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Virtual Reality modalities to reduce fatigue and depressive symptoms in haemodialysis patients: a systematic review

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Introduction

1. All about chronic kidney disease

There are currently two classification systems for chronic kidney disease (CKD). The first one is based on the ICD-11 classification from the World Health Organisation WHO and defines five CKD stages based on the glomerular filtration rate (GFR) which reflects kidney function. They define the disease as *" GFR <60 or presence of kidney damage that is present for more than 3 months. Evidence of kidney damage can include structural abnormalities (imaging or histology), albuminuria above normal limits, urinary sediment abnormalities or electrolyte disturbances due to tubular disorders."* (World Health Organisation, 2024).

The second one is based on the KDIGO 2012 guidelines that define the five stages of CKD as follows: *"CKD is classified based on cause, glomerular filtration rate category, and albuminuria category"* (fig. 1). They define the disease as*: "CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health"* (Stevens et al., 2024).

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73 m²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Fig. 1. The colours show the risk of CKD. The darker the colour is (orange, red), the higher the risk is. On the contrary, the lighter and brighter the colour is (green, yellow), the lower the risk is (Stevens et al., 2024).

The KDIGO 2012 guidelines have made a conceptual model of CKD, currently used in the science world (fig. 2). This model shows that there are earlier stages to CKD: normal kidney function but with some CKD risk factors, increased risk for kidney dysfunction, kidney damage (abnormality in kidney structure), decrease in glomerular filtration rate (kidney function), kidney failure. Chronic kidney failure, which represents end-stage renal disease (ESRD), also called CKD 5D, needs kidney transplantation or dialysis (peritoneal or haemodialysis). Normal/high and mildly decreased GFR with no other marker is not associated with CKD (green).

According to these guidelines, CKD is either a primary disease due to *"a known or presumed pathologic-anatomic abnormality"* (Stevens et al., 2024), or a secondary disease due to an *"underlying systematic disease"* (Stevens et al., 2024) (Table 1).

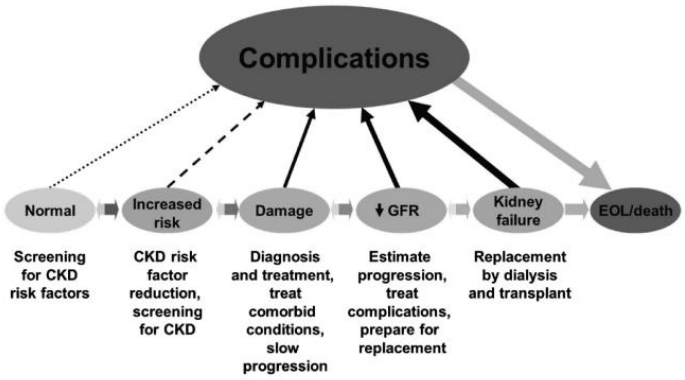

Fig. 2. Conceptual model of CKD where every stage of CKD is paired with the prevention strategies. The size and the shade of the colour used for the arrows pointed to the complications show the greater or lesser incidence of complications. The arrows pointing to the left are in a lighter shade to show that progression is more recurrent than remission. Adapted from Levey AS et al (Stevens et al., 2024).

Table 1. Classification of CKD based on presence or absence of systematic disease and location within the kidney of pathologic-anatomic findings

	Examples of systemic diseases affecting the kidney	Examples of primary kidney diseases (absence of systemic diseases affecting the kidney)
Glomerular diseases	Diabetes, systemic autoimmune diseases, systemic infections, drugs, neoplasia (including amyloidosis)	Diffuse, focal or crescentic proliferative GN; focal and segmental glomerulosclerosis, membranous nephropathy, minimal change disease
Tubulointerstitial diseases	Systemic infections, autoimmune, sarcoidosis, drugs, urate, environmental toxins (lead, aristolochic acid), neoplasia (myeloma)	Urinary-tract infections, stones, obstruction
Vascular diseases	Atherosclerosis, hypertension, ischemia, cholesterol emboli, systemic vasculitis, thrombotic microangiopathy, systemic sclerosis	ANCA-associated renal limited vasculitis, fibromuscular dysplasia
Cystic and congenital diseases	Polycystic kidney disease, Alport syndrome, Fabry disease	Renal dysplasia, medullary cystic disease, podocytopathies

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; CKD, chronic kidney disease, GN, glomerulonephritis (Stevens et al., 2024).

Another review regroups the etiologies of CKD in three categories: prerenal regrouping diseases resulting in a decreased renal perfusion pressure, intrinsic renal regrouping the pathologies of the vessels, glomeruli, or tubules-intestitium, and postrenal diseases causing chronic obstruction (Vaidya & Aeddula, 2024). This review showed that prerenal disease causes for a persistent decrease in renal perfusion leading to multiple episodes of intrinsic kidney injury (acute tubular necrosis). Over time, this results in a loss of kidney function. An example of intrinsic renal disease is vascular diseases such as arterosclerosis and fibro-muscular dysplasia characterized by glomerulosclerosis and tubulointerstitial fibrosis. Lastly, postrenal diseases are for example abdominal/pelvic tumor, nephrolithiasis and prostatic disease (Vaidya & Aeddula, 2024).

The majors risk factors for CKD are classically hypertension and diabetes (Kakitapalli et al., 2019). Other risk factors are kidney stones, low birth weight/prematurity/small for gestational age, preeclampsia/eclampsia, HIV, Hepatitis B/C, bacterial skin disease, schistosomiasis, diarrheal illnesses, malaria, tuberculosis, acute kidney illness (AKI) and more. Detecting the risk factors that are modifiable can help prevent the development of kidney damage and in the end, kidney failure (Luyckx et al., 2017).

CKD is characterized by progressive kidney fibrosis and destruction of a normal kidney architecture due to the loss of renal cells and deposition of the extracellular matrix (Vaidya & Aeddula, 2024; Yang & He, 2020). All compartments are affected:

glomeruli, the tubules, the interstitium and the vessels (Vaidya & Aeddula, 2024). It is manifested by glomerulosclerosis, tubulointerstitial fibrosis and vascular sclerosis. First, due to prolonged kidney injury, there is infiltration of extrinsic inflammatory cells. This causes the intrinsic renal cells to eventually die through apoptosis, necrosis, mesangiolysis and podocytopenia. Extracellular matrix producing cells are then activated and proliferate. These cells are deposited in the damaged kidney and change the architecture (Vaidya & Aeddula, 2024). The events leading to this dysfunctional architecture are complex and will not be seen further in details. Fig. 3, is a more detailed schematic presentation of the different events involved, retrieved from a third review (Yang & He, 2020).

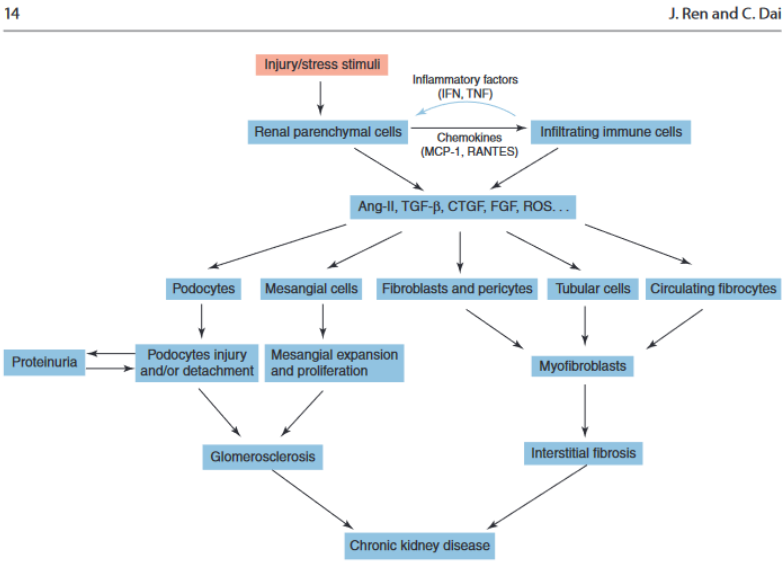

Fig. 3. Schematic presentation for cellular events involved in the progression of chronic kidney disease (Yang & He, 2020).

The clinical presentation varies according to the etiology. Many are asymptomatic until the disease has advanced in the latter stages. As CKD progresses, uraemic toxins accumulate in the body. These toxins can affect all systems and organs. Fig. 4 shows the most common symptoms present in CKD (Webster et al., 2017).

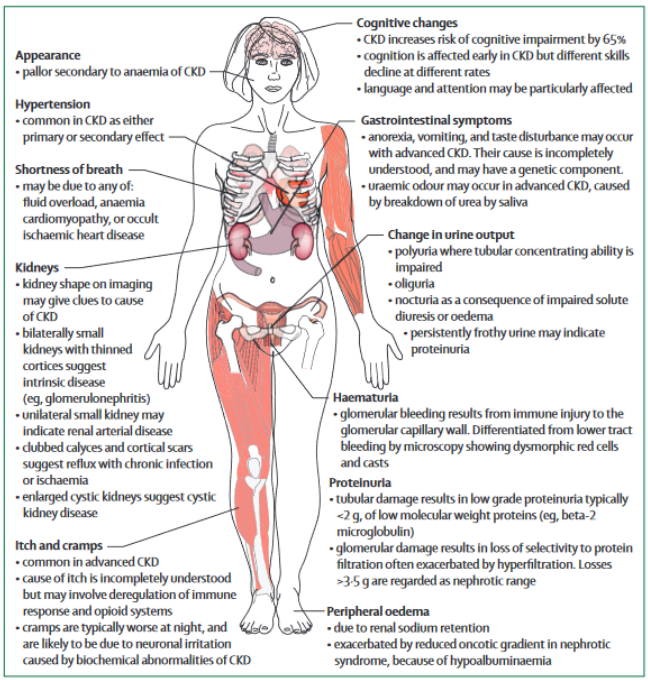

Fig. 4. Symptoms and signs of CKD (Webster et al., 2017).

In 2017, the total numbers of individuals suffering from CKD (stages 1-5) worldwide was estimated by Jager et al., (2019) to be 843.6 million (Kovesdy, 2022). Moreover, this disease is recognised to be a leading cause of death worldwide. It occupied the 13th place in 2016 (GBD 2016 Causes of Death Collaborators, 2017) and 12th place in 2017 (GBD Chronic Kidney Disease Collaboration, 2020) on the list of cause of death (Kovesdy, 2022). A recent review found a controversial finding stating that even though the global population has been expanding and thus the absolute numbers of CKD patients too, the overall prevalence of individuals suffering from this disease has been variable (Kovesdy, 2022). Indeed, the review shows that in several countries such as the US, Norway and the UK it was noted that for several years the percentage increased, followed by the next few years with a stabilisation or even a decrease for some (Kovesdy, 2022). The reason behind this discrepancy is difficult to determine but is probably due to a combination of factors according to Kovesdy, (2022).

2. Haemodialysis: definition and indication

Haemodialysis (HD) is a type of dialysis used for ESDR patients and is executable at home or in centre. Maintenance HD or chronic HD is usually followed for at least

3 months since the definition of CKD states that the kidney failure lasts for at least 3 months.

"Haemodialysis is an extracorporeal process in which the blood is cleansed via removal of uraemic retention products by a semipermeable membrane", as stated by Ronco & Clark, (2018). There are different components to the HD system: dialysers which are the semi-permeable membranes designed to let dialysate fluid and blood circulate on either side of it and in opposite direction, extracorporeal blood circuit which brings the arterial blood to the dialysers and returns the veinous blood to the body, the dialysis machine which supplies the dialysate fluids at a certain temperature/flow rate and chemical composition and monitors the extracorporeal blood circuit (Wong et al., 2015). The dialysate fluid is what draws the excess electrolytes, waste products and excess fluid out of the blood as explained by Fielding, (2019). The author continues by saying that the removed products are brought to the waste system of the dialysis machine through the extracorporeal circuit. Finally, the machine then replaces it with new dialysate fluid and the circuit continues (Fielding, 2019). Fluids and solutes are removed from the blood to the dialysate fluid by diffusion, convection and UltraFiltration (UF) (Fielding, 2019; Swift et al., 2019; Wong et al., 2015). Indeed, diffusion refers to the removal of the solutes and is based on a concentration gradient between the two solutions. Convection refers to the movement of solvent and its solutes and is based on a hydrostatic pressure gradient. Lastly, UltraFiltration refers to the movement of water and is also according to a hydrostatic pressure gradient.

The indicator to begin dialysis is a GFR between 5-15 ml/min per 1.73 m^2 of body surface area (kidney failure) (Wong et al., 2015). Conventional practice of HD is thrice per week for four to five hours. There exist alternative HD schedules called short-daily HD (four to six times per week for two to three hours) and nocturnal HD (three to seven times per week for six to eight hours) (Toussaint, 2010) since the conventional practice may not be appropriate for all patients (Wong et al., 2015).

3. Consequences of haemodialysis

Patients following a dialysis treatment suffer from several symptoms such as headache, coughs, muscle cramps (Karadeniz Teknik Universitesi Saglik

Bilimleri Fakultesi, Hemsirelik Bolumu, Trabzon, Turkiye et al., 2018) and depression (Teles et al., 2018) as well as fatigue (Bossola et al., 2023).

In a study conducted on 200 HD patients, 29% had depression assessed by the Beck Depression Inventory (Teles et al., 2018). This study also showed that all patients with depression had worse results on the SF-36 questionnaire (quality of life) than the non-depressive patients. Another study showed that depression and anxiety in HD patients have a negative impact on all domains of the KDQOL-SF scale (quality of life) (Al-Nashri & Almutary, 2022).

Fatigue is also a common symptom in HD treatment. There is no consensus on the definition of fatigue although researchers seem to agree that fatigue is multidimensional (Billones et al., 2021). In a recent scoping review, 8 dimensions have been identified: psychological, emotional, motivational, cognitive, mental, physical, central and peripheral fatigue (Billones et al., 2021). In a recent review, the author differentiated fatigue that can occur before the HD session and during the HD session (IntraDialytic Fatigue, IDF) and fatigue that persist after the session (Post Dialysis Fatigue, PDF) (Bossola et al., 2023). In that same review, PDF prevalence was estimated between 20%-86%. In another study, a correlation between fatigue and quality of life was observed (Georgios, 2015). Patients with higher score on the FAS questionnaire (fatigue) had lower scores on the MVQOL-15 scale (quality of life) than patients with lower scores on the FAS questionnaire (Georgios, 2015). An additional study also found that fatigue, among other symptoms, was one of the strongest predictors of a deterioration in quality of life (Almutary et al., 2017).

4. Definition of virtual reality

Over the years, there has been more and more research about the use of virtual reality (VR) in healthcare. However, currently there is no consensus about the definition (Kardong-Edgren et al., 2019). This is why, Abbas et al., (2023) has tried to present an evidenced based definition for the term: *"VR is a three-dimensional computer-generated simulated environment, which attempts to replicate real world or imaginary environments and interactions, thereby supporting work, education, recreation, and health"*. This systematic review claims that 2D and 3D experiences

differ too much to be considered both within the context of VR. Nevertheless, since the consensus is not yet made and this definition is not worldwide recognised, for this review, we will consider 2D experience to be a non-immersive VR: *"a computer-generated environment with no immersion into the virtual world"* (Afridi et al., 2022). This type of VR uses game consols, digital screens, keyboards etc (Afridi et al., 2022). Some authors, such as Afridi et al., (2022) and Nadeem, (2019), refer to semi-immersive as another type of VR. It is mostly used in the context of rehabilitation (Nadeem, 2019). they defined it as a VR that immerses participants in a virtual world while also being able to interact with the real world.

5. Positive effect of VR on fatigue and depressive symptoms in different populations

VR has popularly shown its efficiency to reduce symptoms such as fatigue and depression on several study population. Indeed, this has been observed in patients with multiple sclerosis, cancer, stroke and Parkinson patients (Elhusein et al., 2024; Ioannou et al., 2020). In the 2020 review results, it was found that of the four studies (Cho & Sohng, 2014; Schneider et al., 2003, 2004; Schneider & Hood, 2007) that evaluated the efficiency of VR on fatigue, three (Cho & Sohng, 2014; Schneider et al., 2004; Schneider & Hood, 2007) had significant improvement of this symptom. The population involved were cancer patients (Schneider et al., 2004; Schneider & Hood, 2007). Of the fourteen studies that evaluated the efficiency of VR on depression and anxiety, four (Lee et al., 2015; Riva et al., 2003; Shah et al., 2015; Song & Park, 2015) had a significant decrease of the depressive symptoms. The population involved were patients with eating disorders, inpatients diagnosed with major depressive disorder, stroke and Parkinson patients (Ioannou et al., 2020). A 2021 review found that VR was overall more effective than conventional therapy (physiotherapy, balance and strength exercises, and stretching or physical activity, among others) to reduce fatigue symptoms VR-based therapy (Cortés-Pérez et al., 2021).

6. Positive effect of VR on fatigue and depressive symptoms in HD patients

The positive effects of VR discussed above have also been studies in HD patients (Gurz et al., 2023; Marin et al., 2023; Omonaiye et al., 2021). These three reviews show that VR can reduce fatigue and depression in HD patients. All three reviews

base their conclusion on the same pool of studies. Furthermore, several protocols on the same subject are in process (Burrai et al., 2019; Hernandez et al., 2023; Meléndez-Oliva et al., 2023; Segura-Ortí et al., 2023; Smyth et al., 2022).

The aim of this review is to collect the current data to summarize what modalities (type of VR-content, frequency, duration) previously used helped to specifically reduce fatigue and depressive symptoms in patients on maintenance HD. There are currently two recent studies from 2023 that have not been included in any review so far. This is why, in this review we will also reassess whether or not the hypothesis stating that VR can help reduce fatigue and depressive symptoms in chronic HD patients is valid. This review hopes to guide future clinical practice.

Methods

1. Protocol

This systematic review was conducted following the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) published in 2020 (Page et al., 2021). The items 12,13d-15 were not completed for this review.

2. Eligibility criteria

We used the PICOS tool which contains 5 indicators: Population, Intervention, Comparison, Outcome, Study design. Population (P): haemodialysis patients suffering from chronic kidney disease that are above 18 years old (haemodialysis >3 months). Intervention (I): virtual reality. Comparison (C): none. Outcomes (O): scales for fatigue and depressive symptoms. Study designs (S): all types of clinical trials. The following question was established: which modalities of virtual reality used in previous studies helped to reduce depressive and fatigue symptoms in haemodialysis patients?

We selected the studies that fulfil the following criteria: respecting the PICOS criteria, studies between 2014 and 2024, in English or French, full text available for free.

The exclusion criterion was: when the record was a protocol for an ongoing clinical trial.

3. Information sources

A computer-based research strategy using an equation was performed in order to select the current studies in the following databases: Embase, PubMed, PsychInfo, and Scopus. Additional studies were afterwards included through Google Scholar based on their relevancy. This research was performed during a specific timeframe, from September 2023 to March 2024.

4. Search strategy

On Embase, PubMed, PsychInfo and Scopus, an equation was used. On Embase, in the search bar we typed:

('hemodialysis'/exp OR 'blood dialysis' OR 'chronic haemodialysis' OR 'chronic hemodialysis' OR 'chronic intermittent haemodialysis' OR 'chronic intermittent hemodialysis' OR 'dialysis center' OR 'dialysis, blood' OR 'extracorporeal blood cleansing' OR 'extracorporeal dialysis' OR 'haemodialysis' OR 'haemodialysis center' OR 'haemodialysis centre' OR 'haemodialysis department' OR 'haemodialysis unit' OR 'haemodialysis units, hospital' OR 'hemodialyse' OR 'hemodialysis' OR 'hemodialysis center' OR 'hemodialysis department' OR 'hemodialysis unit' OR 'hemodialysis units, hospital' OR 'hemorenodialysis' OR 'hemotrialysate' OR 'hospital haemodialysis units' OR 'hospital hemodialysis units' OR 'intermittent chronic haemodialysis' OR 'intermittent chronic hemodialysis' OR 'intermittent haemodialysis' OR 'intermittent hemodialysis' OR 'renal dialysis' OR 'renal replacement therapy'/exp OR 'dialysis therapy' OR 'dialysis treatment' OR 'kidney dialysis' OR 'kidney replacement therapy' OR 'kidney support' OR 'renal replacement therapy' OR 'renal support' OR 'dialysis') AND ('virtual reality'/exp OR 'virtual reality' OR 'virtual reality simulator'/exp OR 'vr simulation system' OR 'vr simulator' OR 'virtual reality simulation devices' OR 'virtual reality simulation system' OR 'virtual reality simulator' OR 'virtual reality exposure therapy'/exp OR 'vr exposure therapy' OR 'vr immersion therapy' OR 'vret (virtual reality exposure therapy)' OR 'virtual reality exposure therapy' OR 'virtual reality immersion therapy' OR 'exergaming'/exp OR 'vr exercise' OR 'vr exergaming' OR 'vr-based exercise' OR 'active video gaming' OR 'active videogaming' OR 'exer-gaming' OR 'exergaming' OR 'virtual reality (vr) -based exercise' OR 'virtual reality (vr) exergaming' OR 'virtual reality exercise' OR 'virtual reality-based exercise' OR 'wii'/exp OR 'nintendo wii'/exp OR 'serious game'/exp OR 'video game'/exp OR 'tv games' OR 'computer game' OR 'computergame' OR 'television game' OR 'video game' OR 'video games' OR 'videogame' OR 'videogames' OR 'game therapy') AND ('depression'/exp OR 'clinical depression' OR 'depression' OR 'depressive disease' OR 'depressive disorder' OR 'depressive episode' OR 'depressive illness' OR 'depressive personality disorder' OR 'depressive state' OR 'depressive symptom' OR 'depressive syndrome' OR 'mental depression' OR 'depression assessment'/exp OR 'depression assessment' OR 'fatigue'/exp OR 'fatigue' OR 'tiredness').

The equation was then adapted to the other databases, using their own mesh terms for the blue terms and completing it with the missing terms from our original equation.

In Google Scholar, we used the following terms: "hemodial*" OR "haemodial*" OR "renal replacement therapy" OR "dialysis*" OR "kidney*" OR "renal*" AND "virtual reality*" OR "virtual reality exposure therapy" OR "exergam*" OR "wii" OR "nintendo*" OR "game therapy" OR "serious gam* " OR "video gam*" AND

"depress*" OR "depression*" OR "depressive*" OR "fatigue*" OR "tired*". Relevant studies were handpicked by one student.

For PubMed and Scopus, filters were used. We selected "clinical trial", the years "2014-2024" for PubMed and "articles" as well as "2014-2024" for Scopus.

5. Selection process

We used the bibliographic management software Zotero to group the references. The screening process was performed by one student (LZ). Firstly, all duplicates were removed. Afterwards, every study was individually screened based on their title and abstract and the inclusion/exclusion criteria. Then, the remaining studies where no full text was found were excluded. Finally, the final ones were assessed for eligibility based on their full text and the inclusion/exclusion criteria.

For Google Scholar, the same student first screened all studies only based on title. Those with relevant titles were then screened based on their abstract/full free text. Only new studies, not included in the PRISMA diagram pool, were added.

6. Data collection process and items

The same student that did the selection process extracted the relevant data from the remaining studies. The extracted data was summarized in a Power Point table: author, date of publication, the modalities used for the VR (frequency, duration, type-content), outcomes, sample size (n), sex, mean age, mean (x) and standard deviation (SD) before and after intervention, their key findings/conclusions, the PEDro or Downs and Black checklist score for each study, and their study design. When only the standard error was available, we multiplied it by the square root of the sample size to obtain the standard deviation.

Eligible outcomes were grouped in 2 categories: fatigue and depression. Results could be reported as an overall test score that measures fatigue or depression, or as a subscore. There was no restriction concerning the length of follow-up, or the number of times outcomes were measured except for the baseline measure and the final post-intervention measure. The following outcomes were retained: NFSHD, item 2 from the SSQ, MCS energy and fatigue, VAS, SONG-HD to measure fatigue

and Depression-SF8A, CES-D, GDS-15, BDI to measure depressive symptoms. MCS stands for mental composite summary and is a sub score from the KDQOL-SF scale. Energy and fatigue are the last items of the MCS sub score. SSQ is a larger scale that contains 16 items from which fatigue is the second one.

7. Studies Risk of bias assessment

The Modified Downs and Black checklist (Downs & Black, 1998) was used to assess the risk of bias of all the non-randomized studies (appendix 2). Through 27 questions, the scale assesses four domains: reporting, internal validity (bias and confounding), external validity, and power. When an item was hard to fill in, due to the difficulty to interpret a study, the item was answered as 'unable to determine'. The PEDro scale was used to assess the risk of bias of all RCT's. The studies that were not registered in the PEDro database were evaluated using the French version of the PEDro checklist (appendix 3) which included 11 questions. Studies where the randomisation was not explicitly written in the paper, were evaluated with the modified Downs and Black checklist. All studies with fair quality and above were included in the analysis.

8. Synthesis methods

No meta-analysis was conducted. Only a narrative synthesis was undertaken to present all selected studies, data items, risk of bias, results of individual studies and synthesis of the results. The synthesis will first involve each outcome and then what modality (type-content, frequency, duration) helped to improve those outcomes. This is why items 20b-22 of the PRISMA guidelines were not completed for this review.

Results

1. Study selection

A total of 203 references were identified by the four selected databases (Scopus, Embase, PsychInfo, PubMed). After removal of 26 duplicates, 177 records remained. Of those 177 articles, 159 were excluded for not meeting the inclusion criteria and five were excluded for being a protocol for an ongoing clinical trial. The remaining 13 records were sought for retrieval. Four of those were excluded

for not finding their full free text. Finally, the full text analysis of the remaining nine records resulted in the exclusion of three more records. In the end, six studies were retained for the qualitative synthesis (see fig. 5).

Two additional records were identified through google scholar and added at the end, resulting in eight final studies for this review (see fig. 5).

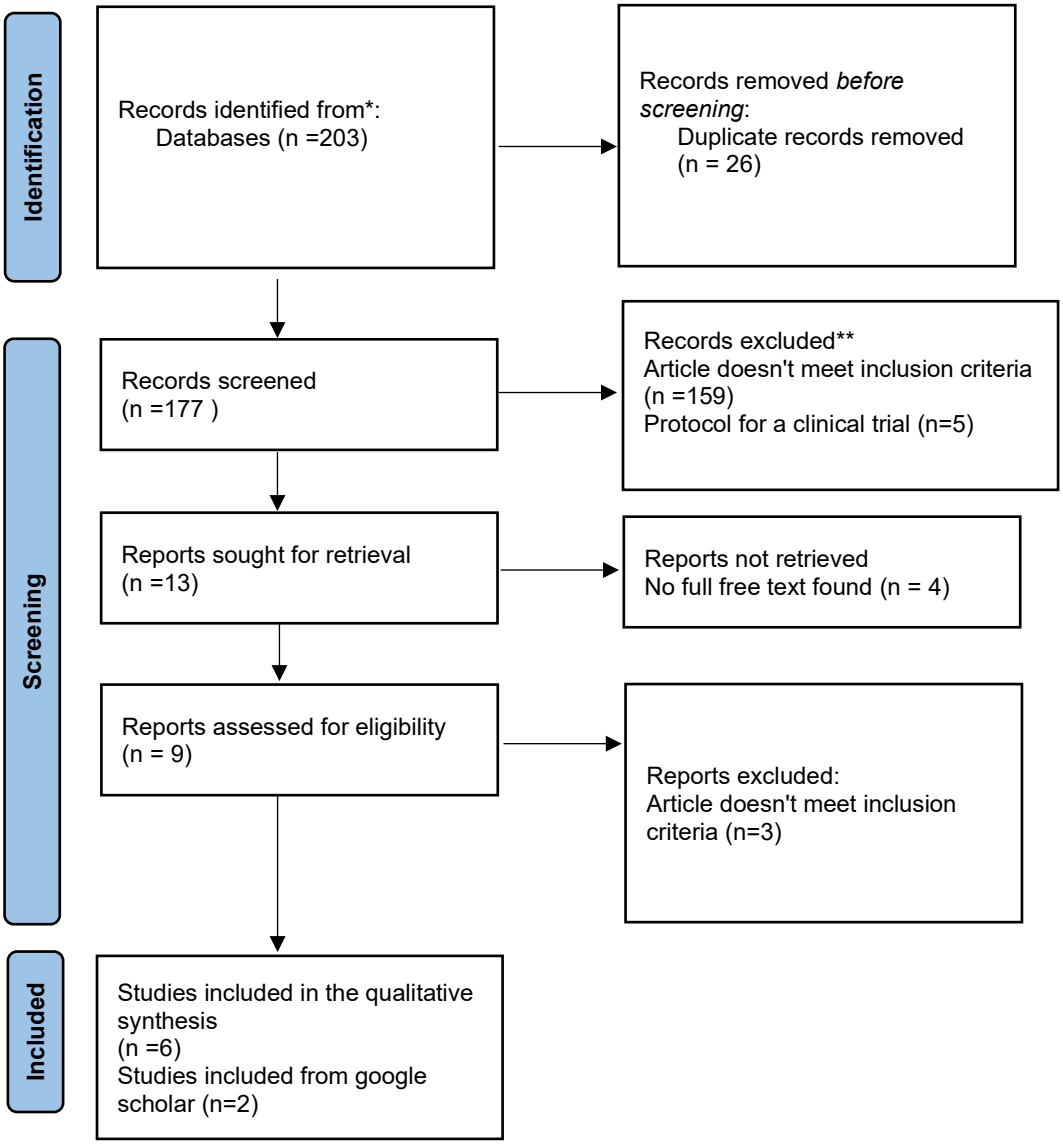

Fig. 5. Prisma Flow diagram of the article selection process

2. Study characteristics

All extracted data from the selected studies were summarized (see table 2). The following modalities were extracted from the studies: the type of VR, the content, the duration and frequency. Concerning the type of VR used, three studies used the Nintendo Wii games (Cho & Sohng, 2014; Chou et al., 2020; Maynard et al., 2019), one study used the prototype of the NefroVR system (Turoń-Skrzypińska et al., 2023), two studies used the Jovialty VR program (Burrows et al., 2023; Hernandez et al., 2021), one study used a guided meditation VR application (Burrows et al., 2023), one study used a non-weight-bearing VR program (Zhou et al., 2020), and one study used the Godot Game Engin to create their own computer-based VR program (Bento et al., 2018).

Six studies performed their VR program three times per week (Burrows et al., 2023; Cho & Sohng, 2014; Chou et al., 2020; Maynard et al., 2019; Turoń-Skrzypińska et al., 2023; Zhou et al., 2020). One study performed their program on two separate occasions during two consecutive HD sessions (Hernandez et al., 2021). Two studies used a four-week program (Chou et al., 2020; Zhou et al., 2020), two studies used a 12-week or three months program (Maynard et al., 2019; Turoń-Skrzypińska et al., 2023), one study used an eight-week program (Cho & Sohng, 2014), one study used a one-week program (Hernandez et al., 2021), one study used a 10-week program with a two-week VR-based-mindfulness program prehabilitation (Burrows et al., 2023) and one study didn't specify the duration or frequency of their VR program (Bento et al., 2018).

The content of the VR was very variable: motor and cognitive dual task exercises (Zhou et al., 2020), Nintendo Wii Fit games with boxing (Chou et al., 2020), Nintendo Wii Fit Plus and Sports with endurance and strength exercises (Maynard et al., 2019), Nintendo Wii Fit Plus with stretching positions, games, muscle strengthening exercises and yoga movements (Cho & Sohng, 2014), VR games using a prototype with a rehabilitation rotor, a panoramic screen, a touch control screen, a digital joystick and button (Turoń-Skrzypińska et al., 2023), VR mindfulness training and guided meditation using the Oculus Rift head-mounted display (Joviality) (Burrows et al., 2023; Hernandez et al., 2021), a guided meditation VR application with virtual environments for meditation (Burrows et al.,

2023). There was even a study that used a VR computer-based program stimulating every-day activities in order to vehicle positive messages as an aim to reduce depression symptoms (Bento et al., 2018).

The scales used by the studies, their mean (x) and standard deviation (SD) before and after intervention we also extracted (see table 2). Sample size varied between 20-85 participants. Only one study had nine participants (Burrows et al., 2023). The average age range for participants was mid to late fifties and mid-sixties. One study had participants in their forties (Maynard et al., 2019). Six studies divided their sample into two groups (Burrows et al., 2023; Cho & Sohng, 2014; Chou et al., 2020; Maynard et al., 2019; Turoń-Skrzypińska et al., 2023; Zhou et al., 2020). The last two studies had only an intervention group (Bento et al., 2018; Hernandez et al., 2021).

The key findings/conclusions of the studies are also presented in the tables. These are complementary to the results of individuals studies, summarized in section 4 of this review.

Finally, we extracted the data concerning the study design and risk of bias score of these studies (see table 2). Four are RCT's (Burrows et al., 2023; Maynard et al., 2019; Turoń-Skrzypińska et al., 2023; Zhou et al., 2020), two are quasi-experimental trials (Bento et al., 2018; Chou et al., 2020), one is an uncontrolled pilot trial (Hernandez et al., 2021) and one is a non-equivalent control group pre-test/post-test trial (Cho & Sohng, 2014). Four studies have fair quality (Bento et al., 2018; Hernandez et al., 2021; Turoń-Skrzypińska et al., 2023; Zhou et al., 2020), two studies have 'high quality' (Burrows et al., 2023; Maynard et al., 2019) and two studies have 'good quality' (Cho & Sohng, 2014; Chou et al., 2020).

Table 2. Study characteristics

Date of publication + author	Modalities of VR (type, frequency, duration, content)	Outcomes	Sample size (n), mean age ±SD	Mean ± (SD) before intervention	Mean ± (SD) after intervention	Key findings/conclusions	Study design and Risk of bias score
(Zhou et al., 2020)	Program with non-weight-bearing condition: dual-task exercise combining motor and cognitive (working memory) tasks. Four weeks, three times per week, during HD session, 30 minutes per session. *"By rotating their foot, the participant could navigate the laptop cursor to execute a simple reaching task game on a computer screen: with the cursor, reaching for the circles that appeared on the same screen."* The games involved simple and complex foot movements.	CES-D scale for depression symptoms	n =73 Exergroup (EG): n=37 62.7 ± 6.8 years Nurse-supervised intradialytic exercise group (SG): n = 36, 66.5 ± 10.0 years	EG: 12.9 ± 6.0 SG: 16.8 ± 11.0	EG: 8.1 ± 7.8 SG: 9.9 ± 10.5	*"Virtually supervised intradialytic exercise therapy appears to be as effective as nurse-supervised intradialytic exercise therapy to reduce depression symptom". "Higher reduction in depression symptoms was observed for those with more severe depression symptoms."*	RCT: PEDro 5/10 = fair quality

(Chou et al., 2020)	VRT[$] program: using Nintendo Wii Fit, game-based training with boxing. Based on the standard Nintendo Wii exercise guidelines. Four weeks, three times per week, 30 minutes per session, alternating with HD. *"Boxing was picked for the swinging, pitching and punching activities."*	NFSHD for fatigue	n= 64 Intervention group (IG): n=32 58 ± 15.75 years Control group (CG): n=32 60.61 ±10.71 years	IG: 1.91 ± 0.96 CG: 2.34 ± 0.96	IG: 1.72 ± 0.72 CG: 2.17 ± 0.96	*"The results of this study indicated that the overall fatigue of patients in both groups declined significantly from the pretest to the posttest, although the decline was greater in the experimental group than in the control group"* *"4 weeks of a virtual reality-based exercise program resulted in no significant differences in overall fatigue and different domains of fatigue between the experimental and control groups." "Indeed, this finding suggests that fatigue is a chronic problem in patients with ESRD who require long-term HD."*	Quasi experimental trial with control group and pretest: 20/28 = good quality

(Maynard et al., 2019)	Endurance and strength exercises in combination with VR Nintendo Wii games (Wii Sports and Wii Fit Plus). Twelve weeks, three times per week, during the first two hours of HD, 30-60 minutes per session, progress in level of difficulty every two weeks. *"During the activities the individual maintained the sitting position working on the coordination, balance, and resistance of the lower limbs and the upper limb."*	CES-D for depression symptoms Item 4 of MCS sub score in KDQOL-SF for fatigue and energy	n =40 IG: n= 20, 49 ± 15.2 years CG: n= 20 43.9 ± 11.7 years	IG: 12.7 ± 7.8 for CES-D, 71.7 ± 21 for MCS CG: 15.8 ± 7.8 for CES-D, 68.7 ± 29.8 for MCS	IG: 7.1 ± 7.3 for MCS, 73 ± 22.7 for MCS CG: 13.1 ± 9.4 for CES-D, 61.50 ± 29 for MCS	*"VR training therapy minimized depressive symptoms (P = 0.154) although it was not statistically significant. "*	RCT: PEDro 7/10= high quality

(Turoń-Skrzypińska et al., 2023)	VR exercises using the prototype of the NefroVR system. Twenty minutes per session during first hours of HD, three times per week, for three months. *"The device operated on the basis of audio-visual stimulation that provoked the patient's physical activity. Prototype contains following components: a base unit, a rehabilitation rotor with a flywheel and a manually adjustable load, a panoramic screen for the patient, a touch control screen, a control kit (for the patient)—digital joystick and one button. Patients played a game where movement was only possible with the rehabilitation rotor, speed and resistance was adjustable".*	Beck depression inventory (BDI)	n= 85 Study group(SG): n= 39, 57.56 ± 17.61 years CG: n= 46, 62.63 ± 15.47 years	SG: 9.53 ± 6.43 CG: 9.09 ± 8.25	SG: 8.31 ± 6.29 CG: 11.64 ± 10.25	"*after a 3-month exercises on a bicycle with the use of low-intensity virtual reality, a decrease in depression symptoms measured by the Beck Depression Inventory (BDI) was observed"* *"The research showed that regular physical activity using virtual reality may be associated with a reduction in the occurrence of anxiety and depression symptoms in patients included in the chronic hemodialysis program."*	RCT: PEDro 4/10 = fair quality

(Hernandez et al., 2021)	Joviality VR program with mindfulness training and guided meditation using the Oculus Rift head-mounted display. Twenty-five minutes per session, VR immersion occurred on two separate occasions during two consecutive HD session, 30 minutes after HD treatment initiation or during the final hour of dialysis. *"The finished program places end-users in an armchair within a virtual living room, where they follow visual and auditory stimuli and instructions on a flatscreen television for the mindfulness training/education".* Followed by 12 minutes guided meditation to finish the 25minutes session.	Item 2 of SSQ for fatigue	IG: n= 20 55.25 ± 13.12	Exposure 1: 5.31± 6.07 Exposure 2: 3.41 ± 5.75	Exposure 1: 1.14 ± 2.78 Exposure 2: 2.65 ± 5.08	"*Significant decreases were observed during exposure one for fatigue, nausea, oculomotor symptoms, disorientation, and total symptomology before versus after VR, P,0.05. No statistically significant differences in scores were observed during exposure two."* *"Patients on hemodialysis routinely suffer from fatigue, nausea, lightheadedness, and headaches that often manifest during their dialysis sessions. Our Joviality VR program decreased symptom severity without adverse effects. VR programs may be a safe platform to improve the experience of patients on dialysis."*	Uncontrolled pilot trial: 19/28 = fair quality

(Cho & Sohng, 2014)	VREP[$] program was accomplished using Nintendo's Wii Fit Plus. Forty minutes per session, three times per week, for eight weeks. Three sections: warm-up, main exercise, and cool-down segment. Warm-up and cool-down segment (five minutes each): eight stretching positions, 5-10 seconds for each position, to do twice. Main exercise (30 minutes): three games, two muscle strengthening movements, and two yoga movements.	VAS for fatigue	n = 46 IG: n =23, 60.8 ± 6.9 years CG: n= 23 57.7 ± 9.5 years	IG: 6.7 ± 0.8 CG: 6.8 ± 1.0	IG: 4.9 ± 1.1 CG: 6.7 ± 1.2	*"Fatigue in the exercise group after taking part in the VREP decreased noticeably, and this was thought to be due to the general improvement in physical fitness in the patients, which reduced the amount of fatigue perceived."*	A nonequivalent control group pretest-posttest design:21/27 = good quality
(Bento et al., 2018)	*« Playing is good for you ! »* is a VR program using the Godot Game Engin that consisted of five modules: 1) dressing room, 2) Garden, 3) Lake, 4) Kitchen and garage. Each module stimulates every-day activities in order to vehicle positive messages as an aim to reduce depressive symptoms.	GDS-15 scale for depression	IG: n = 26, 66.7 ± 5.8 years	IG: 3.9 ± 3.0	IG: 2.8 ± 2.9	*"Playing is good for you! was found to be important in the improvement of depressive symptoms in elderly people undergoing hemodialysis, but did not achieve significant results in relation to cognitive performance. Studies that further investigate effects on cognition, with longer time periods, are required"*	Quasi experimental without control groups: 18/28 = fair quality

	Five individual sessions of 60 minutes during the first two hours of the hemodialysis session, time period unknown.						
(Burrows et al., 2023)	The study is a 10-week program with two-week VR-based-mindfulness program prehabilitation and an eight-week personalised exercise program. VR three times per week for two weeks, 25 minutes per session. the VR-based mindfulness program consisted of: -a Jovialty program: *"25 minutes VRM$ with didactic material for mindfulness training and a 12 minutes guided meditation."*	SONG-HD for fatigue Depression-SF8a for depression symptoms	n = 9 PARx$: n =4, 59.50 ± 15.07 years VRM + PARx$: n=5, 59.67 ± 14.12 years	PARx: at T1: 3.50 ± 1.92 for SONG-HD, 57.10 ± 3.03 for DSF8A PARx + VRM: at T1: 4.40 ± 2.20 for SONG –HD, 56.72 ± 1.33 for DSF8a	PARx: at $T2_2$ (after two weeks of VR prehabilitation): 3.25 ± 1.26 for SONG-HD, 57.50 ± 3.35 for DSF8a at T3 (after 10-week program): 4.25 ± 2.75 for SONG-HD, 41.43 ± 5.38 for DSF8a PARx +VRM: at $T2_1$ (after two weeks of VR prehabilitation): 3.40 ± 1.67 for SONG-HD, 49.48 ± 6.94 for DSF8a	*" In a secondary analysis, we found that our VRM program enhanced mindfulness and reduced depressive symptoms, which were associated with a significant increase in PA levels."* *"While the majority of participants self-reported improvement in energy levels from PARx, fatigue was unchanged. Thus, SONG-HD Fatigue may not be sensitive enough to detect changes in fatigue over time"*	RCT = PEDro 7/10 = high quality

	- a Guided Meditation VR: *"VR meditation application where end-users can self-select from 29 virtual environments (the beach, mountains, a forest trail, etc.) to meditate."* They combined the two to create a new VRM program: the first session was Jovialty, the five others were guided meditation VR. For more details on the Jovialty program, see Hernandez et al.				at T3 (after 10-week program): 4.00 ± 2.24 for SONH-HD, 45.42 ± 6.20 for DSF8a		

[$]VRT = virtual reality therapy, VREP = virtual reality exercise program, VRM = virtual reality-based mindfulness program, PARx = personalized activity prescription.

3. Risk of bias in studies

All the selected studies had the required quality. Four studies (Bento et al., 2018; Cho & Sohng, 2014; Chou et al., 2020; Hernandez et al., 2021) were evaluated using the Downs and Black checklist (see table 3)(Downs & Black, 1998). Expect for one item within the "Reporting" domain (which assesses adverse events), all other items were respected by all the selected studies. Adversely, within the "External validity" domain, no item was respected by all four studies. Furthermore, for the "Internal validity-bias" domain, two items were not respected. Indeed, no study made an attempt to blind participants, nor those measuring the main outcomes. Concerning the "Internal validity-confounding" domain, only the item evaluating whether or not all participants were recruited from the same population was respected by all studies. Lastly, Cho & Sohng, (2014) and Chou et al., (2020) respected the "Power" domain as they included a control group in their protocol, as opposed to Bento et al., (2018) and Hernandez et al., (2021).

Four studies (Burrows et al., 2023; Maynard et al., 2019; Turoń-Skrzypińska et al., 2023; Zhou et al., 2020) were evaluated using the PEDro scale (*PEDro scale,* 1999). The only RCT study (Burrows et al., 2023) that was not registered in the database got evaluated using the French version of the scale (*PEDro scale french(France)*, 2010). All RCT's didn't respect the items evaluating whether or not all subjects and the therapists administrating the treatment were blinded (Burrows et al., 2023; Maynard et al., 2019; Turoń-Skrzypińska et al., 2023; Zhou et al., 2020). Two other items were not respected by the studies. Indeed, three studies did not respect the item evaluating whether or not the staff measuring one of the main outcomes was blinded (Burrows et al., 2023; Turoń-Skrzypińska et al., 2023; Zhou et al., 2020). Furtermore, three studies did not respect the item evaluating whether or not subjects received either a control or treatment condition as allocated, when outcomes were available, and when subjects did not receive their allocated condition, data for at least one main outcome was analyzed by "intention to treat" (*PEDro scale,* 1999) (Maynard et al., 2019; Turoń-Skrzypińska et al., 2023; Zhou et al., 2020).

Table 3. Scores of the studies with the modified Downs and Black

Items Yes =1 No=0	(Chou et al., 2020)	(Hernandez et al., 2021)	(Bento et al., 2018)	(Cho & Sohng, 2014)
Reporting				
1	1	1	1	1
2	1	1	1	1
3	1	1	1	1
4	1	1	1	1
5	2**	1	1	1
6	1	1	1	1
7	1	1	1	1
8	0	0	0	0
9	1	1	1	1
10	1	1	1	1
External validity				
11	0	0	0	0*
12	0*	0*	0*	0*
13	1	1	0*	1
Internal validity-bias				
14	0*	0	0	0*
15	0*	0	0	0*
16	1	1	1	1
17	1	1	0*	1
18	1	1	1	1
19	1	1	1	1
20	1	1	1	1
Internal validity-confounding				
21	1	1	1	1
22	1	1	0*	1
23	0	0	0	0*
24	0	0	0	0*
25	1	0*	0*	1
26	0*	1	1	1
Power				
27	1	0*	0*	1
Score total	20/28	19/28	18/28	21/20

*Unable to determine, **only item where YES=2, Partially=1 and NO=0

Table 4. Scores of the studies with PEDro scale

Items Yes=1 No=0	1	2	3	4	5	6	7	8	9	10	11	Score total
(Burrows et al., 2023)	Yes	1	1	1	0	0	0	1	1	1	1	7/10
(Turoń-Skrzypińska et al., 2023)	Yes	1	0	1	0	0	0	0	0	1	1	4/10
(Maynard et al., 2019)	Yes	1	1	1	0	0	1	1	0	1	1	7/10
(Zhou et al., 2020)	Yes	1	0	1	0	0	0	1	0	1	1	5/10

4. Results of individual studies

The results of each selected study are summarized in table 5.

Table 5. Results of individual studies

(Bento et al., 2018)	GDS-15: Significant decrease of the scores after VR intervention.
(Burrows et al., 2023)	Depression-SF8a: Significant decrease of scores in the PARx+VRM group between T1$^{\$\$\$}$ and T2$^{\$\$\$}$ and between T1 and T3$^{\$\$\$}$. No significant difference between groups between T1-T2 (p=0.07). For the PARx alone group, there is a significant decrease between T1-T3 and T2-T3. No significant difference between groups after the 10 weeks (T1-T3). SONG-HD: No significant difference in both groups and no significant

	difference between groups at any given time.
(Zhou et al., 2020)	CES-D: Significant decrease of depressive symptoms in both EG[$]. and SG[$]. groups. No significant difference between the two groups.
(Chou et al., 2020)	NFSHD: Significant decrease of overall fatigue in both intervention and control group. No significant difference between the two groups.
(Maynard et al., 2019)	CES-D: Significant decrease of depressive symptoms in the intervention group only. However, no significant difference between the two groups. MCS: No significant decrease of the energy and fatigue item in both intervention and control group. No significant difference between the two groups.
(Turoń-Skrzypińska et al., 2023)	BDI: Significant decrease of the BDI scores in the study group while there is a significant increase in the control group. Significant difference between groups.
(Hernandez et al., 2021)	SSQ: Significant decrease of fatigue during the first exposure. No significant decrease of fatigue during the second exposure
(Cho & Sohng, 2014)	VAS: Significant decrease of fatigue in the exercise group (VREP[$$]) only.

[$$$]T1 = at baseline, T2 = after the 2-week VR prehabilitation (VRM), T3: after the 8-week personalized activity prescription (PARx), [$$]VREP = virtual reality exercise program, [$]EG = exergame group, SG = supervised exercise group, Green = studies confirming the hypothesis stating

that VR can help reduce fatigue and depressive symptoms, Red= studies infirming the hypothesis stating that VR car help reduce fatigue and depressive symptoms

5. Synthesis of results

The results of each study are first presented according to each outcome. Then we will present which modalities helped to improve those outcomes.

Fatigue

Five studies (Burrows et al., 2023; Cho & Sohng, 2014; Chou et al., 2020; Hernandez et al., 2021; Maynard et al., 2019) presented results for fatigue. They used the following outcomes: SONG-HD, VAS, item 2 of SSQ, item 4 of MCS and NFSHD. Two studies, one using MCS (Maynard et al., 2019) and the other SONG-HD (Burrows et al., 2023), showed no significant decrease of fatigue in both control and intervention group. In both studies, there was no significant difference of scores between the two groups. The study that used VAS (Cho & Sohng, 2014) showed a significant decrease of scores for the VR exercise group while no changes were noted in the control group. The study that used the item 2 of the SSQ sub score (Hernandez et al., 2021) had only an intervention group undergoing VR program at two different points in times. A significant decrease of fatigue was noted during the first exposure of VR but not during the second exposure. Finally, the study that used the NFSHD scale (Chou et al., 2020) showed a significant decrease of overall fatigue in both intervention and control group.

According to these results it can be concluded that three studies (Cho & Sohng, 2014; Chou et al., 2020; Hernandez et al., 2021) out of five (60%) showed significant decrease of fatigue after the VR intervention. Two used a control group that received no VR intervention (Cho & Sohng, 2014; Chou et al., 2020). Out of the two, one showed an improvement in both VR and non-VR groups but no significant difference was noted between groups (Chou et al., 2020).

Modalities of VR for fatigue improvement

According to the results in the previous section, the modalities from Cho & Sohng, (2014) and Hernandez et al., (2021) seem to have helped the most in reducing fatigue since those are the only studies with statistical proof that VR contributed in

reducing this symptom. Although the study design of Hernandez et al., (2021) did not have a control group to corroborate those results and the results were only observed after the first exposure of VR.

The first modality is an eight-week Nintendo Wii Fit Plus program composed of three sections: warm-up, main exercise and a cool-down segment which in stretching positions, games, strengthening exercises and yoga movements (Cho & Sohng, 2014). The second modality is a VR program called Jovialty with mindfulness training and guided meditation using the Oculus Rift head-mounted display taking place on two separate exposures during two consecutive HD sessions (Hernandez et al., 2021). For each study, the VR sessions lasted 40 and 25 minutes respectively. Cho & Sohng, (2014) did their VR sessions three times per week.

It is also worth mentioning the modalities from Chou et al., (2020), since their within-intervention group comparison showed the same tendency as the two previous studies, however, their between-group comparison was not statistically significant. They used a four-week Nintendo Wii Fit game-based training with boxing (swinging, punching, pitching). Each session lasted 30 minutes and was repeated three times per week.

Depressive symptoms

Five studies (Bento et al., 2018; Burrows et al., 2023; Maynard et al., 2019; Turoń-Skrzypińska et al., 2023; Zhou et al., 2020) presented results for depression. They used the following outcomes: Depression-SF8a, GDS-15 scale, BDI, and CES-D scale. Two studies used the CES-D scale. One compared nurse-supervised non-weight-bearing exercises without assistance of technology to non-weight-bearing exercises assisted by VR and their effect on depressive symptoms (Zhou et al., 2020). They noted a significant decrease of depressive symptoms in both groups but no significant difference between groups (Zhou et al., 2020). The other study compared a VR training therapy group to a control group that underwent no physical effort (Maynard et al., 2019). They noted a significant decrease in depressive symptoms only in the intervention group but no significant difference between groups (Maynard et al., 2019). The study using the BDI showed a significant decrease of scores in the study group (following a VR program) while

the control group showed a significant increase of scores (Turoń-Skrzypińska et al., 2023). The study using the GDS-15 scale was a quasi-experimental study without control group (Bento et al., 2018). They noted a significant decrease of the depressive symptoms after the VR intervention (Bento et al., 2018). Finally, the study that used the Depression-SF8a noted a significant decrease of depressive symptoms at $T2_1$ (after the two-week VR prehabilitation) in the VR intervention group while there was no significant decrease of symptoms in the control group at $T2_2$ (after the two-week prehabilitation with the usual care routine) (Burrows et al., 2023). However, there was no significant difference between groups at $T2_{1,2}$, although it considerably leaned towards between-group significance with a p-value of 0.07. Although not significant, there was a continued decrease of symptoms in the intervention group at T3 (after the eight-week personalized exercise program) and a significant decrease of symptoms in the control group. After the 10-week program, both groups had a significant decrease of depressive symptoms, however no significant between-group difference.

According to these results it can be concluded that four out the five studies (Bento et al., 2018; Maynard et al., 2019; Turoń-Skrzypińska et al., 2023; Zhou et al., 2020) showed a significant decrease of depressive symptoms after the VR intervention. Although two studies both used a non-VR control group (Maynard et al., 2019; Turoń-Skrzypińska et al., 2023) only one (Turoń-Skrzypińska et al., 2023) found a significant difference between groups. Moreover, one study compared a VR exercise program to a non-VR exercise program (Zhou et al., 2020). Through this comparison, they noted that a nurse-supervised intradialytic exercise program is as effective as a VR-supervised intradialytic exercise program in reducing depressive symptoms (Zhou et al., 2020).

Additionally, Burrows et al., (2023) showed the same positive tendency of VR to reduce depressive symptoms, however when comparing their VR intervention group to their non-VR intervention group, their results were not statistically significant (p-value of 0.07).

Modalities for improvement in depressive symptoms

According to the results stated above, the modalities from (Bento et al., 2018; Turoń-Skrzypińska et al., 2023; Zhou et al., 2020) seem to have helped the most in reducing depressive symptoms since those are the only studies with statistical proof that VR contributed in reducing this symptom. The first modality, from Bento et al., (2018), is a VR computer-based program stimulating every-day activities through five modules that each contained a positive message aiming to reduce depressive symptoms and was spread out over five individual sessions lasting each one hour. The frequency of the VR sessions and the duration of their program remain unknown for this study (Bento et al., 2018). Next is a three months VR game-based exercise program using the NefroVR system where the player could only move using the rehabilitation rotor (which is a component of the prototype) (Turoń-Skrzypińska et al., 2023). Finally, a four-week non-weight-bearing VR program where the participant could move the laptop cursor on the screen with their ankle to complete reaching tasks games (Zhou et al., 2020). All studies performed their VR session three times per week except for Bento et al., (2018) who did not mention anything time period-wise other than spreading their VR program over five individual sessions. Each session lasted 60, 20 and 30 minutes respectively.

It is also worth mentioning the modalities from Burrows et al., (2023) and Maynard et al., (2019) since both studies were able to show a significant reduction of depressive symptoms, however, only between the participants of the intervention group. The modalities from Burrows et al., (2023) consisted of a two-week prehabilitation program combining the Jovialty program and a guided meditation VR application as part of a 10-week program. Also, their VR sessions lasted 25 minutes and were repeated three times per week. The modalities from Maynard et al., (2019) consisted of a 12-week VR program using Nintendo Wii Fit Plus/Wii Sports combined with endurance and strength exercises, and their VR sessions lasted 30-60 minutes and were repeated three times per week.

Discussion

1. Results

The main objective of this review was to highlight the modalities previously used that potentially helped to reduce fatigue and depressive symptoms in HD patients suffering from CKD. Since new studies were published and had not been included in any review regarding this topic (Burrows et al., 2023; Turoń-Skrzypińska et al., 2023), we first wanted to confirm or infirm the hypothesis of previous reviews stating that VR can help reduce fatigue and depressive symptoms in this population.

This systematic review included eight studies that measured the effect of VR on fatigue and/or depressive symptoms in patients on maintenance HD. The quality of the studies was fair (n=4) and above (n=4). Two studies showed that VR had a positive impact on fatigue in HD patients (Cho & Sohng, 2014; Hernandez et al., 2021) and three studies showed the positive impact of VR on depressive symptoms in HD patients (Bento et al., 2018; Turoń-Skrzypińska et al., 2023; Zhou et al., 2020). Zhou et al., (2020) also showed that a VR exercise program is as effective as a non-VR exercise program in reducing depressive symptoms. Two studies showed the tendency of VR to reduce depressive symptoms in HD patients (Burrows et al., 2023; Maynard et al., 2019) and another (Chou et al., 2020) showed the tendency of VR to reduce fatigue in HD patients, however none found a significant effect. The modalities collected from all of these studies included type-content of VR used, the frequency and duration of the VR sessions. One study lacked information regarding the frequency of VR sessions and the duration of their VR program (Bento et al., 2018).

The three reviews that previously covered this topic (Gurz et al., 2023; Marin et al., 2023; Omonaiye et al., 2021) share the same pool of studies as our review. This can explain why all the results are very similar. However, one review (Marin et al., 2023) had a different conclusion regarding a study. Indeed, Marin et al., (2023) states in their results that Maynard et al., (2019) found that VR had the tendency to reduce the depressive symptoms in the intervention group, although this was not significant. In a further section, the review contradicts itself by saying that Maynard et al., (2019) demonstrates that VR significantly reduces fatigue and depression.

However, when going back to the original study, they note a significant reduction of depressive symptoms within the intervention group, but no between-group significance when comparing to the control group. They also note no change in fatigue scores.

Gurz et al., (2023) mentions one study that was not detected through our articles selection process (Zhou et al., 2018). The study indicates that the VR intervention group and the standard exercise group both showed a significant improvement of depressive symptoms after a four-week program (Zhou et al., 2018). This finding resembles what our review already mentions. However, Gurz et al., (2023) doesn't mention whether or not the groups of this study had a significant between-group difference and since we cannot access this particular study for free, we can't conclude whether or not the VR intervention was more effective than the standard exercise group in reducing depressive symptoms.

Additionally, the most recent studies (Burrows et al., 2023; Turoń-Skrzypińska et al., 2023) both contributed to confirm the hypothesis stating that VR helps to reduce fatigue and depressive symptoms. Indeed, as previously said, Turoń-Skrzypińska et al., (2023) is part of our four final studies providing statistical proof that VR helped to improve the outcomes. Furthermore, Burrows et al., (2023) results showed the same tendency although their results for between-group difference were not significant.

It is worth to mention that there exists a systematic review and meta-analysis of RCT's that covers the same topic (Yangöz et al., 2023). The abstract states that VR has no effect on depressive symptoms. However, since there is no full free text available, it is impossible to compare it with our review results.

Overall, these findings show the potential of VR to improve psychological well-being in HD patient by improving their fatigue and depressive symptoms and thus also improving their quality of life.

To our knowledge, no study has tried to identify which modalities of VR are the most effective to reduce fatigue and depressive symptoms in HD patients or in any

other chronic illness population. This is the first review that tries to present the modalities of VR that potentially helped to improve those symptoms in HD patients.

2. Within a broader context

Omonaiye et al., (2021) review has also browsed the scientific literature regarding the safety and engagement of the patients. Their work shows that VR can enhance patient's adherence and engagement to their HD treatment program. One study (Segura-Ortí & García-Testal, 2019) even mentions that this could be one of the potential benefits VR has over traditional exercise programs. Regarding safety, the review also concluded that VR, whether it is immersive or not, does not cause adverse effects on paediatric or adult HD patients (Omonaiye et al., 2021). This was later confirmed by a pilot study on users perception and safety (Hernandez et al., 2021). The latter also concludes that VR is capable of reducing other dialysis-symptoms such as headache, nausea, and light-headedness. Moreover, Marin et al., (2023) and Omonaiye et al., (2021) both found evidence that VR was considered safe by patients and staff.

Gurz et al., (2023) and Omonaiye et al., (2021) also found evidence that VR is considered fun by the patients and staff. Indeed, the results of the systematic review show that the participants found it enjoyable. One study also mentions that participants did not find it difficult to use (Zhou et al., 2020). Maynard et al., (2019) states that their findings such as improvement of physical capacity and some domains of HRQOL (physical functioning, role physical and physical composite summary) is similar to the findings described in the literature regarding conventional exercise therapy. The major difference lies with the playfulness of the therapy.

VR therapy has also been studied in HD patients in the context of pain felt during cannulation or venipuncture. The many studies concern adults, adolescents and children (Ahmed Mokbel et al., 2022; Atzori et al., 2022; Kaheni et al., 2016; Nasirzadeh et al., 2019). All four studies report the positive impact of VR on those outcomes. A narrative review (Kassim et al., 2023) states that VR could be used as a distraction tool to reduce procedure-related pain in HD patients.

Overall, the results show the potential of VR to become a tool to boost motivation, enhance compliance to treatment and make HD more bearable for the patients.

When considering all the information above, it shows the importance to invest in research that is willing to uncover all the ways VR could be useful to HD patients. Especially since VR does not need close supervision and thus could reduce the medical staff's workload (Gurz et al., 2023).

3. Limitations and implications

3.1 Selection and data extraction

We selected the studies according to our inclusion/exclusion criteria's. However, one study was included in our review despite not entirely meeting our criteria. Indeed, Bento et al., (2018) neither specified that the included HD patients suffer from CKD nor does he specify that they needed to have been following HD for at least three months. Furthermore, in the table summarizing the results of clinical characteristics, nine participants were following their HD treatment between one and twelve months. However, since they mentioned CKD illness in their text and keywords, we included the study. This implicates that even though we can assume that in the pool of participants CKD patients were included, some might've suffered from acute kidney injury instead.

The second limitation concerns the selection process. Although this is a systematic review, the study selection and data selection process were both only done by one student. This causes for a high risk of bias and errors.

Another limitation concerns the scales used to evaluate fatigue and depression. Almost all the scales used in this review were tested and validated either in chronic HD patients or chronic renal patients. However, three scales (Depression-SF8a, SSQ and VAS) have not been validated in this population. Indeed, the Depression-SF8a has been tested and approved in patients with chronic disease such as multiple sclerosis (Marrie et al., 2018). Regarding the SSQ scale, it's originally used to screen symptoms related to simulation sickness (Stone Iii, 2017). However since HD-related symptoms and simulation sickness symptoms overlap, the study (Hernandez et al., 2021) used it for both. Additionally, even though the VAS scale

is used to measure fatigue in HD patients, no study has yet tested and thus validated this tool in HD patients (Ju et al., 2018). Furthermore, in our review, we didn't compare psychometric properties of the scales and questionaries used by the included studies. Future research should compare the properties of all the tools used to evaluate fatigue and depressive symptoms and assess whether or not they are equivalent and appropriate to use for this particular topic.

Furthermore, the protocols of all the studies were very different from one another. The differences lied within the used study design, the used outcomes, the number of participants as well as their age and the used modalities of VR. This causes problems of relevancy and accuracy when comparing the results of the studies. However, this problem could not be avoided since this is a very recent topic, hence not well documented. Therefore, at this stage, adding inclusion/exclusion criteria would not have been the most appropriate choice.

On the same note, another implication of the limited research available is that our research started off with 203 records identified through four databases, yet we still ended up at eight final articles included in our review. Despite having tried to broaden our equation, we could not find any more studies appropriate for our synthesis.

Considering the positive results of VR described above and the lack of studies on this present day, we encourage research to focus more on this particular topic.

3.2 Study characteristics

Since we included all type of study designs as long as they had fair quality and above, the scores of some items on the risk of bias scales were poor. More high quality RCT's study designs are needed. However, it is important to keep in mind that proper blinding of everyone involved in a VR study is almost impossible since everyone has an idea what VR assisted therapy looks like, especially when compared to the HD usual care. This implicates that regardless of the new and better study design that are proposed, a perfect score of 10/10 on the PEDro scale is impossible.

In response to the need of new studies, there are currently several RCT protocols for ongoing research (Burrai et al., 2019; Hernandez et al., 2023; Meléndez-Oliva et al., 2023; Segura-Ortí et al., 2023; Smyth et al., 2022). All evaluate the effect of VR on fatigue or depressive symptoms in HD patients.

Conclusion

Through this review we were able to highlight the positive impact of virtual reality on fatigue and depressive symptoms in patients on maintenance haemodialysis. We were also able to highlight the modalities (content and type of VR used, frequency and duration of VR sessions) that potentially helped to obtain those positive results.

The majority of the studies contributed to the confirmation of our hypothesis stating that VR helps to reduce fatigue and depressive symptoms. In addition, we also concluded that a VR-supervised intradialytic exercise program is as effective as a nurse-supervised intradialytic exercise program in reducing depressive symptoms.

To our knowledge, this is the first review that tries to present the modalities of VR that potentially helped to improve those symptoms in HD patients. Future research should focus on developing more RCT's, with better scores in the risk of bias scales, in order to better understand how VR helps reducing fatigue and depressive symptoms in patients on maintenance HD. In order for researchers to evaluate whether their scales are equivalent and appropriate, they should compare the measuring tool's psychometric properties. More research is needed to fully develop the knowledge surrounding this problematic. Especially since VR has the potential to aid medical staff in HD care in a number of ways. We hope that our review will be a beneficial tool for future clinicians working with HD patients.

Appendices

Appendix 1: list of abbreviations

2D	Two Dimensions
3D	Three Dimensions
AKI	Acute Kidney Injury
BDI	Beck Depression Inventory
CES-D	Centre for epidemiologic studies-Depression scale
CG	Control group
CKD	Chronic Kidney Disease
CKD 5D	Chronic Kidney Disease end-stage
Depression-SF8a	The PROMIS-Depression—Short Form 8a
EG	Exergame Group
ESRD	End-Stage Renal Disease
FAS	Fatigue Assessment Scale
GDS-15	Geriatric Depression Scale
GFR	Glomerular Filtration Rate
HD	Haemodialysis
HRQOL	Health-Related Quality Of Life
ICD-11	International statistical Classification of Diseases and related health problems (11th ed.)
IDF	Intradialytic Fatigue
IG	Intervention Group
KDQOL-SF	Kidney Disease and Quality Of Life Short Form
MCS	Mental Composite Summary
MVQOL-15	Missoula–Vitas Quality of Life Index-15
PARx	Personalized Exercise Prescription
PDF	Post Dialysis Fatigue

PEDro	Physiotherapy Evidence Database
PICOS	Population, Intervention, Comparator, Outcomes, Study design
PRISMA,	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT,	Randomized Control Trial
SF-36	Medical Outcomes Study Short Form 36
SG	Study Group or Supervised-exercise Group
SONG-HD	Standardized Outcomes in Nephrology-Hemodialysis
SSQ	Simulator Sickness Questionnaire
UF	Ultrafiltration
VAS	Visual Analoge scale
VR	Virtual Reality
VREP	Virtual Reality Exercise Program
VRM	Virtual Reality-based mindfulness program
VRT	Virtual Reality Therapy

Appendix 2: Modified Downs and Black

Item	Criteria	Possible Answers
Reporting		
1	*Is the hypothesis/aim/objective of the study clearly described?*	Yes = 1 No = 0
2	*Are the main outcomes to be measured clearly described in the Introduction or Methods section?* If the main outcomes are first mentioned in the Results section, the question should be answered no.	Yes = 1 No = 0
3	*Are the characteristics of the patients included in the study clearly described?* In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.	Yes = 1 No = 0
4	*Are the interventions of interest clearly described?* Treatments and placebo (where relevant) that are to be compared should be clearly described.	Yes = 1 No = 0
5	*Are the distributions of principal confounders in each group of subjects to be compared clearly described?* A list of principal confounders is provided.	Yes = 2 Partially = 1 No = 0
6	*Are the main findings of the study clearly described?* Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).	Yes = 1 No = 0
7	*Does the study provide estimates of the random variability in the data for the main outcomes?* In non-normally distributed data the interquartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.	Yes = 1 No = 0
8	*Have all important adverse events that may be a consequence of the intervention been reported?* This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).	Yes = 1 No = 0
9	*Have the characteristics of patients lost to follow-up been described?* This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.	Yes = 1 No = 0
10	*Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*	Yes = 1 No = 0

External validity		
11	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.	Yes = 1 No = 0 Unable to determine = 0
12	*Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.	Yes = 1 No = 0 Unable to determine = 0
13	*Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?* For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.	Yes = 1 No = 0 Unable to determine = 0
Internal validity - bias		
14	*Was an attempt made to blind study subjects to the intervention they have received?* For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
15	*Was an attempt made to blind those measuring the main outcomes of the intervention?*	Yes = 1 No = 0 Unable to determine = 0
16	*If any of the results of the study were based on "data dredging", was this made clear?* Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.	Yes = 1 No = 0 Unable to determine = 0
17	*In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?* Where follow-up was the same for all study patients the answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.	Yes = 1 No = 0 Unable to determine = 0
18	*Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
19	*Was compliance with the intervention/s reliable?* Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
20	*Were the main outcome measures used accurate (valid and reliable)?* For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.	Yes = 1 No = 0 Unable to determine = 0

Internal validity - confounding (selection bias)		
21	*Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?* For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study.	Yes = 1 No = 0 Unable to determine = 0
22	*Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?* For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.	Yes = 1 No = 0 Unable to determine = 0
23	*Were study subjects randomized to intervention groups?* Studies which state that subjects were randomized should be answered yes except where method of randomization would not ensure random allocation. For example alternate allocation would score no because it is predictable.	Yes = 1 No = 0 Unable to determine = 0
24	*Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?* All non-randomized studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.	Yes = 1 No = 0 Unable to determine = 0
25	*Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.	Yes = 1 No = 0 Unable to determine = 0
26	*Were losses of patients to follow-up taken into account?* If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
Power		
27*	*Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?* Sample sizes have been calculated to detect a difference of x% and y%.	Yes = 1 No = 0 Unable to determine = 0

Appendix 12 from (Trac et al., 2016): Trac, M. H., McArthur, E., Jandoc, R., Dixon, S. N., Nash, D. M., Hackam, D. G., & Garg, A. X. (2016). Macrolide antibiotics and the risk of ventricular arrhythmia in older adults. *CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne*, *188*(7), E120–E129. https://doi.org/10.1503/cmaj.150901

Appendix 3: French version of PEDro scale

Échelle PEDro – Français

1.	les critères d'éligibilité ont été précisés	non ❑	oui ❑	où:
2.	les sujets ont été répartis aléatoirement dans les groupes (pour un essai croisé, l'ordre des traitements reçus par les sujets a été attribué aléatoirement)	non ❑	oui ❑	où:
3.	la répartition a respecté une assignation secrète	non ❑	oui ❑	où:
4.	les groupes étaient similaires au début de l'étude au regard des indicateurs pronostiques les plus importants	non ❑	oui ❑	où:
5.	tous les sujets étaient "en aveugle"	non ❑	oui ❑	où:
6.	tous les thérapeutes ayant administré le traitement étaient "en aveugle"	non ❑	oui ❑	où:
7.	tous les examinateurs étaient "en aveugle" pour au moins un des critères de jugement essentiels	non ❑	oui ❑	où:
8.	les mesures, pour au moins un des critères de jugement essentiels, ont été obtenues pour plus de 85% des sujets initialement répartis dans les groupes	non ❑	oui ❑	où:
9.	tous les sujets pour lesquels les résultats étaient disponibles ont reçu le traitement ou ont suivi l'intervention contrôle conformément à leur répartition ou, quand cela n'a pas été le cas, les données d'au moins un des critères de jugement essentiels ont été analysées "en intention de traiter"	non ❑	oui ❑	où:
10.	les résultats des comparaisons statistiques intergroupes sont indiqués pour au moins un des critères de jugement essentiels	non ❑	oui ❑	où:
11.	pour au moins un des critères de jugement essentiels, l'étude indique à la fois l'estimation des effets et l'estimation de leur variabilité	non ❑	oui ❑	où:

https://pedro.org.au/wp-content/uploads/PEDro_scale_french(france).pdf

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Abstract:

Background: In recent years, there has been an accrued interest in virtual reality (VR) and its potential role in reducing fatigue and depressive symptoms in HD patients. It is important to review the current knowledge on this subject.

Objectives: The first objective was to confirm or infirm the hypothesis stating that VR can help reduce fatigue and depressive symptoms in patients on chronic HD. The second objective was to highlight the modalities previously used that could be responsible for these results.

Methods: This systematic review was conducted based on the 2020 PRISMA guidelines. We established an equation based on the PICOS criteria. Four databases were used to identify all articles.

Results: Out of 203 studies**,** eight were selected. The majority of the studies showed either a significant reduction of fatigue or of depressive symptoms after a VR intervention. The remaining studies showed the same tendency; however, the results were not significant. The modalities from all these studies included type-content of VR used, the frequency and duration of the VR sessions.

Conclusion: We were able to confirm the hypothesis stating that VR helps to reduce fatigue and depressive symptoms. To our knowledge, this is the first review that tries to present the modalities of VR that potentially helped to improve those symptoms in HD patients. More research is needed to fully develop the knowledge surrounding this problematic.