kidney and dialysis

MDPI

Review

Targeted Non-Pharmacological Interventions for People Living with Frailty and Chronic Kidney Disease

Juliet Mayes [1,*], Hannah M. L. Young [2,3,4], Rochelle M. Blacklock [5], Courtney J. Lightfoot [6,7], Joseph Chilcot [8] and Andrew C. Nixon [9]

1 Department of Therapies, King's College Hospital NHS Foundation Trust, London SE5 9RS, UK
2 Lifestyle and Health Research Group, Leicester Diabetes Research Centre, University of Leicester, Leicester LE5 4PW, UK; hy162@leicester.ac.uk
3 Leicester Diabetes Centre, University Hospitals of Leicester, Leicester LE5 4PW, UK
4 Department of Respiratory Sciences, University of Leicester, Leicester LE1 7RH, UK
5 Department of Nutrition and Dietetics, King's College Hospital, London SE5 9RS, UK; rochelle.blacklock@nhs.net
6 Leicester Kidney Lifestyle Team, Department of Health Sciences, University of Leicester, Leicester LE5 4PW, UK; courtney.lightfoot@leicester.ac.uk
7 Leicester NIHR Biomedical Research Centre, Leicester LE5 4PW, UK
8 Health Psychology Section, Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, 5th Floor Bermondsey Wing, Guy's Campus, London SE19RT, UK; joseph.chilcot@kcl.ac.uk
9 Department of Renal Medicine, Lancashire Teaching Hospitals NHS Foundation Trust, Preston PR2 9HT, UK; andrew.nixon@lthtr.nhs.uk
* Correspondence: juliet.mayes@nhs.net

Abstract: Frailty is highly prevalent within people living with chronic kidney disease (CKD) and is associated with the increased risk of falls, hospitalisation, and mortality. Alongside this, individuals with CKD report a high incidence of depression and reduced quality of life. The identification of frailty within nephrology clinics is needed to establish comprehensive management plans to improve clinical outcomes and quality of life for people with CKD. Current research exploring the role of non-pharmacological management has primarily focussed on exercise and physical activity interventions in the frail CKD population. However, there is a growing evidence base and interest in this area. This review provides an up-to-date overview of the literature into frailty assessment in CKD and subsequent non-pharmacological treatment approaches.

Keywords: frailty; lifestyle; intervention; chronic kidney disease; review; non-pharmacological

Citation: Mayes, J.; Young, H.M.L.; Blacklock, R.M.; Lightfoot, C.J.; Chilcot, J.; Nixon, A.C. Targeted Non-Pharmacological Interventions for People Living with Frailty and Chronic Kidney Disease. *Kidney Dial.* **2022**, *2*, 245–261. https://doi.org/10.3390/kidneydial2020025

Academic Editors: Roman-Ulrich Müller, Sharlene A. Greenwood and Ellen M. Castle

Received: 28 February 2022
Accepted: 13 May 2022
Published: 20 May 2022

1. Introduction

Frailty, a reduction in physiological reserve and multi-system imbalance, when exposed to stressors, is highly prevalent in people with chronic kidney disease (CKD) [1]. Several studies have shown the association between individuals living with chronic disease and frailty, for example, cardiovascular [2] and neurological diseases [3], cancer [4], and diabetes [5]. Alongside this, individuals who live with multiple chronic diseases, known as multi-morbidity, have been shown to have a higher incidence of frailty, shown by increasing disability, hospitalisation, mortality, and healthcare utilisation [6].

Within CKD, recent systematic reviews estimate the prevalence of frailty in the haemodialysis and pre-transplant CKD populations to be 46% and 17%, respectively [7,8]. Outcomes are poor for people with frailty and CKD, including increased risk of mortality, hospitalisation, falls, high symptom burden, health care utilisation, reduced health-related quality of life (HRQoL), and depression [9,10]. Other geriatric impairments, including impaired functional status, mobility, cognition, and mood, are also highly prevalent and similarly associated with adverse outcomes [11,12]. A holistic multi-disciplinary approach

is needed to identify and manage frailty and associated geriatric impairments and to address preventable risk factors for frailty.

Frailty is not a static state, and a transition between frailty states is possible, particularly in those classed as 'pre-frail' [11–13]. Such findings suggest that at least some factors associated with frailty may be reversible or responsive to change. Abundant guidance advocates a life course approach to the management of frailty, by promoting healthy lifestyles in those with risk factors for frailty and enhancing access to proactive, integrated, and personalised care for those with established frailty [14–18]. Existing reviews of non-pharmacological interventions in the frail CKD population have primarily focussed on physical activity and exercise interventions. The majority of included interventions have been extrapolated from robust populations in the absence of research focussing specifically on people with frailty and CKD. Table 1 summarises the current research being undertaken in this area. Despite limited previous research, there is a growing evidence base in this area, and the aim of this review is to provide an updated overview of frailty identification and assessment and subsequent self-management, physical activity, and dietary and psychological interventions for people with frailty and CKD.

Table 1. Current research investigating non-pharmacological interventions in frailty and CKD.

Author and Country	Study Type	Sample Size	Population	Frailty Measure(s) Used	Aims	Intervention	Results
Suzuki et al., 2019 Japan	RCT protocol	20	Maintenance haemodialysis. Aged 65 years or more. SPPB Score 4–9	Short Physical Performance Battery (SPPB)	To evaluate whether electrical muscle stimulation (EMS) during dialysis may be beneficial to reduce physical function impairment in frail elderly haemodialysis patients.	EMS performed on each leg using belt electrode skeletal muscle electrical stimulation.	To be determined—this is a protocol paper.
Nixon et al., 2021 United Kingdom	Pilot RCT	35	Age >65 years old CKD G3b-5 (not receiving dialysis or received a kidney transplant); Clinical Frailty Scale score > 4	Clinical Frailty Scale	To inform the design of a definitive RCT that evaluates the effectiveness of a home-based exercise intervention in pre-frail and frail older adults with CKD.	Multi-component Home Based Exercise Intervention	Feasibility Outcomes: - Met for eligibility, adherence, and outcome completion. - Losses to follow-up and recruitment did not meet the criteria. - Qualitative Outcome: - Recruitment challenged by concerns about participating in exercise because of mobility and worries about risk of pain. Intervention: - Preliminary evidence that home-based exercise may be beneficial for people living with frailty and CKD.
Wytsma-fisher et al., 2021 Canada	Pilot RCT Protocol	24–36	Maintenance dialysis Current inpatients with discharge date > 7 days	Frailty Phenotype	To assess the feasibility and preliminary efficacy of an early physical activity intervention in the care of kidney failure inpatients.	Early physical activity/mobility intervention	To be determined—this is a protocol paper.
Perez-Saez et al., 2021 Spain	RCT Protocol	38 frail and 76 non-frail participants	Waitlist for deceased donor kidney transplant (KT).	Frailty Phenotype	To study the potential effects of multi-modal prehabilitation as a prognostic variable to predict the 90-day primary endpoint based on clinical and functional outcomes achieved in frail and non-frail KT candidates.	Multi-modal exercise intervention with nutritional supplementation.	To be determined—this is a protocol paper.
Anderson et al., 2018 United Kingdom	Pilot RCT	50	Haemodialysis	Frailty Phenotype	To explore a multi-disciplinary clinical intervention to improve frailty status among patients receiving haemodialysis	Dietetic advice Cognitive Behavioural Therapy Goal Setting	To be determined—this is a protocol paper.
Young et al., 2020 United Kingdom	Feasibility RCT	64	Haemodialysis	Clinical Frailty Scale	To determine the feasibility of conducting a randomised controlled trial (RCT) investigating the effects of Intra- Dialytic Cycling (IDC) for HD patients living with frailty.	Intra-dialytic cycling	• RCT of IDC is feasible for frail HD patients with adaptation to increase outcome acceptability and eligibility rates. • Adherence to IDC was high and it was viewed as a safe and efficient use of HD treatment time. • IDC may mitigate deterioration in exercise capacity, endurance, and functional muscle strength, increased PA behaviour (steps/day), and reduced fall incidence. • Preference for a multi-component programme • Tailored intervention is better suited to frail HD patients' needs.
Chang et al., 2020 China	RCT Protocol	242	CKD stage 3–5 without dialysis Aged > 65 years	Frailty Phenotype	To explore the risk factors related to frailty in elderly CKD patients without dialysis. To investigate the effect of individualised interventions of frailty on the prognosis of elderly patients with CKD who did not undergo dialysis.	Nutrition, psychology, and exercise intervention.	To be determined—this is a protocol paper.

2. Frailty Identification and Assessment

First and foremost, the proactive identification of frailty, prompting the timely consideration of targeted interventions, is essential to improving outcomes for this vulnerable population. Clinical acumen alone is unreliable when identifying frailty in people with CKD; frailty measures that can either replace or guide clinical judgement can improve the accuracy of assessment [19]. Most frailty screening tools and measures used in clinical practice are derived from two conceptual models of frailty, the Frailty Phenotype [1] and the deficit accumulation model, also known as the Frailty Index [20,21]. The Frailty Phenotype is defined as a clinical syndrome of physical frailty involving at least three of the following criteria: unintentional weight loss, self-reported exhaustion, weakness (measured by grip strength), slow walking speed, and low physical activity [1]. It has been most well studied in CKD populations [22] and is predictive of adverse outcomes [23,24]. However, it can be unwieldy outside the research environment, requiring a combination of self-report questionnaires and objective assessments. A frailty index takes a more holistic approach to frailty assessment, considering deficits across various domains, including disease states, physical function, cognition, and functional status [20,21]. It is predictive of adverse outcomes in CKD [25], although its use in clinical practice is hampered by the volume of data required to generate a frailty index score. The electronic Frailty Index (eFI) has circumnavigated this limitation within the general older population by using existing electronic primary care health record data to generate a score [26]. Additional validation studies are needed before its use can be recommended within routine nephrology practice; however, preliminary data suggests that the eFI has prognostic value in CKD populations [27].

Multiple frailty screening tools have been evaluated in CKD populations and perform reasonably well [28–32]. Notably, the widely cited Clinical Frailty Scale (CFS) [21,33], a global 9-point scale that guides the clinical judgement of an individual's frailty status, has been shown to be associated with adverse outcomes in Australian, Canadian, Japanese, South Korean, and UK CKD populations [34–44]. A limitation of the CFS is that it relies on a healthcare professional to make a subjective assessment, albeit an informed one. The screening tool selected for use in clinical practice will be influenced by the familiarity of local geriatric medicine and primary care services, given the importance of communicating readily interpretable frailty status assessments in the multi-disciplinary and multi-professional management of people living with frailty. Arguably, it is more important that frailty is proactively identified, regardless of the method used, rather than delaying the implementation of frailty screening within nephrology services as a consequence of over-deliberation.

Once frailty is identified, a holistic assessment can inform the implementation of targeted interventions. Comprehensive Geriatric Assessment (CGA) is considered the 'gold standard' of care for older adults [45]. CGA is defined as 'a multidimensional, multidisciplinary process which identifies medical, social and functional needs, and the development of an integrated/co-ordinated care plan to meet those needs' [46]. CGA or modified versions, which often involve one assessor performing a multi-domain assessment, have been used to successfully identify geriatric impairments in older adults with advanced CKD [36,47,48]. Using a structured geriatric assessment, van Loon et al. [47] demonstrated that nearly half of older people starting dialysis had three or more geriatric impairments. Voorend et al. [49] demonstrated that geriatric assessment was useful to identify trends in geriatric domains and provided a reason to set targeted interventions. In addition, geriatric assessment helped to initiate dialogue on treatment decisions, including prompting the consideration of different treatment options [49]. It is not yet known if CGA leads to improved outcomes in people with CKD; however, studies are underway [49–51]. Existing evidence suggests that CGA or modified versions can be used to assess people with frailty and CKD to identify associated geriatric impairments, which in turn can guide future targeted interventions. Figure 1 details a pathway for the identification, assessment, and management of frailty in CKD.

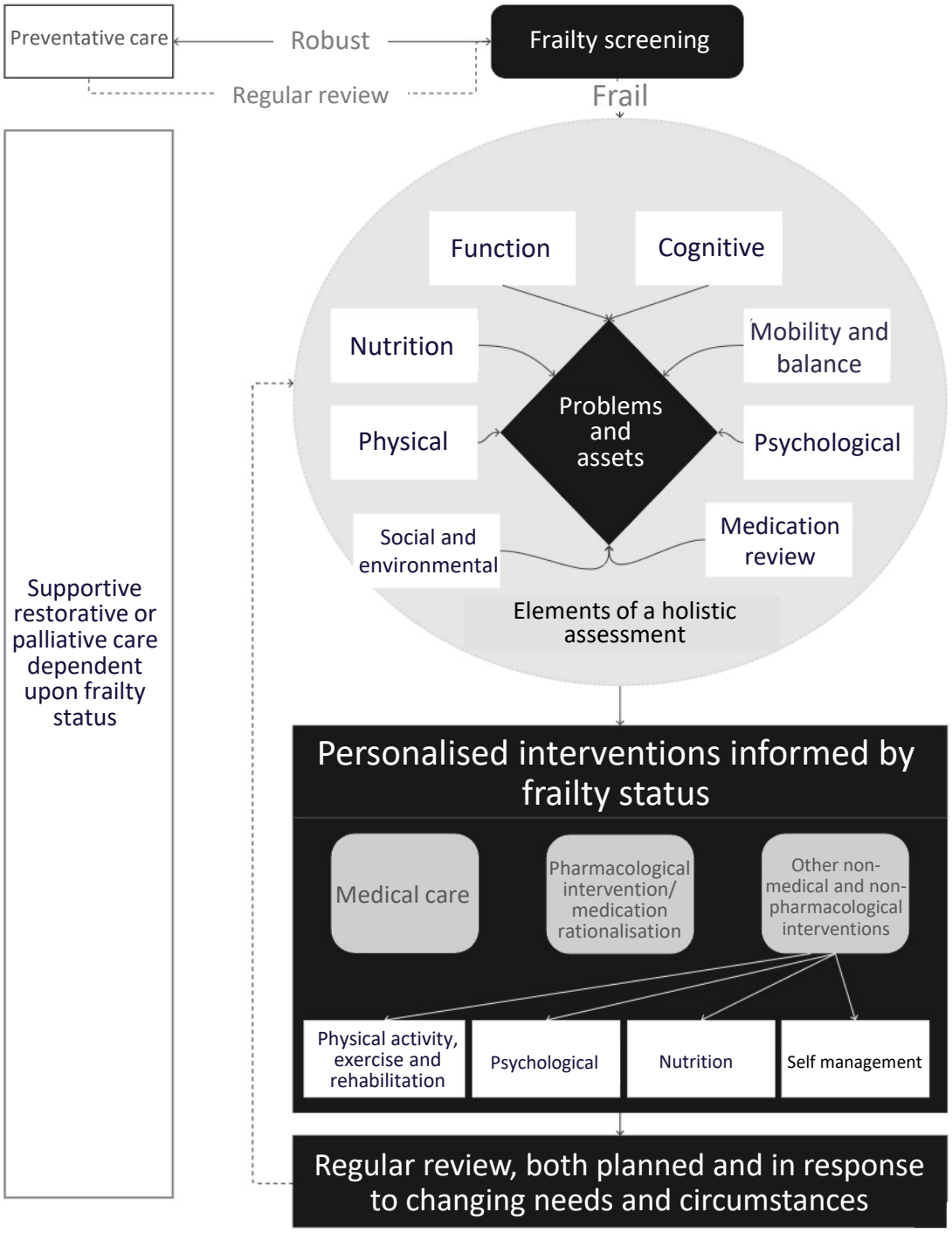

Figure 1. Pathways for the identification and management of frailty in CKD.

3. Self-Management Interventions

Self-management comprises of three core tasks (medical management, role or behavioural management, and emotional management) [52], which are underpinned by five key processes (decision making, utilising resources, forming partnerships with healthcare professionals, problem solving, and taking action) [53]. Lightfoot et al. described these core tasks and processes in detail, outlining them in a figure [54]. For people with CKD, self-management behaviours range from the management of medication adherence, health monitoring, and symptom monitoring to lifestyle modifications (e.g., increasing physical activity and eating an appropriate diet) and learning to live and cope with the emotional consequences associated with CKD [54].

Self-management consists of a diverse repertoire of cognitive and behavioural abilities to manage resources for fulfilling needs and managing losses [55]. The ability to appropriately self-manage is important for people with long-term conditions but becomes especially so when there are changes in health associated with frailty [55,56]. Declines in physical and cognitive condition can negatively impact an individual's ability to manage their health, potentially leading to further deterioration [57]. Whilst frailty is not a significant predictor of self-care behaviours [58], impaired self-management abilities are negatively associated with physical, psychological, and social frailty [59].

Individuals who are vulnerable to or have established frailty may have a lack of reserves in important resources (e.g., health, social support, social roles, etc.) or have losses in such resources [55]. Supported self-management can prevent dependence and increase one's ability to adapt and self-manage long-term condition(s) and their associated consequences [57]. There is a dearth of evidence specifically relating to the benefits of supported self-management in people with frailty and CKD. However, interventions that influence the physical, psychological, and social dimensions of frailty are likely to be beneficial in delaying the onset of frailty or reducing the risk of adverse outcomes associated with it [60,61]. Support should target problem-solving skills, self-efficacy, and coping skills [55]. Future interventions should aim to strengthen the self-management abilities of people with CKD to prevent or delay the onset of frailty. As self-management abilities can be influenced by psychological health, socio-economic factors, and health literacy, interventions need to be tailored to the individual.

4. Physical Activity and Exercise-Based Rehabilitation

Addressing sedentary behaviour, encouraging physical activity, and supporting participation in structured exercise are key components in the holistic care of people with frailty and CKD at all stages and levels of severity, although the focus and aims of these interventions may differ, as outlined within Figure 2.

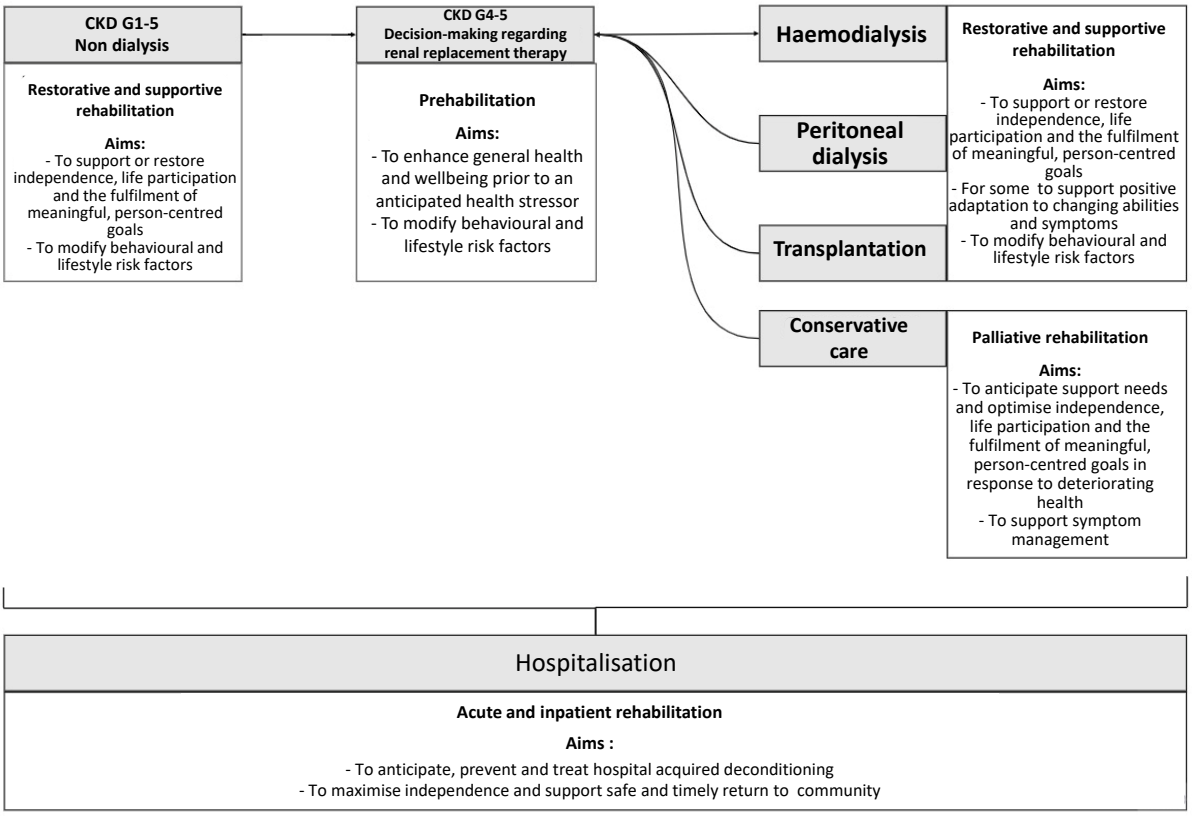

Figure 2. Key timepoints and aims for the provision of physical activity, exercise, and rehabilitation interventions for people with frailty and CKD.

Observational data support the high prevalence of physical frailty characteristics, particularly sarcopenia and physical inactivity, in the CKD population, underlining the possible mediating role of physical activity and exercise in the development and progression of frailty [12,62]. National and international guidance recommend that all people with CKD undertake exercise for cardiovascular and HRQoL benefits [63,64]. In addition, exercise is particularly recommended for older people with CKD because of its positive impact upon function [32].

Despite these recommendations, to date, only three feasibility trials focusing on exercise interventions have been conducted with people with frailty and CKD [65,66]. A small non-randomised pilot of 12 weeks of IDC combined with lower limb strengthening during dialysis in older people aged 75–95 found that those who exercised had improved Fried phenotype scores and function measured by the sit-stand 5 test, although clinically, the significance of these findings is unclear [67,68]. Young et al. (2021) found that six months of moderate-intensity, thrice-weekly intradialytic cycling (IDC) was safe and feasible for frail people receiving HD and may allay deterioration in exercise capacity, endurance, and function [66,67]. Participants, however, described IDC as limited and wanted a more comprehensive programme. Nevertheless, the intradialytic period offers an attractive opportunity to encourage activity without increasing burden. Suzuki et al. (2019) are undertaking a cross-over trial examining the effects of intradialytic electrical muscle stimulation, which may offer a useful adjunct for frailer people who find exercise challenging [69].

A more varied programme comprising twelve weeks of home-based, moderate-intensity resistance, aerobic, and balance training was also feasible and safe for people with frailty and CKD stages 3–5, leading to potential improvements in function and symptoms [65]. Similar programmes are known to be effective in older people with frailty in the general population [70–74]. These findings suggest that, irrespective of stage of CKD and mode of RRT, a focus on a range of exercises may be more effective and acceptable to frailer people who can undertake exercise. Within these programmes, progressive resistance training to enhance muscle mass, strength, and function is of particular importance [75]. Compelling evidence from community-dwelling older populations indicates that strength training alongside balance exercise significantly reduces the rate and number of falls [76]. To date, a limited number of studies have explored the impact of exercise upon falls and falls-related outcomes in the CKD population [77–80].

Evidence to date highlights the challenges of exercise for this population [65,66]. Reducing sedentary behaviour and increasing light physical activity may represent a more achievable first step and segue into exercise for frailer people [81,82]. Levels of sedentary behaviour and physical inactivity are high across the spectrum of CKD and are also key characteristics of frailty [12,83–86]. Several studies indicate that walking is a feasible and acceptable form of physical activity for people with CKD, which can lead to the preservation of muscle mass and improvements in exercise capacity and function, even in older participants [87,88]. Whether walking interventions are acceptable to those with frailty, who may be particularly functionally impaired, remains to be explored. Qualitative evidence suggests that people with CKD and frailty prefer activity with 'purpose' [66]. Increasing functional daily activities may be easier to incorporate into daily routines and is more likely to be viewed as purposeful, potentially promoting sustained change [89]. For those unable to achieve this, even regular standing to break up sedentary periods can lead to functional improvement, and preliminary evidence indicates that this approach is useful for those with CKD [81,90].

Admission to hospital and the transition to end-stage kidney disease represent two significant health stressors, which can trigger increasing dependence and the onset of additional support needs [91]. The introduction of exercise programmes to prevent or allay this decline is an area of growing interest. One small study regarding four weeks of thrice-weekly inpatient exercise training led to improvements in fatigue [92], whilst an ongoing study will explore the feasibility and preliminary efficacy of a tailored inpatient exercise intervention on frailty levels, length of stay, readmissions, HRQoL, and function [93]. How

to effectively support frail people to regain function and fitness post-hospital discharge is also an area requiring further research. For those making decisions regarding RRT, 'prehabilitation', which aims to improve tolerance to an upcoming physiologic stressor, may be beneficial [94]. Existing prehabilitation studies have predominantly focused on those awaiting transplant or approaching dialysis, concluding that prehabilitation has a positive influence on physical activity, frailty status, function, and strength [95–97]. Further definitive trials are required; an ongoing study by Perez-Saez et al. will provide additional information on the role of prehabilitation, specifically in frail kidney transplant candidates [98]. Interestingly, no research has been conducted for those opting for conservative care. In other conditions, palliative prehabilitation helps maintain independence and supports symptom management and the achievement of meaningful goals, as well as reducing carer and family burden [99,100].

5. Nutrition

Poor nutritional status has been identified as a key contributor, and potentially modifiable risk factor, for frailty [1,101,102]. Malnutrition, poor quality diet, and the low intake of specific macro- or micronutrients have been associated with frailty [102,103]. For people with advanced CKD, nutritional status and diet quality may be negatively impacted by a reduced dietary intake driven by uraemic symptoms (e.g., anorexia, nausea, and taste disturbance), financial constraints, low mood, or poor dentition [101,104]. Dietary restrictions may further compromise intake; as such, guidelines on the management of older people with CKD recommend that preserving nutritional status should take precedence over these [32]. Intercurrent illnesses, nutrient losses into dialysate, inflammation, and acidaemia may also be superimposed on reduced dietary intake and further contribute to protein-energy wasting and frailty [104,105].

Screening for risk of malnutrition is recommended for people at risk of frailty [106]. The identification of those at risk of malnutrition can then prompt further nutrition assessment and intervention. For adults with CKD, no gold standard nutrition screening tool exists; however, modified tools are available [107,108]. Comprehensive nutrition assessment (using tools such as the Subjective Global Assessment) can then be conducted to provide a more in-depth assessment of an individual's nutritional state and to help guide a treatment plan [107,108].

Interventions to correct nutritional deficits and weight loss may present the opportunity to reverse or modify frailty in people with CKD. However, currently, there is a paucity of studies exploring the effectiveness of nutritional interventions (nutrition education and/or supplementation) for people with frailty and CKD. Within older populations with frailty, evidence of the benefits of nutritional intervention is also lacking. International guidelines on the management of frailty recommend the use of protein/calorie supplementation when undernutrition or weight loss has been diagnosed, although the low certainty of the evidence on which this recommendation is based is highlighted [109]. Evidence from systematic reviews have suggested that although nutritional interventions delivered in isolation may not show a beneficial effect [110], when used as part of multi-component interventions incorporating physical exercise, they may provide an additive effect, yielding greater improvement in frailty status and physical functioning [111]. For people with frailty and CKD, several such trials are currently underway and will begin to shed light on the impact of multi-component interventions on frailty in people with CKD stage 3–5 [51], those receiving haemodialysis [112], and in kidney transplant recipients [98].

6. Non-Pharmacological Interventions for Depression

Depression is commonly experienced by people with CKD and is associated with poorer health-related outcomes, including increased mortality [113–115]. Across the spectrum of advanced CKD, the prevalence of depression is estimated to be between 26.5 and 39.3% depending on CKD severity and modality [116].

In community settings, depression and frailty often co-occur [117]. The relationship between frailty and depression appears reciprocal since both are associated with the incidence and prevalence of each other [117]. It is likely that both depression and frailty have shared risk factors, including multi-morbidity and chronic inflammation, particularly in the context of CKD. For example, recent meta-analytic evidence found that higher interleukin-6 and lower albumin were associated with the prevalence and severity of depression in people with CKD [118]. Furthermore, symptom clusters of both depression and frailty overlap, including the presence of fatigue, weight loss, and decreased activity [1], which can complicate the assessment of both conditions.

Among people with CKD, both frailty and depression are significant determinants of HRQoL [38,119]. Cross-sectional data from both dialysis and kidney transplant recipients found that depression symptoms are associated with a respective 2.14 and 3.97 increase in the odds of frailty [120,121]. In a prospective study regarding people receiving dialysis, Sy et al. [120] found that depression symptoms were associated with the incidence of frailty, whereas frailty was not found to predict incident depression. In the same study, both frailty and depression were independent predictors of mortality in time-varying survival models [120]. A study regarding kidney transplant recipients found that those with co-existing depression and frailty had a 6.20-fold increased risk of death-censored graft failure and a 2.62-fold increased risk of all-cause mortality, compared to non-depressed non-frail recipients [121]. Furthermore, data from a relatively small study regarding people receiving peritoneal dialysis showed poorer nutritional status and greater hospitalisation and mortality in those with co-existing depression and frailty [122]. A more recent study showed that the association between depression and mortality was attenuated once frailty was adjusted for [123]. Taken together, both depression and frailty appear to be associated with adverse clinical outcomes, with some evidence to suggest that comorbid frailty and depression are particularly important prognostic factors.

Despite the co-occurrence of frailty and depression in CKD, little research has focused on psychosocial and behavioural interventions to support management. Whilst recent meta-analytic evidence suggests that exercise training improves symptoms of depression in people receiving HD, further research is needed to understand the psychosocial factors associated with frailty in order to inform multi-component interventions designed to improve symptoms of frailty and depression. There is a particular need to understand how people with CKD think and respond to symptoms of frailty and how these factors are associated with subsequent self-management behaviours, symptom severity, and impairment. In kidney transplant recipients, psychological resilience has been found to be associated with frailty [124], and in community-dwelling older adults, self-efficacy and a sense of mastery have been found to reduce the odds of functional decline [125]. Such factors are also commonly associated with depression. Improving the early identification and treatment of depression might help reduce functional decline in people with CKD. Future research is needed to develop and test multi-component interventions, which include elements designed to help support the management of both depression and frailty and the impact these symptoms have on HRQoL. At present, there are three multi-component research trials underway, which will go some way to addressing this gap [51,98,112].

7. Digital Health Interventions

With increasing burden placed upon healthcare systems, there is a growing focus on leveraging digital technology as a means of delivering health interventions [126]. Digital technologies may increase synergy across healthcare systems and empower people to manage their long-term physical and mental health [127]. As the number of individuals with frailty and CKD increases, it is imperative that access to appropriately tailored healthcare interventions, irrespective of geographical location, is widened. Digital health interventions (DHIs) are defined as services delivered electronically to deliver health and health-related care [128] and have the potential to improve access to services and reduce health inequalities [129].

There has been an increase in the number and types of DHIs in recent years. DHIs may increase capacity, drive efficiencies, and improve clinical outcomes [129]. DHIs specifically designed for people with frailty is a growing area of interest. DHIs can support frailty detection and the assessment and monitoring of health status and enhance communication between healthcare professionals and people with frailty. They have also been used to provide falls prevention and rehabilitation interventions [130]. To our knowledge, there is limited evidence that specifically focusses on DHIs to support lifestyle interventions for people with frailty and CKD.

The delivery of physical activity and exercise rehabilitation may be particularly amenable to online or app-based delivery. Research indicates that DHIs have the potential to reduce barriers to participating in physical activity, increasing physical activity levels in the shorter term [131–135]. This is particularly relevant within the context of the ongoing coronavirus-19 (COVID-19) pandemic. Frail older adults' levels of physical activity reduced during this time, with a resultant negative impact upon deconditioning and falls [136], and physical activity levels in shielding adults with ESKD also declined [137]. A newly established online platform, which aims to enhance physical activity and emotional wellbeing in people with CKD, 'Kidney Beam', may prove beneficial for people with frailty and CKD [138]. Indeed, a 6-month clinical pilot demonstrated an increase in the number of participants self-reporting that they were meeting national physical activity guidelines, as well as demonstrating an increase in perceived energy levels [139]. A multi-centre, randomised, controlled trial is currently underway to evaluate the clinical effectiveness of this digital platform for individuals living with CKD.

The potential of DHIs for individuals with frailty and CKD is clear; however, is it essential that further research is undertaken to understand how best to tailor DHIs for those living with CKD and frailty. Whilst people with CKD have described their experiences of DHIs as positive [137], some found the loss of non-verbal communication associated with remote telemedicine challenging [137]. Additionally, current DHIs typically provide general advice and feedback, which people with frailty and CKD feel is not always appropriate for their complex needs [140]. DHI designed specifically for this population may benefit from a co-design approach to ensure the content and methods of delivery are in line with users' needs [130].

8. Considerations

This review provides an overview of current evidence on the importance of identifying frailty in those with CKD, alongside targeted non-pharmacological interventions. Individualised holistic assessment and management is required to provide care for this group, to maximise HRQoL, support independence, and minimise the risk of adverse health outcomes.

Frailty is a dynamic state, and frailty status can improve as well as worsen in people with advanced CKD. McAdams-DeMarco et al. [13] demonstrated an improvement in frailty scores three months following transplantation. A recent study by Rampersad et al. [141] found that there is an accelerated decline in physical function with transition to dialysis for older adults. However, Johansen et al. [12] demonstrated that frailty status can fluctuate in the prevalent haemodialysis population, and whilst in some cases, the severity increases, and many also improve. Hospitalisation was associated with worsening frailty status over time [12], highlighting the importance of minimising unplanned hospitalisations. Management strategies should be proactive, aiming to maintain or improve nutritional and functional status, minimise fall risk, and promptly treat infection. Advanced care planning should also be considered, particularly for those with more severe frailty.

Non-pharmacological interventions can prevent or delay dependence. However, it is important to note that prioritising such interventions can be challenging, particularly for those with complex healthcare needs [142,143]. Decisions about which care tasks or activities to prioritise can be influenced by social and economic factors [144], and individuals who are more highly educated or from a higher socio-economic status have

more resources available to enable them to manage their conditions and the impacts of frailty [56,58]. Greater health and technology literacy [58] may also support the use of DHIs to support self-management [145]. Self-management abilities may also be made more challenging in this group by high levels of depression and emotional distress as well as physical and cognitive impairments [142,146,147]. Therefore, disadvantaged groups may require additional support to ensure they achieve the best possible outcomes.

To date, research has focussed primarily on exercise interventions to address the impact of physical frailty and CKD. Future research should focus on understanding the role of multi-component interventions that aim to target the multiple drivers of frailty. This may include a combination of exercise, nutritional, pharmacological, and psychological interventions and could logically lead to greater improvements in outcomes. Evidence for the effectiveness of combined interventions in the general older population appears to be inconclusive, although exercise seems be a key component [70,94,111]. Beetham et al. [147] recently demonstrated the benefits of a multi-component lifestyle intervention, which also included an exercise component, for people with CKD. There are three ongoing studies utilising exercise programmes in conjunction with nutrition and psychological components that will provide further evidence for the frail CKD population [51,98,112].

Current research has identified the need for a holistic, multi-disciplinary approach to both frailty identification and management. Promisingly, there is a growing evidence base in this area, but whilst further research is awaited, there are several practical applications that can be implemented into routine kidney care. These are highlighted in Table 2. Future research should focus on establishing interventions to manage the complications and components of frailty that are specific to the complex needs of those with CKD, particularly those from disadvantaged backgrounds.

Table 2. Practical applications to support the care of people with frailty and CKD.

Areas of Focus	Practical Applications
Frailty identification and assessment	• Proactive frailty identification using a validated screening tool, e.g., Clinical Frailty Scale, within inpatient and outpatient areas. • Offer a holistic multi-domain assessment to people with frailty that aims to identify associated geriatric impairments. • Consider Clinical Champions and/or incorporate responsibilities within existing roles, e.g., Supportive Care Lead, Advanced Kidney Care Clinic MDT members, Dialysis Unit HCPs, etc.
Self-management support	• Support individuals with CKD to set personalised goals to support lifestyle changes. • Provide specific education and facilitate the modelling of behaviour. • Train clinicians in supporting efforts to increase each individual's confidence and self-efficacy. • In clinical settings, allow dedicated time to address treatment concerns.
Exercise/physical activity	• Routinely discuss the importance of exercise and physical activity for maintaining independence, especially during episodes of physiological stress (e.g., initiation of dialysis, hospitalisation, or transplantation). • Dependent upon needs and resources, provide opportunities to become more physically active, and refer into existing strength- and balance-based fall prevention programmes. • Sign-post to local physical activity and exercise groups within the community. • For those unable to undertake exercise, consider supporting them to increase daily physical activity within their usual routine or to reduce sedentary behaviour.

Table 2. *Cont.*

Areas of Focus	Practical Applications
Nutrition	• Routine screening for the risk of undernutrition. • Identify and address treatable causes of weight loss. • Referral to specialist renal dietitians when the risk of undernutrition is identified for further assessment and individualised interventions.
Psychological management	• Screening for psychological distress, depression, or anxiety. • Psychological interventions delivered by renal specialist psychologists, therapists, and counsellors. • Psychoeducation. • Increased integration of psychosocial and physical health care.
Digital health interventions (DHIs)	• Sign-post to DHIs that are specific to frailty and CKD populations. • Identify those who would benefit from the use of DHIs, such as low physical activity levels, psychological wellbeing needs, or specific educational or peer support needs. • Embed the use of renal-specific DHIs within Kidney Units. • Assign Digital Champions within units to promote appropriate resources, educate on safe and researched specific DHIs, and support individuals to access these platforms with digital devices.

9. Conclusions

Frailty is highly prevalent in individuals with CKD and is directly linked to poor HRQoL, reduced physical function, risk of hospitalisation, and mortality. It is therefore essential that individuals are screened in kidney clinics to identify frailty and facilitate discussions around future treatment plans, and that holistic treatment pathways for management are established. Frailty identification and management in CKD is complex and requires a multi-disciplinary approach. Non-pharmacological interventions are a promising area for routine clinical implementation, and future research should focus on targeted interventions for those with frailty and CKD.

Author Contributions: Conceptualisation, A.C.N., H.M.L.Y., J.M., C.J.L., J.C. and R.M.B.; Writing—Original Draft Preparation, A.C.N., H.M.L.Y. and J.M.; Writing—Review and Editing, A.C.N., H.M.L.Y., J.M., C.J.L., J.C. and R.M.B. All authors have read and agreed to the published version of the manuscript.

Funding: H.M.L.Y. and J.M. are supported by grants from the NIHR (H.M.L.Y.—NIHR301593 and J.M.—NIHR301893). C.J.L. is supported by the Stoneygate Trust as part of the Kidney Lifestyle Research Programme Grant. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care. The funders had no role in the study design; collection, analysis, and interpretation of the data; writing the report; and the decision to submit the report for publication.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Fried, L.P.; Tangen, C.M.; Walston, J.; Newman, A.B.; Hirsch, C.; Gottdiener, J.; Seeman, T.; Tracy, R.; Kop, W.J.; Burke, G.; et al. Frailty in older adults: Evidence for a phenotype. *J. Gerontol. A Biol. Sci. Med. Sci.* **2001**, *56*, M146–M156. [CrossRef] [PubMed]
2. Stewart, R. Cardiovascular Disease and Frailty: What Are the Mechanistic Links? *Clin. Chem.* **2019**, *65*, 80–86. [CrossRef] [PubMed]
3. Palmer, K.; Vetrano, D.L.; Padua, L.; Romano, V.; Rivoiro, C.; Scelfo, B.; Marengoni, A.; Bernabei, R.; Onder, G. Frailty Syndromes in Persons With Cerebrovascular Disease: A Systematic Review and Meta-Analysis. *Front. Neurol.* **2019**, *10*, 1255. [CrossRef]

4. El Haddad, K.; Rolland, Y.; Gérard, S.; Mourey, L.; Sourdet, S.; Vellas, B.; Stephan, E.; Abellan Van Kan, G.; de Souto Barreto, P.; Balardy, L. No Difference in the Phenotypic Expression of Frailty among Elderly Patients Recently Diagnosed with Cancer Vs Cancer Free Patients. *J. Nutr. Health Aging* **2020**, *24*, 147–151. [CrossRef] [PubMed]
5. Bilgin, S.; Aktas, G.; Kurtkulagi, O.; Atak, B.M.; Duman, T.T. Edmonton frail score is associated with diabetic control in elderly type 2 diabetic subjects. *J. Diabetes Metab. Disord.* **2020**, *19*, 511–514. [CrossRef] [PubMed]
6. Vetrano, D.L.; Palmer, K.; Marengoni, A.; Marzetti, E.; Lattanzio, F.; Roller-Wirnsberger, R.; Lopez Samaniego, L.; Rodríguez-Mañas, L.; Bernabei, R.; Onder, G. Frailty and Multimorbidity: A Systematic Review and Meta-analysis. *J. Gerontol. Ser. A* **2018**, *74*, 659–666. [CrossRef]
7. Lee, H.-J.; Son, Y.-J. Prevalence and Associated Factors of Frailty and Mortality in Patients with End-Stage Renal Disease Undergoing Hemodialysis: A Systematic Review and Meta-Analysis. *Int. J. Environ. Res. Public Health* **2021**, *18*. [CrossRef] [PubMed]
8. Quint, E.E.; Zogaj, D.; Banning, L.B.D.; Benjamens, S.; Annema, C.; Bakker, S.J.L.; Nieuwenhuijs-Moeke, G.J.; Segev, D.L.; McAdams-DeMarco, M.A.; Pol, R.A. Frailty and Kidney Transplantation: A Systematic Review and Meta-analysis. *Transpl. Direct* **2021**, *7*, e701. [CrossRef]
9. Brown, S.A.; Tyrer, F.C.; Clarke, A.L.; Lloyd-Davies, L.H.; Stein, A.G.; Tarrant, C.; Burton, J.O.; Smith, A.C. Symptom burden in patients with chronic kidney disease not requiring renal replacement therapy. *Clin. Kidney J.* **2017**, *10*, 788–796. [CrossRef]
10. Gregg, L.P.; Jain, N.; Carmody, T.; Minhajuddin, A.T.; Rush, A.J.; Trivedi, M.H.; Hedayati, S.S. Fatigue in Nondialysis Chronic Kidney Disease: Correlates and Association with Kidney Outcomes. *Am. J. Nephrol.* **2019**, *50*, 37–47. [CrossRef]
11. Goto, N.A.; van Loon, I.N.; Morpey, M.I.; Verhaar, M.C.; Willems, H.C.; Emmelot-Vonk, M.H.; Bots, M.L.; Boereboom, F.T.J.; Hamaker, M.E. Geriatric Assessment in Elderly Patients with End-Stage Kidney Disease. *Nephron* **2019**, *141*, 41–48. [CrossRef] [PubMed]
12. Johansen, K.L.; Dalrymple, L.S.; Delgado, C.; Chertow, G.M.; Segal, M.R.; Chiang, J.; Grimes, B.; Kaysen, G.A. Factors Associated with Frailty and Its Trajectory among Patients on Hemodialysis. *Clin. J. Am. Soc. Nephrol.* **2017**, *12*, 1100–1108. [CrossRef] [PubMed]
13. McAdams-DeMarco, M.A.; Isaacs, K.; Darko, L.; Salter, M.L.; Gupta, N.; King, E.A.; Walston, J.; Segev, D.L. Changes in Frailty After Kidney Transplantation. *J. Am. Geriatr. Soc.* **2015**, *63*, 2152–2157. [CrossRef] [PubMed]
14. NHS England. *Supporting Routine Frailty Identification and Frailty through the GP Contract*; NHS England: Leeds, UK, 2017. Available online: https://www.england.nhs.uk/publication/supporting-routine-frailty-identification-and-frailty-through-the-gp-contract-20172018/ (accessed on 16 May 2022).
15. National Institute for Health and Care Excellence. Multimorbidity: Clinical Assessment and Management. 2017. Available online: https://www.nice.org.uk/guidance/qs153 (accessed on 19 January 2022).
16. National Institute for Health and Care Excellence. Falls in Older People. 2015. Available online: https://www.nice.org.uk/guidance/cg161 (accessed on 19 January 2022).
17. NHS England. Personalised Care. 2019. Available online: https://www.england.nhs.uk/personalisedcare/ (accessed on 19 January 2022).
18. NHS England. The NHS Long Term Plan. 2019. Available online: https://www.england.nhs.uk/long-term-plan/ (accessed on 19 January 2022).
19. Salter, M.L.; Gupta, N.; Massie, A.B.; McAdams-DeMarco, M.A.; Law, A.H.; Jacob, R.L.; Gimenez, L.F.; Jaar, B.G.; Walston, J.D.; Segev, D.L. Perceived frailty and measured frailty among adults undergoing hemodialysis: A cross-sectional analysis. *BMC Geriatr* **2015**, *15*, 52. [CrossRef]
20. Mitnitski, A.B.; Mogilner, A.J.; Rockwood, K. Accumulation of deficits as a proxy measure of aging. *Sci. World J.* **2001**, *1*, 323–336. [CrossRef]
21. Rockwood, K.; Song, X.; MacKnight, C.; Bergman, H.; Hogan, D.B.; McDowell, I.; Mitnitski, A. A global clinical measure of fitness and frailty in elderly people. *CMAJ* **2005**, *173*, 489–495. [CrossRef]
22. Zhao, Y.; Liu, Q.; Ji, J. The prevalence of frailty in patients on hemodialysis: A systematic review and meta-analysis. *Int. Urol. Nephrol.* **2020**, *52*, 115–120. [CrossRef]
23. Zhang, Q.; Ma, Y.; Lin, F.; Zhao, J.; Xiong, J. Frailty and mortality among patients with chronic kidney disease and end-stage renal disease: A systematic review and meta-analysis. *Int. Urol. Nephrol.* **2020**, *52*, 363–370. [CrossRef]
24. Mei, F.; Gao, Q.; Chen, F.; Zhao, L.; Shang, Y.; Hu, K.; Zhang, W.; Zhao, B.; Ma, B. Frailty as a Predictor of Negative Health Outcomes in Chronic Kidney Disease: A Systematic Review and Meta-Analysis. *J. Am. Med. Dir. Assoc.* **2021**, *22*, 535–543. [CrossRef]
25. Vezza, C.; Vettoretti, S.; Caldiroli, L.; Bergamaschini, L.; Messa, P.; Cesari, M. Use of the Frailty Index in Older Persons With Chronic Kidney Disease. *J. Am. Med. Dir. Assoc.* **2019**, *20*, 1179–1180. [CrossRef]
26. Clegg, A.; Bates, C.; Young, J.; Ryan, R.; Nichols, L.; Ann Teale, E.; Mohammed, M.A.; Parry, J.; Marshall, T. Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age Ageing* **2016**, *45*, 353–360. [CrossRef] [PubMed]
27. Sam, R.; Usha, A.; Kuldeep, S.; John, S.; John, B.; Andy, C.; Robert, W.; Jenny, H.; Mooney, A. The Electronic Frailty Index (EFI) Indicates Mortality Risk in End Stage Kidney Disease Patients on Dialysis. *Nephrol. Dial. Transplant.* **2019**, *34*, gfz096.FO032. [CrossRef]
28. Worthen, G.; Tennankore, K. Frailty Screening in Chronic Kidney Disease: Current Perspectives. *Int. J. Nephrol. Renov. Dis.* **2019**, *12*, 229–239. [CrossRef]

29. Nixon, A.C.; Bampouras, T.M.; Pendleton, N.; Mitra, S.; Dhaygude, A.P. Diagnostic Accuracy of Frailty Screening Methods in Advanced Chronic Kidney Disease. *Nephron* **2019**, *141*, 147–155. [CrossRef] [PubMed]
30. Van Loon, I.N.; Goto, N.A.; Boereboom, F.T.J.; Bots, M.L.; Verhaar, M.C.; Hamaker, M.E. Frailty Screening Tools for Elderly Patients Incident to Dialysis. *Clin. J. Am. Soc. Nephrol.* **2017**, *12*, 1480–1488. [CrossRef]
31. Van Munster, B.C.; Drost, D.; Kalf, A.; Vogtlander, N.P. Discriminative value of frailty screening instruments in end-stage renal disease. *Clin. Kidney J.* **2016**, *9*, 606–610. [CrossRef]
32. Farrington, K.; Covic, A.; Aucella, F.; Clyne, N.; de Vos, L.; Findlay, A.; Fouque, D.; Grodzicki, T.; Iyasere, O.; Jager, K.J.; et al. Clinical Practice Guideline on management of older patients with chronic kidney disease stage 3b or higher (eGFR <45 mL/min/1.73 m^2). *Nephrol. Dial. Transpl.* **2016**, *31*, ii1–ii66. [CrossRef]
33. Church, S.; Rogers, E.; Rockwood, K.; Theou, O. A scoping review of the Clinical Frailty Scale. *BMC Geriatr.* **2020**, *20*, 393. [CrossRef]
34. Kumarasinghe, A.P.; Chakera, A.; Chan, K.; Dogra, S.; Broers, S.; Maher, S.; Inderjeeth, C.; Jacques, A. Incorporating the Clinical Frailty Scale into routine outpatient nephrology practice: An observational study of feasibility and associations. *Intern. Med. J.* **2021**, *51*, 1269–1277. [CrossRef]
35. Alfaadhel, T.A.; Soroka, S.D.; Kiberd, B.A.; Landry, D.; Moorhouse, P.; Tennankore, K.K. Frailty and mortality in dialysis: Evaluation of a clinical frailty scale. *Clin. J. Am. Soc. Nephrol.* **2015**, *10*, 832–840. [CrossRef]
36. Nixon, A.C.; Brown, J.; Brotherton, A.; Harrison, M.; Todd, J.; Brannigan, D.; Ashcroft, Q.; So, B.; Pendleton, N.; Ebah, L.; et al. Implementation of a frailty screening programme and Geriatric Assessment Service in a nephrology centre: A quality improvement project. *J. Nephrol.* **2020**, *34*, 1215–1224. [CrossRef] [PubMed]
37. Pugh, J.; Aggett, J.; Goodland, A.; Prichard, A.; Thomas, N.; Donovan, K.; Roberts, G. Frailty and comorbidity are independent predictors of outcome in patients referred for pre-dialysis education. *Clin. Kidney J.* **2016**, *9*, 324–329. [CrossRef] [PubMed]
38. Iyasere, O.U.; Brown, E.A.; Johansson, L.; Huson, L.; Smee, J.; Maxwell, A.P.; Farrington, K.; Davenport, A. Quality of Life and Physical Function in Older Patients on Dialysis: A Comparison of Assisted Peritoneal Dialysis with Hemodialysis. *Clin. J. Am. Soc. Nephrol.* **2016**, *11*, 423–430. [CrossRef] [PubMed]
39. Van Loon, I.N.; Joosten, H.; Iyasere, O.; Johansson, L.; Hamaker, M.E.; Brown, E.A. The prevalence and impact of falls in elderly dialysis patients: Frail elderly Patient Outcomes on Dialysis (FEPOD) study. *Arch. Gerontol. Geriatr.* **2019**, *83*, 285–291. [CrossRef]
40. Neradova, A.; Vajgel, G.; Hendra, H.; Antonelou, M.; Kostakis, I.D.; Wright, D.; Masson, P.; Milne, S.E.; Jones, G.; Salama, A.; et al. Frailty score before admission as risk factor for mortality of renal patients during the first wave of the COVID pandemic in London. *G Ital. Nefrol.* **2021**, *38*, 2021.
41. Wu, H.H.L.; Van Mierlo, R.; McLauchlan, G.; Challen, K.; Mitra, S.; Dhaygude, A.P.; Nixon, A.C. Prognostic performance of clinical assessment tools following hip fracture in patients with chronic kidney disease. *Int. Urol. Nephrol.* **2021**, *53*, 2359–2367. [CrossRef]
42. Kamijo, Y.; Kanda, E.; Ishibashi, Y.; Yoshida, M. Sarcopenia and Frailty in PD: Impact on Mortality, Malnutrition, and Inflammation. *Perit. Dial. Int. J. Int. Soc. Perit. Dial.* **2018**, *38*, 447–454. [CrossRef]
43. Hwang, D.; Lee, E.; Park, S.; Yoo, B.C.; Park, S.; Choi, K.J.; Oh, S.; Kim, M.J.; Kim, H.; Jeon, J.S.; et al. Validation of risk prediction tools in elderly patients who initiate dialysis. *Int. Urol. Nephrol.* **2019**, *51*, 1231–1238. [CrossRef]
44. Iyasere, O.; Brown, E.A.; Johansson, L.; Davenport, A.; Farrington, K.; Maxwell, A.P.; Collinson, H.; Fan, S.; Habib, A.-M.; Stoves, J.; et al. Quality of life with conservative care compared with assisted peritoneal dialysis and haemodialysis. *Clin. Kidney J.* **2018**, *12*, 262–268. [CrossRef]
45. Ellis, G.; Gardner, M.; Tsiachristas, A.; Langhorne, P.; Burke, O.; Harwood, R.H.; Conroy, S.P.; Kircher, T.; Somme, D.; Saltvedt, I.; et al. Comprehensive geriatric assessment for older adults admitted to hospital. *Cochrane Database Syst. Rev.* **2017**, *9*, Cd006211. [CrossRef]
46. Parker, S.G.; McCue, P.; Phelps, K.; McCleod, A.; Arora, S.; Nockels, K.; Kennedy, S.; Roberts, H.; Conroy, S. What is Comprehensive Geriatric Assessment (CGA)? An umbrella review. *Age Ageing* **2018**, *47*, 149–155. [CrossRef] [PubMed]
47. Hall, R.K.; Haines, C.; Gorbatkin, S.M.; Schlanger, L.; Shaban, H.; Schell, J.O.; Gurley, S.B.; Colón-Emeric, C.S.; Bowling, C.B. Incorporating Geriatric Assessment into a Nephrology Clinic: Preliminary Data from Two Models of Care. *J. Am. Geriatr. Soc.* **2016**, *64*, 2154–2158. [CrossRef] [PubMed]
48. Kojima, G.; Taniguchi, Y.; Iliffe, S.; Jivraj, S.; Walters, K. Transitions between frailty states among community-dwelling older people: A systematic review and meta-analysis. *Ageing Res. Rev.* **2019**, *50*, 81–88. [CrossRef] [PubMed]
49. Voorend, C.G.N.; Joosten, H.; Berkhout-Byrne, N.C.; Diepenbroek, A.; Franssen, C.F.M.; Bos, W.J.W.; Van Buren, M.; Mooijaart, S.P. Design of a consensus-based geriatric assessment tailored for older chronic kidney disease patients: Results of a pragmatic approach. *Eur. Geriatr. Med.* **2021**, *12*, 931–942. [CrossRef]
50. Van Oevelen, M.; Abrahams, A.C.; Bos, W.J.W.; Emmelot-Vonk, M.H.; Mooijaart, S.P.; van Diepen, M.; van Jaarsveld, B.C.; van Eck van der Sluijs, A.; Voorend, C.G.N.; van Buren, M.; et al. DIALysis or not: Outcomes in older kidney patients with GerIatriC Assessment (DIALOGICA): Rationale and design. *BMC Nephrol.* **2021**, *22*, 39. [CrossRef]
51. Chang, J.; Gao, Y.; Fang, X.-Y.; Zhao, S.-M.; Hou, Y.-P.; Sun, Q.-M. Individualized intervention for frail non-dialysis elderly patients with chronic kidney disease: Protocol for a randomized controlled trial. *BMC Geriatr.* **2020**, *20*, 159. [CrossRef]
52. Corbin, J.M.; Strauss, A. *Unending Work and Care: Managing Chronic Illness at Home*, 1st ed.; Jossey-Bass: San Francisco, CA, USA, 1988; ISBN 978-1555420826.
53. Lorig, K.R.; Holman, H. Self-management education: History, definition, outcomes, and mechanisms. *Ann. Behav. Med.* **2003**, *26*, 1–7. [CrossRef]

54. Lightfoot, C.J.; Nair, D.; Bennett, P.N.; Smith, A.C.; Griffin, A.D.; Warren, M.; Wilkinson, T.J. Patient Activation: The Cornerstone of Effective Self-Management in Chronic Kidney Disease? *Kidney Dial.* **2022**, *2*, 91–105. [CrossRef]
55. Steverink, N.; Lindenberg, S.; Slaets, J.P.J. How to understand and improve older people's self-management of wellbeing. *Eur. J. Ageing* **2005**, *2*, 235–244. [CrossRef]
56. Cramm, J.M.; Twisk, J.; Nieboer, A.P. Self-management abilities and frailty are important for healthy aging among community-dwelling older people; a cross-sectional study. *BMC Geriatr.* **2014**, *14*, 28. [CrossRef]
57. Van het Bolscher-Niehuis, M.J.T.; den Ouden, M.E.M.; de Vocht, H.M.; Francke, A.L. Effects of self-management support programmes on activities of daily living of older adults: A systematic review. *Int. J. Nurs. Stud.* **2016**, *61*, 230–247. [CrossRef]
58. Son, Y.-J.; Shim, D.K.; Seo, E.K.; Seo, E.J. Health Literacy but Not Frailty Predict Self-Care Behaviors in Patients with Heart Failure. *Int. J. Environ. Res. Public Health* **2018**, *15*, 2474. [CrossRef]
59. Boersma, P.; Vaalburg, A.M.; Albers, M.; de Boer, C.J.M.; Gobbens, R.J.J. The Implications for Nursing Care of Frail Elderly with Limited Self-Management Abilities: A Cross-Sectional Study in the Netherlands. *Lupine Online J. Nurs. Healthc.* **2021**, *3*, 270–277.
60. Walston, J.; Buta, B.; Xue, Q.L. Frailty Screening and Interventions: Considerations for Clinical Practice. *Clin. Geriatr. Med.* **2018**, *34*, 25–38. [CrossRef] [PubMed]
61. Kojima, G.; Liljas, A.E.M.; Iliffe, S. Frailty syndrome: Implications and challenges for health care policy. *Risk Manag. Healthc. Policy* **2019**, *12*, 23–30. [CrossRef] [PubMed]
62. Kang, S.H.; Do, J.Y.; Lee, S.Y.; Kim, J.C. Effect of dialysis modality on frailty phenotype, disability, and health-related quality of life in maintenance dialysis patients. *PLoS ONE* **2017**, *12*, e0176814. [CrossRef] [PubMed]
63. National Institute for Health and Care Excellence. *Chronic Kidney Disease: Assessment and Management*; NICE Guideline [NG203]; NICE: London, UK, 2014. Available online: https://www.nice.org.uk/guidance/ng203 (accessed on 16 May 2022).
64. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int.* **2021**, *99*, S1–S87. [CrossRef]
65. Nixon, A.C.; Bampouras, T.M.; Gooch, H.J.; Young, H.M.L.; Finlayson, K.W.; Pendleton, N.; Mitra, S.; Brady, M.E.; Dhaygude, A.P. Home-based exercise for people living with frailty and chronic kidney disease: A mixed-methods pilot randomised controlled trial. *PLoS ONE* **2021**, *16*, e0251652. [CrossRef]
66. Young, H.M.L.; March, D.S.; Highton, P.J.; Graham-Brown, M.P.M.; Churchward, D.C.; Grantham, C.; Goodliffe, S.; Jones, W.; Cheung, M.M.; Greenwood, S.A.; et al. Exercise for people living with frailty and receiving haemodialysis: A mixed-methods randomised controlled feasibility study. *BMJ Open* **2020**, *10*, e041227. [CrossRef]
67. Sánchez-Tocino, M.L.; González-Parra, E.; Serrano, B.M.; Gracia-Iguacel, C.; de-Alba-Peñaranda, A.M.; López-González, A.; Olegario, M.G.; Ortíz, A.; Mas-Fontao, S. Evaluation of the impact of an intradialytic exercise program on sarcopenia in very elderly hemodialysis patients. *Clin. Kidney J.* **2022**, sfac046. [CrossRef]
68. Wilkinson, T.J.; Watson, E.L.; Xenophontos, S.; Gould, D.W.; Smith, A.C. The "Minimum Clinically Important Difference" in Frequently Reported Objective Physical Function Tests After a 12-Week Renal Rehabilitation Exercise Intervention in Nondialysis Chronic Kidney Disease. *Am. J. Phys. Med. Rehabil.* **2019**, *98*, 431–437. [CrossRef] [PubMed]
69. Suzuki, Y.; Kamiya, K.; Tanaka, S.; Hoshi, K.; Watanabe, T.; Harada, M.; Matsuzawa, R.; Shimoda, T.; Yamamoto, S.; Matsunaga, Y.; et al. Effects of electrical muscle stimulation in frail elderly patients during haemodialysis (DIAL): Rationale and protocol for a crossover randomised controlled trial. *BMJ Open* **2019**, *9*, e025389. [CrossRef] [PubMed]
70. Kidd, T.; Mold, F.; Jones, C.; Ream, E.; Grosvenor, W.; Sund-Levander, M.; Tingström, P.; Carey, N. What are the most effective interventions to improve physical performance in pre-frail and frail adults? A systematic review of randomised control trials. *BMC Geriatr.* **2019**, *19*, 184. [CrossRef] [PubMed]
71. De Labra, C.; Guimaraes-Pinheiro, C.; Maseda, A.; Lorenzo, T.; Millán-Calenti, J.C. Effects of physical exercise interventions in frail older adults: A systematic review of randomized controlled trials. *BMC Geriatr.* **2015**, *15*, 154. [CrossRef]
72. Giné-Garriga, M.; Roqué-Fíguls, M.; Coll-Planas, L.; Sitjà-Rabert, M.; Salvà, A. Physical exercise interventions for improving performance-based measures of physical function in community-dwelling, frail older adults: A systematic review and meta-analysis. *Arch. Phys. Med. Rehabil.* **2014**, *95*, 753–769. [CrossRef]
73. Puts, M.T.E.; Toubasi, S.; Andrew, M.K.; Ashe, M.C.; Ploeg, J.; Atkinson, E.; Ayala, A.P.; Roy, A.; Rodríguez Monforte, M.; Bergman, H.; et al. Interventions to prevent or reduce the level of frailty in community-dwelling older adults: A scoping review of the literature and international policies. *Age Ageing* **2017**, *46*, 383–392. [CrossRef]
74. Jadczak, A.D.; Makwana, N.; Luscombe-Marsh, N.; Visvanathan, R.; Schultz, T.J. Effectiveness of exercise interventions on physical function in community-dwelling frail older people: An umbrella review of systematic reviews. *JBI Database Syst. Rev. Implement. Rep.* **2018**, *16*, 752–775. [CrossRef]
75. Beckwée, D.; Delaere, A.; Aelbrecht, S.; Baert, V.; Beaudart, C.; Bruyere, O.; de Saint-Hubert, M.; Bautmans, I. Exercise Interventions for the Prevention and Treatment of Sarcopenia. A Systematic Umbrella Review. *J. Nutr. Health Aging* **2019**, *23*, 494–502. [CrossRef]
76. Sherrington, C.; Fairhall, N.J.; Wallbank, G.K.; Tiedemann, A.; Michaleff, Z.A.; Howard, K.; Clemson, L.; Hopewell, S.; Lamb, S.E. Exercise for preventing falls in older people living in the community. *Cochrane Database Syst Rev.* **2019**, *1*, Cd012424. [CrossRef]
77. Young, H.M.L.; March, D.S.; Graham-Brown, M.P.M.; Jones, A.W.; Curtis, F.; Grantham, C.S.; Churchward, D.R.; Highton, P.; Smith, A.C.; Singh, S.J.; et al. Effects of intradialytic cycling exercise on exercise capacity, quality of life, physical function and cardiovascular measures in adult haemodialysis patients: A systematic review and meta-analysis. *Nephrol. Dial. Transpl.* **2018**, *33*, 1436–1445. [CrossRef]

78. Greenwood, S.A.; Koufaki, P.; Macdonald, J.H.; Bulley, C.; Bhandari, S.; Burton, J.O.; Dasgupta, I.; Farrington, K.; Ford, I.; Kalra, P.A.; et al. Exercise programme to improve quality of life for patients with end-stage kidney disease receiving haemodialysis: The PEDAL RCT. *Health Technol. Assess.* **2021**, *25*, 1–52. [CrossRef] [PubMed]
79. Bennett, P.N.; Fraser, S.; Barnard, R.; Haines, T.; Ockerby, C.; Street, M.; Wang, W.C.; Daly, R. Effects of an intradialytic resistance training programme on physical function: A prospective stepped-wedge randomized controlled trial. *Nephrol. Dial. Transpl.* **2016**, *31*, 1302–1309. [CrossRef] [PubMed]
80. Hristea, D.; Deschamps, T.; Paris, A.; Lefrançois, G.; Collet, V.; Savoiu, C.; Ozenne, S.; Coupel, S.; Testa, A.; Magnard, J. Combining intra-dialytic exercise and nutritional supplementation in malnourished older haemodialysis patients: Towards better quality of life and autonomy. *Nephrology* **2016**, *21*, 785–790. [CrossRef] [PubMed]
81. Dogra, S.; Copeland, J.L.; Altenburg, T.M.; Heyland, D.K.; Owen, N.; Dunstan, D.W. Start with reducing sedentary behavior: A stepwise approach to physical activity counseling in clinical practice. *Patient Educ. Couns.* 2021, *in press*. [CrossRef] [PubMed]
82. Lerma, N.L.; Cho, C.C.; Swartz, A.M.; Miller, N.E.; Keenan, K.G.; Strath, S.J. Isotemporal Substitution of Sedentary Behavior and Physical Activity on Function. *Med. Sci. Sports Exerc.* **2018**, *50*, 792–800. [CrossRef] [PubMed]
83. Dempsey, P.C.; Biddle, S.J.H.; Buman, M.P.; Chastin, S.; Ekelund, U.; Friedenreich, C.M.; Katzmarzyk, P.T.; Leitzmann, M.F.; Stamatakis, E.; van der Ploeg, H.P.; et al. New global guidelines on sedentary behaviour and health for adults: Broadening the behavioural targets. *Int. J. Behav. Nutr. Phys. Act.* **2020**, *17*, 151. [CrossRef]
84. Da Silva Coqueiro, R.; de Queiroz, B.M.; Oliveira, D.S.; das Merces, M.C.; Oliveira Carneiro, J.A.; Pereira, R.; Fernandes, M.H. Cross-sectional relationships between sedentary behavior and frailty in older adults. *J Sports Med. Phys. Fit.* **2017**, *57*, 825–830. [CrossRef]
85. Wilkinson, T.J.; Clarke, A.L.; Nixon, D.G.D.; Hull, K.L.; Song, Y.; Burton, J.O.; Yates, T.; Smith, A.C. Prevalence and correlates of physical activity across kidney disease stages: An observational multicentre study. *Nephrol. Dial. Transpl.* **2021**, *36*, 641–649. [CrossRef]
86. Glavinovic, T.; Ferguson, T.; Komenda, P.; Rigatto, C.; Duhamel, T.A.; Tangri, N.; Bohm, C. CKD and Sedentary Time: Results From the Canadian Health Measures Survey. *Am. J. Kidney Dis.* **2018**, *72*, 529–537. [CrossRef]
87. Sheshadri, A.; Kittiskulnam, P.; Lai, J.C.; Johansen, K.L. Effect of a pedometer-based walking intervention on body composition in patients with ESRD: A randomized controlled trial. *BMC Nephrol.* **2020**, *21*, 100. [CrossRef]
88. Baggetta, R.; D'Arrigo, G.; Torino, C.; ElHafeez, S.A.; Manfredini, F.; Mallamaci, F.; Zoccali, C.; Tripepi, G.; Bolignano, D.; Lamberti, N.; et al. Effect of a home based, low intensity, physical exercise program in older adults dialysis patients: A secondary analysis of the EXCITE trial. *BMC Geriatr.* **2018**, *18*, 248. [CrossRef] [PubMed]
89. Tawney, K.W.; Tawney, P.J.; Hladik, G.; Hogan, S.L.; Falk, R.J.; Weaver, C.; Moore, D.T.; Lee, M.Y. The life readiness program: A physical rehabilitation program for patients on hemodialysis. *Am. J. Kidney Dis.* **2000**, *36*, 581–591. [CrossRef] [PubMed]
90. Lyden, K.; Boucher, R.; Wei, G.; Zhou, N.; Christensen, J.; Chertow, G.M.; Greene, T.; Beddhu, S. Targeting Sedentary Behavior in CKD: A Pilot and Feasibility Randomized Controlled Trial. *Clin. J. Am. Soc. Nephrol.* **2021**, *16*, 717–726. [CrossRef] [PubMed]
91. Van Loon, I.N.; Goto, N.A.; Boereboom, F.T.J.; Bots, M.L.; Hoogeveen, E.K.; Gamadia, L.; van Bommel, E.F.H.; van de Ven, P.J.G.; Douma, C.E.; Vincent, H.H.; et al. Geriatric Assessment and the Relation with Mortality and Hospitalizations in Older Patients Starting Dialysis. *Nephron* **2019**, *143*, 108–119. [CrossRef]
92. Chou, H.-Y.; Chen, S.-C.; Yen, T.-H.; Han, H.-M. Effect of a Virtual Reality-Based Exercise Program on Fatigue in Hospitalized Taiwanese End-Stage Renal Disease Patients Undergoing Hemodialysis. *Clin. Nurs. Res.* **2020**, *29*, 368–374. [CrossRef]
93. Wytsma-Fisher, K.; Mustata, S.; Cowan, T.; Ester, M.; Culos-Reed, S.N. A Physical Activity Intervention Feasibility Study for Kidney Inpatients: A Basic Research Protocol. *Can. J. Kidney Health Dis.* **2021**, *8*, 2054358120987052. [CrossRef]
94. Wynter-Blyth, V.; Moorthy, K. Prehabilitation: Preparing patients for surgery. *BMJ* **2017**, *358*, j3702. [CrossRef]
95. Willingham, F.C.; Speelman, I.; Hamilton, J.; von Fragstein, G.; Shaw, S.; Taal, M.W. Feasibility and effectiveness of pre-emptive rehabilitation in persons approaching dialysis (PREHAB). *J. Ren. Care* **2019**, *45*, 9–19. [CrossRef]
96. Lorenz, E.C.; Hickson, L.J.; Weatherly, R.M.; Thompson, K.L.; Walker, H.A.; Rasmussen, J.M.; Stewart, T.L.; Garrett, J.K.; Amer, H.; Kennedy, C.C. Protocolized exercise improves frailty parameters and lower extremity impairment: A promising prehabilitation strategy for kidney transplant candidates. *Clin. Transpl.* **2020**, *34*, e14017. [CrossRef]
97. McAdams-DeMarco, M.A.; Ying, H.; Van Pilsum Rasmussen, S.; Schrack, J.; Haugen, C.E.; Chu, N.M.; González Fernández, M.; Desai, N.; Walston, J.D.; Segev, D.L. Prehabilitation prior to kidney transplantation: Results from a pilot study. *Clin. Transpl.* **2019**, *33*, e13450. [CrossRef]
98. Pérez-Sáez, M.J.; Morgado-Pérez, A.; Faura, A.; Muñoz-Redondo, E.; Gárriz, M.; Muns, M.D.; Nogués, X.; Marco, E.; Pascual, J. The FRAILMar Study Protocol: Frailty in Patients With Advanced Chronic Kidney Disease Awaiting Kidney Transplantation. A Randomized Clinical Trial of Multimodal Prehabilitation. *Front. Med.* **2021**, *8*, 647. [CrossRef] [PubMed]
99. Barawid, E.; Covarrubias, N.; Tribuzio, B.; Liao, S. The benefits of rehabilitation for palliative care patients. *Am. J. Hosp. Palliat. Care* **2015**, *32*, 34–43. [CrossRef] [PubMed]
100. Ramanjulu, R. Palliative Rehabilitation: The Essence of Personalized Care. *Indian J. Palliat. Care* **2020**, *26*, 399–400. [CrossRef] [PubMed]
101. Lorenzo-López, L.; Maseda, A.; de Labra, C.; Regueiro-Folgueira, L.; Rodríguez-Villamil, J.L.; Millán-Calenti, J.C. Nutritional determinants of frailty in older adults: A systematic review. *BMC Geriatr.* **2017**, *17*, 108. [CrossRef]

102. Ni Lochlainn, M.; Cox, N.J.; Wilson, T.; Hayhoe, R.P.G.; Ramsay, S.E.; Granic, A.; Isanejad, M.; Roberts, H.C.; Wilson, D.; Welch, C.; et al. Nutrition and Frailty: Opportunities for Prevention and Treatment. *Nutrients* **2021**, *13*, 2349. [CrossRef] [PubMed]
103. Kim, J.C.; Kalantar-Zadeh, K.; Kopple, J.D. Frailty and protein-energy wasting in elderly patients with end stage kidney disease. *J. Am. Soc. Nephrol.* **2013**, *24*, 337–351. [CrossRef] [PubMed]
104. Carrero, J.J.; Stenvinkel, P.; Cuppari, L.; Ikizler, T.A.; Kalantar-Zadeh, K.; Kaysen, G.; Mitch, W.E.; Price, S.R.; Wanner, C.; Wang, A.Y.; et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: A consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). *J. Ren. Nutr.* **2013**, *23*, 77–90. [CrossRef]
105. Byham-Gray, L.; Burrowes, J.D.; Chertow, G.M. *Nutrition in Kidney Disease*, 3rd ed.; Springer International Publishing: Cham, Switzerland, 2020.
106. NHS RightCare. *NHS RightCare: Frailty Toolkit*; National Institute for Health and Care Excellence: London, UK, 2019. Available online: https://www.england.nhs.uk/rightcare/wp-content/uploads/sites/40/2019/07/frailty-toolkit-june-2019-v1.pdf (accessed on 16 May 2022).
107. Wright, M.; Southcott, E.; MacLaughlin, H.; Wineberg, S. Clinical practice guideline on undernutrition in chronic kidney disease. *BMC Nephrol.* **2019**, *20*, 370. [CrossRef]
108. Ikizler, T.A.; Burrowes, J.D.; Byham-Gray, L.D.; Campbell, K.L.; Carrero, J.-J.; Chan, W.; Fouque, D.; Friedman, A.N.; Ghaddar, S.; Goldstein-Fuchs, D.J.; et al. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. *Am. J. Kidney Dis.* **2020**, *76*, S1–S107. [CrossRef]
109. Dent, E.; Morley, J.E.; Cruz-Jentoft, A.J.; Woodhouse, L.; Rodríguez-Mañas, L.; Fried, L.P.; Woo, J.; Aprahamian, I.; Sanford, A.; Lundy, J.; et al. Physical Frailty: ICFSR International Clinical Practice Guidelines for Identification and Management. *J. Nutr. Health Aging* **2019**, *23*, 771–787. [CrossRef]
110. Moraes, M.B.; Avgerinou, C.; Fukushima, F.B.; Vidal, E.I.O. Nutritional interventions for the management of frailty in older adults: Systematic review and meta-analysis of randomized clinical trials. *Nutr. Rev.* **2021**, *79*, 889–913. [CrossRef] [PubMed]
111. Dedeyne, L.; Deschodt, M.; Verschueren, S.; Tournoy, J.; Gielen, E. Effects of multi-domain interventions in (pre)frail elderly on frailty, functional, and cognitive status: A systematic review. *Clin. Interv. Aging* **2017**, *12*, 873–896. [CrossRef] [PubMed]
112. Anderson, B.M.; Dutton, M.; Day, E.; Jackson, T.A.; Ferro, C.J.; Sharif, A. Frailty Intervention Trial iN End-Stage patientS on haemodialysis (FITNESS): Study protocol for a randomised controlled trial. *Trials* **2018**, *19*, 457. [CrossRef] [PubMed]
113. Chilcot, J.; Guirguis, A.; Friedli, K.; Almond, M.; Day, C.; Da Silva-Gane, M.; Davenport, A.; Fineberg, N.A.; Spencer, B.; Wellsted, D.; et al. Depression Symptoms in Haemodialysis Patients Predict All-Cause Mortality but Not Kidney Transplantation: A Cause-Specific Outcome Analysis. *Ann. Behav. Med.* **2018**, *52*, 1–8. [CrossRef]
114. Tsai, Y.C.; Chiu, Y.W.; Hung, C.C.; Hwang, S.J.; Tsai, J.C.; Wang, S.L.; Lin, M.Y.; Chen, H.C. Association of symptoms of depression with progression of CKD. *Am. J. Kidney Dis.* **2012**, *60*, 54–61. [CrossRef]
115. Farrokhi, F.; Abedi, N.; Beyene, J.; Kurdyak, P.; Jassal, S.V. Association between depression and mortality in patients receiving long-term dialysis: A systematic review and meta-analysis. *Am. J. Kidney Dis.* **2014**, *63*, 623–635. [CrossRef]
116. Palmer, S.; Vecchio, M.; Craig, J.C.; Tonelli, M.; Johnson, D.W.; Nicolucci, A.; Pellegrini, F.; Saglimbene, V.; Logroscino, G.; Fishbane, S.; et al. Prevalence of depression in chronic kidney disease: Systematic review and meta-analysis of observational studies. *Kidney Int.* **2013**, *84*, 179–191. [CrossRef]
117. Soysal, P.; Veronese, N.; Thompson, T.; Kahl, K.G.; Fernandes, B.S.; Prina, A.M.; Solmi, M.; Schofield, P.; Koyanagi, A.; Tseng, P.T.; et al. Relationship between depression and frailty in older adults: A systematic review and meta-analysis. *Ageing Res. Rev.* **2017**, *36*, 78–87. [CrossRef]
118. Gregg, L.P.; Carmody, T.; Le, D.; Martins, G.; Trivedi, M.; Hedayati, S.S. A Systematic Review and Meta-Analysis of Depression and Protein-Energy Wasting in Kidney Disease. *Kidney Int. Rep.* **2019**, *5*, 318–330. [CrossRef]
119. Soni, R.K.; Weisbord, S.D.; Unruh, M.L. Health-related quality of life outcomes in chronic kidney disease. *Curr. Opin. Nephrol. Hypertens.* **2010**, *19*, 153–159. [CrossRef]
120. Sy, J.; McCulloch, C.E.; Johansen, K.L. Depressive symptoms, frailty, and mortality among dialysis patients. *Hemodial. Int.* **2019**, *23*, 239–246. [CrossRef] [PubMed]
121. Konel, J.M.; Warsame, F.; Ying, H.; Haugen, C.E.; Mountford, A.; Chu, N.M.; Crews, D.C.; Desai, N.M.; Garonzik-Wang, J.M.; Walston, J.D.; et al. Depressive symptoms, frailty, and adverse outcomes among kidney transplant recipients. *Clin. Transplant.* **2018**, *32*, e13391. [CrossRef] [PubMed]
122. Szeto, C.C.; Chan, G.C.; Ng, J.K.; Chow, K.M.; Kwan, B.C.; Cheng, P.M.; Kwong, V.W.; Law, M.C.; Leung, C.B.; Li, P.K. Depression and Physical Frailty Have Additive Effect on the Nutritional Status and Clinical Outcome of Chinese Peritoneal Dialysis. *Kidney Blood Press. Res.* **2018**, *43*, 914–923. [CrossRef]
123. Chan, G.C.-K.; Ng, J.K.-C.; Chow, K.-M.; Kwan, B.C.-H.; Kwong, V.W.-K.; Pang, W.-F.; Cheng, P.M.-S.; Law, M.-C.; Leung, C.-B.; Li, P.K.-T.; et al. Depression does not predict clinical outcome of Chinese peritoneal Dialysis patients after adjusting for the degree of frailty. *BMC Nephrol.* **2020**, *21*, 329. [CrossRef] [PubMed]
124. Zhang, B.; Zhao, P.; Wang, H.; Wang, S.; Wei, C.; Gao, F.; Liu, H. Factors associated with frailty in kidney transplant recipients: A cross-sectional study. *J. Ren. Care* **2021**. [CrossRef] [PubMed]
125. Hoogendijk, E.O.; van Hout, H.P.; van der Horst, H.E.; Frijters, D.H.; Dent, E.; Deeg, D.J.; Huisman, M. Do psychosocial resources modify the effects of frailty on functional decline and mortality? *J. Psychosom. Res.* **2014**, *77*, 547–551. [CrossRef]

126. Barnett, K.; Mercer, S.W.; Norbury, M.; Watt, G.; Wyke, S.; Guthrie, B. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *Lancet* **2012**, *380*, 37–43. [CrossRef]
127. Maruthappu, M.; Sood, H.S.; Keogh, B. The NHS Five Year Forward View: Transforming care. *Br. J. Gen. Pract.* **2014**, *64*, 635. [CrossRef]
128. Soobiah, C.; Cooper, M.; Kishimoto, V.; Bhatia, R.; Scott, T.; Maloney, S.; Larsen, D.; Wijeysundera, H.; Zelmer, J.; Steele Gray, C.; et al. Identifying optimal frameworks to implement or evaluate digital health interventions: A scoping review protocol. *BMJ Open* **2020**, *10*, e037643. [CrossRef]
129. WHO. *WHO Guideline: Recommendations on Digital Interventions for Health System Strengthening*; World Health Organization: Geneva, Switzerland, 2019. Available online: https://www.who.int/publications/i/item/9789241550505 (accessed on 16 May 2022).
130. Linn, N.; Goetzinger, C.; Regnaux, J.-P.; Schmitz, S.; Dessenne, C.; Fagherazzi, G.; Aguayo, G.A. Digital Health Interventions among People Living with Frailty: A Scoping Review. *J. Am. Med. Dir. Assoc.* **2021**, *22*, 1802–1812. [CrossRef]
131. Romeo, A.; Edney, S.; Plotnikoff, R.; Curtis, R.; Ryan, J.; Sanders, I.; Crozier, A.; Maher, C. Can Smartphone Apps Increase Physical Activity? Systematic Review and Meta-Analysis. *J. Med. Internet Res.* **2019**, *21*, e12053. [CrossRef] [PubMed]
132. Brickwood, K.-J.; Watson, G.; O'Brien, J.; Williams, A.D. Consumer-Based Wearable Activity Trackers Increase Physical Activity Participation: Systematic Review and Meta-Analysis. *JMIR mHealth uHealth* **2019**, *7*, e11819. [CrossRef] [PubMed]
133. Lobelo, F.; Kelli, H.M.; Tejedor, S.C.; Pratt, M.; McConnell, M.V.; Martin, S.S.; Welk, G.J. The Wild Wild West: A Framework to Integrate mHealth Software Applications and Wearables to Support Physical Activity Assessment, Counseling and Interventions for Cardiovascular Disease Risk Reduction. *Prog. Cardiovasc. Dis.* **2016**, *58*, 584–594. [CrossRef] [PubMed]
134. Muellmann, S.; Forberger, S.; Möllers, T.; Bröring, E.; Zeeb, H.; Pischke, C.R. Effectiveness of eHealth interventions for the promotion of physical activity in older adults: A systematic review. *Prev. Med.* **2018**, *108*, 93–110. [CrossRef] [PubMed]
135. Yerrakalva, D.; Yerrakalva, D.; Hajna, S.; Griffin, S. Effects of Mobile Health App Interventions on Sedentary Time, Physical Activity, and Fitness in Older Adults: Systematic Review and Meta-Analysis. *J. Med. Internet Res.* **2019**, *21*, e14343. [CrossRef]
136. McGarrigle, L.; Boulton, E.; Todd, C. Map the apps: A rapid review of digital approaches to support the engagement of older adults in strength and balance exercises. *BMC Geriatr.* **2020**, *20*, 483. [CrossRef]
137. Antoun, J.; Brown, D.J.; Jones, D.J.W.; Sangala, N.C.; Lewis, R.J.; Shepherd, A.I.; McNarry, M.A.; Mackintosh, K.A.; Mason, L.; Corbett, J.; et al. Understanding the Impact of Initial COVID-19 Restrictions on Physical Activity, Wellbeing and Quality of Life in Shielding Adults with End-Stage Renal Disease in the United Kingdom Dialysing at Home versus In-Centre and Their Experiences with Telemedicine. *Int. J. Environ. Res. Public Health* **2021**, *18*, 3144. [CrossRef]
138. Kidney Beam. Available online: https://beamfeelgood.com/kidney%20disease2020 (accessed on 19 January 2022).
139. Mayes, J.; Billany, R.E.; Vadaszy, N.; Young, H.M.L.; Castle, E.M.; Bishop, N.C.; Bramham, K.; Nixon, A.C.; Wilkinson, T.J.; Hamilton, A.; et al. The rapid development of a novel kidney-specific digital intervention for self-management of physical activity and emotional wellbeing during the COVID-19 pandemic and beyond: Kidney Beam. *Clin. Kidney J.* **2021**, *15*, 571–573. [CrossRef]
140. Weber, M.B.; Ziolkowski, S.; Bootwala, A.; Bienvenida, A.; Anand, S.; Lobelo, F. Perceptions of physical activity and technology enabled exercise interventions among people with advanced chronic kidney disease: A qualitative study. *BMC Nephrol.* **2021**, *22*, 373. [CrossRef]
141. Rampersad, C.; Darcel, J.; Harasemiw, O.; Brar, R.S.; Komenda, P.; Rigatto, C.; Prasad, B.; Bohm, C.; Tangri, N. Change in Physical Activity and Function in Patients with Baseline Advanced Nondialysis CKD. *Clin. J. Am. Soc. Nephrol.* **2021**, *16*, 1805. [CrossRef]
142. Gobeil-Lavoie, A.P.; Chouinard, M.C.; Danish, A.; Hudon, C. Characteristics of self-management among patients with complex health needs: A thematic analysis review. *BMJ Open* **2019**, *9*, e028344. [CrossRef] [PubMed]
143. Hanlon, P.; Nicholl, B.I.; Jani, B.D.; Lee, D.; McQueenie, R.; Mair, F.S. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: A prospective analysis of 493 737 UK Biobank participants. *Lancet Public Health* **2018**, *3*, e323. [CrossRef]
144. Lindsay, S. The influence of childhood poverty on the self-management of heart disease in later life. *Res. Sociol. Health Care* **2009**, *27*, 161–183. [CrossRef]
145. Anand, S.; Johansen, K.L.; Kurella Tamura, M. Aging and chronic kidney disease: The impact on physical function and cognition. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **2014**, *69*, 315–322. [CrossRef]
146. Mallappallil, M.; Friedman, E.A.; Delano, B.G.; McFarlane, S.I.; Salifu, M.O. Chronic kidney disease in the elderly: Evaluation and management. *Clin. Pract.* **2014**, *11*, 525–535. [CrossRef]
147. Beetham, K.S.; Krishnasamy, R.; Stanton, T.; Sacre, J.W.; Douglas, B.; Isbel, N.M.; Coombes, J.S.; Howden, E.J. Effect of a 3-Year Lifestyle Intervention in Patients with Chronic Kidney Disease: A Randomized Clinical Trial. *J. Am. Soc. Nephrol.* **2022**, *33*, 431. [CrossRef]