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Physical exercise and cognitive training interventions to improve cognition in hemodialysis patients: A systematic review

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Introduction: Patients with chronic kidney disease treated with hemodialysis (HD) have lower cognitive abilities compared to the age-matched healthy population. Recently, physical exercise and cognitive training have been presented as possible interventions to improve cognitive abilities both in the general population and in patients with chronic diseases. To date, there is no general overview of the current knowledge on how these interventions affect cognitive abilities in HD patients and what tests are used to measure these effects.

Methods: Three electronic databases were searched for randomized controlled studies of physical exercise or cognitive training interventions that examined effects on cognitive abilities/performance in HD patients.

Results: Six articles were included. All included studies used physical exercise as an intervention, with one study also including tablet-based cognitive training. Four studies included an intradialytic approach and two included a home-based intervention. Intervention lasted. A significant intervention effect was observed in three studies compared with the control condition.

Conclusion: The present review suggests that physical exercise might improve or at least not worsen cognitive performance in HD patients, whereas the effect of cognitive training has not yet been adequately studied. There is a need for more sensitive and specific cognitive tests to adequately measure the effects of interventions in the HD population.

KEYWORDS

cognitive performance, hemodialysis, physical exercise, cognitive training, cognitive tests, intervention

Introduction

It is well-documented that cognitive deficits cause progression toward dementia (1, 2). This phenomenon is even more pronounced in clinical populations (3). An example of a vulnerable population with an increased incidence of cognitive impairment is patients with kidney disease treated with hemodialysis (HD). The cognitive decline in HD patients is not only the result of underlying and concomitant diseases but can also be attributed to their changed lifestyle after starting HD. These patients have to travel to a dialysis center every other day, where they spend 4–5 h in a sedentary position during a HD procedure. Many reports a post-dialysis burnout and fatigue lasting for up to 24 h post-dialysis (4). As a result, these patients are less physically active and activate their mental functions to a lesser extent. Moreover, in HD patients, diabetes, a common chronic kidney disease (CKD) comorbidity, was significantly associated with larger cognitive impairment (5). HD treatment itself also contributes to a higher risk of developing dementia by causing ischemic stunning of the brain (6). In addition, dementia risk factors such as obesity, depression, and social isolation are common in the HD population.

It was found that only 13% of HD patients have a normal cognitive function (7). Moreover, clinicians usually fail to recognize declining cognitive performance in these patients; therefore, cognitive impairment is critically underestimated and not appropriately treated (8). It has been reported that <5% of all patients with kidney disease with cognitive impairment have been evaluated or received a medical diagnosis (9). Measurement of cognitive function is not currently part of the physical examination and medical history of CKD patients.

Lately, non-pharmacological interventions have been introduced as possible approaches to mitigate cognitive decline and dementia (3). Studies that examined the effect of exercise interventions on cognitive performance showed conflicting results. A systematic review of exercise intervention studies on cognition in older adults did not provide sufficient evidence that exercise affects cognitive performance (10). Another systematic review concluded that physical activity could delay the progression of cognitive decline in the elderly (11). In a recent study, the authors reported the results of a 6-month aerobic exercise intervention in older adults (>60 years) on cognitive function. Compared to control subjects, participants in the training group showed broad improvement in cognitive abilities, including processing speed, episodic memory, executive functions, and updating (12).

In addition to physical activity, cognitive training programs to improve general and specific cognitive domains are being increasingly used in research on cognitive decline. A meta-analysis of 17 controlled interventional trials of computer-assisted cognitive training in subjects with mild cognitive

impairment showed a moderate effect on general cognition (13). In community-dwelling older adults, the ACTIVE trial demonstrated long-term retention of a benefit of 10–14 weeks' cognitive training with significant improvement in cognitive abilities and maintenance of functional status after a 10-year period (14).

Despite the fact that there is a plethora of research on physical and cognitive interventions, most of the focus has been on the general population. There is little research addressing the clinical population. In addition, there is no systematic review of the effect of physical exercise and cognitive training that focuses on patients with CKD undergoing HD. Therefore, the aim of this systematic review was to examine the effects of non-pharmacological interventions in the form of cognitive and physical exercise training on different domains of cognitive performance.

Materials and methods

The review methods and reporting were performed according to the preferred reporting items in systematic review and meta-analyses (PRISMA) guidelines (15).

Eligibility criteria

The PICOS search tool (participant, intervention, comparison, outcome, and study design) was used to determine keywords (Table 1).

Studies were included in the systematic review if they met the following criteria: (a) randomized controlled trials, (b) published in academic journals, (c) written in English, (d) with participants on hemodialysis and (e) studies that included physical exercise or cognitive training interventions with (f) outcome of cognitive performance. Studies were excluded if study population were CKD patients without kidney replacement therapy or patients on peritoneal dialysis, animal studies, and individual case studies.

TABLE 1 "PICOS" items (participants, intervention, comparisons, outcomes, study designs) used to select keywords.

PICOS item	Detail
Participants	Hemodialysis patients
Interventions	Physical exercise training or/and cognitive training
Comparisons	Active or inactive control group
Outcomes	Cognitive performance
Study designs	RCTs

RCT, randomized controlled trial.

Search strategy

To identify potentially relevant studies, we performed a comprehensive literature search in electronic databases including PsycInfo, PubMed and MEDLINE (Ovid) from the database's inception to the final update in August 2022. Medical subject heading (mesh) terms were used, if available, for a qualitative search of potential studies. Search strategies utilized a combination of key words to represent definitions of hemodialysis, cognitive functioning, physical activity interventions and cognitive training. Terms were combined using the "AND" and "OR" Boolean operator (for the

full list of search phrases and terms, see [Table 2](#)). To increase the likeliness of including all relevant trials, a backward and forward search were performed by screening the citations and references list of the included studies. A flow diagram of the search is presented in [Figure 1](#).

Study selection and data collection procedure

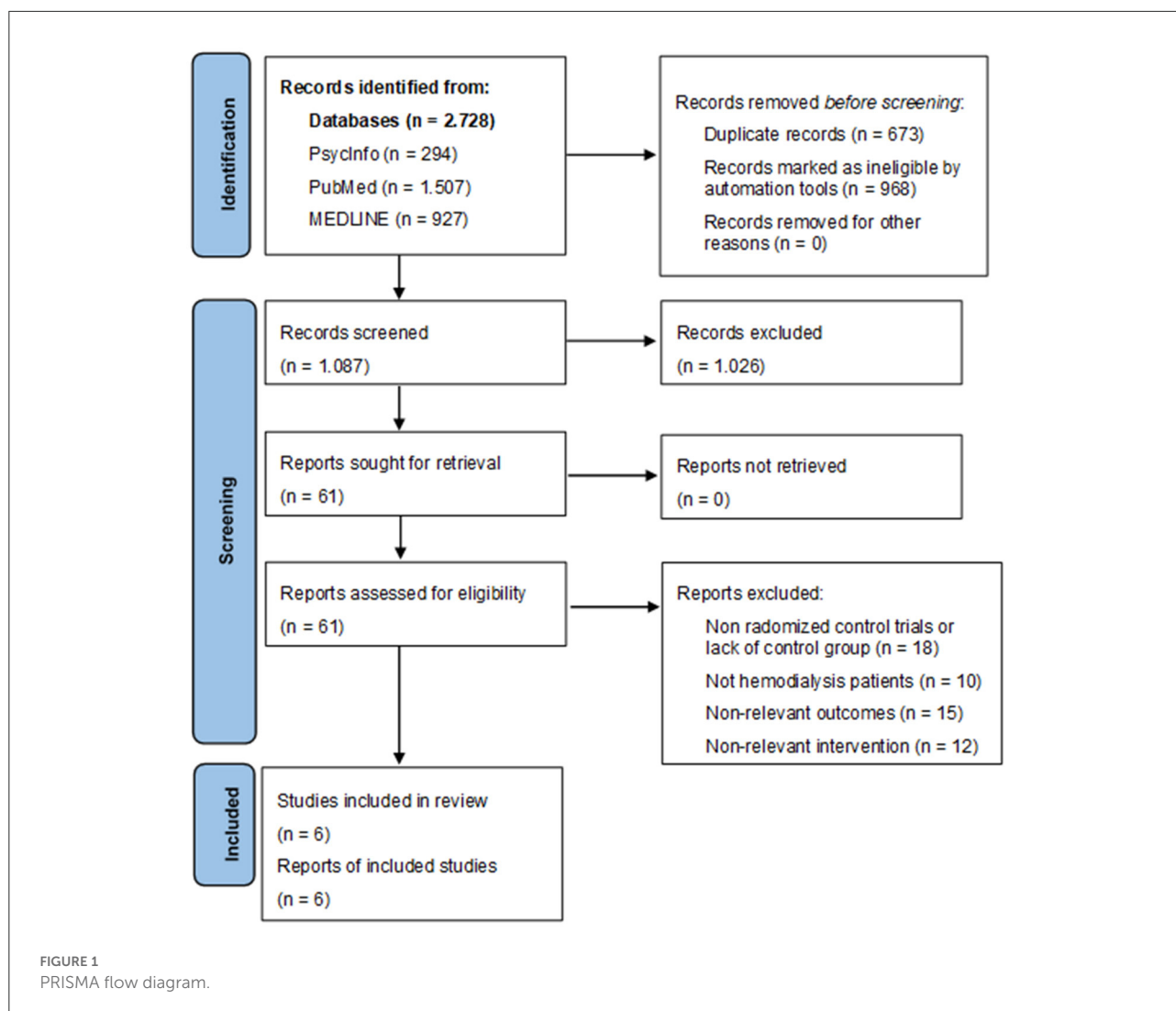
Articles from the above databases were checked for duplicates using EndNote X9. Subsequently, all articles were

TABLE 2 Search strategy.

Literature search

PsycInfo	Hemodialysis OR haemodialysis AND cognition OR cognitive function OR cognitive performance OR cognitive abilities OR cognitive ability Hemodialysis OR haemodialysis AND cognition OR cognitive function OR cognitive performance OR cognitive abilities OR cognitive ability AND intervention Hemodialysis OR haemodialysis AND cognitive training Hemodialysis OR haemodialysis AND physical activity OR exercise OR fitness OR physical exercise Hemodialysis OR haemodialysis AND physical activity OR exercise OR fitness OR physical exercise AND intervention Hemodialysis OR haemodialysis AND cognitive intervention Renal dialysis AND cognition OR cognitive function OR cognitive performance OR cognitive abilities OR cognitive ability AND intervention Renal dialysis AND cognition OR cognitive function OR cognitive performance OR cognitive abilities OR cognitive ability AND intervention AND physical activity OR exercise OR fitness OR physical exercise Renal dialysis AND cognition OR cognitive function OR cognitive performance OR cognitive abilities OR cognitive ability Renal dialysis AND physical activity OR exercise OR fitness OR physical exercise AND intervention Renal dialysis AND cognitive training
Filters	English, academic journals
PubMed	Hemodialysis AND cognition [MeSH] Hemodialysis [MeSH] AND cognitive training Hemodialysis [MeSH] AND physical activity intervention and cognition [MeSH] Hemodialysis [MeSH] AND exercise [MeSH] AND cognition [MeSH] Renal dialysis [MeSH] AND cognition AND intervention Renal dialysis [MeSH] AND physical activity AND cognition AND intervention Renal dialysis [MeSH] AND cognitive training Renal dialysis [MeSH] AND exercise [MeSH]
Filters	English, randomized controlled trials
Medline (OVID)	Renal dialysis AND cognition AND exercise Renal dialysis AND cognitive training Renal dialysis AND cognitive training OR physical exercise intervention Hemodialysis OR renal dialysis AND cognitive training Renal dialysis AND physical activity intervention OR fitness intervention OR physical exercise intervention Renal dialysis AND cognitive intervention Renal dialysis AND cognitive intervention OR physical exercise intervention Renal dialysis AND cognit*
Filters	English, academic journals, expand term finder

*Wildcard that finds variant spellings of words.



screened using the Rayyan app (16). In the app, two reviewers (ŠB and KKM) independently reviewed the titles and abstracts of each article in a blinded manner. The decision to include an article was made at the research team meeting. Articles that met the inclusion criteria underwent quality assessment.

Risk of bias assessment

The quality of the included studies was evaluated using the revised Cochrane Collaboration's risk of bias tool (17). The following biases were evaluated: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result and overall bias. Risk of bias was assessed as low, some concerns or high for each domain and for overall bias.

Results

Study selection

The flow of studies through the review process is reported in Figure 1. Automation tools used in databases were language (English), type of publication (Academic journals) and if possible study type (randomized controlled trial). Duplicate records were removed once the search strategy outputs were combined. Titles and abstracts were screened to identify studies that administered physical activity interventions or cognitive training/interventions to promote cognitive functioning. Full-texts of these articles were read to see whether full inclusion criteria were met. All studies that met inclusion criteria were again screened to determine eligibility for the systematic literature review.

Quality assessment

The bias risks are presented using a risk of bias summary in Figure 2. In the aspects of measurement of outcome, two of the studies were assessed as high risk (18, 19), in the aspects of randomization process three of six included studies were assessed with some concerns (18–20). Three of all included studies were assessed as low risk on all domains and overall (21–23).

Study characteristics

The six included studies were published between 2015 and 2021. They included a total of 466 HD patients. Two hundred fourteen patients received a physical exercise intervention and seven patients received a cognitive training intervention. The control group, which received standard treatment or stretching exercises, consisted of 245 HD patients. The average age of participants in the included studies ranged from 48 to 75 years. The youngest patients were in the exercise group of the study by McAdams-DeMarco et al. (20), and the oldest were in the control group of the study by Baggetta et al. (18). Two studies did not report the frequency of exercise. The remaining physical activity studies reported that exercise was performed three times per week. The duration of the intervention ranged from 12 to 24 weeks. The characteristics of the included studies are shown in Table 3.

Two included studies examined the effect of a 6-month home-based walking program on self-reported cognitive function as measured by KDQOL-SF (18, 19). In one study, there was a significant increase in cognitive function (19) and in the other study the control group experienced a decline while an experimental group preserved self-reported cognitive function in older dialysis patients (>65 years) (18). An intradialytic exercise program in the form of stretching exercises

and cycling significantly improved cognitive performance as measured by the MMSE in the experimental group compared to the standard care control group (23). Contraindicatory, intradialytic resistance exercise (22) and chair stand exercise program (21) showed no significant effect on cognitive ability as measured by MoCA and 3MS. Only one included pilot study examined the effects of cognitive training (20) with 20 HD patients randomly assigned to a cognitive training group (brain games on tablet computers, $n = 7$), an intradialytic cycling group ($n = 6$), or to standard treatment group ($n = 7$). The intervention lasted 3 months and showed a decline in executive functions and psychomotor speed in the control group, whereas the decline was not observed in either the cycling or cognitive training groups.

Regarding the duration of the intervention, in two studies (20, 21), the 12-week intervention did not result in significant improvement in selected cognitive domains. In the remaining studies, the intervention was delivered for 16 weeks or longer and showed either significant improvement (19, 23) or maintenance of cognitive performance compared to the control group (18, 22).

Cognitive performance/ability was assessed using various validated cognitive tests/questionnaires: Modified Mini-Mental State (3MS), Trail-Making Test A and B (TMTA and TMTB), Kidney Disease Quality of Life Short Form (KDQOL-SF), Montreal Cognitive Assessment (MoCA), and Mini-Mental State Examination (MMSE). Brief description of used tests and questionnaires is offered in Table 4.

The MoCA test is a cognitive screening test that has good sensitivity (76.7%) and specificity (78.6%) for assessing cognitive performance in HD patients (29). Another screening test, the MMSE, showed a sensitivity of 55.2% and specificity of 75% (29). The 3MS is a modified version of the MMSE, which showed a sensitivity of 88% and a specificity of 90% as a screening test for dementia in a study of elderly residents (30). In a study by Dobbs and Shergill (31) examining the predictive power of the TMT for

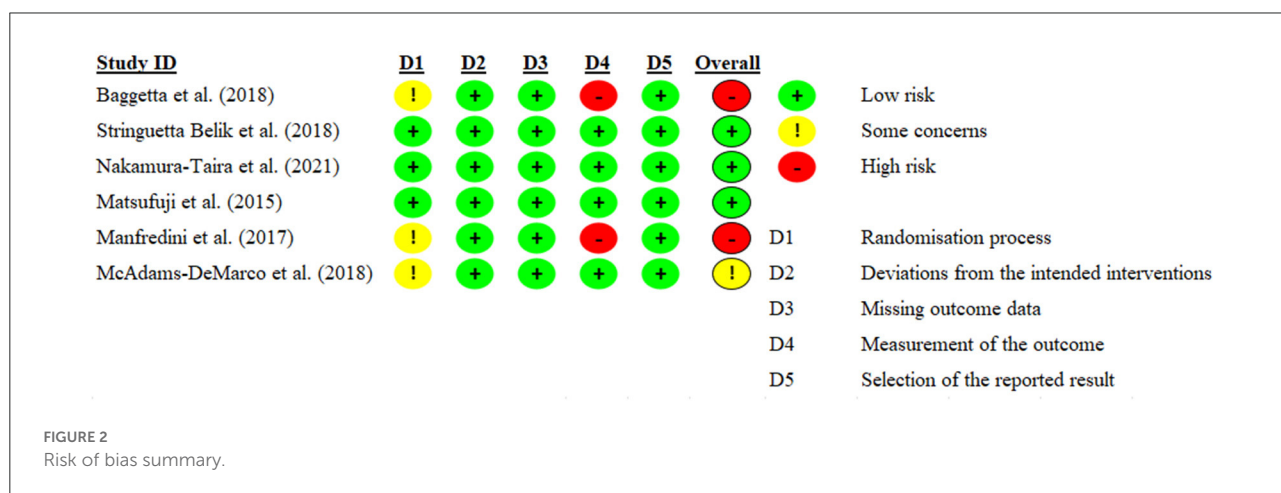


TABLE 3 Characteristics of included studies.

Study	Sample size	Age (mean \pm SD)	Intervention	Duration	Measures	Outcomes
McAdams-DeMarco et al. (20)	CT = 7 EX = 6 CON = 7	CT = 48.9 \pm 12.2 EX = 48.0 \pm 7.0 CON = 55.0 \pm 9.7	CT = intradialytic cognitive training EX = intradialytic cycling CON = standard care	3x/week 12 weeks	3 MS TMTA TMTB	3 MS (score) mean change from baseline CT: -3.4 (9.2); $p = 0.24$; ES = -0.36 EX: 4.3 (5.4); $p = 0.17$; ES = +0.7 CON: -0.1 (7.0); $p = 0.96$; ES = -0.01 TMTA (s) mean change from baseline CT: -0.2 (14.7); $p = 0.98$; ES = -0.01 EX: -2.5 (9.3); $p = 0.77$; ES = -0.15 CON: 15.0 (25.8); $p = 0.055$; ES = +0.76 TMTB (s) mean change from baseline CT: 0.6 (29.1); $p = 0.97$; ES = +0.02 EX: -8.9 (24.4); $p = 0.63$; ES = -0.46 CON: 47.4 (45.7); $p = 0.006$; ES = +1.1
Manfredini et al. (19)	EX = 104 CON = 123	EX = 63 \pm 13 CON = 64 \pm 14	EX = walking exercise program CON = standard care	24 weeks	KDQOL-SF cognitive function	Change from baseline (range) EX: +0.3 (-3.2 to 3.8); $p = 0.87$; ES = +0.03 CON: -6.4 (-11.9 to -0.9); $p = 0.02$; ES = -0.44 Changes between groups (range) -6.7 (-13.2 to -0.2); p (EX vs. CON) = 0.04
Matsufuji et al. (21)	EX = 15 CON = 17	EX = 69 \pm 11 CON = 69 \pm 13	EX = chair stand exercise CON = stretch exercise	EX: 3x/week CON: 1x/week 12 weeks	3MS	Change from baseline (range) EX: 6 (0-17) CON: 2 (-5 to 12) Comparison between groups $p = 0.40$
Nakamura-Taira et al. (22)	EX = 21 CON = 21	EX = 74.9 \pm 2.23 CON = 72.57 \pm 2.26	EX = intradialytic resistance exercise CON = stretch exercise	3x/week 24 weeks	MoCA	Result at baseline and after 24 weeks EX: 18.45 \pm 0.63 (baseline), 18.87 \pm 0.71 (at 24 weeks); ES = +0.63 CON: 18.48 \pm 0.77 (baseline), 18.09 \pm 0.94 (at 24 weeks); ES = -0.45 Comparison between groups SMD = 0.86 95% CI = 0.23-1.5 ES = -0.13 $p > 0.05$
Stringuetta Belik et al. (23)	EX = 15 CON = 15	EX = 50.3 \pm 17.24 CON = 57.8 \pm 15.01	EX = intradialytic stretch exercises and cycling CON = standard care	3x/week 16 weeks	MMSE	Result at baseline and after 16 weeks

(Continued)

TABLE 3 (Continued)

Study	Sample size	Age (mean ± SD)	Intervention	Duration	Measures	Outcomes
Baggetta et al. (18)	EX = 53 CON = 62	EX = 73 ± 5 CON = 75 ± 6	EX = walking exercise program CON = standard care	24 weeks	KDQOL-SF cognitive function	EX: 24.0 ± 3.0 (baseline), 26.4 ± 2.92 (at 16 weeks); ES = +0.81; <i>p</i> < 0.001 CON: 22.4 ± 4.98 (baseline), 23.0 ± 5.09 (at 16 weeks); ES = +0.12; <i>p</i> > 0.05 Comparison between groups <i>p</i> = 0.023 Within group change EX: 0.8 (from -4.9 to 6.5); ES = +0.18; <i>p</i> = 0.78 CON: -9.6 (from -18.5 to -0.7); ES = -1.74; <i>p</i> = 0.04 Between-group difference in change (EX vs. CON) -10.4 (from -21.6 to 0.8); <i>p</i> = 0.05

CI, cognitive training group; EX, physical exercise group; CON, control group; 3MS, Modified Mini-Mental State; TMT, Trail-Making Test; KDQOL-SF, Kidney Disease Quality of Life Short Form; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; ES, Cohen's d effect size; SMD, standardized mean difference; CI, confidence interval; *p*, statistical significance.

TABLE 4 Description of cognitive tests/questionnaires.

Test/questionnaire	Description
Trail-making test A and B (TMTA and TMTB)	TMT is a neuropsychological test that involves visual attention and task switching. It offers information about mental flexibility, visual search speed, speed of processing and executive functioning (24).
Kidney disease quality of life short form (KDQOL-SF)	KDQOL-SF offers disease specific quality of life measure for patients with end-stage renal disease. It includes generic and disease specific components. The scales of KDQOL-SF are: symptoms, effects of kidney disease, burden of kidney disease, work status, cognitive function, quality of social interaction, sexual function, sleep, social support, dialysis staff encouragement and patient satisfaction (25).
Montreal cognitive assessment (MoCA)	MoCA test is screening instrument for mild cognitive dysfunction, and it offers information about cognitive domains of attention and concentration, executive functioning, memory, language, orientation, visuospatial abilities, conceptual thinking and orientation (26).
Mini-mental state examination (MMSE)	MMSE is a set of 11 tasks that can be used for assessing cognitive impairment (27). It offers a brief assessment of several cognitive domains: orientation, memory, attention, calculation, language and constructional ability.
Modified mini-mental state (3MS)	3MS is modified MMSE, it includes four additional items, and it extends scoring range. It can be used as a brief cognitive assessment or as a screening test. It offers a brief assessment of following cognitive domains: orientation, attention, concentration, calculation, language abilities, long-term and short-term memory, abstract thinking, and verbal fluency (28).

driving performance, the TMTA had a sensitivity of 77% and a specificity of 62%, while the TMTB had a sensitivity of 50% and a specificity of 88%. The cognitive domain of the KDQOL-SF had poor sensitivity (range, 28–36%) and modest specificity (range, 77–81%) for identifying poorer memory and executive function in the HD population (32).

Discussion

In the present review, we highlighted the effects of non-pharmacological interventions (physical exercise or cognitive training) on cognitive performance in HD patients. In addition, we presented and described the cognitive tests used in the included studies. The results of a limited number of studies

show that physical exercise may significantly improve cognitive performance or at least mitigate cognitive decline in HD patients. Furthermore, there is insufficient evidence to conclude that cognitive training can attenuate cognitive decline in this population.

Lower cognitive functioning is often seen in HD patients (33–35). It has been documented that impaired cognitive abilities limit the ability to adhere to dialysis activities, make informed decisions, follow food and fluid restrictions, and are a risk factor for mortality in HD patients (36–39). Therefore, the recognition of poor cognitive function is crucial for the implementation of prevention and coping strategies to delay patients' cognitive decline. Furthermore, it is well-known that HD patients have poorer physical function compared to healthy individuals (40) and are mostly physically inactive (41), leading to a decreased quality of life (42). A growing number of randomized controlled trials of exercise training in the HD population show improvement in physical performance (43–46), dialysis symptoms (47), bone mineral density (48, 49), dialysis adequacy (50, 51), and quality of life (52). The highest adherence to physical exercise programs was observed in interventions performed during dialysis (53–55) and these interventions generally appear safe. Notwithstanding the positive effects of physical exercise mentioned above, randomized controlled trials investigating the effects on cognitive performance in HD patients are lacking. However, the limited number of studies included in this review suggests that patients may also benefit in this area.

There are several reasons for the positive association between physical activity and improved cognitive performance. Physical activity has been found to prevent cerebral atrophy or even increase hippocampal volume (56). Furthermore, a recent review found that up to 82% of total brain gray matter volume can be altered by physical activity (57). People in good physical condition can tolerate a higher neuropathological load without suffering cognitive impairment (58). The association between a low cognitive score and high risk or incidence of injury indicates a direct relationship between higher cognitive control and executive function (59, 60). Physical exercise may also have a positive effect on patients' cognitive performance by reducing inflammation and thus improving brain plasticity (61, 62). The results of the present review support the findings of the aforementioned studies in HD patients and contribute to the understanding of the relationship between physical exercise and cognitive performance in this population.

Cognitive training is another non-pharmacological intervention that has received attention in the scientific community. In healthy older adults, cognitive training prevented cognitive decline in executive functions, including working memory, abstracting ability, attentional control, inhibitory control, and verbal reasoning (63–65). Studies investigating cognitive training approaches to combat cognitive decline in HD patients are lacking.

This systematic review has its pitfalls, mainly related to the limitations of the included studies. Limitations include the small number of eligible studies, the small sample size of most included studies leading to low statistical power and possibly associated with potential imbalances in the study groups. The appropriateness of cognitive tests used to measure intervention effects is questionable. The instruments used in the included studies (3MS, MoCA, MMSE, KDQOL-SF) are predominantly screening tests to detect mild cognitive impairment, which are vulnerable to learning effects and may lack sensitivity and specificity (32, 66, 67). Therefore, the aforementioned tests are not the best option to detect the effects of the training interventions presented. Future studies should consider using more sensitive and specific tests instead of using tests that only measure global cognitive performance and are subject to the learning effect. It is proposed to develop a neurocognitive battery to systematically assess various cognitive abilities. Suggested cognitive tests with low learning effect, high sensitivity, validity, and reliability could be the Symbol Digit Modalities Test (SDMT), the Computerized Test of Attentional Performance (TAP), and the Trail Making Test (TMTA and TMTB) (24, 68, 69).

This is the first systematic review to demonstrate the effect of non-pharmacological interventions in the form of physical exercise and cognitive training in HD patients. It also provides insight into the instruments used to measure cognitive performance. These results from a small number of studies suggest that physical exercise training may have a positive effect on cognitive performance in HD patients. The effects of cognitive training or a combination of both approaches should be further investigated (70). Intra-dialysis period provides a unique opportunity to study these effects. Patients could use the time spent during the HD session to replace passive activities with activities that benefit their cognitive status. Research in nephrology has only begun to examine the short-term effects of exercise and cognitive training on cognition. Further studies are needed to replicate these findings and to investigate different strategies to maintain or improve cognitive function not only in HD patients but also in pre-dialysis CKD patients and in transplant recipients. In addition, long-term outcomes such as prevention of dementia should also be investigated. Furthermore, more sensitive and reliable instruments are needed to evaluate the effects of interventions on cognitive performance in this population.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

Author contributions

ŠB designed the search strategy. JP, KM, TP, and MP revised the design. Title and abstract screening was performed by ŠB and KM. Full text screening was performed by ŠB and JP. MP and TP performed data analysis. Quality assessment was performed by KM and ŠB. ŠB drafted the manuscript, which was revised by JP, KM, TP, and MP. All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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