Identifying Research Priorities for Cognition in CKD
A Delphi Study

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Key Points
- Cognitive impairment is prevalent in CKD, affecting quality of life, self-management, and decision-making. It worsens with disease progression.
- This Delphi study engaged diverse stakeholders to identify 27 critical research questions on cognitive impairment in CKD for future focus.
- Top priorities include preventing cognitive decline, preserving cognition, routine monitoring, and adjusting dialysis treatment to reduce cognitive impairment.

Abstract
Background Cognition is a research priority for people living with CKD, but identification of critical research questions is lacking. This study aimed to determine which cognition-related research questions are most important to CKD stakeholders.

Methods A modified Delphi technique with three survey rounds was used. The study sample included three panels (*People with lived CKD experience, Researchers, and Clinicians*) recruited through international patient and kidney research networks, kidney societies, and snowball sampling with email invitations. Survey rounds were distributed electronically through Research Electronic Data Capture. In round 1 (October 2021–May 2022), respondents contributed three important research questions regarding cognition in CKD (free text). After deduplication and qualitative synthesis, respondents ranked the importance of these questions on a nine-point Likert scale in round 2 (February–April 2023). Questions with mean and median ratings of >7 by at least two respondent panels or rated critically important by the lived experience panel were reranked in round 3 (August–September 2023) and assessed for consensus to identify the final list of priority research questions.

Results Respondents (n=152) identified 125 and 44 discrete questions after rounds 1 and 2, respectively. The final shortlist included 27 questions in eight categories. The most critical research question identified was "What factors *prevent* cognitive impairment in people receiving dialysis?" Overall, respondents prioritized questions focusing on prevention and treatment of cognitive impairment. Scores between the panels were significantly different for 16 questions. Those with lived CKD experience prioritized quality of life, researchers emphasized developing interventions to mitigate cognitive impairment, and clinicians prioritized the effect of CKD treatment on cognitive impairment.

Conclusions Through an established consensus methodology involving key stakeholder groups, we identified 27 critical research questions about cognition in CKD. These questions should guide future study design and outcome selection.

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Introduction

Cognitive impairment is defined as difficulty remembering, learning new things, focusing, and making everyday life decisions.[1] It ranges in severity from mild, which involves a modest decline in cognitive abilities that does not significantly affect daily function, to major (dementia), in which declines in cognitive abilities interfere substantially with daily function and independence.[2] The prevalence of cognitive impairment is higher in people living with CKD compared with the general population, increases with CKD progression, and is highest in people with kidney failure receiving dialysis.[3–9] Previous research has shown an 11% higher risk of cognitive impairment with each 10 ml/min per 1.73 m^2 decrease in eGFR in individuals with eGFR <60 ml/min per 1.73 m^2.[10] Cognitive impairment is present in 77.2% of individuals receiving hemodialysis.[11]

Although its etiology in the CKD population remains unclear,[12] cognitive impairment can lead to challenges in decision-making, self-management practices, and communication with health care providers and is associated with reduced quality of life and increased mortality.[3,13,14] Addressing cognitive impairment has been previously identified as a research priority by people living with CKD and their caregivers, but identification of critical knowledge gaps and research questions is lacking.[15–17]

The goal of our study was to address this knowledge gap and inform future research on cognitive impairment in CKD by gathering perspectives on important cognition-related research priorities from people living with CKD, clinicians, researchers, and other stakeholders.

Methods

Study Design

We used a modified Delphi technique using an iterative *a priori* process in which a group of stakeholders reach consensus on a topic through several survey rounds with controlled feedback. In this study, we used three survey rounds and a steering committee to guide consensus achievement.[18] We chose three rounds to prevent participant attrition, which can occur when the number of survey rounds is unknown or extensive, and to establish the stability of responses across time points.[18,19] We followed the Guidance on Conducting and REporting DElphi Studies' guidelines.[20]

Participant Selection

Recruitment for round 1 occurred through international patient networks and advisory groups, kidney research networks, national and international kidney societies, snowball sampling, and email invitations by study coinvestigators. We aimed to recruit a sample of content experts that included clinicians, researchers, administrators, decision-makers, people living with CKD (including nondialysis CKD and kidney failure requiring dialysis or kidney transplant), and their family members or caregivers (Supplemental Material 1.1). Criteria for being classified as a content expert and definitions of each type of stakeholder are outlined in Supplemental Material 1.2. Recruitment for round 2 involved reinviting participants from round 1 and new participants identified from the same sources as round 1. Round 3 included only individuals who had participated in either previous round.[21]

Steering Committee

A project steering committee composed of two clinicians (D. Collister and S. Thompson), two researchers (B. Tarca and N. Chu), and two patient partners (B. Corradetti and K. Fowler) guided all phases of the study. They reviewed results after each round and finalized the list of questions sent out in subsequent rounds to ensure accessible language and question cohesiveness.

Sample Size

The Delphi process relies on group dynamics to reach consensus rather than statistical power. The literature varies widely regarding the number of recommended experts on a Delphi panel, but in a recent review, Shang suggested including 8–23 participants per panel.[22,23] We aimed to recruit approximately 15 researchers, clinicians, and decision-makers, which falls in the middle of the recommended range and totals approximately 50.[23] For individuals with lived experience, we prioritized their inclusion to highlight patient perspectives. We targeted 100 participants to ensure the representation of diverse views. This number was chosen to reflect an international scope, with approximately ten participants per region where the research team had established contacts (the United Kingdom, Portugal, Italy, Canada, the United States, Australia, and South America), and a goal to recruit ten for each of people with nondialysis CKD, people on dialysis, and people who live with a kidney transplant.

Data Collection

Surveys were piloted by people living with CKD, clinicians, and researchers before the distribution of each round. Round 1 surveys were distributed from October 2021 to May 2022 and were administered in English, Spanish, Portuguese, and French. Surveys were translated into Spanish (S.J. Leon), Portuguese (H. Ribeiro), and French (S.J. Leon) and back-translated to English (Figure 1). Owing to low response rates for non-English surveys, surveys were only disseminated in English for rounds 2 and 3. Round 2 was distributed from February 2023 to April 2023 and round 3 from August 2023 to September 2023. Data were collected and managed using Research Electronic Data Capture tools, a secure, web-based software platform designed to support data capture for research studies, hosted at the University of Manitoba.[24,25] All surveys were distributed electronically through Research Electronic Data Capture. All surveys were completed independently online. Individuals who could not read or write or who did not have online access were not included in this study.

Round 1

Participants provided demographic information in the first survey (Supplemental Material 2.1). They were asked to provide three potential research questions using free-form text about cognition and cognitive impairment in CKD and kidney failure. Responses could pertain to

prevention, diagnosis and treatment or how cognitive impairment affects the lives of patients and caregivers. Participants were encouraged to be specific when describing the population or outcomes in their responses. At the end of the survey, participants were able to provide additional feedback about the study or what could be addressed in subsequent rounds. Surveys that included at least one research question were included in the analyses.

Round 2

In round 2, a list of categorized questions derived from the analysis of the open-ended responses in round 1 was distributed (Supplemental Material 2.2). Participants were invited to score each question using a Likert scale of 1–9, with scores of 1–3 indicating that the topic was not important, scores of 4–6 indicating that the topic was important but not critical, and scores of 7–9 indicating that the topic was critical.[26] After the ranking of the generated questions, participants had the opportunity to suggest additional research questions. Participants could abstain from scoring any questions throughout the survey. Round 2 responses were sorted into three respondent panels based on stakeholder type: lived experience (people with kidney disease or caregivers), clinicians (clinicians and decision-makers), and researchers. Questions with a mean and median rating of seven or more by at least two of the three panels or rated as critically important by the lived experience panel were included in round 3 of the survey. More weight was given to the lived experience panel to ensure their priorities were not eliminated by other panels when perceived importance differed, countering the inherent power imbalance in clinician-patient or researcher-patient relationships.[27,28] Questions deemed as duplicates or already addressed in previous studies were eliminated.

Round 3

Using the list of streamlined questions from round 2, participants were again asked to score each question using

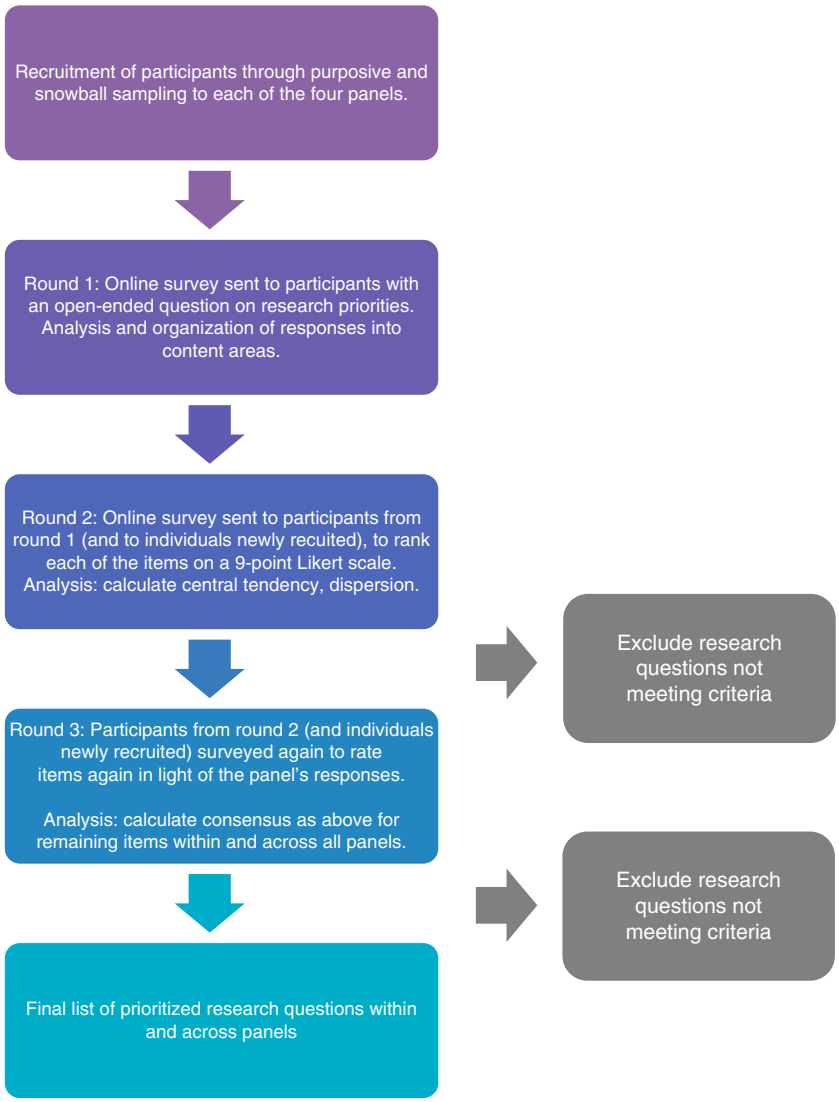

Figure 1. High-level overview of the Delphi process.

the same Likert scale of 1–9 as described above.[26] An unsure option was also introduced based on participant feedback requesting its inclusion. If this option was selected, those responses would be excluded from the calculations for consensus. Participants were given the round 2 mean scores for each question as part of the survey. Questions with a mean and median rating of seven or more by at least two of the three panels or rated critically important by the lived experience panel in round 3 were included in the final list of questions.

Analyses

Qualitative Data—*Categorizing Research Priorities from Round 1*

Questions submitted by respondents in round 1 were independently reviewed by two authors (C. Bohm/D. Verrelli, J. Vanderlinden/O. Harasemiw). Questions were categorized inductively based on the overall theme (*e.g.*, cardiovascular, patient-reported) and/or key concept (*e.g.*, safety, counseling) and condensed by omitting redundancies, expanding questions to incorporate concepts with the same meaning, and removing questions outside the scope cognition in CKD. The revised list of questions was compared with the initial list by steering committee members to ensure credibility. Any disagreements were resolved by consensus.

Quantitative Data

Descriptive data for participant demographics were calculated as a proportion of total respondents. The mean and median score of each question and the proportion of questions identified as critically important overall and for each of the three panels were calculated, with missing responses excluded. Differences in scores between the three respondent panels were determined using the Kruskall–Wallis test with Dunn correction, computed using R software, version 4.3.1 (Vienna, Austria). Subgroup analyses by sex and geographic location were also performed.

Consensus for Critical Importance

Consensus was defined *a priori* using criteria from previously published research.[29,30] Although specific thresholds are somewhat arbitrary, the consensus is met when most participants strongly favor a position and a minority are strongly opposed.[30] For each question, if >70% of scores were between 7 and 9 and <15% of scores were 1–3, consensus ranked that question as critically important. Consensus that a research question was unimportant was reached if >70% of scores were 1–3 and <15% were 7–9.

Ethical Considerations

Ethics approval was obtained from the University of Manitoba Health Research Ethics Board (HS24827 [H2021: 152]). The survey accompanied an information/consent page that provided the rationale and explained the Delphi procedure. Completing each survey round indicated consent for participation.

Results

A total of 152 discrete participants responded to at least one of the three rounds of the survey (Figure 2). Round 1 included 138 respondents, 26.8% of whom were living with CKD (n=37), 3.6% caregivers of those with CKD (n=5), 38.4% clinicians (n=53), 25.4% researchers (n=35), 2.2% health care administrators (n=3), and 3.6% (n=5) self-identified as other, which included allied health providers and exercise professionals. Respondents originated from 13 countries, with the highest proportions coming from Canada (36.2%), Italy (13.0%), and the United Kingdom (12.3%); 49.6% of the respondents were female and 50.4% were male (Table 1).

Round 2 included 73 respondents, including clinicians (which included health care administrators and other for ease of analysis; 24.3%, n=18), researchers (33.8%, n=25), and lived experience (people living with CKD and caregivers; 41.9%, n=31). Of the 73 respondents, 59 had participated in round 1. Round 3 included 63 participants, all of whom had completed either round 1, round 2, or both. Additional demographic data can be found in Supplemental Tables 1 and 2.

Round 1 Priorities

In total, 447 initial questions were received in round 1; after deduplication and qualitative synthesis, 125 unique research questions within ten categories were identified (Table 2).

Round 2 Priorities

Of the 125 questions in round 2, 46 received a mean and median score of seven or higher across all three panels, indicating critical importance (Supplemental Table 3). The lived experience panel identified the highest number of questions as critical (63), followed by researchers (45), then clinicians (25). Between panels, there was disagreement on the level of importance for almost half (43.2%) of the questions (*i.e.*, differed in being ranked *important but not critical* versus *critical* across panels). Researchers ranked five of the six questions in the Exercise and Other Therapies category as critical compared with zero questions ranked critical in this category by the other panels. Clinicians identified the Patient-Oriented Outcomes and Natural History of Cognition categories as less critical than the other panels, only ranking three of 27 and three of 33 of the questions as critical, respectively. None of the questions received an overall or panel ranking of unimportant (*i.e.*, mean and median score ≤3). Ultimately, no questions in the Exercise and Other Therapies and Healthcare Costs categories met the criteria to move forward, and both categories were eliminated.

In round 2, participants also had the opportunity to suggest additional research questions. Of the eight respondents who provided additional questions or comments, no new questions were suggested.

A total of 44 questions met the criteria to move to round 3 for final reranking.

Round 3 Priorities

Table 3 shows the final top three questions per panel. Table 4 shows the complete list of questions, median scores, and proportion of participants scoring each question as critically important (7–9). The overall median score for the questions in round 3 was 7 (interquartile range, 7–8). Ultimately, all 44 questions were deemed critically important.

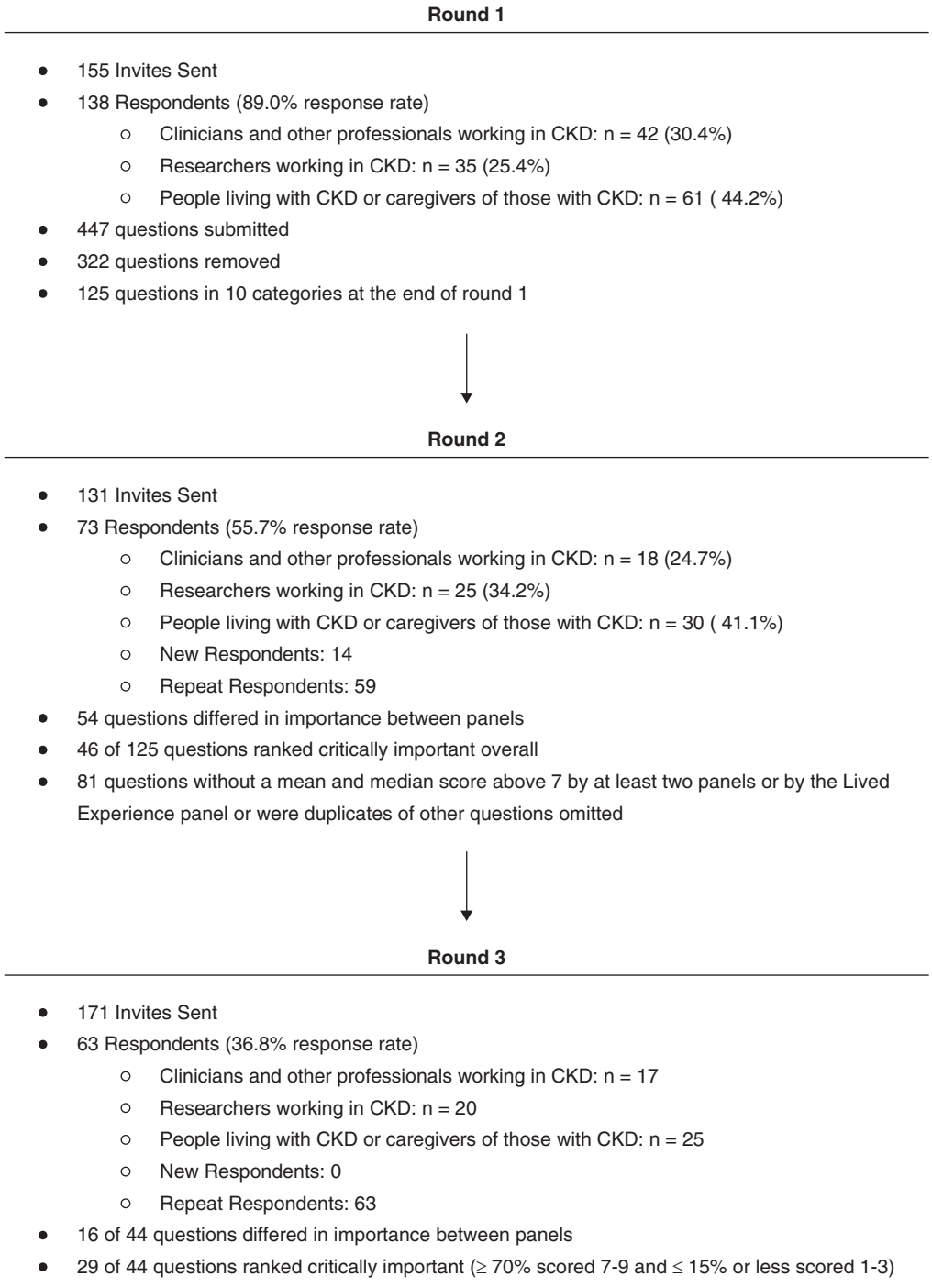

Figure 2. Participant flow chart.

Consensus

Consensus that a question was critically important was achieved on 27 of 44 questions (Table 4). Consensus was reached in 100% of questions in categories of *Uremia* (n=2), *Prevention of Cognitive Impairment* (n=5), *Dialysis Treatment Impact* (n=1), and *Cognitive Assessment* (n=4). The category with the lowest proportion of questions reaching consensus was the *Impact of CKD Management on Cognitive Impairment*, with only two of six (33.3%) of the questions agreed upon as critically important across panels. The top questions, as ranked by consensus rating, were as follows:

1. What factors *prevent* cognitive impairment in people receiving dialysis? (93.6% consensus)
2. What strategies and interventions can *maintain* cognition in all stages of CKD, including dialysis? (93.6%)
3. What can be done to *prevent* cognitive impairment in children living with any stage of CKD, including dialysis and transplant? (91.9%)

Table 1. Participant demographics

Characteristic	Round 1	Round 2	Round 3
N	138	74	63
Occupation/role			
Health care administrator	3 (2.2)	1 (1.4)	0 (0)
Researcher	35 (25.4)	25 (33.8)	19 (30.2)
Clinician	53 (38.4)	16 (21.6)	16 (25.4)
Caregivers or family of someone living with CKD	5 (3.6)	1 (1.4)	1 (1.6)
Person living with CKD[a]	37 (26.8)	30 (40.5)	25 (39.7)
Other	5 (3.6)	1 (1.4)	2 (3.2)
Sex			
Female	67 (49.6)	40 (54.8)	32 (50.8)
Male	68 (50.4)	33 (45.2)	31 (49.2)
Gender identity			
Woman	68 (49.6)	40 (54.8)	31 (49.2)
Man	67 (48.9)	33 (45.2)	31 (49.2)
Gender diverse	1 (0.7)	0 (0)	1 (1.6)
Unknown	1 (0.7)	0 (0)	0 (0)
Age, yr			
18–34	41 (29.7)	10 (13.7)	7 (11.1)
35–49	46 (33.3)	28 (38.4)	22 (34.9)
50–64	41 (29.7)	27 (37.0)	25 (39.8)
65–79	9 (6.5)	7 (9.6)	8 (12.7)
80+	1 (0.7)	1 (1.4)	1 (1.6)
Continent			
Africa	1 (0.7)	0 (0)	0 (0)
Asia	17 (12.3)	2 (2.7)	0 (0)
Europe	39 (28.3)	26 (35.1)	19 (30.1)
North America	53 (38.4)	36 (48.6)	37 (58.7)
Oceania	14 (10.1)	6 (8.1)	4 (6.3)
South America	14 (10.1)	4 (5.4)	3 (4.8)

Values are presented as *N* (%) for each round.
[a]Role can be subdivided into stages of CKD. Round 1: 33.3% CKD not on dialysis, 23.1% CKD on dialysis, 43.6% transplant recipients; round 2: 40.0% CKD not on dialysis, 10.0% CKD on dialysis, 50.0% transplant recipients; round 3: 40.0% CKD not on dialysis, 16.0% CKD on dialysis, 44.0% transplant recipients.

4. Should *routine monitoring* of cognition be implemented as part of routine clinical care for people with CKD? (89.5%)
5. Can improving clearance of toxins that build up in kidney failure during hemodialysis *reduce the risk* of impaired cognition? (88.7%)

The complete list of questions meeting consensus is available in Supplemental Material 1.3.

Differences between Stakeholder Groups

Table 5 shows differences in median scores between all stakeholder groups in the final analysis. Sixteen questions differed significantly in ranking between the stakeholder groups. The clinician and lived experience panels differed significantly on 15 questions, while the researcher and lived experience panels differed on seven. The clinician and researcher panels differed significantly on just one question.

Six questions had scores that differed significantly between male (n=31) and female (n=32) participants. Four questions differed significantly between respondents from Canada (n=34) and the United Kingdom (n=32), the countries with the highest number of respondents (Supplemental Tables 4 and 5).

Changes in Scores from Rounds 2–3

Figure 3 shows changes in the overall median scores between rounds 2 and 3. The median score remained the same in 30 questions, increased in four, and decreased in eight.

Discussion

This is the first study to incorporate perspectives from diverse stakeholders to identify critical research questions regarding cognitive impairment in people with CKD. The identified questions reflect the perceived importance of preventing and managing cognitive impairment in CKD, which was generally deemed more critical than questions about the etiology of cognitive impairment.

Interestingly, questions characterizing the relationship between uremia and cognitive impairment were also identified as critically important. Numerous studies have identified uremic toxins as a potential underlying mechanism that contributes to cognitive impairment, in part because of observations that cognitive impairment tends to improve once people with kidney failure initiate dialysis initially.[12,31–33] However, dialysis may not wholly mitigate cognitive impairment because of its ineffectiveness at removing larger, protein-bound metabolites, such

Table 2. Round 1 question categories and priorities

Question Category	No. of Questions	Proportion of Questions	Exemplar Question
Uremia	6	4.8%	Can improving clearance of toxins that build up in kidney failure during hemodialysis reduce the risk of impaired cognition?
Prevention of cognitive impairment	6	4.8%	At what stage or grade of CKD should treatments be implemented to prevent cognitive impairment?
Patient-oriented outcomes	27	21.6%	Does decreased kidney function impact emotional regulation abilities?
Comparisons in cognition between stages of CKD and treatment modalities	14	11.2%	What is the difference in cognitive status across different CKD stages?
Dialysis treatment effect	8	6.4%	What is the effect of low BP during hemodialysis on cognitive impairment?
Understanding the natural history of cognition in CKD	33	26.4%	What are early signs of worsening cognitive impairment in people with CKD?
Effect of CKD management on cognition	8	6.4%	How does cognitive impairment across the spectrum of CKD affect self-management practices (*e.g.*, ability to take medications as prescribed, attend medical appointments)?
Cognitive assessment	14	11.2%	Should routine monitoring of cognition be implemented as part of routine clinical care for people with CKD?
Exercise and other therapies for impaired cognition	7	5.6%	Can exercise be used to prevent worsening cognitive impairment in people receiving dialysis?
Health care costs	2	1.6%	Can preventing cognitive impairment in people with CKD decrease health care costs?

as phosphate and indoxyl sulfate, which have been implicated in cognitive impairment.[31–33] Currently, few evidence-based interventions to address cognitive impairment in CKD cohorts exist. Although there is a sizable body of evidence to support kidney transplantation as a method of improving or reversing cognitive impairment in those previously on dialysis, transplantation is not a viable alternative for all individuals.[34–41] As identified by the highest priority research question (What factors *prevent* cognitive impairment in people receiving dialysis?), future translational research should continue to identify candidate metabolites and characterize these molecules' role in cognitive impairment. Investigations into the effect of novel dialysis treatment methods, including expanded hemodialysis with medium cut-off membranes and hemodiafiltration, on solute clearance and cognitive impairment in people receiving hemodialysis should also be considered.[42]

Research regarding testing and monitoring of cognitive impairment in CKD populations was also identified as critical. It is unknown how often people living with CKD are screened for cognitive impairment because this likely differs widely between settings and CKD stage. Most research experts agree that routine monitoring should be implemented in CKD.[3,33] By contrast, people living with CKD have reservations about routine screening in clinical care because of the implications of a diagnosis of cognitive impairment on mental health, lack of clear correlations of test scores with cognitive function, and lack of effective evidence-based interventions.[43] Further information regarding the accuracy and impact of a diagnosis of cognitive impairment with current tests would be prudent before launching large-scale screening efforts in a clinical setting. In addition, there is a lack of certainty on when and how to assess cognitive impairment in clinical care, and although several tools exist, there is no clear consensus on which is best.[44] Future research should identify whether different tools are appropriate in various stages of CKD and create a more optimal comprehensive screening tool for those living with CKD. In addition, to move research in this area forward, there is a need for validated, reliable, responsive cognition instruments for outcome ascertainment in clinical trials.

We observed differences in the perception of importance between male and female respondents for questions about brain fog, cognition, and menopause, and developing standard definitions and tests for cognitive impairment. There is currently limited evidence available to help explain why these differences may have occurred. That said, it is known that, in general, male and female participants differ in health-seeking behaviors and that biological and sociocultural differences between male and female participants can influence how individuals experience disease.[45,46] In addition, we can assume that female participants would naturally prioritize female-specific reproductive issues, such as menopause, more than male participants. This highlights the importance of considering different preferences by sex and gender when developing studies in this area.

Consistent with previous literature ranking disease and treatment preferences in different populations, we observed differences in priorities between stakeholder panels.[47–49] Specifically, clinicians tended to place more importance on objective health outcomes and treatment success and less importance on subjective quality of life compared with people with lived experience.[28,47–51] This emphasizes the importance of incorporating patient

Table 3. Top three responses per panel and across all respondents

Rank	Category[a]	Research Question	Mean (SD)	Median (IQR)	% Ranked as Critical[b]
Lived experience panel					
1	Prevention	What can be done to prevent cognitive impairment in children living with any stage of CKD, including dialysis and transplant?	8.04 (1.08)	8 (8–9)	92.00
2	Comparison	Do kidney transplant medications that are given to prevent rejection worsen brain fog?	8.10 (1.04)	8 (8–9)	83.33
3	Cognitive assessment	Should routine monitoring of cognition be implemented as part of routine clinical care for people with CKD?	8.04 (0.75)	8 (7.75–9)	100
Researchers					
1	Prevention	What can be done to prevent cognitive impairment in children living with any stage of CKD, including dialysis and transplant?	8.11 (0.81)	8 (8–9)	90.00
2	Prevention	What factors prevent cognitive impairment in people receiving dialysis?	7.90 (0.97)	8 (7.75–8.25)	95.00
3	Natural history	What are potential treatments to improve cognitive impairment in people with CKD?	8.00 (1.00)	8 (7.5–9)	89.47
Clinicians					
1	Prevention	What factors prevent cognitive impairment in people receiving dialysis?	7.67 (0.54)	8 (8–8)	100
2	Uremia	Can improving clearance of toxins that build up in kidney failure during hemodialysis reduce the risk of impaired cognition?	7.65 (0.70)	8 (7–8)	94.12
3	Comparison	Does cognitive impairment improve after initiating dialysis?	7.29 (1.14)	8 (7–8.25)	87.50
Across panels					
1	Prevention	What can be done to prevent cognitive impairment in children living with any stage of CKD, including dialysis and transplant?	7.92 (0.96)	8 (8–8.25)	91.94
2	Natural history	What are potential treatments to improve cognitive impairment in people with CKD?	7.88 (0.99)	8 (7–9)	87.93
3	Prevention	What factors prevent cognitive impairment in people receiving dialysis?	7.84 (0.86)	8 (7–8)	93.55

IQR, interquartile range.
[a]Category names have been shortened to save space in the table. Prevention refers to Prevention of Cognitive Impairment. Natural History refers to Natural History of Cognitive Impairment in CKD. Comparison refers to Comparisons in Cognition between Stages of CKD and Treatment Modalities.
[b]Percentage of questions ranked with both a mean and median of 7 or higher per panel.

perspectives when designing research studies to capture patient-oriented priorities.

The strengths of this study include the use of pre-established Delphi methodology and the incorporation of unique perspectives from people living with kidney disease.[52,53] Encouraging active patient participation in discussions is crucial in decision-making, treatment planning, and uptake of research findings.[28] Next, individuals with diverse roles, from varied geographic locations were involved in the synthesis of the responses for the multiple rounds of the survey. This ensured collection of diverse perspectives, fairness, and that all questions deemed critical remained in the survey and were not swayed by one perspective.

Limitations of the study include low response rates from decision-makers, who accounted for only one of the participants in the first round and did not participate in the last two rounds, despite numerous invitations to

Table 4. Scores given on all round 3 questions per panel and overall

Category	Question	Mean (SD)				Median (IQR)				Proportion for Consensus			
		Overall	Clinicians	Researchers	Lived Experience	Overall	Clinicians	Researchers	Lived Experience	Overall	Clinicians	Researchers	Lived Experience
Uremia	How does the build-up of toxins due to kidney failure (*i.e.*, uremia) affect different aspects of cognition in people with CKD?	7.48 (1.10)	7.47 (0.87)	7.55 (1.19)	7.42 (1.21)	8 (7–8)	7 (7–8)	8 (7–8)	8 (7–8)	83.87%	88.24%	85.00%	80.00%
	Can improving clearance of toxins that build up in kidney failure during hemodialysis reduce the risk of impaired cognition?	7.68 (0.85)	7.65 (0.70)	7.70 (0.98)	7.70 (0.88)	8 (7–8)	8 (7–8)	8 (7.25–8)	8 (7–8)	88.71%	94.12%	90.00%	84.00%
Prevention of cognitive impairment in CKD	At what stage of CKD should potential treatments be implemented to prevent cognitive impairment?	7.16 (1.47)	6.11 (1.12)	7.55 (1.5)	7.36 (1.52)	8 (7–8)	7 (5.25–7)	8 (7.25–8.75)	8 (7–8)	75.81%	58.82%	80.00%	84.00%
	What strategies and interventions can maintain cognition in all stages of CKD, including dialysis?	7.82 (0.78)	7.33 (0.79)	7.85 (0.88)	7.92 (0.70)	8 (7–8)	8 (7–8)	8 (8–8)	8 (8–8)	93.55%	94.12%	90.00%	96.00%
	What factors prevent cognitive impairment in people receiving dialysis?	7.84 (0.86)	7.67 (0.54)	7.90 (0.97)	7.71 (0.95)	8 (7–8)	8 (8–8)	8 (7.25–8)	8 (7–8)	93.55%	100%	95.00%	88.00%
	What can be done to prevent cognitive impairment in children living with any stage of CKD, including dialysis and transplant?	7.92 (0.96)	7.33 (0.87)	8.11 (0.81)	8.04 (1.08)	8 (8–8.25)	8 (7–8)	8 (8–9)	8 (8–9)	91.94%	94.12%	90.00%	92.00%
	What are cost-effective strategies to prevent cognitive impairment in people living with CKD who live in low- and low-middle-income countries?	7 (1.40)	6.89 (1.28)	7.05 (1.28)	6.96 (1.60)	7 (7–8)	7 (6.25–7.75)	7 (6–8)	7 (7–8)	75.81%	76.47%	70.00%	80.00%
Patient-oriented outcomes	What is the relationship between cognitive impairment and quality of life in people with CKD?	6.98 (1.43)	6.12 (1.55)	7.00 (1.52)	7.33 (1.20)	7 (6–8)	7 (6–7)	7 (6–8)	7.5 (6–8)	65%	56.25%	60.00%	75.00%
	What tools (if any) are there to help with memory issues for people with predialysis CKD?	7.10 (1.17)	7.00 (1.26)	6.85 (1.23)	7.41 (1.01)	7 (6–8)	7 (6.25–8)	7 (6–8)	7.5 (7–8)	68.33%	75.00%	60.00%	70.83%
	How does cognitive impairment affect daily function and activities in people living with CKD?	7.1 (1.41)	6.50 (1.63)	7.05 (1.54)	7.54 (0.98)	7 (6.75–8)	7 (5.25–7)	7 (6.25–8)	8 (7–8)	75.00%	62.50%	70.00%	87.50%
	What is the relationship between cognitive impairment and mental health?	6.90 (1.40)	6.38 (1.20)	6.85 (1.60)	7.30 (1.26)	7 (6–8)	6.5 (5–7)	7 (6.25–8)	8 (7–8)	66.67%	50.00%	70.00%	75.00%
	What is the relationship between socioeconomic status, education, and cognitive impairment in people with all stages of CKD, including dialysis?	6.57 (1.68)	6.25 (1.61)	6.35 (1.37)	7.00 (1.51)	6.5 (6–8)	6.5 (5.25–7)	7 (6–8)	7 (6–8)	57.00%	50.00%	55.00%	62.50%
	How can we assist caregivers to identify cognitive impairment, seek help, and provide support to people with any stage of CKD and cognitive impairment?	7.17 (1.40)	7.19 (1.05)	7.15 (1.18)	7.17 (1.79)	7 (6.75–8)	7 (7–7.75)	7 (7–8)	8 (6–8)	75.00%	81.25%	75.00%	70.83%
	What causes brain fog and self-perceived losses in cognition in all stages of CKD?	7.15 (1.23)	7.13 (0.89)	6.40 (1.43)	7.83 (1.03)	7 (6.5–8)	7 (7–7.75)	7 (6–7)	8 (7–9)	73.33.%	75.00%	60.00%	83.33%
	What is the relationship between cognitive impairment and fatigue/low energy levels in people receiving dialysis?	6.68 (1.62)	6.06 (1.61)	6.35 (1.39)	7.39 (1.62)	7 (6–8)	6 (5.25–7)	6 (6–7)	8 (7–8)	53.00%	37.50%	40.00%	75.00%
	Does decreased physical activity impact cognition in hemodialysis?	7.26 (1.21)	6.94 (1.18)	7.60 (1.14)	7.18 (1.26)	7 (7–8)	7 (6–7)	8 (7–8)	7 (7–8)	74.58%	68.75%	80.00%	73.91%
	What is the effect of cognitive impairment on dialysis decision making (starting and stopping treatment)?	7.12 (1.51)	6.94 (1.61)	7.00 (1.49)	7.35 (1.50)	7 (6.5–8)	7.5 (6–8)	7 (7–8)	8 (7–8)	73.33%	56.25%	80.00%	79.17%
Comparison between stages of CKD or treatment modality	Does cognitive impairment improve after initiating dialysis?	7.28 (1.18)	7.29 (1.14)	7.16 (1.01)	7.09 (1.31)	8 (7–8)	8 (7–8)	7 (7–8)	8 (6–8)	76.27%	87.50%	73.68%	70.83%
	How do we differentiate cognitive impairment related to toxin build-up in kidney failure from other causes of cognitive impairment in older adults (*e.g.*, normal memory decline with aging and/or dementia/ Alzheimer disease)?	7.02 (1.56)	7.13 (1.67)	6.58 (1.54)	7.32 (1.49)	8 (6–8)	8 (6.25–8)	7 (5.25–8)	8 (6.75–8)	67.80%	75.00%	57.89%	70.83%
	How does cognition differ between people with different stages of CKD, including those receiving hemodialysis, peritoneal dialysis, and transplant recipients?	6.80 (1.53)	6.75 (1.44)	6.56 (1.69)	7.05 (1.50)	7 (6–8)	7 (6–7.75)	7 (5.25–8)	7 (6–8)	60.34%	56.25%	66.67%	58.33%
	In people receiving dialysis, does cognitive impairment improve after having a kidney transplant?	7.03 (1.43)	7.06 (1.53)	6.79 (1.72)	7.22 (1.09)	7 (6.25–8)	7 (7–7.75)	7 (6–8)	7 (6.75–8)	72.88%	87.50%	63.16%	70.83%
	Do kidney transplant medications that are given to prevent rejection worsen brain fog?	7.80 (1.73)	5.94 (1.73)	6.11 (1.52)	8.10 (1.04)	7 (6–8)	6.5 (4.25–7)	6 (6–7)	8 (8–9)	62.71%	50.00%	47.37%	83.33%

Table 4. (Continued)

Category	Question	Mean (SD)				Median (IQR)				Proportion for Consensus			
		Overall	Clinicians	Researchers	Lived Experience	Overall	Clinicians	Researchers	Lived Experience	Overall	Clinicians	Researchers	Lived Experience
Dialysis treatment impact	Are there treatments (*e.g.*, medications, dialysate temperature, dialysis prescription) specifically related to kidney failure and dialysis that are associated with worsening cognitive impairment over time?	7.48 (0.96)	7.00 (0.81)	7.47 (0.96)	7.57 (1.08)	8 (7–8)	7 (7–8)	7 (7–8)	8 (7–8)	83.05%	87.50%	84.21%	79.17%
Natural history of cognitive impairment in CKD	What are early signs of worsening cognitive impairment in people with CKD?	7.05 (1.37)	5.94 (1.39)	7.33 (1.24)	7.33 (1.31)	7 (6–8)	6 (5.25–7.75)	8 (6–8)	7.5 (7–8)	68.42%	40.00%	66.67%	87.50%
	What cognitive impairment screening tools in CKD can be easily used in different stages of CKD?	7.30 (1.11)	7.33 (1.05)	7.21 (1.08)	7.36 (1.22)	7 (7–8)	7 (7–8)	7 (7–8)	7.5 (7–8)	81.03%	86.67%	73.68%	83.33%
	What are the risk factors and causes of cognitive impairment among individuals living with all stages of CKD, including dialysis and transplant?	7.16 (1.17)	6.87 (1.25)	7.11 (1.33)	7.41 (0.96)	7 (7–8)	7 (6–8)	7 (7–8)	7.5 (7–8)	77.00%	66.67%	78.95%	82.61%
	What is the long-term kidney health prognosis in people with CKD who experience cognitive impairment?	6.81 (1.42)	5.80 (1.57)	6.95 (1.47)	7.33 (0.92)	7 (6–8)	6 (4.25–7)	7 (6–8)	7 (7–8)	69.00%	40.00%	68.42%	87.50%
	What domains of cognition (*e.g.*, memory, attention, reasoning, judgment abilities) are most affected in people with different stages of CKD, including those on dialysis and with kidney transplant?	7.22 (1.18)	7.13 (1.19)	7.22 (1.06)	7.27 (1.32)	7 (7–8)	7 (6.25–8)	7 (7–8)	8 (6–8)	72.41%	73.33%	78.95%	66.67%
	At what stage of CKD does brain fog start?	6.39 (1.67)	5.73 (1.75)	6.00 (1.60)	7.13 (1.42)	7 (5–7)	6 (4–7)	6 (5.25–7)	7 (6–8.25)	55.17%	46.67%	47.37%	66.67%
	What is the relationship between menopause and cognitive impairment in female participants living with all stages of CKD including those on dialysis and with a kidney transplant?	6.05 (1.60)	5.20 (1.57)	5.58 (1.22)	7.05 (1.43)	6 (5–7)	5 (4–6.75)	6 (5–6)	7 (6–8)	36.21%	26.67%	21.05%	54.17%
	What are potential treatments to improve cognitive impairment in people with CKD?	7.88 (0.99)	7.47 (1.06)	8.00 (1.00)	8.05 (0.90)	8 (7–9)	8 (7–8)	8 (7.25–9)	8 (7–9)	87.93%	86.67%	89.47%	87.50%
	Is cognitive impairment reversible in CKD (all stages including dialysis and transplant)?	7.53 (1.18)	6.87 (1.41)	7.47 (0.96)	8.00 (1.00)	8 (7–8)	7 (6.25–8)	8 (7–8)	8 (7–9)	84.48%	73.33%	89.47%	87.50%
	How can cognition be improved in children at all stages of CKD, including transplant?	7.31 (1.27)	6.60 (1.35)	7.61 (0.61)	7.57 (1.47)	7 (7–8)	7 (6–7)	8 (7–8)	8 (7–9)	78.95%	60.00%	94.74%	78.26%
	How common is cognitive impairment in children in all stages of CKD, including among those who have received a transplant?	6.93 (1.50)	6.20 (1.52)	6.67 (0.61)	7.67 (1.28)	7 (6–8)	6 (6–7)	7 (6–7)	8 (7–9)	63.79%	46.67%	63.16%	75.00%
Effect of CKD management on cognitive impairment	What medications affect (either improve or worsen) cognition in people with CKD?	7.30 (1.05)	7.0 (1.0)	6.95 (1.13)	7.78 (0.85)	7 (7–8)	7 (7–7.75)	7 (7–7.75)	8 (7–8)	87.72%	80.00%	84.21%	95.65%
	How does cognitive impairment across the spectrum of CKD affect adherence and self-management practices (*e.g.*, ability to take medications as prescribed, attend medical appointments)?	6.81 (1.66)	6.33 (1.84)	7.05 (1.51)	6.92 (1.67)	7 (6–8)	7 (4.5–7.75)	7 (6.25–8)	7 (6–8)	62.07%	53.33%	68.42%	62.50%
	How do hemoglobin levels affect cognition in hemodialysis?	6.34 (1.69)	5.33 (1.68)	5.84 (1.61)	7.38 (1.17)	6 (6–8)	6 (4–6)	6 (5–7)	8 (6–8)	46.55%	26.67%	31.58%	70.83%
	How do iron levels affect cognition in people receiving hemodialysis?	6.28 (1.72)	5.20 (1.66)	5.58 (1.50)	7.50 (1.10)	6 (5–8)	5 (4.25–6)	6 (5–6.75)	8 (7–8)	46.55%	20.00%	26.32%	79.17%
	How do albumin levels affect cognition in CKD?	5.89 (1.86)	4.60 (1.76)	5.26 (1.48)	7.26 (1.25)	6 (5–7)	5 (4–5.75)	6 (5–6)	7 (6–8)	36.21%	6.67%	21.05%	66.67%
	How does polypharmacy (which when an individual takes multiple medications—including opiates, gabapentinoids [gabapentin, pregabalin] and sedative/hypnotics) affect cognition in people receiving dialysis?	7.09 (1.19)	6.87 (1.06)	6.79 (1.44)	7.47 (0.98)	7 (7–8)	7 (6.25–7)	7 (7–7)	8 (7–8)	77.59%	73.33%	73.68%	83.33%

Table 4. (Continued)

Category	Question	Mean (SD)				Median (IQR)				Proportion for Consensus			
		Overall	Clinicians	Researchers	Lived Experience	Overall	Clinicians	Researchers	Lived Experience	Overall	Clinicians	Researchers	Lived Experience
Cognitive assessment	Is it possible to develop a test for cognition that can accurately and reproducibly diagnose cognitive impairment across all stages of CKD, including dialysis and transplant?	7.24 (1.30)	7.43 (1.02)	6.79 (1.44)	7.50 (1.30)	8 (7–8)	8 (7–8)	7 (6–8)	8 (7–8)	77.19%	85.71%	63.16%	83.33%
	What currently available standardized cognition tests are the best tools to assess cognitive status in people living with CKD in clinical and research settings?	7.23 (1.22)	7.50 (0.52)	7.16 (1.17)	7.13 (1.55)	7 (7–8)	7.5 (7–8)	7 (7–8)	7 (7–8)	84.21%	100%	78.95%	79.17%
	Should routine monitoring of cognition be implemented as part of routine clinical care for people with CKD?	7.60 (1.21)	6.93 (1.38)	7.53 (1.35)	8.04 (0.75)	8 (7–8)	7 (7–8)	8 (7–8)	8 (7–9)	89.47%	78.57%	84.21%	100%
	What is the standard definition of cognitive impairment in people with all stages of CKD, including dialysis and transplant?	7.15 (1.13)	7.00 (1.11)	6.89 (1.24)	7.45 (1.01)	7 (7–8)	7 (7–7)	7 (6.25–7.75)	8 (6.75–8)	73.68%	85.71%	68.42%	70.83%

IQR, interquartile range.

Table 5. Questions differing significantly on importance between panels

Questions Differing Significantly between Panels	Median Score			*P* Value		
Question	LE	R	C	LE versus R	LE versus C	C versus R
At what stage of CKD should potential treatments be implemented to prevent cognitive impairment?	8	8	7	0.9	0.02	0.005
How does cognitive impairment affect daily function and activities in people living with CKD?	8	7	7	0.8	0.02	0.1
What is the relationship between cognitive impairment and mental health?	8	7	6.5	0.7	0.005	0.04
What causes brain fog and self-perceived losses in cognition in all stages of CKD?	8	7	7	<0.001	0.05	0.3
What is the relationship between cognitive impairment and fatigue/low energy levels in people receiving dialysis?	8	6	6	0.02	0.002	0.6
Do kidney transplant medications that are given to prevent rejection worsen brain fog?	8	6	6.5	<0.001	<0.001	0.6
What is the long-term kidney health prognosis in people with CKD who experience cognitive impairment?	7	7	6	0.4	0.002	0.05
At what stage of CKD does brain fog start?	7	6	6	0.07	0.02	0.8
What is the relationship between menopause and cognitive impairment in female participants living with all stages of CKD, including those on dialysis and with a kidney transplant?	7	6	5	0.01	0.003	0.8
Is cognitive impairment reversible in CKD (all stages, including dialysis and transplant)?	8	8	7	0.3	0.02	0.4
How can cognition be improved in children at all stages of CKD, including transplant?	8	8	7	0.9	0.02	0.05
How common is cognitive impairment in children in all stages of CKD, including among those who have received a transplant?	8	7	6	0.08	0.005	0.4
How do hemoglobin levels affect cognition in hemodialysis?	8	6	6	0.007	0.0004	0.5
How do iron levels affect cognition in people receiving hemodialysis?	8	6	5	<0.001	<0.001	0.5
How do albumin levels affect cognition in CKD?	7	6	5	0.001	<0.001	0.3
Should routine monitoring of cognition be implemented as part of routine clinical care for people with CKD?	8	8	7	0.5	0.02	0.2

C, Clinicians; LE, Lived Experience; R, Researchers.

individuals working in these roles. However, our study sample may have captured decision-makers with multiple roles (*e.g.*, clinician decision-makers). In addition, respondents were predominately from Western, high-economic regions, limiting generalizability to low-middle-income countries. Furthermore, most of the lived experience panel comprised people with nondialysis CKD and transplant recipients. People with dialysis-dependent CKD may have unique perspectives and may not have been fully represented in this study. Finally, because the

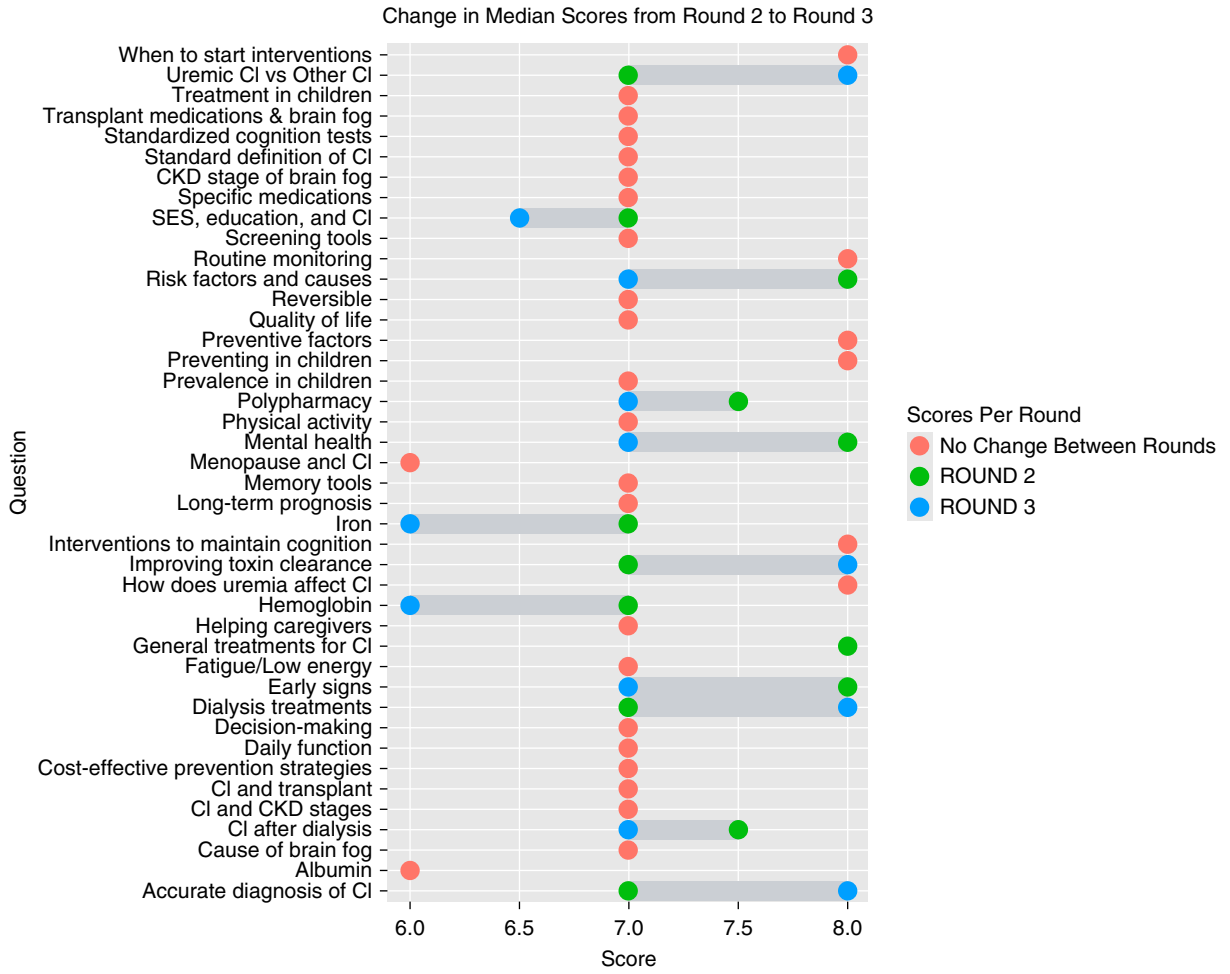

Figure 3. Change in median scores from round 2 to round 3. CI, cognitive impairment; SES, socioeconomic status.

established consensus criteria using the Likert scale did not further narrow down critical questions from round 2 to round 3, another approach may have been more effective in establishing priorities.

In conclusion, the major stakeholder groups in CKD identified 27 questions spanning eight different categories as critical for future research in cognition and cognitive impairment. Researchers, clinicians, and policymakers are encouraged to use this list to inform future research and decision-making related to cognitive impairment in all stages of CKD.

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Data Sharing Statement

All data are included in the manuscript and/or supporting information. Partial restrictions to the data and/or materials apply. The data underlying this article are available in the article and in its online supplementary material. Additional data underlying this article will be shared on reasonable request to the corresponding author.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/A869.

1.1. Participant Recruitment

1.2. Criterion as Being a "Content Expert"

1.3. Questions Meeting Consensus Following Round 3

Supplemental Table 1. Geographic location of participants.

Supplemental Table 2. Demographic information by panel.

Supplemental Table 3. Round 1 and round 2 interim results by panel. Values represent the number of questions identified per panel.

Supplemental Table 4. Questions differing significantly on importance between male and female respondents in round 3.

Supplemental Table 5. Questions differing significantly on importance between Canada and the United Kingdom in round 3.

2.1. Round 1 Survey

2.2. Round 2 Survey

2.3. Round 3 Survey

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