao and Xiaohua Pei. Data curation: Nazia Begum Bakerally and Xiaohua Pei. Formal analysis: Xiaohua Pei, Fei Gao, and Yao Ma. Funding acquisition: Weihong Zhao and Xiaohua Pei. Methodology: Xiaohua Pei and Zhan Wang. Project administration: Weihong Zhao. Resources: Nazia Begum Bakerally, Sizhu Zhu, and Yun Bo. Supervision: Weihong Zhao. Writing – original draft: Nazia Begum Bakerally, Xiaohua Pei, and Zhenzhu Yong. Writing – review and editing: Xiaohua Pei, Nazia Begum Bakerally, and Zhu Bei.

Ethical approval

No ethical approval was required for this review.

Consent form

No patients consent was required for this review.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data used to support the findings of this study are included within the article. Supplements are available from the corresponding author.

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