A COMPARISON OF FRAILTY TOOLS IN HAEMODIALYSIS: A PROSPECTIVE COHORT STUDY

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Abstract

Frailty is a syndrome of increased vulnerability to poor resolution of homeostasis after stressor event, and is associated with poor patient outcomes such as mortality, hospitalisation, and disability, including in haemodialysis recipients. It has, however, been subject to heterogenous reporting. Commonly cited frailty tools include the Frailty Phenotype (FP), Frailty Index (FI), Edmonton Frail Scale (EFS), and Clinical Frailty Scale (CFS). Each of these utilises different methodologies to determine frailty, and it is not known how they relate to one another in haemodialysis recipients.

The aims of this thesis are to explore frailty by each of these tools in prevalent haemodialysis recipients, both in relationship to one another, and their association with important patient-centred outcomes.

In our single-centre prospective cohort of prevalent (>3-months) haemodialysis recipients, we observed that correlations between frailty tools are modest, and agreement between them upon frailty status was weak. Each of the frailty tools associated with mortality hazard during follow-up. The CFS was the only tool to associate with rates of admission, but equally was the only tool not to associate with length of stay. We identified variable association between frailty tools and ultrasound-derived sarcopenia, and have highlighted that sarcopenia appears to be differentially expressed between males and females receiving haemodialysis. We also identified a novel patient-reported outcome – change in health over the past year – that modulates

the association of frailty with mortality, and independently associates with hospitalisation. We propose a notional model of how this may be integrated into frailty assessment for haemodialysis recipients. We have also demonstrated that depression and cognitive impairment are associated with frailty in haemodialysis recipients, and that admissions amongst haemodialysis recipients are highest when cognitive and frailty scores are most discordant.

Frailty is associated with many poor patient outcomes in these analyses, but different frailty tools may be identifying different frailty subtypes. Consensus is required on the optimal frailty tool in haemodialysis recipients to allow comparison and extrapolation of findings across patient cohorts. The Clinical Frailty Scale likely represents the optimal tool in terms of association with negative outcomes and simplicity of use. An evidence-based frailty intervention is urgently required for haemodialysis recipients.

Acknowledgements

Firstly, I wish to thank my ever-patient wife Miriam and my extended family for acquiescing to my near-constant need to be working on this PhD.

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I must extend special thanks to Dr Sharif for his wise counsel on all matters of research, clinical medicine, careers, ethics, philosophy, and politics, although I probably won't follow his lead on the latter. Dr Sharif was in many ways the ideal PhD supervisor; he was always available to offer guidance when asked but would otherwise leave me to it to work it out for myself. This meant I gained the maximum exposure to all aspects of

research design, delivery, analysis, and dissemination, and have gained a host of new skills as a result.

I am extremely grateful to the late Sr Mary Dutton for her guidance and support, especially in the early design phase of the FITNESS study. Sr Dutton was unfailingly generous with her time, and in sharing the wisdom of her hard-earned experience in renal research. Through her insights, we shaped the FITNESS study to be as pragmatic as possible. Sr Dutton was fearsomely protective of research fellows, formidable in all the right ways, and had intimate knowledge of the practical and political considerations of research in a large organisation such as UHB. As such, her counsel saved many hours of my time. Furthermore, her critical insight into the trial protocol and ethics submissions were fundamental to the smooth passage of FITNESS through the relevant ethical and regulatory consents. I will forever be grateful to her, and was deeply saddened to hear of her passing.

Finally, none of this would be possible without the kind study participants who gave their time and energy to be a part of FITNESS. Haemodialysis recipients receive a raw deal when it comes to research. Due to their thrice weekly haemodialysis commitment, transport issues, and in many cases longstanding ill-health, recruiting haemodialysis recipients to prospective research is often said to be challenging. This dogma can be challenged the fact that by my estimate, >50% of prevalent haemodialysis recipients under UHB willingly gave their time to FITNESS. Sadly, as we will learn, many of those who joined this project have now passed away. A common refrain from those who

consented was “I’ll do anything that has a chance to make things better for future dialysis patients”. This always seemed like rather a lofty goal, but I hope that this body of work may make a small positive difference to haemodialysis research.

Extent of Personal Contribution

The work in this thesis was carried out by myself with the following exceptions. Dr Adnan Sharif had the original concept, with subsequent development by Dr Sharif and myself. This process was supported by Dr Thomas Jackson, Dr Edward Day, and Sister Mary Dutton. I obtained Research Ethics Committee and study sponsor approvals for the study with important contributions from Dr Sharif and Sister Mary Dutton. Grant funding was applied for and obtained by myself and Dr Adnan Sharif from Queen Elizabeth Hospital Charities (Fund Number 17-3-886). I obtained all study amendments, maintained all paper and electronic study and regulatory records, and completed sponsor-requested study audits.

I designed, wrote the code for, and maintained the FITNESS database on REDCap. Mr Zaib Khawaja provided technical support throughout this process.

Participants were screened and recruited by me, with important contributions from Dr Gonzalo Correa. Baseline data collections were performed by me, with contributions – under my supervision – from Dr Correa, Dr Muhammad Qasim, and Dr Sharif.

The ultrasound protocol was heavily based upon one developed by Dr Daisy Wilson in the Institute of Inflammation and Ageing. I co-ordinated procurement of the ultrasound scanner and consumables. All ultrasound scans were performed and interpreted by me,

with a few training scans performed by Dr Qasim and Dr Correa under my direct supervision.

Electronic patient record data were captured by Ms Felicity Evison and Ms Suzy Gallier in University Hospitals Birmingham Department of Health Informatics. All subsequent data handling, analysis and interpretation were performed by me, under supervision from Dr Sharif and with the advice and guidance of Mr James Hodson and Ms Evison.

Dr Adnan Sharif, Dr Thomas Jackson, and Professor Charles Ferro provided advice, guidance and critical appraisal throughout all manuscript preparations and submissions. Dr Daisy Wilson provided further critical appraisal, expert insight and data interpretation for the submissions and chapters upon ultrasound quadriceps assessment.

Abbreviations

95% C.I.	95% Confidence Interval
AAV	ANCA-associated vasculitis
ADL	Activities of Daily Living
AE	Adverse Event
AHP	Allied Health Professional
AKI	Acute Kidney Injury
ANCA	Anti-Neutrophil Cytoplasmic Antibody
BAME	Black, Asian, and Minority Ethnic
BATT	Bilateral Anterior Thigh Thickness
BDI	Beck Depression Inventory
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
CFS	Clinical Frailty Scale
CFS-MDT	Clinical Frailty Scale from Multi-Disciplinary Team
CGA	Comprehensive Geriatric Assessment
CI	Cognitive Impairment
CKD	Chronic Kidney Disease
cm-RCT	Cohort Multiple Randomised Controlled Trial
COVID-19	Coronavirus Disease – 19
CT	Computed Tomography
DEXA	Dual Energy X-ray Absorptiometry

EFS	Edmonton Frailty Scale
eGFR	Estimated Glomerular Filtration Rate
EPR	Electronic Patient Record
EQ-5D	EuroQol EQ-5D-3L Score
ESKD	End-Stage Kidney Disease
FI	Frailty Index
FITNESS	Frailty Intervention Trial in End-Stage Patients on Haemodialysis
FP	Frailty Phenotype
FSGS	Focal Segmental Glomerulosclerosis
GPPAQ	General Practice Physical Activity Questionnaire
HD	Haemodialysis
HES	Hospital Episode Statistics
HR	Hazard Ratio
HRA	Health Research Authority
HRQOL	Health-Related Quality of Life
IADL	Instrumental Activities of Daily Living
ICD-10	International Classification of Diseases – 10
IgA	IgA Nephropathy
IMD	Indices of Multiple Deprivation
IQR	Inter-Quartile Range
IRR	Incidence Rate Ratio
LMM	Low Muscle Mass

MACE	Major Adverse Cardiovascular Events
MDT	Multi-Disciplinary Team
MI	Myocardial Infarction
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NLM	Node Link Mapping
ONS	Office of National Statistics
OR	Odds Ratio
PAI	Physical Activity Index
PHQ-9	Patient Health Questionnaire – 9
PIL	Patient Information Leaflet
PKD	Polycystic Kidney Disease
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PVD	Peripheral Vascular Disease
QA	Quality Assurance
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SBNT	Social Behaviour and Network Therapy
SF-12	Short Form Questionnaire - 12

STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UK	United Kingdom
US	United States
USS	Ultrasound
WTE	Whole Time Equivalent

ABSTRACT I

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Chapter 1:
General Introduction

1.1 Chronic Kidney Disease

Chronic Kidney Disease (CKD) is defined as reduced kidney function for at least 3-months, with an estimated glomerular filtration rate (eGFR) of <60ml/min/$m^{2,}$, or markers of kidney damage (typically urinary albumin: creatinine ratio [ACR]), or both.[1] It affects 9.1% of the population worldwide;[2] in the United Kingdom (UK), prevalence of CKD stages 3-5 is estimated at between 4% and 8.5%.[3,4] The histological hallmarks of advanced CKD include glomerulosclerosis, interstitial fibrosis, and tubular atrophy, leading to reduced functional nephron mass and poorer filtration capability.[1] This results in the biochemical hallmark of advanced CKD: the accumulation of uraemic solutes, leading to a clinical syndrome that includes chronic inflammation, cardiovascular calcification, increased bleeding risk, and mineral bone disease (CKD-MBD), amongst others.[5] CKD is associated with poorer health-related quality of life (HRQOL) and reduced survival, including a greatly increased risk of cardiovascular disease, cancer, infection, and diabetes mellitus.[6,7]

1.2 End-Stage Kidney Disease and Renal Replacement Therapy

End-stage kidney disease (ESKD) is commonly thought of as the point at which kidney function has failed, though a unifying definition of what exactly this means remains elusive. Most would consider the onset of chronic renal replacement therapy (RRT) as defining ESKD, though there is debate over what represents “chronic”. Furthermore, there is legitimate uncertainty about how to define ESKD in the context of maximal supportive – also known as “conservative” or “palliative” – kidney care, where a renal replacement therapy is either not offered or declined.[8] A review of ESKD falls outside

the scope of this study, so we shall instead turn our attention to the prevalence of ESKD and RRT in the UK.

According to the Renal Registry in the UK, 7945 people started RRT in 2019. Of these 71.6% started on haemodialysis, 20.1% on peritoneal dialysis (PD), and 8.3% received a pre-emptive kidney transplant.[9] As we can see in Figure 1-1, prevalence of RRT has risen persistently over the past decade, so there are around 1300 people receiving RRT per million people in the UK.

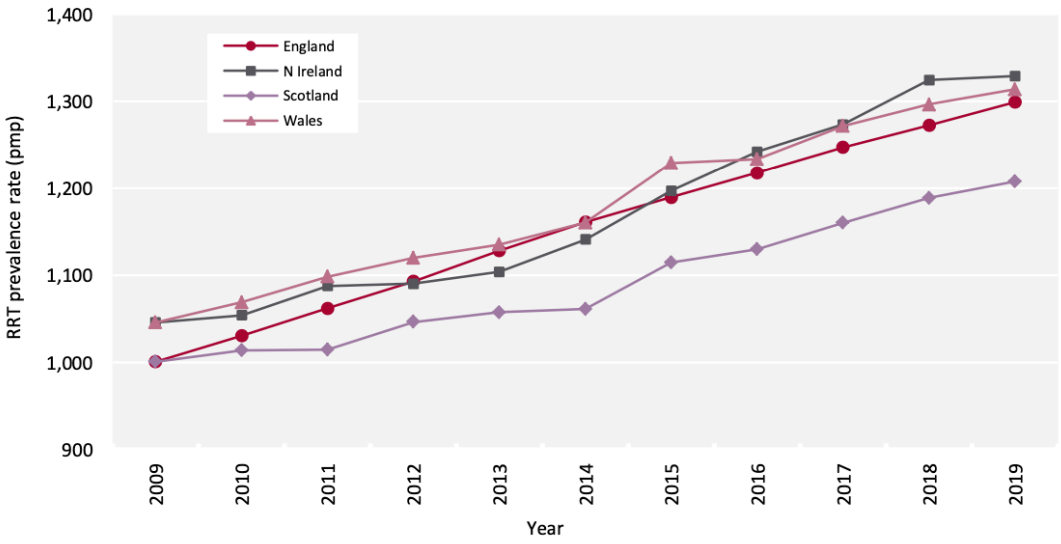


Figure 1-1: Increasing prevalence of renal replacement therapy in the UK From UK Renal Registry 23rd Annual Report.[9]

Figure 1-2 demonstrates that this expansion in RRT prevalence is largely driven by increases in prevalence amongst middle and older age groups, with RRT in persons < 45-years static over the same time period.

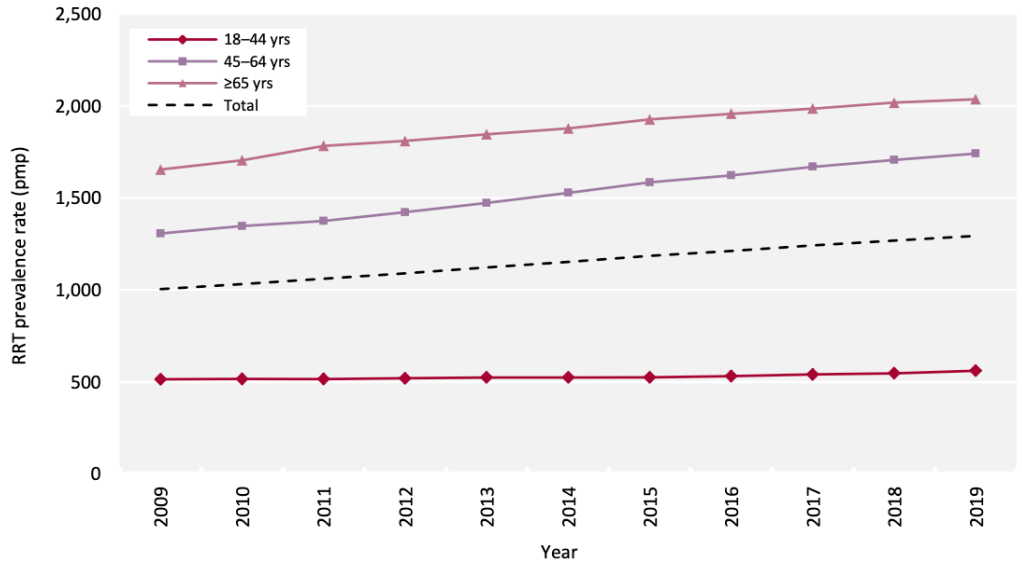


Figure 1-2: Adult prevalence of RRT by age group between 2009 and 2019. From UK Renal Registry 23rd Annual Report [9]

Figure 1-3 shows that haemodialysis is the second most prevalent RRT modality after transplantation, and all modalities have increased in prevalence over the past decade.

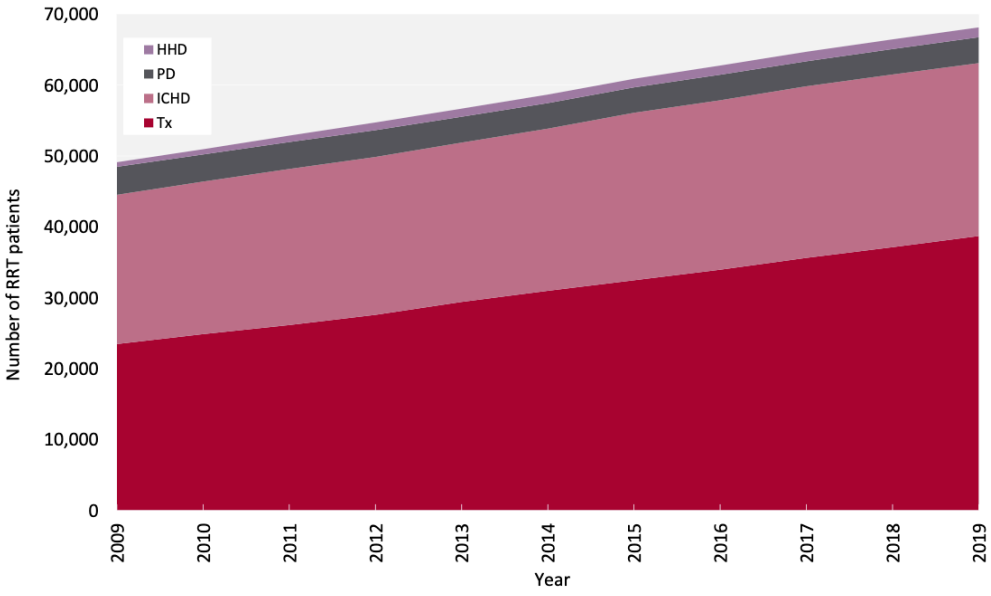


Figure 1-3: Prevalence of RRT by modality between 2009 and 2019.From UK Renal Registry 23rd Annual Report [9]

1.3 Haemodialysis

Haemodialysis is the process of removing accumulated solutes and fluid from blood via a semi-permeable membrane via a combination of diffusion and convection.[10] A minimum of 12 hours per week is considered standard practice, typically delivered three times per week for four hours.[11] The majority of haemodialysis is delivered "in centre", in a hospital or clinic setting on either Mondays, Wednesdays, and Fridays, or alternatively Tuesdays, Thursdays and Saturdays. A minority of haemodialysis recipients are managed with Home Haemodialysis (HHD), with a haemodialysis machine in their home for personal use.[9] Whilst haemodialysis can remove excess fluid and toxic solutes, there are many functions of the kidney that cannot be replaced with dialysis. These include endocrine functions, such as activation of 25-hydroxyvitamin D (25(OH)D) and production of Erythropoietin (EPO), crucial in bone metabolism and bone marrow signalling respectively. Secondary hyperparathyroidism is common amongst people living with ESKD, and this is typically managed with active vitamin D replacement and/or direct parathyroid suppression or parathyroidectomy.[12] Anaemia is another common complication of ESKD, and haemodialysis recipients typically require high dose IV iron regularly alongside exogenous Erythropoietin Stimulating Agents to maintain adequate circulating haemoglobin.[13] Blood pressure derangement is another common feature of ESKD, due to a combination of volume overload, renin angiotensin aldosterone system dysfunction, and vascular calcification.[14]

The haemodialysis population also lives with a high burden of comorbidity – over and above the original cause for their kidney failure. Mortality amongst haemodialysis

recipients is high; the Renal Registry reported that prevalent RRT recipients an annual mortality relative risk of 6.6 overall, but with much higher relative risk amongst younger patients compared with age-matched peers.[9] Normalised to age 60, a haemodialysis recipient is estimated to have a 12.3% annual mortality risk.[9] Furthermore, whilst standardised mortality has been falling in those with ESKD, still 25.9% of new starters to RRT (excluding transplantation) die within 3 years.[15]

We must interrogate why this may be the case. To this end, there has been increasing interest in investigating the underlying mechanisms behind the high mortality burden in this patient group. A longstanding anecdotal refrain amongst nephrologist has been that haemodialysis recipients are – almost by definition – more frail than their counterparts. Perhaps due to this suspicion, or the increasing prevalence of frailty research in other areas of medicine, there is now increasing interest in a formal assessment of frailty in dialysis recipients, as well as in CKD and transplantation.

1.4 What is Frailty?

Frailty is an emerging concept within medicine, typically described amongst older adults. Frailty is a syndrome of increased vulnerability to poor resolution of homeostasis after a stressor event,[16] associated with negative outcomes including mortality, hospitalisation and disability.[17]

Frailty in older adults is associated with a host of poor health outcomes, including mortality, depression, worsening mobility, ADL disability, hospitalisation, post-operative

complications, post-operative length of stay, falls and fractures, and increased care needs[18-29]. Frailty is typically considered to be a syndrome of progressive decline,[30] and progression of frailty with age is also associated with mortality risk.[31]

The gold standard frailty diagnostic tool is the Comprehensive Geriatric Assessment (CGA).[32] This is an assessment, treatment plan, and review delivered by a specialist multi-disciplinary team (MDT). It comprises iterative assessments across multiple domains, including physical and mental health conditions, functional abilities (for example ADLs/IADLs), social support, and environmental considerations.[33] Originally operationalised as an inpatient tool, the CGA has been shown to reduce mortality and maintain functional independence,[34,35] and there is increasing evidence of its efficacy in the outpatient setting.[33]

The CGA does however come with significant cost and logistical challenges, hence it is not commonly used in research practice to identify frailty. Instead, an ever-increasing number of frailty screening and diagnostic tools have been proposed. These include the Frailty Phenotype (FP),[19] Frailty Index (FI),[36,37] Edmonton Frail Scale (EFS),[38] and Clinical Frailty Scale (CFS).[27] Between them, these represent competing paradigms of how to approach frailty. The Frailty Phenotype considers frailty as a physical syndrome, whereas the Frailty Index – and by extension the Edmonton Frailty Scale and Clinical Frailty Scale – considers frailty as an accumulation of deficits. We shall discuss each in turn, before later considering their use in renal clinical and research practice.

1.4.1 Frailty Phenotype

The Frailty Phenotype proposed by Fried and colleagues described frailty as any three of slowness, weakness, exhaustion, low physical activity, and weight loss [19]. This model is attractive as it distinguishes frailty from disability and comorbidity, allowing study of frailty as a distinct entity whilst acknowledging the interplay between these important geriatric syndromes.[39] Simplicity is another important feature, helping it become the predominant frailty measure used in research practice.[40] However, its face validity is hampered by the relatively low number of variables, and a focus upon musculoskeletal determinants of frailty. As such, it is sometimes referred to as the "Physical Frailty Phenotype". Many consider frailty to be a multidimensional syndrome, including psychological and social dimensions, and would criticise the FP for the lack of provision for these important factors.[41-43] Despite these limitations, the Frailty Phenotype has been shown to be predictive of falls, disability, poor mobility, hospitalisation and death in the Cardiovascular Health Study cohort.[19] The FP has been amended by multiple studies to reflect methodological constraints, notably by using self-reported measures of all five frailty discriminators with comparable results to those found in the original CHS cohort,[44-46] though as we will see later, with mixed results elsewhere.

1.4.2 Frailty Index

Contrary to the phenotypic model is the "Frailty Index" proposed by Rockwood and colleagues, originally conceived and validated against the CGA.[47] In many ways, the FI can be considered a different paradigm to FP; its authors felt that frailty cannot be

separated from disability or comorbidity, and therefore defined frailty as a series of clinical and biochemical "Deficits". This model of frailty assigns scores of between zero and one to ≥ 30 of these deficits, to give a mean composite score of between zero and one, with higher scores representing increasing frailty.[37] It is more comprehensive and multidimensional than the FP, and is modifiable to incorporate disease-specific elements.[48] This feature of the FI lends itself to use in kidney disease, which by virtue of its different stages and patient groups – CKD, haemodialysis, PD, and transplantation to name but a few – contains several linked but distinct patient groups with differing characteristics and risk profiles. However, such an approach also lends itself to variability and difficulty in comparing across cohorts. Furthermore, the use of over 30 data points is not practical in everyday clinical practice, so whilst the FI may represent a potentially "truer" reflection of the multidimensional nature of frailty, and offers greater granularity to researchers, the FP is undoubtedly easier to administer.

The difficulties inherent in the FI led the authors to conceive of two further screening tools based upon the deficit model: the Clinical Frailty Scale and the Edmonton Frail Scale, both of which we shall discuss shortly. Further efforts at simplifying the FI have resulted in the development of the electronic Frailty Index (eFI), an entirely electronic Frailty Index using General Practice (GP) coding data. Increasing eFI frailty has been associated with increased mortality hazard, hospitalisation, and nursing home admission in an English cohort of unselected older persons.[49,50] However, the capacity of the eFI to predict mortality at the individual level was poor, with 76% sensitivity and 53% specificity for mortality in a validation sample.[51] We must caution against

discounting the eFI as an important risk-stratification tool on the basis of these results; rather they demonstrate some of the difficulties inherent in translating population risk into meaningful individual discussion and decision-making.

1.4.3 Clinical Frailty Scale

The Clinical Frailty Scale was originally conceived as a seven-point scale of increasing frailty, and was latterly expanded to include nine categories.[21,27] It ranges from 1) "Very Fit" to 8) "Very Severe Frailty", with a further category 9) for those who are terminally ill, but not otherwise living with severe frailty, as shown in Figure 1-4. It was originally conceived and validated following detailed clinical interview at CGA and included Multidisciplinary Team (MDT) discussion,[27] but subsequent guidance acknowledges the *de facto* use as an individual clinician appraisal without the requirement for MDT discussion in everyday practice.[52]

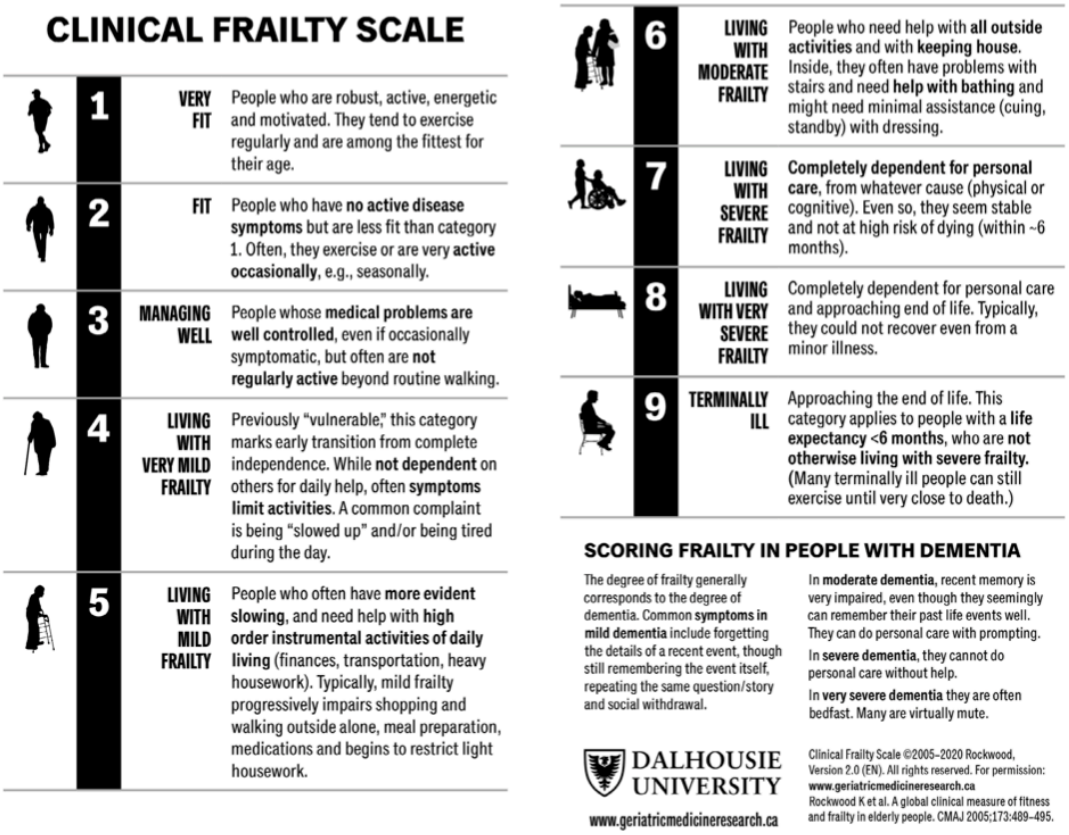


Figure 1-4: Categories of the Clinical Frailty Scale. Reproduced with permission from Rockwood and Theou (2020)[52]

The CFS has risen to particular prominence during the early phases of the COVID-19 pandemic, where it was used – to much criticism – as a screening tool for treatment escalation.[52-54]

1.4.4 Edmonton Frailty Scale

The Edmonton Frail Scale could be said to incorporate both the deficit accumulation and phenotypic definitions of frailty and has been shown to predict outcomes after surgical procedures[18,38]. We may alternatively consider it to be an abridged version of the FI, in that it covers multiple domains including physical health, mental health, ADL disability, and polypharmacy. It comprises a number of questions and tasks for participants, with

a total composite score of between 0 to 17. It has been validated against domains of the CGA,[55] and is recommended by the British Geriatric Society for frailty screening in elective surgical patients.[56]

1.4.5 Comparison of frailty tools

The Frailty Phenotype is the predominant frailty score in haemodialysis research.[57] Comparison of the Phenotypic versus Index definitions of frailty have shown reasonable correlation between the two; the phenotypic model was purported to give broad estimations of risk, whereas the index model required greater interpretation but allowed greater precision.[58]

In an elegant study in a US older adult cohort, Xue and colleagues showed that agreement between FI and FP frailty was minimal (Cohen's κ= 0.16). Furthermore, agreement remained poor even when the FI frailty threshold was manipulated to allow equivalent frailty prevalence with FP. Factors associated with discordant frailty status included male gender, high income, low ADL/IADL disability, and black ethnicity.[59] The authors concluded that the screening tools were identifying different subsets of frailty within the cohort. This is important, as the current literature base includes any number of different frailty screening tools, which does somewhat suggest an assumption of homogeneity of the syndrome across these definitions. The analysis of Xue *et al.* challenges this underlying assumption, though no such detailed appraisal of the agreement between frailty scores currently exists in haemodialysis cohorts.

1.5 Sarcopenia

1.5.1 What is sarcopenia?

Sarcopenia is a progressive and generalised disorder of skeletal muscle, defined by low muscle mass and low muscle strength, and is considered a contributor to the development of frailty.[60-62] Whilst it has been a subject of interest over the past two decades, it was only relatively recently that a consensus definition was proposed which included specific criteria for diagnosis of sarcopenia,[61,63] which have since been revised to include a greater emphasis on muscle strength and function.[60] Prior to these consensus statements, sarcopenia definitions used in the literature were heterogeneous, but generally included DEXA scanning for muscle mass approximation alongside either gait speed, hand grip strength or both as tests of function.[62] The importance of measuring muscle strength and function is underlined when one considers that associations between muscle mass and negative outcomes are lost after adjustment for muscle strength.[64,65]

Studies have demonstrated an association between advancing age and diminishing strength[66], and subsequent association between this loss of strength and disability[64,67-69], frailty[67], falls[70] and mortality[65].

1.6 Frailty in CKD

1.6.1 Scope of the problem

Until recently, the association between advancing CKD and frailty was not well established. Indeed, CKD was excluded as a comorbid condition in Fried's seminal

phenotype-defining study[19]. Later analysis on the same cohort, however, found that chronic renal insufficiency was associated with an odds ratio of 1.76 for frailty.[71] This work has been corroborated by studies in other cohorts showing prevalence of frailty increases with advancing CKD, and furthermore that frailty predicts progression to death or dialysis in multivariate analysis of CKD patients[72-76]. The European Renal Best Practice Working Group released a guideline on management of older persons with advanced CKD, but concluded there was insufficient evidence to recommend a specific screening tool.[77]

There has been much speculation about the potential overlap in aetiology between frailty and CKD, with advanced CKD also said to represent a state of accelerated aging[78]. We may consider the uraemic and frailty syndromes to have many commonalities in both clinical phenotypes and underlying mechanisms. There is much symptomatic overlap between frailty and CKD; weight loss, general decline, fatigue and functional disability would be at home amongst a description of either the uraemic or frailty syndromes. It can therefore be confusing for clinicians and patients alike to distinguish between the two in practice. Indeed, in a cohort study of nursing home residents with CKD, weight loss and loss of functional ability were significantly associated with earlier dialysis initiation.[79] Frail patients are more likely to start dialysis at higher GFR thresholds, and the association between dialysis initiation at higher GFR and mortality is lost when adjusted for frailty.[23] It may therefore be that clinicians are responding to symptoms such as weight loss and low energy and concluding they are uraemic in origin, whereas they may be – at least in part – a consequence of frailty.[80]

1.6.2 CKD, uraemia, and frailty: common underlying mechanisms?

A detailed review of the cellular and molecular mechanisms underlying frailty falls outside of the scope of this review, however we shall consider briefly some of the common pathological pathways associated with CKD and frailty.

Uraemia, much like frailty, is an acquired immunodeficiency state,[81] in which patients are more susceptible to infections,[82] respond poorly to vaccinations,[83,84] and have higher prevalence of cancers, in particular those which are virus-associated.[85] Cellular phenotypes appear to overlap between frailty and CKD/uraemia. As seen in advancing age and frailty, haemodialysis patients have been shown to have reduced central memory and naïve CD4 and CD8 cell populations, alongside a reduced CD4/CD8 ratio.[86] Peritoneal dialysis patients have also shown increased populations of CD4+CD28- cells, compared to healthy controls.[87] CD4+CD28- cells have been shown to exhibit a cytotoxic phenotype, destabilising atherosclerotic plaques,[88] and have been shown to be an independent risk factor for cardiovascular disease.[89]

Inflammation is also prominent in both the CKD and frailty syndromes. Il-6 is a pro-inflammatory cytokine which has been associated with frailty,[90] as has CRP.[91] Both high and low white cell counts have been associated with frailty.[92] IL-6 increases with falling GFR, but this association is lost for patients with age-related diseases/disability, whereas CRP increases with falling GFR, and retains this association in multivariate analysis.[93,94] Raised inflammatory markers in CKD are associated with endothelial dysfunction,

suggesting a possible pathophysiological mechanism behind the high prevalence of cardiovascular disease in this cohort.[94] This endothelial dysfunction has also been shown to be associated with frailty in a pre-dialysis CKD cohort.[95]

There are also overlaps in endocrine dysfunction between frailty and CKD. Dehydroepiansterone Sulfate (DHEAS) is lower in dialysis patients, and a lower DHEAS level is associated with a greater mortality risk amongst men, but not women.[96] Testosterone insufficiency has also been associated with greater arterial stiffness, alongside higher rates of infection and mortality in male haemodialysis recipients.[97,98] Furthermore, testosterone replacement was associated with reduced erythropoietin stimulating agent (ESA) dose and modest increases in serum albumin amongst male haemodialysis recipients in a small study of males receiving haemodialysis.[99] The pathogenic effects of low testosterone may not be limited to males. Low testosterone was more common in post-menopausal female haemodialysis recipients than age-matched controls, and this was associated with greater evidence of atherosclerosis.[100]

There is also a significant trend towards insulin resistance with falling GFR, and the correlates of insulin resistance are similar between those with and without CKD.[101] There is also an association between CKD with oxidative stress and accumulation of advanced glycation end products, resulting in inhibition of endothelial nitric oxide expression and endothelial dysfunction alongside other systems-wide effects.[102,103] This endothelial dysfunction has been associated with frailty status in CKD patients.[95] CKD-

MBD and associated risk factors also lead to accelerated vascular calcification in CKD patients.[104]

Whilst the extent to which frailty and CKD are interlinked has yet to be fully established, these factors combined point to the premise of CKD as a state of accelerated aging, much like frailty, and with many overlapping concepts and pathophysiological mechanisms.

1.7 Sarcopenia in CKD

1.7.1 The importance of sarcopenia in CKD

Physical activity declines with age, and this phenomenon is accelerated in CKD.[105,106] Roshanravan and colleagues have shown that poor performance in TUGT and gait speed are powerful predictor of mortality in non-dialysis CKD.[107] Haemodialysis recipients also demonstrate lower physical activity than healthy sedentary controls, in an effect that is increased with age.[108,109] Inactivity is associated with mortality in people living with CKD.[105,107]

Any cursory reading of the available literature on mechanisms underlying frailty in CKD and uraemia may lead one to the conclusion that sarcopenia and frailty are essentially the same. This is understandable; much of the literature is focussed upon FP frailty, which as we have discussed, is the most physically-mediated frailty screen. Indeed, low grip strength is fundamental to both, and slow walking speed helps to define both FP frailty and severe sarcopenia.[19,60] On the contrary, if we were to consider the deficit accumulation model of frailty, there is much yet to establish regarding the non-

musculoskeletal determinants of frailty. Furthermore, recent work has illustrated that concordance between frailty and sarcopenia in older adults is weak, even for those considered frail by the "Physical" FP.[110] We must therefore exercise caution when considering the mechanistic interplay between frailty and sarcopenia. Updated European Working Group on Sarcopenia in Older Persons (EWGSOP) guidance has reiterated that, whilst sarcopenia can be considered a contributor to the frailty syndrome, frailty and sarcopenia are distinct clinical entities.[60] It is clear that much further work is required to elucidate underlying mechanisms, both shared and distinct, of sarcopenia and frailty. With this in mind, we shall now turn our attention to the common mechanisms underlying sarcopenia and CKD. In so doing, it is important to recognise that much of the literature uses frailty and sarcopenia as interchangeable – or at least very similar – terms. For the purposes of clarity and readability (not to mention terminological rectitude), we shall consider mechanisms underlying poor muscle health as 'sarcopenic', rather than 'frail'. However we must acknowledge that just as sarcopenia can be a part of the frailty syndrome, there is much yet to learn as to whether the following pathophysiological mechanisms can lead to frailty in the absence of clinical sarcopenia.

1.7.2 Sarcopenia, CKD and Protein Energy Wasting

There is considerable overlap between frailty, the sarcopenic phenotype and the protein energy wasting (PEW) phenomenon observed in chronic kidney disease. Each are thought to be multifactorial in aetiology and share common underlying factors, such as inflammation, oxidative stress and comorbidities, and also common sequelae such as

increased hospitalisation and mortality[111]. It may be that protein energy wasting at least in part underlies sarcopenia and frailty in chronic kidney disease and dialysis patients. In a narrative review, Kim and colleagues postulated that the extent to which ESKD contributes to PEW may be influenced by numerous individual differences in genotype, medical history, psychosocial factors, and lifestyle.[112]

Undernutrition in CKD and ESKD may be driven in part by anorexia, which has been identified in 35-50% of ESKD patients.[113] It is however clear that other mechanisms, such as chronic inflammation, are implicated in muscle wasting and poor muscle strength exhibited in CKD and ESKD.

We have previously seen that high inflammatory burden is associated with frailty. High levels of TNF-α and IL-6 have also been associated with long-term reductions in muscle strength and muscle mass.[114] There is impaired clearance of pro-inflammatory cytokines in CKD, and there may also be dialysis-specific drivers of inflammation, such as the dialysis membrane – which is not immunologically inert – to consider.[112] Furthermore, impairments in immunity render those with CKD and ESKD more liable to infection, further increasing inflammatory burden.[112,113] Muscle size decreases with age, but there are also changes in the structure of the muscle, with smaller type II "fast twitch" muscle fibres and replacement of these fibres with fat and connective tissue.[115] Furthermore, there is a reduction in the numbers of satellite cells in type II muscle fibres in sarcopenia, which can be reversed with exercise.[116,117] It has been suggested that TNF-α may play a role in this preferential loss of type II fibres.[112,118]

Reduced GFR is associated with impaired insulin-like growth factor 1 (IGF-1) signalling, thought to be due to a combination of the accumulation of pro-inflammatory cytokines we have already described, as well as uraemia and metabolic acidosis.[112,119] Whilst there is increasing Growth Hormone (GH), insulin and IGF-1 resistance with uraemia, free GH is increased. As a consequence of these combined phenomena, free IGF-1 is reduced, and IGF-1 resistance increases.[120-123] Furthermore, IGF-1 levels appear to drop further on dialysis initiation.[124] Low levels of – and resistance to – the anabolic stimulation from insulin, GH, and IGF-1 helps to incite muscle protein breakdown.[125] In parallel with frailty and older adults, a combination of low IGF-1 and high IL-6 levels confer higher mortality risk in CKD patients, predominantly cardiovascular risk,[126] as does low IGF-1 individually.[127]

There has been considerable interest in the potential for testosterone as a mediator for sarcopenia and frailty in males. There is markedly decreased function of hypothalamic-pituitary-gonadal system in CKD, with consequent reduced testosterone synthesis.[128] Testosterone is a noted inhibitor of catabolism within muscle, as such low testosterone may potentiate the catabolic effects of low IGF-1, GH and insulin upon muscle breakdown in sarcopenia.[128] Testosterone insufficiency is present in the majority of men with CKD,[129] and men receiving haemodialysis,[130] and testosterone is inversely correlated with CRP and IL-6.[131] Chiang and colleagues found that low free testosterone in males receiving haemodialysis was associated with higher odds of both frailty and

sarcopenia at baseline, and of developing frailty and/or sarcopenia in the following 12 months.[132]

1.7.3 "Sarcopenic Obesity"

There has been considerable recent insight into the relationship between obesity and sarcopenia, resulting in the term "Sarcopenic Obesity". Higher fat mass is associated with frailty in haemodialysis patients.[133] Direct measures of fat mass and body composition perform better in predicting outcomes in older adults and haemodialysis recipients than BMI measurement.[134,135] Furthermore central obesity can be present with a normal BMI in people living with ESKD.[136] Low lean mass, high fat mass, and intramuscular fat deposition have been associated with self-reported loss of function and poorer mobility. [64,137] Furthermore, frail patients who were normal or underweight had higher mortality than those who were overweight, and that overweight (though not obese) status appeared to be relatively protective against frailty, and against mortality amongst those who were frail.[138] It may be therefore, that BMI provides too crude a measure of body composition to be of benefit in the study of frailty and sarcopenia; it is certainly true from the evidence to date that inter- and intra-muscular fat deposition is a much more sensitive discriminator.

The complex pathophysiology of sarcopenic obesity has been reviewed in detail by Tchkonia and colleagues[139], and more recently by Kalinkovich and Livshits[140]. In summary, a potential pathophysiological mechanism has been proposed, which includes; age and obesity related increases in fatty acids in the blood, followed by

increased inter- and intra-muscular uptake. This in turn leads to mitochondrial dysfunction and production of reactive oxygen species, poor lipid metabolism and further accumulation of lipids and inflammatory dysregulation in a "vicious cycle". This in turn leads to insulin resistance and decline in muscle mass and strength[140]. This hypothesis is strengthened by results from a small study showing signs that exercise, but not diet-induced weight loss reduces IL-6 and other inflammatory cytokine expression.[141] A subgroup analysis of the Cardiovascular Health Study cohort found that self-reported exercise was associated with lower levels of CRP and white blood cells amongst other markers of inflammation.[142]

1.7.4 Identifying sarcopenia in haemodialysis recipients

As we have discussed, sarcopenia is under-recognised in part due to difficulties confirming low muscle mass.[60] Gold standard assessments such as whole-body magnetic resonance imaging (MRI), computed tomography (CT) and dual-energy x-ray absorptiometry (DEXA) are expensive, time-consuming and onerous for patients.[143] Additional hospital visits for scans may be unacceptable for many haemodialysis recipients, given the already burdensome requirements of thrice-weekly dialysis. Furthermore, exposure to ionising radiation from CT and DEXA scans is also potentially controversial, particularly in the context of research. Despite these barriers, where DEXA has been used in research, prevalence of sarcopenia has been estimated at 37% and 40% in European and Japanese haemodialysis cohorts respectively,[144,145] and has been associated with hospitalisation and mortality in haemodialysis patients.[144]

1.7.5 Use of ultrasound

Ultrasound (US) is portable, often used on dialysis units for vascular access assessments, and has been validated for assessment of muscle size in older adults.[146,147] Recent work has suggested cut-offs for low muscle size – determined in the healthy young – according to ultrasound-derived bilateral anterior thigh thickness (BATT), a sum of the bilateral anterior-posterior depth of vastus intermedius and rectus femoris. BATT correlates with muscle strength and function, with high inter-rater reliability.[148] US has also shown good agreement with CT measurements of mid-thigh quadriceps thickness and with bioimpedance,[149,150] and demonstrated little loss of precision by comparison to CT scanning in acute kidney injury patients.[151] Furthermore, good correlation between MRI and ultrasound measures of rectus femoris hypertrophy in response to exercise in non-dialysis CKD,[152] suggesting it has value in assessing response to intervention. Importantly, no significant differences have been identified in femoral muscle thickness before and after dialysis, indicating that fluid overload does not significantly influence results.[153,154] Recent reports have shown that ultrasound-derived measures of quadriceps size are associated with both muscle function[155] and mortality[156] in haemodialysis recipients.

Muscle quality may also be obtained using ultrasonography, with higher echo intensity of the muscles being associated with poorer muscle strength independently of muscle size,[147,157] and may also increase with worsening CKD.[5] Recent analyses have shown however that inter-rater reliability for muscle echo intensity on ultrasound is poor,[148] so

this may not represent a feasible measure of muscle quality at a scale suitable for clinical use.

The combination of availability, cost, and simplicity suggest that ultrasonographic assessment may be an attractive option for assessing sarcopenia in haemodialysis recipients but many questions remain unanswered. Firstly, bilateral anterior thigh thickness has not specifically been investigated in the setting of haemodialysis. Secondly, the relationship between ultrasound-derived muscle parameters and frailty has yet to be explored in haemodialysis patients.

1.8 Frailty, ESKD, and Haemodialysis

1.8.1 Importance of frailty in an ageing kidney population

The RRT population is getting older, with the median age of UK RRT patients increasing from 53 to 57 years between 2000 and 2014, and the number of RRT patients over the age of 75 was 16%.[158] Those on dialysis treatment are older than those with functioning transplants (haemodialysis 67 years, PD 64 years, transplant 53 years)[158]. An ageing and expanding ESKD population presents an increasing challenge to both resource allocation and in providing individualised care that elderly patients can often require. It has been argued that a combination of an ageing population and an increasing burden of frailty and disability in ESKD patients of all ages presents a significant ethical challenge to nephrology practice. Specifically, discussions regarding potential RRT modalities versus conservative care, both for incident ESKD patients and indeed longstanding dialysis recipients can be challenging in an era of increasing burden of frailty and age-related

comorbidity, allied to an increasing societal and cultural expectation of intervention upon disease.[159,160] In this context, it is crucial to understand the role frailty plays within ESKD and dialysis to be able to best inform patient and clinician shared decision-making.

Elderly haemodialysis patients have been found to have high rates of dependency for ADLs such as climbing stairs and particularly for complex tasks such as housework,[161,162] indicating a high level of disability. Furthermore, patients over the age of 80 experience precipitous declines in functional independence following initiation of both peritoneal and haemodialysis.[163] Similarly, nursing home residents showed functional decline after dialysis initiation.[164] Frail haemodialysis patients have lower physical activity[165]are at much greater risk of ADL disability than non-frail counterparts (OR 11.35).[166] Burns and colleagues further demonstrated the negative associations of ESKD and dialysis by estimating when conservative care patients may have started dialysis based upon biochemical measurements. They found that dialysis patients lived longer than their conservative care counterparts, but at the expense of days spent on dialysis, and were more likely to be admitted to hospital.[167] These factors combined suggest a need to stratify patients according to risk of adverse outcomes when considering RRT modality choices, and to hold frank bilateral discussions with patients both approaching and at ESKD about goals of care.

1.8.2 Measurement and prevalence of frailty in haemodialysis

Frailty is present in a greater proportion of the dialysis population than the general elderly population. In the United States, frailty prevalence was 6.9% in community

dwelling older adults,[19] and 16.3% in the Women's Health initiative study.[44] This contrasts with 67.7% of dialysis patients in the DMMS Wave 2. [168] This is despite both the former studies being performed exclusively in an elderly population, whilst the dialysis study included all adults over 18 years. Frailty is more common in haemodialysis versus peritoneal dialysis patients,[168] and has also been associated with female sex, increasing age, lower serum albumin, white ethnicity, peripheral vascular disease and cardiac dysrhythmias in dialysis patients.[168-170]

As we have previously discussed, a multitude of frailty screening tools are available; until recently, there was little exploration of which tool may be optimal in haemodialysis recipients. Drost et al found that estimates of frailty prevalence were higher for FI than for FP in a mixed group of PD, haemodialysis and pre-dialysis patients, but they did not seek to quantify the agreement between FI and FP.[171] Imamura and colleagues conducted a cohort study of prevalent Japanese haemodialysis recipients, assessed for frailty by FP, CFS, Study of Osteoporotic Fractures (SOF) index,[172] Short Physical Performance Battery (SPPB),[173] FRAIL scale,[174] and Frail Screening Index.[175,176] They found frailty prevalence of between 15% to 34% in this sample, and fair to moderate agreement upon frailty status between FP and other tools. They also reported that rates of hospitalisation/mortality composite were higher for those with frailty by FP, SOF index, and CFS, but not the Frail Screening Index or FRAIL scale.[175] Whilst this is an important recent addition to the literature on haemodialysis and frailty assessment, it has a number of important limitations. First, the SPPB may be more accurately defined as a measure of muscle performance, specifically lower limb performance rather than a

multidimensional frailty assessment.[173] Second, the SOF and Frail Screening Index are not in wide use in nephrology for frailty screening. Third, the use of a composite measure of hospitalisation, fractures, and mortality – whilst understandable to increase statistical power – lacks granular detail for these distinct negative sequelae of frailty. Furthermore, comparing rates of mortality (a definitive end point), with fractures and hospitalisation (which can occur multiple times each during follow-up) introduces the potential for survivor bias in the analyses.

In a qualitative study of clinicians and ESKD patients, discrepancy was observed between the proportion of clinicians (97.6%) and patients (60.2%) who felt that ESKD made patients frail. Furthermore, clinicians appeared more likely to consider the components of the FP to be relevant to frailty, though a high proportion of clinicians felt weight loss was not relevant.[177]

Self-report measures of frailty involving questionnaires have poorer accuracy than performance-based measures in haemodialysis patients, tending to demonstrate lower estimated frailty prevalence[45,178,179]. Haemodialysis patients who meet self-reported but not performance-based frailty criteria were at no greater mortality risk than those not classified as frail in either scale[46]. Physician, nursing and patient perceptions of frailty have been shown to be inaccurate, as around a third of prevalent haemodialysis patients were misclassified as frail, when compared with the Fried scale. Black and older patients were at higher risk of being misclassified as frail[180]. These data combined suggest that physicians are likely to be both under and overestimating frailty in their patient groups,

which may then influence clinical decision making regarding treatment options. A standardised and validated frailty scoring system has a role to play in day-to-day clinical practice, rather than just as a research tool. Zanotto and colleagues found that the timed up and go test (TUGT) and gait speed showed good diagnostic accuracy for frailty.[181] We may argue however, that given these are constituents of the FP and FES respectively, it may be preferable to spend the modest extra time in completing a formal frailty assessment.

Chao and colleagues observed poor correlation between two laboratory based laboratory frailty indices ("LFI 1" and "LFI-2") against a self-reported version of the EFS and no significant correlation against a self-reported FP.[182] However, given what we have already discussed regarding the accuracy of self-reported surrogates for formal frailty assessment, we may question whether these represented suitable comparators. They also found that participants with high LFI-1 scores had greater mortality on univariable analysis, but did not include any adjusted analyses in their published analyses.[182]

1.8.3 Frailty and mortality in haemodialysis recipients

Frailty has been associated with a hazard ratio of 2.24 for 1 year mortality.[168] Frailty has separately been associated with increased mortality and hospitalisation in the incident dialysis population independently of age, dialysis modality and comorbidity, with the mortality risk increasing in a dose-dependent manner with degree of frailty.[21,170]

In a small Spanish haemodialysis cohort >69-years, FP frailty was associated with increased mortality hazard, but interestingly, frail participants who survived one year showed stable physical function and improved depression scores. Non-frail survivors however, showed significant worsening of these domains,[183] suggesting that frailty is a dynamic construct.

Recent analysis in a Spanish prevalent haemodialysis cohort found frailty prevalence using the EFS was 29.6%,[184] compared with 38.3% in a Brazilian haemodialysis cohort over 60 years of age.[185] In the Spanish study, frailty was associated with a mortality hazard ratio of 2.34 (95% C.I. 1.39 to 3.95; p=0.001). Furthermore, hospitalisations were higher in the frail group.[184]

The CFS was associated with a mortality hazard ratio of 1.59 (95% C.I. 1.10-2.58; p<0.001) in a Japanese incident haemodialysis cohort >75 years.[186] In a recent analysis of COVID-19 admissions in UK renal patients – of which 88.5% were dialysis recipients – prior CFS frailty was associated with an odd ratio for mortality of 3.3 (95% C.I. 1.0-10.6; P=0.044).[187]

1.8.4 Frailty and hospitalisation in haemodialysis recipients

Frailty has principally been studied in haemodialysis with regards to mortality,[21,170,184] but this is not the only important negative outcome for haemodialysis recipients; hospitalisation occurs at a rate of > 1 admission per patient-year[188]. Frailty has been shown to increase hospitalisation risk, both in general elderly populations[17] and in

haemodialysis recipients assessed with the FP and EFS[170,184]. To our knowledge, these data have not been validated in a different haemodialysis cohort and the associations between the FI and CFS with hospitalisation have not been tested. It is therefore important to compare the association of these tools with hospitalisation, to allow a more holistic view of both the burden of frailty and the performance of the individual frailty screening tools.

1.8.5 Frailty, falls, and fractures in haemodialysis recipients

A self-reported surrogate for FP frailty is associated with increased risk of fractures or medically urgent falls in US new starters to dialysis.[24] The FP itself is also independently predictive of falls in prevalent haemodialysis patients.[189] This may be in part explained by the sarcopenia demonstrated in dialysis patients.[190]

A mixed cohort of assisted PD and haemodialysis recipients ≥60- years found frequent falls, which in turn led to reduced activity.[191] There is evidence that fractures in this population may not simply be due to a confluence of poor functional status and CKD-MBD. In a prevalent Japanese haemodialysis cohort, FP frailty was associated with lower calcaneus bone mass assessed by ultrasound, independently of traditional markers of CKD-MBD.[192]

1.8.6 Frailty and depression in haemodialysis recipients

Depression also impacts upon quality of life in haemodialysis recipients,[193,194] but is generally under-recognised in haemodialysis populations.[195] The Patient Health

Questionnaire-9 (PHQ-9) has been validated in dialysis recipients, with 92% sensitivity and 92% specificity for detection of depression.[196] Depression of at least moderate severity was present in 28% of participants of a large prospective cohort, and both moderate depression and continuous PHQ-9 scores have been associated with mortality.[197-199] In a systematic review and meta-analysis of published observational studies, depression was associated with increased mortality hazard for dialysis recipients.[200] A diagnosis of depression has also been associated with greater hospitalisation, but lower mortality within hospital admission episodes in retrospective cohorts.[201,202]

Despite the high prevalence of both frailty and depression, there has been little exploration of the relationship between the two in haemodialysis recipients. A systematic review of depression and frailty in non-dialysis older adults has suggested a reciprocal relationship between frailty and depression, with each being a risk factor for the other.[203] However, Sy and colleagues found prevalent depression was associated with incident frailty, but not vice versa in a prevalent United States (US) dialysis cohort.[204] US and European dialysis demographics and outcomes differ significantly,[205] therefore these relationships require further study in non-US haemodialysis populations. Chi and colleagues assessed the relationship between depression and frailty in a Taiwanese prevalent haemodialysis cohort. They assessed the EFS, FRAIL scale, and SOF for association with Geriatric Depression Scale (GDS) depression. They found that however defined, frailty was associated with increased odds of depression,[206] though the GDS is less sensitive for depression in haemodialysis recipients than other

scores such as the PHQ-9.[207] There is clear overlap between symptoms of frailty and depression, the relationship between them and their associations with patient-centred outcomes requires scrutiny.

There has been interest in categorising depression scores into somatic and cognitive symptom components.[208] The somatic symptom subset of the Beck Depression Inventory (BDI) has been associated with mortality and hospitalisation in haemodialysis recipients in Dutch[209] and Jordanian[210] haemodialysis recipients. In the Dutch cohort, depression, somatic symptoms, and cognitive symptoms were all associated with lower quality of life.[209] We may speculate that the somatic depression symptoms – fatigue, lack of sleep, poor appetite – show considerable overlap with those of frailty, yet no exploration of the interplay between the two has been attempted in haemodialysis recipients. This is important, as we cannot therefore be certain that the association somatic symptoms are not simply a surrogate of frailty in their association with mortality.

1.8.7 'Cognitive frailty' in haemodialysis recipients

Cognitive impairment is common in haemodialysis recipients,[211,212] with up to 73.4% of prevalent patients having moderate to severe cognitive impairment in one cross-sectional study,[213] and cognition declines in both incident and prevalent haemodialysis recipients.[211,214,215] Cognitive impairment among haemodialysis patients is associated with poor outcomes like mortality,[216-220] with little data into associations with other adverse outcomes like risk for hospitalisation. Many aetiological factors contribute to

development of cognitive impairment, which are common in both general population and haemodialysis cohorts with frailty.[215,221,222]

In a systematic review and meta-analysis, Borges and colleagues identified a relationship between incident cognitive impairment and frailty in the general population (pooled Odds Ratio 1.80, 95% CI 1.11-2.92, p=0.02). Relatively little is known about the interplay between frailty and cognition in the setting of haemodialysis. McAdams-DeMarco and colleagues showed FP frailty was associated with cognitive impairment in incident haemodialysis recipients.[223] An Indian cohort demonstrated FP was associated with cognitive impairment by Montreal Cognitive Assessment (MoCA)[224] in prevalent haemodialysis recipients over 75 years, though inferences may be limited by small numbers.[225]

1.8.8 Frailty and health-related quality of life in haemodialysis recipients

There is increasing acknowledgement within the kidney community of an unmet need to address health-related quality of life (HRQOL) amongst ESKD patients.[226] The EuroQol EQ-5D is a brief multidimensional measure of HRQOL,[227] that is widely used, including in haemodialysis studies,[228] though it must be said that the Short Form-36 questionnaire – and its kidney-specific variation the KDQOL-36 – is more commonly used in this population.[229]

In a cross-sectional study of prevalent haemodialysis recipients, Warsame and colleagues observed that higher levels of intra-dialytic activity – for example chatting or

playing games – were associated with better HRQOL via the KDQOL-36 score.[230] The authors rightly concluded that further prospective work was required to confirm such an association.

Hall and colleagues highlighted the limitations in quantitation of HRQOL in a small qualitative study of haemodialysis recipients ≥75 years. They found that frail and non-frail participants had different perspectives on what constituted quality of life. Furthermore, many of the subthemes identified within their analysis were not adequately explored using existing quantitative HRQOL measures.[231] Whilst qualitative assessments of HRQOL fall outside the scope of the FITNESS project, it is important to recognise the limitations of a broadly quantitative approach.

Lower bodily pain, and physical function domains of the SF-36 have been associated with mortality in a long-term Brazilian haemodialysis cohort, though the statistical significance of these were lost upon multivariable analyses.[232] In a retrospective analysis of the DOPPS study, Perl and colleagues found that lower HRQOL was associated with mortality in haemodialysis recipients, but this effect was retained only for the most recent measure, indicating that changes in HRQOL are less important to mortality association.[233]

Frailty has been associated with poorer quality of life in Brazilian[234] and UK[235] non-dialysis CKD cohorts. McAdams-DeMarco and colleagues found that self-rated fair/poor quality of life was more likely in frail haemodialysis recipients, and that frailty was

associated with worsening quality of life over time.[236] A decline in quality of life in frail haemodialysis recipients was also observed in a small Canadian cohort.[237] In a mixed sample of advanced CKD and dialysis recipients, Nixon and colleagues found FP frailty was independently associated with poorer physical conditioning, emotional problems, energy/fatigue, social functioning, and pain domains of the SF-36.[235]

There is emerging interest in HRQOL as an outcome in discussion regarding renal replacement therapy (RRT) modality decisions. In the GOLD study, EQ-5D HRQOL fell in patients receiving maximal conservative care for their ESKD, whereas scores were not significantly different for those initiating dialysis treatment after one year. Baseline frailty was higher, and HRQOL lower in the conservative care group however, so we must exercise caution in drawing causative conclusions.[238]

1.8.9 Frailty Intervention in ESKD

As we have seen, much of the work into frailty in ESKD has focussed upon associations and – to a lesser extent – mechanisms of frailty. These are of undoubted value to the kidney community, but we must also acknowledge the need for high quality evidence into potential frailty interventions within this high-risk patient group. For example, patients and clinicians alike felt that intradialytic exercise may reduce frailty in ESKD.[177] Currently, however no evidence exists to support any intervention targeted to improve frailty in haemodialysis recipients.

In the general elderly population, there is some evidence of the utility of a multi-disciplinary approach to intervene on frailty. For example, the FIT study utilised a multifactorial inter-disciplinary intervention which reduced frailty among older people by 14.7% at 12-months,[239] however there were no other outcomes measured, such as quality of life, mortality or hospital admissions. The majority of frailty intervention studies performed in both general and dialysis populations do not use validated measures of frailty for either inclusion criteria or outcome measures, but show that functional outcomes (i.e. disability) can be improved with exercise.[240-242] For those patients proceeding to kidney transplantation, frailty at the time of transplantation has been associated with poorer post-transplant outcomes,[243-246] although there have not been any published attempts at "prehab" in prospective transplant recipients. Therefore, whether such a strategy would lead to more haemodialysis patients being deemed suitable to benefit from transplantation remains to be seen.

A small feasibility study of intradialytic exercise found modest stabilisations and/or improvements in muscle function compared to usual care, but also barriers to recruitment in female, older, more frail, and black and minority ethnic group participants.[247] The authors recognised these limitations to external validity, but also proposed a number of interesting potential mitigations for future large-scale RCTs. These included peer and family involvement, and Partial Randomisation, to allow participants with a strong preference for a particular exercise modality to be allowed to choose their intervention.

In a small RCT, Jeong at colleagues found no difference in physical function or quality of life with either oral protein supplementation, or a combination of intradialytic exercise with oral protein supplementation,[248] although this was in a relatively young and nutritionally well group of haemodialysis recipients, and it may therefore have lacked power to detect the subtle changes one would expect in this group. [249]

Further difficulty is suggested by work in a Polish cohort, which demonstrated frail haemodialysis recipients were much less likely to adhere to guidance on physical activity recommendations.[250] This highlights the need for strategies to help participants engage with any intervention trial.

The DiaTT study is a Randomised Controlled Trial (RCT) that will assess the benefits of intradialytic exercise in a large prevalent haemodialysis cohort (n=1100). Primary outcome will be a 60 second sit-to-stand test, a measure of muscle function, but frailty will comprise one of the secondary outcomes, alongside mortality.[251] Frailty will be assessed by the Multidimensional Prognostic Index (MPI), which whilst has shown mortality association in non-dialysis CKD,[252] has yet to be validated as a measure of frailty in a haemodialysis cohort. However, as a large prospective exercise trial, with a 12-month intervention period, it has the potential to offer definitive evidence of the efficacy or otherwise of intradialytic exercise upon improving functional impairment.

We speculate that patient behaviours can be modified to impact upon frailty. To the best of our knowledge, there have not been any published attempts to intervene upon

frailty using behavioural change. Meta-analysis and meta-regression have shown that behavioural change techniques (BCTs) congruent with Control Theory[253] are significantly more effective than those that are not[254-256]. These include Node-Link Mapping (NLM), which incorporates visual representations of behavioural change, alongside potential aids and barriers to this change with strategies to overcome these[257]. NLM is a technique already successfully used in addiction psychiatry[258]. Social Behaviour and Network Therapy (SBNT) seeks to identify the level of social support for an individual, and aims to include significant supportive others in setting and monitoring goals, and has been successfully used in alcohol abstinence after liver transplantation[259]. Long-term changes in behaviour and activity are likely to be required to impact upon frailty, and as such BCTs may have a role to play in frailty interventions.

1.9 Unanswered questions

To summarise the evidence to date, frailty is much more prevalent amongst dialysis patients of all ages than unselected elderly. It is associated with multiple negative health and quality of life outcomes within the haemodialysis population, and the underlying processes behind it appear congruous with frailty seen in older adults. However, many questions regarding frailty in ESKD remain unanswered, and it is to these that we shall now turn our attention.

1.9.1 Which Frailty Tool to use in ESKD?

So far we have seen that frailty by each of the FP, FI, EFS, and CFS is associated with mortality in haemodialysis recipients, whereas only the FP and EFS have been associated with greater hospitalisation.[21,45,46,49,170,184] Recent work from Imamura *et al* compared the FP and CFS amongst other less used frailty tools for association with a composite of hospitalisation, fractures and mortality.[175] However, no such comparison exists between frailty tools for their associations with mortality and hospitalisation as individual outcomes. This is important, as patients and providers alike may not view these as equivalent outcomes, and as such further detail is required to elucidate which frailty screening tool is optimal for use in haemodialysis recipients.

1.9.2 What are the outcomes associated with Frailty in ESKD?

Detail is also lacking into the interplay between frailty and its associated syndromes in ESKD. Whilst we have seen that there is little concordance between frailty and sarcopenia in older adults, such analysis in haemodialysis recipients is lacking. In a further important consideration, little is known whether the associations of cognitive impairment, depression, and low HRQOL with poor patient outcomes are maintained when adjusted for frailty.

1.9.3 Can Frailty be mitigated in ESKD?

Perhaps the greatest unanswered question in frailty amongst those living with ESKD is what can be done about it. As we have seen, the kidney community has yet to benefit from a large-scale RCT of frailty intervention. A further complication is the choice of

outcome measures. Is a reduction in frailty a meaningful patient-centred outcome? What about mortality, hospitalisation, HRQOL, or ADL disability? Any frailty intervention trial must address these issues, whilst maintaining acceptability to participants.

1.10 Limitations of this review

This review attempts to give a broad and representative overview of the literature regarding frailty in haemodialysis. Furthermore, we have identified gaps in the literature base that require further exploration. This is limited however, by its narrative nature rather than applying a more systematic approach. A scoping review, conforming to PRISMA-ScR methodology,[260] would aid in the examination of the breadth of frailty research in ESKD, and to highlight gaps in the knowledge base.[261] This would be a necessary first step in identifying any areas that may be amenable to systematic review,[262] although as frailty in ESKD is an emerging field with few interventional studies, a systematic review may not yet be a high priority.

1.11 Hypotheses

1. Frailty is highly prevalent in a UK haemodialysis cohort
2. One of the frailty tools is superior to others for association with mortality and hospitalisation in haemodialysis recipients.
3. Syndromes and conditions that contribute towards frailty, such as depression and cognitive impairment, lose their association with negative outcomes when adjusted for frailty

There was originally a fourth hypothesis, which has not yet been tested in part due to the COVID-19 pandemic, this will be discussed in Chapter 13:.

4. A clinical intervention study incorporating multidisciplinary, psychologically-supported lifestyle intervention is feasible and tolerable to participants.

1.12 Aims

In Chapter 3: – the first of the experimental chapters – we will explore the relationship between frailty scores within the FITNESS haemodialysis cohort, comparing correlations of raw scores and agreement upon frailty status of individuals. Chapters 4 and 5 explore the relationship between ultrasound-derived sarcopenia and frailty in haemodialysis recipients. In Chapter 6: and 7, we will assess the associations between frailty scores and mortality and hospitalisation respectively within the FITNESS cohort. We will then in Chapter 8 propose and assess the utility of a novel patient reported outcome measure – self-reported health change – and how it may interact with frailty scores to influence the association of frailty with mortality and hospitalisation. Chapter 9 examines an alternative method of obtaining a CFS via haemodialysis MDT discussion, comparing frailty scores and associations with outcomes for this method compared with a CFS derived from clinical interview. We then turn our focus to depression and frailty in chapters 10 and 11, examining the relationship between depression and frailty and the effect this has upon outcome association. In Chapter 12 – the final experimental chapter – we will assess the interplay between cognitive impairment and frailty in haemodialysis recipients, and their combined association with mortality and hospitalisation.

Chapter 2:
General Methods

2.1 Extent of Personal Contribution

This protocol was designed and developed by myself for the FITNESS study. Study funding was secured by myself, under Dr Adnan Sharif's supervision, and I liaised directly with Queen Elizabeth Hospital Birmingham Charity in grant application and subsequent submissions. The first draft of this study protocol was compiled by myself in concert with oversight from Dr Adnan Sharif. Sister Mary Dutton, Dr Thomas Jackson and Prof. Charlie Ferro provided critical reviews of protocol content and design. Dr Edward Day provided the insight into Control Theory and BCT methodology. Ethical approval was obtained by myself through the Integrated Research Application System and I presented the study to the West Midlands-South Birmingham Research Ethics Committee for final approval. I liaised directly with University Hospitals Birmingham Department of Research and Development during and after the ethical approval process. All regulatory documents, audits and correspondence with the sponsor were my primary responsibility. I maintained the site file and dealt with and documented any protocol deviations and adverse events. I was responsible for training and supervising colleagues who supported in data collection.

The first draft of the manuscript was written by myself and I was responsible for all edits and revisions. This chapter is based upon work published in Trials Journal, on which I am first author.[263]

2.2 Study Design

The FITNESS study was originally designed as a prospective, single centre, open-label, cohort multiple randomised controlled (cm-RCT) study[264] , split into two elements. Work Package 1 was a cohort study of prevalent haemodialysis patients which aims to identify the prevalence of frailty amongst this population and outcomes associated with frailty such as mortality, hospitalisation and quality of life. Work Package 2 did not proceed as planned, however, as detailed in Chapter 13:. Therefore this chapter will describe the cohort study (Work Package 1) phase of the FITNESS study.

2.3 Participants and Study Setting

Patients were recruited from a single nephrology centre located in Birmingham, England. The centre consists of one in-hospital dialysis unit and ten private-provider satellite units distributed around the region, and provides haemodialysis to 1000 patients. Birmingham and the West Midlands is a diverse, multicultural population and as such we aimed to recruit proportionate numbers of Black, Asian and Minority Ethnic (BAME) participants to the study to accurately represent the community our hospital serves.

2.3.1 Inclusion Criteria

- Aged 18 and over
- Received regular haemodialysis for at least 3 months' duration
- Able to provide informed consent

2.3.2 Exclusion criteria

- Received inpatient care within 4-weeks of recruitment (unless for vascular access)

2.3.3 Screening and Consent

Potential participants were identified through a review of all patients attending haemodialysis sessions, currently available from electronic patient records (EPR) and from clinicians in charge of each haemodialysis unit. Patient information leaflets (PIL) were given to the patients in advance of a discussion with the researcher in person. Individuals were approached at their usual dialysis unit appointment for discussion and potential recruitment to the study. Potential participants were given the opportunity to reflect on the information given both verbally and within the PIL. No fixed time was specified for the length or timing of this prior interview as it was dependent upon the patient's understanding of their underlying disease and of the research project. It was important that non-English speaking patients are given full opportunity to be informed and recruited to the study, to accurately reflect the demographics of the haemodialysis population. In these instances, we used any possibility to discuss the study with patients to aid participation and consent. This included using family, friends, dialysis staff or the investigator team who may be proficient in the patients preferred language (e.g. Urdu, Punjabi). Written consent was received from each patient entering the study.

2.4 Baseline Assessment

Prior to the patient being connected to the dialysis machine, the following assessments took place.

- Timed walk over 4 metres
- Assessment of grip strength with a dynamometer.
- Montreal Cognitive Assessment (MoCA)

Once dialysis started, patients were clinically interviewed, including a series of questionnaires including assessments of activities of daily living (ADL) disability, demography, social history, and frailty-specific questionnaires. Electronic Patient Records were interrogated for comorbidities, drug history, dialysis vintage and adequacy, previous transplantation, and biochemical data. Self-reported change in health (henceforth "health change") was obtained by asking "How has your health changed in the last year?", potential responses were "Better" "The Same" or "Worse". Socio-economic deprivation was based upon the Index of Multiple Deprivation (IMD), a model calculated according to local area, with 1 representing the most deprived and 5 the least deprived area respectively.

2.4.1 Muscle strength and function

Physical assessments took place immediately before connection to dialysis on the participants routine dialysis session. Grip strength was assessed using hand grip Dynamometer (Grip-D, Takei Scientific Instruments, Japan), with arm resting at the side of the patient with elbow in extension and wrist in the neutral resting position. A practice grip was taken with results discarded, then one summative grip on each hand, for which the participant was encouraged to give maximum effort. Both scores were noted, but the greater of the two scores taken for subsequent analysis. Adjusted hand-grip strength was calculated as fold change from the lowest 20% by gender and BMI in the original Fried frailty phenotype cohort[19].

Walking speed was measured over 4m from a standing start; usual walking aids were permitted. If the participant was not able to complete the 4m distance, no walking speed was calculated, and a deficit registered for this component of the relevant frailty scores.

2.4.2 Ultrasonographic measurements

Following baseline frailty assessment, further verbal consent was sought for ultrasound assessment. Consenting participants had thickness of their anterior thigh muscles measured bilaterally, or unilaterally in the case of unilateral lower limb amputation. Ultrasonographic measurement took place during the participants' regular dialysis session. Patients were positioned sitting at an angle of ≤45° with knees resting comfortably upon a cushion near the natural 10° to 20° resting position. Participants were instructed to relax during the examination. Scanning followed a protocol established in previous work,[148] with subcutaneous tissue, vastus intermedius and rectus femoris depth all captured in a single transverse plane at anterior mid-thigh. This was defined as 50% of the measured distance between greater trochanter and lateral epicondyle of the femur. Images and depth measurements were obtained using Phillips Lumify L12-4 transducer via the Phillips Lumify app (Koninklijke Philips, Netherlands) on its factory musculoskeletal settings, with a power of -0.3dB and gain of 50. The bilateral anterior thigh thickness was calculated as the sum of bilateral rectus femoris and vastus intermedius anterior-posterior depth, or double the unilateral rectus femoris and vastus intermedius depth in instances of unilateral lower limb amputation, or of dialysis access (e.g. femoral line or arteriovenous graft) restricting adequate exposure of the area to be scanned. Thresholds for low muscle mass (LMM) were 38.53m and

54.36mm for females and males respectively, as per previous work in healthy volunteers.[148] Low grip strength was <27kg for males and <16kg for females; slow walking speed was set as <0.8ms^{-1}.[60] Sarcopenia was defined as low muscle mass and low grip strength, severe sarcopenia was assigned when low muscle mass, low grip strength and slow walking speed were all present.

2.4.3 Montreal Cognitive Assessment

Study participants completed a MoCA prior to dialysis connection.[224] Scores on the MoCA range from zero to 30, with a score of <26 indicating cognitive impairment. The MoCA has been validated in abridged form for the visually impaired by omitting the executive function and naming sections.[265] This protocol was used for participants with visual impairment. A further protocol was devised to perform MoCA without executive function only for participants with difficulties with manual dexterity. MoCA scores were treated both as raw scores and as a binary measure of cognitive impairment, defined as <26 for participants completing the full MoCA protocol, <21 for participants lacking dexterity, and <18 for visually impaired. Moderate cognitive impairment was defined as MoCA ≤21 for full completion, or ≤18 for participants lacking dexterity, and ≤15 for visually impaired.[266]

2.4.4 PHQ-9 Depression Scores

PHQ-9 scores were obtained by patient questionnaire with comprised 9 questions each scored between 0-3 for frequency of depression symptoms, giving a total score of between 0-27. Moderate depression was defined as a PHQ-9 score of ≥10[196].A PHQ-9 score of 20 or over may

indicate depression and a discussion was held with the patient asking whether they would like a discussion with their nephrologist or a referral to the renal psychology service.

Electronic patient records will be interrogated for data upon comorbidities, dialysis parameters, previous transplantation, biochemical data, medication history and social deprivation score.

2.4.5 Health-Related Quality of Life

Health-related quality of life was assessed using Euroqol EQ-5D-3L. This was converted into the single-measure EQ-5D Summary Index via a standardised formula.[267] This results in a potential score of between 1 (if no HRQOL deficits identified) and -0.716 (if extreme deficit in every domain), and has been validated in UK populations.

2.4.6 GP Physical Activity Questionnaire and Physical Activity Index

The GP Physical Activity Questionnaire (GPPAQ) was used to obtain patient-reported physical activity levels. The Physical Activity Index was derived from the GPPAQ via a validated formula.[268,269]

2.5 Frailty Definitions

2.5.1 Frailty Phenotype

The Frailty Phenotype was determined as a score between zero and five, with participants receiving one point for each of the following: slow walking speed, weak grip strength, exhaustion, weight loss, and low physical activity. Slow walking speed was assessed from a

standing start over 4 metres, and participants scored one point if their time was over or equal to prespecified values stratified by height and gender or if they were unable to undertake the test. These values were determined by the original FP described by Fried and colleagues[19], with times reduced in proportion to the reduced distance of 4m in this study versus 15 feet in the FP study. Poor grip strength was evaluated with dynamometer (Takei Grip D, Takei Scientific Instruments, Niigata, Japan); participants scored one point if their grip strength in either hand was not above cut-off values as per the original FP[19] stratified by BMI and gender, or if they were unable to perform the test in either hand. Unintentional weight loss of greater than 4.5kg in the past year scored one point. To characterise exhaustion, participants were asked whether they felt that a) everything was an effort or b) they felt they could not get going within the past week. The possible responses were “Rarely”, “Some of the time”, and “Most of the time”. Participants scored one point for exhaustion if they responded that they felt either statement was true either most of the time or - if they answered “Some of the time” – they felt it was the case on more than 3 days in the week prior to recruitment. Physical activity was assessed by response to the question “How often do you engage in activities that require a low or moderate level of energy such as gardening, cleaning the car, or going for a walk?”. Possible responses were “More than once per week”, “Once per week”, “One to three times per month”, and “Hardly ever or never”. Participants scored one point for low physical activity if they responded “One to three times per month” or “Hardly ever or never”. Participants were considered not frail by FP if their total score was 0, vulnerable if their total score was 1-2 and frail if their score was 3-5.

2.5.2 Frailty Index

A Frailty Index score was based upon previous work from van Munster and colleagues conducted in an elderly haemodialysis cohort.[270] The FI therefore consisted of 32 variables measuring deficits across multiple body systems. Each variable was scored out of one by pre-determined cut-offs and the FI comprised a mean average of these scores, giving a continuous variable between zero and one. A score of ≥0.24 was considered frail by FI; a score of ≥0.12 but <0.24 was considered vulnerable and the rest considered robust.

2.5.3 Clinical Frailty Scale

Clinical Frailty Scale (CFS) was derived from interrogation and interpretation of independent activity of daily living questionnaire responses, which were administered by the investigators and interpreted by the lead investigator. Scores can range between 1 to 9, with a threshold score ≥5 considered frail, 4 considered vulnerable and <4 considered robust. A score of 9 represents terminal illness without apparent frailty. No FITNESS participants fell into this category.

2.5.4 Clinical Frailty Scale from MDT Discussion

A Clinical Frailty Scale from MDT (CFS-MDT) was ascertained as a result of MDT discussion at the participants' monthly dialysis quality assurance (QA) meeting. Present at this QA meeting were the patients' nephrologist, dialysis unit nurses, and dietitian; each had a copy of the CFS at the time of the meeting. CFS-MDT scores were arrived at by consensus from this MDT discussion; in the event of intractable MDT disagreement, the patients' nephrologist had the casting vote on CFS-MDT frailty status. The lead investigator was present in this meeting to

offer guidance and clarification of specific queries regarding the CFS instrument, but did not otherwise contribute to the MDT discussion. Frailty score cut-offs were identical to the CFS as outlined above.

2.5.5 Edmonton Frailty Scale

The Edmonton Frailty Scale was determined according to the original study[38], but in order to reduce test burden on participants, a 4 metre walk was substituted for the timed up and go test. The results were split into terciles and attributed zero points to those in the lowest tercile, one point to those in the middle tercile and two points to those in the top tercile. To satisfy EFS scoring criteria, the resulting times were split into terciles, with the fastest tercile assigned zero points, the middle tercile one point and the slowest tercile (or unable to walk) two points. A score of ≥8 was considered frail, and a score of 6 or seven vulnerable by EFS.

2.6 Data Handling

Data collected throughout the study was entered onto a study specific data base REDCap™ (Research Electronic Data Capture)[271] with secure storage and full oversight from information governance. Any paper records which formed part of the source data for the study will be retained securely at site.

Patients were consented for electronic data capture of clinical parameters (e.g. biochemical data) from University Hospitals Birmingham EPR at 1-month, 3-months, 1-year, 3-years and

5-years post-recruitment (facilitated through informatics linkage utilising Hospital Patient Registration number). In addition, clinical outcomes (e.g. hospital admissions, medical events, surgical procedures, death etc.) were electronically captured from Hospital Episodes Statistics for the same time points (facilitated through informatics data linkage utilising NHS number). This allowed long-term data capture of important clinical outcomes without direct patient involvement.

2.6.1 Data Monitoring and Risk

There were no specific risks anticipated with this study. However, any study-related adverse events would have been documented and reported to the steering committee. Should a participant report any thoughts of deliberate self-harm or suicide, or complete a PHQ-9 score of over 20 during the study, a discussion was held with the patient asking whether they would like a referral to the patient's nephrologist or psychology services at the trust.

2.6.2 Participant Withdrawal

In the event of patients wishing to discontinue in the trial, the participant would be withdrawn from the study with the assurance that their usual care will continue unaffected. Identifiable data already collected with consent was retained and used in the study. No further data or tissue was collected, or any other research procedures carried out on or in relation to the participant. If the patient consented to have long term electronic tracking of their outcomes, this was continued.

2.7 Statistics and power calculation

The principal parameters being examined in work package 1 were hospitalisation, mortality and their association with frailty. Based upon US data,[168] we have assumed an adjusted risk ratio of 2.24 for 1-year mortality and 1.56 for 1-year mortality and/or hospitalisation for frail versus non-frail patients receiving haemodialysis. We have assumed a baseline (non-frail) risk of 5% for 1-year mortality and a 40% risk of 1-year mortality/hospitalization, powered to 0.8 and with confidence interval of 0.95. We therefore calculate a sample size of 602 to be adequately powered to demonstrate a difference in 1-year mortality or 150 patients to be powered for 1-year mortality/hospitalization. However, in agreement with the sponsor, a target of 602 was not considered feasible within this single centre study, so a revised target of 500 participants was set with data capture beyond one year.

Statistical analyses were performed using STATA (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) unless otherwise stated. Detailed explanations of statistical methods are found in the experimental chapters and as such will not be repeated here.

Supplementary Table 2-1: Frailty Phenotype

Domain	Parameter	Detail	Score 1 point if:	Modification
Slowness	4m Walk	Standing start, time taken to walk between marks 4m apart. Walking aids allowed. Instructed to "Walk at a brisk, but safe pace"	Male > 173cm AND time ≥ 5.25s Male ≤173cm AND time ≥ 6.13s Female >159cm AND time ≥ 5.25s Female ≤159cm AND time ≥ 6.13s Unable to walk	Times reduced proportionately to walk over 4m rather than 4.57m (15ft)
Weakness	Hand-Grip Strength	Takei Grip-D Dynamometer. One practice grip before measured maximal grip strength on each hand (if able). Best result used for analysis.	Unable to attempt on either side **OR** Male: BMI ≤24 AND Grip ≤29kg BMI 24.1-26 AND Grip ≤30kg BMI 26.1-28 AND Grip ≤ 30kg BMI >28 AND Grip ≤ 32kg Female: BMI ≤23 AND Grip ≤ 17kg BMI 23.1-26 AND Grip ≤ 17.3kg BMI 26.1-29 AND Grip ≤ 18kg BMI > 29 AND Grip ≤ 21kg	-
Exhaustion	Questionnaire Response	How often in the past week have you felt that everything was an effort? How often in the past week have you felt like you couldn't get going?	Response to either question: Most of the time OR Some of the time (≥3 days per week)	-
Low Physical Exertion	Questionnaire Response	How often do you engage in activities that require a low or moderate amount of energy, such as gardening, cleaning the car, or going for a walk?	One to three times per month OR Hardly ever or never	Replaces Minnesota Leisure Time Activity questionnaire
Unintentional Weight Loss	EPR/Clinical Interview	Interrogation of electronic patient record followed by confirmation by patient any weight loss was unintentional and not due to appropriate reduction in volume overload (for example in more recent starters to HD)	Reduction in dry weight of > 4.54kg (> 10lb) AND Participant confirms this was unintentional	Use of EPR to verify weight loss

Supplementary Table 2-2: Frailty Index

Domain	Parameter	Detail	Result	Score
Unintentional Weight Loss	EPR/Clinical Interview	Interrogation of electronic patient record followed by confirmation by patient any weight loss was unintentional and not due to appropriate reduction in volume overload (for example in more recent starters to HD)	Reduction in dry weight of > 4.54kg (> 10lb) AND Participant confirms this was unintentional	1
ADL	Do you require help with any of the following?	Bathing Dressing Getting in or out of a chair Walking around the house Eating Grooming Using the toilet Getting up or down stairs Lifting 10 pounds (4.5kg) Meal preparation Shopping Taking Medication Finances Housework Laundry Using the telephone Transportation	Yes	1 point for each ADL
Physical activity	Questionnaire response	In the past month have you cut down on your usual activity? in the past month, have you stayed in bed for at least half the day due to health? How often do you walk outside?	Yes Yes Less than three days per week	1 1 1
Weakness	Hand-Grip Strength	Takei Grip-D Dynamometer. One practice grip before measured maximal grip strength on each hand (if able). Best result used for analysis.	Unable to attempt on either side **OR** Male: BMI ≤24 AND Grip ≤29kg BMI 24.1-26 AND Grip ≤30kg BMI 26.1-28 AND Grip ≤ 30kg BMI >28 AND Grip ≤ 32kg Female: BMI ≤23 AND Grip ≤ 17kg BMI 23.1-26 AND Grip ≤ 17.3kg BMI 26.1-29 AND Grip ≤ 18kg BMI > 29 AND Grip ≤ 21kg	1
Slowness	4m Walk	Standing start, time taken to walk between marks 4m apart. Walking aids allowed. Instructed to "Walk at a brisk, but safe pace"	Male > 173cm AND time ≥ 5.25s Male ≤173cm AND time ≥ 6.13s Female >159cm AND time ≥ 5.25s Female ≤159cm AND time ≥ 6.13s Unable to walk	1
Health Rating	Questionnaire response	How would you rate your health?	Poor Fair Good Very Good Excellent	1 0.75 0.5 0.25 0
Health Change	Questionnaire response	How has your health changed in the last year	Worse The Same Better	1 0 0
Exhaustion	Questionnaire Response	How often in the past week have you felt that everything was an effort?	Most of the time Some of the Time Rarely	1 0.5 0
		How often in the past week have you felt like you couldn't get going?	Most of the time Some of the Time Rarely	1 0.5 0
Depression	Questionnaire response	How often in the past week have you felt depressed?	Most of the time Some of the Time Rarely	1 0.5 0
Loneliness	Questionnaire response	How often in the past week have you felt lonely?	Most of the time Some of the Time Rarely	1 0.5 0
BMI	Electronic patient record	BMI calculated from height and dry weight on electronic patient record	BMI < 18.5 BMI ≥ 30 30 > BMI ≥ 25 18.5 < BMI < 25	1 1 0.5 0
Cognitive Impairment	Montreal Cognitive Assessment	MOCA Test English 7.1 or appropriate language translation. Threshold score for cognitive impairment proportionately reduced for blind participants and particpants unable to complete drawing tasks due to dexterity issues.	Not blind and able to draw: MOCA < 26 If blind: MOCA <19 If not blind but unable to draw: MOCA < 22	1

Supplementary Table 2-3: Edmonton Frailty Scale

Domain	Parameter	Detail	0 points	1 point	2 points	Modification
Cognition	Clock Face	Clock Face task from Montreal Cognitive Asssessment	No Errors	Minor errors in positioning	Other errors	
General health status	Previous admissions	number of previous admissions with previous year derived from EPR	0	1 or 2	> 2	Derived from EPR rather than patient recall
	Self-reported heatlh	How would you rate your health?	Excellent, Very good, Good	Fair	Poor	
ADLs	Total number of ADLs requiring help	Bathing Dressing Getting in or out of a chair Walking around the house Eating Grooming Using the toilet Getting up or down stairs Lifting 10 pounds (4.5kg) Meal preparation Shopping Taking Medication Finances Housework Laundry Using the telephone Transportation	<2	2 to 4	>4	
Social support	When you need help, can you count upon someone who is willing and able to meet your needs?		Always	Sometimes	Never	
Medication Use	Number of drugs	Interrogation of drug history from EPR	<5	≥5		Derived from EPR rather than patient recall
	Forgetting	At times do you forget to take your prescription medications?	No	Yes		
Nutrition	Weight Loss	Have you recently lost weight such that your clothing has become looser?	No	Yes		
Mood		Do you often feel sad or depressed?	No	Yes		
Continence		Do you have a problem with losing control of urine when you don't want to?	No	Yes		
Functional Performance	4m Walk		≤3.98s	>3.98s	>5.37s Unwilling or unable	Replaces timed up and go test. Results of timed walk split into terciles and points awarded according to tercile.

Chapter 3:

Correlations, agreement and utility of frailty instruments in prevalent haemodialysis patients: baseline cohort data from the FITNESS study

Authors: Benjamin M Anderson, Muhammad Qasim, Gonzalo Correa, Felicity Evison, Suzy Gallier, Charles J Ferro, Thomas A Jackson, Adnan Sharif

3.1 Extent of Personal Contribution

I coordinated all study visits with participants and dialysis unit staff. I recruited participants, and collected all baseline data with the support of Dr Gonzalo Correa, Dr Muhammad Qasim, and Dr Adnan Sharif. All colleagues were trained and supervised by me in data collection, and I was responsible for maintaining training and personnel logs in the site file.

Ms Felicity Evison, and Ms Suzy Gallier were responsible for interrogation of EPR for IMD Quintile assessment. I performed all subsequent data cleaning, integrity, and analyses with guidance from Dr Adnan Sharif.

The first draft of the manuscript was written by myself and I was responsible for all edits and revisions. This chapter was published in Clinical Kidney Journal with me as the first author.[272]

3.2 Abstract

3.2.1 Background.

Frailty is associated with poor outcomes for haemodialysis patients, but its prevalence is uncertain due to heterogeneous definitions. The aim of this study was to compare and contrast prevalence and features of commonly used frailty instruments in an English haemodialysis cohort.

3.2.2 Methods.

The FITNESS study recruited adults aged ≥18-years after informed consent, with ≥3-months haemodialysis exposure and no hospital admission within 4-weeks unless for dialysis access. Study participants were clinically phenotyped with frailty instruments including the Frailty Index (FI), Frailty Phenotype (FP), Edmonton Frailty Scale (EFS), and Clinical Frailty Scale (CFS), alongside comprehensive baseline data collection of biochemical, clinical and social characteristics.

3.2.3 Results.

Between 12th January 2018 and 18th April 2019, 485 haemodialysis patients were recruited. Baseline demographics were median age 63 years, male sex 58.6% and non-White ethnicity 42.1%. Prevalence of frailty was high; 41.9% of participants were frail by FP, 63.3% by FI, 50.2% by EFS, and 53.8% by CFS. Female gender was associated with increased frailty, with no independent association observed with age or ethnicity. While correlation between frailty instruments was strong, intraclass correlation coefficient for frailty agreement was 0.628 (95% C.I. 0.585-0.669) and only weak agreement between instrument pairs.

3.2.4 Conclusion.

Frailty is highly prevalent among haemodialysis patients regardless of criteria used. However, our data suggests caution when interpreting heterogenous definitions of frailty for haemodialysis patients as they are not inter-changeable. Consensus agreement on the optimal frailty definition for haemodialysis patients must balance ease of use with predictive ability for adverse outcomes before determining clinical application.

3.3 Introduction

Frailty is a syndrome of accelerated ageing, characterised by multisystem dysregulation and vulnerability to stressor events such as infections or surgery.[273] Best studied in the general population, frailty is associated with poor outcomes including mortality, hospitalisation, cognitive impairment, and disability.[17] However, heterogenous use of frailty tools is a major limitation for research investigation and clinical application.

The gold standard frailty definition is the Comprehensive Geriatric Assessment (CGA),[32] but this has significant cost and logistic implications. Consequently, screening tools have been proposed; including the Fried Frailty Phenotype (FP),[19] Rockwood Frailty Index (FI),[47] Edmonton Frailty Scale (EFS),[55] and Clinical Frailty Scale (CFS).[27] The FP distinguishes frailty from disability and comorbidity[39] and has been the predominant frailty measure used in research practice.[40] It is simple to administer but focuses upon measures of sarcopenia rather than a multidimensional approach.[41-43] Conversely, the FI does not distinguish frailty from disability or comorbidity, defining frailty as a composite of "deficits" across multiple clinical, biochemical and social domains.[36,37] This gives greater scope for interpretation but is more complex to administer, hence the same group devised the EFS and CFS as more accessible deficit models.

Lack of diagnostic consensus is important as frailty is a major problem for kidney failure populations, with prevalence amplified compared to the general population independent of age. For example, frailty prevalence by FP criteria amongst community-dwelling elderly in the United States (US) has been estimated between 6.9%-16.3%[19,44] compared with 31%-42% of

US haemodialysis recipients ≥18.[46,49,170] Outcome data, predominantly derived from US cohorts, demonstrate adverse morbidity and mortality outcomes in frail haemodialysis patients of all ages.[168,170,184] In summary, frailty in haemodialysis patients is common, clinically important and warrants further investigation to clarify clinical applications.

Therefore, we require better understanding of how frailty tools can be utilised for haemodialysis populations to improve delivery of care. Instruments define frailty through different mechanisms and there is a need to establish how these compare with each other in this high-risk population. As a first step, we must improve our understanding of prevalence stratified by different frailty instruments. In this report, we describe the prevalence, correlation and interaction between various frailty assessment measures at recruitment.

3.4 Methods

3.4.1 Study design

A detailed description of the FITNESS (**F**railty **I**ntervention **T**rial i**N** **E**nd-**S**tage patient**S** on haemodialysis) study has been reported.[263] Briefly, this first stage is a cross-sectional assessment and long-term follow up of study participants on maintenance haemodialysis with comprehensive frailty and bio-clinical phenotyping.[264] The study protocol was subject to favourable opinion by the South Birmingham Research Ethics Committee (Ref: 17/WM/0381) and institutional review board assessment of University Hospitals Birmingham NHS Foundation Trust (RRK6082).

3.4.2 Study setting

Patients were recruited from a single nephrology centre located in Birmingham, England. The service provides haemodialysis to approximately 1000 patients in a mixture of urban and rural settings, with a diverse range of ethnic and socioeconomic groups. Eligible patients were identified by interrogation of hospital electronic patient records (EPR) and from discussion with clinicians at each dialysis unit. Eligible patients were approached, given written and verbal information about the study, and given sufficient opportunity to consider the information before giving consent for recruitment.

3.4.3 Eligibility criteria

Inclusion criteria included adults aged ≥18, receiving regular haemodialysis for at least 3 months' duration and ability to give informed consent. The only exclusion criterion was inpatient care within 4-weeks of recruitment unless for vascular access purposes, to avoid confounding of baseline data with frailty secondary to recent hospitalisation.

3.4.4 Baseline assessment

Baseline assessments took place at individual dialysis units before and during their usual dialysis session. To negate potential effects of the long break from dialysis, we avoided the first haemodialysis session after the long weekend interval.

Prior to connection to dialysis, participants underwent a timed walk over 4 metres, and grip strength dynamometer assessment. As the 4 metre timed walk replaced the timed up-and-go test in the case of the EFS, we split the results into terciles and attributed zero points to those

in the lowest tercile, one point to those in the middle tercile and two points to those in the top tercile. Once dialysis started, participants completed questionnaires upon disability (activities of daily living; ADL), demography, social history and frailty-specific questionnaires. EPR was interrogated for comorbidities, drug history, dialysis vintage/adequacy, previous transplantation and biochemical data, providing sufficient data to calculate FP, FI, EFS assessments. Determination of socio-economic deprivation was based upon the Index of Multiple Deprivation, a multiple deprivation model calculated at the local area level, with 1 representing the most deprived and 5 the least deprived area respectively.[274]

3.4.5 Frailty Definitions

3.4.5.1 Frailty Phenotype

The Frailty Phenotype was determined as a score between zero and five, with participants receiving one point for each of the following: slow walking speed, weak grip strength, exhaustion, weight loss, and low physical activity. Slow walking speed was assessed from a standing start over 4 metres, and participants scored one point if their time was over or equal to prespecified values stratified by height and gender or if they were unable to undertake the test. These values were determined by the original FP described by Fried and colleagues[19], with times reduced in proportion to the reduced distance of 4m in this study versus 15 feet in the FP study. Poor grip strength was evaluated with dynamometer (Takei Grip D, Takei Scientific Instruments, Niigata, Japan); participants scored one point if their grip strength in either hand was not above cut-off values as per the original FP[19] stratified by BMI and gender, or if they were unable to perform the test in either hand. Unintentional weight loss of greater

than 4.5kg in the past year scored one point. To characterise exhaustion, participants were asked whether they felt that a) everything was an effort or b) they felt they could not get going within the past week. The possible responses were “Rarely”, “Some of the time”, and “Most of the time”. Participants scored one point for exhaustion if they responded that they felt either statement was true either most of the time or - if they answered “Some of the time” – they felt it was the case on more than 3 days in the week prior to recruitment. Physical activity was assessed by response to the question “How often do you engage in activities that require a low or moderate level of energy such as gardening, cleaning the car, or going for a walk?”. Possible responses were “More than once per week”, “Once per week”, “One to three times per month”, and “Hardly ever or never”. Participants scored one point for low physical activity if they responded “One to three times per month” or “Hardly ever or never”. Participants were considered not frail by FP if their total score was 0, vulnerable if their total score was 1-2 and frail if their score was 3-5. The FP is summarised in Supplementary Table 2-1.

3.4.5.2 Frailty Index

A Frailty Index score was based upon previous work from van Munster and colleagues conducted in an elderly haemodialysis cohort[270]. The FI consisted of 32 variables across measuring deficits across multiple body systems. Each variable was scored out of one by pre-determined cut-offs and the FI comprised a mean average of these scores, giving a continuous variable between zero and one. The FI was not originally designed to be split into categories, though many groups have subsequently done so to aid interpretation. For example, the primary care eFI (electronic Frailty Index)[49,50] categorised scores of robust ($\leq$0.12), mildly frail (>0.12 to $\leq$0.24), moderately frail (>0.24 to $\leq$0.36) and severely frail (>0.36). Due to the

relatively low numbers of non-frail participants using this classification, and the lack of a "vulnerable" category present in the other instruments, we reclassified the mildly frail group (>0.12 to ≤0.24) as vulnerable and scores ≥0.24 were classed as frail (≥0.24 mildly, ≥0.36 moderately, and ≥0.48 severely frail). The Frailty Index is summarised in Supplementary Table 2-2

3.4.5.3 Clinical Frailty Scale

Clinical Frailty Scale (CFS) was derived from interrogation and interpretation of independent activity of daily living questionnaire responses, which were administered by the investigators and interpreted by the lead investigator. Scores can range between 1 to 9, with a threshold score ≥5 considered frail, 4 considered vulnerable and <4 considered robust.

3.4.5.4 Edmonton Frailty Scale

The Edmonton Frailty Scale was determined according to the original study[38], but in order to reduce test burden on participants, a 4 metre walk was substituted for the timed up and go test. The results were split into terciles and attributed zero points to those in the lowest tercile, one point to those in the middle tercile and two points to those in the top tercile. To satisfy EFS scoring criteria, the resulting times were split into terciles, with the fastest tercile assigned zero points, the middle tercile one point and the slowest tercile (or unable to walk) two points. A score of ≥8 was considered frail, and a score of 6 or seven vulnerable by EFS. The EFS is summarised in Supplementary Table 2-3.

3.4.6 Statistics

Statistical analysis was performed using STATA (StataCorp 2019, Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC) and R Studio (version 1.3.959). Categorical data was presented as numbers and percentages, with continuous variables reported as medians and interquartile ranges (IQRs).

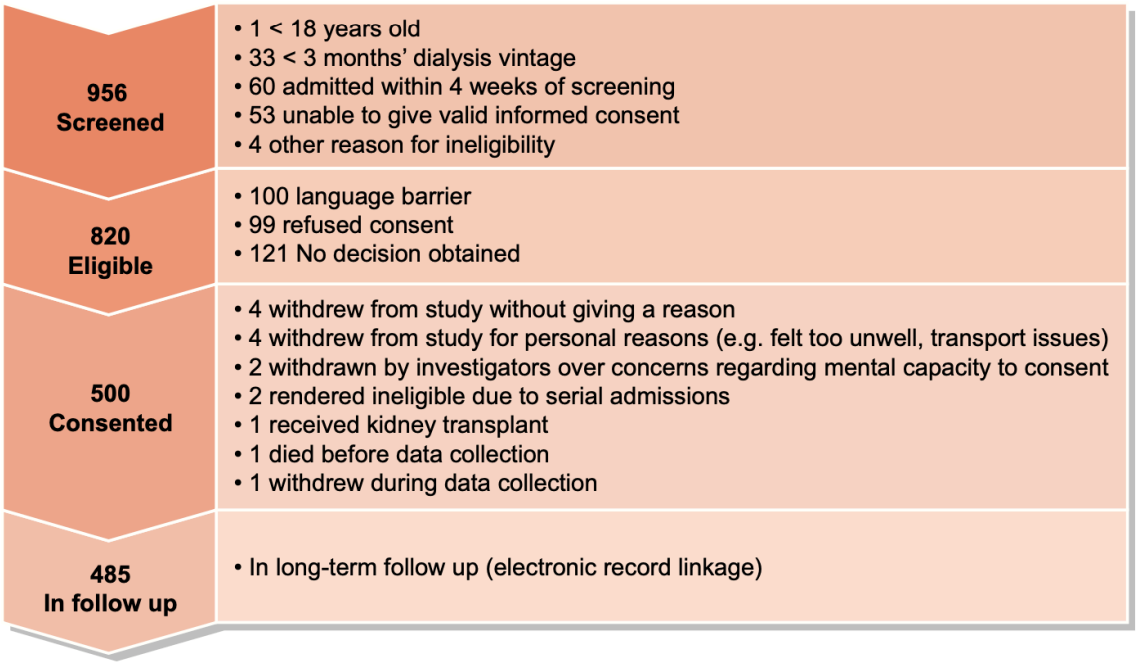


Figure 3-1: PRISMA flowchart of study participation in the FITNESS study. The numbers for specific exclusion criteria do not add up to the total excluded number as some participants had more than one reason for ineligibility. Reproduced from Anderson et al[272]. CKJ 2021. Open Access under Creative Commons License.

Differences between groups were compared using chi-square or Fisher's Exact tests for categorical variables and student t-tests or Mann-Whitney tests (parametric or non-parametric data respectively) for all continuous variables. Correlations were analysed using Spearman's test. Odds ratios were calculated using logistic regression, with adjustment against clinically important variables including age, gender, ethnicity, Charlson Comorbidity

Score and social deprivation. Agreement between frailty scores were analysed using Cohen's Kappa or Intraclass coefficient as appropriate. Strength of agreement was rated as >0.90 almost perfect agreement, 0.80-0.90 strong, 0.60-0.79 moderate, 0.40-0.59 weak, 0.21-0.39 minimal and ≤0.20 no agreement.[275]

Missing data was assumed missing at random and handled via listwise deletion. A p value < 0.05 was considered significant in the statistical analysis.

3.5 Results

3.5.1 Recruitment

In total, 500 participants gave informed consent to participate in the FITNESS study between 12th January 2018 and 18th April 2019. After initial approach, 15 patients withdrew from the study either prior to or during baseline recruitment, leaving 485 with data available for analysis. Figure 3-1 shows a PRISMA flowchart outline study recruitment.

3.5.2 Baseline demographics and co-morbidities

Table 3-1 highlights baseline demographics and co-morbidities of our study participants. We identified significant health and socio-economic burden in our overall study cohort, but no difference between frailty instruments.

A notable demographic feature of our study recruits was a significant proportion of individuals of non-White ethnicity (comprising 42.1% of total study cohort). In Table 3-2, we highlight significant differences between ethnic groups in reasons for non-recruitment after invitation.

For example, difficulty with language barrier was recorded particularly highly in South Asian and other ethnicity (not White, South Asian or Black) patients, while declined invitations and lack of mental capacity were proportionally higher in White and Black patients. However, our study participant cohort is broadly representative of our local haemodialysis population by ethnicity, gender and age as confirmed by comparison with registry data.[276]

3.5.3 Prevalence of frailty by instrument

Figure 3-2summarises prevalence of frailty, vulnerability and robustness using the different instruments. The median FP was 2 (interquartile range [IQR]: 1-3), with 63 (13.0%) participants categorised as robust, 219 (45.2%) vulnerable and 203 (41.9%) as frail.

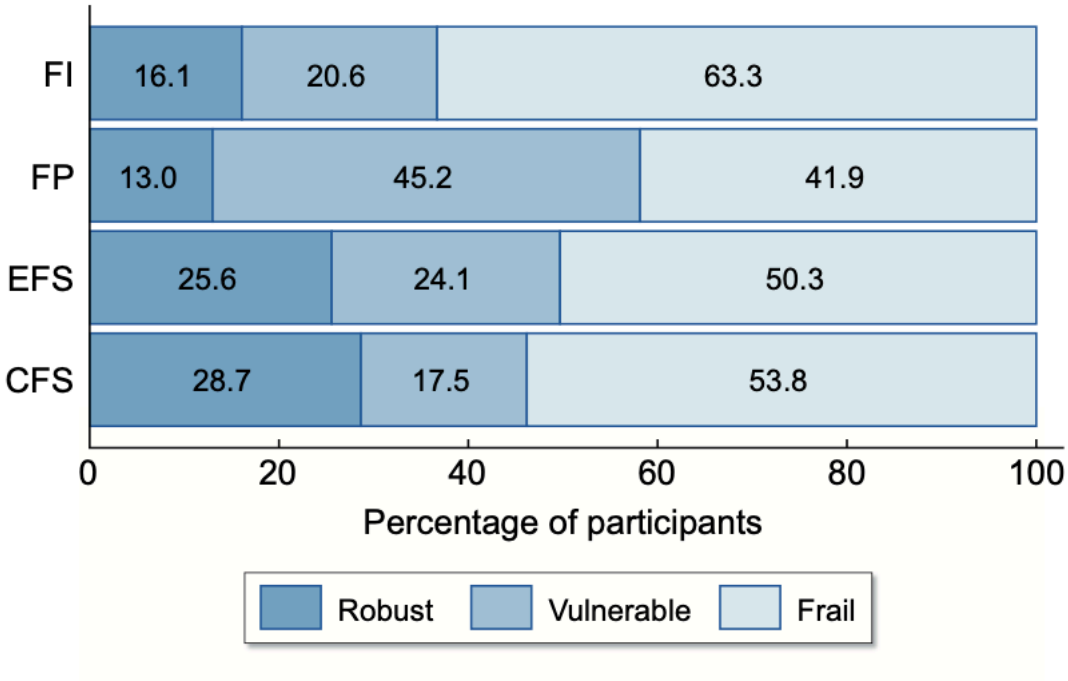


Figure 3-2: Percentage of participants classified as robust, vulnerable or frail by different frailty instruments: FI, FP, EFS and CFS. Reproduced from Anderson et al[272]. CKJ 2021. Open Access under Creative Commons License.

The median FI was 0.305 (IQR: 0.164-0.477). Using the eFI thresholds[49,50] in our cohort, 78 (16.1%) of participants were robust, 100 (20.6%) were mildly frail, 116 (23.9%) moderately

frail, and 191 (39.4%) severely frail. Due to the relatively low numbers of non-frail participants using this classification, and the lack of a "vulnerable" category present in the other instruments, we reclassified the mildly frail group (>0.12 to ≤0.24) as vulnerable. Using this FI classification 16.1% of participants were robust, 20.6% vulnerable and 63.3% frail (comprising 23.9% mildly frail, 14.6% moderately frail, and 24.7% severely frail). This new FI classification was used in all further analyses.

The median EFS was 8 (IQR: 5-10), with 124 (25.6%) classed as robust, 117 (24.1%) vulnerable, 114 (23.5%) mildly frail, 93 (19.2%) moderately frail and 37 (7.6%) severely frail.

Finally, the median CFS was 5 (IQR 3-6), with 139 (28.66%) classed as robust, 85 (17.5%) vulnerable, 131 (27.0%) mildly frail, 103 (21.2%) moderately frail, and 27 (5.6%) severely frail.

3.5.4 Association between frailty and key demographics

Frail participants by FP had a significantly higher median age in years than non-frail participants (67 versus 60 respectively, p<0.001), as did frail participants adjudged by CFS (65 versus 60 respectively, p=0.002). Those aged ≥65 years were more likely to be characterised as frail by CFS (Odds Ratio [OR]1.50, 95% C.I. 1.05-2.16, p=0.025) and FP (OR 1.82, 95% C.I. 1.27-2.63, p=0.001) on univariable analysis. However, these associations were no longer significant when adjusted for clinically important variables such as Charlson Comorbidity Score, gender, ethnicity and social deprivation. There was no significant association between age ≥65 and FI (OR 1.14, 95% C.I. 0.79-1.65, p=0.49) or EFS (OR 0.95, 95% C.I. 0.66-1.35, p=0.76) on either univariable or adjusted analyses. Frailty remained prevalent in younger

patients, with 49.0% of participants <65 years being characterised as frail by CFS, 51% frail by EFS, 35% by FP, and 61.9% by FI.

Female participants were more likely to be frail by all frailty instruments, with OR of 1.57 (95% C.I. 1.09-2.26, p=0.016) for FP frailty, 1.74 (95% C.I. 1.18-2.55, p=0.005) for FI frailty, 1.72 (95% C.I. 1.20-2.48, p=0.004) for EFS frailty, and 1.79 (95% C.I. 1.24-2.59, p=0.002) for CFS frailty. These associations were retained upon adjustment for Charlson Comorbidity Score, social deprivation, age ≥65, and ethnicity; ORs were 1.76 for FP (95% C.I. 1.17-2.67, p=0.007), 1.87 for FI (95% C.I. 1.22-2.85, p=0.004), 1.72 for EFS (95% C.I. 1.16-2.58, p=0.008), and 2.06 for CFS (95% C.I. 1.37-3.12, p=0.001).

Table 3-3 demonstrates that increasing frailty was variable associated with other physical and physiological parameters. Table 3-3: Correlation between baseline frailty instruments and physical/psychological parameters

	Frailty Phenotype	Frailty Index	Edmonton Frailty Scale	Clinical Frailty Scale
Charlson score	0.265	0.226	0.175	0.275
Number of admissions previous 12-months	0.099	0.103	0.344	0.047
Number of drugs	0.280	0.362	0.324	0.352
Dialysis vintage (years)	0.129	0.077	-0.039	0.087
Grip strength (strongest hand)	-0.576	-0.470	-0.398	-0.434
Grip strength (weakest hand)	-0.547	-0.481	-0.392	-0.440
MOCA	-0.295	-0.346	-0.364	-0.310
PHQ9 score	0.419	0.537	0.477	0.361
Health rate score	0.421	0.513	0.587	0.387
EQ5D	-0.434	-0.494	-0.411	-0.392

Spearman's Rho. All values significant at P<0.001 level.

Table 3-4 shows there was no significant difference between ethnicities in frailty status regardless of the instrument used, despite variation in ranges of frailty prevalence estimates between ethnicities.

3.5.5 Correlation between frailty instruments

Table 3-5 shows correlations between frailty instruments. The FI showed strong correlation with both the CFS (Spearman's ρ=0.884, p<0.001) and FP (Spearman's ρ=0.790, p<0.001). The EFS showed strong correlation with the FI (ρ=0.755, p<0.001) and moderately strong correlation with the FP (ρ=0.666, p<0.001). The CFS was moderately correlated with FP (ρ=0.665, p<0.001), and the EFS (ρ=0.646, p<0.001).

3.5.6 Agreement between instruments on severity of frailty

Figure 3-3 gives a visual representation of the agreement between scores of frailty severity. The Intraclass Correlation Coefficient across the scores was 0.628 (95% C.I. 0.585-0.669). The FI showed weak agreement with FP (κ=0.409; p<0.001), EFS (κ=0.414; p<0.001), and CFS (κ=0.539; p<0.001). The FP showed minimal agreement with EFS (κ=0.0.334; p<0.001) and CFS (κ=0.317; p<0.001). The EFS and CFS showed minimal agreement (κ=0.392; p<0.001). Agreement between frailty instruments was weakest in the vulnerable category. Intraclass correlation coefficients by ethnicity were 0.622 (95% C.I. 0.566-0.676) for white, 0.645 (95% C.I. 0.562-0.721) for South Asian, 0.602 (95% C.I. 0.495-0.702) for black, and 0.688 (95% C.I. 0.449-0.873) for other ethnicity participants.

3.6 Discussion

FITNESS is the largest European, prospective cohort study with detailed baseline frailty phenotyping of haemodialysis patients linked to long-term outcomes. In our first analysis, we aim to compare and contrast multiple frailty instruments to determine agreement, correlation and utility for haemodialysis patients. Our main finding is a high prevalence of frailty among haemodialysis patients regardless of actual instrument used. Females are more likely to be classified as frail regardless of instrument used independent of other demographic characteristics. Finally, while we highlight strong correlation between raw frailty scores, agreement of frailty status between instruments is weak at best and suggests frailty tools are not inter-changeable.

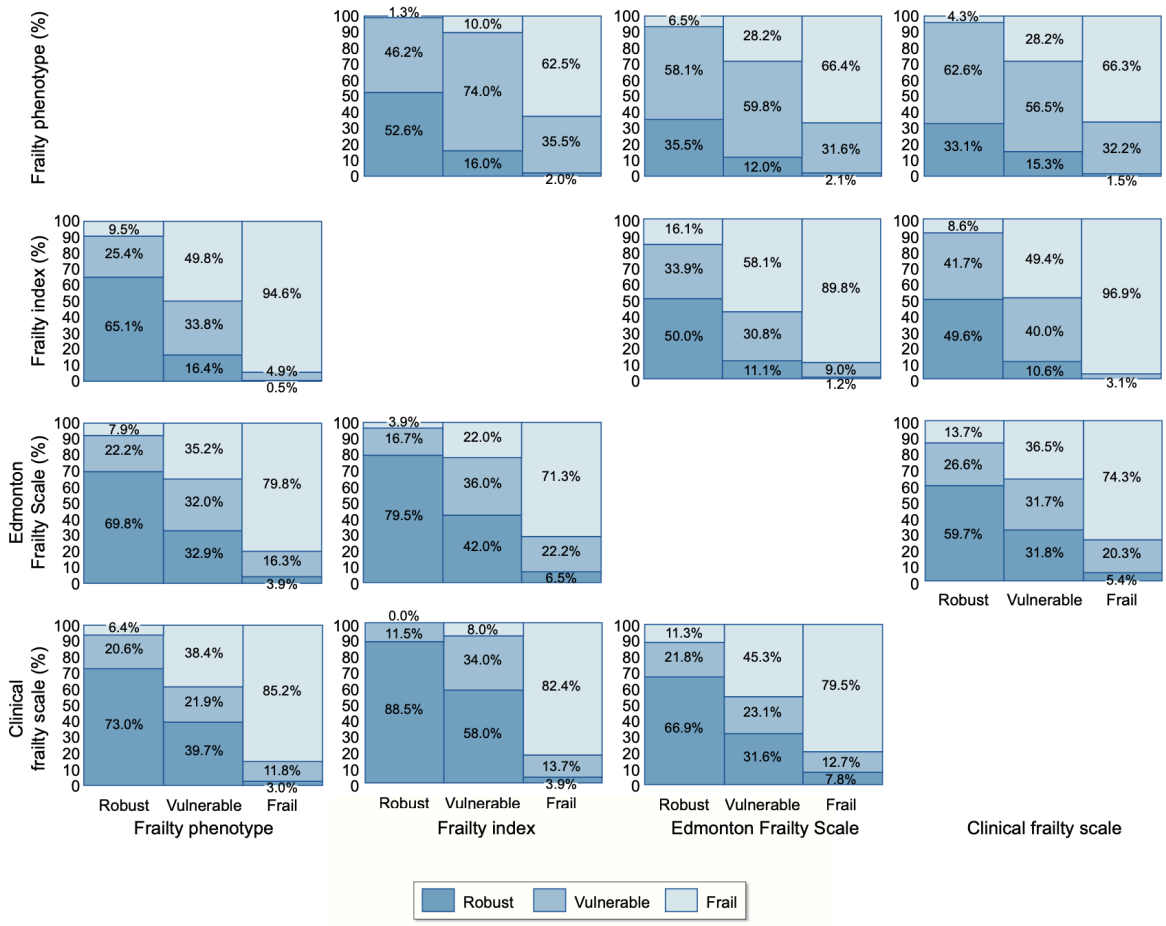


Figure 3-3: Composite of agreement upon frailty status. Percentages shown indicated the proportion of participants considered frail, vulnerable, or robust by the y-axis frailty tool within the categories of frail, vulnerable, and robust of the x-axis frailty tool. Reproduced from Anderson et al[272]. CKJ 2021. Open Access under Creative Commons License.

Our results indicate a higher burden of frailty than that reported in some studies. A recent Spanish study categorised 26.5% of 277 prevalent haemodialysis patients as frail by EFS,[184] compared to 50.2% using the same measure in our cohort. A Dutch study found 48% of 125 incident HD recipients ≥65 were frail by FP.[277] While this appears similar to our 42%, our cohort was not limited to older dialysis patients. Our prevalence appears more comparable to US cohorts, where between 31% and 42% of haemodialysis recipients are categorised as frail by FP regardless of age.[46,170] We must exercise caution when comparing cohorts; there are likely to be many reasons why burden of frailty can differ between countries, including demographics, socio-cultural and/or environmental differences.

Frailty prevalence was significantly higher in females across all instruments studied in our haemodialysis cohort. Our data do not offer clues as to why females may be frailer than males, but this phenomenon is not limited to the haemodialysis population.[19] It is interesting to observe that in this multi-ethnic cohort, frailty instruments did not show any significant difference in prevalence between ethnic groups, which aligns with data from non-English dialysis cohorts. This is contrary to a study in the general population, where frailty prevalence (by electronic FI) varied between 14.0% in Black to 32.9% in Bangladeshi patients aged ≥65 in England (overall prevalence of 18.1%).[278] The underlying reasons for this discrepancy require further investigation, but may be related to the known reverse epidemiology and/or survival paradox observed for non-White patients on haemodialysis.[279] It is reassuring that there was no meaningful difference in frailty agreement between ethnicities; the original validation cohorts were North American with different ethnic breakdowns to the UK.[19,27,47,55] As expected, frailty greatly increased with age but remained a significant burden among younger haemodialysis patients.

We observed a large spread of prevalence across the different frailty instruments. Correlation between raw frailty scores was stronger than the agreement between these same instruments when divided into frailty categories. This suggests instruments are classifying large numbers of participants with frailty differently. This assertion is supported by the 21.5% difference in frailty prevalence between the highest and lowest estimations, the FI and FP, respectively. Our data demonstrated weakest agreement between frailty instruments in the vulnerable category. This is of particular concern as this is the 'decision zone' where clinical conclusions

may be drawn based upon whether a patient is frail or not-frail (i.e., vulnerable), which may lead to detrimental consequences for HD recipients. Discrepancy between estimated frailty prevalence and agreement between instruments demonstrates the difficulties in attempting to divide frailty into neat 'silos' and is in keeping with a syndrome which defies easy clinical – and indeed mechanistic – definition. The weak agreement between instruments on frailty classification suggests caution be applied when attempting to dichotomise individual patients into frailty groups.

Achieving consensus on the optimal frailty screening tool for haemodialysis patients requires a balance between ease of use versus utility. Frailty instruments range from quick (e.g., CFS) to more time consuming (FI). Usability will be centre-specific and dependent upon infrastructure, multi-disciplinary support and EPR capabilities. A more important question is whether a frailty instrument that characterises two-thirds of haemodialysis recipients as 'frail' provides added value to clinical decision-making. For example, if these instruments are used as screening tools for referral to support networks, then referring over half of dialysis recipients of all ages for further assessment would be impractical and counterproductive. Conversely, a frailty prevalence less than observed here would be more manageable but may risk underestimating 'true' frailty in our patients and depriving at-risk individuals from potential intervention. Van Loon and colleagues demonstrated a frailty prevalence of 75% in incident elderly (aged ≥65 years) haemodialysis patients by the gold-standard CGA, with the FP displaying good positive predictive value but poor negative predictive value for CGA-defined frailty.[277] We can speculate that the instruments returning higher rates of frailty within the FITNESS cohort, such as the FI, may represent a closer estimate of 'true' frailty

prevalence in this cohort. However, the very strong correlation between raw FI and CFS scores may suggest that the CFS, properly applied using assessment of ADL disability, may be a suitable alternative. The CFS is simple and speedy to use, and therefore carries significant advantage in clinical practice over the more detailed FI. However, true prognostication value will be determined by linkage of each frailty instrument to long-term adverse outcomes and that is planned as part of the FITNESS study.

To the best of our knowledge, this study is the first to directly compare commonly used frailty instruments in a large prevalent haemodialysis cohort. One of its major strengths is study recruitment representative of the local cohort, featuring a diverse mix of demographics, co-morbidities and socio-economic backgrounds. This should provide reassurance for translation of these findings to clinical application in real-world cohorts. Limitations include the use of frailty assessment as a single baseline measure in a cross-sectional analysis rather than prospective serial measurements over time. This is important as the frailty syndrome appears to be a dynamic process.[280] Frailty characteristics may also not be translatable across different cohorts and should be interpreted with caution in non-English populations.

To conclude, our work identifies a high burden of frailty in a large prospective cohort of prevalent English haemodialysis patients regardless of frailty definition. At present, lack of consensus in frailty assessment for haemodialysis patients limits translatability between cohorts, prohibiting collaborations for clinical research. Our data, highlighting significant variability between different measures, reinforces the importance of achieving consensus on this issue. However, the optimal instrument requires a balance between ease of use, utility

and predictive value for adverse outcomes. Prospective monitoring of the FITNESS cohort, with record linkage to clinical outcomes, will provide further insight into the clinical sequelae associated with different frailty instruments and aid such discussions to achieve consensus.

3.7 Tables

Table 3-1: Baseline demographics of FITNESS study participants

Parameter		Total cohort	Participants identified as frail by:				P value
			FP	FI	EFS	CFS	
Participants identified as frail (% of total cohort)		-	203 (41.9%)	307 (63.3%)	244 (50.3%)	261 (53.8%)	-
Median Age		63 (53-74)	67 (56-77)	63 (54-75)	63 (53-74.5)	65 (55-76)	0.125
Ethnicity	*White*	281 (57.9%)	121 (59.6%)	174 (56.7%)	132 (54.1%)	144 (55.2%)	0.909
	South Asian	115 (23.7%)	51 (25.1%)	80 (26.1%)	61 (25.0%)	71 (27.2%)	
	Black	76 (15.7%)	27 (13.3%)	46 (15.0%)	47 (19.3%)	41 (15.7%)	
	Other	13 (2.7%)	4 (2.0%)	7 (2.3%)	4 (1.6%)	5 (1.9%)	
Male		284 (58.6%)	106 (52.2%)	165 (53.8%)	127 (52.1%)	136 (52.1%)	0.974
Median BMI		26.8 (23.2-32.4)	27.8 (22.7-33.6)	27.9 (23.1-33.2)	27.7 (23.1-33.6)	27.9 (23.2-33.7)	0.967
Cause of kidney failure*	*Diabetes*	114 (23.5%)	64 (31.5%)	86 (28.0%)	71 (29.1%)	81 (31.0%)	0.800
	Ischaemic	38 (7.8%)	18 (8.9%)	27 (8.8%)	20 (8.2%)	24 (9.2%)	0.983
	Hypertension	39 (8.4%)	14 (6.9%)	22 (7.2%)	21 (8.6%)	17 (6.5%)	0.823
	IgA	37 (7.6%)	12 (5.9%)	21 (6.8%)	19 (7.8%)	17 (6.5%)	0.882
	PKD	28 (5.8%)	7 (3.5%)	14 (4.6%)	11 (4.5%)	11 (4.2%)	0.933
	FSGS	24 (5.0%)	10 (4.9%)	13 (4.2%)	13 (5.3%)	10 (3.8%)	0.852
	Reflux	17 (3.5%)	11 (5.4%)	12 (3.9%)	10 (4.1%)	10 (3.8%)	0.826
	Obstructive	16 (3.3%)	7 (3.5%)	8 (2.6%)	7 (2.9%)	6 (2.3%)	0.896
	AAV	15 (3.1%)	5 (2.5%)	6 (2.0%)	5 (2.1%)	4 (1.5%)	0.741
	Interstitial Nephritis	10 (2.1%)	4 (2.0%)	5 (1.6%)	3 (1.2%)	4 (1.5%)	0.946
	Myeloma	10 (2.1%)	2 (1.0%)	5 (1.6%)	3 (1.2%)	2 (0.8%)	0.835
	Other	86 (17.7%)	36 (17.7%)	60 (19.5%)	46 (18.9%)	47 (18.0%)	0.950
	Unknown	68 (14.0%)	23 (11.3%)	40 (13.0%)	28 (11.5%)	37 (14.2%)	0.749
Medical co-morbidities	*MI*	98 (20.2%)	53 (26.1%)	73 (23.8%)	61 (25.0%)	64 (24.5%)	0.946
	Heart failure	52 (10.7%)	24 (11.8%)	35 (11.4%)	31 (12.7%)	33 (12.6%)	0.958
	Stroke	57 (11.8%)	36 (17.7%)	43 (14.0%)	37 (15.2%)	40 (15.3%)	0.725
	PVD	47 (9.7%)	27 (13.3%)	36 (11.7%)	26 (10.7%)	32 (12.3%)	0.854
	Cancer	56 (11.6%)	18 (8.9%)	34 (11.1%)	25 (10.3%)	26 (10.0%)	0.881

Smoking history	*Current*	68 (14.1%)	28 (13.9%)	41 (13.4%)	36 (14.8%)	30 (11.5%)	0.971
	Previous	132 (27.3%)	51 (25.3%)	78 (25.5%)	59 (24.3%)	68 (26.2%)	
	Never	284 (58.7%)	123 (60.9%)	187 (61.1%)	148 (60.9%)	162 (62.3%)	
Median Charlson Score**		4 (3-6)	5 (4-7)	5 (3-6)	5 (3-6)	5 (4-7)	0.235
Dialysis details	*Dialysis vintage (median in months)*	37 (17-76)	49 (22-93)	41 (18-82)	35 (16-77)	41 (20-81)	0.219
	Line	113 (23.3%)	54 (26.6%)	77 (25.1%)	67 (27.5%)	66 (25.3%)	0.916
	Kt/V	1.6 (1.4-1.9)	1.6 (1.4-1.9)	1.6 (1.4-1.9)	1.6 (1.4-1.9)	1.6 (1.4-1.9)	0.835
Transplant list status	*Active*	58 (12.0%)	11 (5.4%)	27 (8.8%)	20 (8.2%)	22 (8.4%)	0.592
	Suspended	15 (3.1%)	2 (1.0%)	9 (2.9%)	6 (2.5%)	6 (2.3%)	
	Not listed	412 (85%)	190 (93.6%)	271 (88.3%)	218 (89.4)	233 (89.3%)	
% Employment Status	*Employed*	69 (14.3%)	5 (2.5%)	16 (5.2%)	13 (5.4%)	8 (3.1%)	0.337
	Unemployed	148 (30.6%)	67 (33.2%)	114 (37.3%)	94 (38.7%)	90 (34.6%)	
	Retired	267 (55.2%)	130 (64.4%)	176 (57.5%)	136 (56.0%)	162 (62.3%)	
% Job Role***	*Unskilled Manual*	181 (39.3%)	93 (48.4%)	131 (45.8%)	101 (44.5%)	111 (45.7%)	0.999
	Skilled Manual	101 (21.9%)	37 (19.3%)	58 (20.3%)	49 (21.6%)	51 (21.0%)	
	Clerical	52 (11.3%)	24 (12.5%)	33 (11.5%)	27 (11.9%)	24 (9.9%)	
	Managerial	46 (10.0%)	14 (7.3%)	21 (7.3%)	18 (7.9%)	20 (8.2%)	
	Professional	81 (17.6%)	24 (12.5%)	43 (15.0%)	32 (14.1%)	37 (15.2%)	
% Education Level	*High School*	342 (70.7%)	153 (75.7%)	229 (74.8%)	185 (76.1%)	196 (75.4%)	0.884
	College/Sixth Form	92 (19.0%)	39 (19.3%)	54 (17.7%)	41 (16.9%)	43 (16.5%)	
	University	50 (10.3%)	10 (5.0%)	23 (7.5%)	17 (7.0%)	21 (8.1%)	
Residence	*Own home*	462 (95.9%)	188 (93.1%)	288 (94.4%)	224 (93.0%)	244 (94.2%)	0.993
	Warden-Controlled Flat	12 (2.5%)	7 (3.5%)	10 (3.3%)	11 (4.6%)	9 (3.5%)	
	Residential Home	5 (1.0%)	4 (2.0%)	4 (1.3%)	4 (1.7%)	3 (1.2%)	
	Nursing Home	3 (0.6%)	3 (1.5%)	3 (1.0%)	2 (0.8%)	3 (1.2%)	
% With Professional Carers****		36 (7.8%)	31 (16.1%)	35 (12.0%)	30 (13.0%)	36 (14.6%)	0.607

P values for differences between those classified as Frail by each of the frailty scores studied. P values obtained by Chi square or Fischer's exact as appropriate for categorical data, Kruskal-Wallis or Rank Sum test as appropriate for continuous data. *Some participants had >1 cause of kidney failure listed. **CKD omitted from Charlson Score. ***Current job or previous job if unemployed/retired. ****For those living in own home.

Table 3-2: Reasons for non-recruitment by ethnicity

	White		South Asian		Black		Other		p
	n	% of ethnicity	n	% of ethnicity	n	% of ethnicity	n	% of ethnicity	
Screened	474	-	285	-	142	-	41	-	0.0013
Recruited	281	59.3	115	40.4	77	54.2	13	31.7	
Reason for Non-Recruitment									
Under 18	0	0	1	0.6	0	0	0	0	0.577
Lacking mental capacity	26	13.5	11	6.5	16	24.6	0	0	**<0.001**
Dialysis vintage <3 months	18	9.3	6	3.5	5	7.7	4	14.3	0.052
Inpatient <4 weeks	35	18.1	11	6.5	9	13.8	5	17.9	**0.005**
Language barrier	6	3.1	83	48.8	3	4.6	14	50	**<0.001**
Declined approach	64	33.2	20	11.8	17	26.2	1	3.6	**<0.001**
Other reason	57	29.5	42	24.7	20	30.8	12	42.9	0.234

P values obtained by chi-squared or Fisher's Exact as appropriate. Bold text indicates significant at P<0.05 level. Categories not mutually exclusive; some recruits had >1 reason for ineligibility.

Table 3-3: Correlation between baseline frailty instruments and physical/psychological parameters

	Frailty Phenotype	Frailty Index	Edmonton Frailty Scale	Clinical Frailty Scale
Charlson score	0.265	0.226	0.175	0.275
Number of admissions previous 12-months	0.099	0.103	0.344	0.047
Number of drugs	0.280	0.362	0.324	0.352
Dialysis vintage (years)	0.129	0.077	-0.039	0.087
Grip strength (strongest hand)	-0.576	-0.470	-0.398	-0.434
Grip strength (weakest hand)	-0.547	-0.481	-0.392	-0.440
MOCA	-0.295	-0.346	-0.364	-0.310
PHQ9 score	0.419	0.537	0.477	0.361
Health rate score	0.421	0.513	0.587	0.387
EQ5D	-0.434	-0.494	-0.411	-0.392

Spearman's Rho. All values significant at P<0.001 level.

Table 3-4: Proportion of frailty within ethnicities

	Percentage of ethnicity classed as frail				P value
	White	South Asian	Black	Other	
Frailty Phenotype	43.1	44.4	35.5	30.8	0.499
Frailty Index	61.9	69.6	60.5	53.9	0.388
Edmonton Frailty Scale	47.0	53.0	61.8	30.8	0.054
Clinical Frailty Scale	51.3	61.7	54.0	38.5	0.180

P values derived from Chi-squared or Fisher's Exact as appropriate

Table 3-5: Correlation of raw frailty scores by Spearman's Rho

	Frailty Phenotype	Frailty Index	Edmonton Frailty Scale	Clinical Frailty Scale
Frailty Phenotype		0.790	0.666	0.665
Frailty Index	0.790		0.755	0.884
Edmonton Frailty Scale	0.666	0.755		0.646
Clinical Frailty Scale	0.665	0.884	0.646	

All results significant at $p<0.001$

Chapter 4:

Ultrasound quadriceps muscle thickness is variably associated with frailty in haemodialysis recipients

Authors: Benjamin M Anderson, Daisy V Wilson, Muhammad Qasim, Gonzalo Correa, Felicity Evison, Suzy Gallier, Charles J Ferro, Thomas A Jackson, Adnan Sharif

4.1 Extent of Personal Contribution

I coordinated all study visits with participants and dialysis unit staff. I recruited participants, and collected all baseline data with the support of Dr Gonzalo Correa, Dr Muhammad Qasim, and Dr Adnan Sharif. All colleagues were supervised by me in their data collection, and I was responsible for maintaining training and personnel logs in the site file. All ultrasound measures were taken and analysed by me.

The ultrasound protocol was originally developed by Dr Daisy Wilson, who kindly trained me in quadriceps ultrasound prior to the study. Dr Wilson also provided critical appraisal and insight into the statistical analyses and interpretation for this chapter.

Ms Felicity Evison, and Ms Suzy Gallier were responsible for interrogation of EPR for IMD Quintile assessment. I performed all subsequent data cleaning, integrity, and analyses with guidance from Dr Adnan Sharif.

The first draft of the manuscript was written by myself and I was responsible for all edits and revisions. This chapter has been submitted as a manuscript for consideration of peer-reviewed publication to BMC Nephrology on 28th July 2022, Submission ID c0f4e70c-bf44-4b7b-8bea-70dae6fa502a

4.1 Abstract

4.1.1 Background

Ultrasonographic quantitation of quadriceps muscle mass is increasingly used for assessment of sarcopenia, but its relationship with frailty in haemodialysis recipients is not known. This study explores the relationship between ultrasound-derived bilateral anterior thigh thickness (BATT), sarcopenia, and frailty by common frailty tools (Frailty Phenotype [FP], Frailty Index [FI], Edmonton Frailty [EFS], and Clinical Frailty Scale [CFS]).

4.1.2 Methods

This was an exploratory analysis of a subgroup of adult prevalent (≥3 months) haemodialysis recipients deeply phenotyped for frailty. Ultrasound assessment of BATT was obtained with participants at an angle of ≤45°, with legs outstretched and knees resting at 10°-20°, according to an established protocol. Associations with frailty were explored via both linear and logistic regressions for BATT, Low Muscle Mass (LMM), and sarcopenia with stepwise adjustment for *a priori* covariables.

4.1.3 Results

In total 223 study participants had ultrasound measurements. Frailty ranged from 34% for FP to 58% for FI. BATT was associated with increasing frailty on simple linear regression by all frailty tools, but lost significance on addition of covariables. Upon dichotomising frailty tools into Frail/Not Frail, BATT was associated with frailty by all tools on univariable analyses, but only retained association for EFS on the fully adjusted model (OR 0.97, 95% C.I. 0.94-1.00, P=0.05).

4.1.4 Conclusions

Ultrasound measures of quadriceps thickness is variably associated with frailty in prevalent haemodialysis recipients, dependent upon the frailty tool used, but not independent of other variables. Further work is required to establish the added value of sarcopenia measurement in frail haemodialysis patients.

4.1.5 Trial Registration

Clinicaltrials.gov : NCT03071107 registered 6th March 2017

4.2 Keywords

Sarcopenia, Frailty, Ultrasound, Epidemiology

4.2.1.1

4.3 Introduction

Frailty is associated with negative outcomes including mortality, hospitalisation and disability.[17] As we have seen, however, it is subject to heterogenous reporting. We have identified that the Frailty Phenotype (FP),[19] Frailty Index (FI),[36,37] Edmonton Frail Scale (EFS),[38] and Clinical Frailty Scale (CFS) demonstrate different frailty prevalence within the same cohort.[27] We have also demonstrated that correlation is weak and agreement minimal between these scores in haemodialysis recipients.[272] It appears likely therefore, that these frailty tools are in fact measuring different subsets of frailty, as previously postulated in older adult cohorts.[59] Thus, it is prudent to consider the ways in which these frailty scores may differ within haemodialysis recipients. To do so, we shall turn our attention to some of the common contributors to the frailty syndrome, starting with sarcopenia.

Sarcopenia is a progressive and generalised disorder of skeletal muscle, defined by low muscle mass and low muscle strength, and is considered a contributor to the development of frailty.[60] Sarcopenia is under-recognised, in part due to difficulties confirming low muscle mass.[60] Gold standard assessments such as whole-body magnetic resonance imaging (MRI), computed tomography (CT) and dual-energy x-ray absorptiometry (DEXA) are expensive, time-consuming and onerous for patients.[143] Additional hospital visits for scans will be unacceptable for many haemodialysis recipients, given the already burdensome requirements of thrice-weekly dialysis. Despite these barriers, where DEXA has been used in research, prevalence of sarcopenia has been estimated at 37% and 40% in European and Japanese haemodialysis cohorts respectively,[144,145] and has been associated with hospitalisation and mortality in haemodialysis patients.[144]

Ultrasound (US) is portable, often used on dialysis units for vascular access assessments, and has been validated for assessment of muscle size in older adults.[146,147] Recent work has suggested cut-offs for low muscle size – determined in the healthy young – according to ultrasound-derived bilateral anterior thigh thickness (BATT), a sum of the bilateral anterior-posterior depth of vastus intermedius and rectus femoris. BATT correlates with muscle strength and function, with high inter-rater reliability.[148] Ultrasound has also shown good agreement with CT measurements of mid-thigh quadriceps thickness and with bioelectrical impedance analysis (BIA),[149,150] and demonstrated little loss of precision by comparison to CT scanning in acute kidney injury patients.[151] Importantly, no significant differences have been identified in femoral muscle thickness before and after dialysis, indicating that fluid overload does not significantly influence results.[153,154] Recent reports have shown that ultrasound-derived measures of quadriceps size are associated with both muscle function[155] and mortality[156] in haemodialysis recipients.

The combination of availability, cost, and simplicity therefore suggests that ultrasonographic assessment may be an attractive option for assessing sarcopenia in haemodialysis recipients but many questions remain unanswered. Firstly, bilateral anterior thigh thickness has not specifically been investigated in the setting of haemodialysis. Secondly, the relationship between US-derived muscle parameters and frailty has yet to be explored in haemodialysis patients. Therefore, the aims of this study were to; 1) explore the relationship between BATT with measures of muscle function, and 2) assess the relationship between muscle size,

sarcopenia and frailty by common frailty tools both in the setting of prevalent haemodialysis patients.

4.4 Methods

Full details of study setting, eligibility criteria, and recruitment and consent are detailed in Chapters Chapter 2: and 2.2.

4.4.1 Recruitment

As this was an exploratory study on a subgroup of FITNESS participants, no power calculation was applied to this part of the study.

4.4.1.1

4.4.2 Statistics

Statistical analyses were performed using STATA 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Correlations between observations were calculated using Spearman rank correlation coefficient. Agreement was assessed with Cohen's Kappa, and was rated as >0.9 almost perfect agreement, 0.8-0.9 strong, 0.6-0.79 moderate, 0.4-0.59 weak, 0.21-0.39 minimal, and ≤0.2 no agreement.

Associations with continuous frailty scores were analysed using linear regression, having satisfied the linear assumption via visual comparison of observed versus Lowess fit lines on scatter plot and augmented component plus residual plots. Robust standard errors were specified to account for heteroscedasticity. Multicollinearity was excluded on all analyses by variance inflation factor <10. Odds ratios for frailty were obtained by logistic regression.

Linear and logistic regressions were performed both unadjusted and adjusted for *a priori* covariables chosen for proven or suspected association with frailty. These were introduced in a stepwise manner; Model 1 included age, ethnicity, gender, education level, IMD quintile, self-reported social support (Yes/No), and haemodialysis vintage. Model 2 added to these self-reported health today (Euroqol 5D Visual Analogue Scale),[227] self-reported health change, PHQ-9 score, cognitive impairment, and Charlson Comorbidity Index (CKD omitted). Model 3 added self-reported slow walking speed (from GPPAQ), and use of walking aids (yes/no), which to avoid bias were chosen as – unlike grip strength and walking speed – they did not comprise a component of the frailty scores under investigation.

For association with walking speed or grip strength, the following covariables were selected: age, gender, ethnicity, IMD quintile, BMI, remaining ultrafiltration volume at time of scan, self-reported health change, Physical Activity Index (PAI) from GPPAQ,[268,269] Charlson Index (CKD omitted), self-reported health today from Euroqol EQ-5D visual analogue scale out of 100 (EQ-5D VAS), self-reported use of walking aids, and haemodialysis vintage.

As statistical significance was lost for many frailty associations with stepwise addition of covariables, a further analysis was performed whereby the order of addition of covariables was reversed to explore the likelihood of type II error. Therefore, Model A included self-reported slow walking speed, and use of walking aids. Model B added self-reported health today,[227] self-reported health change, PHQ-9 score, cognitive impairment, and Charlson

Comorbidity Index (CKD omitted). Model C added age, ethnicity, gender, education level, IMD quintile, self-reported social support, and haemodialysis vintage.

Missing IMD quintiles were handled via a dummy variable. All other missing data were handled via listwise deletion, as <1% of other data were missing. A P value < 0.05 was considered significant.

4.5 Results

Figure 4-1 shows a flowchart of recruitment to the FITNESS study. 485 participants underwent frailty assessment and entered follow-up, of which 223 had valid ultrasound measurements. Of those with valid US measurements, the median FP was 2 (IQR 1-3), FI 0.266 (IQR 0.148-0.430), EFS 7 (IQR 5-10, and CFS 4 (3-5). Table 4-1 shows key demographics; the percentage determined to be frail ranged from 34% for the FP to 58% for FI.

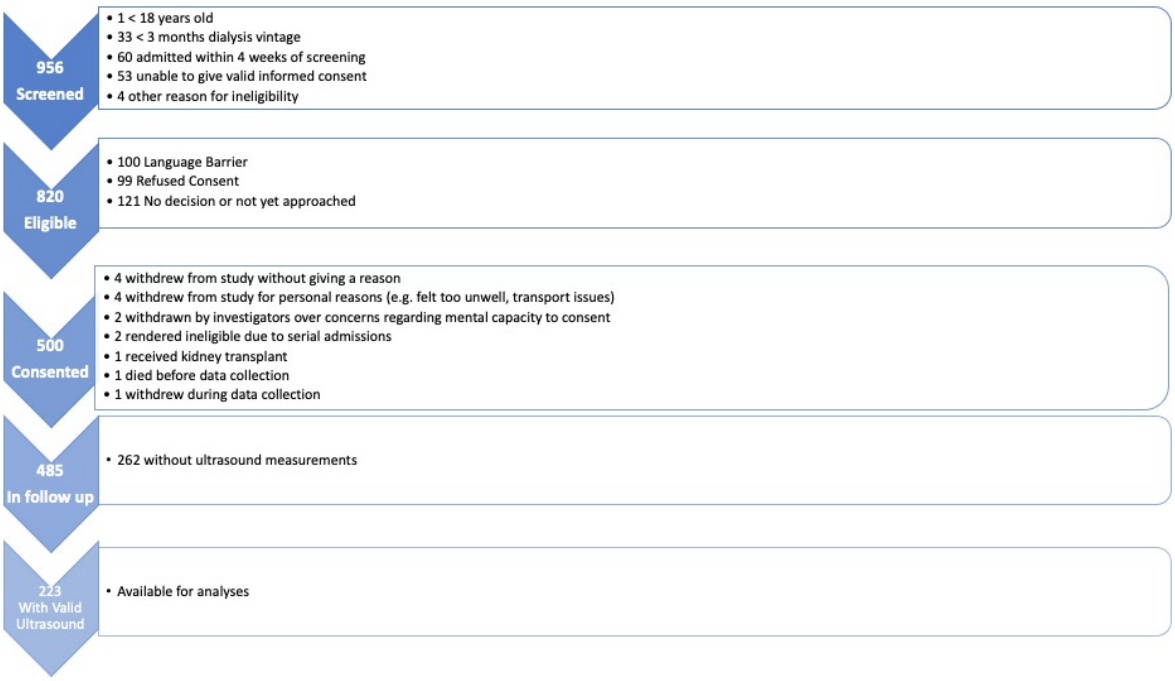


Figure 4-1: PRISMA flow diagram of study participation

4.5.1 Prevalence of low muscle mass, and concordance with frailty

Low muscle mass was present in 119 participants (53.4%). Sarcopenia was identified in 71 participants (31.8%). Table 4-2 shows that concordance of both LMM and sarcopenia with frailty was poor regardless of frailty definition. Agreement between frailty and sarcopenia was minimal, Cohen's Kappa was 0.381 for FP (P<0.001), 0.219 for FI (P<0.001), 0.245 for EFS (P<0.001), and 0.240 for CFS (P<0.001).

4.5.2 Association between muscle size, sarcopenia, and frailty

A composite forest plot of simple and multiple linear regressions between each of BATT, LMM and sarcopenia with each frailty tool is shown in Figure 4-2 to Figure 4-4. Figure 4-2 shows that increasing BATT was associated with lower scores on each frailty tool on simple linear regression.

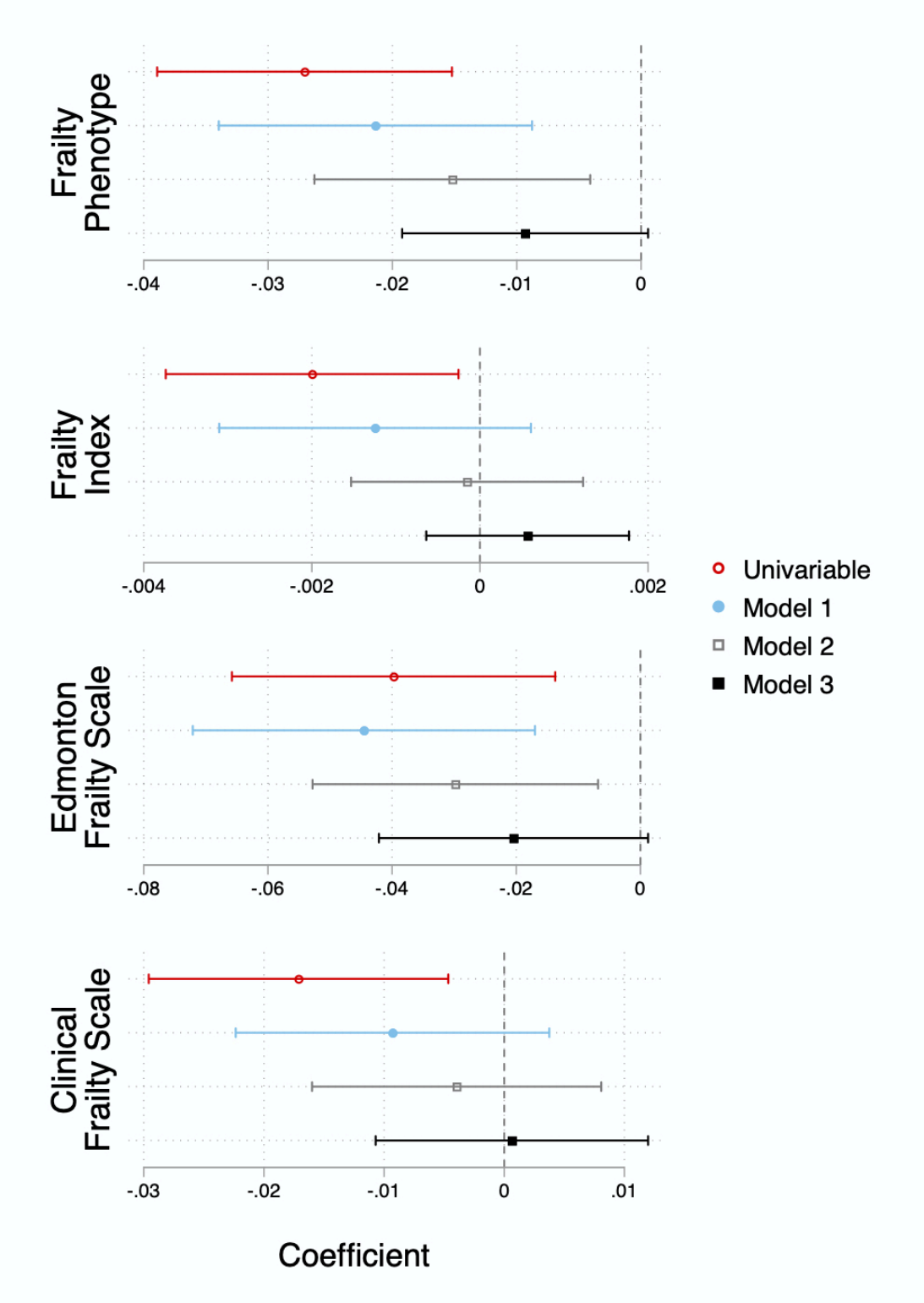


Figure 4-2: Composite forest plot of simple and multiple linear regressions of change in frailty score with increase in BATT

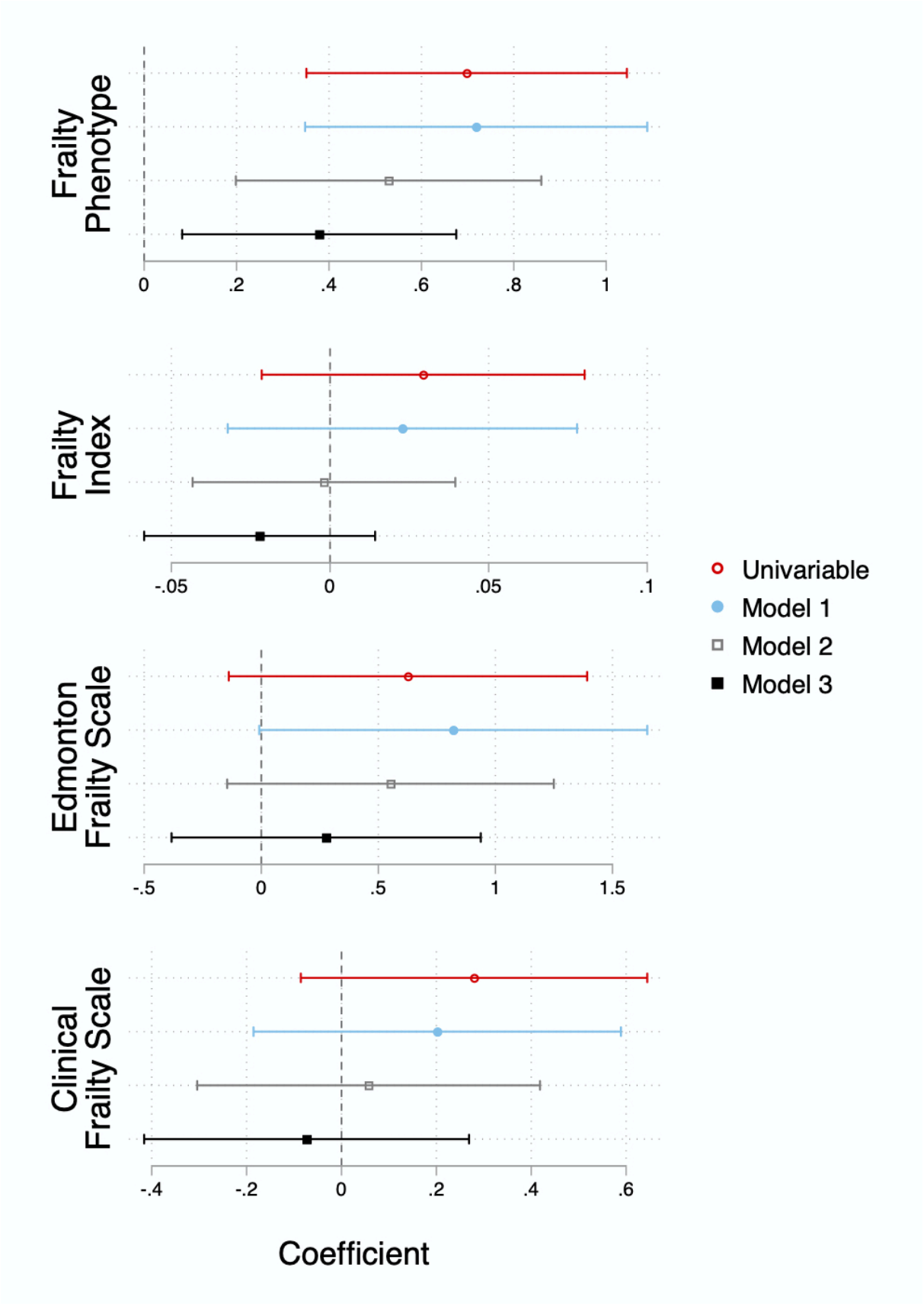


Figure 4-3: Composite forest plot of simple and multiple linear regressions of frailty scores associated with low muscle mass

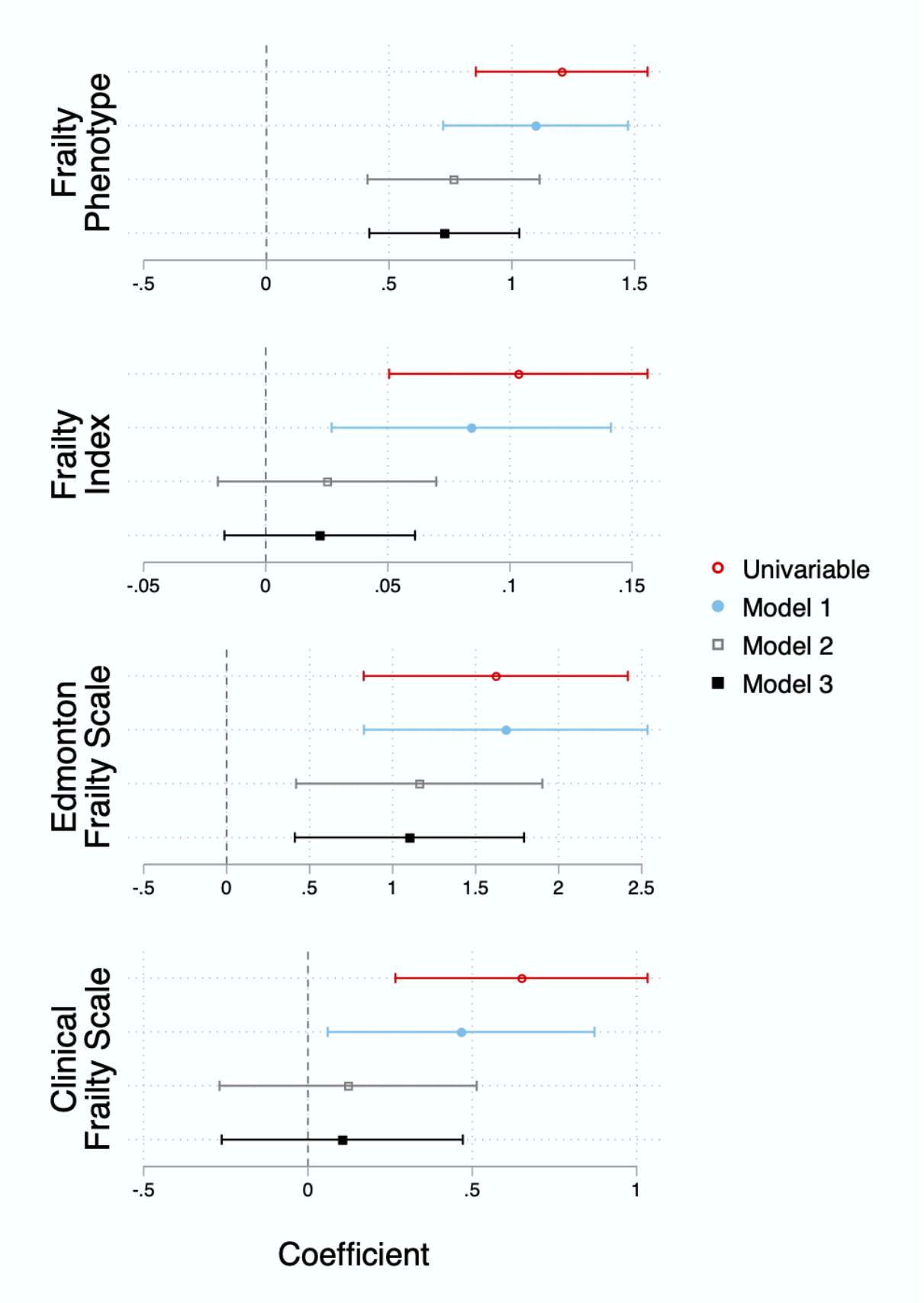


Figure 4-4: Composite forest plot of simple and multiple linear regressions of frailty scores associated with sarcopenia

However, upon stepwise addition of covariables to the models, BATT lost its association with decreasing frailty by each tool. LMM was associated with increasing FP frailty on all linear regression models but was not significantly associated with any other frailty score. Sarcopenia was associated with increasing frailty on all models for the FP and EFS, but lost significance of association upon addition of Model 2 covariables for FI and CFS. All Model 3 results are detailed in Supplementary Table 4-1 to Supplementary Table 4-12.

Odds ratios for frailty associated with BATT, LMM and sarcopenia are shown in Figure 4-5 to Figure 4-7. Increasing BATT was associated with lower odds of frailty for FP and EFS on univariable analyses and in Models 1 and 2 but lost the association on addition of surrogates of muscle function in Model 3. Neither frailty by FI nor CFS showed any significant associations with BATT on univariable or multivariable logistic regression.

A similar pattern was observed for LMM, which was associated with higher odds of FP frailty on all analyses, and for EFS frailty until addition of Model 3 covariables. It did not associate with FI or CFS frailty on any model. Sarcopenia was associated with increased odds of frailty on unadjusted and all adjusted models for FP, FI, and EFS, but lost significance for this association on Model 2 for CFS. All Model 3 results are shown in Supplementary Table 4-13 to Supplementary Table 4-24.

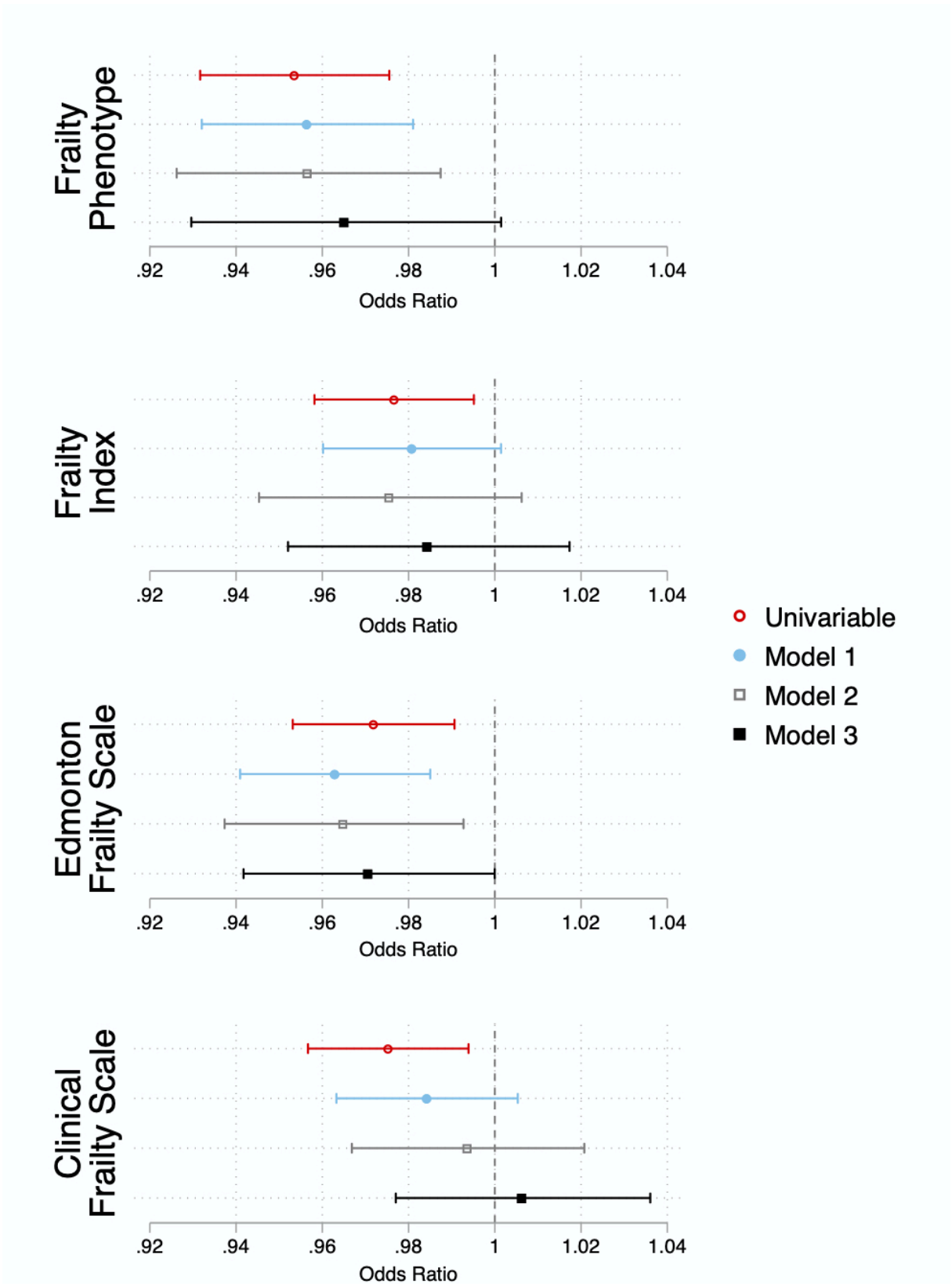
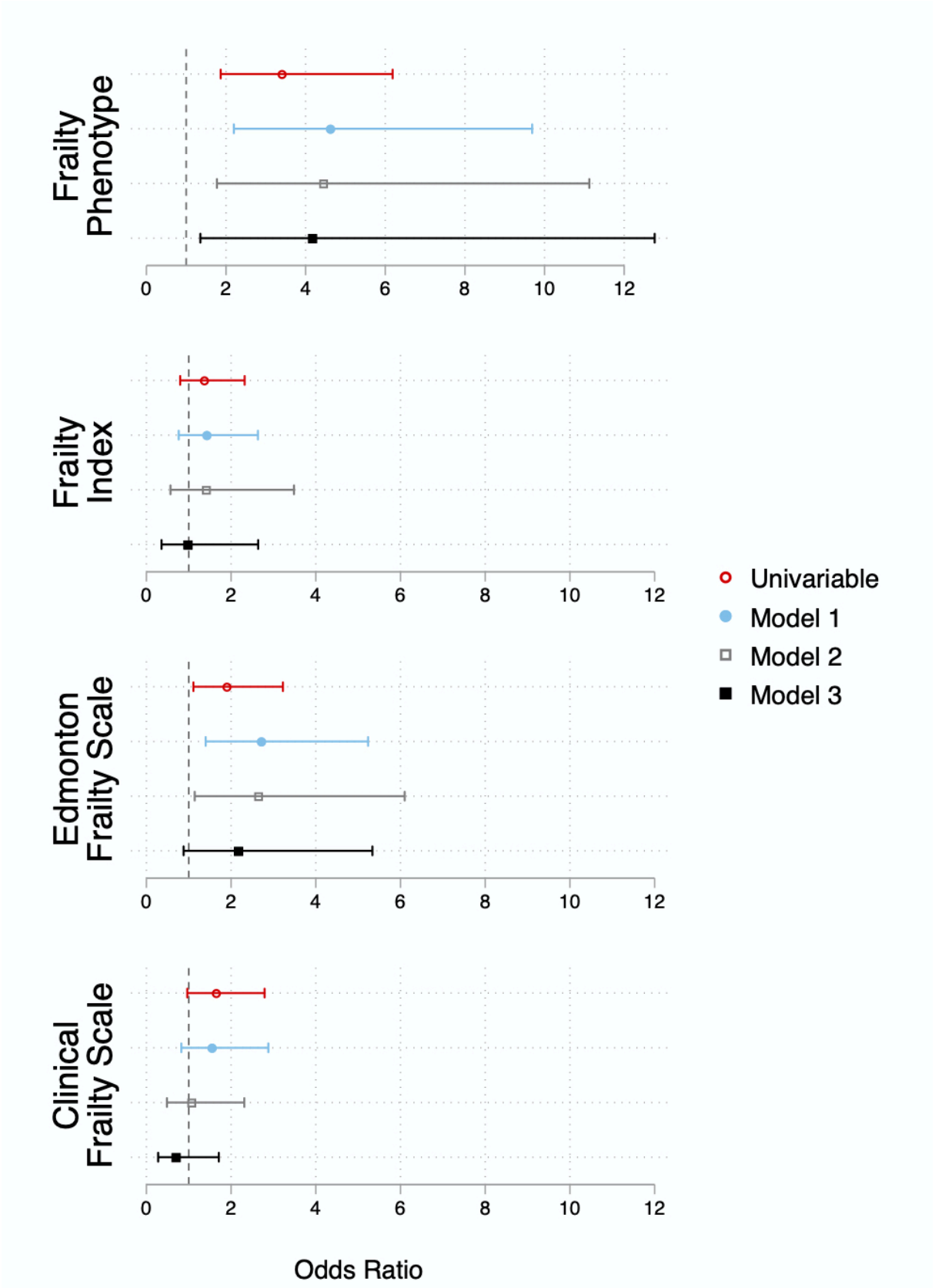
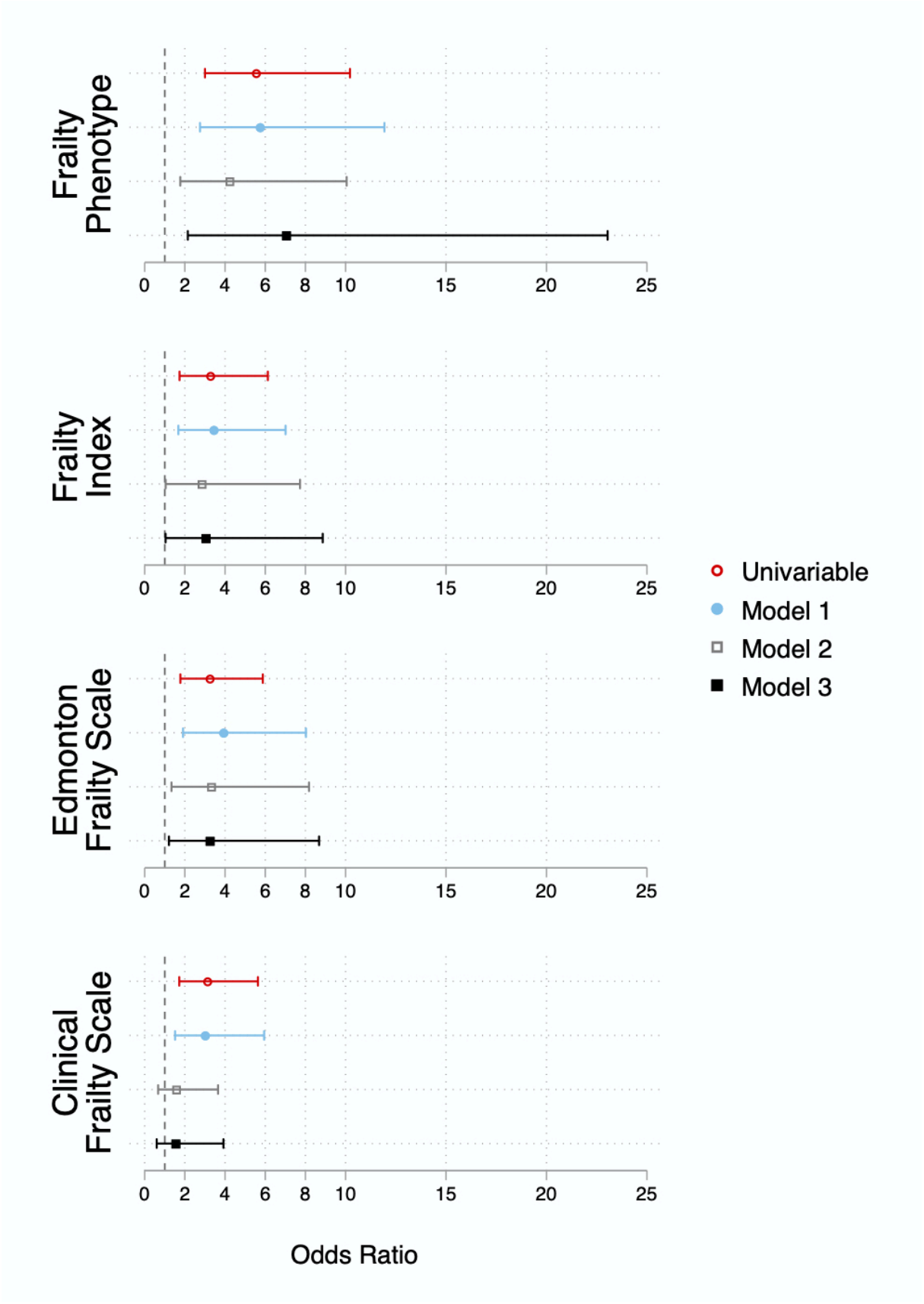


Figure 4-5: Univariable and adjusted logistic regression of frailty associated with BATT



4.5.2.1

Figure 4-6: Univariable and adjusted logistic regression of frailty associated with low muscle mass.



4.5.2.2

Figure 4-7: Univariable and adjusted logistic regression of frailty associated with sarcopenia

4.5.3 Sensitivity Analyses

Supplementary Table 4-25 and Supplementary Table 4-26 show that changing the order of covariable addition did not materially change the interpretation of results. The only exceptions were for linear and logistic regressions for association between FP and BATT; significant results were maintained until the final model on both forward and backward stepwise regression, suggesting the loss of statistical significance for Model 3 could be due to Type II error for the FP.

4.6 Discussion

Ultrasonography has shown promise in assessing muscle size in frail older adults,[146,148] and in haemodialysis recipients,[144,145] but its relationship to frailty in haemodialysis is not known. Here we have shown in a large prevalent haemodialysis cohort that BATT associates with poorer grip strength and walking speed. Ultrasound-derived BATT, low muscle size,[148] and sarcopenia that incorporates BATT criteria are associated with frailty in haemodialysis recipients, but consistency of these associations upon multivariable analyses are dependent upon the frailty measure used. The most persistent associations were seen with the FP, a primarily physically-focussed frailty score, whereas weakest associations were seen with CFS. Further work should include the assessment of long-term outcomes associated with BATT in haemodialysis, and to establish whether sarcopenia associates with negative outcomes in haemodialysis recipients when adjusted for frailty.

Ultrasound-derived quadriceps muscle mass has been validated against CT and BIA in haemodialysis recipients,[149,155] and is not affected by volume overload.[153,154] Our findings

corroborate and build-upon work from Matsuzawa and colleagues, who found that cross-sectional area of rectus femoris associated with grip strength and walking speed.[155] Associations of ultrasound-derived muscle mass and frailty in haemodialysis have to the best of our knowledge not been examined until now. Here we show that quadriceps muscle thickness is associated with frailty to a variable degree, and almost universally lost association with frailty on addition of surrogates of muscle function (self-reported walking speed and use of walking aids) to the models. Our finding that sarcopenia – the addition of low grip strength to low muscle mass – was more robustly associated with frailty is consistent with these results: indeed low grip strength is a component of the FP, FI (by our definition), and EFS. Whilst we must exercise caution when comparing across different regression models, it is interesting that the strength and reliability of association between muscle mass and frailty appear highest where the frailty tool most relies upon musculoskeletal constituents. The proportion of each frailty score ascribed to markers of muscle function ranges from FP (which almost exclusively relies upon markers of musculoskeletal function) at the highest, via the EFS, FI, to CFS (which does not include any direct assessment of muscle function) at the lowest. It is therefore unsurprising that the FP retained the strongest association with muscle mass and sarcopenia, but to our knowledge this is the first study to confirm this in haemodialysis recipients.

Despite sharing some mechanistic and clinical similarities, we must not conflate sarcopenia and frailty. Rather sarcopenia is considered a contributor to – but not a requirement of – frailty.[60] Reijnierse and colleagues reported that in older adults referred to a geriatric clinic, there was little concordance between sarcopenia and frailty,[110] which we have corroborated in haemodialysis recipients here. The potential utility of sarcopenia assessment therefore depends upon additive risk stratification for important outcomes. Sabatino and colleagues

found that distal vastus intermedius thickness – normalised for height – was independently associated with increased mortality in haemodialysis.[156] These results have yet to be repeated in other haemodialysis cohorts, but are in keeping with the association found between CT-derived thigh muscle mass and mortality in a Japanese haemodialysis cohort.[281] It remains to be established, however, whether the association with mortality is maintained when frailty is accounted for. If so, we can be confident that ultrasound measures of muscle mass offer prognostic detail that merit the logistical challenges. This question will be addressed as the FITNESS cohort matures.

Limitations of this study include the fact that the whole FITNESS cohort did not complete ultrasound assessment. The ultrasound scanner was not procured until after the first 193 participants were recruited, and a further 69 refused or were unable to be scanned. Scanning took place during haemodialysis sessions, in order to reduce the time commitment of each participant for the study. This may have resulted in the frailest being unable to participate in this aspect of the study due to concerns regarding mobility and adequate exposure for scanning. This potential discrepancy reduces the generalisability of our findings. The utility of quantifying muscle mass using this approach may be in identifying those at risk of progressive sarcopenia and/or frailty, rather than those with already advanced frailty. Barriers to scanning frail participants may persist in other cohorts using an intra-dialytic scanning approach, limiting utility as a screening tool in haemodialysis populations. Scanning either before or after dialysis would potentially mitigate many of these weaknesses. Scanning in a separate office would reduce concerns regarding privacy (many dialysis units utilise temporary curtains only), and in protecting dialysis access and connection to the dialysis machine. However, this would

also increase substantially the time spent on the dialysis unit for each participant, impacting the acceptability of investigation to potential participants.

4.6.1 Conclusions

To conclude, a thigh ultrasound-derived sarcopenia associates with frailty in haemodialysis recipients, but association between frailty and muscle size alone is much more variable. Our study results suggest the utility of quadriceps ultrasound in risk assessment of haemodialysis recipients currently lacks utility in the clinical setting and requires further investigation.

4.7 Tables

Table 4-1: Baseline characteristics of the FITNESS subgroup with valid ultrasound measurements

	(n=223)	
	n	% of cohort/IQR
Male	138	61.9
FP	76	34.1
FI	129	57.9
EFS	111	49.8
CFS	109	48.9
Albumin*	39	35-42
MoCA*	22	18-25
Age*	63	54-74
BMI*	27.0	23.4-32.1
Charlson Index* **	5	3-6
HD Vintage (months)*	33	14-65
Kt/V*	1.58	1.37-1.82
Ethnicity		
White	136	61.0
South Asian	51	22.9
Black	32	14.4
Other	4	1.8
Smoking Status		
Current	33	14.8
Ex	67	30.0
Never	123	55.2
Active on transplant list?		
No	195	87.4
Yes	28	12.6
Employment Status		
Employed	32	14.4
Unemployed	74	33.2
Retired	117	52.5
Occupation***		
Unskilled Manual	92	43.4
Skilled Manual	32	15.1
Clerical	25	11.8
Managerial	31	14.6
Professional	32	15.1
Education level		
High School	154	69.1

College/6th form	47	21.1
University	22	9.9
Type of residence		
Own Home	219	98.2
Warden-Controlled	3	1.4
Residential Home	1	0.5
Nursing Home	0	0.0
Professional Carer Use?****		
No	209	94.1
Yes	13	5.9
Physical Activity Index		
Inactive	184	82.5
Moderately Inactive	18	8.1
Moderately Active	5	2.2
Active	16	7.2
IMD Quintile		
1	101	45.3
2	29	13.0
3	36	16.1
4	19	8.5
5	22	9.9
Unknown	16	7.2

All values n and percentages except *=median and interquartile range; **=CKD omitted; ***=or previous occupation if unemployed/retired; ****=if not in residential/nursing accommodation.

Table 4-2: Concordance between frailty status with low muscle mass and sarcopenia

Frailty Tool	Frailty Status	Low Muscle Mass?		Sarcopenia?		Row Total (n)
		No	Yes	No	Yes	
FP	Not Frail	83	64	119	28	147
		56.5%	43.5%	81.0%	19.1%	
	Frail	21	55	33	43	76
		27.6%	72.4%	43.4%	56.6%	
FI	Not Frail	48	46	77	17	94
		51.1%	48.9%	81.9%	18.1%	
	Frail	56	73	75	54	129
		43.4%	56.6%	58.1%	41.9%	
EFS	Not Frail	61	51	90	22	112
		54.5%	45.5%	80.4%	19.6%	
	Frail	43	68	62	49	111
		38.7%	61.3%	55.9%	44.1%	
CFS	Not Frail	60	54	91	23	114
		52.6%	47.4%	79.8%	20.2%	
	Frail	44	65	61	48	109
		40.4%	59.6%	56.0%	44.0%	

Table 4-3: Simple and multiple linear regression of Grip and Walking Speed associated with BATT and Low Muscle Mass

		Coef.	Lower 95% C.I.	Upper 95% C.I.	P
BATT	Grip				
	Univariable	0.29	0.21	0.37	<0.001
	Multivariable	0.10	0.02	0.19	0.019
	Walk Speed				
	Univariable	0.007	0.004	0.010	<0.001
	Multivariable	0.005	0.002	0.008	0.001
Low Muscle Mass	Grip				
	Univariable	-3.36	-5.99	-0.73	0.013
	Multivariable	-3.23	-5.65	-0.82	0.009
	Walk Speed				
	Univariable	-0.155	-0.244	-0.066	0.001
	Multivariable	-0.115	-0.202	-0.028	0.010

Multivariable analyses adjusted for: age, gender, ethnicity, IMD quintile, BMI, remaining ultrafiltration volume at time of scan, self-reported health change, Physical Activity Index (PAI) from GPPAQ,[268,269] Charlson Index (CKD omitted), self-reported health today from Euroqol EQ-5D visual analogue scale out of 100 (EQ-5D VAS), self-reported use of walking aids, and haemodialysis vintage.

4.8 Supplementary Tables

Supplementary Table 4-1: Multiple linear regression of FP by BATT. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	-0.009	-0.019	0.001	0.064
Age	0.001	-0.013	0.015	0.935
Ethnicity				
White		REFERENCE		
South Asian	**0.406**	**0.014**	**0.798**	**0.043**
Black	-0.142	-0.550	0.267	0.495
Other	-0.418	-1.442	0.606	0.421
Education Level				
High School		REFERENCE		
College/6th form	0.003	-0.344	0.350	0.988
University	-0.099	-0.585	0.387	0.688
IMD Quintile				
1		REFERENCE		
2	0.164	-0.251	0.580	0.436
3	-0.014	-0.416	0.388	0.945
4	-0.293	-0.808	0.222	0.263
5	-0.425	-0.900	0.050	0.079
Unknown	0.047	-0.501	0.596	0.865
Gender				
Male		REFERENCE		
Female	0.236	-0.061	0.532	0.119
Social Support				
Yes		REFERENCE		
No	-0.312	-0.894	0.271	0.292
HD Vintage	0.001	-0.002	0.004	0.481
Charlson Index	0.069	-0.014	0.152	0.104
Cognitive Impairment				
No		REFERENCE		
Yes	0.036	-0.329	0.400	0.847
PHQ-9 Score	**0.061**	**0.031**	**0.091**	**<0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	-0.093	-0.489	0.303	0.643
Worse	-0.095	-0.483	0.293	0.630
Self-Reported Health Today	**-0.011**	**-0.018**	**-0.003**	**0.006**
Walking Aid Use				
No		REFERENCE		
Yes	**0.848**	**0.532**	**1.163**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**0.625**	**0.305**	**0.945**	**<0.001**
Constant	**1.548**	**0.377**	**2.719**	**0.010**

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-2: Multiple linear regression of Frailty Phenotype by Low Muscle Mass. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	**0.379**	**0.082**	**0.676**	**0.013**
Age	0.002	-0.012	0.015	0.829
Ethnicity				
White		REFERENCE		
South Asian	**0.418**	**0.030**	**0.806**	**0.035**
Black	-0.116	-0.523	0.290	0.573
Other	-0.424	-1.439	0.591	0.411
Education Level				
High School		REFERENCE		
College/6th form	0.040	-0.307	0.387	0.821
University	-0.073	-0.557	0.410	0.765
IMD Quintile				
1		REFERENCE		
2	0.095	-0.321	0.510	0.653
3	-0.041	-0.441	0.360	0.841
4	-0.278	-0.789	0.233	0.284
5	**-0.486**	**-0.958**	**-0.014**	**0.044**
Unknown	0.042	-0.502	0.587	0.879
Gender				
Male		REFERENCE		
Female	**0.392**	**0.098**	**0.686**	**0.009**
Social Support				
Yes		REFERENCE		
No	-0.309	-0.886	0.269	0.293
HD Vintage	0.001	-0.002	0.003	0.634
Charlson Index	0.070	-0.012	0.152	0.094
Cognitive Impairment				
No		REFERENCE		
Yes	0.035	-0.325	0.396	0.847
PHQ-9 Score	**0.062**	**0.032**	**0.092**	**<0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	-0.117	-0.510	0.277	0.559
Worse	-0.078	-0.463	0.307	0.690
Self-Reported Health Today	**-0.010**	**-0.017**	**-0.002**	**0.012**
Walking Aid Use				
No		REFERENCE		
Yes	**0.814**	**0.499**	**1.130**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**0.657**	**0.341**	**0.974**	**<0.001**
Constant	0.717	-0.322	1.756	0.175

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-3: Multiple linear regression of Frailty Phenotype by Sarcopenia. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**0.725**	**0.420**	**1.030**	**<0.001**
Age	0.000	-0.013	0.013	0.995
Ethnicity				
White		REFERENCE		
South Asian	0.360	-0.014	0.733	0.059
Black	-0.068	-0.459	0.323	0.732
Other	-0.508	-1.484	0.468	0.306
Education Level				
High School		REFERENCE		
College/6th form	0.007	-0.322	0.335	0.969
University	-0.065	-0.529	0.398	0.781
IMD Quintile				
1		REFERENCE		
2	0.153	-0.243	0.548	0.448
3	0.115	-0.268	0.499	0.553
4	-0.198	-0.689	0.294	0.429
5	-0.372	-0.826	0.081	0.107
Unknown	0.034	-0.489	0.557	0.897
Gender				
Male		REFERENCE		
Female	**0.347**	**0.072**	**0.622**	**0.014**
Social Support				
Yes		REFERENCE		
No	-0.425	-0.982	0.132	0.134
HD Vintage	0.000	-0.002	0.003	0.885
Charlson Index	0.057	-0.022	0.135	0.159
Cognitive Impairment				
No		REFERENCE		
Yes	0.007	-0.338	0.352	0.968
PHQ-9 Score	**0.059**	**0.030**	**0.087**	**<0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	-0.176	-0.555	0.204	0.362
Worse	-0.075	-0.445	0.295	0.689
Self-Reported Health Today	**-0.007**	**-0.014**	**0.000**	**0.049**
Walking Aid Use				
No		REFERENCE		
Yes	**0.850**	**0.551**	**1.149**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**0.663**	**0.359**	**0.967**	**<0.001**
Constant	0.773	-0.206	1.752	0.121

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-4: Multiple linear regression of Frailty Index by BATT. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	0.001	-0.001	0.002	0.355
Age	-0.001	-0.003	0.000	0.109
Ethnicity				
White		REFERENCE		
South Asian	**0.061**	**0.013**	**0.109**	**0.012**
Black	0.010	-0.039	0.060	0.682
Other	0.009	-0.116	0.134	0.889
Education Level				
High School		REFERENCE		
College/6th form	-0.005	-0.048	0.037	0.806
University	-0.012	-0.072	0.047	0.679
IMD Quintile				
1		REFERENCE		
2	0.016	-0.035	0.067	0.536
3	0.019	-0.030	0.068	0.438
4	-0.005	-0.068	0.058	0.881
5	-0.012	-0.070	0.046	0.691
Unknown	0.012	-0.055	0.079	0.728
Gender				
Male		REFERENCE		
Female	**0.048**	**0.012**	**0.084**	**0.010**
Social Support				
Yes		REFERENCE		
No	**-0.103**	**-0.174**	**-0.032**	**0.005**
HD Vintage	0.000	0.000	0.000	0.556
Charlson Index	**0.017**	**0.007**	**0.027**	**0.001**
Cognitive Impairment				
No		REFERENCE		
Yes	**0.060**	**0.015**	**0.104**	**0.009**
PHQ-9 Score	**0.012**	**0.009**	**0.016**	**<0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	-0.048	-0.096	0.000	0.051
Worse	0.023	-0.025	0.070	0.343
Self-Reported Health Today	-0.001	-0.002	0.000	0.100
Walking Aid Use				
No		REFERENCE		
Yes	**0.124**	**0.085**	**0.162**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**0.069**	**0.030**	**0.108**	**0.001**
Constant	0.090	-0.052	0.233	0.213

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-5: Multiple linear regression of Frailty Index by Low Muscle Mass. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	-0.022	-0.059	0.014	0.230
Age	-0.001	-0.003	0.000	0.094
Ethnicity				
White		REFERENCE		
South Asian	**0.060**	**0.013**	**0.108**	**0.013**
Black	0.009	-0.041	0.059	0.724
Other	0.009	-0.116	0.134	0.886
Education Level				
High School		REFERENCE		
College/6th form	-0.007	-0.050	0.035	0.734
University	-0.014	-0.073	0.045	0.645
IMD Quintile				
1		REFERENCE		
2	0.020	-0.031	0.071	0.440
3	0.021	-0.028	0.070	0.405
4	-0.006	-0.068	0.057	0.858
5	-0.008	-0.066	0.050	0.783
Unknown	0.012	-0.055	0.079	0.721
Gender				
Male		REFERENCE		
Female	**0.039**	**0.002**	**0.075**	**0.036**
Social Support				
Yes		REFERENCE		
No	**-0.103**	**-0.174**	**-0.032**	**0.005**
HD Vintage	0.000	0.000	0.000	0.492
Charlson Index	**0.017**	**0.007**	**0.027**	**0.001**
Cognitive Impairment				
No		REFERENCE		
Yes	**0.060**	**0.016**	**0.104**	**0.008**
PHQ-9 Score	**0.012**	**0.008**	**0.016**	**<0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	-0.047	-0.095	0.002	0.058
Worse	0.022	-0.025	0.069	0.364
Self-Reported Health Today	-0.001	-0.002	0.000	0.080
Walking Aid Use				
No		REFERENCE		
Yes	**0.126**	**0.087**	**0.164**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**0.067**	**0.028**	**0.106**	**0.001**
Constant	**0.140**	**0.013**	**0.268**	**0.031**

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-6: Multiple linear regression of Frailty Index by Sarcopenia. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	0.022	-0.017	0.061	0.265
Age	-0.001	-0.003	0.000	0.086
Ethnicity				
White		REFERENCE		
South Asian	**0.057**	**0.010**	**0.105**	**0.019**
Black	0.014	-0.036	0.064	0.576
Other	0.000	-0.125	0.124	0.994
Education Level				
High School		REFERENCE		
College/6th form	-0.001	-0.043	0.041	0.962
University	-0.009	-0.068	0.050	0.771
IMD Quintile				
1		REFERENCE		
2	0.016	-0.035	0.066	0.539
3	0.020	-0.029	0.069	0.430
4	-0.003	-0.066	0.060	0.918
5	-0.008	-0.066	0.050	0.776
Unknown	0.011	-0.056	0.078	0.739
Gender				
Male		REFERENCE		
Female	**0.045**	**0.010**	**0.080**	**0.012**
Social Support				
Yes		REFERENCE		
No	**-0.106**	**-0.177**	**-0.035**	**0.004**
HD Vintage	0.000	0.000	0.000	0.820
Charlson Index	**0.016**	**0.006**	**0.026**	**0.002**
Cognitive Impairment				
No		REFERENCE		
Yes	**0.063**	**0.019**	**0.107**	**0.006**
PHQ-9 Score	**0.012**	**0.009**	**0.016**	**<0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	**-0.051**	**-0.100**	**-0.003**	**0.038**
Worse	0.022	-0.025	0.069	0.364
Self-Reported Health Today	-0.001	-0.002	0.000	0.204
Walking Aid Use				
No		REFERENCE		
Yes	**0.121**	**0.082**	**0.159**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**0.068**	**0.029**	**0.107**	**0.001**
Constant	0.116	-0.009	0.241	0.069

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-7: Multiple linear regression of Edmonton Frailty Scale by BATT. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	-0.020	-0.042	0.001	0.064
Age	-0.017	-0.047	0.014	0.288
Ethnicity				
White		REFERENCE		
South Asian	0.477	-0.382	1.337	0.274
Black	**0.908**	**0.012**	**1.804**	**0.047**
Other	-1.760	-4.005	0.484	0.123
Education Level				
High School		REFERENCE		
College/6th form	-0.290	-1.050	0.471	0.453
University	-0.539	-1.605	0.527	0.320
IMD Quintile				
1		REFERENCE		
2	0.651	-0.259	1.561	0.160
3	-0.403	-1.285	0.478	0.368
4	-0.187	-1.316	0.942	0.744
5	0.431	-0.610	1.472	0.415
Unknown	-0.492	-1.695	0.711	0.421
Gender				
Male		REFERENCE		
Female	0.187	-0.463	0.838	0.570
Social Support				
Yes		REFERENCE		
No	0.958	-0.318	2.234	0.140
HD Vintage	-0.004	-0.010	0.002	0.150
Charlson Index	0.182	0.000	0.363	0.050
Cognitive Impairment				
No		REFERENCE		
Yes	0.681	-0.118	1.481	0.094
PHQ-9 Score	**0.130**	**0.064**	**0.196**	**<0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	**-1.289**	**-2.156**	**-0.421**	**0.004**
Worse	0.209	-0.642	1.060	0.628
Self-Reported Health Today	-0.014	-0.030	0.003	0.099
Walking Aid Use				
No		REFERENCE		
Yes	**1.551**	**0.860**	**2.242**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**0.824**	**0.123**	**1.525**	**0.021**
Constant	**7.429**	**4.863**	**9.995**	**<0.001**

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-8: Multiple linear regression of Edmonton Frailty Scale by Low Muscle Mass. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	0.277	-0.383	0.938	0.408
Age	-0.015	-0.046	0.016	0.350
Ethnicity				
White		REFERENCE		
South Asian	0.524	-0.340	1.388	0.233
Black	0.901	-0.004	1.806	0.051
Other	-1.659	-3.919	0.600	0.149
Education Level				
High School		REFERENCE		
College/6th form	-0.329	-1.101	0.444	0.402
University	-0.563	-1.639	0.513	0.304
IMD Quintile				
1		REFERENCE		
2	0.596	-0.328	1.521	0.205
3	-0.365	-1.256	0.526	0.420
4	-0.154	-1.291	0.983	0.790
5	0.359	-0.691	1.409	0.501
Unknown	-0.494	-1.706	0.718	0.422
Gender				
Male		REFERENCE		
Female	0.400	-0.254	1.055	0.229
Social Support				
Yes		REFERENCE		
No	0.955	-0.331	2.241	0.145
HD Vintage	-0.004	-0.010	0.002	0.194
Charlson Index	**0.198**	**0.016**	**0.380**	**0.033**
Cognitive Impairment				
No		REFERENCE		
Yes	0.621	-0.182	1.424	0.129
PHQ-9 Score	**0.126**	**0.059**	**0.192**	**<0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	**-1.295**	**-2.171**	**-0.420**	**0.004**
Worse	0.248	-0.609	1.105	0.568
Self-Reported Health Today	-0.014	-0.030	0.003	0.099
Walking Aid Use				
No		REFERENCE		
Yes	**1.575**	**0.873**	**2.278**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**0.876**	**0.171**	**1.581**	**0.015**
Constant	**6.034**	**3.721**	**8.347**	**<0.001**

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-9: Multiple linear regression of Edmonton Frailty Scale by Sarcopenia. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**1.101**	**0.411**	**1.791**	**0.002**
Age	-0.017	-0.047	0.013	0.268
Ethnicity				
White		REFERENCE		
South Asian	0.425	-0.420	1.270	0.323
Black	**1.008**	**0.124**	**1.892**	**0.026**
Other	-1.848	-4.053	0.357	0.100
Education Level				
High School		REFERENCE		
College/6th form	-0.314	-1.056	0.427	0.404
University	-0.507	-1.554	0.540	0.340
IMD Quintile				
1		REFERENCE		
2	0.631	-0.264	1.526	0.166
3	-0.180	-1.046	0.686	0.682
4	-0.032	-1.144	1.080	0.955
5	0.498	-0.526	1.523	0.339
Unknown	-0.511	-1.693	0.671	0.395
Gender				
Male		REFERENCE		
Female	0.402	-0.220	1.024	0.204
Social Support				
Yes		REFERENCE		
No	0.783	-0.476	2.042	0.221
HD Vintage	-0.005	-0.011	0.001	0.079
Charlson Index	0.170	-0.008	0.349	0.061
Cognitive Impairment				
No		REFERENCE		
Yes	0.610	-0.170	1.390	0.125
PHQ-9 Score	**0.125**	**0.060**	**0.189**	**<0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	**-1.409**	**-2.266**	**-0.552**	**0.001**
Worse	0.251	-0.584	1.087	0.554
Self-Reported Health Today	-0.009	-0.025	0.007	0.273
Walking Aid Use				
No		REFERENCE		
Yes	**1.577**	**0.901**	**2.253**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**0.895**	**0.207**	**1.583**	**0.011**
Constant	**5.889**	**3.677**	**8.101**	**<0.001**

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-10: Multiple linear regression of Clinical Frailty Scale by BATT. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	0.001	-0.011	0.012	0.912
Age	0.001	-0.015	0.018	0.858
Ethnicity				
White		REFERENCE		
South Asian	**0.549**	**0.099**	**0.998**	**0.017**
Black	-0.070	-0.539	0.398	0.768
Other	0.378	-0.796	1.552	0.526
Education Level				
High School		REFERENCE		
College/6th form	0.126	-0.271	0.524	0.531
University	-0.123	-0.680	0.435	0.665
IMD Quintile				
1		REFERENCE		
2	0.065	-0.411	0.541	0.788
3	0.226	-0.235	0.687	0.334
4	-0.472	-1.062	0.119	0.117
5	-0.309	-0.853	0.235	0.264
Unknown	0.102	-0.527	0.731	0.749
Gender				
Male		REFERENCE		
Female	**0.368**	**0.028**	**0.708**	**0.034**
Social Support				
Yes		REFERENCE		
No	-0.727	-1.394	-0.059	0.033
HD Vintage	0.000	-0.003	0.003	0.977
Charlson Index	**0.097**	**0.002**	**0.192**	**0.045**
Cognitive Impairment				
No		REFERENCE		
Yes	0.391	-0.027	0.809	0.066
PHQ-9 Score	**0.057**	**0.022**	**0.091**	**0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	-0.250	-0.703	0.204	0.279
Worse	-0.042	-0.487	0.403	0.853
Self-Reported Health Today	-0.006	-0.014	0.003	0.166
Walking Aid Use				
No		REFERENCE		
Yes	**0.828**	**0.467**	**1.190**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**0.417**	**0.050**	**0.783**	**0.026**
Constant	**2.776**	**1.434**	**4.118**	**<0.001**

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-11: Multiple linear regression of Clinical Frailty Scale by Low Muscle Mass. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	0.001	-0.011	0.012	0.912
Age	0.001	-0.015	0.018	0.858
Ethnicity				
White		REFERENCE		
South Asian	**0.549**	**0.099**	**0.998**	**0.017**
Black	-0.070	-0.539	0.398	0.768
Other	0.378	-0.796	1.552	0.526
Education Level				
High School		REFERENCE		
College/6th form	0.126	-0.271	0.524	0.531
University	-0.123	-0.680	0.435	0.665
IMD Quintile				
1		REFERENCE		
2	0.065	-0.411	0.541	0.788
3	0.226	-0.235	0.687	0.334
4	-0.472	-1.062	0.119	0.117
5	-0.309	-0.853	0.235	0.264
Unknown	0.102	-0.527	0.731	0.749
Gender				
Male		REFERENCE		
Female	**0.368**	**0.028**	**0.708**	**0.034**
Social Support				
Yes		REFERENCE		
No	-0.727	-1.394	-0.059	0.033
HD Vintage	0.000	-0.003	0.003	0.977
Charlson Index	**0.097**	**0.002**	**0.192**	**0.045**
Cognitive Impairment				
No		REFERENCE		
Yes	0.391	-0.027	0.809	0.066
PHQ-9 Score	**0.057**	**0.022**	**0.091**	**0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	-0.250	-0.703	0.204	0.279
Worse	-0.042	-0.487	0.403	0.853
Self-Reported Health Today	-0.006	-0.014	0.003	0.166
Walking Aid Use				
No		REFERENCE		
Yes	**0.828**	**0.467**	**1.190**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**0.417**	**0.050**	**0.783**	**0.026**
Constant	**2.776**	**1.434**	**4.118**	**<0.001**

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-12: Multiple linear regression of Clinical Frailty Scale by Sarcopenia. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	0.104	-0.263	0.471	0.575
Age	0.001	-0.015	0.017	0.883
Ethnicity				
White		REFERENCE		
South Asian	**0.536**	**0.087**	**0.986**	**0.020**
Black	-0.056	-0.526	0.414	0.814
Other	0.350	-0.823	1.522	0.557
Education Level				
High School		REFERENCE		
College/6th form	0.136	-0.258	0.531	0.495
University	-0.111	-0.668	0.445	0.693
IMD Quintile				
1		REFERENCE		
2	0.064	-0.412	0.539	0.792
3	0.236	-0.224	0.697	0.312
4	-0.461	-1.052	0.130	0.125
5	-0.298	-0.842	0.247	0.282
Unknown	0.100	-0.528	0.729	0.753
Gender				
Male		REFERENCE		
Female	**0.370**	**0.039**	**0.700**	**0.029**
Social Support				
Yes		REFERENCE		
No	**-0.742**	**-1.411**	**-0.073**	**0.030**
HD Vintage	0.000	-0.003	0.003	0.924
Charlson Index	0.093	-0.002	0.188	0.054
Cognitive Impairment				
No		REFERENCE		
Yes	0.396	-0.019	0.810	0.061
PHQ-9 Score	**0.057**	**0.023**	**0.091**	**0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	-0.263	-0.718	0.192	0.256
Worse	-0.043	-0.487	0.401	0.849
Self-Reported Health Today	-0.005	-0.014	0.003	0.224
Walking Aid Use				
No		REFERENCE		
Yes	**0.822**	**0.462**	**1.181**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**0.418**	**0.053**	**0.784**	**0.025**
Constant	**2.779**	**1.603**	**3.955**	**<0.001**

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-13: Multivariable logistic regression of Frailty Phenotype by BATT. Model 3

	Odds Ratio	Lower 95% C.I.	Upper 95% C.I.	P
BATT	0.965	0.930	1.001	0.060
Age	1.002	0.953	1.054	0.938
Ethnicity				
White		REFERENCE		
South Asian	1.383	0.353	5.409	0.642
Black	0.456	0.111	1.866	0.275
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	0.508	0.171	1.510	0.223
University	0.087	0.006	1.265	0.074
IMD Quintile				
1		REFERENCE		
2	1.898	0.476	7.569	0.364
3	0.661	0.184	2.374	0.526
4	0.170	0.024	1.231	0.079
5	0.204	0.037	1.136	0.070
Unknown	2.108	0.169	26.280	0.562
Gender				
Male		REFERENCE		
Female	1.673	0.588	4.757	0.335
Social Support				
Yes		REFERENCE		
No	0.378	0.059	2.418	0.304
HD Vintage	1.005	0.997	1.014	0.215
Charlson Index	1.204	0.913	1.586	0.188
Cognitive Impairment				
No		REFERENCE		
Yes	0.258	0.061	1.097	0.067
PHQ-9 Score	**1.147**	**1.032**	**1.275**	**0.011**
Self-Reported Health Change				
Better		REFERENCE		
The Same	1.664	0.383	7.236	0.497
Worse	0.814	0.209	3.178	0.767
Self-Reported Health Today	0.979	0.955	1.004	0.095
Walking Aid Use				
No		REFERENCE		
Yes	**6.657**	**2.435**	**18.199**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**11.458**	**3.044**	**43.123**	**<0.001**
Constant	0.271	0.004	18.611	0.545

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-14: Multivariable logistic regression of Frailty Phenotype by Low Muscle Mass. Model 3

	Odds Ratio	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	**4.160**	**1.356**	**12.765**	**0.013**
Age	1.005	0.955	1.058	0.848
Ethnicity				
White		REFERENCE		
South Asian	1.537	0.395	5.987	0.535
Black	0.515	0.125	2.126	0.359
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	0.633	0.207	1.943	0.424
University	0.100	0.007	1.503	0.096
IMD Quintile				
1		REFERENCE		
2	1.392	0.343	5.650	0.643
3	0.558	0.148	2.099	0.388
4	0.138	0.018	1.080	0.059
5	**0.150**	**0.025**	**0.882**	**0.036**
Unknown	1.972	0.163	23.844	0.594
Gender				
Male		REFERENCE		
Female	**3.155**	**1.082**	**9.194**	**0.035**
Social Support				
Yes		REFERENCE		
No	0.308	0.046	2.064	0.225
HD Vintage	1.004	0.995	1.013	0.374
Charlson Index	1.225	0.932	1.609	0.146
Cognitive Impairment				
No		REFERENCE		
Yes	0.245	0.057	1.060	0.060
PHQ-9 Score	**1.153**	**1.038**	**1.282**	**0.008**
Self-Reported Health Change				
Better		REFERENCE		
The Same	1.629	0.371	7.154	0.518
Worse	0.813	0.210	3.146	0.765
Self-Reported Health Today	0.983	0.959	1.009	0.195
Walking Aid Use				
No		REFERENCE		
Yes	**6.219**	**2.232**	**17.326**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**12.938**	**3.450**	**48.509**	**<0.001**
Constant	**0.011**	**0.000**	**0.504**	**0.021**

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-15: Multivariable logistic regression of Frailty Phenotype by Sarcopenia. Model 3

	Odds Ratio	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**7.034**	**2.147**	**23.042**	**0.001**
Age	0.991	0.939	1.046	0.756
Ethnicity				
White		REFERENCE		
South Asian	1.145	0.276	4.743	0.852
Black	0.618	0.145	2.632	0.515
Other	1.000			
Education Level				
High School		REFERENCE		
College/6th form	0.517	0.168	1.585	0.248
University	0.085	0.005	1.440	0.088
IMD Quintile				
1		REFERENCE		
2	1.816	0.463	7.119	0.392
3	1.006	0.268	3.769	0.993
4	0.191	0.024	1.543	0.120
5	0.190	0.030	1.221	0.080
Unknown	2.124	0.184	24.579	0.546
Gender				
Male		REFERENCE		
Female	2.652	0.927	7.589	0.069
Social Support				
Yes		REFERENCE		
No	0.225	0.029	1.738	0.153
HD Vintage	1.003	0.995	1.012	0.476
Charlson Index	1.227	0.925	1.627	0.156
Cognitive Impairment				
No		REFERENCE		
Yes	0.241	0.051	1.145	0.073
PHQ-9 Score	**1.144**	**1.029**	**1.271**	**0.013**
Self-Reported Health Change				
Better		REFERENCE		
The Same	1.533	0.328	7.156	0.587
Worse	0.966	0.240	3.893	0.961
Self-Reported Health Today	0.990	0.964	1.017	0.472
Walking Aid Use				
No		REFERENCE		
Yes	**8.121**	**2.790**	**23.642**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**16.034**	**3.928**	**65.447**	**<0.001**
Constant	**0.016**	**0.000**	**0.812**	**0.039**

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-16: Multivariable logistic regression of Frailty Index by BATT. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	0.984	0.952	1.017	0.345
Age	1.014	0.968	1.063	0.554
Ethnicity				
White		REFERENCE		
South Asian	**5.488**	**1.171**	**25.714**	**0.031**
Black	0.748	0.204	2.743	0.662
Other	2.680	0.118	60.795	0.536
Education Level				
High School		REFERENCE		
College/6th form	1.302	0.402	4.220	0.660
University	1.178	0.253	5.492	0.835
IMD Quintile				
1		REFERENCE		
2	0.733	0.197	2.724	0.643
3	2.041	0.518	8.050	0.308
4	0.289	0.054	1.542	0.146
5	0.650	0.159	2.651	0.548
Unknown	0.443	0.055	3.578	0.445
Gender				
Male		REFERENCE		
Female	1.896	0.668	5.381	0.230
Social Support				
Yes		REFERENCE		
No	0.408	0.074	2.252	0.304
HD Vintage	0.999	0.990	1.008	0.811
Charlson Index	1.106	0.833	1.468	0.485
Cognitive Impairment				
No		REFERENCE		
Yes	**8.406**	**2.450**	**28.837**	**0.001**
PHQ-9 Score	**1.294**	**1.137**	**1.473**	**<0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	0.488	0.139	1.719	0.264
Worse	1.482	0.440	4.992	0.525
Self-Reported Health Today	**0.965**	**0.942**	**0.989**	**0.005**
Walking Aid Use				
No		REFERENCE		
Yes	**5.212**	**1.836**	**14.796**	**0.002**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	2.020	0.784	5.204	0.145
Constant	0.107	0.002	5.886	0.275

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-17: Multivariable logistic regression of Frailty Index by Low Muscle Mass. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	0.971	0.357	2.639	0.955
Age	1.014	0.968	1.063	0.554
Ethnicity				
White		REFERENCE		
South Asian	**5.734**	**1.233**	**26.666**	**0.026**
Black	0.788	0.217	2.856	0.717
Other	2.797	0.119	65.470	0.523
Education Level				
High School		REFERENCE		
College/6th form	1.180	0.367	3.794	0.781
University	1.086	0.232	5.092	0.917
IMD Quintile				
1		REFERENCE		
2	0.765	0.197	2.965	0.699
3	2.262	0.567	9.026	0.248
4	0.308	0.057	1.664	0.171
5	0.640	0.159	2.586	0.531
Unknown	0.468	0.057	3.801	0.477
Gender				
Male		REFERENCE		
Female	2.202	0.813	5.961	0.120
Social Support				
Yes		REFERENCE		
No	0.384	0.069	2.136	0.275
HD Vintage	1.000	0.991	1.009	0.954
Charlson Index	1.141	0.858	1.518	0.365
Cognitive Impairment				
No		REFERENCE		
Yes	**7.555**	**2.232**	**25.571**	**0.001**
PHQ-9 Score	**1.283**	**1.129**	**1.459**	**<0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	0.489	0.139	1.718	0.264
Worse	1.504	0.447	5.058	0.509
Self-Reported Health Today	**0.965**	**0.942**	**0.989**	**0.005**
Walking Aid Use				
No		REFERENCE		
Yes	**5.576**	**1.924**	**16.162**	**0.002**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	2.124	0.832	5.421	0.115
Constant	0.042	0.001	1.396	0.076

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-18: Multivariable logistic regression of Frailty Index by Sarcopenia. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	0.022	-0.017	0.061	0.265
Age	-0.001	-0.003	0.000	0.086
Ethnicity				
White		REFERENCE		
South Asian	**0.057**	**0.010**	**0.105**	**0.019**
Black	0.014	-0.036	0.064	0.576
Other	0.000	-0.125	0.124	0.994
Education Level				
High School		REFERENCE		
College/6th form	-0.001	-0.043	0.041	0.962
University	-0.009	-0.068	0.050	0.771
IMD Quintile				
1		REFERENCE		
2	0.016	-0.035	0.066	0.539
3	0.020	-0.029	0.069	0.430
4	-0.003	-0.066	0.060	0.918
5	-0.008	-0.066	0.050	0.776
Unknown	0.011	-0.056	0.078	0.739
Gender				
Male		REFERENCE		
Female	**0.045**	**0.010**	**0.080**	**0.012**
Social Support				
Yes		REFERENCE		
No	**-0.106**	**-0.177**	**-0.035**	**0.004**
HD Vintage	0.000	0.000	0.000	0.820
Charlson Index	**0.016**	**0.006**	**0.026**	**0.002**
Cognitive Impairment				
No		REFERENCE		
Yes	**0.063**	**0.019**	**0.107**	**0.006**
PHQ-9 Score	**0.012**	**0.009**	**0.016**	**<0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	**-0.051**	**-0.100**	**-0.003**	**0.038**
Worse	0.022	-0.025	0.069	0.364
Self-Reported Health Today	-0.001	-0.002	0.000	0.204
Walking Aid Use				
No		REFERENCE		
Yes	**0.121**	**0.082**	**0.159**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**0.068**	**0.029**	**0.107**	**0.001**
Constant	0.116	-0.009	0.241	0.069

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-19: Multivariable logistic regression of Edmonton Frailty Scale by BATT. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	**0.970**	**0.942**	**1.000**	**0.050**
Age	0.987	0.947	1.030	0.558
Ethnicity				
White		REFERENCE		
South Asian	1.802	0.586	5.546	0.304
Black	**4.229**	**1.230**	**14.539**	**0.022**
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	0.598	0.217	1.647	0.320
University	0.575	0.141	2.344	0.440
IMD Quintile				
1		REFERENCE		
2	1.508	0.403	5.640	0.542
3	0.354	0.110	1.138	0.081
4	0.484	0.112	2.100	0.333
5	1.781	0.456	6.951	0.406
Unknown	0.642	0.131	3.158	0.586
Gender				
Male		REFERENCE		
Female	1.035	0.422	2.541	0.940
Social Support				
Yes		REFERENCE		
No	5.070	0.705	36.483	0.107
HD Vintage	0.994	0.987	1.002	0.144
Charlson Index	1.225	0.952	1.576	0.115
Cognitive Impairment				
No		REFERENCE		
Yes	1.785	0.605	5.263	0.294
PHQ-9 Score	**1.113**	**1.016**	**1.220**	**0.022**
Self-Reported Health Change				
Better		REFERENCE		
The Same	0.378	0.117	1.228	0.106
Worse	0.512	0.159	1.647	0.261
Self-Reported Health Today	**0.972**	**0.952**	**0.994**	**0.012**
Walking Aid Use				
No		REFERENCE		
Yes	**4.512**	**1.828**	**11.134**	**0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	2.005	0.856	4.695	0.109
Constant	6.501	0.196	215.239	0.294

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-20: Multivariable logistic regression of Edmonton Frailty Scale by Low Muscle Mass. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	2.165	0.878	5.336	0.093
Age	0.991	0.951	1.032	0.661
Ethnicity				
White		REFERENCE		
South Asian	1.881	0.616	5.748	0.267
Black	**4.101**	**1.218**	**13.811**	**0.023**
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	0.629	0.226	1.751	0.374
University	0.583	0.145	2.349	0.448
IMD Quintile				
1		REFERENCE		
2	1.247	0.329	4.724	0.745
3	0.344	0.104	1.136	0.080
4	0.487	0.109	2.167	0.345
5	1.553	0.405	5.953	0.520
Unknown	0.645	0.135	3.078	0.582
Gender				
Male		REFERENCE		
Female	1.570	0.657	3.750	0.310
Social Support				
Yes		REFERENCE		
No	5.565	0.714	43.364	0.101
HD Vintage	0.994	0.986	1.002	0.124
Charlson Index	1.231	0.959	1.580	0.102
Cognitive Impairment				
No		REFERENCE		
Yes	1.761	0.600	5.165	0.303
PHQ-9 Score	**1.108**	**1.014**	**1.212**	**0.024**
Self-Reported Health Change				
Better		REFERENCE		
The Same	0.364	0.114	1.169	0.090
Worse	0.547	0.173	1.726	0.303
Self-Reported Health Today	**0.974**	**0.953**	**0.996**	**0.019**
Walking Aid Use				
No		REFERENCE		
Yes	**4.201**	**1.702**	**10.368**	**0.002**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	2.201	0.937	5.168	0.070
Constant	0.621	0.033	11.815	0.751

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-21: Multivariable logistic regression of Edmonton Frailty Scale by Sarcopenia. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**3.238**	**1.207**	**8.681**	**0.020**
Age	0.987	0.947	1.029	0.542
Ethnicity				
White		REFERENCE		
South Asian	1.706	0.544	5.352	0.359
Black	**4.131**	**1.221**	**13.975**	**0.023**
Other	1.000			
Education Level				
High School		REFERENCE		
College/6th form	0.564	0.207	1.534	0.262
University	0.522	0.126	2.155	0.369
IMD Quintile				
1		REFERENCE		
2	1.366	0.356	5.235	0.649
3	0.431	0.135	1.370	0.153
4	0.531	0.117	2.412	0.413
5	1.722	0.435	6.826	0.439
Unknown	0.641	0.132	3.126	0.583
Gender				
Male		REFERENCE		
Female	1.480	0.625	3.508	0.373
Social Support				
Yes		REFERENCE		
No	4.206	0.548	32.273	0.167
HD Vintage	0.993	0.986	1.001	0.101
Charlson Index	1.216	0.947	1.561	0.126
Cognitive Impairment				
No		REFERENCE		
Yes	1.618	0.543	4.823	0.387
PHQ-9 Score	**1.102**	**1.009**	**1.203**	**0.030**
Self-Reported Health Change				
Better		REFERENCE		
The Same	0.345	0.105	1.138	0.081
Worse	0.546	0.170	1.748	0.308
Self-Reported Health Today	**0.977**	**0.955**	**0.999**	**0.037**
Walking Aid Use				
No		REFERENCE		
Yes	**4.556**	**1.830**	**11.341**	**0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	2.182	0.917	5.194	0.078
Constant	0.878	0.047	16.299	0.930

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-22: Multivariable logistic regression of Clinical Frailty Scale by BATT. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	1.006	0.977	1.036	0.684
Age	1.005	0.963	1.048	0.831
Ethnicity				
White		REFERENCE		
South Asian	**3.647**	**1.026**	**12.961**	**0.046**
Black	0.884	0.276	2.832	0.835
Other	2.638	0.152	45.912	0.506
Education Level				
High School		REFERENCE		
College/6th form	1.012	0.362	2.827	0.982
University	2.306	0.599	8.875	0.225
IMD Quintile				
1		REFERENCE		
2	2.558	0.779	8.399	0.122
3	**3.743**	**1.089**	**12.867**	**0.036**
4	0.433	0.090	2.077	0.295
5	1.015	0.262	3.932	0.983
Unknown	1.909	0.298	12.223	0.495
Gender				
Male		REFERENCE		
Female	**2.701**	**1.085**	**6.727**	**0.033**
Social Support				
Yes		REFERENCE		
No	**0.147**	**0.030**	**0.725**	**0.019**
HD Vintage	1.002	0.994	1.010	0.588
Charlson Index	**1.322**	**1.008**	**1.733**	**0.044**
Cognitive Impairment				
No		REFERENCE		
Yes	2.937	0.971	8.885	0.056
PHQ-9 Score	**1.144**	**1.045**	**1.252**	**0.004**
Self-Reported Health Change				
Better		REFERENCE		
The Same	0.727	0.233	2.270	0.583
Worse	0.949	0.315	2.862	0.926
Self-Reported Health Today	0.985	0.964	1.005	0.148
Walking Aid Use				
No		REFERENCE		
Yes	**6.370**	**2.557**	**15.871**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**2.840**	**1.178**	**6.845**	**0.020**
Constant	**0.007**	**0.000**	**0.304**	**0.010**

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-23: Multivariable logistic regression of Clinical Frailty Scale by Low Muscle Mass. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	0.690	0.278	1.709	0.422
Age	1.003	0.962	1.047	0.876
Ethnicity				
White		REFERENCE		
South Asian	**3.677**	**1.032**	**13.101**	**0.045**
Black	0.868	0.269	2.801	0.813
Other	2.576	0.143	46.387	0.521
Education Level				
High School		REFERENCE		
College/6th form	0.972	0.344	2.749	0.957
University	2.219	0.567	8.692	0.252
IMD Quintile				
1		REFERENCE		
2	2.854	0.838	9.717	0.093
3	**3.988**	**1.147**	**13.864**	**0.030**
4	0.437	0.090	2.114	0.303
5	1.060	0.272	4.131	0.933
Unknown	1.963	0.309	12.463	0.475
Gender				
Male		REFERENCE		
Female	2.397	0.982	5.856	0.055
Social Support				
Yes		REFERENCE		
No	**0.146**	**0.030**	**0.719**	**0.018**
HD Vintage	1.003	0.995	1.011	0.517
Charlson Index	1.332	1.017	1.746	0.038
Cognitive Impairment				
No		REFERENCE		
Yes	2.925	0.966	8.862	0.058
PHQ-9 Score	**1.141**	**1.042**	**1.249**	**0.004**
Self-Reported Health Change				
Better		REFERENCE		
The Same	0.737	0.235	2.315	0.601
Worse	0.937	0.309	2.835	0.908
Self-Reported Health Today	0.983	0.963	1.004	0.122
Walking Aid Use				
No		REFERENCE		
Yes	**6.712**	**2.652**	**16.989**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**2.790**	**1.165**	**6.683**	**0.021**
Constant	**0.014**	**0.000**	**0.378**	**0.011**

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-24: Multivariable logistic regression of Clinical Frailty Scale by Sarcopenia. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	0.104	-0.263	0.471	0.575
Age	0.001	-0.015	0.017	0.883
Ethnicity				
White		REFERENCE		
South Asian	**0.536**	**0.087**	**0.986**	**0.020**
Black	-0.056	-0.526	0.414	0.814
Other	0.350	-0.823	1.522	0.557
Education Level				
High School		REFERENCE		
College/6th form	0.136	-0.258	0.531	0.495
University	-0.111	-0.668	0.445	0.693
IMD Quintile				
1		REFERENCE		
2	0.064	-0.412	0.539	0.792
3	0.236	-0.224	0.697	0.312
4	-0.461	-1.052	0.130	0.125
5	-0.298	-0.842	0.247	0.282
Unknown	0.100	-0.528	0.729	0.753
Gender				
Male		REFERENCE		
Female	**0.370**	**0.039**	**0.700**	**0.029**
Social Support				
Yes		REFERENCE		
No	**-0.742**	**-1.411**	**-0.073**	**0.030**
HD Vintage	0.000	-0.003	0.003	0.924
Charlson Index	0.093	-0.002	0.188	0.054
Cognitive Impairment				
No		REFERENCE		
Yes	0.396	-0.019	0.810	0.061
PHQ-9 Score	**0.057**	**0.023**	**0.091**	**0.001**
Self-Reported Health Change				
Better		REFERENCE		
The Same	-0.263	-0.718	0.192	0.256
Worse	-0.043	-0.487	0.401	0.849
Self-Reported Health Today	-0.005	-0.014	0.003	0.224
Walking Aid Use				
No		REFERENCE		
Yes	**0.822**	**0.462**	**1.181**	**<0.001**
Self-Reported Slow Walk Speed				
No		REFERENCE		
Yes	**0.418**	**0.053**	**0.784**	**0.025**
Constant	**2.779**	**1.603**	**3.955**	**<0.001**

Charlson Index with CKD omitted. Self-reported health today from EQ-5D VAS

Supplementary Table 4-25: Sensitivity Analyses of Frailty Score by multiple linear regression models in reverse order.

		Model	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Frailty Phenotype	BATT	A	**-0.013**	**-0.023**	**-0.003**	**0.009**
		B	**-0.012**	**-0.022**	**-0.003**	**0.010**
		C	-0.009	-0.019	0.001	0.064
	LMM	A	**0.380**	**0.102**	**0.657**	**0.008**
		B	**0.334**	**0.061**	**0.606**	**0.017**
		C	**0.379**	**0.082**	**0.676**	**0.013**
	Sarcopenia	A	**0.818**	**0.536**	**1.100**	**<0.001**
		B	**0.740**	**0.448**	**1.032**	**<0.001**
		C	**0.725**	**0.420**	**1.030**	**<0.001**
Frailty Index	BATT	A	0.000	-0.001	0.002	0.888
		B	0.000	-0.001	0.001	0.815
		C	0.001	-0.001	0.002	0.355
	LMM	A	-0.019	-0.060	0.022	0.368
		B	-0.021	-0.054	0.013	0.227
		C	-0.022	-0.059	0.014	0.230
	Sarcopenia	A	**0.047**	**0.004**	**0.091**	**0.033**
		B	0.020	-0.018	0.058	0.304
		C	0.022	-0.017	0.061	0.265
Edmonton Frailty Scale	BATT	A	-0.012	-0.034	0.011	0.300
		B	-0.015	-0.036	0.006	0.151
		C	-0.020	-0.042	0.001	0.064
	LMM	A	-0.031	-0.683	0.620	0.924
		B	0.125	-0.481	0.732	0.684
		C	0.277	-0.383	0.938	0.408
	Sarcopenia	A	**0.840**	**0.150**	**1.530**	**0.017**
		B	**0.951**	**0.283**	**1.618**	**0.005**
		C	**1.101**	**0.411**	**1.791**	**0.002**
Clinical Frailty Scale	BATT	A	-0.004	-0.015	0.007	0.493
		B	-0.003	-0.014	0.008	0.597
		C	0.001	-0.011	0.012	0.912
	LMM	A	-0.033	-0.346	0.281	0.838
		B	-0.084	-0.400	0.232	0.601
		C	-0.074	-0.416	0.269	0.672
	Sarcopenia	A	0.293	-0.042	0.627	0.086
		B	0.113	-0.241	0.467	0.530
		C	0.104	-0.263	0.471	0.575

Bold text indicates significant at P<0.05 level. See materials and methods section for model definitions.

Supplementary Table 4-26: Sensitivity analyses of multivariable logistic regression models of frailty. Multivariable models reversed.

	Model	OR	Lower 95% C.I.	Upper 95% C.I.	P
BATT	A	**0.959**	**0.932**	**0.987**	**0.004**
	B	**0.954**	**0.923**	**0.987**	**0.006**
	C	0.965	0.930	1.001	0.060
LMM	A	**3.259**	**1.561**	**6.804**	**0.002**
	B	**3.520**	**1.497**	**8.273**	**0.004**
	C	**4.160**	**1.356**	**12.765**	**0.013**
Sarcopenia	A	**5.961**	**2.671**	**13.305**	**<0.001**
	B	**6.334**	**2.434**	**16.484**	**<0.001**
	C	**7.034**	**2.147**	**23.042**	**0.001**
BATT	A	0.992	0.971	1.014	0.491
	B	0.981	0.953	1.010	0.192
	C	0.984	0.952	1.017	0.345
LMM	A	0.891	0.469	1.694	0.725
	B	1.023	0.442	2.367	0.957
	C	0.971	0.357	2.639	0.955
Sarcopenia	A	**2.426**	**1.181**	**4.985**	**0.016**
	B	**2.722**	**1.035**	**7.160**	**0.042**
	C	**3.033**	**1.038**	**8.862**	**0.043**
BATT	A	0.986	0.964	1.008	0.211
	B	0.983	0.958	1.008	0.187
	C	0.970	0.942	1.000	0.050
LMM	A	-0.031	-0.683	0.620	0.924
	B	0.125	-0.481	0.732	0.684
	C	0.277	-0.383	0.938	0.408
Sarcopenia	A	**0.840**	**0.150**	**1.530**	**0.017**
	B	**0.951**	**0.283**	**1.618**	**0.005**
	C	**1.101**	**0.411**	**1.791**	**0.002**
BATT	A	0.992	0.970	1.014	0.463
	B	0.992	0.967	1.018	0.541
	C	1.006	0.977	1.036	0.684
LMM	A	1.096	0.579	2.074	0.779
	B	0.907	0.433	1.899	0.795
	C	0.690	0.278	1.709	0.422
Sarcopenia	A	**2.297**	**1.154**	**4.570**	**0.018**
	B	1.577	0.698	3.564	0.273
	C	1.533	0.600	3.919	0.372

Bold text indicates significant at P<0.05 level. See materials and methods section for model definitions.

Chapter 5:

Gender disparity in expression of sarcopenia in haemodialysis recipients: analysis from the FITNESS cohort

Authors: Benjamin M Anderson, Daisy V Wilson, Muhammad Qasim, Gonzalo Correa, Felicity Evison, Suzy Gallier, Charles J Ferro, Thomas A Jackson, Adnan Sharif

5.1 Extent of Personal Contribution

I coordinated all study visits with participants and dialysis unit staff. I recruited participants, and collected all baseline data with the support of Dr Gonzalo Correa, Dr Muhammad Qasim, and Dr Adnan Sharif. All colleagues were supervised by me in their data collection, and I was responsible for maintaining training and personnel logs in the site file. All ultrasound measures were taken and analysed by me.

The ultrasound protocol was originally developed by Dr Daisy Wilson, who kindly trained me in quadriceps ultrasound prior to the study. Dr Wilson also provided critical appraisal and insight into the statistical analyses and interpretation for this chapter.

Ms Felicity Evison, and Ms Suzy Gallier were responsible for interrogation of EPR for IMD Quintile assessment. I performed all subsequent data cleaning, integrity, and analyses with guidance from Dr Adnan Sharif.

The first draft of the manuscript was written by myself and I was responsible for all edits and revisions. This chapter is based upon a manuscript submitted for peer-review to Hemodialysis International on 31st August 2022, reference HDI-22-0266.

5.2 Abstract

5.2.1 Background

There has been little exploration of the interplay between sarcopenia and frailty in haemodialysis, particularly regarding gender difference. We aimed to 1) assess whether ultrasound-derived low muscle mass (LMM) and sarcopenia are more common in male or female haemodialysis recipients; 2) whether age influences any observed gender difference, and 3) explore the interplay between sarcopenia, frailty and gender in haemodialysis recipients.

5.2.2 Materials and Methods

This was an exploratory analysis of a subgroup of adult prevalent (≥3 months) haemodialysis with frailty phenotype (FP) scores. Bilateral Anterior Thigh Thickness (BATT) was obtained according to an established ultrasound protocol. Associations with frailty were explored via both linear and logistic regressions for BATT, LMM, and sarcopenia with *a priori* covariables, stratified by gender.

5.2.3 Results

In total 223 study participants had ultrasound measurements. Males showed greater prevalence of LMM. On adjusted analyses, LMM was associated with lower hand grip strength in males (β=-4.17; 95% C.I. -7.57 to -0.77; P=0.017), but not females (β=-1.88; 95% C.I. -5.41 to 1.64; P=0.289). LMM was also associated with slower walking speed in both males (β-0.115; 95% C.I. -0.258 to -0.013; P=0.03) and females (β=-0.152; 95% C.I. -0.300 to -0.005; P=0.04).

Sarcopenia was associated with greater odds of frailty on adjusted models in males (OR=9.86; 95% C.I. 1.8 to 54.0; P=0.008), but not females (OR=5.16; 95% C.I. 0.22 to 124; P=0.312).

5.2.4 Conclusion

The clinical expression and significance of sarcopenia differs substantially between males and females on haemodialysis. Further work is required to elucidate underlying mechanisms and guide tailored treatment.

5.3 Background

As we have seen, frailty is variably associated with BATT, LMM and sarcopenia. We also noted that females showed greater prevalence of LMM than males the FITNESS cohort, which we shall consider in more detail in this chapter.

There is heterogeneity in reports of gender differences in prevalence of both LMM and sarcopenia. Data from the NHANES study has shown that more females than males had DEXA-derived low muscle mass in non-CKD participants aged >50-years,[282] but this difference was not observed when the sample included participants aged ≥20-years.[283] However, systematic reviews of studies in nursing home residents[284] and the general population[285] found sarcopenia rates were similar between genders.

Heterogeneity is also observed in haemodialysis recipients, with reports of DEXA data ranging from females having higher proportions of sarcopenia,[286] to LMM and sarcopenia being more prevalent in males,[144] to no gender difference at all.[287] There is disagreement between studies as to whether BIA-derived LMM and sarcopenia is[6 288] or is not[289-291] more common in males than females on haemodialysis, though studies observing no significant difference may have lacked power. Other studies have defined LMM/sarcopenia from within-cohort medians rather than from healthy young adults as per European Working Group on Sarcopenia in Older Adults (EWGSOP) guidelines.[60,292,293]

Therefore, questions remain unanswered about the gender-specific prevalence of LMM and sarcopenia in haemodialysis recipients. To address this uncertainty, the aims of this study were to; 1) assess whether ultrasound-derived LMM and sarcopenia are more common in

male or female haemodialysis recipients; 2) assess whether age may influence any observed gender difference, and; 3) explore the interplay between sarcopenia, frailty and gender.

5.4 Methods

Full details of study setting, eligibility criteria, and recruitment and consent are detailed in Chapters Chapter 2: and 2.2. The Frailty Phenotype showed the most robust association with measures of muscle size in this cohort, as detailed in Chapter Chapter 4: hence we have used this as our primary frailty tool for the purposes of this analysis.[19]

5.4.1 Recruitment

As this was an exploratory study on a subgroup of FITNESS participants, no power calculation was applied to this part of the study.

5.4.2 Statistics

Statistical analyses were performed using STATA 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Correlations were calculated using Spearman's rank correlation coefficient. Agreement was assessed with Cohen's Kappa, and was rated as >0.9 almost perfect agreement, 0.8-0.9 strong, 0.6-0.79 moderate, 0.4-0.59 weak, 0.21-0.39 minimal, and ≤0.2 no agreement. Differences between groups were assessed using unpaired T-tests on transformed-normal continuous data, and Chi-squared or Fisher's Exact for proportions as appropriate.

Associations with continuous frailty scores were analysed using linear regression, having satisfied the linear assumption via visual comparison of observed versus Lowess fit lines on

scatter plot and augmented component plus residual plots. Robust standard errors were specified to account for heteroscedasticity. Multicollinearity was excluded on all analyses by variance inflation factor <10. Odds ratios for frailty were obtained by logistic regression.

Linear and logistic regressions were performed both unadjusted and adjusted for *a priori* covariables chosen for proven or suspected association with frailty. These were introduced in a stepwise manner; Model 1 included age, ethnicity, gender, education level, Index of Multiple Deprivation (IMD) quintile[294,295], self-reported social support (Yes/No), and haemodialysis vintage. Model 2 added to these self-reported health today (Euroqol 5D Visual Analogue Scale)[227], self-reported health change, PHQ-9 score,[196] cognitive impairment (Montreal Cognitive Assessment [MoCA])[224], and Charlson Comorbidity Index (CKD omitted). Model 3 added self-reported slow walking speed (from GP Physical Activity Questionnaire)[269], and use of walking aids (yes/no).

Missing IMD quintiles were handled via a dummy variable. All other missing data were handled via listwise deletion, as <1% of these data were missing. A P value < 0.05 was considered significant.

5.5 Results

Figure 4-1 shows a flowchart of recruitment to the FITNESS study. In total, 485 participants underwent frailty assessment and entered follow-up, of which 223 had valid ultrasound measurements. Of those with valid ultrasound measurements, the median FP was 2 (IQR 1-3) and 34% of participants were frail. Table 5-1 shows key demographics stratified by gender.

5.5.1 Prevalence of low muscle mass and sarcopenia

Mean BATT was 49.4mm (95% C.I. 47.0 to 51.8) in males and 44.6mm (95% C.I. 41.7 to 47.6) in females (P for difference: 0.014). Table 5-2 shows that LMM was significantly more prevalent in males. There were no statistically significant differences in muscle function between genders, but there was a non-significant trend towards sarcopenia in males (36.2% versus 24.7%; P=0.073). BATT was associated with walking speed for males (Spearman's ρ=0.362; P<0.001) but not females (ρ=0.126; P=0.280). BATT was associated with HGS in both males (ρ=0.447; P<0.001) and females (ρ=0.295; P=0.006).

Supplementary Table 5-1 shows higher prevalence of frailty, low grip strength, and slow walking speed in participants without ultrasound measurements versus those with ultrasound data. These differences were similarly maintained between genders.

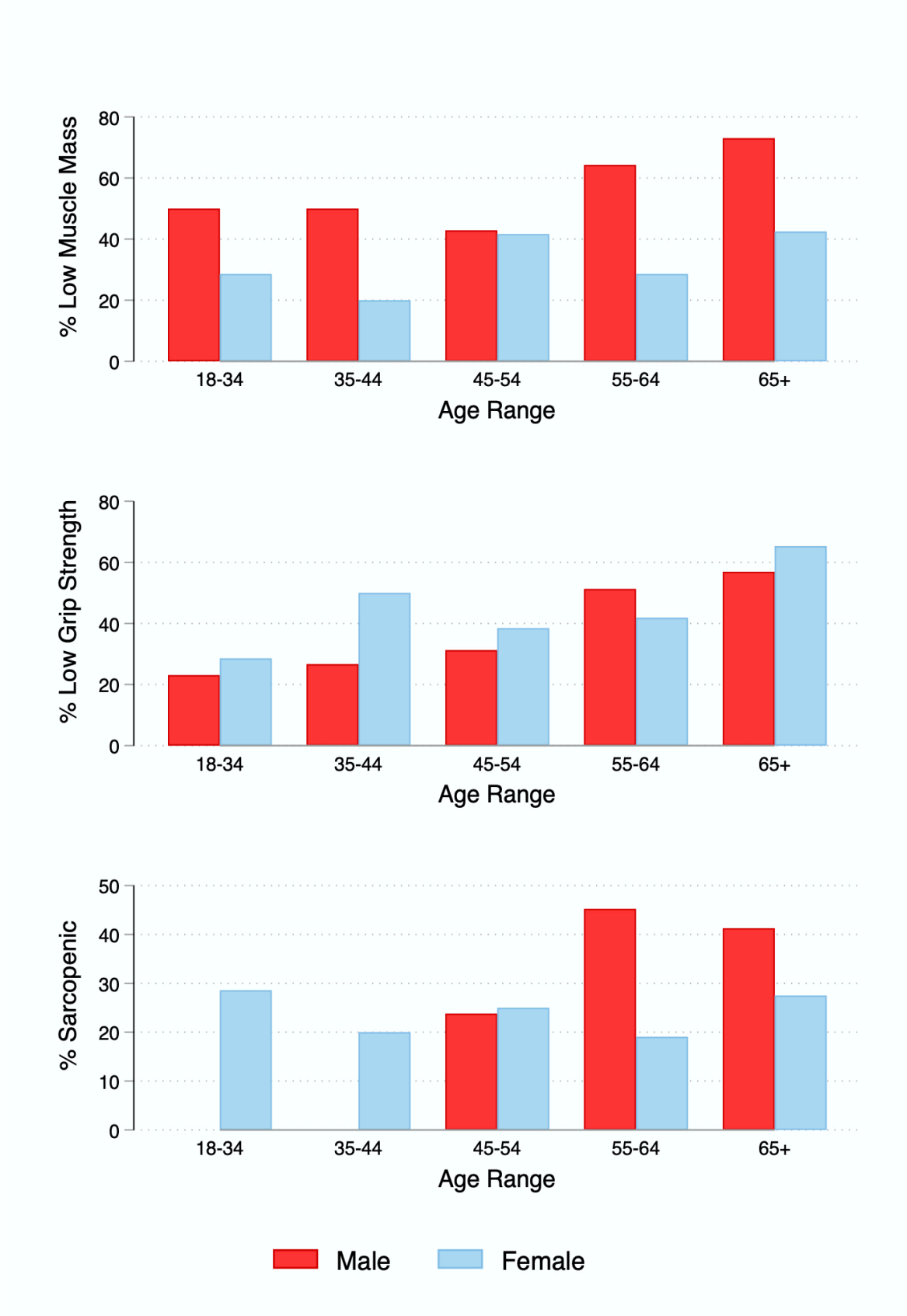


Figure 5-1: Age and gender-specific prevalence of low muscle mass, low grip strength, and sarcopenia

5.5.2 Influence of age on gender difference

Figure 5-1 shows that prevalence of low grip strength, LMM and sarcopenia all remained relatively stable for females across age ranges, whereas for males prevalence of each rose with age. When divided into age categories, males in the 54-65 and >65 age groups had significantly higher prevalence of LMM than females as shown in Table 5-3. As there were relatively few participants in each of the youngest three age categories, analyses were rerun by age tercile which demonstrated a similar pattern of LMM prevalence across genders, as shown in Table 5-4.

5.5.3 Association between muscle size and function

Low muscle mass was associated with slower walking speed for males (β=-0.226; 95% C.I. -0.347 to -0.105; P<0.001), but not females (β=-0.122; 95% C.I. -0.254 to 0.009; P=0.068) on simple linear regression. Low muscle mass was associated with poorer HGS on simple linear regression for both males (β=-7.64; 95% C.I. -10.7 to -4.62; P<0.001) and females (β=-5.19; 95% C.I. -8.17 to -2.20; P=0.001).

Table 5-5 and Figure 5-2 show that walking speed was lower in both males and females with LMM on multiple linear regression, but only males with LMM showed lower HGS. Full multiple linear regression models, including those with BATT as an independent variable, are shown in Supplementary Table 5-2 to Supplementary Table 5-5

5.5.4 Association between muscle size and frailty

Figure 5-3 shows that in males, LMM and sarcopenia were associated with higher FP scores on all simple and multiple linear regression models. In females, LMM did not demonstrate

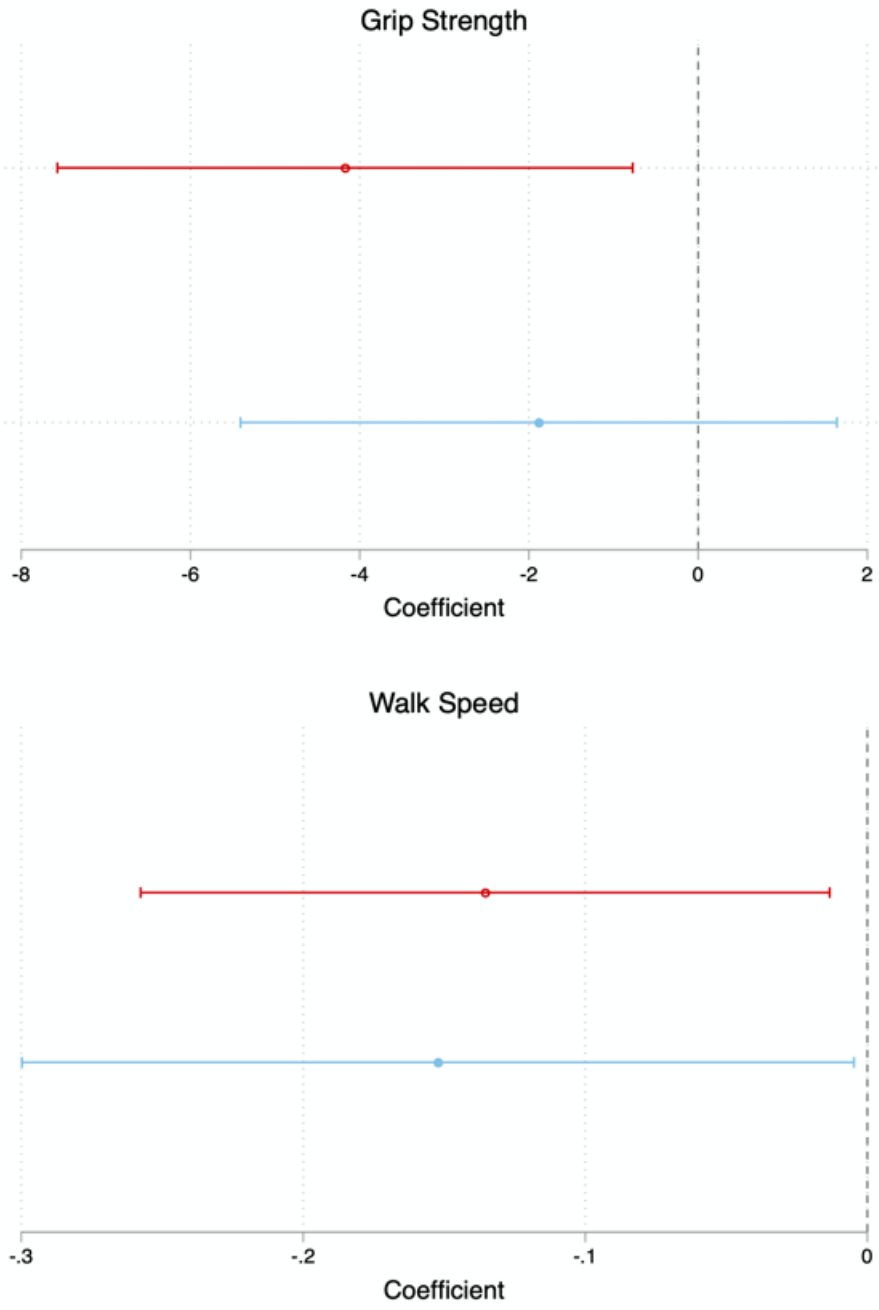


Figure 5-2: Change in grip strength and walking speed associated with low muscle mass on multiple linear regression

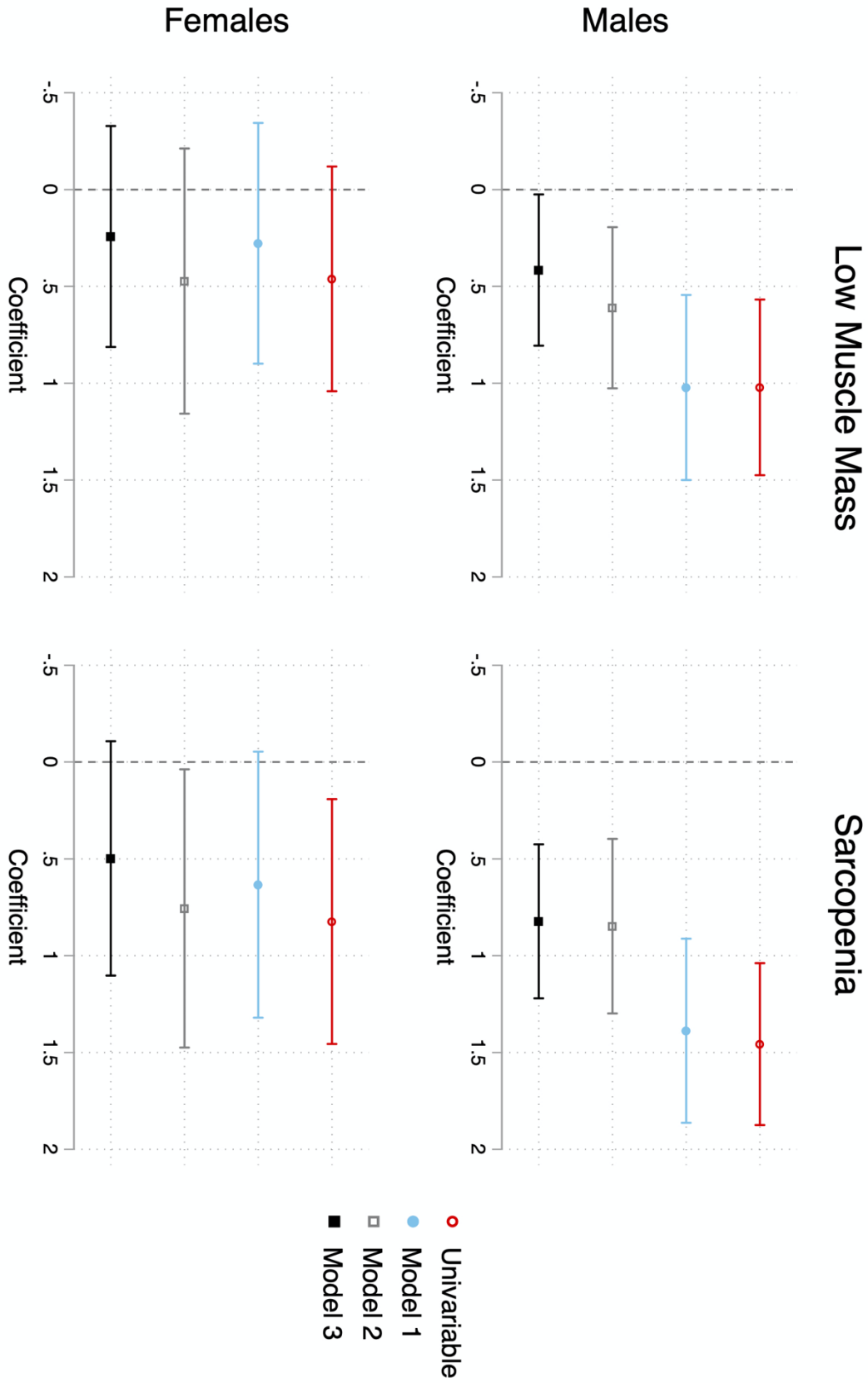


Figure 5-3: Change in Frailty Phenotype score associated with low muscle mass and sarcopenia in males and females on simple and multiple linear regression

significant association with FP scores on any model, whereas sarcopenia was associated with

increased FP scores for simple linear regression and Model 2 only. Full model results, including models involving BATT, are shown in Supplementary Table 5-6 to Supplementary Table 5-29.

Figure 5-4 shows that on logistic regression in males, LMM and sarcopenia were associated with increased odds of frailty on all models. Females with LMM were more likely to be frail on unadjusted analyses but lost this association on all adjusted models. Sarcopenia in females was associated with increased odds of frailty on unadjusted analysis and Model 1 but lost this association in Models 2 and 3. Full models are shown in Supplementary Table 5-30 to Supplementary Table 5-53

5.5.5 Constituents of Frailty Phenotype

Table 5-6 shows a slow walking speed was more common amongst females than in males. Furthermore, there was greater prevalence of low energy expenditure amongst females in the total FITNESS cohort, and those without ultrasound measurements, but there was no difference in energy expenditure between males and females for participants with valid ultrasound measures.

5.6 Discussion

There are conflicting reports of gender-specific prevalence of sarcopenia and LMM in haemodialysis recipients, and the relationship between gender and age upon sarcopenia has yet to be fully explored. This is important as the greater prevalence of LMM and sarcopenia in males described in haemodialysis literature is incongruent with the general population, where

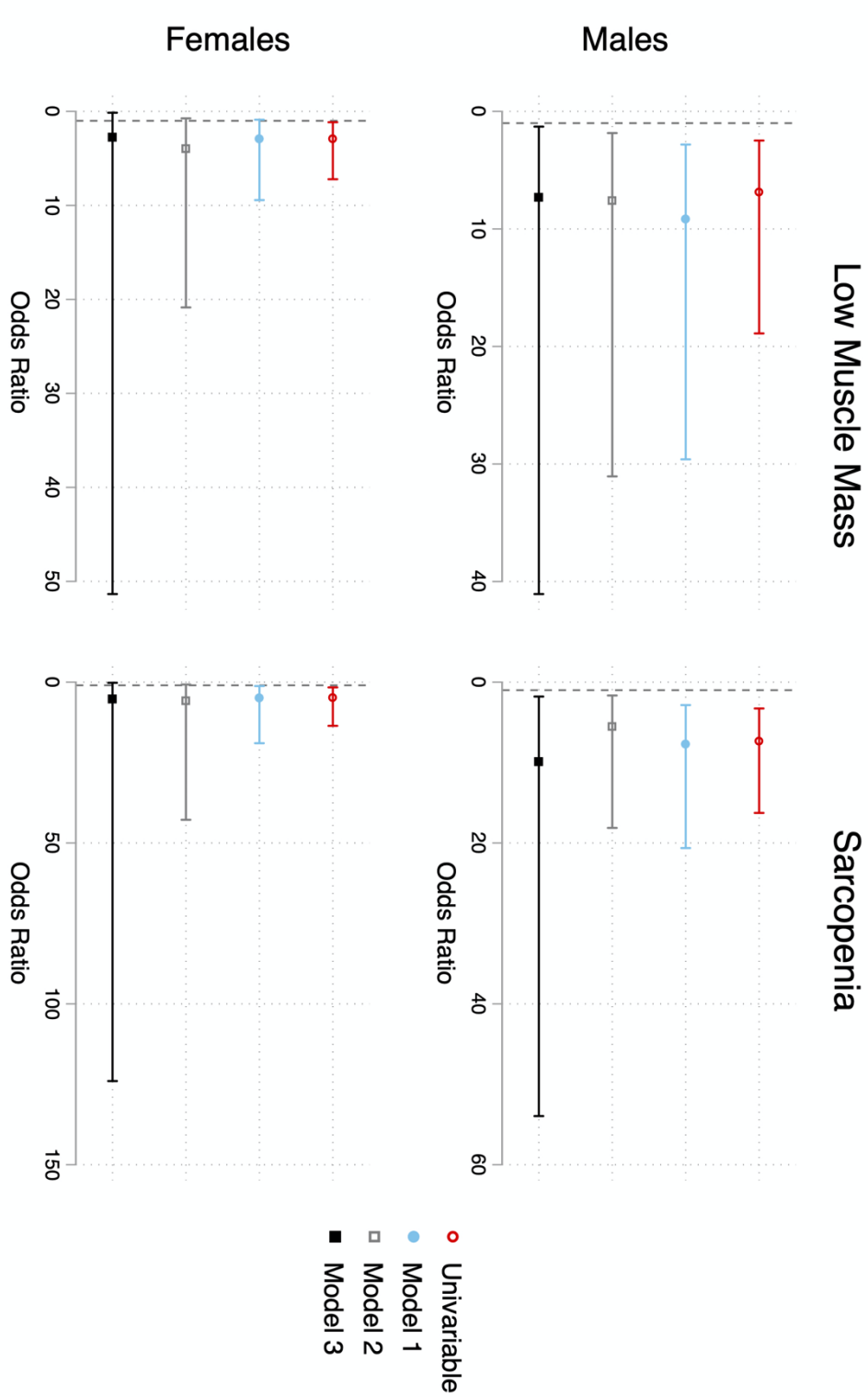


Figure 5-4: Univariable and multivariable Odds Ratios of FP frailty associated with low muscle mass and sarcopenia in males and females

there is greater prevalence of LMM in females in older age groups.[282,283] In this study, we confirm that LMM is more common in male haemodialysis recipients, and that there are also trends towards greater prevalence of sarcopenia in males. These gender differences appear

driven by significant differences in older age groups; in younger haemodialysis recipients, no such differences between genders were observed. The links between muscle mass and function are stronger in males than females on haemodialysis. Furthermore, there are robust associations between frailty and LMM/sarcopenia in males, but these associations are lost upon multivariable analyses in females. These results suggest that the sarcopenic and frailty phenotypes differ between genders; we can speculate that there may be a protective mechanism in younger male haemodialysis recipients that is lost with age. Further work should explore any mechanistic differences in sarcopenia between genders, and potential gender-specific mitigation for this important syndrome.

There is much interest in testosterone as a protective mechanism against sarcopenia and frailty. The majority of males receiving haemodialysis are testosterone-deficient, and testosterone levels fall with age.[131,296,297] Conversely, in a small observational study of haemodialysis recipients, all females enrolled had normal or supra-normal testosterone levels.[298] Chiang et al. found low free testosterone in male haemodialysis recipients was associated with low muscle mass, sarcopenia, and FP frailty both at baseline and at 12 months.[132] Our analyses demonstrate gender differences in LMM among haemodialysis recipients appear to be driven largely by high prevalence in older men. In the context of current research into testosterone deficiency in haemodialysis, we may speculate that the effects of advanced CKD, uraemia, and of haemodialysis itself may be synergistic with age to drive testosterone levels in older male haemodialysis recipients below protective levels. However, whilst testosterone replacement has been shown to increase muscle mass, HGS and physical function scores in men and women on haemodialysis,[240,299] and quality of life in men,[300] no large scale studies have explored the relationship between frailty and testosterone

deficiency in haemodialysis recipients. Furthermore, studies of testosterone replacement in older men in the general population have failed to demonstrate improved muscle performance (e.g., walking speed) despite improvements in strength and muscle mass.[295,301,302] We must therefore be cautious in ascribing gender differences to testosterone alone. Furthermore, there are legitimate concerns regarding the cardiovascular risk associated with testosterone supplementation in an already high-risk cohort.[295]

Our work raises an interesting question - if testosterone deficiency is associated with sarcopenia and/or frailty in males on haemodialysis then what of females? Female haemodialysis recipients exhibit higher prevalence of frailty compared to males; true even of the FP, the most physically mediated frailty score.[272] Males in our cohort exhibit higher prevalence of LMM, and a trend towards greater sarcopenia. Furthermore, the link between sarcopenia and frailty appears more robust in males. We must take care not to conflate sarcopenia and frailty,[60] but we must also question how a disparity in prevalence of LMM, sarcopenia and FP frailty arises between genders. One explanation may be selection bias; FITNESS participants with ultrasound measures were less frail than those without, but this was true of both males and females and would not satisfactorily explain the discrepancy. Our data also show that female haemodialysis recipients are more likely to have slow walking speed and low energy expenditure than their male counterparts. This may explain why FP frailty is higher in females despite the lower prevalence of sarcopenia, but in turn raises questions about the mechanisms behind such differences. On this issue there is remarkably little in the available literature to guide us. In the general population, Choe and colleagues found that resistance exercise but not moderate-to-high physical activity reduced incident sarcopenia for men, but the opposite was true for women.[303] An English older adult cohort

found moderate and vigorous activity in males, but only vigorous activity in females, was associated with reduced sarcopenia.[304] Therefore there may be gender differences in sarcopenia expression and mitigation in non-renal populations, which appears congruent with our findings. We suggest that further work is required to elucidate the differential mechanisms behind frailty and sarcopenia in males and females receiving haemodialysis, and why there appears to be such a different epidemiological pattern to sarcopenia in haemodialysis compared with other populations. A comprehensive systematic review from March and colleagues have shown that intradialytic exercise shows promise in mitigating for many components of the sarcopenia phenotype in all genders combined.[305] Clinicians may therefore feel this represents a pragmatic approach whilst detailed mechanistic study of gender differences are awaited to guide more tailored management.

Limitations of this study include that the whole FITNESS cohort did not complete ultrasound assessment. The ultrasound scanner was not procured until after the first 193 participants were recruited, and a further 69 refused or were unable to be scanned. Those not scanned were significantly frailer than those with ultrasound measurements. Scanning took place during haemodialysis sessions, in order to reduce the time commitment of each participant for the study. This may have resulted in the frailest being unable to participate in this aspect of the study due to concerns regarding mobility and adequate exposure for scanning, reducing the generalisability of our findings. In a further limitation, some of the 95% confidence intervals cross the point of no effect by small margins, most notably in the trend towards greater sarcopenia in males, raising the possibility of type II error. Participant numbers in younger adult age groups were also low. We attempted to mitigate for this by additional analyses using age terciles, but in so doing combined all participants <57-years into one group.

It therefore remains challenging to draw conclusions on the nature of sarcopenia in young adult haemodialysis recipients on these data alone.

5.7 Conclusions

To conclude, low muscle mass is more common and there is a trend towards greater sarcopenia in male versus female haemodialysis recipients. However, frailty is more common in female haemodialysis recipients, driven by significantly greater prevalence of slow walking speed and low energy expenditure. Our work suggests there is a need to explore the mechanisms of gender difference underlying sarcopenia and frailty in haemodialysis recipients, and to consider gender-specific management strategies.

5.8 Tables

Table 5-1: Baseline characteristics of the FITNESS cohort and subgroup with valid ultrasound measurements

	Total		Males		Females	
	n	%/IQR	n	%/IQR	n	%/IQR
Male	138	61.9	-	-	-	-
Frailty	76	34.1	43	31.2	33	38.8
Albumin*	39	35-42	40	36-42	38	34-38
MoCA*	22	18-25	22	19-25	22	17-25
Age*	63	54-74	63	55-72	63	53-75
BMI*	27.0	23.4-32.1	26.9	23.9-32.1	27.3	22.7-32.4
Charlson Index* **	5	3-6	5	3-6	4	3-5
HD Vintage (months)*	33	14-65	31	12-64	37	17-66
Kt/V*	1.58	1.37-1.82	1.48	1.32-1.69	1.80	1.52-2.00
Ethnicity						
White	136	61.0	75	54.4	61	71.8
South Asian	51	22.9	42	30.4	9	10.6
Black	32	14.4	19	13.8	13	15.3
Other	4	1.8	2	1.5	2	2.4
Smoking Status						
Current	33	14.8	16	11.6	17	30.0
Ex	67	30.0	48	34.8	19	22.4
Never	123	55.2	74	53.6	49	57.7
Active on transplant list?						
No	195	87.4	122	88.4	73	85.9
Yes	28	12.6	16	11.6	12	14.1
Employment Status						
Employed	32	14.4	24	17.4	8	9.4
Unemployed	74	33.2	48	34.8	26	30.6
Retired	117	52.5	66	47.8	51	60.0
Occupation***						
Unskilled Manual	92	43.4	61	45.9	31	39.2
Skilled Manual	32	15.1	27	20.3	5	6.3
Clerical	25	11.8	6	4.5	19	24.1
Managerial	31	14.6	23	17.3	8	10.1
Professional	32	15.1	16	12	16	20.3
Education level						
High School	154	69.1	99	71.7	55	64.7
College/6th form	47	21.1	26	18.8	21	24.7
University	22	9.9	13	9.4	9	10.6
Type of residence						
Own Home	219	98.2	135	97.8	84	98.8
Warden-Controlled	3	1.4	3	2.2	0	0

Residential Home	1	0.5	0	0	1	1.2
Professional Carer Use?****						
No	209	94.1	130	94.2	79	94.1
Yes	13	5.9	8	5.8	5	6.0
Physical Activity Index						
Inactive	184	82.5	108	78.3	76	89.4
Moderately Inactive	18	8.1	14	10.1	4	4.7
Moderately Active	5	2.2	2	1.5	3	3.5
Active	16	7.2	14	10.1	2	2.4
IMD Quintile						
1	101	45.3	64	46.4	37	43.5
2	29	13.0	16	11.6	13	15.3
3	36	16.1	26	18.8	10	11.8
4	19	8.5	9	6.5	10	11.8
5	22	9.9	13	9.4	9	10.6
Unknown	16	7.2	10	7.3	6	7.1

All values n and percentages except *=median and interquartile range. Frailty assessed by Frailty Phenotype. **=CKD omitted; ***=or previous occupation if unemployed/retired; ****=if not in residential/nursing accommodation.

Table 5-2: Prevalence of low muscle mass, low muscle function and sarcopenia by gender

	Male	Female	P
Low Muscle Mass			
No	**50**	**54**	**<0.001**
	36.2%	**63.5%**	
Yes	**88**	**31**	
	63.8%	**36.5%**	
Sarcopenia			
No	88	64	0.073
	63.8%	75.3%	
Yes	50	21	
	36.2%	24.7%	
Severe Sarcopenia			
No	104	70	0.221
	75.4%	82.4%	
Yes	34	15	
	24.6%	17.7%	
Low Grip Strength			
No	78	46	0.726
	56.5%	54.1%	
Yes	60	39	
	43.5%	45.9%	
Slow Walk Speed			
No	78	40	0.169
	56.5%	47.1%	
Yes	60	45	
	43.5%	52.9%	

Percentages within gender shown. P-values obtained by Chi-Squared.

Table 5-3: Proportions of low muscle mass, low grip strength, slow walking speed, sarcopenia and severe sarcopenia by gender.

	Male (n=138)		Female (n=85)		P
	n	% age group	n	% age group	
Low Muscle Mass					
18-34	2	50%	2	29%	0.576
35-44	4	50%	1	20%	0.565
45-54	9	43%	5	42%	0.947
55-64	**27**	**64%**	**6**	**29%**	**0.007**
≥65	**46**	**73%**	**17**	**43%**	**0.002**
Low Grip Strength					
18-34	0	0%	3	43%	0.236
35-44	1	13%	3	60%	0.217
45-54	5	24%	4	33%	0.690
55-64	24	57%	7	33%	0.075
≥65	30	48%	22	55%	0.465
Slow Walking Speed					
18-34	0	0%	2	29%	0.237
35-44	2	25%	3	60%	0.293
45-54	6	29%	5	42%	0.471
55-64	17	40%	10	48%	0.589
≥65	35	56%	25	63%	0.486
Sarcopenia					
18-34	0	0%	2	29%	0.237
35-44	0	0%	1	20%	0.188
45-54	5	23%	3	25%	0.939
55-64	**19**	**45%**	**4**	**19%**	**0.042**
≥65	26	41%	11	28%	0.156
Severe Sarcopenia					
18-34	0	0%	1	14%	1.000
35-44	0	0%	1	20%	0.385
45-54	2	10%	2	17%	0.610
55-64	10	24%	2	10%	0.307
≥65	22	35%	9	23%	0.180

Number of participants and percentage within age and gender group shown. Bold text indicates significance at <0.05 level.

Table 5-4: Proportions of low muscle mass, low grip strength, slow walking speed, sarcopenia and severe sarcopenia by age tercile.

	Male (n=138)		Female (n=85)		P
	n	% age group	n	% age group	
Low Muscle Mass					
<57	19	45%	8	30%	0.195
57-70	**39**	**72%**	**9**	**32%**	**<0.001**
>70	**30**	**71%**	**14**	**47%**	**0.034**
Low Grip Strength					
<57	12	29%	10	37%	0.461
57-70	27	50%	11	39%	0.356
>70	21	50%	18	60%	0.401
Slow Walking Speed					
<57	11	26%	10	37%	0.339
57-70	25	46%	16	57%	0.352
>70	24	57%	19	63%	0.597
Sarcopenia					
<57	9	21%	6	22%	0.938
57-70	23	43%	6	21%	0.057
>70	18	43%	9	30%	0.267
Severe Sarcopenia					
<57	3	71%	4	15%	0.420
57-70	16	30%	4	14%	0.177
>70	15	36%	7	23%	0.261

All definitions by EQGSOP guidelines. P-values for difference obtained via chi-squared or Fisher's Exact as appropriate. Bold text indicates significant at P<0.05 level.

Table 5-5: Multiple linear regressions of grip strength and walking speed by low muscle mass.

		β	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass	Grip Strength				
	All	**-3.23**	**-5.65**	**-0.82**	**0.009**
	Males	**-4.17**	**-7.57**	**-0.77**	**0.017**
	Females	-1.88	-5.41	1.64	0.289
	Walking Speed				
	All	**-0.115**	**-0.202**	**-0.028**	**0.010**
	Males	**-0.136**	**-0.258**	**-0.013**	**0.030**
	Females	**-0.152**	**-0.300**	**-0.005**	**0.043**

Grip strength in kg. Walking speed in ms^{-1}. Bold text indicates significant at P<0.05 level. Multivariable analyses adjusted for: age, ethnicity, IMD quintile, BMI, remaining ultrafiltration volume at time of scan, self-reported health change, Physical Activity Index (PAI) from GPPAQ,[268,269] Charlson Index (CKD omitted), self-reported health today from Euroqol EQ-5D visual analogue scale out of 100 (EQ-5D VAS), self-reported use of walking aids, and haemodialysis vintage.

Table 5-6: Comparison of constituents of the Frailty Phenotype by gender.

	Males		Females		P
	n	%	n	%	
Whole Cohort (n=485)					
Slow Walking Speed	**102**	**35.92%**	**104**	**51.74%**	**0.001**
Weak Grip	184	64.79%	134	66.67%	0.668
Weight Loss	36	12.68%	25	12.44%	0.938
Exhaustion	131	46.13%	106	52.74%	0.151
Low Energy Expenditure	**123**	**43.31%**	**109**	**54.23%**	**0.018**
With valid US (n=223)					
Slow Walking Speed	**42**	**30.43%**	**37**	**43.53%**	**0.047**
Weak Grip	86	62.32%	51	60.00%	0.730
Weight Loss	17	12.32%	8	9.41%	0.504
Exhaustion	62	44.93%	47	55.29%	0.133
Low Energy Expenditure	54	39.13%	35	41.18%	0.762
Without Valid US (n=262)					
Slow Walking Speed	**60**	**41.10%**	**67**	**57.76%**	**0.007**
Weak Grip	98	67.12%	83	71.55%	0.441
Weight Loss	19	13.01%	17	14.66%	0.701
Exhaustion	69	47.26%	59	50.86%	0.562
Low Energy Expenditure	**69**	**47.26%**	**74**	**63.79%**	**0.008**

Whole FITNESS cohort, and those with and without ultrasound measurements shown. P-values obtained by Chi-squared. %=within group percentage. n= number of participants with attribute. Bold text indicates significant at P<0.05 level.

5.9 Supplementary Tables

Supplementary Table 5-1: Proportions of participants with frailty, low grip strength, and slow walking speed by ultrasound assessment status.

Supplementary Table 5-1	Without US (n=262)		With US (n=223)		P
	n	%	n	%	
Combined					
Frail	**127**	**48%**	**76**	**34%**	**0.001**
Low Grip Strength	**143**	**55%**	**99**	**44%**	**0.025**
Slow Walking Speed	**158**	**60%**	**105**	**47%**	**0.004**
Males					
Frail	**63**	**43%**	**43**	**31%**	**0.037**
Low Grip Strength	76	52%	60	43%	0.148
Slow Walking Speed	79	54%	60	43%	0.073
Females					
Frail	**64**	**55%**	**33**	**39%**	**0.022**
Low Grip Strength	67	58%	39	46%	0.096
Slow Walking Speed	**79**	**68%**	**45**	**53%**	**0.029**

% = prevalence within group. P value for difference obtained via Chi-squared.

Supplementary Table 5-2: Multiple linear regression model of grip strength associated with BATT in males.

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	**0.13**	**0.01**	**0.24**	**0.030**
BMI	0.09	-0.17	0.35	0.501
UF (ml/kg)*	-0.08	-0.21	0.06	0.272
Ethnicity				
White		REFERENCE		
South Asian	-2.95	-6.31	0.41	0.085
Black	2.82	-1.62	7.27	0.210
Other	**12.1**	**0.22**	**23.91**	**0.046**
Age	-0.13	-0.29	0.03	0.111
IMD Quintile				
1		REFERENCE		
2	1.91	-2.61	6.43	0.404
3	2.47	-1.48	6.43	0.218
4	-2.30	-8.56	3.96	0.468
5	1.24	-4.02	6.49	0.642
Unknown	1.57	-4.07	7.21	0.581
Charlson Index**	-0.14	-0.94	0.67	0.735
Health Change				
Better		REFERENCE		
The Same	-2.06	-6.10	1.98	0.314
Worse	-0.91	-4.72	2.90	0.636
Physical Activity Index				
Inactive		REFERENCE		
Moderately Inactive	1.72	-3.10	6.54	0.481
Moderately Active	3.42	-8.09	14.94	0.557
Active	3.16	-1.65	7.97	0.196
Walking Aid Use				
No		REFERENCE		
Yes	-2.81	-6.08	0.46	0.091
EQ-5D Health Today	0.04	-0.03	0.11	0.271
HD Vintage	-0.02	-0.05	0.00	0.092
Constant	**28.9**	**15.3**	**42.5**	**<0.001**

Bold text indicates significance at P<0.005 level. *=Remaining fluid removal via ultrafiltration to be completed at time of ultrasound assessment. **=CKD omitted.

Supplementary Table 5-3: Multiple linear regression model of grip strength associated with BATT in females.

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	0.03	-0.10	0.15	0.655
BMI	0.29	-0.01	0.58	0.056
UF (ml/kg)*	-0.01	-0.23	0.22	0.953
Ethnicity				
White		REFERENCE		
South Asian	-4.89	-10.05	0.26	0.062
Black	1.12	-3.31	5.55	0.614
Other	-0.95	-12.2	10.31	0.866
Age	0.00	-0.13	0.13	0.973
IMD Quintile				
1		REFERENCE		
2	-1.74	-6.22	2.74	0.441
3	-1.41	-6.45	3.63	0.577
4	2.12	-2.88	7.12	0.399
5	4.60	-0.34	9.54	0.067
Unknown	3.12	-3.17	9.40	0.325
Charlson Index**	-0.67	-1.62	0.29	0.166
Health Change				
Better		REFERENCE		
The Same	0.93	-3.73	5.60	0.691
Worse	0.73	-3.90	5.35	0.755
Physical Activity Index				
Inactive		REFERENCE		
Moderately Inactive	**9.98**	**2.33**	**17.63**	**0.011**
Moderately Active	0.67	-7.27	8.61	0.867
Active	0.58	-10.06	11.22	0.913
Walking Aid Use				
No		REFERENCE		
Yes	**-3.66**	**-7.05**	**-0.27**	**0.035**
EQ-5D Health Today	0.03	-0.04	0.10	0.407
HD Vintage	0.00	-0.03	0.03	0.980
Constant	9.11	-3.86	22.1	0.165

Bold text indicates significance at P<0.005 level. *=Remaining fluid removal via ultrafiltration to be completed at time of ultrasound assessment. **=CKD omitted.

Supplementary Table 5-4: Multiple linear regression model of walking speed associated with BATT in males.

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	**0.006**	**0.002**	**0.010**	**0.004**
BMI	**-0.013**	**-0.023**	**-0.004**	**0.006**
UF (ml/kg)*	-0.003	-0.008	0.002	0.193
Ethnicity				
White		REFERENCE		
South Asian	**-0.127**	**-0.241**	**-0.013**	**0.029**
Black	-0.015	-0.168	0.138	0.845
Other	0.140	-0.245	0.524	0.473
Age	0.000	-0.006	0.005	0.962
IMD Quintile				
1		REFERENCE		
2	0.089	-0.062	0.241	0.244
3	0.099	-0.035	0.233	0.145
4	0.154	-0.062	0.370	0.160
5	0.041	-0.145	0.227	0.663
Unknown	-0.060	-0.245	0.124	0.520
Charlson Index**	-0.028	-0.056	0.000	0.050
Health Change				
Better		REFERENCE		
The Same	-0.108	-0.243	0.028	0.118
Worse	-0.049	-0.179	0.080	0.454
Physical Activity Index				
Inactive		REFERENCE		
Moderately Inactive	0.149	-0.013	0.311	0.070
Moderately Active	0.117	-0.257	0.491	0.535
Active	**0.214**	**0.057**	**0.372**	**0.008**
Walking Aid Use				
No		REFERENCE		
Yes	**-0.197**	**-0.309**	**-0.084**	**0.001**
EQ-5D Health Today	0.002	0.000	0.004	0.107
HD Vintage	0.000	-0.001	0.000	0.339
Constant	**1.170**	**0.709**	**1.632**	**<0.001**

Bold text indicates significance at P<0.005 level. *=Remaining fluid removal via ultrafiltration to be completed at time of ultrasound assessment. **=CKD omitted.

Supplementary Table 5-5: Multiple linear regression model of walking speed associated with BATT in females.

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	0.003	-0.002	0.008	0.269
BMI	-0.009	-0.023	0.005	0.187
UF (ml/kg)*	0.000	-0.009	0.009	0.946
Ethnicity				
White		REFERENCE		
South Asian	-0.063	-0.287	0.160	0.574
Black	-0.018	-0.186	0.150	0.830
Other	0.260	-0.167	0.686	0.227
Age	-0.002	-0.008	0.004	0.470
IMD Quintile				
1		REFERENCE		
2	-0.043	-0.222	0.136	0.632
3	0.083	-0.102	0.269	0.373
4	0.115	-0.069	0.300	0.214
5	0.072	-0.114	0.259	0.441
Unknown	-0.095	-0.365	0.174	0.481
Charlson Index**	-0.005	-0.045	0.034	0.790
Health Change				
Better		REFERENCE		
The Same	-0.028	-0.215	0.159	0.763
Worse	-0.008	-0.192	0.176	0.929
Physical Activity Index				
Inactive		REFERENCE		
Moderately Inactive	**0.382**	**0.088**	**0.676**	**0.012**
Moderately Active	-0.064	-0.356	0.228	0.663
Active	0.014	-0.377	0.405	0.942
Walking Aid Use				
No		REFERENCE		
Yes	**-0.235**	**-0.362**	**-0.109**	**<0.001**
EQ-5D Health Today	0.001	-0.002	0.004	0.465
HD Vintage	-0.001	-0.002	0.001	0.395
Constant	**1.133**	**0.599**	**1.668**	**<0.001**

Bold text indicates significance at P<0.005 level. *=Remaining fluid removal via ultrafiltration to be completed at time of ultrasound assessment. **=CKD omitted.

Supplementary Table 5-6: Simple Linear Regression of Frailty Phenotype score associated with BATT in males.

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	**-0.034**	**-0.049**	**-0.019**	**<0.001**
Constant	**3.628**	**2.840**	**4.415**	**<0.001**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-7: Multiple Linear Regression of Frailty Phenotype scores associated with BATT in males. Model 1

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	**-0.031**	**-0.047**	**-0.015**	**<0.001**
Age	**0.020**	**0.001**	**0.038**	**0.038**
Ethnicity				
White		REFERENCE		
South Asian	0.325	-0.212	0.862	0.233
Black	-0.351	-1.052	0.350	0.323
Other	-0.789	-2.814	1.236	0.442
Education Level				
High School		REFERENCE		
College/6th form	-0.121	-0.687	0.445	0.673
University	-0.684	-1.511	0.142	0.104
IMD Quintile				
1		REFERENCE		
2	-0.577	-1.284	0.130	0.109
3	-0.416	-1.048	0.217	0.196
4	0.028	-0.925	0.981	0.954
5	-0.679	-1.498	0.140	0.103
Unknown	-0.770	-1.646	0.107	0.085
Social Support				
Yes		REFERENCE		
No	0.089	-0.845	1.023	0.851
HD vintage (months)	-0.002	-0.006	0.002	0.420
Constant	**2.610**	**0.906**	**4.313**	**0.003**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-8: Multiple Linear Regression of Frailty Phenotype scores associated with BATT in males. Model 2

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	**-0.020**	**-0.034**	**-0.007**	**0.003**
Age	0.019	-0.002	0.040	0.078
Ethnicity				
White		REFERENCE		
South Asian	0.424	-0.075	0.922	0.095
Black	-0.258	-0.829	0.312	0.372
Other	-1.376	-3.028	0.276	0.101
Education Level				
High School		REFERENCE		
College/6th form	-0.033	-0.515	0.449	0.892
University	-0.344	-1.053	0.365	0.338
IMD Quintile				
1		REFERENCE		
2	-0.005	-0.629	0.619	0.987
3	-0.094	-0.618	0.430	0.722
4	-0.187	-0.996	0.621	0.646
5	-0.210	-0.908	0.488	0.552
Unknown	-0.139	-0.930	0.651	0.727
Social Support				
Yes		REFERENCE		
No	-0.354	-1.170	0.462	0.392
HD vintage (months)	-0.002	-0.005	0.002	0.377
Charlson Index*	0.063	-0.046	0.172	0.257
Cognitive Impairment				
No		REFERENCE		
Yes	-0.081	-0.614	0.452	0.763
PHQ-9 score	**0.075**	**0.033**	**0.117**	**0.001**
Self-reported health change				
Better		REFERENCE		
The Same	-0.058	-0.598	0.483	0.832
Worse	0.245	-0.272	0.762	0.350
Self-reported health today/100	**-0.021**	**-0.031**	**-0.012**	**<0.001**
Constant	**2.370**	**0.728**	**4.013**	**0.005**

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-9: Multiple Linear Regression of Frailty Phenotype scores associated with BATT in males. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	**-0.015**	**-0.028**	**-0.003**	**0.018**
Age	0.005	-0.015	0.025	0.620
Ethnicity				
White		REFERENCE		
South Asian	0.454	0.006	0.901	0.047
Black	-0.111	-0.644	0.422	0.680
Other	**-1.633**	**-3.122**	**-0.145**	**0.032**
Education Level				
High School		REFERENCE		
College/6th form	-0.198	-0.648	0.253	0.387
University	0.064	-0.594	0.723	0.847
IMD Quintile				
1		REFERENCE		
2	0.033	-0.531	0.597	0.908
3	0.053	-0.422	0.528	0.826
4	0.027	-0.705	0.759	0.942
5	-0.077	-0.709	0.554	0.809
Unknown	0.045	-0.670	0.761	0.900
Social Support				
Yes		REFERENCE		
No	-0.432	-1.172	0.308	0.250
HD vintage (months)	0.000	-0.003	0.003	0.969
Charlson Index*	0.067	-0.031	0.165	0.178
Cognitive Impairment				
No		REFERENCE		
Yes	-0.234	-0.718	0.250	0.340
PHQ-9 score	**0.068**	**0.029**	**0.106**	**0.001**
Self-reported health change				
Better		REFERENCE		
The Same	-0.119	-0.606	0.368	0.630
Worse	0.062	-0.408	0.532	0.793
Self-reported health today/100	**-0.013**	**-0.023**	**-0.004**	**0.007**
Walking Aid Use				
No		REFERENCE		
Yes	**0.653**	**0.233**	**1.074**	**0.003**
Self-reported slow walking				
No		REFERENCE		
Yes	**0.697**	**0.268**	**1.126**	**0.002**
Constant	**1.884**	**0.391**	**3.376**	**0.014**

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-10: Simple Linear Regression of Frailty Phenotype score associated with BATT in females.

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	-0.013	-0.033	0.007	0.206
Constant	**2.684**	**1.721**	**3.647**	**<0.001**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-11: Multiple Linear Regression of Frailty Phenotype scores associated with BATT in females. Model 1

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	-0.007	-0.030	0.015	0.501
Age	0.008	-0.012	0.029	0.432
Ethnicity				
White			REFERENCE	
South Asian	0.237	-0.711	1.185	0.619
Black	-0.494	-1.360	0.371	0.259
Other	-1.400	-3.394	0.594	0.166
Education Level				
High School			REFERENCE	
College/6th form	0.392	-0.303	1.086	0.264
University	-0.319	-1.360	0.722	0.543
IMD Quintile				
1			REFERENCE	
2	0.300	-0.537	1.137	0.477
3	-0.577	-1.543	0.389	0.238
4	-1.352	-2.304	-0.400	0.006
5	**-1.081**	**-2.047**	**-0.114**	**0.029**
Unknown	0.472	-0.743	1.686	0.441
Social Support				
Yes			REFERENCE	
No	0.161	-1.036	1.358	0.789
HD vintage (months)	-0.001	-0.008	0.006	0.768
Constant	**2.256**	**0.403**	**4.109**	**0.018**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-12: Multiple Linear Regression of Frailty Phenotype scores associated with BATT in females. Model 2

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	-0.011	-0.034	0.013	0.370
Age	0.009	-0.018	0.036	0.498
Ethnicity				
White		REFERENCE		
South Asian	0.644	-0.472	1.759	0.253
Black	-0.266	-1.128	0.596	0.539
Other	-0.559	-2.607	1.488	0.587
Education Level				
High School		REFERENCE		
College/6th form	0.550	-0.198	1.297	0.147
University	-0.269	-1.429	0.890	0.644
IMD Quintile				
1		REFERENCE		
2	0.282	-0.587	1.151	0.519
3	-0.440	-1.451	0.571	0.387
4	**-1.024**	**-2.015**	**-0.033**	**0.043**
5	-0.784	-1.751	0.184	0.110
Unknown	0.335	-0.950	1.620	0.604
Social Support				
Yes		REFERENCE		
No	0.267	-1.027	1.561	0.681
HD vintage (months)	-0.001	-0.008	0.006	0.771
Charlson Index*	0.081	-0.138	0.299	0.464
Cognitive Impairment				
No		REFERENCE		
Yes	0.314	-0.495	1.124	0.440
PHQ-9 score	0.074	0.007	0.140	0.031
Self-reported health change				
Better		REFERENCE		
The Same	-0.096	-1.064	0.873	0.844
Worse	-0.350	-1.327	0.626	0.476
Self-reported health today/100	-0.012	-0.029	0.004	0.146
Constant	1.956	-0.563	4.475	0.126

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-13: Multiple Linear Regression of Frailty Phenotype scores associated with BATT in females. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
BATT	0.001	-0.019	0.021	0.903
Age	0.003	-0.020	0.025	0.797
Ethnicity				
White		REFERENCE		
South Asian	0.292	-0.641	1.225	0.534
Black	-0.392	-1.102	0.319	0.274
Other	-0.206	-1.912	1.499	0.810
Education Level				
High School		REFERENCE		
College/6th form	0.265	-0.361	0.890	0.401
University	-0.290	-1.249	0.670	0.548
IMD Quintile				
1		REFERENCE		
2	0.277	-0.439	0.993	0.442
3	-0.155	-0.992	0.683	0.713
4	**-0.908**	**-1.726**	**-0.090**	**0.030**
5	**-1.029**	**-1.829**	**-0.229**	**0.013**
Unknown	0.181	-0.877	1.239	0.733
Social Support				
Yes		REFERENCE		
No	-0.073	-1.174	1.028	0.894
HD vintage (months)	-0.001	-0.006	0.005	0.840
Charlson Index*	-0.013	-0.196	0.170	0.890
Cognitive Impairment				
No		REFERENCE		
Yes	0.262	-0.406	0.930	0.436
PHQ-9 score	0.039	-0.017	0.095	0.169
Self-reported health change				
Better		REFERENCE		
The Same	-0.008	-0.805	0.790	0.985
Worse	-0.202	-1.010	0.606	0.619
Self-reported health today/100	-0.006	-0.020	0.008	0.365
Walking Aid Use				
No		REFERENCE		
Yes	**1.087**	**0.567**	**1.607**	**<0.001**
Self-reported slow walking				
No		REFERENCE		
Yes	**0.726**	**0.181**	**1.272**	**0.010**
Constant	1.259	-0.880	3.397	0.244

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-14: Simple linear regression of Frailty Phenotype score by LMM in males.

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	**1.021**	**0.568**	**1.475**	**<0.001**
Constant	**1.240**	**0.878**	**1.602**	**<0.001**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-15: Multiple linear regression of Frailty Phenotype score by LMM in males. Model 1

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	**1.022**	**0.544**	**1.500**	**<0.001**
Age	**0.024**	**0.006**	**0.042**	**0.008**
Ethnicity				
White		REFERENCE		
South Asian	0.330	-0.198	0.858	0.218
Black	-0.308	-0.999	0.383	0.379
Other	-0.599	-2.596	1.398	0.554
Education Level				
High School		REFERENCE		
College/6th form	-0.002	-0.564	0.559	0.994
University	-0.562	-1.375	0.252	0.174
IMD Quintile				
1		REFERENCE		
2	**-0.736**	**-1.437**	**-0.035**	**0.040**
3	-0.546	-1.179	0.087	0.090
4	0.004	-0.936	0.945	0.993
5	**-1.059**	**-1.880**	**-0.238**	**0.012**
Unknown	**-0.889**	**-1.753**	**-0.024**	**0.044**
Social Support				
Yes		REFERENCE		
No	0.091	-0.830	1.012	0.845
HD vintage (months)	-0.002	-0.006	0.002	0.332
Constant	0.190	-0.978	1.358	0.748

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-16: Multiple linear regression of Frailty Phenotype score by LMM in males. Model 2

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	**0.610**	**0.194**	**1.026**	**0.004**
Age	0.020	-0.001	0.041	0.059
Ethnicity				
White		REFERENCE		
South Asian	0.433	-0.065	0.932	0.088
Black	-0.218	-0.788	0.353	0.451
Other	-1.228	-2.888	0.432	0.145
Education Level				
High School		REFERENCE		
College/6th form	0.051	-0.435	0.537	0.835
University	-0.282	-0.988	0.425	0.431
IMD Quintile				
1		REFERENCE		
2	-0.134	-0.763	0.494	0.673
3	-0.167	-0.700	0.366	0.537
4	-0.172	-0.983	0.639	0.675
5	-0.428	-1.139	0.282	0.235
Unknown	-0.203	-0.994	0.588	0.611
Social Support				
Yes		REFERENCE		
No	-0.349	-1.167	0.469	0.399
HD vintage (months)	-0.002	-0.005	0.002	0.360
Charlson Index*	0.076	-0.032	0.185	0.165
Cognitive Impairment				
No		REFERENCE		
Yes	-0.047	-0.584	0.489	0.861
PHQ-9 score	**0.073**	**0.031**	**0.115**	**0.001**
Self-reported health change				
Better		REFERENCE		
The Same	-0.049	-0.591	0.493	0.859
Worse	0.288	-0.231	0.807	0.274
Self-reported health today/100	**-0.021**	**-0.031**	**-0.011**	**<0.001**
Constant	0.730	-0.695	2.155	0.312

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-17: Multiple linear regression of Frailty Phenotype score by LMM in males. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	**0.415**	**0.025**	**0.806**	**0.037**
Age	0.006	-0.014	0.026	0.545
Ethnicity				
White		REFERENCE		
South Asian	**0.466**	**0.016**	**0.917**	**0.042**
Black	-0.069	-0.604	0.466	0.799
Other	**-1.538**	**-3.040**	**-0.035**	**0.045**
Education Level				
High School		REFERENCE		
College/6th form	-0.128	-0.589	0.333	0.584
University	0.111	-0.547	0.770	0.738
IMD Quintile				
1		REFERENCE		
2	-0.054	-0.624	0.516	0.850
3	0.011	-0.475	0.498	0.963
4	0.036	-0.702	0.774	0.923
5	-0.223	-0.870	0.424	0.495
Unknown	0.000	-0.719	0.719	0.999
Social Support				
Yes		REFERENCE		
No	-0.442	-1.186	0.303	0.242
HD vintage (months)	0.000	-0.003	0.003	0.953
Charlson Index*	0.078	-0.020	0.176	0.117
Cognitive Impairment				
No		REFERENCE		
Yes	-0.214	-0.703	0.276	0.389
PHQ-9 score	**0.066**	**0.027**	**0.105**	**0.001**
Self-reported health change				
Better		REFERENCE		
The Same	-0.116	-0.607	0.374	0.639
Worse	0.095	-0.380	0.571	0.691
Self-reported health today/100	**-0.013**	**-0.022**	**-0.003**	**0.010**
Walking Aid Use				
No		REFERENCE		
Yes	**0.629**	**0.199**	**1.059**	**0.005**
Self-reported slow walking				
No		REFERENCE		
Yes	**0.719**	**0.287**	**1.151**	**0.001**
Constant	0.681	-0.620	1.981	0.301

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-18: Simple linear regression of frailty phenotype score by LMM in females.

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	0.461	-0.119	1.041	0.118
Constant	**1.926**	**1.576**	**2.276**	**<0.001**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-19: Multiple linear regression of Frailty Phenotype score by LMM in females. Model 1

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	0.277	-0.344	0.899	0.376
Age	0.009	-0.011	0.029	0.385
Ethnicity				
White		REFERENCE		
South Asian	0.233	-0.713	1.179	0.625
Black	-0.499	-1.353	0.356	0.248
Other	-1.429	-3.419	0.561	0.156
Education Level				
High School		REFERENCE		
College/6th form	0.396	-0.294	1.087	0.256
University	-0.314	-1.337	0.709	0.542
IMD Quintile				
1		REFERENCE		
2	0.262	-0.573	1.096	0.534
3	-0.584	-1.548	0.380	0.231
4	**-1.362**	**-2.312**	**-0.412**	**0.006**
5	**-1.062**	**-2.028**	**-0.095**	**0.032**
Unknown	0.494	-0.719	1.707	0.420
Social Support				
Yes		REFERENCE		
No	0.119	-1.083	1.322	0.844
HD vintage (months)	-0.001	-0.008	0.005	0.685
Constant	**1.798**	**0.382**	**3.215**	**0.014**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-20: Multiple linear regression of Frailty Phenotype score by LMM in females. Model 2

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	0.473	-0.212	1.157	0.172
Age	0.011	-0.016	0.038	0.415
Ethnicity				
White		REFERENCE		
South Asian	0.779	-0.352	1.910	0.173
Black	-0.241	-1.094	0.612	0.574
Other	-0.644	-2.674	1.386	0.528
Education Level				
High School		REFERENCE		
College/6th form	0.581	-0.150	1.311	0.117
University	-0.251	-1.351	0.849	0.650
IMD Quintile				
1		REFERENCE		
2	0.189	-0.680	1.059	0.665
3	-0.430	-1.431	0.572	0.394
4	**-1.021**	**-2.003**	**-0.038**	**0.042**
5	-0.775	-1.734	0.184	0.111
Unknown	0.399	-0.880	1.677	0.535
Social Support				
Yes		REFERENCE		
No	0.225	-1.060	1.510	0.727
HD vintage (months)	-0.002	-0.009	0.005	0.608
Charlson Index*	0.084	-0.132	0.299	0.441
Cognitive Impairment				
No		REFERENCE		
Yes	0.271	-0.502	1.044	0.486
PHQ-9 score	**0.078**	**0.012**	**0.144**	**0.022**
Self-reported health change				
Better		REFERENCE		
The Same	-0.231	-1.218	0.755	0.641
Worse	-0.429	-1.409	0.550	0.384
Self-reported health today/100	-0.011	-0.027	0.006	0.206
Constant	1.213	-1.264	3.691	0.331

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-21: Multiple linear regression of Frailty Phenotype score by LMM in females. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	0.242	-0.328	0.813	0.399
Age	0.004	-0.019	0.026	0.738
Ethnicity				
White		REFERENCE		
South Asian	0.394	-0.554	1.343	0.409
Black	-0.338	-1.042	0.367	0.342
Other	-0.359	-2.047	1.330	0.672
Education Level				
High School		REFERENCE		
College/6th form	0.352	-0.256	0.961	0.251
University	-0.149	-1.058	0.760	0.744
IMD Quintile				
1		REFERENCE		
2	0.236	-0.483	0.954	0.514
3	-0.165	-0.996	0.667	0.694
4	-0.915	-1.728	-0.102	0.028
5	**-1.022**	**-1.817**	**-0.226**	**0.013**
Unknown	0.227	-0.829	1.283	0.668
Social Support				
Yes		REFERENCE		
No	-0.097	-1.192	0.997	0.859
HD vintage (months)	-0.001	-0.007	0.005	0.687
Charlson Index*	-0.015	-0.197	0.167	0.868
Cognitive Impairment				
No		REFERENCE		
Yes	0.304	-0.338	0.946	0.348
PHQ-9 score	0.047	-0.009	0.102	0.098
Self-reported health change				
Better		REFERENCE		
The Same	-0.094	-0.909	0.721	0.818
Worse	-0.296	-1.106	0.515	0.468
Self-reported health today/100	-0.005	-0.019	0.009	0.507
Walking Aid Use				
No		REFERENCE		
Yes	**1.062**	**0.543**	**1.580**	**<0.001**
Self-reported slow walking				
No		REFERENCE		
Yes	**0.702**	**0.172**	**1.232**	**0.010**
Constant	1.090	-0.988	3.167	0.298

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-22: Simple linear regression of frailty phenotype score by sarcopenia (EWGSOP definition) in males.

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**1.456**	**1.038**	**1.874**	**<0.001**
Constant	**1.364**	**1.112**	**1.615**	**<0.001**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-23: Multiple linear regression of frailty phenotype score by sarcopenia (EWGSOP definition) in males. Model 1

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**1.387**	**0.912**	**1.863**	**<0.001**
Age	0.016	-0.002	0.033	0.077
Ethnicity				
White		REFERENCE		
South Asian	0.151	-0.359	0.661	0.558
Black	-0.282	-0.937	0.374	0.397
Other	-0.681	-2.577	1.215	0.479
Education Level				
High School		REFERENCE		
College/6th form	-0.080	-0.611	0.451	0.766
University	-0.478	-1.251	0.294	0.223
IMD Quintile				
1		REFERENCE		
2	-0.493	-1.156	0.170	0.144
3	-0.012	-0.606	0.582	0.968
4	-0.063	-0.956	0.830	0.889
5	-0.444	-1.218	0.330	0.258
Unknown	**-0.896**	**-1.717**	**-0.076**	**0.033**
Social Support				
Yes		REFERENCE		
No	-0.043	-0.916	0.830	0.923
HD vintage (months)	-0.003	-0.007	0.001	0.158
Constant	0.792	-0.330	1.914	0.165

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-24: Multiple linear regression of frailty phenotype score by sarcopenia (EWGSOP definition) in males. Model 2

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**0.847**	**0.397**	**1.298**	**<0.001**
Age	0.017	-0.003	0.038	0.101
Ethnicity				
White		REFERENCE		
South Asian	0.382	-0.107	0.871	0.124
Black	-0.207	-0.764	0.349	0.462
Other	-1.270	-2.887	0.347	0.122
Education Level				
High School		REFERENCE		
College/6th form	-0.040	-0.511	0.432	0.868
University	-0.292	-0.982	0.397	0.402
IMD Quintile				
1		REFERENCE		
2	0.003	-0.608	0.614	0.993
3	0.104	-0.408	0.617	0.687
4	-0.193	-0.983	0.597	0.629
5	-0.140	-0.825	0.545	0.687
Unknown	-0.302	-1.076	0.471	0.440
Social Support				
Yes		REFERENCE		
No	-0.433	-1.230	0.364	0.284
HD vintage (months)	-0.002	-0.005	0.001	0.252
Charlson Index*	0.059	-0.048	0.165	0.277
Cognitive Impairment				
No		REFERENCE		
Yes	-0.114	-0.635	0.406	0.664
PHQ-9 score	**0.065**	**0.023**	**0.107**	**0.002**
Self-reported health change				
Better		REFERENCE		
The Same	-0.135	-0.664	0.395	0.616
Worse	0.285	-0.221	0.792	0.266
Self-reported health today/100	**-0.018**	**-0.028**	**-0.008**	**<0.001**
Constant	1.073	-0.299	2.444	0.124

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-25: Multiple linear regression of frailty phenotype score by sarcopenia (EWGSOP definition) in males. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**0.822**	**0.425**	**1.220**	**<0.001**
Age	0.002	-0.017	0.020	0.869
Ethnicity				
White		REFERENCE		
South Asian	0.389	-0.038	0.815	0.074
Black	-0.043	-0.549	0.463	0.866
Other	**-1.519**	**-2.936**	**-0.101**	**0.036**
Education Level				
High School		REFERENCE		
College/6th form	-0.199	-0.628	0.229	0.358
University	0.118	-0.501	0.737	0.705
IMD Quintile				
1		REFERENCE		
2	0.038	-0.498	0.574	0.888
3	0.224	-0.227	0.676	0.327
4	0.055	-0.642	0.751	0.876
5	0.005	-0.598	0.607	0.987
Unknown	-0.094	-0.775	0.587	0.785
Social Support				
Yes		REFERENCE		
No	-0.492	-1.195	0.211	0.168
HD vintage (months)	-0.001	-0.004	0.002	0.706
Charlson Index*	0.058	-0.035	0.151	0.223
Cognitive Impairment				
No		REFERENCE		
Yes	-0.250	-0.709	0.210	0.283
PHQ-9 score	**0.060**	**0.023**	**0.097**	**0.002**
Self-reported health change				
Better		REFERENCE		
The Same	-0.191	-0.655	0.274	0.417
Worse	0.091	-0.357	0.538	0.688
Self-reported health today/100	-0.009	-0.018	0.000	0.057
Walking Aid Use				
No		REFERENCE		
Yes	**0.757**	**0.363**	**1.151**	**<0.001**
Self-rated slow walking				
No		REFERENCE		
Yes	**0.688**	**0.279**	**1.096**	**<0.001**
Constant	0.893	-0.316	2.102	0.146

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-26: Simple linear regression of frailty phenotype score by sarcopenia (EWGSOP definition) in females.

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**0.824**	**0.192**	**1.456**	**0.011**
Constant	**1.891**	**1.576**	**2.205**	**<0.001**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-27: Multiple linear regression of frailty phenotype score by sarcopenia (EWGSOP definition) in females. Model 1

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	0.633	-0.053	1.320	0.070
Age	0.010	-0.010	0.029	0.323
Ethnicity				
White		REFERENCE		
South Asian	0.233	-0.696	1.161	0.619
Black	-0.401	-1.248	0.446	0.348
Other	-1.550	-3.505	0.405	0.118
Education Level				
High School		REFERENCE		
College/6th form	0.406	-0.269	1.080	0.234
University	-0.204	-1.209	0.801	0.687
IMD Quintile				
1		REFERENCE		
2	0.290	-0.529	1.108	0.482
3	-0.474	-1.427	0.478	0.324
4	**-1.205**	**-2.152**	**-0.257**	**0.013**
5	**-1.055**	**-2.003**	**-0.108**	**0.030**
Unknown	0.605	-0.594	1.804	0.318
Social Support				
Yes		REFERENCE		
No	-0.039	-1.235	1.156	0.948
HD vintage (months)	-0.002	-0.008	0.005	0.627
Constant	**1.632**	**0.226**	**3.039**	**0.024**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-28: Multiple linear regression of frailty phenotype score by sarcopenia (EWGSOP definition) in females. Model 2

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**0.756**	**0.038**	**1.474**	**0.039**
Age	0.011	-0.016	0.037	0.424
Ethnicity				
White		REFERENCE		
South Asian	0.784	-0.311	1.878	0.157
Black	-0.148	-0.992	0.697	0.728
Other	-0.795	-2.790	1.201	0.429
Education Level				
High School		REFERENCE		
College/6th form	0.548	-0.148	1.245	0.121
University	-0.162	-1.233	0.909	0.764
IMD Quintile				
1		REFERENCE		
2	0.243	-0.602	1.088	0.567
3	-0.341	-1.326	0.644	0.491
4	-0.805	-1.789	0.178	0.107
5	-0.803	-1.743	0.138	0.093
Unknown	0.592	-0.683	1.867	0.357
Social Support				
Yes		REFERENCE		
No	0.116	-1.151	1.383	0.855
HD vintage (months)	-0.002	-0.009	0.005	0.530
Charlson Index*	0.103	-0.108	0.315	0.331
Cognitive Impairment				
No		REFERENCE		
Yes	0.291	-0.466	1.048	0.445
PHQ-9 score	**0.078**	**0.014**	**0.142**	**0.017**
Self-reported health change				
Better		REFERENCE		
The Same	-0.287	-1.249	0.675	0.553
Worse	-0.493	-1.450	0.464	0.307
Self-reported health today/100	-0.010	-0.026	0.006	0.219
Constant	1.099	-1.309	3.508	0.365

*Bold text indicates significance at P<0.05 level. *=CKD omitted.*

Supplementary Table 5-29: Multiple linear regression of frailty phenotype score by sarcopenia (EWGSOP definition) in females. Model 3

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	0.498	-0.108	1.103	0.105
Age	0.004	-0.018	0.026	0.719
Ethnicity				
White		REFERENCE		
South Asian	0.421	-0.498	1.339	0.363
Black	-0.259	-0.961	0.443	0.463
Other	-0.481	-2.143	1.181	0.564
Education Level				
High School		REFERENCE		
College/6th form	0.353	-0.228	0.934	0.229
University	-0.066	-0.953	0.821	0.883
IMD Quintile				
1		REFERENCE		
2	0.255	-0.446	0.956	0.469
3	-0.116	-0.935	0.704	0.778
4	-0.772	-1.589	0.045	0.064
5	**-1.034**	**-1.816**	**-0.251**	**0.010**
Unknown	0.368	-0.690	1.426	0.489
Social Support				
Yes		REFERENCE		
No	-0.147	-1.227	0.932	0.786
HD vintage (months)	-0.002	-0.007	0.004	0.584
Charlson Index*	-0.002	-0.181	0.177	0.984
Cognitive Impairment				
No		REFERENCE		
Yes	0.331	-0.300	0.963	0.298
PHQ-9 score	0.049	-0.005	0.103	0.072
Self-reported health change				
Better		REFERENCE		
The Same	-0.154	-0.951	0.644	0.701
Worse	-0.358	-1.152	0.435	0.370
Self-reported health today/100	-0.004	-0.017	0.010	0.581
Walking Aid Use				
No		REFERENCE		
Yes	**1.005**	**0.489**	**1.522**	**<0.001**
Self-rated slow walking				
No		REFERENCE		
Yes	0.725	0.205	1.245	0.007
Constant	0.928	-1.108	2.964	0.366

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-30: Logistic Regression of FP frailty by BATT in males. Univariable

	OR	Lower 95% C.I.	Upper 95% C.I.	P
BATT	**0.936**	**0.906**	**0.968**	**<0.001**
Constant	**10.550**	**2.183**	**50.987**	**0.003**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-31: Multivariable Logistic Regression of FP frailty by BATT in males. Model 1

	OR	Lower 95% C.I.	Upper 95% C.I.	P
BATT	**0.933**	**0.898**	**0.969**	**<0.001**
Age	**1.046**	**1.004**	**1.090**	**0.032**
Ethnicity				
White		REFERENCE		
South Asian	1.020	0.352	2.951	0.971
Black	0.409	0.089	1.883	0.251
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	0.586	0.183	1.869	0.366
University		OMITTED		
IMD Quintile				
1		REFERENCE		
2	0.385	0.090	1.646	0.198
3	0.317	0.089	1.128	0.076
4	0.719	0.103	5.030	0.740
5	0.215	0.040	1.166	0.075
Unknown	0.271	0.033	2.211	0.223
Social Support				
Yes		REFERENCE		
No	0.759	0.116	4.964	0.774
HD vintage (months)	0.999	0.992	1.006	0.749
Constant	1.915	0.062	58.702	0.710

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-32: Multivariable Logistic Regression of FP frailty by BATT in males. Model 2

	OR	Lower 95% C.I.	Upper 95% C.I.	P
BATT	**0.922**	**0.876**	**0.971**	**0.002**
Age	**1.097**	**1.014**	**1.187**	**0.021**
Ethnicity				
White		REFERENCE		
South Asian	2.625	0.528	13.046	0.238
Black	0.514	0.089	2.978	0.457
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	0.308	0.073	1.303	0.109
University		OMITTED		
IMD Quintile				
1		REFERENCE		
2	1.747	0.316	9.656	0.522
3	0.443	0.093	2.118	0.308
4	0.419	0.038	4.581	0.476
5	0.207	0.023	1.886	0.162
Unknown	0.151	0.004	5.327	0.299
Social Support				
Yes		REFERENCE		
No	0.243	0.017	3.570	0.302
HD vintage (months)	0.997	0.988	1.006	0.524
Charlson Index*	1.020	0.753	1.380	0.900
Cognitive Impairment				
No		REFERENCE		
Yes	0.440	0.074	2.610	0.366
PHQ-9 score	1.144	0.996	1.314	0.058
Self-reported health change				
Better		REFERENCE		
The Same	0.791	0.144	4.348	0.788
Worse	1.475	0.312	6.974	0.624
Self-reported health today/100	**0.954**	**0.921**	**0.988**	**0.009**
Constant	1.352	0.008	219.061	0.907

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-33: Multivariable Logistic Regression of FP frailty by BATT in males. Model 3

	OR	Lower 95% C.I.	Upper 95% C.I.	P
BATT	**0.935**	**0.884**	**0.988**	**0.017**
Age	1.062	0.972	1.161	0.183
Ethnicity				
White		REFERENCE		
South Asian	4.935	0.462	52.658	0.186
Black	0.496	0.050	4.906	0.549
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	**0.128**	**0.022**	**0.761**	**0.024**
University		OMITTED		
IMD Quintile				
1		REFERENCE		
2	3.335	0.314	35.402	0.318
3	0.903	0.137	5.943	0.915
4	0.551	0.033	9.276	0.679
5	0.170	0.012	2.439	0.192
Unknown	0.511	0.001	209.505	0.827
Social Support				
Yes		REFERENCE		
No	0.136	0.007	2.774	0.194
HD vintage (months)	1.005	0.994	1.017	0.374
Charlson Index*	1.157	0.789	1.698	0.455
Cognitive Impairment				
No		REFERENCE		
Yes	0.130	0.011	1.599	0.111
PHQ-9 score	1.139	0.955	1.357	0.147
Self-reported health change				
Better		REFERENCE		
The Same	1.876	0.200	17.598	0.582
Worse	1.121	0.167	7.502	0.906
Self-reported health today/100	0.968	0.930	1.008	0.112
Walking Aid Use				
No		REFERENCE		
Yes	**6.594**	**1.438**	**30.238**	**0.015**
Self-reported slow walking				
No		REFERENCE		
Yes	**46.923**	**2.815**	**782.145**	**0.007**
Constant	0.027	0.000	14.213	0.258

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-34: : Logistic Regression of FP frailty by BATT in females. Univariable

	OR	Lower 95% C.I.	Upper 95% C.I.	P
BATT	0.976	0.944	1.009	0.153
Constant	1.885	0.404	8.797	0.420

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-35:Multivariable Logistic Regression of FP frailty by BATT in females. Model 1

	OR	Lower 95% C.I.	Upper 95% C.I.	P
BATT	0.979	0.938	1.022	0.331
Age	1.005	0.966	1.046	0.803
Ethnicity				
White		REFERENCE		
South Asian	0.991	0.197	4.978	0.991
Black	0.220	0.041	1.176	0.077
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	3.338	0.812	13.722	0.095
University	0.321	0.029	3.598	0.357
IMD Quintile				
1		REFERENCE		
2	1.092	0.241	4.956	0.909
3	0.192	0.033	1.131	0.068
4	0.050	0.005	0.541	0.014
5	0.106	0.011	1.019	0.052
Unknown	2.821	0.324	24.599	0.348
Social Support				
Yes		REFERENCE		
No	2.758	0.217	35.037	0.434
HD vintage (months)	0.999	0.987	1.011	0.859
Constant	2.222	0.063	78.080	0.660

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-36: Multivariable Logistic Regression of FP frailty by BATT in females. Model 2

	OR	Lower 95% C.I.	Upper 95% C.I.	P
BATT	0.974	0.918	1.033	0.377
Age	0.989	0.923	1.060	0.756
Ethnicity				
White		REFERENCE		
South Asian	1.038	0.097	11.133	0.975
Black	0.678	0.065	7.037	0.745
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	5.344	0.682	41.859	0.111
University	0.058	0.001	3.937	0.186
IMD Quintile				
1		REFERENCE		
2	3.980	0.443	35.762	0.218
3	**0.031**	**0.002**	**0.479**	**0.013**
4	**0.017**	**0.001**	**0.560**	**0.022**
5	0.239	0.017	3.317	0.286
Unknown	4.403	0.242	79.9	0.316
Social Support				
Yes		REFERENCE		
No	5.274	0.185	150.0	0.330
HD vintage (months)	0.995	0.980	1.010	0.498
Charlson Index*	1.599	0.851	3.004	0.145
Cognitive Impairment				
No		REFERENCE		
Yes	0.144	0.011	1.947	0.145
PHQ-9 score	**1.311**	**1.078**	**1.594**	**0.007**
Self-reported health change				
Better		REFERENCE		
The Same	10.396	0.518	208.5	0.126
Worse	1.078	0.072	16.073	0.957
Self-reported health today/100	0.972	0.928	1.018	0.229
Constant	0.967	0.001	856.4	0.992

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-37: Multivariable Logistic Regression of FP frailty by BATT in females. Model 3

	OR	Lower 95% C.I.	Upper 95% C.I.	P
BATT	1.055	0.934	1.193	0.388
Age	0.954	0.830	1.096	0.504
Ethnicity				
White		REFERENCE		
South Asian	0.090	0.002	4.952	0.239
Black	0.001	0.000	2.055	0.075
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	3.46	0.063	189.1	0.543
University	0.018	0.000	4.833	0.159
IMD Quintile				
1		REFERENCE		
2	13.7	0.185	1017	0.233
3	0.000	0.000	0.256	0.018
4	0.000	0.000	0.166	0.024
5	0.003	0.000	3.456	0.105
Unknown	1.920	0.008	479	0.817
Social Support				
Yes		REFERENCE		
No	9.966	0.022	4587	0.462
HD vintage (months)	1.009	0.979	1.040	0.548
Charlson Index*	0.879	0.268	2.882	0.831
Cognitive Impairment				
No		REFERENCE		
Yes	**0.009**	**0.000**	**0.921**	**0.046**
PHQ-9 score	1.406	0.945	2.093	0.093
Self-reported health change				
Better		REFERENCE		
The Same	48.3	0.275	8483	0.141
Worse	0.155	0.001	46.694	0.522
Self-reported health today/100	0.957	0.875	1.045	0.326
Walking Aid Use				
No		REFERENCE		
Yes	**496.1**	**2.197**	**112027**	**0.025**
Self-reported slow walking				
No		REFERENCE		
Yes	**353**	**2.242**	**55556**	**0.023**
Constant	0.217	0.000	268830	0.831

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-38: Univariable logistic regression of FP frailty by low muscle mass in males

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	**6.840**	**2.477**	**19**	**<0.001**
Constant	**0.111**	**0.044**	**0.280**	**<0.001**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-39: Multivariable logistic regression of FP frailty by low muscle mass in males. Model 1

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	**9.136**	**2.820**	**30**	**<0.001**
Age	**1.055**	**1.012**	**1.100**	**0.012**
Ethnicity				
White		REFERENCE		
South Asian	1.051	0.361	3.064	0.927
Black	0.462	0.101	2.117	0.320
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	0.765	0.240	2.434	0.650
University		OMITTED		
IMD Quintile				
1		REFERENCE		
2	0.332	0.078	1.408	0.135
3	**0.259**	**0.071**	**0.954**	**0.042**
4	0.614	0.081	4.671	0.638
5	**0.113**	**0.020**	**0.632**	**0.013**
Unknown	0.215	0.025	1.878	0.165
Social Support				
Yes		REFERENCE		
No	0.690	0.097	4.930	0.712
HD vintage (months)	0.998	0.991	1.006	0.658
Constant	**0.009**	**0.001**	**0.158**	**0.001**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-40: Multivariable logistic regression of FP frailty by low muscle mass in males. Model 2

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	**7.560**	**1.840**	**31**	**0.005**
Age	**1.099**	**1.019**	**1.186**	**0.014**
Ethnicity				
White		REFERENCE		
South Asian	2.649	0.580	12	0.209
Black	0.560	0.098	3.198	0.515
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	0.466	0.116	1.865	0.280
University		OMITTED		
IMD Quintile				
1		REFERENCE		
2	1.232	0.231	6.579	0.807
3	0.360	0.070	1.857	0.222
4	0.421	0.037	4.825	0.487
5	0.123	0.013	1.169	0.068
Unknown	0.148	0.004	4.970	0.287
Social Support				
Yes		REFERENCE		
No	0.330	0.024	4.460	0.404
HD vintage (months)	0.997	0.987	1.006	0.485
Charlson Index*	1.069	0.797	1.432	0.657
Cognitive Impairment				
No		REFERENCE		
Yes	0.535	0.097	2.953	0.473
PHQ-9 score	1.115	0.974	1.277	0.113
Self-reported health change				
Better		REFERENCE		
The Same	0.960	0.190	4.863	0.961
Worse	1.506	0.328	6.909	0.599
Self-reported health today/100	**0.957**	**0.925**	**0.990**	**0.011**
Constant	**0.004**	**0.000**	**0.287**	**0.012**

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-41: Multivariable logistic regression of FP frailty by low muscle mass in males. Model 3

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	**7.290**	**1.294**	**41.067**	**0.024**
Age	1.078	0.985	1.180	0.102
Ethnicity				
White		REFERENCE		
South Asian	6.403	0.671	61	0.107
Black	0.645	0.068	6.134	0.703
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	0.215	0.038	1.208	0.081
University		OMITTED		
IMD Quintile				
1		REFERENCE		
2	2.464	0.260	23	0.432
3	0.645	0.089	4.648	0.663
4	0.387	0.022	6.848	0.517
5	0.084	0.005	1.393	0.084
Unknown	0.322	0.002	59	0.670
Social Support				
Yes		REFERENCE		
No	0.118	0.007	2.027	0.141
HD vintage (months)	1.005	0.992	1.019	0.449
Charlson Index*	1.224	0.844	1.775	0.287
Cognitive Impairment				
No		REFERENCE		
Yes	0.122	0.011	1.309	0.082
PHQ-9 score	1.133	0.955	1.344	0.152
Self-reported health change				
Better		REFERENCE		
The Same	1.772	0.206	15	0.602
Worse	0.935	0.150	5.846	0.943
Self-reported health today/100	0.971	0.934	1.010	0.144
Walking Aid Use				
No		REFERENCE		
Yes	**5.372**	**1.197**	**24**	**0.028**
Self-reported slow walking				
No		REFERENCE		
Yes	**63.511**	**4.263**	**946**	**0.003**
Constant	**0.000**	**0.000**	**0.040**	**0.003**

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-42: Univariable logistic regression of FP frailty by low muscle mass in females

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	**2.884**	**1.152**	**7.217**	**0.024**
Constant	**0.421**	**0.235**	**0.755**	**0.004**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-43: Multivariable logistic regression of FP frailty by low muscle mass in females. Model 1

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	2.888	0.884	9.432	0.079
Age	1.005	0.966	1.046	0.795
Ethnicity				
White		REFERENCE		
South Asian	0.980	0.186	5.154	0.981
Black	0.244	0.046	1.295	0.098
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	3.513	0.863	14	0.079
University	0.384	0.034	4.30	0.437
IMD Quintile				
1		REFERENCE		
2	0.950	0.200	4.511	0.948
3	0.174	0.028	1.096	0.063
4	**0.047**	**0.004**	**0.505**	**0.012**
5	**0.100**	**0.010**	**0.998**	**0.050**
Unknown	3.074	0.336	28	0.320
Social Support				
Yes		REFERENCE		
No	2.484	0.157	39	0.519
HD vintage (months)	0.998	0.986	1.010	0.694
Constant	0.618	0.040	9.645	0.731

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-44: Multivariable logistic regression of FP frailty by low muscle mass in females. Model 2

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	3.925	0.739	21	0.109
Age	0.990	0.923	1.061	0.769
Ethnicity				
White		REFERENCE		
South Asian	1.538	0.132	18	0.731
Black	0.765	0.074	7.956	0.823
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	6.504	0.774	55	0.085
University	0.100	0.001	7.433	0.295
IMD Quintile				
1		REFERENCE		
2	3.314	0.350	31	0.296
3	**0.041**	**0.003**	**0.626**	**0.022**
4	**0.019**	**0.001**	**0.607**	**0.025**
5	0.172	0.011	2.719	0.211
Unknown	5.069	0.240	107	0.297
Social Support				
Yes		REFERENCE		
No	4.949	0.152	161	0.368
HD vintage (months)	0.992	0.977	1.008	0.321
Charlson Index*	1.658	0.872	3.151	0.123
Cognitive Impairment				
No		REFERENCE		
Yes	0.159	0.011	2.363	0.182
PHQ-9 score	**1.327**	**1.086**	**1.621**	**0.006**
Self-reported health change				
Better		REFERENCE		
The Same	9.225	0.392	217	0.168
Worse	1.004	0.061	17	0.998
Self-reported health today/100	0.977	0.931	1.025	0.339
Constant	0.107	0.000	125	0.536

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-45: Multivariable logistic regression of FP frailty by low muscle mass in females. Model 3

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Low Muscle Mass				
No		REFERENCE		
Yes	2.717	0.144	51	0.505
Age	0.947	0.823	1.090	0.449
Ethnicity				
White		REFERENCE		
South Asian	0.104	0.002	6.464	0.283
Black	0.006	0.000	3.503	0.115
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	5.546	0.110	281	0.392
University	0.138	0.001	29	0.469
IMD Quintile				
1		REFERENCE		
2	15.222	0.177	1311	0.231
3	0.002	0.000	0.299	0.016
4	**0.000**	**0.000**	**0.097**	**0.014**
5	0.007	0.000	6.298	0.154
Unknown	5.282	0.026	1093	0.541
Social Support				
Yes		REFERENCE		
No	6.457	0.017	2395	0.537
HD vintage (months)	1.001	0.973	1.029	0.966
Charlson Index*	0.889	0.291	2.714	0.836
Cognitive Impairment				
No		REFERENCE		
Yes	0.037	0.001	2.030	0.107
PHQ-9 score	1.436	0.994	2.074	0.054
Self-reported health change				
Better		REFERENCE		
The Same	58.672	0.208	16512	0.157
Worse	0.213	0.001	58.114	0.589
Self-reported health today/100	0.970	0.889	1.059	0.497
Walking Aid Use				
No		REFERENCE		
Yes	**236**	**2.692**	**20605**	**0.017**
Self-reported slow walking				
No		REFERENCE		
Yes	**90.4**	**2.252**	**3630**	**0.017**
Constant	0.599	0.000	167009	0.936

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-46: Univariable logistic regression of FP frailty by sarcopenia (EWGSOP definition) in males.

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**7.299**	**3.276**	**16.262**	**<0.001**
Constant	**0.189**	**0.107**	**0.335**	**<0.001**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-47: Multivariable logistic regression of FP frailty by sarcopenia (EWGSOP definition) in males. Model 1

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**7.673**	**2.854**	**20.627**	**<0.001**
Age	1.037	0.994	1.082	0.093
Ethnicity				
White		REFERENCE		
South Asian	0.878	0.285	2.712	0.822
Black	0.636	0.138	2.922	0.561
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	0.576	0.174	1.901	0.365
University		OMITTED		
IMD Quintile				
1		REFERENCE		
2	0.612	0.146	2.566	0.502
3	0.918	0.264	3.196	0.893
4	0.612	0.078	4.789	0.640
5	0.372	0.064	2.170	0.272
Unknown	0.238	0.030	1.910	0.177
Social Support				
Yes		REFERENCE		
No	0.595	0.086	4.100	0.598
HD vintage (months)	0.998	0.991	1.006	0.623
Constant	0.038	0.002	0.655	0.024

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-48: Multivariable logistic regression of FP frailty by sarcopenia (EWGSOP definition) in males. Model 2

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**5.490**	**1.663**	**18.123**	**0.005**
Age	**1.079**	**1.003**	**1.162**	**0.042**
Ethnicity				
White		REFERENCE		
South Asian	2.530	0.545	11.746	0.236
Black	0.753	0.125	4.528	0.757
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	0.404	0.103	1.578	0.192
University		OMITTED		
IMD Quintile				
1		REFERENCE		
2	2.101	0.358	12.338	0.411
3	1.103	0.258	4.703	0.895
4	0.470	0.047	4.693	0.520
5	0.394	0.048	3.202	0.383
Unknown	0.192	0.007	5.380	0.332
Social Support				
Yes		REFERENCE		
No	0.257	0.018	3.726	0.319
HD vintage (months)	0.997	0.988	1.007	0.585
Charlson Index*	1.013	0.757	1.355	0.932
Cognitive Impairment				
No		REFERENCE		
Yes	0.539	0.096	3.031	0.483
PHQ-9 score	1.100	0.968	1.249	0.145
Self-reported health change				
Better		REFERENCE		
The Same	0.772	0.146	4.093	0.761
Worse	1.819	0.407	8.123	0.433
Self-reported health today/100	**0.964**	**0.933**	**0.996**	**0.026**
Constant	0.015	0.000	1.038	0.052

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-49: Multivariable logistic regression of FP frailty by sarcopenia (EWGSOP definition) in males. Model 3

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**9.855**	**1.800**	**53.950**	**0.008**
Age	1.039	0.947	1.140	0.420
Ethnicity				
White		REFERENCE		
South Asian	5.015	0.476	52.849	0.180
Black	1.277	0.124	13.143	0.837
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	**0.152**	**0.025**	**0.909**	**0.039**
University		OMITTED		
IMD Quintile				
1		REFERENCE		
2	4.460	0.462	43.015	0.196
3	2.605	0.378	17.940	0.331
4	0.473	0.025	9.010	0.618
5	0.329	0.021	5.051	0.425
Unknown	0.421	0.001	159.369	0.775
Social Support				
Yes		REFERENCE		
No	0.128	0.008	2.110	0.151
HD vintage (months)	1.005	0.993	1.018	0.395
Charlson Index*	1.221	0.823	1.811	0.320
Cognitive Impairment				
No		REFERENCE		
Yes	0.160	0.011	2.407	0.185
PHQ-9 score	1.132	0.961	1.334	0.137
Self-reported health change				
Better		REFERENCE		
The Same	1.524	0.176	13.168	0.702
Worse	1.207	0.191	7.612	0.841
Self-reported health today/100	0.982	0.940	1.026	0.421
Walking Aid Use				
No		REFERENCE		
Yes	**10.050**	**1.852**	**54.524**	**0.007**
Self-rated slow walking				
No		REFERENCE		
Yes	**71.284**	**3.876**	**1310.861**	**0.004**
Constant	**0.000**	**0.000**	**0.100**	**0.007**

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-50: Univariable logistic regression of FP frailty by sarcopenia (EWGSOP definition) in females.

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**4.737**	**1.651**	**13.589**	**0.004**
Constant	**0.422**	**0.247**	**0.722**	**0.002**

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-51: Multivariable logistic regression of FP frailty by sarcopenia (EWGSOP definition) in females. Model 1

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	**4.823**	**1.225**	**18.994**	**0.024**
Age	1.010	0.971	1.051	0.621
Ethnicity				
White		REFERENCE		
South Asian	1.056	0.191	5.834	0.950
Black	0.283	0.052	1.551	0.146
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	3.536	0.855	14.628	0.081
University	0.424	0.037	4.818	0.489
IMD Quintile				
1		REFERENCE		
2	1.044	0.215	5.075	0.958
3	0.221	0.035	1.396	0.108
4	**0.067**	**0.006**	**0.712**	**0.025**
5	**0.084**	**0.008**	**0.898**	**0.040**
Unknown	4.041	0.425	38.395	0.224
Social Support				
Yes		REFERENCE		
No	1.830	0.093	35.988	0.691
HD vintage (months)	0.997	0.985	1.009	0.635
Constant	0.427	0.025	7.161	0.554

Bold text indicates significance at P<0.05 level.

Supplementary Table 5-52: Multivariable logistic regression of FP frailty by sarcopenia (EWGSOP definition) in females. Model 2

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	5.709	0.762	42.804	0.090
Age	0.988	0.920	1.061	0.735
Ethnicity				
White		REFERENCE		
South Asian	1.261	0.113	14.047	0.851
Black	0.846	0.073	9.801	0.894
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	5.187	0.677	39.733	0.113
University	0.096	0.001	6.525	0.276
IMD Quintile				
1		REFERENCE		
2	3.537	0.402	31.103	0.255
3	**0.054**	**0.003**	**0.876**	**0.040**
4	**0.026**	**0.001**	**0.963**	**0.048**
5	0.110	0.005	2.262	0.152
Unknown	8.708	0.359	211.062	0.183
Social Support				
Yes		REFERENCE		
No	3.367	0.100	113.068	0.498
HD vintage (months)	0.991	0.975	1.007	0.277
Charlson Index*	1.735	0.896	3.363	0.102
Cognitive Impairment				
No		REFERENCE		
Yes	0.162	0.011	2.428	0.188
PHQ-9 score	**1.300**	**1.078**	**1.567**	**0.006**
Self-reported health change				
Better		REFERENCE		
The Same	9.149	0.406	206.277	0.164
Worse	0.968	0.061	15.371	0.982
Self-reported health today/100	0.976	0.930	1.025	0.328
Constant	0.145	0.000	148.212	0.585

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Supplementary Table 5-53: Multivariable logistic regression of FP frailty by sarcopenia (EWGSOP definition) in females. Model 3

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Sarcopenia				
No		REFERENCE		
Yes	5.159	0.215	123.994	0.312
Age	0.952	0.830	1.094	0.490
Ethnicity				
White		REFERENCE		
South Asian	0.081	0.001	4.956	0.231
Black	0.006	0.000	2.648	0.100
Other		OMITTED		
Education Level				
High School		REFERENCE		
College/6th form	5.775	0.113	293.965	0.382
University	0.193	0.001	42.934	0.551
IMD Quintile				
1		REFERENCE		
2	11.474	0.152	868.188	0.269
3	**0.002**	**0.000**	**0.266**	**0.013**
4	**0.000**	**0.000**	**0.181**	**0.019**
5	0.006	0.000	4.809	0.132
Unknown	6.327	0.033	1202.284	0.491
Social Support				
Yes		REFERENCE		
No	5.228	0.014	2021.490	0.586
HD vintage (months)	0.999	0.973	1.027	0.965
Charlson Index*	0.845	0.275	2.595	0.769
Cognitive Impairment				
No		REFERENCE		
Yes	0.051	0.001	2.552	0.136
PHQ-9 score	1.420	1.000	2.016	0.050
Self-reported health change				
Better		REFERENCE		
The Same	43.373	0.203	9244.579	0.168
Worse	0.189	0.001	40.533	0.543
Self-reported health today/100	0.974	0.894	1.060	0.541
Walking Aid Use				
No		REFERENCE		
Yes	**189.217**	**2.662**	**13449.290**	**0.016**
Self-rated slow walking				
No		REFERENCE		
Yes	**101.312**	**2.517**	**4077.688**	**0.014**
Constant	0.426	0.000	87320.960	0.891

Bold text indicates significance at P<0.05 level. *=CKD omitted.

Chapter 6: Frailty associates with but does not predict mortality in haemodialysis: a comparison of frailty screening tools.

6.1 Extent of Personal Contribution

I coordinated all study visits with participants and dialysis unit staff. I recruited participants, and collected all baseline data with the support of Dr Gonzalo Correa, Dr Muhammad Qasim, and Dr Adnan Sharif. All colleagues were supervised by me in their data collection, and I was responsible for maintaining training and personnel logs in the site file.

Ms Felicity Evison, and Ms Suzy Gallier were responsible for interrogation of EPR for IMD Quintile assessment and HES/OPCS/ONS data for mortality follow-up. I performed all subsequent data cleaning, integrity, and analyses with guidance from Dr Adnan Sharif.

The first draft of the manuscript was written by myself and I was responsible for all edits and revisions.

6.2 Abstract

6.2.1 Introduction

With heterogenous definitions in use, the optimal frailty tool to for use in high-risk haemodialysis patients is unknown.

6.2.2 Methods

We performed a prospective cohort study of prevalent haemodialysis recipients linked to national datasets for long-term clinical outcomes including mortality. The following frailty instruments were compared; 1) Frailty Phenotype (FP), 2) Frailty Index (FI), 3) Edmonton Frail Scale (EFS) and 4) Clinical Frailty Scale (CFS). Time-to-event outcomes analysed with Cox's Proportional Hazards Model, treating frailty variables as ordinal (classified as Frail, Vulnerable and Robust) and continuous variables.

6.2.3 Findings

We observed 111 (22.9%) deaths over a median follow up of 678 days. In unadjusted and adjusted models, frailty defined by FP (HR 3.74, 95% CI 1.25-13.64), FI (HR 8.20, 95% CI 1.94-34.57), EFS (HR 3.12, 95% CI 1.41-8.91) and CFS (HR 2.84, 95% CI 1.38-5.84) were all associated with mortality. Apart from FP (HR 1.91, 95% CI 0.66-5.52), vulnerability defined by FI (HR 4.83, 95% CI 1.10-21.25), EFS (HR 3.27, 95% CI 1.48-7.25) and CFS (HR 2.36, 95% CI 1.07-5.18) were independently associated with mortality. However, univariable C-statistics for mortality prediction were poor; 0.653 for FP, 0.630 for FI, 0.620 for EFS and 0.619 for CFS.

6.2.4 Conclusion

Frailty is strongly associated with mortality in haemodialysis but cannot be extrapolated to probabilities. Further work is warranted to understand how best to integrate use of frailty tools in this high-risk population for meaningful clinical application.

Keywords:

Haemodialysis, Frailty, Epidemiology, Survival Analysis

6.3 Introduction

We have previously discussed work both within the general elderly population and from the FITNESS cohort has demonstrated that agreement upon frailty status is poor.[59,272] Variation in frailty definition leads to disparate estimates of prevalence, limiting our understanding of frailty-associated adverse outcomes such as mortality. While heterogenous frailty definitions demonstrate strong association with increased mortality,[21,45,46,49,170] it is unclear if mortality association is comparable across different frailty tools in haemodialysis patients.

Each of the Frailty Phenotype (FP)[19], Frailty Index[47], Edmonton Frail Scale[55], and Clinical Frailty Scale[27] have been studied in haemodialysis populations[21,170,184,270] though their clinical utility has not been directly compared. The optimal frailty instrument requires a balance between ease of use, utility and predictive value for adverse outcomes. With regards to the latter, the lack of data comparing the discriminatory ability of commonly used frailty instruments for prediction of mortality is a limitation. Therefore, the aim of this study is to report the short-term mortality associated with frailty by commonly employed tools and to compare the probabilities of each instrument in prevalent haemodialysis patients.

6.4 Materials and Methods

6.4.1 Study design

FITNESS study design, eligibility, consent and baseline data acquisition are presented in detail in Chapters Chapter 2: and Chapter 3:.

6.4.2 Frailty definitions

Frailty definitions are detailed in Chapter 2: with baseline assessments used to determine frailty status. In summary the following frailty instruments were used; 1) Frailty Phenotype (FP), 2) Frailty Index (FI)[270], 3) Edmonton Frail Scale (EFS) and 4) Clinical Frailty Scale (CFS). Patients were classified at baseline with the following frailty definitions; FP range 0-5 (frail ≥3, vulnerable 1-2, robust 0), FI range 0-1 (frail ≥0.24, vulnerable >0.12 to ≤0.24, robust ≤0.12), EFS range 0-17 (frail ≥8, vulnerable 6-7, robust <6), and CFS range 1-9 (frail ≥5, vulnerable 4, robust <4).

6.4.3 Outcomes

The main outcome under investigation was all-cause mortality, with data obtained by electronic record linkage of all FITNESS study recruits to Office of National Statistics (ONS), a UK-wide repository of death certificate data. This ensures robust coverage of mortality data capture and comprehensive description of causality.

6.4.4 Recruitment

A power calculation was originally performed based upon US data,[168] assuming adjusted risk ratio of 2.24 for 1-year mortality and 1.56 for 1-year mortality and/or hospitalisation for frail versus non-frail patients receiving haemodialysis. A non-frail risk of 5% for 1-year mortality and a 40% risk of 1-year mortality/hospitalisation was assumed, powered to 0.8 and with a confidence interval of 0.95. A sample size of 602 was therefore considered to be robustly powered to demonstrate a difference in 1-year mortality or 150 patients to be powered for 1-year mortality/hospitalisation. However, in agreement with the sponsor, recruitment of 602

participants was not felt to be feasible in this single centre, and a revised target of 500 participants to be recruited was set with follow up beyond 1-year.

6.4.5 Statistics

Statistical analysis was performed using STATA 17 (StataCorp 2020, Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) and R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). Categorical data was presented as numbers and percentages, with continuous variables reported as medians and interquartile ranges (IQRs). Differences between groups were compared using chi-square tests or Fisher's Exact test for categorical variables and student t-tests or Mann-Whitney tests (parametric or non-parametric data respectively) for all continuous variables.

Survival analyses were performed by generation of Kaplan-Meier curve estimates and time-to-event outcomes were analysed with the Cox's Proportional Hazards Model, treating frailty variables both as ordinal – Frail, Vulnerable and Robust – and continuous variables. The proportional hazard assumption was checked and satisfied by examination of plots of the log-negative-log of the within-group survivorship functions versus log time as well as comparing Kaplan-Meier (observed) with Cox (expected) survival curves with our study variables, alongside selected covariables for adjusted analyses (reported as Hazard Ratios [HR] with 95% Confidence Intervals [CI]). Survival time was accrued from the day of baseline data collection and was censored for end of follow-up. Multiple models for adjustment were considered; unadjusted, model 1 (adjusted for age, gender, ethnicity, IMD quintile), model 2 (adjusted for age, gender, ethnicity, IMD quintile, BMI, Charlson Index [CKD omitted], number of admissions in year prior to recruitment, haemodialysis vintage, medication number, smoking

status [current, ex-, or never], serum albumin) A list of candidate baseline prediction variables for model 3 was established *a priori* and considered on the basis of a known or suspected relationship with dialysis-related mortality (age, sex, ethnicity, body mass index, index of multiple deprivation, Charlson comorbidity index, number of hospitalisation episodes, polypharmacy, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status). Trends of survivor function across the continuous frailty scores were tested using log-rank tests on the fully adjusted model. Mortality probabilities were calculated using sensitivity, specificity, positive predictive value and negative predictive value. Harrell's C statistic was calculated from unadjusted Cox proportional hazard models. Further analyses were run using Fine and Gray's competing risks model for all mortality models to ascertain whether controlling for kidney transplantation as a competing event affected results.

Missing IMD quintile data were handled via a dummy variable. Other missing data were assumed missing at random and handled via listwise deletion as all other covariables had <1% data missing.

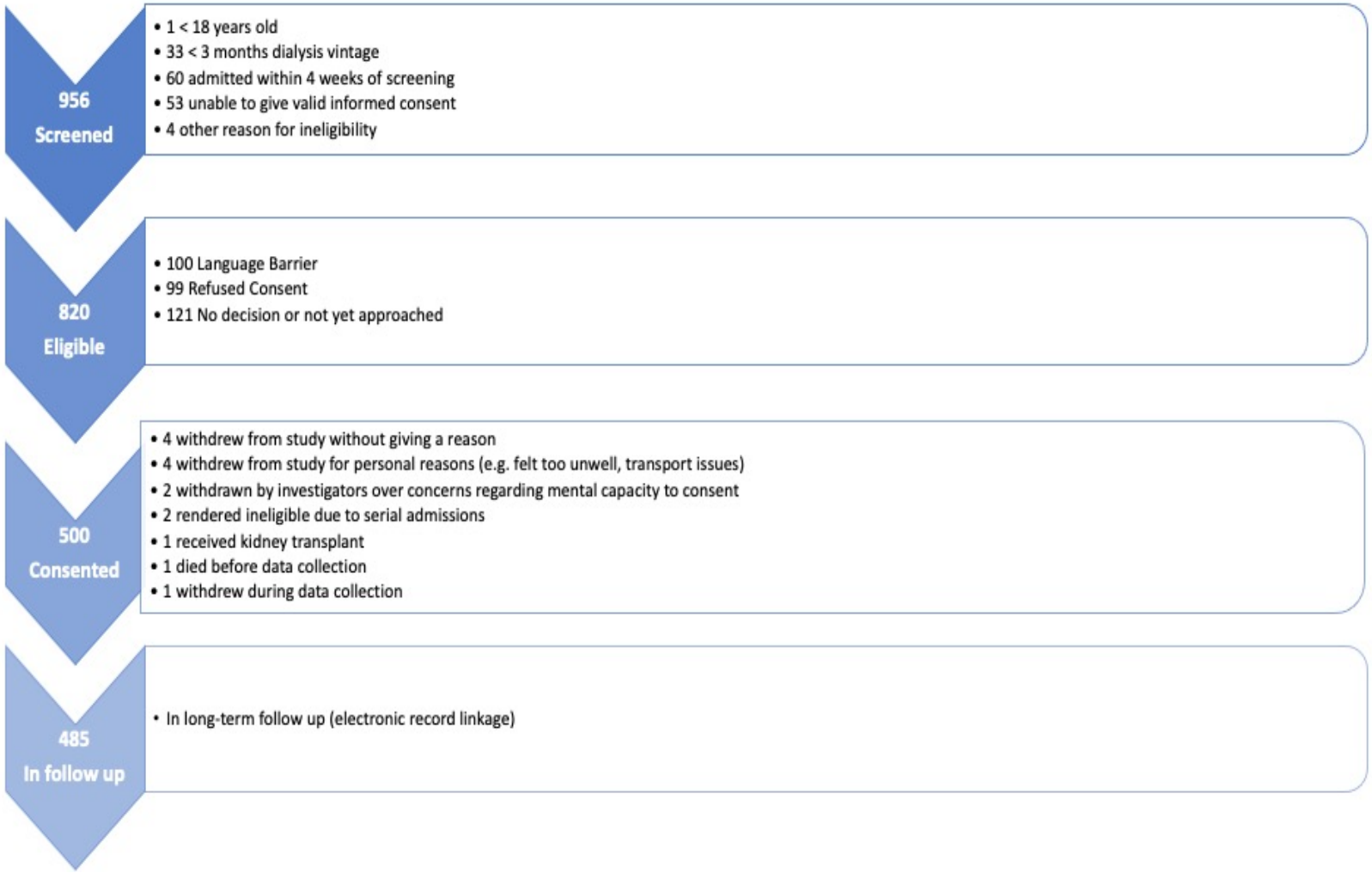


Figure 6-1: PRISMA flow chart of study participation

6.5 Results

6.5.1 Study cohort demographics

Figure 6-1 shows the PRISMA study flow of participant recruitment to the FITNESS study, with 485 prevalent haemodialysis patients with baseline frailty assessments and linkage to local electronic patient records and national datasets. Follow up was 678 days (interquartile range: 531-812 days), with all participants receiving a minimum potential follow-up of 365 days from recruitment. Table 6-1 shows key demographics stratified by different frailty instruments at study recruitment.

6.5.2 Baseline frailty assessment

The proportion of participants classified as frail was 41.9% by FP, 63.3% by FI, 50.3% by EFS and 53.8% by CFS. The proportion of participants classified as vulnerable was 45.3% by FP, 20.6% by FI, 24.1% by EFS and 17.5% by CFS. This is summarised in detail in Chapter 3:.

6.5.3 Mortality outcomes.

There were 111 (22.9%) deaths during the follow-up period, of which 47 (42.3% of total deaths) occurred within the first year of follow-up. Kidney transplantation occurred for 34 (6.6%) participants during follow-up, of which 2 (5.9%) subsequently died. Primary cause of death was listed as infection in 22 participants (19.8%), ischaemic heart disease 17 (15.4%) cancer 10 (9.0%), cerebrovascular disease 4 (3.6%), peripheral vascular disease 2 (1.8%), and other causes of death 35 (31.5%). Cause of death data were not available for 21 (18.9%) of deaths. Of the infection-related deaths, 8 (7.2% of total deaths) were due to COVID-19 (primary cause of death code U07.1).

Table 6-2 highlights mortality outcomes for each frailty instrument, stratified into robust, vulnerable and frail classification. Figure 6-2 to Figure 6-5 show unadjusted cumulative survival was lower for frail and vulnerable participants when compared with the robust group for each frailty instrument ($p<0.001$ for each instrument by log-rank test).

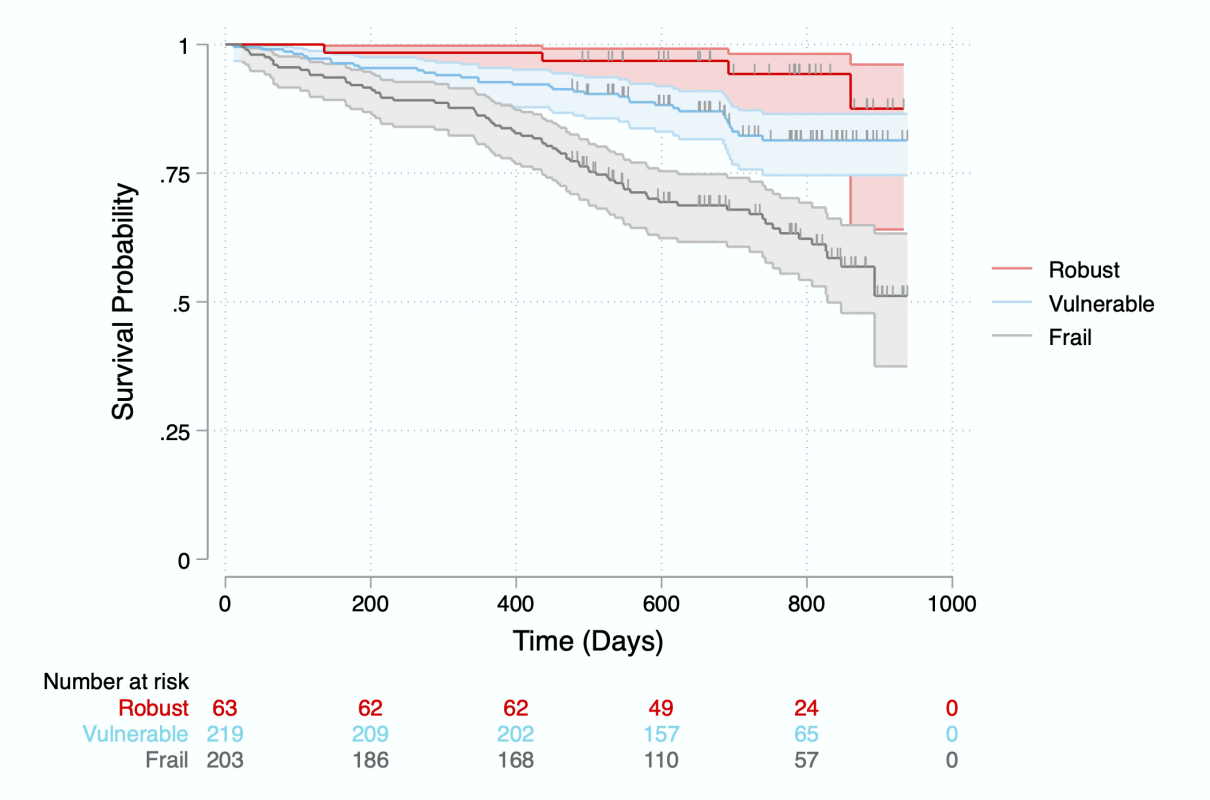


Figure 6-2: Unadjusted Kaplan-Meier of participant survival by FP frailty status

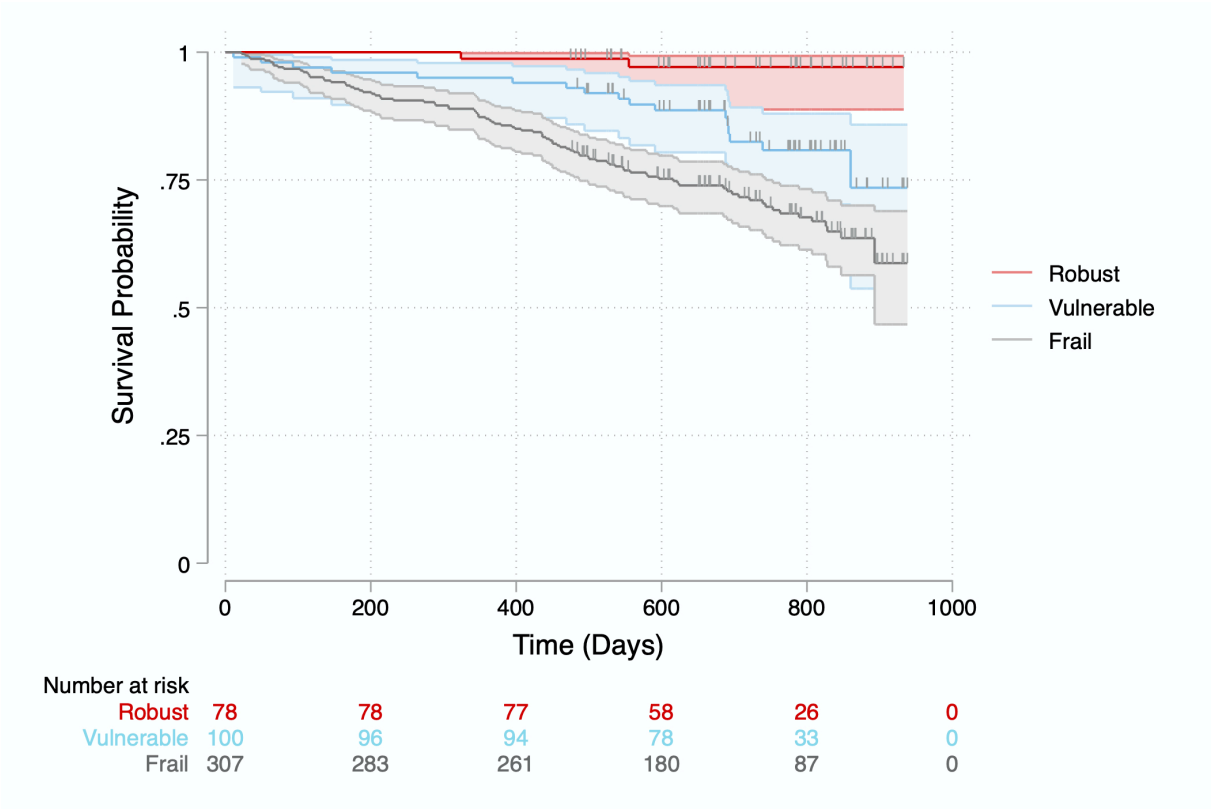


Figure 6-3: Unadjusted Kaplan-Meier of participant survival by FI frailty status

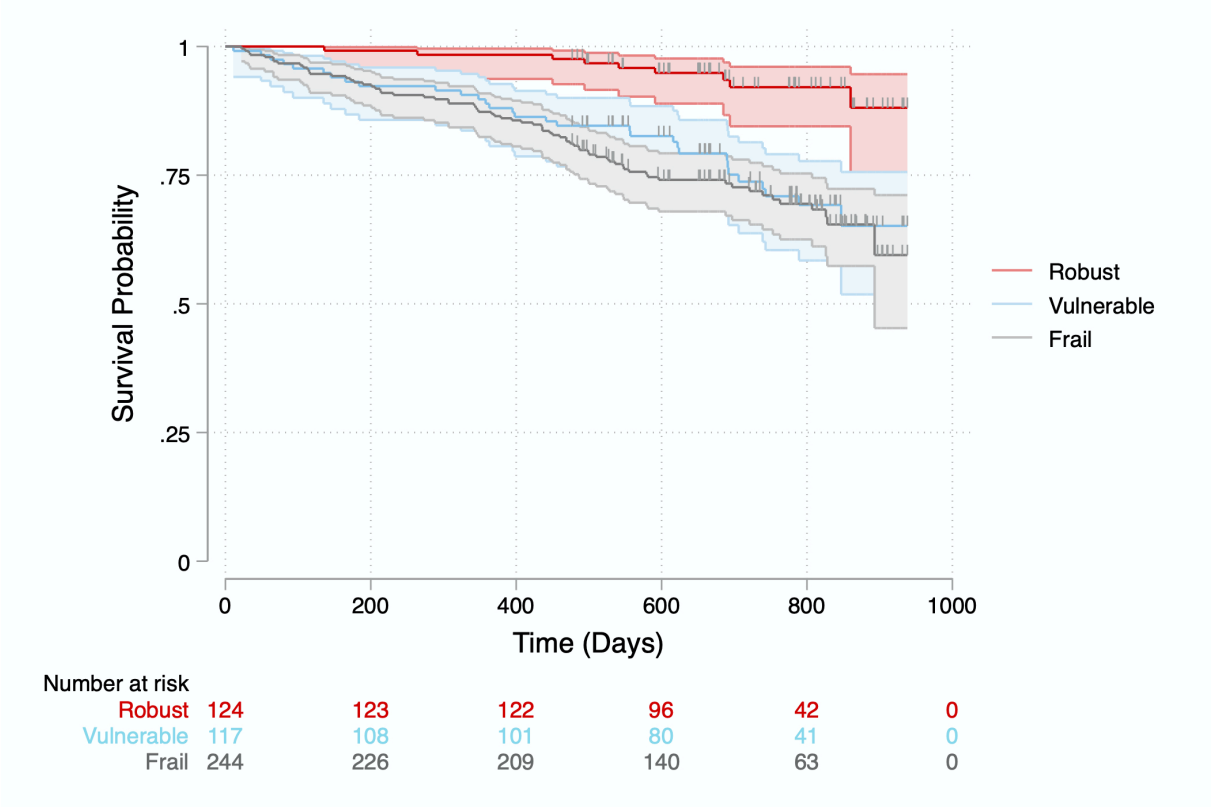


Figure 6-4: Unadjusted Kaplan-Meier of participant survival by EFS frailty status

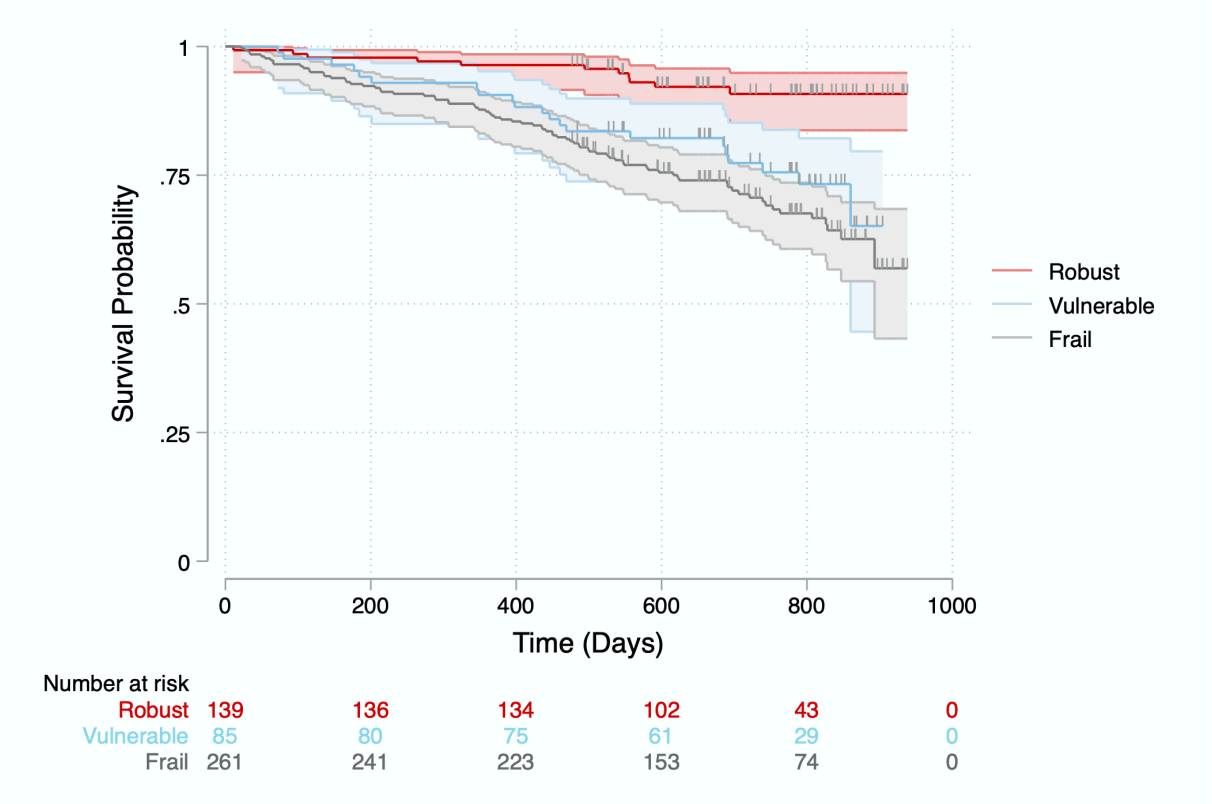


Figure 6-5: Unadjusted Kaplan-Meier of participant survival by CFS frailty status

6.5.4 Unadjusted and adjusted hazards for mortality

The Cox proportional hazards model was adjusted for the *a priori* variables as discussed in the methodology section, with results shown in Table 6-3 for the different models. In the models adjusting for basic demographics or incorporating measures to reflect co-morbidity and disability, all frailty instruments were associated with mortality. In a fully adjusted model as described in the methodology, all frailty instruments retained statistical significance (see Table 6-4 for full model results). Vulnerability defined by FI, EFS and CFS had a statistically significant association with mortality, both in unadjusted and every adjusted model, while vulnerability defined by FP had no association with mortality in any model. Fully adjusted Cox regression curves are shown in Figure 6-6 to Figure 6-9. All instruments retained their

mortality association when treated as continuous variables, as shown in Bold text indicates significance at P<0.05 level. *CKD omitted.

Table 6-5. A trend of the survivor function was observed for each increase in frailty for all instruments studied (p<0.001). Table 6-6 and Table 6-7 show that upon re-running the analyses using Fine and Gray's competing risks model with kidney transplantation as the competing event, FP vulnerability gained statistical significance for association with mortality subhazard on unadjusted analysis, whereas FI vulnerability lost statistical significance for the same on the fully adjusted model. No other differences in statistical significance were observed on either continuous or ordinal analyses.

6.5.5 Probability accuracy for mortality

Table 6-8 shows the diagnostic probability of each of the frailty instruments for mortality. It shows that positive predictive values (PPV) and negative predictive values (NPV) were not significantly different across the frailty instruments, but sensitivities and specificities differed significantly. To explore this further, sensitivities and specificities were compared between frailty instrument pairs. At 87.2%, the FI demonstrated a significantly higher sensitivity for mortality than the FP at 63.8% (p=0.008), the EFS (66.0% p=0.015), but was not significantly different to the CFS sensitivity of 72.3% (p=0.072). There were no significant differences between the sensitivities of FP and EFS (63.8% versus 66.0%, p=0.829), or FP and CFS (63.8% versus 72.3%, p=0.376). There was no significant difference between the sensitivities for the EFS and CFS (66.0% versus 72.3%, p=0.503).

The FI had significantly lower specificity than the FP (39.3% versus 60.5%, p<0.001), EFS (39.3% versus 51.4%, p<0.001) and CFS (39.3% versus 49.3%, p=0.003). The FP showed significantly higher specificity than EFS (60.5% versus 51.4%, p = 0.006), and CFS (60.5% versus

49.3%, p=0.001). There was no significant difference between the specificity of the EFS and CFS (51.4% versus 49.3%, p=0.544).

On univariable analysis, Harrell's C statistic was 0.630 for FI, 0.653 for FP, 0.620 for EFS and 0.619 for CFS.

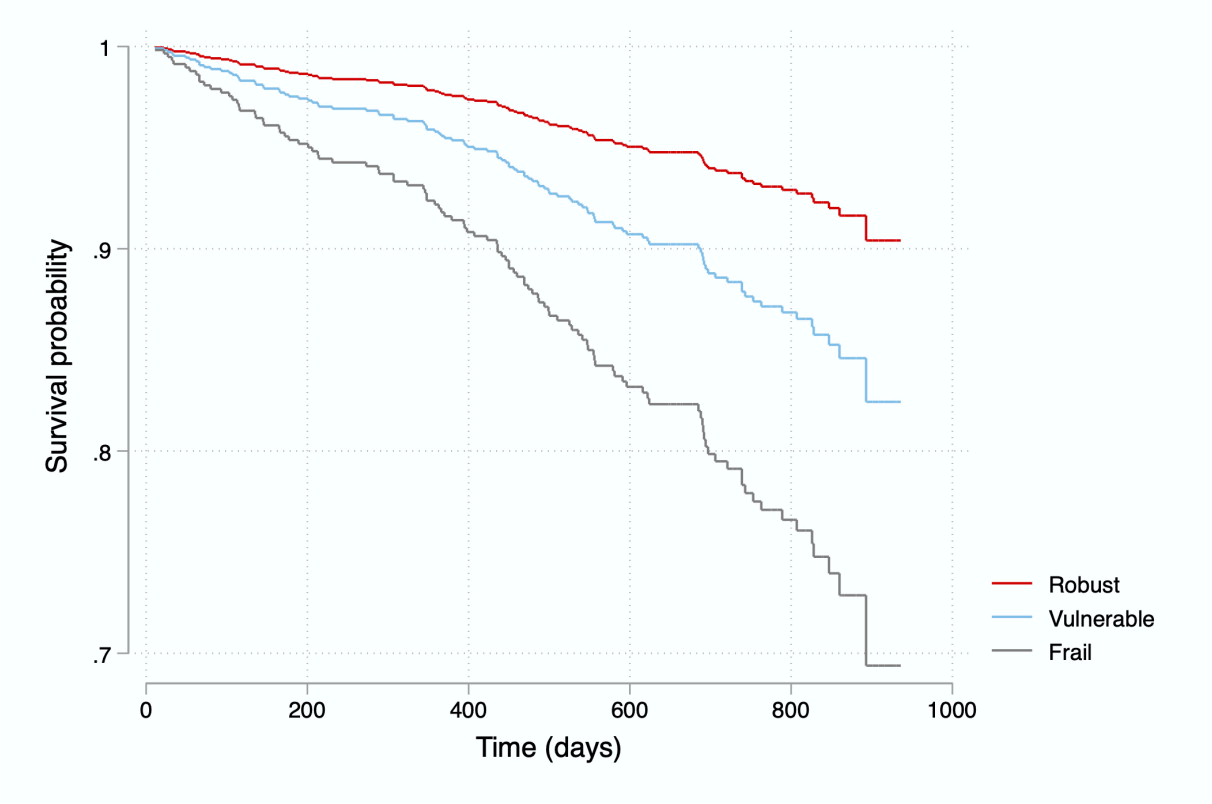


Figure 6-6: Fully adjusted Cox regression curve of participant survival by FP frailty status

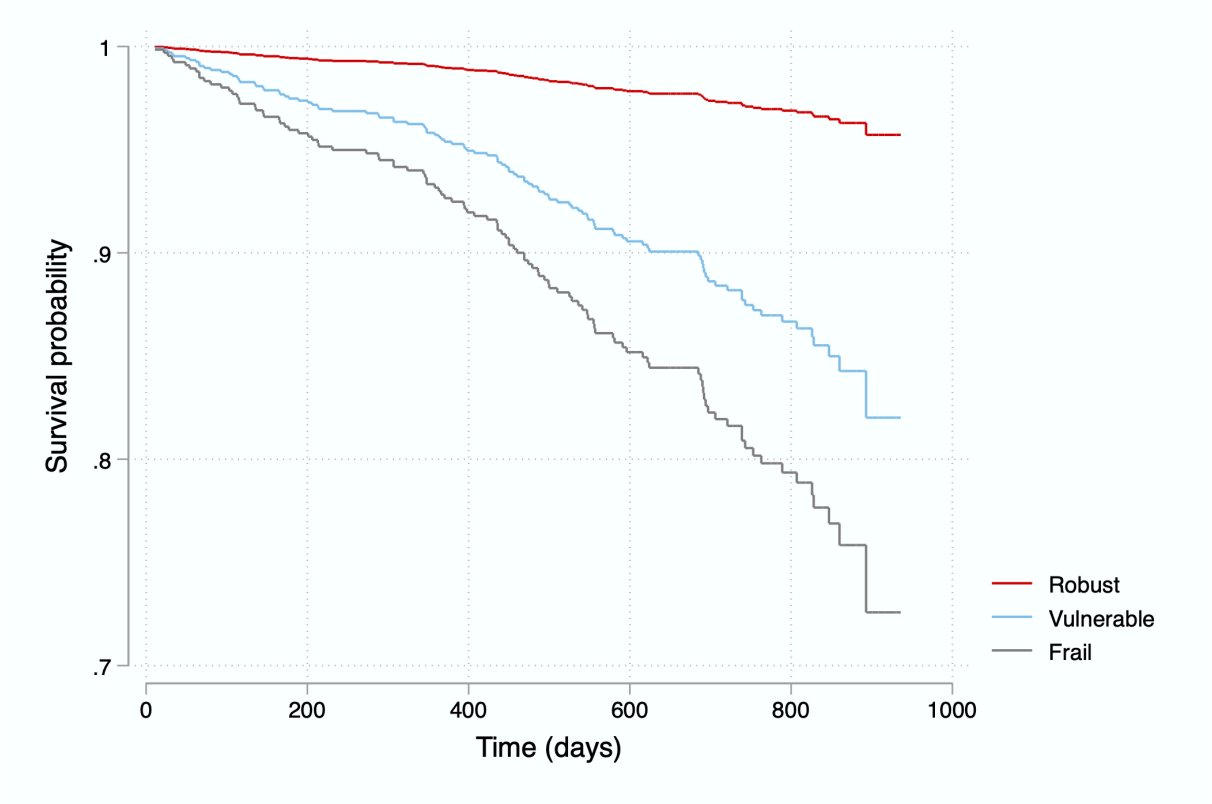


Figure 6-7: Fully adjusted Cox regression curve of participant survival by FI frailty status

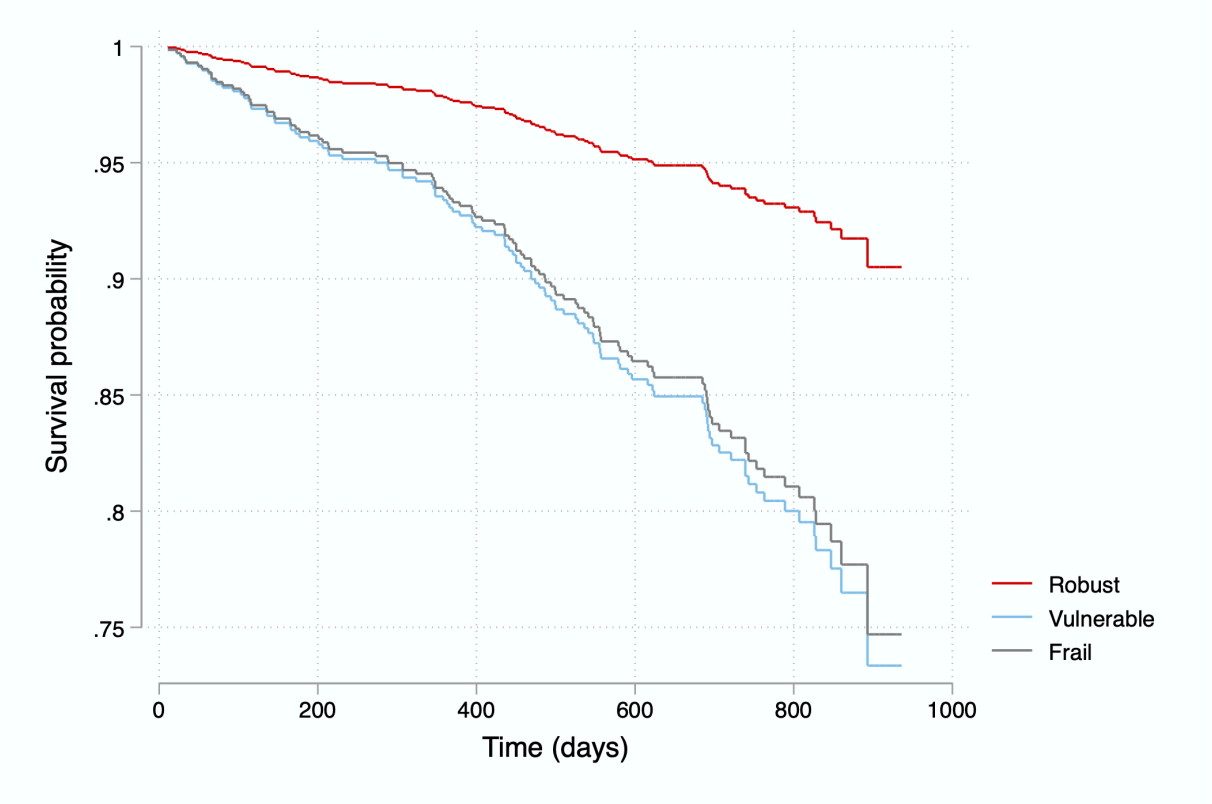


Figure 6-8: Fully adjusted Cox regression curve of participant survival by EFS frailty status

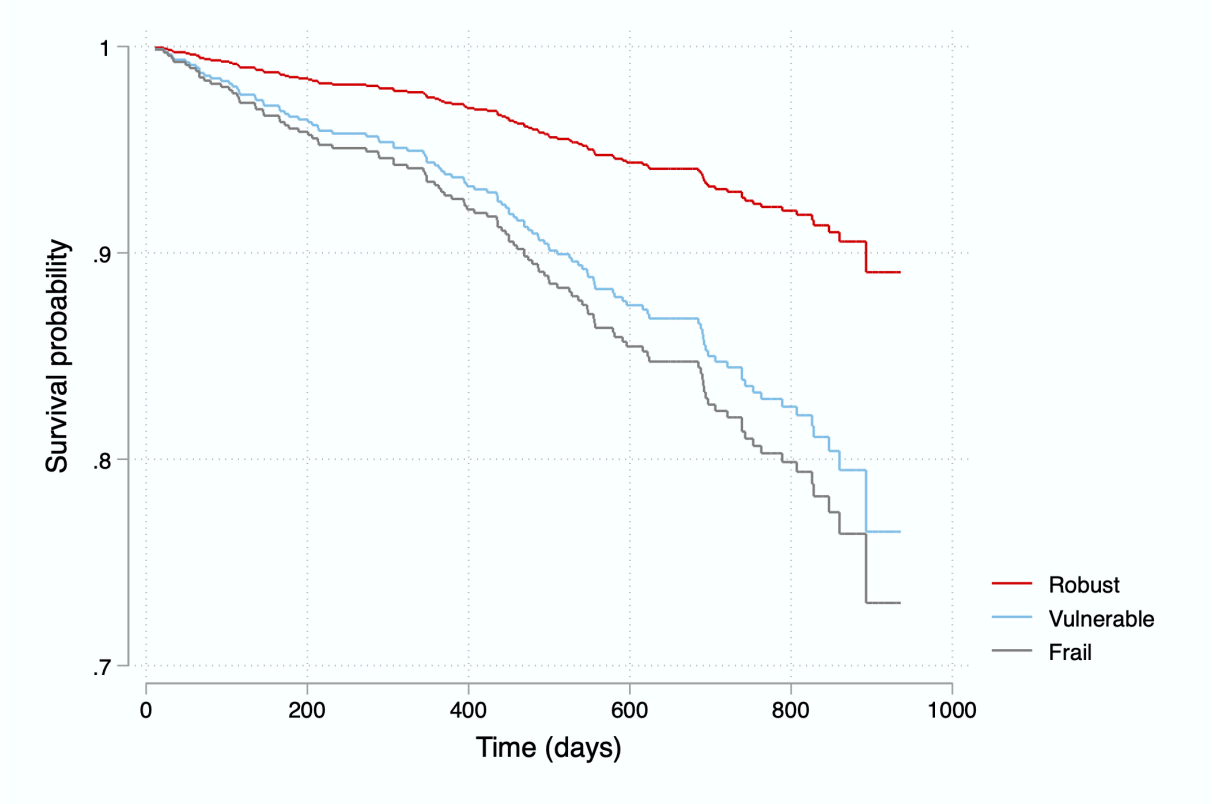


Figure 6-9: Fully adjusted Cox regression curve of participant survival by CFS frailty status

6.6 Discussion

Frailty is associated with mortality in haemodialysis patients, but studies to date have used heterogenous definitions that limit generalisability. Previous work from this cohort has demonstrated good correlation but poor agreement upon frailty between these frailty instruments.[272] In this prospective-cohort study of a large, prevalent haemodialysis population, we report a high frailty prevalence and association with mortality, regardless of frailty definition and after adjustment for clinically-relevant risk factors. Furthermore, vulnerability (or pre-frailty) was also associated with increased mortality for all tools except FP. Despite this strong association, probability for mortality was universally poor across all frailty tools. This suggests that whilst frailty can indicate increased mortality risk, it should not be considered a predictor of such an outcome. This should stimulate debate as to which frailty

instrument is optimal for kidney failure patients, and for what specific purpose, before considering their potential clinical application.

Our findings linking frailty defined by FP[170], EFS[184] and CFS[21] in haemodialysis patients with mortality are well described, but this study is the first to also confirm an association between FI and mortality. The association between vulnerability (also defined as intermediate frailty or pre-frail) and mortality is not as clear. While an association between vulnerability defined by FP and mortality was previously described,[170] no such association was observed by Garcia-Canton and colleagues using EFS (Hazard Ratio 1.45, 95% CI 0.75-2.79).[184] This may simply reflect an under-powered sample, with only 53/277 (19.1%) prevalent haemodialysis patients being defined as vulnerable. Identifying vulnerability status may be important as published studies from systematic reviews suggest intervention to prevent rather than reverse established frailty is likely to be more effective.[306-308] However, the evidence-base is limited to within community-dwelling older adults only and it is unclear if this evidence is directly translatable to haemodialysis patients. Identifying vulnerability is therefore likely to be important in identifying suitable candidate for multi-disciplinary intervention, but also (in the case of FI, EFS and CFS) help identify populations at risk for increased mortality independent of other factors.

Alfaadhel and colleagues explored CFS as a continuous scale as per original recommendations, observing an increasing Hazard Ratio of 1.22 (95% CI 1.04-1.43) for every 1-point increase in CFS.[21] In our cohort, frailty as a continuous variable retained a significant association with mortality and a significant trend of increasing hazard for death for each instrument studied. However, we cannot make any direct comparison between the strengths of these

associations, not least because each instrument operates on a different scale. Therefore, comparing like-for-like analyses between frailty tools and different cohorts is difficult and may explain some of the heterogenous outcomes observed in the literature.[17]

One of the important considerations in our analysis is that studying associations and probabilities is not inter-changeable with studying prediction. Association provides a measure that relates to statistical inference for the overall population, while prediction for a binary outcome evaluates the correct classification of individual patients. Conflating the two can lead to confusion and erroneous interpretation of the data. Different techniques exist to ensure accurate estimates of predictive accuracy are reported but a review of the current scientific literature demonstrates significant overlap.[309] For clinical decision-makers, strong claims on the predictive utility of a frailty tool in haemodialysis patients might result in increased willingness to screen high-risk patients to predict mortality. However, if the original study claimed predictive utilities based on association statistics (related to a population sample), it is impossible to determine how well a frailty tool will classify patients individually without performing the appropriate analyses. Thus, conflating association with prediction could potentially subject patients to unnecessary screening and lead to significant resource wastage. In the FITNESS cohort, mortality probabilities as evidenced by C-statistics appear comparably unsatisfactory across all tools. All instruments demonstrated good NPV but poor PPV for mortality, suggesting they are much better at identifying individuals within this cohort at least risk of dying than those who may be at greater risk. It is important to note that frailty instruments were not originally designed to be predictors of poor outcomes, although they are increasingly used as such in clinical settings. This is most overt in recent guidance upon

treatment escalation decision-making for inpatients with COVID-19, which has since been amended significantly.[53]

Should this approach be extended to the haemodialysis setting, this may risk excluding patients from potentially appropriate intervention - including transplantation - based upon an incomplete understanding of frailty and its sequelae. McAdams-DeMarco and colleagues found that transplant recipients initially became frailer before improving to above pre-transplant levels of function,[310] further complicating the notion of frailty as a barrier to intervention. Whilst categorising frailty is of undoubted use in epidemiological study, our analyses should prompt critical discussion about the use of frailty as a surrogate for futility in individual patients, lest frailty become a self-fulfilling prophecy for adverse outcomes.

While any measurement must accurately identify frailty, they require additional qualities as reported by Clegg and colleagues;[311] (1) an ability to reliably predict adverse clinical outcomes; (2) an ability to reliably predict response to potential therapies; and, (3) be supported by a biological causative theory. Our data do not support or study the use of frailty tools as predictors of mortality, but there are many other relevant outcomes to be explored such as quality of life, cognition, disability, and hospital admission. Further work with the FITNESS project will examine associations with these other important outcomes, explore predictive discriminatory abilities using additional data sets and study the response to potential therapies. However, our current understanding of the underlying biological mechanisms of frailty remain poorly understood.[312] It is also unclear if the underlying biology of frailty is different for haemodialysis patients versus the general population. Further work is required across all three of the above domains to allow frailty scoring to be of value in the

delivery of care for kidney failure patients. We may speculate that frailty could be a useful tool to identify populations and/or individual haemodialysis recipients that may benefit from further targeted intervention, such as physiotherapy or exercise programs. Unless, and until, such interventions are proven to be beneficial, the kidney community risks screening our patients for a condition we do not fully understand and cannot yet effectively treat.

One of the major strengths of our study is the multitude of frailty tools under comparison in a large prevalent cohort, featuring a diverse mix of demographics, co-morbidities and socio-economic backgrounds representative of local demographics as per registry data.[276] This provides reassurance our research findings are translatable to real-world cohorts locally and nationally. However, frailty characteristics may not be translatable across international cohorts and our data should be interpreted with caution in non-English populations. Our work should stimulate interest in multinational studies of frailty to compare frailty status by standardised criteria, to understand to what extent the burden and sequelae of frailty differ between populations. Other limitations include the single cross-sectional assessment of frailty, which is important as frailty is a dynamic state. For example, Johansen and colleagues observed year-by-year variability in frailty status defined by surrogates and components of the Fried Phenotype, with equal numbers improving or worsening.[313] Our work focussed on a prevalent population and, considering the significant burden of frailty identified, it may be prudent in future to consider incident haemodialysis patients or people approaching kidney failure for further investigation as a strategy to prevent frailty in this high-risk cohort. Our assessment of CFS was based upon analysis of responses to ADL questionnaires, rather than from clinical interview followed by MDT discussion as originally designed,[27] which may limit applicability to other studies. However, we would argue that given the increasing use of ADLs

to guide CFS in clinical practice, we would argue the potential for undue bias in our approach is small. In a further limitation, frailty was conceived and validated in elderly cohorts, whereas this cohort included haemodialysis recipients >18 years. It should be noted that in so doing we may dilute the impact of frailty upon mortality; the effect of frailty may be more keenly felt in older haemodialysis recipients. Finally, while identifying frailty is important from a risk counselling perspective alone, identifying frailty/vulnerability for risk stratification will have greater value by identifying high-risk individuals for targeted interventions but no evidence-base for this currently exists. The feasibility of facilitating exercise[247] or nutritional[314] interventions on frail haemodialysis patients to improve frailty scores have been observed but the benefits of a multi-disciplinary intervention, combining physical and psychological components, currently lacks evidence.

To conclude, frailty in haemodialysis cohorts is both highly prevalent and associated with mortality, independent of demographics, co-morbidity and disability. However, mortality probabilities are poor across all frailty instruments studied. As such, grouping frailty into categories may be more useful at a population level than for guiding individual clinical decisions, where considering frailty as a continuum may be more meaningful. Further study is warranted, to both understand the underlying biological mechanisms of the significant burden of frailty among haemodialysis populations and to consider the most appropriate interventional strategy and/or target to improve outcomes. In the meantime, we would caution against using frailty as a surrogate for futility or convoluting associations with prediction capability.

6.7 Tables

Table 6-1: Baseline demographics of FITNESS study participants

Parameter		Total cohort	Participants identified as frail by:			
			FP	FI	EFS	CFS
Participants identified as frail (% of total cohort)		-	203 (41.9%)	307 (63.3%)	244 (50.3%)	261 (53.8%)
Median Age		63 (53-74)	67 (56-77)	63 (54-75)	63 (53-74.5)	65 (55-76)
Ethnicity	*White*	281 (57.9%)	121 (59.6%)	174 (56.7%)	132 (54.1%)	144 (55.2%)
	South Asian	115 (23.7%)	51 (25.1%)	80 (26.1%)	61 (25.0%)	71 (27.2%)
	Black	76 (15.7%)	27 (13.3%)	46 (15.0%)	47 (19.3%)	41 (15.7%)
	Other	13 (2.7%)	4 (2.0%)	7 (2.3%)	4 (1.6%)	5 (1.9%)
Male		284 (58.6%)	106 (52.2%)	165 (53.8%)	127 (52.1%)	136 (52.1%)
Median BMI		26.8 (23.2-32.4)	27.8 (22.7-33.6)	27.9 (23.1-33.2)	27.7 (23.1-33.6)	27.9 (23.2-33.7)
Cause of kidney failure*	*Diabetes*	114 (23.5%)	64 (31.5%)	86 (28.0%)	71 (29.1%)	81 (31.0%)
	Ischaemic	38 (7.8%)	18 (8.9%)	27 (8.8%)	20 (8.2%)	24 (9.2%)
	Hypertension	39 (8.4%)	14 (6.9%)	22 (7.2%)	21 (8.6%)	17 (6.5%)
	IgA	37 (7.6%)	12 (5.9%)	21 (6.8%)	19 (7.8%)	17 (6.5%)
	PKD	28 (5.8%)	7 (3.5%)	14 (4.6%)	11 (4.5%)	11 (4.2%)
	FSGS	24 (5.0%)	10 (4.9%)	13 (4.2%)	13 (5.3%)	10 (3.8%)
	Reflux	17 (3.5%)	11 (5.4%)	12 (3.9%)	10 (4.1%)	10 (3.8%)
	Obstructive	16 (3.3%)	7 (3.5%)	8 (2.6%)	7 (2.9%)	6 (2.3%)
	AAV	15 (3.1%)	5 (2.5%)	6 (2.0%)	5 (2.1%)	4 (1.5%)
	Interstitial Nephritis	10 (2.1%)	4 (2.0%)	5 (1.6%)	3 (1.2%)	4 (1.5%)
	Myeloma	10 (2.1%)	2 (1.0%)	5 (1.6%)	3 (1.2%)	2 (0.8%)
	Other	86 (17.7%)	36 (17.7%)	60 (19.5%)	46 (18.9%)	47 (18.0%)
	Unknown	68 (14.0%)	23 (11.3%)	40 (13.0%)	28 (11.5%)	37 (14.2%)
Medical co-morbidities	*MI*	98 (20.2%)	53 (26.1%)	73 (23.8%)	61 (25.0%)	64 (24.5%)
	Heart failure	52 (10.7%)	24 (11.8%)	35 (11.4%)	31 (12.7%)	33 (12.6%)
	Stroke	57 (11.8%)	36 (17.7%)	43 (14.0%)	37 (15.2%)	40 (15.3%)

	PVD	47 (9.7%)	27 (13.3%)	36 (11.7%)	26 (10.7%)	32 (12.3%)
	Cancer	56 (11.6%)	18 (8.9%)	34 (11.1%)	25 (10.3%)	26 (10.0%)
Smoking history	*Current*	68 (14.1%)	28 (13.9%)	41 (13.4%)	36 (14.8%)	30 (11.5%)
	Previous	132 (27.3%)	51 (25.3%)	78 (25.5%)	59 (24.3%)	68 (26.2%)
	Never	284 (58.7%)	123 (60.9%)	187 (61.1%)	148 (60.9%)	162 (62.3%)
Median Charlson Score**		4 (3-6)	5 (4-7)	5 (3-6)	5 (3-6)	5 (4-7)
Dialysis details	*HD vintage (median months)*	37 (17-76)	49 (22-93)	41 (18-82)	35 (16-77)	41 (20-81)
	Line	113 (23.3%)	54 (26.6%)	77 (25.1%)	67 (27.5%)	66 (25.3%)
	Kt/V	1.6 (1.4-1.9)	1.6 (1.4-1.9)	1.6 (1.4-1.9)	1.6 (1.4-1.9)	1.6 (1.4-1.9)
Transplant list status	*Active*	58 (12.0%)	11 (5.4%)	27 (8.8%)	20 (8.2%)	22 (8.4%)
	Suspended	15 (3.1%)	2 (1.0%)	9 (2.9%)	6 (2.5%)	6 (2.3%)
	Not listed	412 (85%)	190 (93.6%)	271 (88.3%)	218 (89.4)	233 (89.3%)
% Employment Status	*Employed*	69 (14.3%)	5 (2.5%)	16 (5.2%)	13 (5.4%)	8 (3.1%)
	Unemployed	148 (30.6%)	67 (33.2%)	114 (37.3%)	94 (38.7%)	90 (34.6%)
	Retired	267 (55.2%)	130 (64.4%)	176 (57.5%)	136 (56.0%)	162 (62.3%)
% Job Role***	*Unskilled Manual*	181 (39.3%)	93 (48.4%)	131 (45.8%)	101 (44.5%)	111 (45.7%)
	Skilled Manual	101 (21.9%)	37 (19.3%)	58 (20.3%)	49 (21.6%)	51 (21.0%)
	Clerical	52 (11.3%)	24 (12.5%)	33 (11.5%)	27 (11.9%)	24 (9.9%)
	Managerial	46 (10.0%)	14 (7.3%)	21 (7.3%)	18 (7.9%)	20 (8.2%)
	Professional	81 (17.6%)	24 (12.5%)	43 (15.0%)	32 (14.1%)	37 (15.2%)
% Education Level	*High School*	342 (70.7%)	153 (75.7%)	229 (74.8%)	185 (76.1%)	196 (75.4%)
	College/Sixth Form	92 (19.0%)	39 (19.3%)	54 (17.7%)	41 (16.9%)	43 (16.5%)
	University	50 (10.3%)	10 (5.0%)	23 (7.5%)	17 (7.0%)	21 (8.1%)
Residence	*Own home*	462 (95.9%)	188 (93.1%)	288 (94.4%)	224 (93.0%)	244 (94.2%)
	Warden-Controlled Flat	12 (2.5%)	7 (3.5%)	10 (3.3%)	11 (4.6%)	9 (3.5%)
	Residential Home	5 (1.0%)	4 (2.0%)	4 (1.3%)	4 (1.7%)	3 (1.2%)
	Nursing Home	3 (0.6%)	3 (1.5%)	3 (1.0%)	2 (0.8%)	3 (1.2%)

% With Professional Carers****	36 (7.8%)	31 (16.1%)	35 (12.0%)	30 (13.0%)	36 (14.6%)

*Some participants had >1 cause of kidney failure listed. **Chronic kidney disease omitted from Charlson Score. ***Current job or previous job if unemployed/retired. ****For those living in own home.

Table 6-2: Frailty status and mortality status during follow up

Frailty instrument	Frailty status	Alive	Dead	p-value
Frailty Index	Robust	59 (93.7%)	4 (6.3%)	<0.001
	Vulnerable	185 (84.5%)	34 (15.5%)	
	Frail	130 (64.0%)	73 (36.0%)	
Frailty Phenotype	Robust	77 (97.5%)	2 (2.5%)	<0.001
	Vulnerable	82 (82.8%)	12 (17.2%)	
	Frail	215 (70.0%)	92 (30.0%)	
Edmonton Frail Scale	Robust	115 (92.7%)	9 (7.3%)	<0.001
	Vulnerable	86 (73.5%)	31 (26.5%)	
	Frail	173 (70.9%)	71 (29.1%)	
Clinical Frailty Scale	Robust	30 (90.9%)	3 (9.1%)	<0.001
	Vulnerable	162 (84.8%)	29 (15.2%)	
	Frail	182 (69.7%)	79 (30.3%)	

P-values obtained by Chi-squared.

Table 6-3: Cox Regression model of predictors for mortality (different models)

Model	Frailty Status	HR	Lower 95% C.I.	Upper 95% C.I.	P
Frailty Phenotype					
Unadjusted	*Vulnerable*	2.68	0.95	7.56	0.062
	Frail	**6.91**	**2.53**	**18.92**	**<0.001**
Model 1	*Vulnerable*	2.40	0.85	6.83	0.099
	Frail	**6.36**	**2.30**	**17.61**	**<0.001**
Model 2	*Vulnerable*	2.11	0.74	6.04	0.165
	Frail	**4.49**	**1.58**	**12.81**	**0.005**
Model 3	*Vulnerable*	1.91	0.66	5.52	0.234
	Frail	**3.74**	**1.25**	**11.16**	**0.018**
Frailty Index*					
Unadjusted	*Vulnerable*	**6.79**	**1.57**	**29.37**	**0.010**
	Frail	**13.60**	**3.35**	**55.20**	**<0.001**
Model 1	*Vulnerable*	**6.46**	**1.49**	**28.04**	**0.013**
	Frail	**14.07**	**3.45**	**57.40**	**<0.001**
Model 2	*Vulnerable*	**5.63**	**1.29**	**24.61**	**0.022**
	Frail	**10.13**	**2.45**	**41.95**	**0.001**
Model 3	*Vulnerable*	**4.83**	**1.10**	**21.25**	**0.037**
	Frail	**8.20**	**1.94**	**34.57**	**0.004**
Edmonton Frailty Scale					
Unadjusted	*Vulnerable*	**4.05**	**1.93**	**8.51**	**<0.001**
	Frail	**4.72**	**2.36**	**9.45**	**<0.001**
Model 1	*Vulnerable*	**4.03**	**1.91**	**8.49**	**<0.001**
	Frail	**5.38**	**2.66**	**10.92**	**<0.001**
Model 2	*Vulnerable*	**3.59**	**1.63**	**7.93**	**0.002**
	Frail	**3.64**	**1.67**	**7.94**	**0.001**
Model 3	*Vulnerable*	**3.27**	**1.48**	**7.25**	**0.003**
	Frail	**3.12**	**1.41**	**6.91**	**0.005**
Clinical Frailty Scale					
Unadjusted	*Vulnerable*	**3.23**	**1.56**	**6.70**	**0.002**
	Frail	**4.34**	**2.31**	**8.15**	**<0.001**
Model 1	*Vulnerable*	**2.88**	**1.37**	**6.05**	**0.005**
	Frail	**4.25**	**2.24**	**8.08**	**<0.001**
Model 2	*Vulnerable*	**2.60**	**1.19**	**5.69**	**0.017**
	Frail	**3.40**	**1.69**	**6.83**	**0.001**
Model 3	*Vulnerable*	**2.36**	**1.07**	**5.18**	**0.032**
	Frail	**2.84**	**1.38**	**5.84**	**0.005**

Model 1 Adjusted for age, gender, ethnicity, IMD quintile

Model 2 Adjusted for age, gender, ethnicity, IMD quintile, BMI, Charlson Index [CKD omitted], number of admissions in year prior to recruitment, haemodialysis vintage, medication number, smoking status [current, ex-, or never], serum albumin

Model 3 Adjusted for age, sex, ethnicity, body mass index, index of multiple deprivation, Charlson comorbidity index, number of hospitalisation episodes, polypharmacy, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status

Table 6-4: Cox Regression model of predictors for mortality (fully adjusted model)

Variable		FP	FI	EFS	CFS
Frailty status	Robust (REF)	-	-	-	-
	Vulnerable	1.91 (0.66-5.52)	**4.83 (1.10-21.25)**	**3.27 (1.48-7.25)**	**2.36 (1.07-5.18)**
	Frail	**3.74 (1.25-11.16)**	**8.20 (1.94-34.57)**	**3.12 (1.41-6.91)**	**2.84 (1.38-5.84)**
Age (in years)		0.99 (0.97-1.01)	1.00 (0.98-1.02)	1.00 (0.97-1.02)	0.99 (0.97-1.01)
Female sex		0.90 (0.60-1.34)	0.88 (0.59-1.31)	0.89 (0.59-1.33)	0.89 (0.59-1.33)
Ethnicity	White (REF)	-	-	-	-
	South Asian	0.58 (0.32-1.05)	0.58 (0.32-1.04)	0.57 (0.31-1.03)	**0.55 (0.31-1.00)**
	Black	0.98 (0.56-1.72)	0.94 (0.54-1.64)	0.88 (0.51-1.55)	0.92 (0.53-1.62)
	Other	0.54 (0.07-4.07)	0.53 (0.07-3.99)	0.62 (0.08-4.66)	0.63 (0.08-4.80)
Body mass index (kg/m^2)		1.00 (0.97-1.02)	0.99 (0.97-1.02)	0.99 (0.97-1.02)	1.00 (0.97-1.02)
Index of multiple deprivation	1 (REF)	-	-	-	-
	2	1.01 (0.59-1.74)	1.04 (0.60-1.78)	1.12 (0.65-1.92)	1.03 (0.60-1.77)
	3	1.39 (0.80-2.40)	1.37 (0.80-2.34)	1.31 (0.76-2.25)	1.28 (0.75-2.20)
	4	0.76 (0.34-1.74)	0.75 (0.33-1.71)	0.76 (0.34-1.74)	0.78 (0.34-1.78)
	5	0.84 (0.37-1.92)	0.82 (0.36-1.89)	0.82 (0.35-1.89)	0.81 (0.35-1.85)
	Unknown	0.93 (0.36-2.40)	1.09 (0.42-2.83)	1.07 (0.41-2.77)	0.99 (0.38-2.57)
Charlson co-morbidity index*		**1.18 (1.06-1.32)**	**1.16 (1.04-1.29)**	**1.16 (1.04-1.30)**	**1.17 (1.05-1.31)**
Hospitalisation episode within 12-months		1.07 (0.98-1.17)	1.08 (0.98-1.18)	1.05 (0.96-1.15)	1.07 (0.98-1.17)
Number of medications		1.01 (0.95-1.07)	1.01 (0.95-1.07)	1.02 (0.96-1.08)	1.01 (0.95-1.07)
Smoking	Smoker (REF)	-	-	-	-
	Ex-smoker	1.29 (0.70-2.38)	1.36 (0.73-2.52)	1.35 (0.73-2.50)	1.28 (0.69-2.37)
	Never smoked	0.80 (0.44-1.45)	0.84 (0.46-1.55)	0.84 (0.46-1.54)	0.81 (0.44-1.48)
Albumin (g/L)		0.96 (0.92-1.00)	**0.95 (0.91-0.99)**	**0.95 (0.92-0.99)**	**0.95 (0.91-0.99)**
Use of walking aids		1.28 (0.77-2.15)	1.36 (0.84-2.20)	1.56 (0.97-2.53)	1.45 (0.89-2.38)
Time on dialysis (days)		1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Active on transplant waiting list		0.15 (0.02-1.11)	0.17 (0.02-1.26)	0.15 (0.02-1.11)	0.16 (0.02-1.19)

Bold text indicates significance at P<0.05 level. *CKD omitted.

Table 6-5: Cox Regression model of predictors of mortality (different models using frailty scores as continuous variables)

Model	HR	Lower 95% C.I.	Upper 95% C.I.	P
Frailty Phenotype				
Unadjusted	**1.48**	**1.29**	**1.69**	**<0.001**
Model 1	**1.47**	**1.28**	**1.69**	**<0.001**
Model 2	**1.31**	**1.12**	**1.53**	**0.001**
Model 3	**1.25**	**1.05**	**1.48**	**0.011**
*Frailty Index**				
Unadjusted	**1.28**	**1.18**	**1.40**	**<0.001**
Model 1	**1.34**	**1.23**	**1.47**	**<0.001**
Model 2	**1.27**	**1.14**	**1.41**	**<0.001**
Model 3	**1.23**	**1.10**	**1.38**	**<0.001**
Edmonton Frailty Scale				
Unadjusted	**1.18**	**1.10**	**1.26**	**<0.001**
Model 1	**1.20**	**1.12**	**1.28**	**<0.001**
Model 2	**1.12**	**1.03**	**1.22**	**0.006**
Model 3	**1.09**	**1.00**	**1.19**	**0.041**
Clinical Frailty Scale				
Unadjusted	**1.47**	**1.27**	**1.69**	**<0.001**
Model 1	**1.52**	**1.30**	**1.77**	**<0.001**
Model 2	**1.38**	**1.16**	**1.64**	**<0.001**
Model 3	**1.31**	**1.09**	**1.57**	**0.004**

Model 1 Adjusted for age, gender, ethnicity, IMD quintile

Model 2 Adjusted for age, gender, ethnicity, IMD quintile, BMI, Charlson Index [CKD omitted], number of admissions in year prior to recruitment, haemodialysis vintage, medication number, smoking status [current, ex-, or never], serum albumin

Model 3 Adjusted for age, sex, ethnicity, body mass index, index of multiple deprivation, Charlson comorbidity index, number of hospitalisation episodes, polypharmacy, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status

*Scaled for each 0.1 rise in FI.

All results significant at $p<0.05$ level.

Table 6-6: Fine and Gray subdistribution hazards model of mortality, with any kidney transplant as a competing event. Frailty as ordinal variable

Model	Frailty Status	SHR	Lower 95% C.I.	Upper 95% C.I.	P
Frailty Phenotype					
Unadjusted	*Vulnerable*	**3.38**	**1.05**	**10.93**	**0.04**
	Frail	**9.01**	**2.86**	**28.44**	**<0.001**
Model 1	*Vulnerable*	3.06	0.91	10.30	0.071
	Frail	**8.38**	**2.52**	**27.90**	**0.001**
Model 2	*Vulnerable*	2.65	0.78	8.99	0.118
	Frail	**5.77**	**1.67**	**19.90**	**0.006**
Model 3	*Vulnerable*	2.40	0.70	8.15	0.162
	Frail	**4.79**	**1.35**	**16.98**	**0.015**
Frailty Index					
Unadjusted	*Vulnerable*	**6.00**	**1.37**	**26.26**	**0.02**
	Frail	**13.42**	**3.30**	**54.48**	**<0.001**
Model 1	*Vulnerable*	**5.71**	**1.30**	**25.20**	**0.021**
	Frail	**14.02**	**3.38**	**58.23**	**<0.001**
Model 2	*Vulnerable*	**4.87**	**1.10**	**21.63**	**0.037**
	Frail	**9.90**	**2.34**	**41.91**	**0.002**
Model 3	*Vulnerable*	4.08	0.90	18.50	0.068
	Frail	**7.81**	**1.77**	**34.45**	**0.007**
Edmonton Frailty Scale					
Unadjusted	*Vulnerable*	**4.39**	**2.03**	**9.50**	**<0.001**
	Frail	**5.29**	**2.57**	**10.89**	**<0.001**
Model 1	*Vulnerable*	**4.37**	**1.99**	**9.62**	**<0.001**
	Frail	**6.06**	**2.82**	**13.04**	**<0.001**
Model 2	*Vulnerable*	**3.94**	**1.71**	**9.07**	**0.001**
	Frail	**4.08**	**1.79**	**9.27**	**0.001**
Model 3	*Vulnerable*	**3.60**	**1.56**	**8.29**	**0.003**
	Frail	**3.50**	**1.50**	**8.15**	**0.004**
Clinical Frailty Scale					
Unadjusted	*Vulnerable*	**3.36**	**1.57**	**7.18**	**0.002**
	Frail	**4.68**	**2.42**	**9.05**	**<0.001**
Model 1	*Vulnerable*	**2.99**	**1.36**	**6.59**	**0.007**
	Frail	**4.61**	**2.35**	**9.03**	**<0.001**
Model 2	*Vulnerable*	**2.69**	**1.18**	**6.18**	**0.019**
	Frail	**3.66**	**1.76**	**7.62**	**0.001**
Model 3	*Vulnerable*	**2.42**	**1.04**	**5.63**	**0.041**
	Frail	**3.01**	**1.41**	**6.46**	**0.005**

Model 1 Adjusted for age, gender, ethnicity, IMD quintile

Model 2 Adjusted for age, gender, ethnicity, IMD quintile, BMI, Charlson Index [CKD omitted], number of admissions in year prior to recruitment, haemodialysis vintage, medication number, smoking status [current, ex-, or never], serum albumin

[Model 3] Adjusted for age, sex, ethnicity, body mass index, index of multiple deprivation, Charlson comorbidity index, number of hospitalisation episodes, polypharmacy, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status

Bold text indicates significant at P <0.05 level

Table 6-7: Fine and Gray subdistribution hazards model of mortality, with any kidney transplant as a competing event. Frailty as continuous variable

Model	SHR	Lower 95% C.I.	Upper 95% C.I.	P
Frailty Phenotype				
Unadjusted	1.51	1.33	1.71	<0.001
Model 1	1.50	1.31	1.72	<0.001
Model 2	1.33	1.13	1.56	0.001
Model 3	1.27	1.06	1.52	0.011
*Frailty Index**				
Unadjusted	1.30	1.20	1.40	<0.001
Model 1	1.36	1.25	1.48	<0.001
Model 2	1.28	1.16	1.42	<0.001
Model 3	1.24	1.11	1.38	<0.001
Edmonton Frailty Scale				
Unadjusted	1.19	1.12	1.26	<0.001
Model 1	1.21	1.13	1.29	<0.001
Model 2	1.13	1.04	1.22	0.006
Model 3	1.10	1.00	1.20	0.041
Clinical Frailty Scale				
Unadjusted	1.51	1.31	1.73	<0.001
Model 1	1.56	1.34	1.81	<0.001
Model 2	1.42	1.20	1.68	<0.001
Model 3	1.34	1.13	1.59	0.001

Model 1 Adjusted for age, gender, ethnicity, IMD quintile

Model 2 Adjusted for age, gender, ethnicity, IMD quintile, BMI, Charlson Index [CKD omitted], number of admissions in year prior to recruitment, haemodialysis vintage, medication number, smoking status [current, ex-, or never], serum albumin

Model 3 Adjusted for age, sex, ethnicity, body mass index, index of multiple deprivation, Charlson comorbidity index, number of hospitalisation episodes, polypharmacy, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status. *Scaled for each 0.1 rise in FI. All results significant at $p<0.05$ level.

Table 6-8: Sensitivity, specificity, positive predictive value and negative predictive value of frailty instruments for 1-year mortality.

	Sensitivity	**Specificity**	**PPV**	**NPV**
Frailty Index	87.23%	39.27%	13.36%	96.63%
Frailty Phenotype	63.83%	60.50%	14.78%	93.97%
Edmonton Frail Scale	65.96%	51.37%	12.70%	93.36%
Clinical Frailty Scale	72.34%	49.33%	13.03%	94.20%
P	**0.049**	**<0.001**	0.950	0.975

P-values shown for within-column differences, obtained by chi-squared.

Chapter 7:

Frailty and hospitalisation in haemodialysis recipients: A comparison of commonly used frailty tools.

7.1 Extent of Personal Contribution

I coordinated all study visits with participants and dialysis unit staff. I recruited participants, and collected all baseline data with the support of Dr Gonzalo Correa, Dr Muhammad Qasim, and Dr Adnan Sharif. All colleagues were supervised by me in their data collection, and I was responsible for maintaining training and personnel logs in the site file.

Ms Felicity Evison, and Ms Suzy Gallier were responsible for interrogation of EPR for IMD Quintile assessment and HES/OPCS/ONS data for mortality and hospitalisation follow-up. I performed all subsequent data cleaning, integrity, analyses, and interpretation with guidance from Dr Adnan Sharif.

The first draft of the manuscript was written by myself and I was responsible for all edits and revisions.

7.2 Abstract

7.2.1 Background

Frailty is associated with poor outcomes in haemodialysis recipients, but commonly used frailty tools have not been compared for their association with hospitalisation.

7.2.2 Methods

We performed a prospective cohort study of prevalent haemodialysis recipients linked to national datasets for long-term clinical outcomes including hospitalisation. The following frailty instruments were compared; 1) Frailty Phenotype (FP), 2) Frailty Index (FI), 3) Edmonton Frail Scale (EFS) and 4) Clinical Frailty Scale (CFS). Time-to-event outcomes analysed with Cox's Proportional Hazards Model, and count outcomes analysed using negative binomial regression. Frailty tools were treated both as ordinal (classified as Frail, Vulnerable and Robust) and continuous variables.

7.2.3 Results

We observed 111 (22.9%) deaths, 1242 admissions, and 10175 nights spent in hospital over a median follow-up of 678 days. Increasing frailty was associated with admissions, total nights in hospital and nights in hospital per admission on univariable analysis for all tools. On multivariable analysis however, only the CFS showed significant association with total number of admissions during follow-up; conversely, it was also the only tool not to show association with nights spent in hospital. Association between frailty and hospitalisation was more variable between frailty tools when split into categories of increasing frailty.

7.2.4 Conclusion

Frailty was associated with hospitalisation in haemodialysis recipients, with significant variation between frailty tools. Our data supports treating frailty as a continuum rather than splitting into discrete categories for haemodialysis patients. Frailty tools are not analogous in haemodialysis patients, strengthening the case for consensus on the optimal tool for clinical application.

7.3 Introduction

Frailty is highly prevalent in haemodialysis recipients, but due to the lack of consensus on the optimal frailty instrument, has been subject to heterogenous reporting. Our previous work has shown that estimates of frailty prevalence also vary significantly within a haemodialysis population according to the instrument, ranging from 42% for FP to 63% for the FI. Furthermore, agreement between these instruments on individual frailty status was weak.[272]

Any consensus on the optimal frailty instrument in haemodialysis settings needs to consider each tool's association with negative outcomes. Frailty has principally been studied in haemodialysis with regards to mortality[21,170,184], but this is not the only important negative outcome for haemodialysis recipients; hospitalisation occurs at a rate of > 1 admission per patient-year.[188] Frailty has been shown to increase hospitalisation risk, both in general elderly populations[17] and in haemodialysis recipients assessed with the FP and EFS.[170,184] To our knowledge, this data has not been validated in a different haemodialysis cohort and the associations between the FI and CFS with hospitalisation have not been tested. It is therefore important to compare the association of these tools with hospitalisation, to allow a more holistic view of both the burden of frailty and the performance of the individual frailty screening tools. Here we report the associations of frailty by each of the above tools with hospital admission, and length of stay in a large prospective UK haemodialysis cohort.

7.4 Materials and Methods

FITNESS study design, eligibility, consent and baseline data acquisition are presented in detail in Chapters Chapter 2: and 2.2.

7.4.1 Frailty definitions

Frailty definitions are detailed in section 3.7, with baseline assessments used to determine frailty status. In summary the following frailty instruments were used; 1) Frailty Phenotype (FP), 2) Frailty Index (FI)[270], 3) Edmonton Frail Scale (EFS) and 4) Clinical Frailty Scale (CFS). Patients were classified at baseline with the following frailty definitions; FP range 0-5 (frail ≥3, vulnerable 1-2, robust 0), FI range 0-1 (frail ≥0.24, vulnerable >0.12 to ≤0.24, robust ≤0.12), EFS range 0-17 (frail ≥8, vulnerable 6-7, robust <6), and CFS range 1-9 (frail ≥5, vulnerable 4, robust <4).

7.4.2 Recruitment

A power calculation was originally performed based upon US data,[168] assuming adjusted risk ratio of 2.24 for 1-year mortality and 1.56 for 1-year mortality and/or hospitalisation for frail versus non-frail patients receiving haemodialysis. A non-frail risk of 5% for 1-year mortality and a 40% risk of 1-year mortality/hospitalisation was assumed, powered to 0.8 and with a confidence interval of 0.95. A sample size of 602 was therefore considered to be robustly powered to demonstrate a difference in 1-year mortality or 150 patients to be powered for 1-year mortality/hospitalisation. However, in agreement with the sponsor, recruitment of 602 participants was not felt to be feasible in this single centre, and a revised target of 500 participants to be recruited was set with follow up beyond 1-year.

7.4.3 Outcomes

Electronic patient records, Hospital Episode Statistics (HES), and Office of National Statistics data were interrogated for follow-up outcomes including hospitalisation and mortality (reported elsewhere). Attendance to hospital were defined as any hospital episode,

regardless of whether admitted. Admissions were defined as any hospital episode lasting ≥ 1 night. Primary diagnoses for each admission were recorded as these have been shown to be accurate for research purposes.[315] Primary diagnoses are reported both as raw diagnoses and – for ease of reporting and interpretation – grouped into; i) infection, ii) dialysis access, iii) dialysis indications/CKD 5, and iv) major adverse cardiovascular events (MACE). Explanatory notes and constituent HES codes are detailed in Supplementary Table 7-1: Admission groupings with constituent HES/ICD-10 and OPCS-4 codes. Any admissions or attendances involving a transfer between hospitals were considered as one continuous admission, with the length of stay for such admissions considered to be the time from admission to the first hospital to discharge from the final hospital.

7.4.4 Statistics

Statistical analysis was performed using STATA 17 (StataCorp 2021, Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) and R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). Categorical data were presented as numbers and percentages, with continuous variables reported as medians and interquartile ranges (IQRs). Incidence rate ratios were obtained for count data by Negative Binomial Regression, offset by length of follow-up, treating frailty variables both as ordinal – Frail, Vulnerable and Robust – and continuous variables. Negative binomial distribution was confirmed by interrogation of means and variances and visual interpretation of expected versus observed distribution plots. Zero-truncated negative binomial regression was used to calculate incidence rate ratios for length of admission, as by definition all admissions were of one night or more. All regressions were performed unadjusted and adjusted for an *a priori* list of covariables, considered based on a known or suspected relationship with dialysis-related admission (age, sex, ethnicity, body

mass index, index of multiple deprivation, Charlson comorbidity index, number of hospitalisation episodes, polypharmacy, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status).

Missing IMD quintile data were handled via a dummy variable. Other missing data were assumed missing at random and handled via listwise deletion as all other covariables had <1% data missing. A p value < 0.05 was considered significant in the statistical analysis.

7.5 Results

Figure 6-1 shows the PRISMA study flow of participant recruitment to the FITNESS study, with 485 prevalent haemodialysis patients with baseline frailty assessments and linkage to local electronic patient records and national datasets. Table 7-1 shows key demographics stratified by different frailty instruments at study recruitment. Participants were followed-up electronically for a median of 678 (IQR: 531-812) days and all participants had a minimum potential follow-up of 365 days, barring mortality.

7.5.1 Admission Diagnoses

Total participant follow-up was 862.1 patient-years, during which there were 2729 attendances to hospital, 1242 admissions of at least one night's duration, and 10175 nights spent in hospital. 382 (78.8%) participants had at least one hospital admission during follow-up, and the median number of admissions was 2 (IQR: 0-4). There were 700 admissions within one year of recruitment, divided amongst 288 (59.4%) participants; the median number of admissions within one year of recruitment was 1 (IQR: 0-2).

Primary admission diagnoses were related to infection in 270 admissions (22.0%), dialysis access in 269 (21.9%), dialysis indications/CKD5 in 151 (12.3%), and MACE occurred in 46 (3.8%) of admissions. Table 7-2 shows the 10 most common primary diagnoses for all admissions.

7.5.2 Hospital Admissions and nights spent in hospital – frailty as a continuous variable

Incidence rate ratios (IRR) for hospital admission, total nights spent in hospital during follow-up, and mean nights in hospital per admission for frailty treated as a continuous variable are summarised in Table 7-3. Increasing frailty was associated with greater hospitalisations, total nights in hospital and mean nights per admission for all frailty instruments on univariable analysis. On multivariable analysis, only the CFS retained a significant IRR for hospitalisation, but it was also the only frailty tool not to retain significance for total or mean nights spent in hospital.

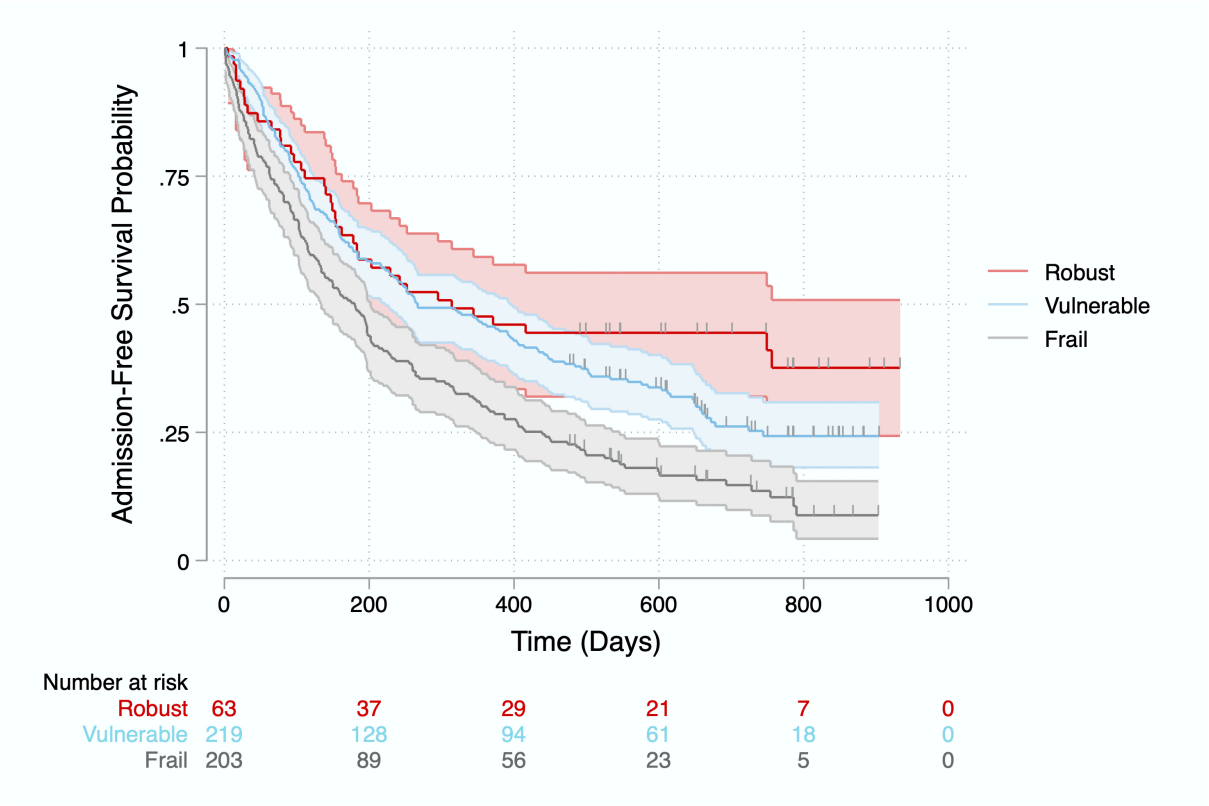


Figure 7-1: Unadjusted Kaplan-Meier of admission-free survival according to FP frailty status

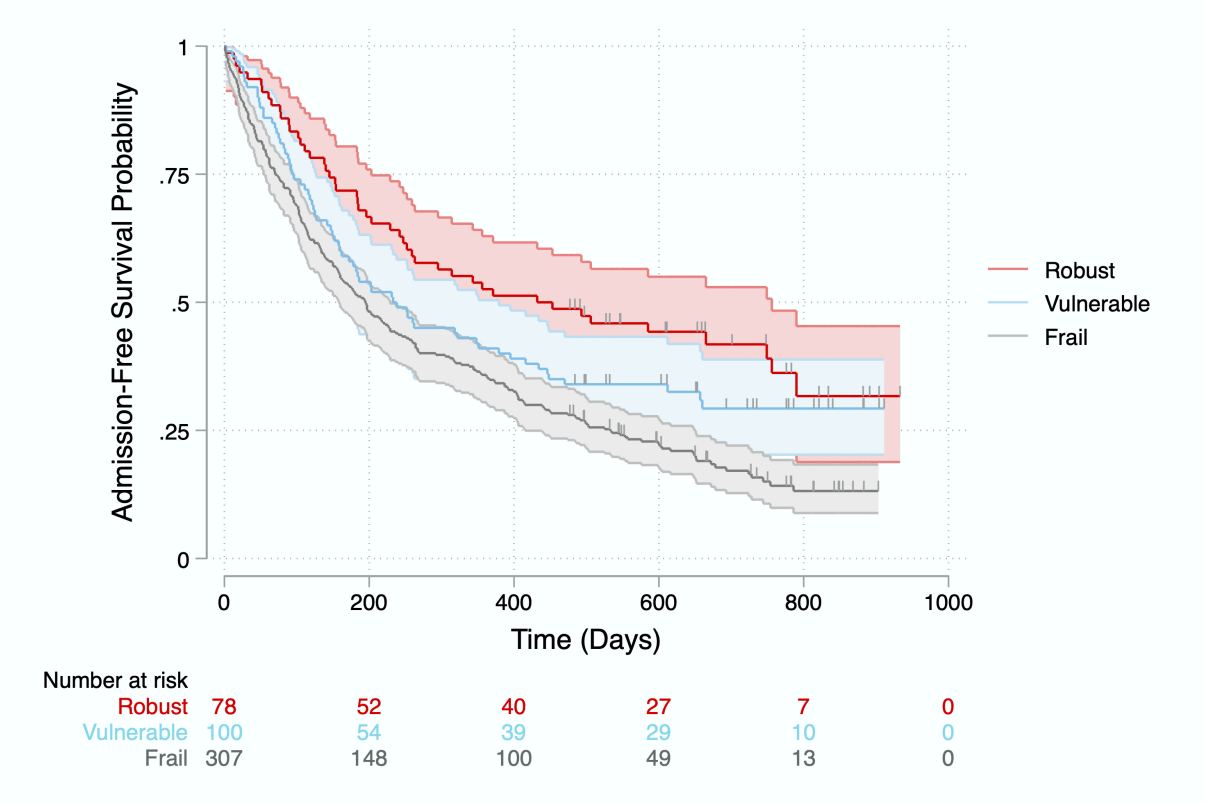


Figure 7-2: Unadjusted Kaplan-Meier of admission-free survival according to FI frailty status

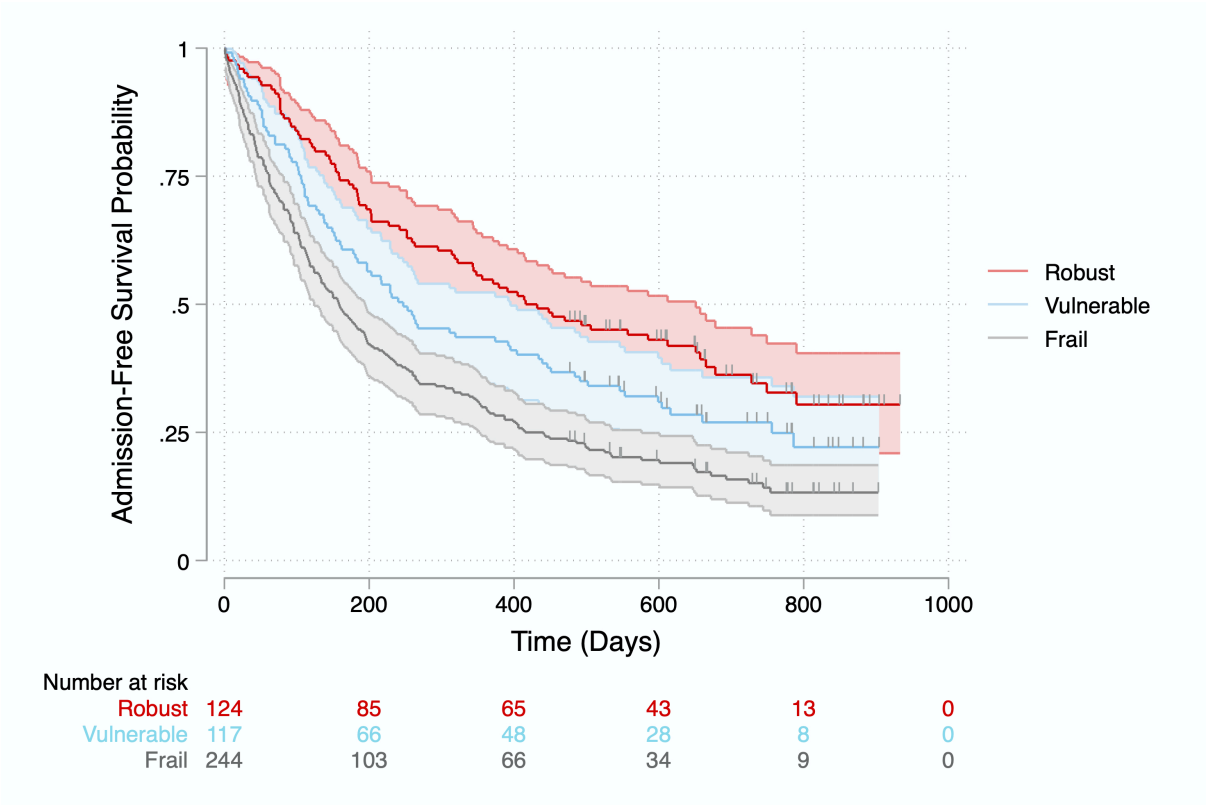


Figure 7-3: Unadjusted Kaplan-Meier of admission-free survival according to EFS frailty status

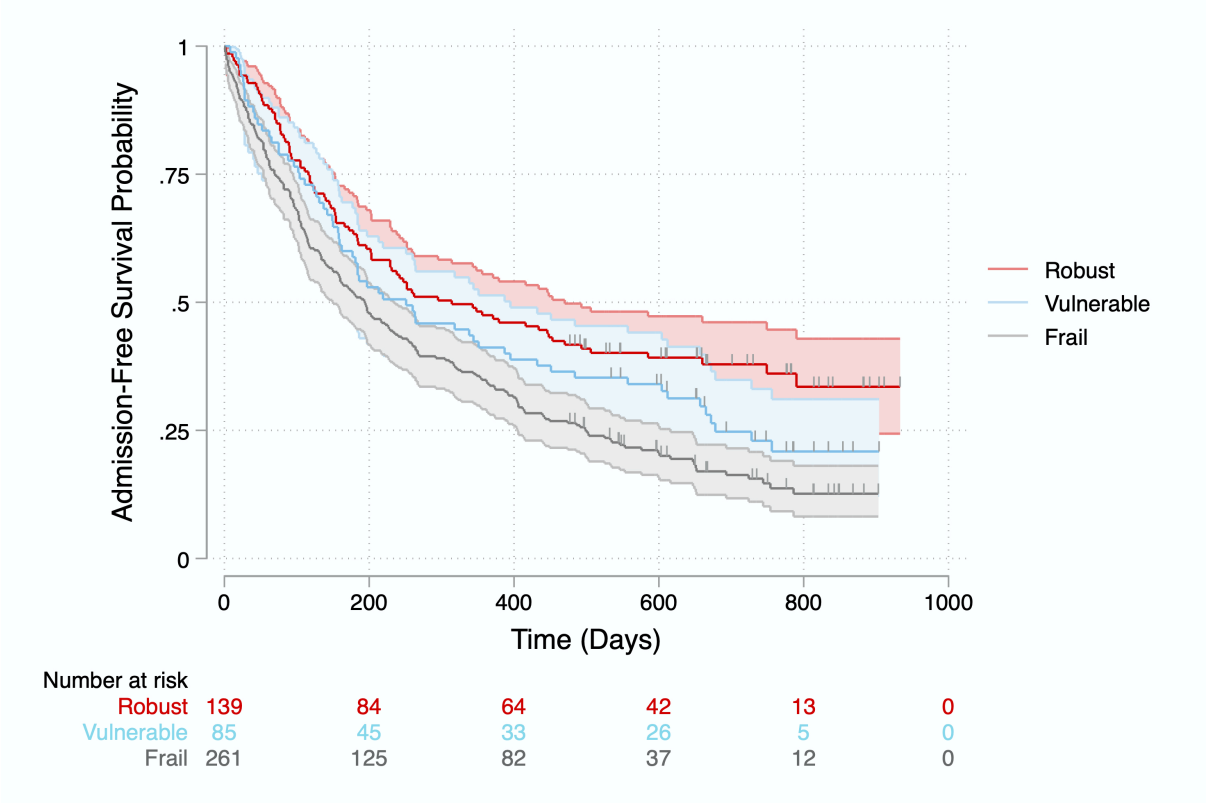


Figure 7-4: Unadjusted Kaplan-Meier of admission-free survival according to EFS frailty status

7.5.3 Hospital Admissions and nights spent in hospital – frailty as a categorical variable

Univariable Kaplan-Meier curves for admission-free survival by frailty status for each frailty tool studied are shown in Figure 7-1 to Figure 7-4. Table 7-3 and Figure 7-5 show that frailty was associated with increased admissions for all instruments on univariable analysis but retained this association only for the FI and CFS when adjusted for *a priori* covariables. Vulnerability was associated with increased hospital admissions on univariable analysis for the FI, EFS, and CFS, but not the FP. Vulnerability did not retain significant association with hospital admissions on multivariable analysis for any frailty tool.

Figure 7-5 also demonstrates that on univariable analysis, total nights in hospital during follow-up were higher for frailty however defined, but this association was only retained for the FI and EFS on multivariable analysis. Vulnerability by EFS and CFS was associated with greater nights spent in hospital, but only the EFS retained this when adjusted for important covariables.

Nights per admission were also associated with frailty on univariable analysis by all measures, but only the FP retained this on multivariable analysis. Only vulnerability by the EFS showed significant association with nights per admission on univariable analysis, but lost significance on adjusted analysis.

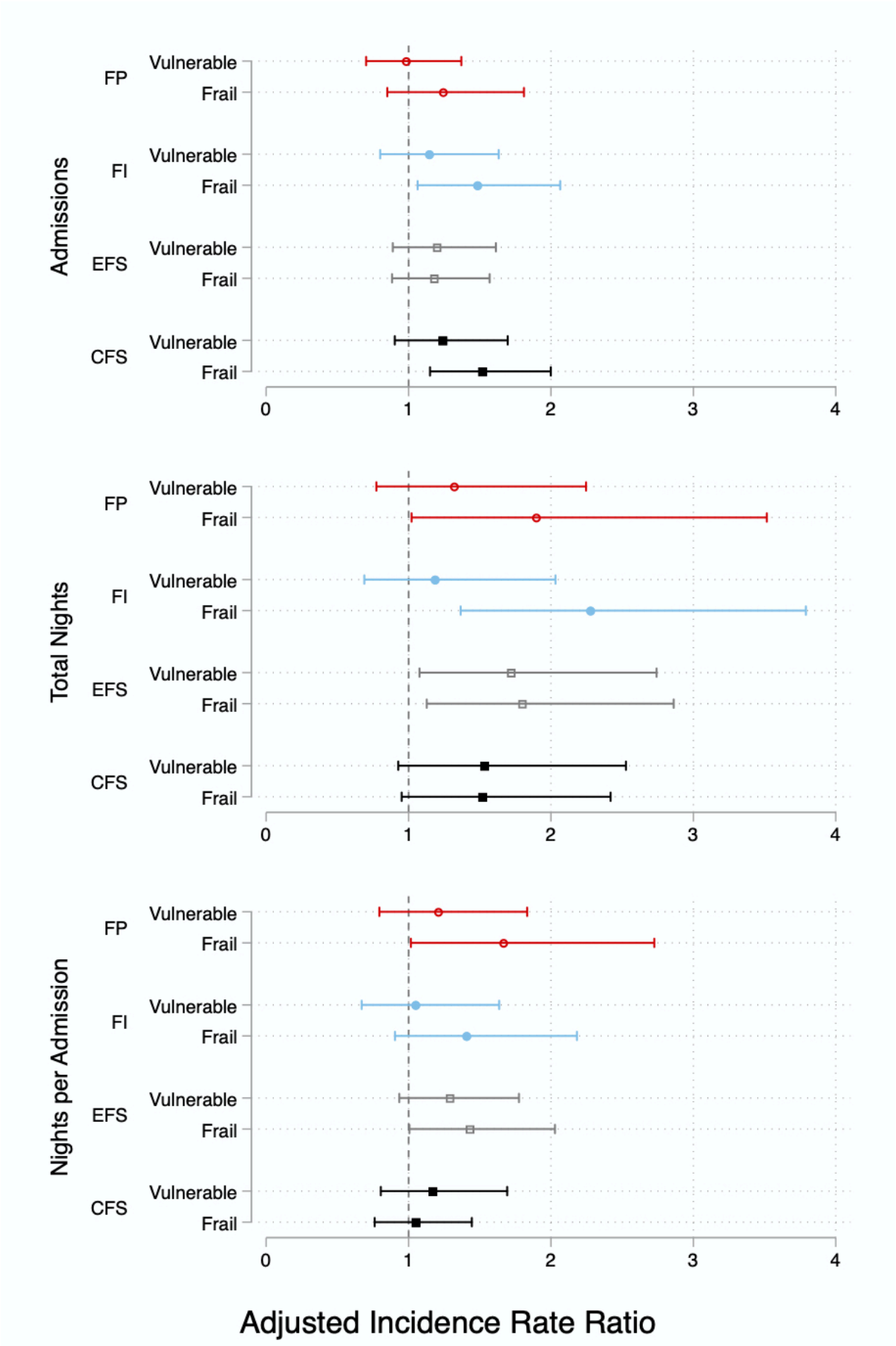


Figure 7-5: Incidence Rate Ratios of hospital admissions ≥ 1 night, total nights in hospital, and nights per hospital admission during follow-up

7.6 Discussion

Frailty is associated with negative outcomes in haemodialysis recipients.[17] However, heterogeneous assessment of frailty limits generalisability of findings across cohorts,[21,46,184,270] and our previous work has shown that agreement between frailty tools is weak.[272] The association between admissions and frailty by these common definitions have not previously been compared in haemodialysis. Here we show in a large single-centre cohort that haemodialysis recipients endure a high burden of hospitalisation regardless of frailty status. We also report differing associations of frailty with admission outcomes dependent upon the frailty tool used. When treated as continuous variables, only the CFS demonstrated association between increasing frailty and hospital admissions on adjusted analysis, but it was also the only tool not to be associated with total nights in hospital nor nights per admission. Interpretation of results becomes yet more challenging when frailty scores were split into robust, vulnerable, and frail categories. No single instrument demonstrated a significant association between frailty with all total admissions, total nights in hospital and nights in hospital per admission. These data prompt questions about the utility of frailty tools in risk assessment; the kidney community must establish what purposes we wish frailty assessment to serve, so that we may be able to reach consensus on which of these non-analogous instruments may be optimal for widespread use.

Frailty in haemodialysis has been principally studied regarding its association with mortality[21,170,184], but the high burden of hospitalisation in haemodialysis requires that frailty scores be assessed for their associations with this important negative outcome. To date, only the FP[170] and EFS[184] have been studied with relation to hospitalisation in haemodialysis, and no data have been published comparing frailty scores with regards to hospitalisation in

haemodialysis recipients. McAdams-DeMarco and colleagues found that hospitalisations were significantly higher in frail haemodialysis recipients by FP[170], but we were unable to replicate these findings on our adjusted analyses.

Garcia-Canton and colleagues found that both vulnerability and frailty by EFS were associated with greater hospitalisation, although there was little difference between the IRRs of these two categories[184]. In the FITNESS cohort by contrast, neither vulnerability nor frailty by EFS were associated with significantly higher rates of hospitalisation on adjusted analysis. It might be argued that for the EFS in FITNESS, the 95% confidence intervals only just cross the point of no effect, however these confidence intervals are not especially wide. Further, the FITNESS cohort is both larger and subject to longer median follow-up than our Spanish counterparts; thus, the likelihood of type 2 error fully explaining the lack of concordance between these two cohorts would appear small.

The inability of FITNESS to replicate results seen both in US and Spanish cohorts may be due to methodological differences. FITNESS controlled for a greater number of *a priori* covariables selected for adjusted analyses than our counterparts, and there were differences in the way frailty was defined between cohorts. Indirect comparison of frailty across different cohorts and healthcare systems is challenging. Apparent differences in observed frailty prevalence and outcomes between these studies therefore strengthen the case for a unified approach to frailty assessment in haemodialysis recipients.

Whilst splitting frailty into discrete categories may be helpful for communicating risk at a population level, these results must call into question the utility of broad frailty

categorisation to support clinical decisions about individual haemodialysis recipients. Far better perhaps to consider frailty as a continuum to support a more nuanced conversation about risk than to consider arbitrary thresholds where certain interventions are no longer considered appropriate. It is simpler however to pursue the latter approach, such as has been used in the context of treatment escalation during the COVID-19 pandemic[53].

Our data support treating frailty as a continuum rather than splitting into discrete categories. As a continuous variable, increasing frailty was associated with hospitalisation/mortality on adjusted analyses for all frailty tools. When split into categories, the associations between the frail groups and admissions and/or nights spent in hospital were frequently – though not always – lost on adjustment for important covariables. By contrast, when treated as a continuous variable, increasing frailty showed a more consistent association with these adverse outcomes on unadjusted and adjusted analyses. This may strengthen the case for widespread use of either the CFS or FI in haemodialysis cohorts; both tools were designed and validated to be used as continuous variables. The FI has the benefit of offering greater detail into frailty, but at the expense of being more challenging to administer and interpret[58]. For use at scale it may be more feasible to use the CFS, which was validated against the FI[27] but is much simpler to use.

FITNESS is to our knowledge the largest prospective cohort study to compare frequently used frailty tools in haemodialysis, and the first to compare their associations with hospitalisation. Further strengths include diversity of demographics, comorbidities and socio-economic backgrounds representative of local demographics.[276] However, the apparent differences in

association between frailty and hospitalisation and/or mortality and US[170] and Spanish[184] cohorts mandates our data should be interpreted with caution in non-English populations. Our work should stimulate interest in multinational studies of frailty to compare frailty status by standardised criteria, to elucidate the burden and associations of frailty across populations. A limitation of FITNESS is the single cross-sectional assessment, as frailty is a dynamic state, with year-by-year variability in frailty observed in a prospective US haemodialysis cohort.[313] There were small variations in application of frailty tool criteria from other studies, as summarised in Section 3.7. The CFS was derived from investigator interrogation of ADL questionnaire responses, rather than via CGA followed by multi-disciplinary discussion as in the original validation cohort.[27] In another limitation, some 95% confidence intervals crossed the point of no effect by small margins. This was particularly true for the IRRs of frailty as a categorical variable and raises the possibility of type II error. Finally, as we saw in the previous chapter, whilst these data describe associations with hospital admissions, they cannot support the notion of frailty as a 'predictor' of such adverse outcomes, and due caution should be exercised when considering the applicability of these findings to the individual haemodialysis recipient in clinical practice.

Further work from the FITNESS cohort will investigate the feasibility of a psychologically supported multi-disciplinary intervention into frailty. The kidney community must address the feasibility and efficacy of frailty intervention so that we may be able to use the results of frailty assessments to the advantage of our patients.

To conclude, this study shows that frailty is associated with hospitalisation/mortality, total number of admissions and nights spent in hospital for haemodialysis recipients. However, as

no individual frailty tool demonstrates association with all the patient-centred outcomes studied here, no firm recommendations can be made regarding the optimal tool to choose on the basis of hospitalisation data alone. Further work should include detailed analysis of other outcomes of interest, including quality of life.

Table 7-1: Baseline demographics of FITNESS study participants

Parameter		Total cohort	Participants identified as frail by:			
			FP	FI	EFS	CFS
Participants identified as frail (% of total cohort)		-	203 (41.9%)	307 (63.3%)	244 (50.3%)	261 (53.8%)
Median Age		63 (53-74)	67 (56-77)	63 (54-75)	63 (53-74.5)	65 (55-76)
Ethnicity	*White*	281 (57.9%)	121 (59.6%)	174 (56.7%)	132 (54.1%)	144 (55.2%)
	South Asian	115 (23.7%)	51 (25.1%)	80 (26.1%)	61 (25.0%)	71 (27.2%)
	Black	76 (15.7%)	27 (13.3%)	46 (15.0%)	47 (19.3%)	41 (15.7%)
	Other	13 (2.7%)	4 (2.0%)	7 (2.3%)	4 (1.6%)	5 (1.9%)
Male		284 (58.6%)	106 (52.2%)	165 (53.8%)	127 (52.1%)	136 (52.1%)
Median BMI		26.8 (23.2-32.4)	27.8 (22.7-33.6)	27.9 (23.1-33.2)	27.7 (23.1-33.6)	27.9 (23.2-33.7)
Cause of kidney failure*	*Diabetes*	114 (23.5%)	64 (31.5%)	86 (28.0%)	71 (29.1%)	81 (31.0%)
	Ischaemic	38 (7.8%)	18 (8.9%)	27 (8.8%)	20 (8.2%)	24 (9.2%)
	Hypertension	39 (8.4%)	14 (6.9%)	22 (7.2%)	21 (8.6%)	17 (6.5%)
	IgA	37 (7.6%)	12 (5.9%)	21 (6.8%)	19 (7.8%)	17 (6.5%)
	PKD	28 (5.8%)	7 (3.5%)	14 (4.6%)	11 (4.5%)	11 (4.2%)
	FSGS	24 (5.0%)	10 (4.9%)	13 (4.2%)	13 (5.3%)	10 (3.8%)
	Reflux	17 (3.5%)	11 (5.4%)	12 (3.9%)	10 (4.1%)	10 (3.8%)
	Obstructive	16 (3.3%)	7 (3.5%)	8 (2.6%)	7 (2.9%)	6 (2.3%)
	AAV	15 (3.1%)	5 (2.5%)	6 (2.0%)	5 (2.1%)	4 (1.5%)
	Interstitial Nephritis	10 (2.1%)	4 (2.0%)	5 (1.6%)	3 (1.2%)	4 (1.5%)
	Myeloma	10 (2.1%)	2 (1.0%)	5 (1.6%)	3 (1.2%)	2 (0.8%)
	Other	86 (17.7%)	36 (17.7%)	60 (19.5%)	46 (18.9%)	47 (18.0%)
	Unknown	68 (14.0%)	23 (11.3%)	40 (13.0%)	28 (11.5%)	37 (14.2%)
Medical co-morbidities	*MI*	98 (20.2%)	53 (26.1%)	73 (23.8%)	61 (25.0%)	64 (24.5%)
	Heart failure	52 (10.7%)	24 (11.8%)	35 (11.4%)	31 (12.7%)	33 (12.6%)
	Stroke	57 (11.8%)	36 (17.7%)	43 (14.0%)	37 (15.2%)	40 (15.3%)
	PVD	47 (9.7%)	27 (13.3%)	36 (11.7%)	26 (10.7%)	32 (12.3%)
	Cancer	56 (11.6%)	18 (8.9%)	34 (11.1%)	25 (10.3%)	26 (10.0%)
Smoking history	*Current*	68 (14.1%)	28 (13.9%)	41 (13.4%)	36 (14.8%)	30 (11.5%)
	Previous	132 (27.3%)	51 (25.3%)	78 (25.5%)	59 (24.3%)	68 (26.2%)

	Never	284 (58.7%)	123 (60.9%)	187 (61.1%)	148 (60.9%)	162 (62.3%)
Median Charlson Score**		4 (3-6)	5 (4-7)	5 (3-6)	5 (3-6)	5 (4-7)
Dialysis details	*Dialysis vintage (median in months)*	37 (17-76)	49 (22-93)	41 (18-82)	35 (16-77)	41 (20-81)
	Line	113 (23.3%)	54 (26.6%)	77 (25.1%)	67 (27.5%)	66 (25.3%)
	Kt/V	1.6 (1.4-1.9)	1.6 (1.4-1.9)	1.6 (1.4-1.9)	1.6 (1.4-1.9)	1.6 (1.4-1.9)
Transplant list status	*Active*	58 (12.0%)	11 (5.4%)	27 (8.8%)	20 (8.2%)	22 (8.4%)
	Suspended	15 (3.1%)	2 (1.0%)	9 (2.9%)	6 (2.5%)	6 (2.3%)
	Not listed	412 (85%)	190 (93.6%)	271 (88.3%)	218 (89.4)	233 (89.3%)
% Employment Status	*Employed*	69 (14.3%)	5 (2.5%)	16 (5.2%)	13 (5.4%)	8 (3.1%)
	Unemployed	148 (30.6%)	67 (33.2%)	114 (37.3%)	94 (38.7%)	90 (34.6%)
	Retired	267 (55.2%)	130 (64.4%)	176 (57.5%)	136 (56.0%)	162 (62.3%)
% Job Role***	*Unskilled Manual*	181 (39.3%)	93 (48.4%)	131 (45.8%)	101 (44.5%)	111 (45.7%)
	Skilled Manual	101 (21.9%)	37 (19.3%)	58 (20.3%)	49 (21.6%)	51 (21.0%)
	Clerical	52 (11.3%)	24 (12.5%)	33 (11.5%)	27 (11.9%)	24 (9.9%)
	Managerial	46 (10.0%)	14 (7.3%)	21 (7.3%)	18 (7.9%)	20 (8.2%)
	Professional	81 (17.6%)	24 (12.5%)	43 (15.0%)	32 (14.1%)	37 (15.2%)
% Education Level	*High School*	342 (70.7%)	153 (75.7%)	229 (74.8%)	185 (76.1%)	196 (75.4%)
	College/Sixth Form	92 (19.0%)	39 (19.3%)	54 (17.7%)	41 (16.9%)	43 (16.5%)
	University	50 (10.3%)	10 (5.0%)	23 (7.5%)	17 (7.0%)	21 (8.1%)
Residence	*Own home*	462 (95.9%)	188 (93.1%)	288 (94.4%)	224 (93.0%)	244 (94.2%)
	Warden-Controlled Flat	12 (2.5%)	7 (3.5%)	10 (3.3%)	11 (4.6%)	9 (3.5%)
	Residential Home	5 (1.0%)	4 (2.0%)	4 (1.3%)	4 (1.7%)	3 (1.2%)
	Nursing Home	3 (0.6%)	3 (1.5%)	3 (1.0%)	2 (0.8%)	3 (1.2%)
% With Professional Carers****		36 (7.8%)	31 (16.1%)	35 (12.0%)	30 (13.0%)	36 (14.6%)

*Some participants had >1 cause of kidney failure listed. **Chronic kidney disease omitted from Charlson Score. ***Current job or previous job if unemployed/retired. ****For those living in own home.

Table 7-2: Top 10 primary causes for emergency attendance and admission by HES code

Primary HES Code	Description	Admissions (n=1228)	
		n	%
T828	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts	229	18.7
N185	Chronic kidney disease, stage 5	103	8.4
A419	Sepsis, unspecified	33	2.7
J181	Lobar pneumonia, unspecified	33	2.7
E877	Fluid overload	30	2.4
U071	Emergency use of U07.1 (COVID-19)	26	2.1
J22	Unspecified acute lower respiratory infection	25	2.0
J189	Pneumonia, unspecified	24	2.0
J440	Chronic obstructive pulmonary disease with acute lower respiratory infection	24	2.0
T827	Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts	20	1.6

Table 7-3: Incidence Rate Ratios of Admissions and Nights in Hospital treating frailty as continuous variables.

	FP	FI	EFS	CFS
Total Number of Admissions				
Univariable	**1.22**	**1.16**	**1.11**	**1.25**
	1.13-1.32	**1.10-1.22**	**1.07-1.15**	**1.15-1.34**
Multivariable	1.05	1.05	1.02	**1.12**
	0.96-1.15	0.98-1.12	0.97-1.06	**1.02-1.22**
Total Nights in Hospital				
Univariable	**1.42**	**12.01**	**1.21**	**1.35**
	1.27-1.59	**5.22-27.60**	**1.14-1.29**	**1.21-1.52**
Multivariable	**1.20**	**1.28**	**1.08**	1.11
	1.04-1.40	**1.18-1.39**	**1.01-1.17**	0.95-1.30
*Nights per admission**				
Univariable	**1.21**	**1.18**	**1.09**	**1.14**
	1.08-1.36	**1.06-1.31**	**1.03-1.16**	**1.03-1.26**
Multivariable	**1.19**	**1.17**	1.06	1.02
	1.06-1.33	**1.04-1.30**	1.00-1.13	0.92-1.14

Bold text indicates significance at p<0.05 level. IRRs and 95% confidence intervals shown. All values calculated by negative binomial regression, except * which was calculated via zero-truncated negative binomial regression. Multivariable models adjusted for: age, sex, ethnicity, body mass index, index of multiple deprivation, Charlson comorbidity index, number of hospitalisation episodes, polypharmacy, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status

Table 7-4: Incidence Rate Ratios for hospital admission and nights spent in hospital by frailty status as a categorical variable

		FP	FI	EFS	CFS
Total number of admissions					
Univariable	Vulnerable	1.16 0.82-1.63	**1.45** **1.01-2.09**	**1.46** **1.07-2.00**	**1.41** **1.01-1.95**
	Frail	**1.99** **1.42-2.80**	**2.24** **1.65-3.06**	**1.93** **1.48-2.51**	**2.04** **1.59-2.63**
Multivariable	Vulnerable	0.98 0.70-1.37	1.14 0.80-1.63	1.20 0.89-1.61	1.24 0.90-1.70
	Frail	1.24 0.85-1.81	**1.48** **1.06-2.06**	1.17 0.88-1.57	**1.52** **1.15-2.00**
Total Nights in Hospital					
Univariable	Vulnerable	1.54 0.93-2.53	1.38 0.81-2.33	**2.22** **1.42-3.48**	**1.90** **1.17-3.09**
	Frail	**3.45** **2.09-5.72**	**3.76** **2.42-5.84**	**3.77** **2.57-5.53**	**2.87** **1.98-4.15**
Multivariable	Vulnerable	1.32 0.77-2.25	1.18 0.69-2.03	**1.72** **1.08-2.74**	1.53 0.93-2.53
	Frail	**1.89** **1.02-3.52**	**2.28** **1.37-3.79**	**1.79** **1.13-2.86**	1.52 0.93-2.53
Nights per Admission*					
Univariable	Vulnerable	1.22 0.73-2.03	1.06 0.69-1.61	**1.45** **1.05-2.01**	1.21 0.82-1.78
	Frail	**1.90** **1.12-3.24**	**1.81** **1.19-2.76**	**1.90** **1.36-2.67**	**1.58** **1.15-2.16**
Multivariable	Vulnerable	1.21 0.79-1.83	1.05 0.67-1.64	1.29 0.93-1.78	1.17 0.81-1.69
	Frail	**1.66** **1.02-2.73**	1.41 0.90-2.18	**1.43** **1.01-2.03**	1.05 0.76-1.44

Bold text indicates significance at p<0.05 level. All IRRs and 95% C.I. calculated using negative binomial regression except * which was calculated by negative-truncated negative binomial regression. Vulnerability and Frailty compared with Robustness for each frailty instrument. Multivariable models adjusted for: age, sex, ethnicity, body mass index, index of multiple deprivation, Charlson comorbidity index, number of hospitalisation episodes, polypharmacy, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status

Supplementary Table 7-1: Admission groupings with constituent HES/ICD-10 and OPCS-4 codes

Admission Type	Explanation	ICD-10/OPCS-4 Codes
Infection	Any infection in any site	A000-B999 E32.1 G000-G090 H00.0 H01.1 H03.0 H03.1 H04.0 H05.0 H05.1 H10.0 H10.2-H10.9 H30.0-H30.1 H30.9 H44.0-H44.1 H60.0-H60.3 H61.0 H62 H65.0-H65.1 I30.1 I320-I339 I38 I39 I40 I41.0-I41.2 I43.0 I52.0-I52.1 I68.1 I79.0-I79.1 I88 I98.0-I98.1 J000-J069 J090-J189 J200-J229 J32 J34.0 J360-J379 J38.3 J38.7 J39.0-J39.1 J44.0 J850-J869 K04.6 K04.7 K11.3 K11.2 K12.2 K14.0 K350-K379 K57.0 K57.2 K57.4 K57.8 K61 K63.0 K65.0 K67 K75.0 K77.0 K81 K83.0 K85 K87.1 L000-L089 M000-M039 M60.0 M63.0-M63.2 N30.0 N30.8 N30.9 N33 N34 N41 N43.1 N45 N48.1 N48.2 N49 N51 N61 N700-N769 U04 U06 U07 U820-U859
Dialysis Access	Any code indicating dialysis access dysfunction	T82.4 T82.5 T82.7 T82.8 T82.9 T85.6
Dialysis Indications/CKD 5	Any code related to dialysis indications (uraemia, hyperkalaemia, hypervolaemia, or acidosis) or to CKD 5	E87.2 E87.5 E87.7 G63.8 G99.8 I32.8 I68.8 N18.5 N18.9 N19
Cancer	Any code relating to any cancer at any site	C000-C979 D000-D099 D100-D369 D370-D489
MACE (Major Adverse Cardiovascular Events)	1. Any code relating to myocardial infarction, cerebrovascular accident in any diagnosis. 2. Heart failure, or unstable angina pectoris if in primary diagnosis. 3. Any coronary revascularisation OPCS-4 code 4. Any cardiovascular underlying cause of death during admission	1. I21-I22 I60-I64 2. I50 I200 3. K75 4. I21 I24 I25 I26 I42 I44 I48 I49 I50 I63 I64 I67 I69

Chapter 8:

Self-reported health change in haemodialysis recipients modulates the effect of frailty upon mortality and hospital admissions

Authors: Benjamin M Anderson, Muhammad Qasim, Gonzalo Correa, Felicity Evison, Suzy Gallier, Charles J Ferro, Thomas A Jackson, Adnan Sharif

8.1 Extent of Personal Contribution

I coordinated all study visits with participants and dialysis unit staff. I recruited participants, and collected all baseline data with the support of Dr Gonzalo Correa, Dr Muhammad Qasim, and Dr Adnan Sharif. All colleagues were supervised by me in their data collection, and I was responsible for maintaining training and personnel logs in the site file.

Ms Felicity Evison, and Ms Suzy Gallier were responsible for interrogation of EPR for IMD Quintile assessment and HES/OPCS/ONS data for mortality and hospitalisation follow-up. I performed all subsequent data cleaning, integrity, and analyses with guidance from Dr Adnan Sharif. Ms Felicity Evison kindly provided her statistical expertise to check the processing and interpretation of the interactions analyses.

The first draft of the manuscript was written by myself and I was responsible for all edits and revisions. This chapter is based upon a manuscript accepted for publication by NDT: Nephrology Dialysis Transplantation on which I am first author.[316]

8.2 Abstract

8.2.1 Background

Frailty among haemodialysis patients is associated with hospitalisation and mortality, but high frailty prevalence suggests further discrimination of risk is required. We hypothesised that incorporation of self-reported health with frailty measurement may aid risk stratification.

8.2.2 Methods

Prospective cohort study of 485 prevalent haemodialysis recipients linked to English national datasets. Frailty Phenotype (FP), Frailty Index (FI), Edmonton Frail Scale (EFS), Clinical Frailty Scale (CFS) and self-reported health change were assessed. Mortality was explored using Fine and Gray regression, and admissions by negative binomial regression.

8.2.3 Results

Over a median 678 (IQR: 531-812) days, there were 111 deaths, and 1241 hospitalisations. Increasing frailty was associated with mortality on adjusted analyses for FP, FI, and CFS, but not EFS. Health change interacted with frailty tools to modify association with mortality; only those who rated their health as the same or worse experienced increased mortality hazard associated with frailty by FP (P = 0.001 and 0.035 respectively), FI (P = 0.002 and 0.007 respectively), and CFS (P = 0.009 and 0.02 respectively). CFS was the only frailty tool associated with hospitalisation (incidence rate ratio 1.12, 95% CI 1.02-1.23, p=0.02).

8.2.4 Conclusions

We confirm the high burden of hospitalisation and mortality associated with haemodialysis patients regardless of frailty tool utilised and introduce the discriminatory ability of self-reported health to identify the most at-risk frail individuals.

8.3 What is already known about this subject

- Frailty is common in haemodialysis recipients, and associated with adverse outcomes
- Heterogeneity of reporting limits generalisability across cohorts.
- There is a need to understand which frailty tool is optimal for use in haemodialysis, and to further stratify risk within this highly frail and comorbid population.
-

8.4 What this study adds

- Clinical Frailty Scale is the only frailty tool to associate with both mortality and hospitalisation in this cohort
- Self-reported change in health associates with hospitalisation, total time in hospital, and appears to modulate the association of frailty with mortality.
- Only those who rated their health as “The Same” or “Worse” over the past year experienced increased mortality hazard associated with frailty
-

8.5 What impact this may have on practice or policy

- A simple patient reported outcome measure of change in health may aid risk stratification in haemodialysis cohorts and to guide frailty intervention.

8.6 Introduction

Frailty is a syndrome of accelerated ageing across multiple physiological systems, characterised by increased vulnerability to stressors, and is common in haemodialysis recipients.[21,46,49,170,184,270,273] Our cohort from the FITNESS (**F**railty **I**ntervention **T**rial i**N** **E**nd-**S**tage patient**S** on haemodialysis) study reported frailty prevalence between 42-63% dependent upon the tool used; previous work both within the general elderly population and from the FITNESS cohort demonstrates poor agreement regarding frailty status.[59,272]

Common frailty assessment tools include the Frailty Phenotype (FP) [19], Frailty Index (FI)[47], Edmonton Frail Scale (EFS)[55], and Clinical Frailty Scale (CFS)[27]. Of these, only the FP and EFS have been associated with increased hospitalisation risk in haemodialysis[170,184], while all frailty tools demonstrate an association with increased mortality.[21,45,46,49,170] Given the very high prevalence of frailty in haemodialysis populations, identifying those most vulnerable to adverse outcomes associated with frailty is critical.

Several Health-Related Quality of Life (HRQOL) domains are associated with mortality and hospitalisation in haemodialysis cohorts.[219,232,317-319] Patient-reported outcome measures (PROMs) in haemodialysis recipients are dynamic, and these changes may aid with risk stratification. Perl *et al.* found that change in SF-12 HRQOL was associated with increased mortality, but lost this association on adjustment for the most recent HRQOL measure.[233] Matsuzawa and colleagues reported that a fall in instrumental activities of daily living (IADL) functional ability was associated with mortality.[320] However, Hall *et al.* found that change in SF-12 physical component summary did not associate with mortality, though as a high proportion of this cohort died prior to repeat SF-12

assessment, this result may have been affected by survivor bias.[321] Frailty has also been shown to be a dynamic state in haemodialysis recipients,[313] and we hypothesise that a simple measure of self-reported health change may capture some of this dynamism in frailty and HRQOL. Furthermore, incorporating health change with frailty assessment may serve as a useful triage for identifying frail patients at highest risk for specific discriminatory targeting.

Therefore, the aim of this study is to report the short-term mortality and hospitalisation associated with frailty by commonly employed frailty tools, and their interaction with self-reported health status, in a prevalent haemodialysis population.

8.7 Methods

The full protocol for the FITNESS study has been described in **Error! Reference source not found.** and Chapter 3:.[263,272] The study is reported in accordance with STROBE guidelines.[322]

Self-reported change in health (henceforth "health change") was obtained by asking "How has your health changed in the last year?", with potential responses of "Better" "The Same" or "Worse". Determination of socio-economic deprivation was based upon the Index of Multiple Deprivation (IMD), a model calculated according to local area, with 1 representing the most deprived and 5 the least deprived area respectively.

Frailty definitions are detailed in Chapter 2:, however for this analysis we omitted health change from the FI as originally described, so that the FI was a composite of 31 variables

rather than 32, but with the same potential score of 0-1 and with the same categorisation thresholds.

8.7.1 Outcomes

Mortality data were obtained by electronic record linkage of all FITNESS study recruits to Office of National Statistics (ONS), a UK-wide repository of death certificate data. This ensures robust coverage of mortality data capture and comprehensive description of causality. Hospital Episode Statistics (HES), a database containing all secondary care episodes in any NHS hospital in England, provided robust national coverage data for all hospitalisation. Hospital admissions were defined as any hospital episode lasting ≥1 night.

8.7.2 Statistics

Statistical analysis was performed using STATA 17 (StataCorp 2021, Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) and R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). Categorical data was presented as numbers and percentages, with continuous variables reported as medians and interquartile ranges (IQRs).

Survival analyses were performed by generation of Kaplan-Meier curve estimates and time-to-event outcomes were analysed with the Fine and Gray Subdistribution Hazards Model, with kidney transplantation as a competing event, and censored for end of follow-up.[323,324] The proportional hazard assumption was checked and satisfied by examination of plots of the log-negative-log of the within-group survivorship functions versus log time as well as comparing observed with expected survival curves with our study variables, alongside selected covariables for adjusted analyses (reported as Hazard Ratios [HR] with 95%

Confidence Intervals [CI]). Trends of survivor function across the continuous frailty scores were tested using log-rank tests on the fully adjusted model.

Incidence rate ratios were obtained for count data by Negative Binomial Regression, death-censored and offset by length of follow-up. Negative binomial distribution was confirmed by over-dispersion and visual interpretation of expected versus observed distribution plots.

All regressions were performed treating frailty as a continuous variable. The FI was scaled so that regression outputs quoted represent the association with each 0.1 rise in FI. All regressions included unadjusted analyses and adjusted for an *a priori* list of covariables, based on a known or suspected relationship with dialysis-related mortality/admission, with stepwise addition of covariables. Model 1 included age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], index of multiple deprivation. Model 2 added body mass index, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, dialysis vintage [continuous]. Model 3 added use of walking aids, and kidney transplant wait-listing [active versus not active].

Interactions between frailty scores and health change are reported as predicted SHRs and marginal effect of frailty upon SHRs shown in graphical format for each level of frailty and health change.

Missing IMD Quintile data were handled via a dummy variable. All other missing data were assumed missing at random and handled via listwise deletion as they had <1% data missing. A p value < 0.05 was considered significant in the statistical analysis.

8.8 Results

Figure 6-1 shows the PRISMA study flow of participant recruitment to the FITNESS study, with 485 prevalent haemodialysis patients with baseline frailty assessments and data linkage. Follow up was 678 days (interquartile range: 531-812 days), with all participants receiving a minimum potential follow-up of 365 days. Baseline demographics are described elsewhere.[272] Table 8-1 shows key demographics stratified by different frailty instruments at study recruitment.

8.8.1 Mortality Outcomes

There were 111 (22.9%) deaths during the follow-up period. Primary cause of death was listed as infection in 22 participants (19.8%), ischaemic heart disease 17 (15.4%) cancer 10 (9.0%), cerebrovascular disease 4 (3.6%), peripheral vascular disease 2 (1.8%), and other causes of death 35 (31.5%). Cause of death data were not available for 21 (18.9%) of deaths. Of the infection-related deaths, 8 (7.2% of total deaths) were due to COVID-19 (primary cause of death code U07.1). Figure 6-2 to Figure 6-5 show unadjusted cumulative survival was lower for frail and vulnerable participants when compared with the robust group for each frailty instrument ($p<0.001$ for each instrument by log-rank test).

Total participant follow-up was 862.1 patient-years, during which there were 1241 admissions of at least one night's duration (1.44 admissions per patient-year), and 10175 nights spent in hospital. 382 (78.8%) participants had at least one hospital admission during follow-up; the median number of admissions was 2 (IQR: 0-4). Table 8-2 shows frequency of admissions within the FITNESS cohort.

8.8.2 Association between frailty, health change, and mortality

Increasing frailty by all frailty tools was associated with increased mortality hazard on univariable and multivariable analysis, as shown in Table 8-3. A trend of the survivor function was observed for each increase in frailty for all instruments studied ($p<0.001$).

On univariable analysis, worse health change was associated with increased mortality, but this was lost on addition of the frailty scores to the model. No health change category was associated with mortality on the adjusted model. Addition of health change into the adjusted model resulted in the EFS losing its association with increased mortality, but the other tools retained their mortality association. Table 8-4 shows stepwise addition of covariables into the mortality model did not appreciably affect results except for the EFS, which lost statistical significance in model 3 only.

Figure 8-1 and Table 8-5 show that only those who rated their health as "The Same" or "Worse" over the past year experienced increased mortality hazard associated with FP, FI or CFS frailty. There was no significant interaction between health change and EFS.

8.8.3 Association between frailty, health change and admissions

Table 8-6 shows that on adjusted analysis, participants reporting their health to be the same or worse over the past year had a higher rate of hospital admissions. This association remained after addition of each of the frailty tools into the model. Of the frailty tools, only

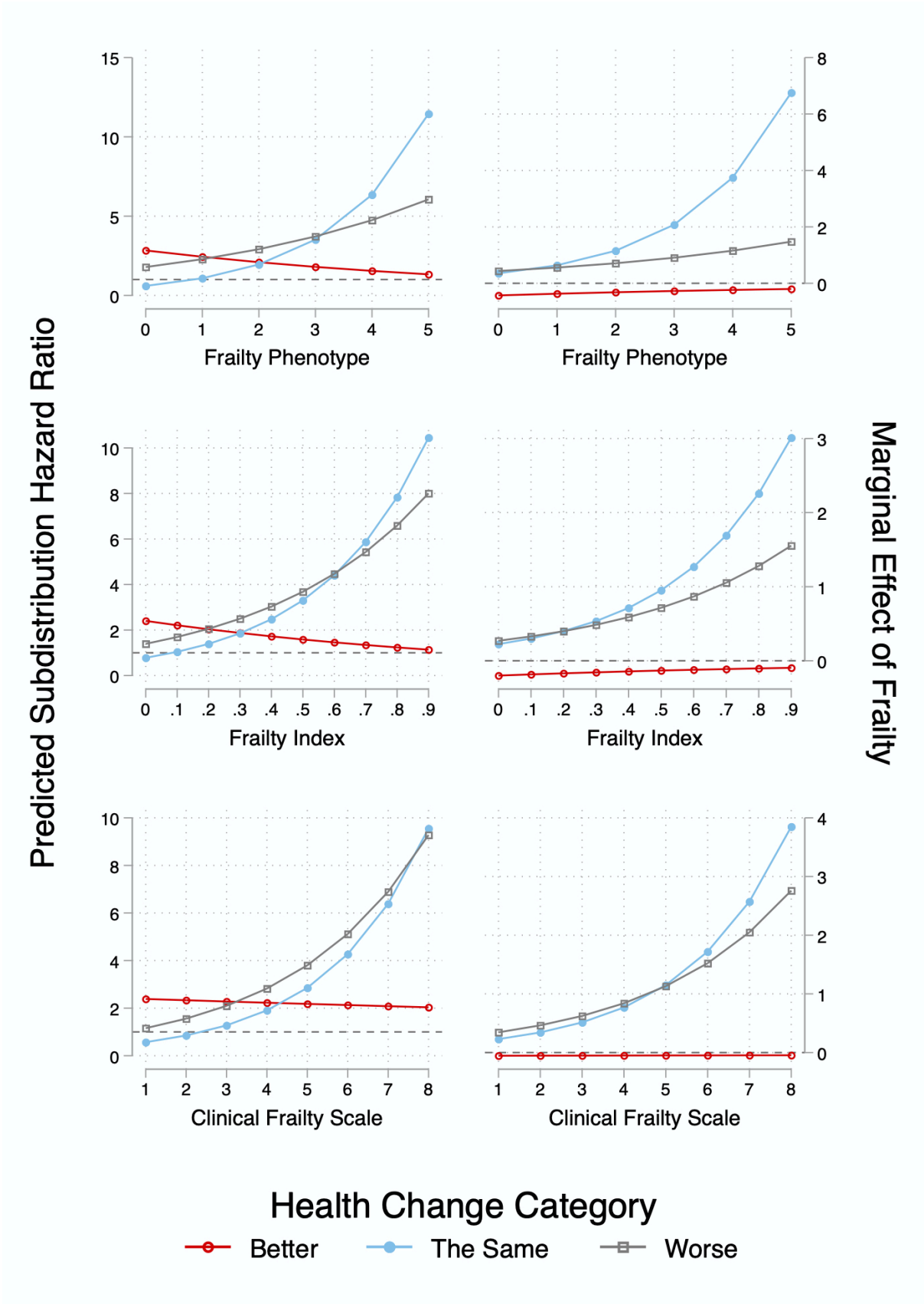


Figure 8-1: Interaction plot between health change and frailty by FP (top row), FI (middle row), and CFS (bottom row). Graphs on the left represent predicted subdistribution hazard ratios for each level of frailty and health change. On the right are graphs of the marginal contribution of increases in frailty to the subdistribution hazard ratio. Marginal effect of FI scaled to each 0.1 rise in FI.

the CFS maintained a significant association with rate of admission upon adjusted analysis. There were no significant interactions between health change and any of the frailty tools for association with admissions.

As we have previously seen in Chapter 7:, Table 8-7 demonstrates that CFS was the only frailty instrument not to associate with total nights in hospital on multivariable analyses. However, it also shows that both the same or worse health change in the past year were both associated with increased rates of nights in hospital. Table 8-8 shows the only significant interaction was between the FP and health change in "the same" category.

8.9 Discussion

Frailty is associated with mortality and hospitalisation in haemodialysis patients, but studies to date have used heterogenous definitions that limit generalisability. Previous work from this cohort has demonstrated good correlation but poor agreement upon frailty between these frailty instruments.[272] Furthermore, high frailty prevalence may render attempts to intervene upon frailty at a population level impractical. Therefore, there is an urgent need to identify haemodialysis patients at greatest risk of developing adverse outcomes from frailty. In this prospective-cohort study of a large, prevalent haemodialysis population, we report association of frailty with mortality, regardless of frailty definition and after adjustment for clinically relevant risk factors. Rate of admissions were only higher for increasing frailty by the CFS, whereas this was the only frailty tool to not associate with rate of nights in hospital during follow-up. We also report that a simple patient-reported outcome measure – health change in the past year – outperforms each frailty tool for association with rates of hospital admission and nights in hospital. Furthermore, health change interacts with FP, FI, and CFS to modulate

their association with mortality, with only those who rate their health as the same or worse over the past year demonstrating increased mortality hazard. Self-reported health change may therefore serve as a useful tool to identify those who are more likely to experience negative outcomes associated with frailty.

Our findings linking frailty defined by FP[170], FI[182,325], EFS[184] and CFS[21] in haemodialysis patients with mortality are well described, but this study is the first to compare these common tools for association with hospitalisation. Imamura and colleagues compared frailty tools including the FP and CFS, but not the FI and EFS for their association with a composite of mortality, hospitalisation and fractures.[175] This analysis was limited by the use of a composite outcome, rather than exploring each of these important but distinct outcomes separately. Addition of health change may provide additional information to frailty assessment; its consistent association with metrics of hospital admissions may counterbalance the inconsistent association of each frailty tool with these same outcomes. Only CFS was associated with hospitalisation, although not nights in hospital, and as a judgment-based frailty tool is the easiest to utilise. A scoping review has highlighted the increasing use of CFS in multiple settings[326], and our data would support CFS being prioritised as the frailty tool of choice for haemodialysis patients, but it requires validation in other cohorts.

Patient reported outcome measures (PROMs) and association with outcomes have largely tended towards domains of health-related quality of life (HRQOL). Several HRQOL domains are associated with mortality in Dutch[317], Brazilian[232] and Irish[318] cohorts and with mortality and hospitalisation in a US cohort[219]. Change in health has been studied less extensively and has yielded conflicting results. Change in serial SF-12 HRQOL scores was

not associated with mortality,[233] nor was self-reported drop in physical function.[321] However Matsuzawa and colleagues reported that a fall in instrumental activities of daily living (IADL) functional ability was associated with mortality.[320] Our findings might appear to corroborate a lack of association between health change and mortality, but – whilst both could be considered PROMs – it is important to acknowledge the difference between HRQOL and self-reported health change. To our knowledge, no group has explored the interplay between health change and frailty upon associations with mortality or hospitalisation. Studies have tended towards investigating PROMs as a surrogate for frailty, with disagreement as to whether they do[45,229] or do not[180] provide a useful proxy for formal frailty assessment. Self-reported frailty was associated with mortality, yet interestingly not in a subgroup of participants who were frail by self-report but non-frail by formal assessment,[46] and there was significant discordance between self-reported and formal FP frailty.[45] Health change has advantages over these self-reported frailty measures. First, it was not conceived as a surrogate for frailty, and as such would be less liable to cause confusion amongst patients or providers in the event of discordant results. Second, it independently associates with hospitalisation, indeed outperforming frailty assessment by any of the included tools. Third, it appears to modulate the effect of frailty on mortality, with only those who report health as the same or worse demonstrating the association between increasing frailty and mortality. Together, these factors posit a screening tool that is not a frailty surrogate, rather it provides additional and synergistic risk stratification alongside frailty assessment.

It is prudent however to be mindful of the limitations of using health change as a screen for formal frailty assessment. Less than 20% of participants reported better health; a small number of exclusions from frailty assessment, albeit with minimal time and monetary cost. Furthermore, as the frailty tools studied here are themselves "screening tools" for frailty, we may be wary of applying a screening tool for a screening tool. Whilst here we report associations with important outcomes of mortality and hospitalisation, there are many more patient-centred outcomes to be considered, such as quality of life, mood, and cognition – the subject of further work. It is also important to recognise that no frailty intervention has yet proven efficacy in the haemodialysis population. As such identifying those at high risk of poor outcomes is of limited benefit to the individual patient. Most importantly, our findings need to be replicated in other cohorts for health change to be considered a useful screen for frailty. Figure 8-2 shows a notional model of

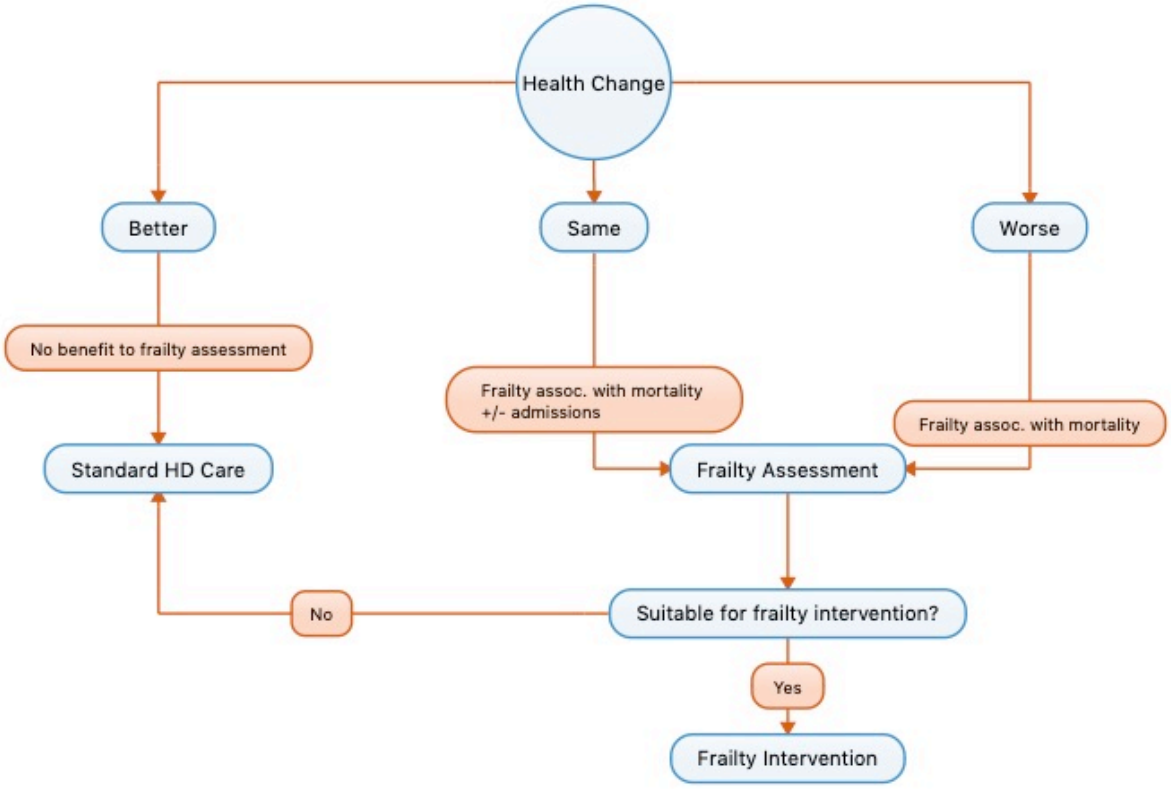


Figure 8-2: Notional model of how self-reported health change may be integrated into frailty assessment

how health change could be integrated into frailty assessment and intervention. For this model to be feasible, the following assumptions must be satisfied: i) validation of our health change findings in other haemodialysis cohorts ii) emergence of a proven frailty intervention in haemodialysis, iii) confirmation that this same frailty intervention also helps reduce admissions.

FITNESS is to our knowledge the largest prospective cohort study to compare frequently used frailty tools in haemodialysis, the first to compare their associations with both mortality and hospitalisation, and the first to propose a PROM that may modulate the associations of frailty. Further strengths include diversity of demographics, comorbidities and socio-economic backgrounds representative of the local population.[327] However our data should be interpreted with caution in non-English populations, and validation of our findings elsewhere is required. We studied ≥3-month prevalent haemodialysis recipients, which introduces a small risk of survivor bias into the analyses, albeit these were adjusted for dialysis vintage. Nevertheless, our findings may not be directly translatable to incident ESKD. A limitation of FITNESS is the single cross-sectional assessment, as frailty is a dynamic state.[313] We may speculate that health change may derive its utility from capturing this dynamism in health and frailty in a one-off assessment. There were also small variations in application of frailty tool criteria from other studies. We adjusted for an extensive list of covariables, which may risk overfitting the mortality models. Supplementary tables show that stepwise addition of covariables led to loss of statistical significance in Model 3 for EFS, but all other models retained significant associations with mortality. Furthermore, some 95% confidence intervals crossed the point of no effect by small margins, raising the possibility of type

II error. Finally, whilst these data describe associations, they cannot support the notion of frailty as a 'predictor' of such adverse outcomes, and caution should be exercised when considering the applicability of these findings to the individual haemodialysis recipient in clinical practice.

To conclude, our work confirms the high burden of hospitalisation and mortality associated with haemodialysis patients regardless of frailty tool utilised but introduces the discriminatory ability of self-reported health to identify the most at-risk frail individuals. The kidney community must address the feasibility and efficacy of frailty intervention among dialysis patients to allow utilisation of frailty assessments to support improvements in clinical outcomes.

8.10 Tables

Table 8-1: Baseline demographics of FITNESS study participants

Parameter		Total cohort	Participants identified as frail by:			
			FP	FI	EFS	CFS
Participants identified as frail (% of total cohort)		-	203 (41.9%)	293 (60.4%)	244 (50.3%)	261 (53.8%)
Median Age		63 (53-74)	67 (56-77)	64 (53-75)	63 (53-74.5)	65 (55-76)
Self-Reported Health Change	Better	94 (19.4%)	27 (13.3%)	48 (16.4%)	43 (17.6%)	42 (16.1%)
	The Same	174 (35.9%)	62 (30.5%)	92 (31.4%)	69 (28.3%)	84 (32.2%)
	Worse	217 (44.7%)	114 (56.2%)	153 (52.2%)	132 (54.1%)	135 (51.7%)
Ethnicity	*White*	281 (57.9%)	121 (59.6%)	167 (57.0%)	132 (54.1%)	144 (55.2%)
	South Asian	115 (23.7%)	51 (25.1%)	77 (26.3%)	61 (25.0%)	71 (27.2%)
	Black	76 (15.7%)	27 (13.3%)	44 (15.0%)	47 (19.3%)	41 (15.7%)
	Other	13 (2.7%)	4 (2.0%)	5 (1.7%)	4 (1.6%)	5 (1.9%)
Male		284 (58.6%)	106 (52.2%)	157 (53.6%)	127 (52.1%)	136 (52.1%)
IMD Quintile	1	212 (43.7%)	95 (46.8%)	137 (46.8%)	177 (48.0%)	116 (44.4%)
	2	87 (17.9%)	40 (19.7%)	50 (17.0%)	43 (17.6%)	44 (16.9%)
	3	85 (17.5%)	29 (14.3%)	49 (16.7%)	34 (13.9%)	47 (18.0%)
	4	38 (7.8%)	15 (7.4%)	21 (7.2%)	17 (7.0%)	18 (6.9%)
	5	33 (6.8%)	12 (5.9%)	20 (6.8%)	19 (7.8%)	19 (7.3%)
	Unknown	30 (6.2%)	12 (5.91%)	16 (5.5%)	14 (5.7%)	17 (6.5%)
Median BMI		26.8 (23.2-32.4)	27.8 (22.7-33.6)	28.1 (23.3-33.5)	27.7 (23.1-33.6)	27.9 (23.2-33.7)
Cause of kidney failure*	*Diabetes*	114 (23.5%)	64 (31.5%)	85 (29.0%)	71 (29.1%)	81 (31.0%)
	Ischaemic	38 (7.8%)	18 (8.9%)	28 (9.6%)	20 (8.2%)	24 (9.2%)
	Hypertension	39 (8.4%)	14 (6.9%)	21 (7.2%)	21 (8.6%)	17 (6.5%)
	IgA	37 (7.6%)	12 (5.9%)	21 (7.2%)	19 (7.8%)	17 (6.5%)
	PKD	28 (5.8%)	7 (3.5%)	10 (3.4%)	11 (4.5%)	11 (4.2%)
	FSGS	24 (5.0%)	10 (4.9%)	14 (4.8%)	13 (5.3%)	10 (3.8%)
	Reflux	17 (3.5%)	11 (5.4%)	12 (4.1%)	10 (4.1%)	10 (3.8%)
	Obstructive	16 (3.3%)	7 (3.5%)	7 (2.4%)	7 (2.9%)	6 (2.3%)
	AAV	15 (3.1%)	5 (2.5%)	6 (2.0%)	5 (2.1%)	4 (1.5%)
	Interstitial Nephritis	10 (2.1%)	4 (2.0%)	5 (1.7%)	3 (1.2%)	4 (1.5%)

	Myeloma	10 (2.1%)	2 (1.0%)	3 (1.0%)	3 (1.2%)	2 (0.8%)
	Other	86 (17.7%)	36 (17.7%)	54 (18.4%)	46 (18.9%)	47 (18.0%)
	Unknown	68 (14.0%)	23 (11.3%)	439 (13.3%)	28 (11.5%)	37 (14.2%)
Medical co-morbidities	*MI*	98 (20.2%)	53 (26.1%)	72 (24.6%)	61 (25.0%)	64 (24.5%)
	Heart failure	52 (10.7%)	24 (11.8%)	37 (12.6%)	31 (12.7%)	33 (12.6%)
	Stroke	57 (11.8%)	36 (17.7%)	43 (14.7%)	37 (15.2%)	40 (15.3%)
	PVD	47 (9.7%)	27 (13.3%)	33 (11.3%)	26 (10.7%)	32 (12.3%)
	Cancer	56 (11.6%)	18 (8.9%)	31 (10.6%)	25 (10.3%)	26 (10.0%)
Smoking history	*Current*	68 (14.1%)	28 (13.9%)	37 (12.7%)	36 (14.8%)	30 (11.5%)
	Previous	132 (27.3%)	51 (25.3%)	75 (25.7%)	59 (24.3%)	68 (26.2%)
	Never	284 (58.7%)	123 (60.9%)	180 (61.6%)	148 (60.9%)	162 (62.3%)
Median Charlson Score**		4 (3-6)	5 (4-7)	5 (4-6)	5 (3-6)	5 (4-7)
Dialysis details	*Dialysis vintage (median in months)*	37 (17-76)	49 (22-93)	41 (19-81)	35 (16-77)	41 (20-81)
	Line	113 (23.3%)	54 (26.6%)	72 (24.6%)	67 (27.5%)	66 (25.3%)
	Kt/V	1.6 (1.4-1.9)	1.6 (1.4-1.9)	1.6 (1.4-1.9)	1.6 (1.4-1.9)	1.6 (1.4-1.9)
Transplant list status	*Active*	58 (12.0%)	11 (5.4%)	27 (9.2%)	20 (8.2%)	22 (8.4%)
	Suspended	15 (3.1%)	2 (1.0%)	6 (2.1%)	6 (2.5%)	6 (2.3%)
	Not listed	412 (85%)	190 (93.6%)	247 (88.3%)	218 (89.4)	233 (89.3%)
% Employment Status	*Employed*	69 (14.3%)	5 (2.5%)	13 (4.5%)	13 (5.4%)	8 (3.1%)
	Unemployed	148 (30.6%)	67 (33.2%)	109 (37.3%)	94 (38.7%)	90 (34.6%)
	Retired	267 (55.2%)	130 (64.4%)	170 (58.2%)	136 (56.0%)	162 (62.3%)
% Job Role***	*Unskilled Manual*	181 (39.3%)	93 (48.4%)	129 (47.3%)	101 (44.5%)	111 (45.7%)
	Skilled Manual	101 (21.9%)	37 (19.3%)	55 (20.2%)	49 (21.6%)	51 (21.0%)
	Clerical	52 (11.3%)	24 (12.5%)	30 (11.0%)	27 (11.9%)	24 (9.9%)
	Managerial	46 (10.0%)	14 (7.3%)	22 (8.1%)	18 (7.9%)	20 (8.2%)
	Professional	81 (17.6%)	24 (12.5%)	37 (13.6%)	32 (14.1%)	37 (15.2%)
% Education Level	*High School*	342 (70.7%)	153 (75.7%)	220 (75.3%)	185 (76.1%)	196 (75.4%)
	College/Sixth Form	92 (19.0%)	39 (19.3%)	50 (17.1%)	41 (16.9%)	43 (16.5%)
	University	50 (10.3%)	10 (5.0%)	22 (7.5%)	17 (7.0%)	21 (8.1%)
Residence	*Own home*	462 (95.9%)	188 (93.1%)	274 (94.2%)	224 (93.0%)	244 (94.2%)

	Warden-Controlled Flat	12 (2.5%)	7 (3.5%)	10 (3.4%)	11 (4.6%)	9 (3.5%)
	Residential Home	5 (1.0%)	4 (2.0%)	4 (1.4%)	4 (1.7%)	3 (1.2%)
	Nursing Home	3 (0.6%)	3 (1.5%)	3 (1.0%)	2 (0.8%)	3 (1.2%)
% With Professional Carers****		36 (7.8%)	31 (16.1%)	36 (13.0%)	30 (13.0%)	36 (14.6%)

*Some participants had >1 cause of kidney failure listed. **Chronic kidney disease omitted from Charlson Score. ***Current job or previous job if unemployed/retired. ****For those living in own home.

Table 8-2: Frequency of admissions during FITNESS cohort follow-up

Number of Admissions	Number of Participants	% of participants
0	131	27.0%
1	103	21.2%
2	71	14.6%
3	42	8.7%
4	43	8.9%
5	27	5.6%
6	22	4.5%
7	16	3.3%
≥8	30	6.2%

Table 8-3: Association of change in health and frailty with mortality on unadjusted and adjusted analyses

Frailty tool in model	Variable	Unadjusted SHR	Unadjusted 95% C.I.	Unadjusted P	Adjusted SHR	Adjusted 95% C.I.	Adjusted P
Frailty Only*	Frailty Phenotype	**1.51**	**1.33-1.71**	**<0.001**	**1.26**	**1.06-1.52**	**0.01**
	Frailty Index	**1.29**	**1.19-1.39**	**<0.001**	**1.23**	**1.10-1.37**	**<0.001**
	Edmonton Frailty Scale	**1.19**	**1.12-1.26**	**<0.001**	**1.1**	**1.00-1.20**	**0.04**
	Clinical Frailty Scale	**1.51**	**1.31-1.73**	**<0.001**	**1.34**	**1.13-1.59**	**0.001**
None	Health Change						
	Better		REFERENCE			REFERENCE	
	Same	1.23	0.66-2.30	0.5	1.13	0.56-2.26	0.7
	Worse	**2.16**	**1.21-3.87**	**0.01**	1.68	0.87-3.26	0.1
Frailty Phenotype	Health Change						
	Better		REFERENCE			REFERENCE	
	Same	1.30	0.67-2.50	0.4	1.36	0.64-2.89	0.4
	Worse	1.81	0.99-3.30	0.06	1.76	0.88-3.53	0.1
	Frailty Phenotype	**1.47**	**1.29-1.68**	**<0.001**	**1.26**	**1.05-1.53**	**0.02**
Frailty Index	Health Change						
	Better		REFERENCE			REFERENCE	
	Same	1.26	0.67-2.38	0.5	1.24	0.60-2.57	0.6
	Worse	1.73	0.96-3.14	0.07	1.57	0.79-3.13	0.2
	Frailty Index	**1.26**	**1.16-1.36**	**<0.001**	**1.21**	**1.09-1.35**	**0.001**
Edmonton Frailty Scale	Health Change						
	Better		REFERENCE			REFERENCE	
	Same	1.35	0.71-2.56	0.4	1.17	0.58-2.38	0.7
	Worse	1.8	1.00-3.27	0.05	1.59	0.80-3.13	0.2
	Edmonton Frailty Scale	**1.17**	**1.10-1.24**	**<0.001**	1.08	0.99-1.18	0.1
Clinical Frailty Scale	Health Change						
	Better		REFERENCE			REFERENCE	
	Same	1.21	0.64-2.29	0.6	1.22	0.59-2.52	0.6
	Worse	1.8	0.99-3.27	0.05	1.64	0.82-3.28	0.2
	Clinical Frailty Scale	**1.47**	**1.28-1.69**	**<0.001**	**1.32**	**1.11-1.58**	**0.002**

Obtained by Fine and Gray Subdistribution Hazards Model, with any kidney transplantation (n=34) as competing risk. 106 deaths in 478 participants in adjusted models. Bold text indicates significance at P<0.05 level. SHR= Subdistribution Hazard Ratio. 95% C.I. = 95% confidence interval. *Separate model for each frailty tool, assessed without health change. SHRs for Frailty Index are scaled for each 0.1 rise in FI. Adjusted analyses (Model 3) covariables: age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin,

use of walking aids, dialysis vintage [continuous] and kidney transplant wait-listing [active versus not active].

Table 8-4: Association of frailty with mortality via stepwise addition of covariables to model

	SHR	Lower 95% C.I.	Upper 95% C.I.	P
Frailty Phenotype				
Univariable	**1.51**	**1.33**	**1.71**	**<0.001**
Model 1	**1.46**	**1.27**	**1.69**	**0.000**
Model 2	**1.32**	**1.11**	**1.56**	**0.001**
Model 3	**1.26**	**1.05**	**1.53**	**0.015**
Frailty Index				
Univariable	**1.29**	**1.19**	**1.39**	**<0.001**
Model 1	**1.32**	**1.21**	**1.44**	**<0.001**
Model 2	**1.25**	**1.13**	**1.39**	**<0.001**
Model 3	**1.21**	**1.09**	**1.35**	**0.001**
Edmonton Frailty Scale				
Univariable	**1.19**	**1.12**	**1.26**	**<0.001**
Model 1	**1.19**	**1.11**	**1.27**	**<0.001**
Model 2	**1.11**	**1.02**	**1.21**	**0.020**
Model 3	1.08	0.99	1.18	0.093
Clinical Frailty Scale				
Univariable	**1.51**	**1.31**	**1.73**	**<0.001**
Model 1	**1.52**	**1.30**	**1.76**	**<0.001**
Model 2	**1.39**	**1.18**	**1.65**	**<0.001**
Model 3	**1.32**	**1.11**	**1.58**	**0.002**

Obtained by Fine and Gray Subdistribution Hazards Model, with any kidney transplantation (n=34) as competing event. 106 deaths in 478 participants in adjusted models. Bold text indicates significant at P<0.05 level. HR= Hazard Ratio. 95% C.I. = 95% confidence intervals. SHRs for Frailty Index are scaled for each 0.1 rise in FI. Model 1 includes: age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], index of multiple deprivation. Model 2 adds: body mass index, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, dialysis vintage [continuous]. Model 3 adds: use of walking aids, and kidney transplant wait-listing

Table 8-5: Interaction between frailty and health change category for association with mortality

		Interaction P-Values		
		Main Effects	Interaction Terms	Effect of Frailty
Frailty Phenotype	Health Change			
	Better	REF	REF	0.3
	The Same	**0.01**	**0.001**	**0.001**
	Worse	0.4	**0.03**	**0.04**
	Frailty Phenotype	0.3	REF	REF
Frailty Index	Health Change			
	Better	REF	REF	0.5
	The Same	**0.04**	**0.004**	**0.001**
	Worse	0.3	**0.03**	**0.005**
	Frailty Index	0.5	REF	REF
Edmonton Frailty Scale	Health Change			
	Better	REF	REF	1.0
	The Same	0.2	0.2	0.06
	Worse	0.9	0.4	0.2
	Edmonton Frailty Scale	1.0	REF	REF
Clinical Frailty Scale	Health Change			
	Better	REF	REF	0.9
	The Same	0.1	**0.03**	**0.01**
	Worse	0.3	0.07	**0.02**
	CFS	0.9	REF	REF

Obtained by Fine and Gray Subdistribution Hazards Model, with any kidney transplantation (n=34) as competing event. 106 deaths in 478 participants in adjusted models. Bold text indicates significant at P<0.05 level. HR= Hazard Ratio. 95% C.I. = 95% confidence intervals. SHRs for Frailty Index are scaled for each 0.1 rise in FI. Adjusted analyses (Model 3) covariables: age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage [continuous] and kidney transplant wait-listing [active versus not active].

Table 8-6: Association of self-reported change in health and frailty with rate of hospital admissions for both unadjusted and adjusted analyses

Frailty tool in model	Variable	Unadjusted			Adjusted		
		IRR	95% C.I.	P	IRR	95% C.I.	P
Frailty Only*	Frailty Phenotype	**1.22**	**1.13-1.32**	**<0.001**	1.05	0.96-1.15	0.28
	Frailty Index	**1.15**	**1.09-1.21**	**<0.001**	1.04	0.98-1.11	0.184
	Edmonton Frailty Scale	**1.11**	**1.07-1.15**	**<0.001**	1.02	0.97-1.06	0.568
	Clinical Frailty Scale	**1.25**	**1.15-1.34**	**<0.001**	**1.12**	**1.02-1.22**	**0.016**
None	Health Change						
	Better		REF			REF	
	Same	1.29	0.95-1.76	0.107	**1.41**	**1.04-1.90**	**0.027**
	Worse	**1.62**	**1.20-2.18**	**0.002**	**1.43**	**1.07-1.92**	**0.016**
Frailty Phenotype	Health Change						
	Better		REF			REF	
	Same	1.25	0.92-1.70	0.15	**1.41**	**1.04-1.91**	**0.026**
	Worse	**1.43**	**1.06-1.93**	**0.018**	**1.41**	**1.05-1.89**	**0.021**
	Frailty Phenotype	**1.2**	**1.11-1.30**	**<0.001**	1.045	0.95-1.14	0.338
Frailty Index	Health Change						
	Better		REF			REF	
	Same	1.28	0.95-1.74	0.104	**1.42**	**1.04-1.92**	**0.023**
	Worse	**1.33**	**0.99-1.80**	**0.062**	**1.38**	**1.02-1.85**	**0.035**
	Frailty Index	**1.13**	**1.07-1.20**	**<0.001**	1.04	0.97-1.11	0.237
Edmonton Frailty Scale	Health Change						
	Better		REF			REF	
	Same	**1.38**	**1.02-1.88**	**0.036**	**1.41**	**1.04-1.91**	**0.026**
	Worse	**1.41**	**1.05-1.90**	**0.022**	**1.42**	**1.05-1.91**	**0.021**
	Edmonton Frailty Scale	**1.1**	**1.06-1.15**	**<0.001**	1.01	0.96-1.06	0.71
Clinical Frailty Scale	Health Change						
	Better		REF			REF	
	Same	**1.31**	**0.97-1.77**	**0.08**	**1.45**	**1.07-1.96**	**0.017**
	Worse	**1.43**	**1.06-1.92**	**0.018**	**1.38**	**1.03-1.85**	**0.029**
	Clinical Frailty Scale	**1.23**	**1.14-1.33**	**0.001**	**1.12**	**1.02-1.23**	**0.016**

1241 admissions in 485 participants. Negative binomial regression model used. Bold indicates significant at P<0.05 level. IRR = incidence rate ratio. 95% C.I. = 95% confidence intervals. IRRs for Frailty Index are scaled for each 0.1 rise in FI. Adjusted analyses (Model 3) covariables: age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage [continuous] and kidney transplant wait-listing [active versus not active].

Table 8-7: Association of self-reported change in health and frailty with total nights in hospital for both unadjusted and adjusted analyses

Frailty tool in model	Variable	Unadjusted			Adjusted		
		IRR	95% C.I.	P	IRR	95% C.I.	P
Frailty Only*	Frailty Phenotype	**1.42**	**1.27-1.59**	**<0.001**	**1.20**	**1.04-1.40**	**0.02**
	Frailty Index	**1.27**	**1.17-1.38**	**<0.001**	**1.14**	**1.02-1.27**	**0.02**
	Edmonton Frailty Scale	**1.21**	**1.14-1.29**	**<0.001**	**1.08**	**1.01-1.17**	**0.04**
	Clinical Frailty Scale	**1.35**	**1.21-1.52**	**<0.001**	1.11	0.95-1.30	0.2
None	Health Change						
	Better		REF			REF	
	Same	1.49	0.94-2.35	0.09	**2.01**	**1.23-3.29**	**0.005**
	Worse	**2.15**	**1.38-3.34**	**0.001**	**2.18**	**1.36-3.50**	**0.001**
Frailty Phenotype	Health Change						
	Better		REF			REF	
	Same	1.33	0.85-2.08	0.2	**1.92**	**1.17-3.13**	**0.01**
	Worse	**1.73**	**1.12-2.67**	**0.01**	**2.05**	**1.27-3.31**	**0.003**
	Frailty Phenotype	**1.39**	**1.24-1.56**	**<0.001**	**1.17**	**1.01-1.36**	**0.04**
Frailty Index	Health Change						
	Better		REF			REF	
	Same	1.32	0.85-2.07	0.2	**1.95**	**1.19-3.19**	**0.008**
	Worse	**1.58**	**1.02-2.46**	**0.04**	**1.92**	**1.17-3.16**	**0.01**
	Frailty Index	**1.25**	**1.15-1.36**	**<0.001**	1.11	0.99-1.24	0.08
Edmonton Frailty Scale	Health Change						
	Better		REF			REF	
	Same	**1.64**	**1.05-2.55**	**0.03**	**2.04**	**1.25-3.32**	**0.004**
	Worse	**1.62**	**1.05-2.50**	**0.03**	**1.99**	**1.23-3.22**	**0.005**
	Edmonton Frailty Scale	**1.21**	**1.13-1.28**	**<0.001**	1.07	0.99-1.16	0.08
Clinical Frailty Scale	Health Change						
	Better		REF			REF	
	Same	1.43	0.92-2.24	0.1	**2.01**	**1.23-3.28**	**0.006**
	Worse	**1.79**	**1.15-2.78**	**0.01**	**2.11**	**1.31-3.40**	**0.002**
	Clinical Frailty Scale	**1.31**	**1.17-1.48**	**<0.001**	1.08	0.92-1.26	0.3

Negative binomial regression model of 10175 nights in hospital in 485 participants. IRRs for Frailty Index are scaled for each 0.1 rise in FI. Adjusted analyses (Model 3) covariables: age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage [continuous] and kidney transplant wait-listing [active versus not active]. Bold text indicates significant at P<0.05 level. IRR = incidence rate ratio. 95% C.I. = 95% confidence intervals.

Table 8-8: Interaction terms between frailty and health change in association with total nights in hospital during follow-up

		Interaction P-Values		
		Main Effects	Interaction Terms	Effect of Frailty
Frailty Phenotype	Health Change			
	Better	REF	REF	0.9
	The Same	0.7	**0.02**	**0.001**
	Worse	0.1	0.6	0.4
	Frailty Phenotype	0.9	REF	REF
Frailty Index	Health Change			
	Better	REF	REF	0.6
	The Same	0.9	0.06	**0.03**
	Worse	0.6	0.21	0.2
	Frailty Index	0.5	REF	REF
Edmonton Frailty Scale	Health Change			
	Better	REF	REF	0.6
	The Same	0.5	0.7	0.2
	Worse	0.6	0.6	0.1
	Edmonton Frailty Scale	0.6	REF	REF
Clinical Frailty Scale	Health Change			
	Better	REF	REF	0.9
	The Same	0.9	0.4	0.2
	Worse	0.5	0.7	0.6
	CFS	0.9	REF	REF

Negative binomial regression model of 10175 nights in hospital in 485 participants. Adjusted analyses (Model 3) covariables: age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage [continuous] and kidney transplant wait-listing [active versus not active]. Bold text indicates significant at P<0.05 level.

Chapter 9:

A Clinical Frailty Scale obtained from MDT discussion performs poorly in assessing frailty in haemodialysis recipients

Authors: Benjamin M Anderson, Muhammad Qasim, Gonzalo Correa, Felicity Evison, Suzy Gallier, Charles J Ferro, Thomas A Jackson, Adnan Sharif

9.1 Extent of Personal Contribution

I coordinated all study visits with participants and dialysis unit staff. I recruited participants, and collected all baseline data with the support of Dr Gonzalo Correa, Dr Muhammad Qasim, and Dr Adnan Sharif. All colleagues were supervised by me in their data collection, and I was responsible for maintaining training and personnel logs in the site file.

Ms Felicity Evison, and Ms Suzy Gallier were responsible for interrogation of EPR for IMD Quintile assessment and HES/OPCS/ONS data for mortality and hospitalisation follow-up. I performed all subsequent data cleaning, integrity, and analyses with guidance from Dr Adnan Sharif.

The first draft of the manuscript was written by myself and I was responsible for all edits and revisions. This chapter is based upon a manuscript submitted for peer-review to BMC Nephrology, submission ID ff76481d-742c-462e-b21c-ecc0835ebff6.

9.2 Abstract

9.2.1 Background

The Clinical Frailty Scale (CFS) is a commonly utilised frailty screening tool that has been associated with hospitalisation and mortality in haemodialysis recipients, but is subject to heterogenous methodologies including subjective clinician opinion. The aims of this study were to i) examine the accuracy of a subjective, multidisciplinary assessment of CFS at haemodialysis Quality Assurance (QA) meetings (CFS-MDT), compared with a standard CFS score via clinical interview, and ii) ascertain the associations of these scores with hospitalisation and mortality.

9.2.2 Methods

We performed a prospective cohort study of prevalent haemodialysis recipients linked to national datasets for outcomes including mortality and hospitalisation. Frailty was assessed using the CFS after structured clinical interview. The CFS-MDT was derived from consensus at haemodialysis QA meetings, involving dialysis nurses, dietitians, and nephrologists.

9.2.3 Results

453 participants were followed-up for a median of 685 days (IQR 544-812), during which there were 96 (21.2%) deaths and 1136 hospitalisations shared between 327 (72.1%) participants. Frailty was identified in 246 (54.3%) participants via CFS, but only 120 (26.5%) via CFS-MDT. There was weak correlation (Spearman Rho 0.485, $P<0.001$) on raw frailty scores and minimal agreement (Cohen's $\kappa= 0.274$, $P<0.001$) on categorisation of frail, vulnerable and robust between the CFS and CFS-MDT. Increasing frailty was associated with higher rates of

hospitalisation for the CFS (IRR 1.26, 95% C.I. 1.17-1.36, P= 0.016) and CFS-MDT (IRR 1.10, 1.02-1.19, P=0.02), but only the CFS-MDT was associated with greater nights in hospital (IRR 1.22, 95% C.I. 1.08-1.38, P=0.001). Both scores were associated with mortality (CFS HR 1.31, 95% C.I. 1.09-1.57, P=0.004; CFS-MDT HR 1.36, 95% C.I. 1.16-1.59, P<0.001).

9.2.4 Conclusions

Assessment of CFS is deeply affected by the underlying methodology, with the potential to profoundly affect decision-making. Standardisation of CFS use is of paramount importance in clinical and research practice in haemodialysis.

9.3 Keywords

Frailty

Haemodialysis

Mortality

Hospitalisation

Clinical Frailty Scale

9.4 Introduction

Our previous work has shown that estimates of frailty prevalence vary significantly between frailty tools within a haemodialysis population, ranging between 42% to 63%.[272] The simplest frailty tool is the Clinical Frailty Scale (CFS);[27] prevalence of frailty among prevalent haemodialysis patients in our cohort was 54% according to CFS, with weak agreement between frailty instruments on individual frailty status.

Other studies have also explored CFS use in haemodialysis patients. Frailty prevalence has been estimated at 26% using CFS in Canada,[21] derived from a subjective clinician judgement of frailty based upon available records, rather than as an adjunct to detailed clinical interview as originally validated.[27]

In haemodialysis patients, frailty is strongly associated with mortality[21,170,184] and increased hospitalisation rates.[170,184,188] Therefore, any consensus on the optimal frailty instrument in haemodialysis settings needs to consider ease of use and association with adverse outcomes for dialysis patients. While the CFS is simple to use, the level of agreement between the CFS obtained from subjective clinician judgment versus the more objective method based upon clinical interview is not known, despite both methods being used in clinical and research practice. Neither is it known whether these different methods of CFS acquisition affect the associations with negative outcomes for haemodialysis patients. It is important to compare the association of these two different methods of obtaining CFS with mortality and hospitalisation, to determine which methodology is best applied for use in haemodialysis recipients, and that was the aim of this analysis.

9.5 Materials and Methods

FITNESS study design, eligibility, consent and baseline data acquisition are presented in detail in Chapters Chapter 2: and 2.2.

9.5.1 Frailty definitions

CFS was calculated using activity of daily living questionnaire results by the first author. CFS-MDT was ascertained as a result of MDT discussion at the participants' monthly dialysis quality assurance (QA) meeting. Present at this QA meeting were the patients' nephrologist, dialysis unit nurses, and dietitian; each had a copy of the CFS at the time of the meeting. CFS-MDT scores were arrived at by consensus from this MDT discussion; in the event of intractable MDT disagreement, the patients' nephrologist had the casting vote on CFS-MDT frailty status. Frailty for both CFS and CFS-MDT was defined as a score of ≥5, vulnerability a score of 4 and robustness a score of ≤3. A score of 9 (end of life but not frail) was considered robust for analysis.

9.5.2 Outcomes

Once more, as in Chapters Chapter 6:, 0, and Chapter 8:, mortality and hospitalisation were the primary outcomes of interest for this analysis. Admissions were again grouped into; i) infection, ii) dialysis access, iii) dialysis indications/CKD 5 (e.g. fluid overload/hyperkalaemia), iv) cancer, and v) major adverse cardiovascular events (MACE). Constituent HES codes are detailed in Supplementary Table 7-1. Transfers between hospitals were considered as one continuous admission, with the length of stay for such admissions considered to be the time from admission to the first hospital to discharge from the final hospital.

9.5.3 Statistics

Statistical analysis was performed using STATA (StataCorp 2021, Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Categorical data was presented as numbers and percentages, with continuous variables reported as medians and interquartile ranges (IQRs).

Correlations were analysed using Spearman's test. Agreement between frailty scores were analysed using Cohen's Kappa. Strength of agreement was rated as >0.90 almost perfect agreement, 0.80-0.90 strong, 0.60-0.79 moderate, 0.40-0.59 weak, 0.21-0.39 minimal and ≤0.20 no agreement.[275]

Survival analyses were performed for both mortality and a composite of mortality/first hospitalisation. Survival analyses were performed by generation of Kaplan-Meier curve estimates and time-to-event outcomes were analysed with the Cox's Proportional Hazards Model. The proportional hazard assumption was satisfied by examination of plots of the log-negative-log of the within-group survivorship functions versus log time as well as comparing Kaplan-Meier (observed) with Cox (expected) survival curves with our study variables, alongside selected covariables for adjusted analyses (reported as Hazard Ratios [HR] with 95% Confidence Intervals [CI]). Survival time was accrued from the day of baseline data collection and was censored for end of follow-up. Incidence rate ratios were obtained for count data by Negative Binomial Regression, offset by length of follow-up. Negative binomial distribution was confirmed by interrogation of means and variances and visual interpretation of expected

versus observed distribution plots. All regressions were performed treating frailty both as continuous and ordinal (Robust, Vulnerable, or Frail) variables; these were performed unadjusted and adjusted for an *a priori* list of covariables, considered based on a known or suspected relationship with dialysis-related admission (age, sex, ethnicity, body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, polypharmacy, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status). No kidney transplants occurred prior to first admission in this cohort, therefore only mortality-alone regressions were re-run according to the Fine and Gray model.

Missing IMD Quintile data were handled via a dummy variable. All other missing data was assumed missing at random and handled via listwise deletion as all other covariables had <1% data missing. A p value < 0.05 was considered significant in the statistical analysis.

9.6 Results

A PRISMA diagram of recruitment is shown in Figure 9-1. In total, 500 participants gave informed consent to participate in the cohort study between 12th January 2018 and 18th April 2019. After initial approach 15 participants withdrew from the study either prior to, or during data collection. A further 32 participants did not get discussed at the relevant dialysis QA (e.g., due to hospital admission after recruitment) and hence did not receive a CFS-MDT score. This

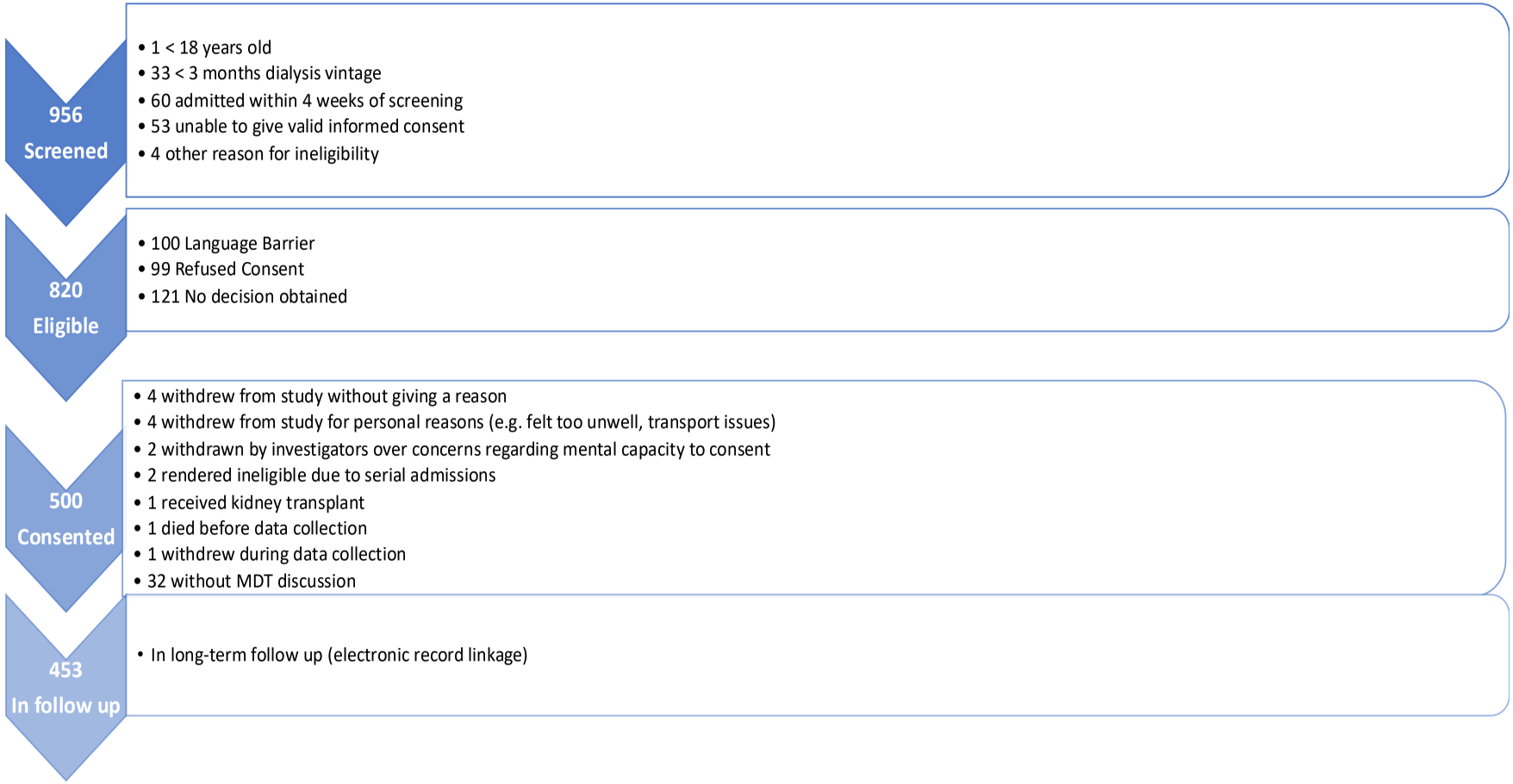


Figure 9-1: PRISMA flow diagram of study participation

left 453 participants with data available for this analysis. Table 9-1 shows baseline demographics and co-morbidities of study participants.

Participants were followed-up through EPR linkage for a median of 685 days (IQR 544-812) and all participants had a minimum potential follow-up of 365 days, barring mortality.

9.6.1 Frailty Prevalence, Correlation and Agreement

Using the CFS, 127 (28.0%) participants were classified as robust, 80 (17.7%) vulnerable, and 246 (54.3%) frail. By contrast, using the CFS-MDT 250 (55.2%) were classified as robust, 83 (18.3%) were vulnerable, and 120 (26.5% were frail).

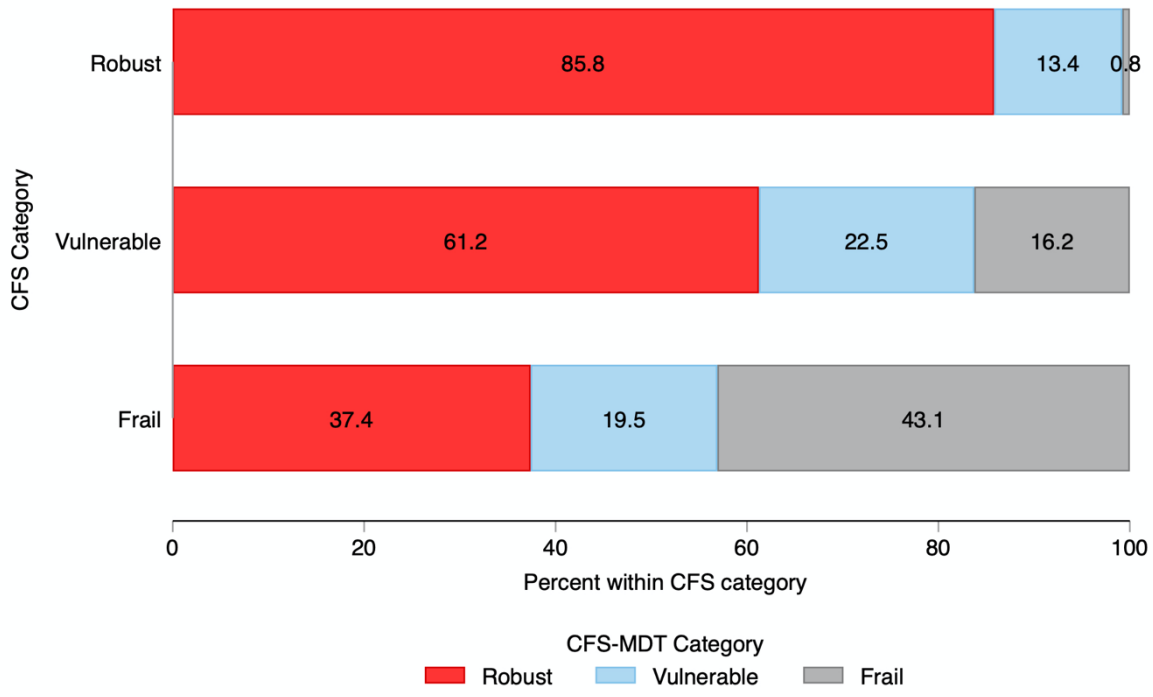


Figure 9-2: CFS-MDT frailty status as a proportion of CFS frailty

The CFS and CFS-MDT were weakly correlated (Spearman Rho 0.485, P<0.001), and agreement was minimal upon splitting into ordinal categories of robust, vulnerable, and frail (Cohen's κ= 0.274, P<0.001). Figure 9-2 demonstrates substantial discrepancy in frailty status between the CFS and CFS-MDT. For example, 37.4% of participants adjudged frail by CFS were considered robust by the CFS-MDT. There was also substantial variation in both correlation and agreement between CFS and CFS-MDT depending upon dialysis unit, as shown in Table 9-2.

9.6.1.1

9.6.2 Mortality

There were 96 deaths (21.2% of total) during follow-up. Infection was the primary cause of death for 20 (20.8%) participants, ischaemic heart disease 10 (10.4%), cerebrovascular disease 3 (3.1%), cancer 10 (10.4%), and CKD or haemodialysis complications in 3 (3.1%). Of the 20 infection-related deaths, 8 (8.3% of total deaths) were due to COVID-19. Cause of death data were not available for 20 (20.8%) participants. The most common causes of death are summarised in Supplementary Table 9-1.

Figure 9-3 and Figure 9-4 show Kaplan-Meier curves for survival by frailty category for both frailty tools. Table 9-3 shows that increasing frailty via both CFS and CFS-MDT was associated with increasing hazard for mortality after adjustment for *a priori* covariables. When split into robust, vulnerable, or frail categories, both frailty and vulnerability were associated with greater hazard for mortality when compared with robustness on multivariable analysis, as shown in Table 9-4. Fully adjusted model results are detailed in Supplementary Table 9-3 to Supplementary Table 9-6. Table 9-5Table 9-6 show interpretation of these data were not affected by treating transplant as a competing event.

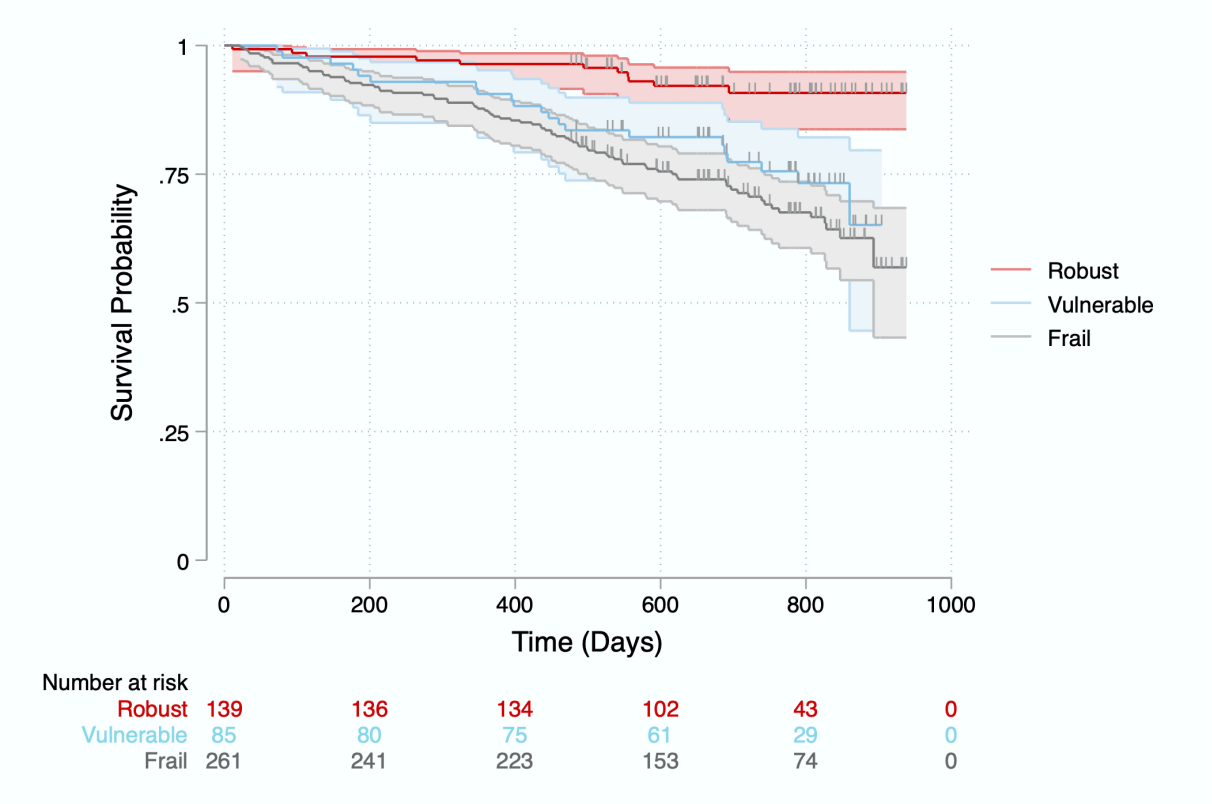


Figure 9-3: Univariable Kaplan-Meier curve of participant survival by CFS frailty status

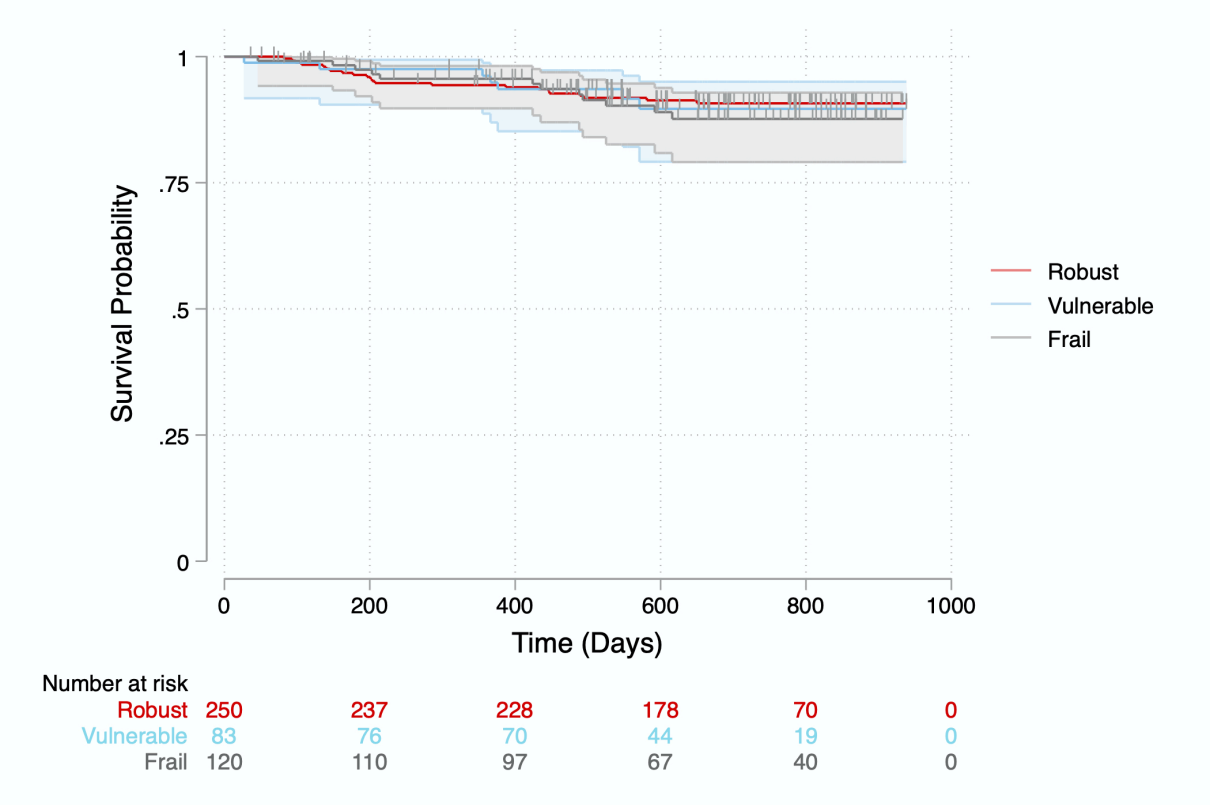


Figure 9-4: Univariable Kaplan-Meier curve of participant survival by CFS-MDT frailty status

9.6.3 Mortality/Hospitalisation

There were 1136 hospital admissions during follow-up, shared between 327 (72.1%) participants; the median number of admissions was 2 (IQR 0-4). Of these, 634 admissions occurred within the first year, split between 263 (58.1%) participants, with a median of 1 admission within 1-year of recruitment (IQR 0-2). Infection was listed as primary diagnosis in 254 (22.6%) admissions, 239 (21.3%) admissions were due to dialysis access, 139 (12.4%) for dialysis-specific indications, there were 41 (3.65%) MACE during admissions.

Figure 9-5 and Figure 9-6 show Kaplan-Meier curves for admission-free survival by frailty category for both frailty tools. Increasing frailty was associated with increased hazard for

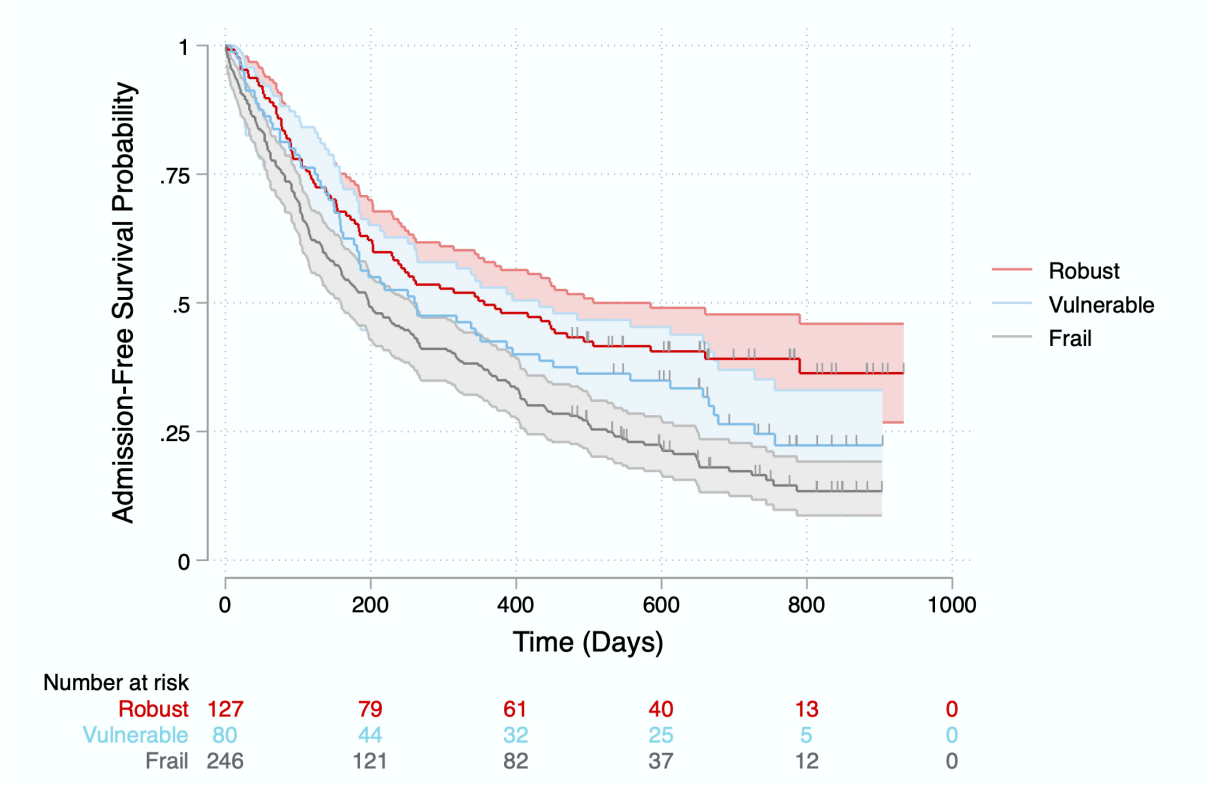


Figure 9-5: Univariable Kaplan-Meier of admission-free survival by CFS frailty status

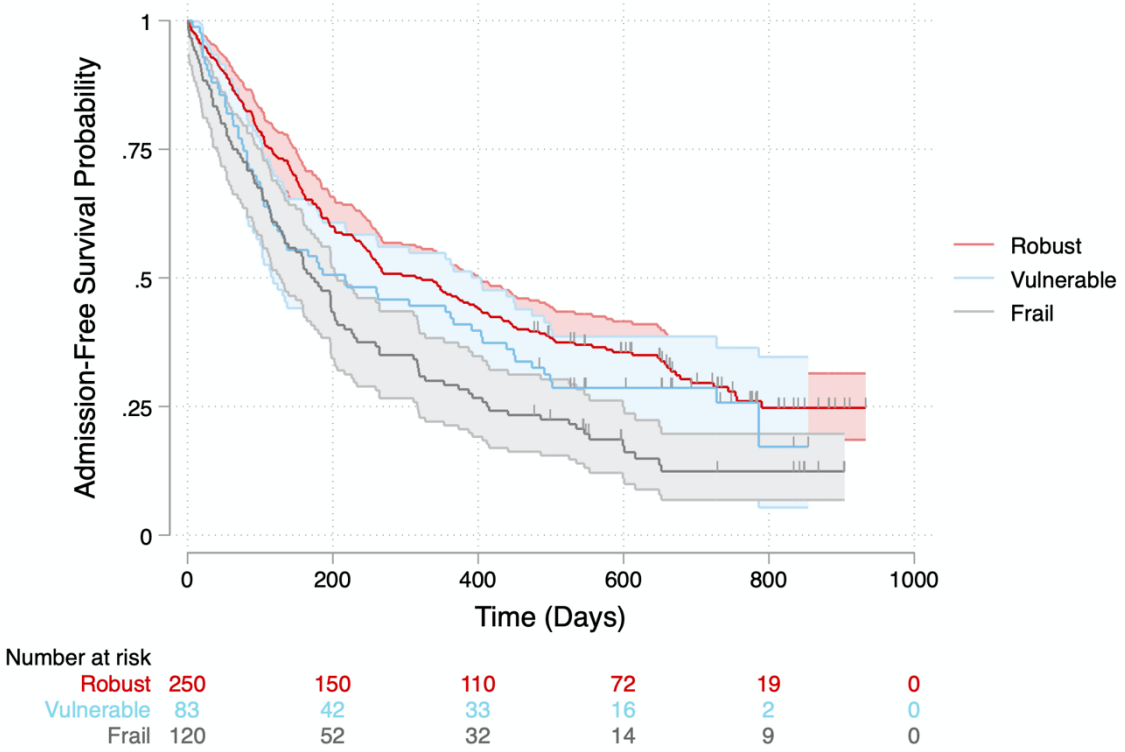


Figure 9-6: Univariable Kaplan-Meier of admission-free survival by CFS-MDT frailty status

mortality/hospitalisation by both CFS and CFS-MDT on both unadjusted and adjusted analysis, as shown in Table 9-3. However, Table 9-4 shows that when split into categories, only frailty was associated with increased hazard of mortality/hospitalisation when compared with robustness for both CFS and CFS-MDT, and this lost significance for the CFS-MDT on adjusted analysis. Fully adjusted Cox regression models for mortality/hospitalisation are shown in Supplementary Table 9-7 to Supplementary Table 9-10.

9.6.4 Rates of admission

Table 9-7 shows that increasing frailty was associated with higher rates of admission during follow up by both tools on adjusted analyses. Both tools demonstrated association with

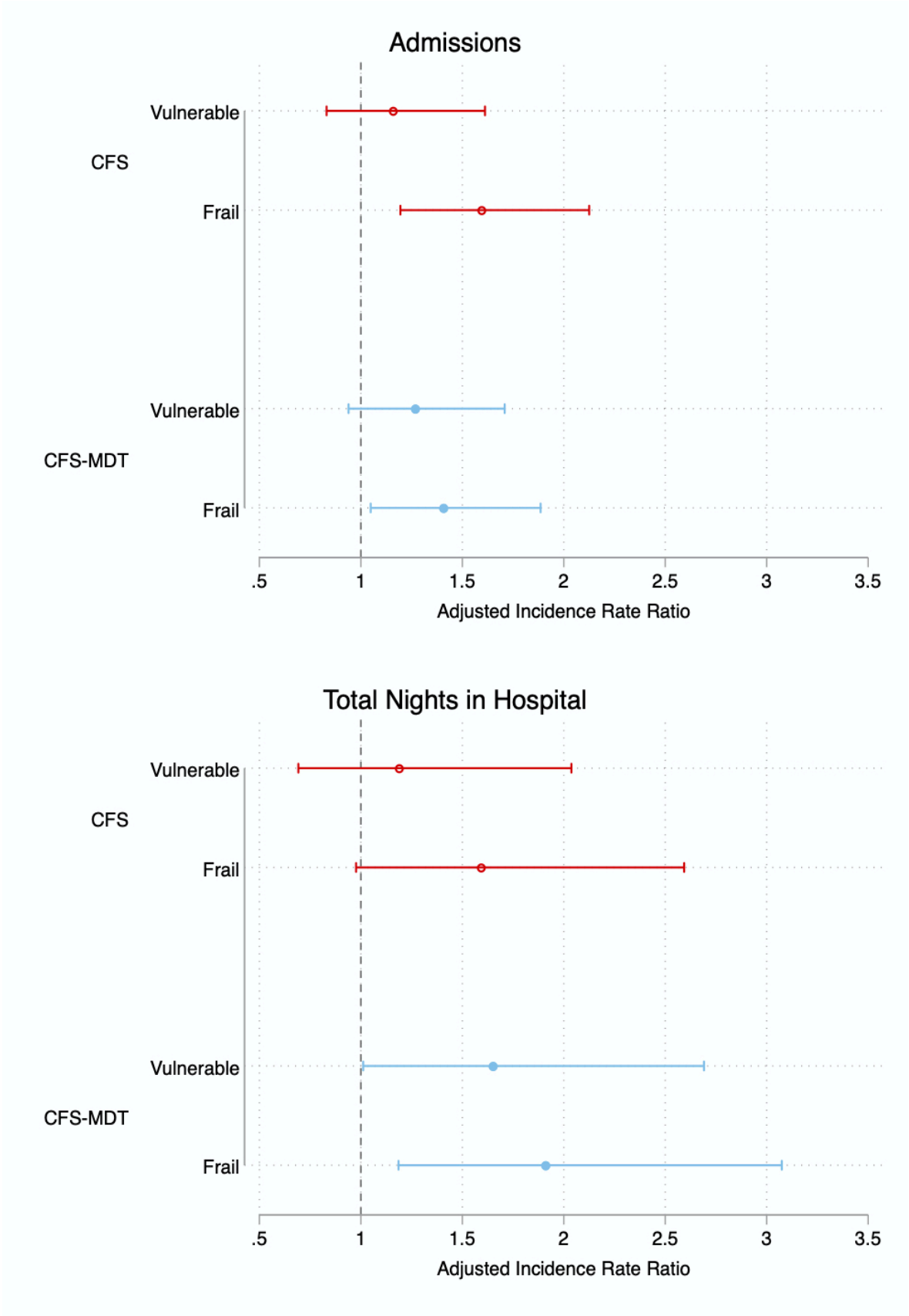


Figure 9-7: Composite forest plot of adjusted Incidence Rate Ratios of hospital admissions and total nights in hospital during follow-up by frailty status

greater nights spent in hospital on univariable analysis, but only the CFS-MDT retained this association on multivariable analysis. Figure 9-7 and Table 9-8 show a similar pattern was observed when the frailty tools were divided into frailty categories. Fully adjusted negative binomial models are shown in Supplementary Table 9-11 to Supplementary Table 9-18.

9.7 Discussion

Frailty is associated with adverse clinical outcomes for haemodialysis patients, including increased risk for hospitalisation and/or mortality, but heterogeneity in application and reporting of frailty tools limits generalisability. The CFS has been studied in haemodialysis, but based upon clinician opinion rather than - as originally operationalised – an adjunct to detailed clinical interview.[21] In this large prospective single centre prevalent haemodialysis cohort, we have shown that CFS derived via MDT discussion yields a much lower frailty prevalence than that based upon responses to clinical interview. Furthermore, there was only weak correlation of raw CFS scores and minimal agreement upon frailty classification between the two approaches. Whilst those adjudged to be frail both CFS and CFS-MDT had greater hazard for mortality/hospitalisation than robust participants, only frailty by CFS retained this association on multivariable analysis. It should be noted that when treated as a continuous variable – as originally intended[27] – increasing frailty by both scores was associated with mortality/hospitalisation and rate of admissions on adjusted analyses. Conversely, only the CFS-MDT was associated with increased nights in hospital on multivariable analysis. These results prompt questions about the validity of using clinician opinion to guide CFS scoring without the initial clinical interview, and highlights difficulties comparing results between cohorts that employ different frailty methodologies.

The CFS was originally conceived as a simple measure of frailty, validated after clinical interview of subjects. In this context, it showed high correlation with other frailty scores.[27] It has subsequently been studied as a subjective measure in incident haemodialysis based upon the opinion of the primary nephrologist,[21] although this measure has not been validated against the CFS as originally conceived. Nevertheless, increasing frailty by this approach was associated with higher mortality. We have previously shown that whilst agreement between the CFS and other validated frailty scores was weak or minimal, correlation of raw CFS scores with the Frailty Index was strong, and moderate correlation was seen between CFS and Frailty Phenotype and Edmonton Frail Scale.[272]

Our findings of wide variation in frailty prevalence, alongside the weak correlation and minimal agreement between the CFS and CFS-MDT, raises concern for clinical application. Figure 9-2 shows that over half of participants adjudged frail and over three-quarters of those adjudged vulnerable were misclassified by the CFS-MDT. Indeed, the frailty prevalence of 26.5% by CFS-MDT is less than half that of the CFS and also substantially lower than prevalence estimates according to the Frailty Phenotype, Frailty Index, and Edmonton Frail Scale in this cohort.[272] This suggests that relying upon clinician judgement alone may not be sufficient to capture all frailty within haemodialysis, which risks leaving behind a significant proportion of potential candidates for frailty intervention. The significant variation between haemodialysis units in both correlation of raw frailty scores and in agreement upon frailty status between the CFS and CFS-MDT suggests unmeasured local factors at individual haemodialysis units may influence interpretation of CFS-MDT and raises questions about inter-rater reliability.

Importantly, both the CFS and CFS-MDT were associated with mortality, mortality/hospitalisation, and total number of hospital admissions after adjustment for important covariables. However, only the CFS-MDT retained significant association with nights spent in hospital upon adjusted analyses. This complicates the notion of the CFS-MDT as an 'inferior' frailty tool. The CFS relies upon a perhaps simplistic decoding of ADL disability, whereas the subjective CFS-MDT may result in a more nuanced reflection of patients' clinical status by the clinical team who know them best. An alternative hypothesis, and one which may explain the lower overall rates of frailty using CFS-MDT, may be that clinicians are liable to compare patients against one another in a haemodialysis unit. This may have the dual effect of pushing down the estimate of frailty prevalence (as patient *x* is not as frail as patient *y*), but also of offering discrimination between those at higher and lower risk of adverse outcomes.

Frailty prevalence by the CFS-MDT in our prevalent haemodialysis cohort is remarkably similar to the 26% obtained from a Canadian incident haemodialysis cohort with a CFS obtained by similar methodology.[21] We must exercise caution when comparing frailty estimates across cohorts as demographics and methodologies may differ significantly. However, the discrepancy observed in the FITNESS cohort between frailty prevalence by CFS-MDT and CFS - alongside other frailty scores[272] - may lead us to speculate whether frailty prevalence might have been higher in the Canadian cohort if assessed by other frailty tools. Certainly, such a discrepancy between frailty prevalence observed between two interpretations of the same frailty instrument in the FITNESS cohort strongly suggests a need for consensus upon 1) which frailty tool is most appropriate for widespread use, and 2) the specific application of said tool.

This would limit what may otherwise be unsatisfactory variation between methodologies and aid the kidney community in comparing the needs of different haemodialysis populations.

To our knowledge, FITNESS is the largest prospective cohort study to compare frequently used frailty tools in haemodialysis, and the first to compare their associations with both mortality and hospitalisation. Further strengths include diversity of demographics, comorbidities and socio-economic backgrounds representative of local demographics.[327] However our data should be interpreted with caution in non-English populations. A limitation of FITNESS is the single cross-sectional assessment, as frailty is a dynamic state, with year-by-year variability in frailty observed in a prospective US haemodialysis cohort.[313] The CFS was derived from investigator interrogation of ADL questionnaire responses, rather than via CGA followed by multi-disciplinary discussion as in the original validation cohort.[27] However, given our ADL questionnaires were administered by research personnel in keeping with CFS clinical use guidance,[52] we would argue the potential for bias in such an approach is small. In another limitation, some 95% confidence intervals crossed the point of no effect by small margins, raising the possibility of type II error. Finally, whilst these data describe associations with mortality and hospital admissions, they cannot support the notion of frailty as a 'predictor' of such adverse outcomes, and due caution should be exercised when considering the applicability of these findings to the individual haemodialysis recipient in clinical practice.

To conclude, assessment of the Clinical Frailty Scale is dramatically affected by the underlying methodology, with the potential to profoundly affect clinical decision making. Agreement between subjective and objective measures of CFS frailty is minimal, with vulnerable patients

at greatest risk of misclassification. Whilst the subjective CFS-MDT showed greater association with some adverse outcomes than the traditional CFS, the minimal agreement and weak correlation between the scores, alongside wide variation in the agreement and correlation between dialysis units suggests the subjective measure of CFS-MDT is a poor alternative to the validated score. Standardisation of CFS use is of paramount importance in clinical and research practice within haemodialysis cohorts so that the lessons of frailty may be more freely applicable across populations.

9.8 Tables

Table 9-1: Baseline characteristics of the FITNESS cohort, including those considered frail by CFS and CFS-MDT

Parameter	Total cohort (n=453)	Participants adjudged as frail by:	
		CFS	CFS-MDT
Frail participants (% of total cohort)	-	246 (54.3%)	120 (26.5%)
Median Age*	63 (54-74)	65 (55-75)	70.5 (59-78.5)
Ethnicity			
White	263 (58.1%)	133 (54.1%)	70 (58.3%)
South Asian	107 (23.6%)	68 (27.6%)	31 (25.8%)
Black	72 (15.9%)	40 (16.3%)	19 (15.8%)
Other ethnicity	11 (2.4%)	5 (2.0%)	0 (0%)
Male	268 (59.2%)	131 (53.3)	61 (50.8%)
Median BMI*	26.9 (23.2-32.3)	27.9 (23.3-33.7)	27.4 (23.6-33.9)
IMD Quintile			
1	199 (43.9%)	111 (45.1%)	52 (43.3%)
2	79 (17.4%)	39 (15.9%)	19 (15.8%)
3	79 (17.4%)	45 (18.3%)	20 (16.7%)
4	36 (7.95%)	17 (6.9%)	11 (9.2%)
5	31 (6.8%)	17 (6.9%)	9 (7.5%)
Unknown	29 (6.4%)	17 (6.9%)	9 (7.5%)
Median Albumin*	39 (35-41)	38 (35-41)	37 (33-40)
Median MoCA Score*	22 (18-25)	20 (16-23)	19 (15-23)
Cause of kidney failure			
Diabetes	107 (23.6%)	74 (30.1%)	45 (37.5%)
Ischaemic	36 (8.0%)	22 (8.9%)	11 (9.2%)
Hypertensive	36 (8.0%)	17 (6.9%)	5 (4.2%)
IgA	35 (7.7%)	15 (6.1%)	6 (5.0%)
PKD	28 (6.2%)	11 (4.5%)	4 (3.3%)
FSGS	22 (4.9%)	10 (4.1%)	5 (4.2%)
Reflux	15 (3.3%)	10 (4.1%)	5 (4.2%)
Obstructive	16 (3.5%)	6 (2.44%)	5 (4.2%)
AAV	15 (3.3%)	4 (1.6%)	3 (2.5%)
Interstitial Nephritis	10 (2.2%)	4 (1.6%)	1 (0.8%)
Myeloma	9 (2.0%)	2 (0.8%)	2 (1.7%)
Other	38 (8.4%)	23 (9.4%)	11 (9.2%)
Unknown	63 (13.9%)	35 (14.2%)	13 (10.8%)
Medical co-morbidities			
MI	87 (19.2%)	57 (23.2%)	30 (25.0%)
Heart failure	46 (10.2%)	32 (13.0%)	13 (10.8%)
Stroke/TIA	53 (11.7%)	36 (14.6%)	25 (20.7%)
PVD	41 (9.1%)	28 (11.4%)	20 (16.7%)
Cancer	53 (11.%)	26 (10.6%)	14 (11.7%)
Smoking history			
Current	63 (13.9%)	29 (11.8%)	13 (10.8%)
Previous	124 (27.4%)	64 (26.0%)	32 (26.7%)

Never	266 (58.7%)	153 (62.2%)	75 (62.5%)
Median Charlson score* **	4 (3-6)	5 (4-6)	6 (4.5-7)
Dialysis details			
Median dialysis vintage (months)	36.2 (17.5-75.6)	40.6 (19.9-79.0)	42.0 (22.0-87.7)
Line access	99 (21.9%)	60 (24.4%)	35 (29.2%)
Median Kt/V	1.60 (1.41-1.85)	1.62 (1.41-1.89)	1.60 (1.38-1.88)
Transplant list status			
Active	54 (11.9%)	22 (8.9%)	1 (0.8%)
Suspended	13 (2.9%)	6 (2.4%)	0 (0%)
Not listed	386 (85.2%)	218 (88.6%)	119 (99.2%)
Employment status			
Employed	62 (13.7%)	8 (3.3%)	2 (1.7%)
Unemployed	136 (30.0%)	84 (34.2%)	27 (22.5%)
Retired	255 (56.3%)	154 (62.6%)	91 (75.8%)
Job role***			
Unskilled Manual	172 (39.5%)	106 (45.9%)	49 (43.0%)
Skilled Manual	99 (22.7%)	50 (21.7%)	27 (23.7%)
Clerical	48 (11.0%)	20 (8.7%)	10 (8.8%)
Managerial	41 (9.4%)	19 (8.2%)	9 (7.9%)
Professional	76 (17.4%)	36 (15.6%)	19 (16.7)
Education level			
High School	322 (71.1%)	186 (75.6%)	98 (81.7)
College/Sixth Form	84 (18.5%)	39 (15.9%)	15 (12.5%)
University	47 (10.4%)	21 (8.5%)	7 (5.8%)
Residence			
Own home	431 (95.6%)	230 (93.9%)	108 (90.0%)
Warden-controlled flat	12 (2.7%)	9 (3.7%)	5 (4.2%)
Residential home	5 (1.1%)	3 (1.2%)	4 (3.3%)
Nursing home	3 (0.7%)	3 (1.2%)	3 (2.5%)
With professional carers****	32 (7.37)	32 (12.7%)	21 (18.8%)

All numbers shown n (%) except * which indicates median (IQR). Percentages shown within CFS and CFS-MDT columns indicate percentage of those considered frail by relevant instrument unless otherwise stated. ** = CKD excluded. *** = Current job role or previous if retired/unemployed. **** = if not in nursing or residential care.

Table 9-2: Agreement and correlation between CFS and CFS-MDT by haemodialysis unit

HD Unit	κ	P	ρ	P
1	**0.510**	**<0.001**	**0.741**	**<0.001**
2	0.053	0.134	0.204	0.174
3	**0.158**	**0.018**	**0.457**	**<0.001**
4	**0.448**	**<0.001**	**0.660**	**<0.001**
5	**0.218**	**0.019**	**0.373**	**0.011**
6	0.076	0.153	**0.491**	**0.013**
7	**0.339**	**<0.001**	**0.634**	**<0.001**
8	**0.322**	**<0.001**	**0.561**	**<0.001**
9	**0.268**	**<0.001**	**0.484**	**<0001**
10	**0.470**	**<0.001**	**0.512**	**0.013**

Figures shown derived from Cohen's κ for agreement and Spearman's ρ for correlation. Dialysis units anonymised.

Table 9-3: Hazard Ratios for mortality and mortality/hospitalisation by frailty tool when treated as a continuous variable.

	CFS		CFS-MDT	
	HR (95% C.I.)	P	HR (95% C.I.)	P
Mortality				
Univariable	1.50 (1.29-1.76)	<0.001	1.54 (1.36-1.73)	<0.001
Multivariable	1.39 (1.13-1.70)	0.002	1.36 (1.16-1.59)	<0.001
Mortality/Hospitalisation				
Univariable	1.19 (1.10-1.29)	<0.001	1.18 (1.10-1.27)	<0.001
Multivariable	1.14 (1.03-1.26)	0.01	1.12 (1.02-1.23)	0.019

Cox's proportional hazards model. Hazard Ratios and 95% confidence intervals shown. All significant at P<0.05 level. Multivariable analyses adjusted for age, sex, ethnicity, body mass index, index of multiple deprivation, Charlson comorbidity index, number of hospitalisation episodes, polypharmacy, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status

Table 9-4: Hazard Ratios for mortality and mortality/hospitalisation for frailty when considered as a categorical variable

		CFS		CFS-MDT	
		HR 95% C.I.	P	HR 95% C.I.	P
Mortality					
Univariable	*Vulnerable*	**3.68 1.60-8.47**	**0.002**	**2.71 1.54-4.76**	**0.001**
	Frail	**5.03 2.42-10.45**	**<0.001**	**3.93 2.44-6.31**	**<0.001**
Multivariable	*Vulnerable*	**2.76 1.12-6.83**	**0.028**	**2.03 1.10-3.77**	**0.024**
	Frail	**3.60 1.56-8.34**	**0.003**	**2.30 1.30-4.07**	**0.004**
Mortality/Hospitalisation					
Univariable	*Vulnerable*	1.28 0.91-1.80	0.151	1.22 0.91-1.63	0.188
	Frail	**1.70 1.30-2.21**	**<0.001**	**1.61 1.26-2.06**	**<0.001**
Multivariable	*Vulnerable*	1.22 0.85-1.75	0.281	1.08 0.79-1.48	0.634
	Frail	**1.56 1.13-2.16**	**0.008**	1.35 0.99-1.85	0.058

Cox's proportional hazards model. Hazard Ratios and 95% confidence intervals shown. All significant at P<0.05 level. Multivariable analyses adjusted for age, sex, ethnicity, body mass index, index of multiple deprivation, Charlson comorbidity index, number of hospitalisation episodes, polypharmacy, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status. Bold text indicates significance at P<0.05 level.

Table 9-5: Fine and Gray regression model of mortality subdistribution hazard associated with frailty as a continuous variable

Model	SHR	Lower 95% C.I.	Upper 95% C.I.	P
Clinical Frailty Scale				
Unadjusted	1.51	1.31	1.73	<0.001
Adjusted	1.34	1.13	1.59	0.001
CFS-MDT				
Unadjusted	1.57	1.39	1.78	<0.001
Adjusted	1.38	1.16	1.64	<0.001

Fine and Gray's subdistribution hazards model with transplantation as a competing event. Subhazard Ratios and 95% confidence intervals shown. All significant at P<0.05 level. Multivariable analyses adjusted for age, sex, ethnicity, body mass index, index of multiple deprivation, Charlson comorbidity index, number of hospitalisation episodes, polypharmacy, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status. Bold text indicates significance at P<0.05 level.

Table 9-6: Fine and Gray regression model of mortality subdistribution hazard associated with frailty as an ordinal variable

Model	Frailty Status	SHR	Lower 95% C.I.	Upper 95% C.I.	P
Clinical Frailty Scale					
Unadjusted	*Vulnerable*	3.36	1.57	7.18	0.002
	Frail	4.68	2.42	9.05	<0.001
Adjusted	*Vulnerable*	2.42	1.04	5.63	0.041
	Frail	3.01	1.41	6.46	0.005
CFS-MDT					
Unadjusted	*Vulnerable*	2.14	1.11	4.10	0.023
	Frail	2.38	1.28	4.42	0.006
Adjusted	*Vulnerable*	2.88	1.63	5.09	<0.001
	Frail	4.21	2.59	6.85	<0.001

Fine and Gray's subdistribution hazards model with transplantation as a competing event. Subhazard Ratios and 95% confidence intervals shown. All significant at P<0.05 level. Multivariable analyses adjusted for age, sex, ethnicity, body mass index, index of multiple deprivation, Charlson comorbidity index, number of hospitalisation episodes, polypharmacy, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status. Bold text indicates significance at P<0.05 level.

Table 9-7: Incidence Rate Ratios of hospital admission, total nights in hospital by frailty as a continuous variable

	CFS		CFS-MDT	
	IRR 95% C.I.	P	IRR 95% C.I.	P
Total Admissions				
Univariable	**1.26** **1.17-1.36**	**<0.001**	**1.22** **1.14-1.30**	**<0.001**
Multivariable	**1.14** **1.04-1.25**	**0.006**	**1.10** **1.02-1.19**	**0.020**
Total Nights in Hospital				
Univariable	**1.34** **1.19-1.51**	**<0.001**	**1.36** **1.24-1.49**	**<0.001**
Multivariable	1.13 0.97-1.33	**0.126**	**1.22** **1.08-1.38**	**0.001**

Incidence Rate Ratios and 95% confidence intervals shown. All values obtained by negative binomial regression except *, which was obtained using zero-truncated negative binomial regression. Multivariable analyses adjusted for age, sex, ethnicity, body mass index, index of multiple deprivation, Charlson comorbidity index, number of hospitalisation episodes, polypharmacy, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status. Bold text indicates significance at P<0.05 level.

Table 9-8: Incidence Rate Ratios of hospital admission, total nights in hospital by frailty as an ordinal variable

		CFS		CFS-MDT	
		IRR 95% C.I.	P	IRR 95% C.I.	P
Total Admissions					
Univariable	Vulnerable	1.35 0.96-1.91	0.084	**1.51** **1.12-2.03**	**0.006**
	Frail	**2.10** **1.61-2.73**	**<0.001**	**1.96** **1.51-2.53**	**<0.001**
Multivariable	Vulnerable	1.16 0.83-1.61	0.387	1.27 0.94-1.71	0.121
	Frail	**1.59** **1.20-2.13**	**0.002**	**1.41** **1.05-1.89**	**0.023**
Total Nights in Hospital					
Univariable	Vulnerable	1.52 0.91-2.53	0.111	1.56 1.00-2.45	0.052
	Frail	**2.71** **1.84-4.01**	**<0.001**	**2.85** **1.92-4.22**	**<0.001**
Multivariable	Vulnerable	1.19 0.69-2.04	0.533	1.52 0.94-2.46	0.090
	Frail	1.59 0.97-2.59	0.062	**1.75** **1.12-2.72**	**0.013**

Incidence Rate Ratios and 95% confidence intervals shown. All values obtained by negative binomial regression. Multivariable analyses adjusted for age, sex, ethnicity, body mass index, index of multiple deprivation, Charlson comorbidity index, number of hospitalisation episodes, polypharmacy, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status. Bold text indicates significance at P<0.05 level.

9.9 Supplementary Materials

Supplementary Table 9-1

Admission Type	Explanation	HES/ICD-10/OPCS-4 Codes
Infection	Any infection in any site	A000-B999 E32.1 G000-G090 H00.0 H01.1 H03.0 H03.1 H04.0 H05.0 H05.1 H10.0 H10.2-H10.9 H30.0-H30.1 H30.9 H44.0-H44.1 H60.0-H60.3 H61.0 H62 H65.0-H65.1 I30.1 I320-I339 I38 I39 I40 I41.0-I41.2 I43.0 I52.0-I52.1 I68.1 I79.0-I79.1 I88 I98.0-I98.1 J000-J069 J090-J189 J200-J229 J32 J34.0 J360-J379 J38.3 J38.7 J39.0-J39.1 J44.0 J850-J869 K04.6 K04.7 K11.3 K11.2 K12.2 K14.0 K350-K379 K57.0 K57.2 K57.4 K57.8 K61 K63.0 K65.0 K67 K75.0 K77.0 K81 K83.0 K85 K87.1 L000-L089 M000-M039 M60.0 M63.0-M63.2 N30.0 N30.8 N30.9 N33 N34 N41 N43.1 N45 N48.1 N48.2 N49 N51 N61 N700-N769 U04 U06 U07 U820-U859
Dialysis Access	Any code indicating dialysis access dysfunction	T82.4 T82.5 T82.7 T82.8 T82.9 T85.6
Dialysis/CKD 5	Any code related to dialysis indications (uraemia, hyperkalaemia, hypervolaemia, or acidosis) or to CKD 5	E87.2 E87.5 E87.7 G63.8 G99.8 I32.8 I68.8 N18.5 N18.9 N19
Cancer	Any code relating to any cancer at any site	C000-C979 D000-D099 D100-D369 D370-D489
MACE	Any code relating to myocardial infarction, cerebrovascular accident, heart failure, or unstable angina pectoris or any procedure code relating to coronary revascularisation	HES: I200 I21-I22 I50 I60-I64 OPCS-4: K75

HES= Hospital Episode Statistics OPCS-4=Office of Population Censuses and Surveys Classification of Interventions and Procedures.. MACE=Major Adverse Cardiovascular Events.

Supplementary Table 9-2: Top 10 causes of death during follow-up

ICD-10 Code	Diagnosis	n
U07.1	COVID-19	8
I25.1	Atherosclerotic heart disease	5
J18.9	Pneumonia, unspecified	5
C90.0	Multiple myeloma	3
E11.2	Type 2 diabetes mellitus: With renal complications	3
E14.2	Unspecified diabetes mellitus: With renal complications	3
I12.0	Hypertensive renal disease with renal failure	3
I25.9	Chronic ischaemic heart disease, unspecified	3
N18.5	Chronic kidney disease, stage 5	3
C64	Malignant neoplasm of kidney, except renal pelvis	2

Supplementary Table 9-3: Fully adjusted Cox Regression Model of mortality associated with CFS frailty status - ordinal variable

	HR	Lower 95% C.I.	Upper 95% C.I.	P
CFS				
Robust		REFERENCE		
Vulnerable	**2.76**	**1.12**	**6.83**	**0.028**
Frail	**3.60**	**1.56**	**8.34**	**0.003**
Age	0.99	0.97	1.02	0.635
Gender				
Male		REFERENCE		
Female	0.89	0.58	1.38	0.608
Ethnicity				
White		REFERENCE		
South Asian	0.68	0.37	1.25	0.214
Black	0.90	0.48	1.66	0.726
Other	0.85	0.11	6.59	0.88
BMI	0.99	0.96	1.02	0.408
IMD Quintile				
1		REFERENCE		
2	0.90	0.50	1.64	0.729
3	1.15	0.64	2.06	0.644
4	0.83	0.36	1.92	0.670
5	0.76	0.31	1.88	0.560
Unknown	0.83	0.29	2.38	0.723
Charlson Index*	**1.18**	**1.05**	**1.33**	**0.006**
Previous admissions	1.03	0.93	1.14	0.562
Number Medications	1.00	0.93	1.07	0.948
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.48	0.75	2.90	0.256
Never Smoked	0.89	0.46	1.73	0.728
Albumin (g/L)	0.94	0.90	0.98	0.005
Walking Aid Use				
No		REFERENCE		
Yes	1.31	0.77	2.22	0.316
HD vintage	1.00	1.00	1.00	0.786
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	0.18	0.02	1.32	0.091

HR = Hazard Ratio. *=CKD omitted. **= Number of admissions in year prior to assessment.

Supplementary Table 9-4: Fully adjusted Cox Regression Model of mortality associated with CFS-MDT frailty status - ordinal variable

	HR	Lower 95% C.I.	Upper 95% C.I.	P
CFS-MDT				
Robust		REFERENCE		
Vulnerable	**2.03**	**1.10**	**3.77**	**0.024**
Frail	**2.30**	**1.30**	**4.07**	**0.004**
Age	0.99	0.97	1.02	0.661
Gender				
Male		REFERENCE		
Female	0.87	0.56	1.36	0.542
Ethnicity				
White		REFERENCE		
South Asian	0.67	0.36	1.23	0.194
Black	0.90	0.49	1.67	0.746
Other	0.85	0.11	6.58	0.878
BMI	0.99	0.96	1.02	0.402
IMD Quintile				
1		REFERENCE		
2	0.85	0.47	1.55	0.604
3	1.04	0.58	1.88	0.884
4	0.77	0.33	1.77	0.534
5	0.73	0.30	1.76	0.478
Unknown	0.79	0.27	2.26	0.659
Charlson Index*	1.16	1.03	1.31	0.015
Previous admissions	1.04	0.94	1.15	0.415
Number Medications	1.01	0.94	1.07	0.878
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.38	0.70	2.72	0.346
Never Smoked	0.84	0.43	1.61	0.592
Albumin (g/L)	**0.94**	**0.90**	**0.98**	**0.008**
Walking Aid Use				
No		REFERENCE		
Yes	1.35	0.79	2.32	0.276
HD vintage	1.00	1.00	1.00	0.583
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	0.20	0.03	1.49	0.116

HR = Hazard Ratio. *=CKD omitted. **= Number of admissions in year prior to assessment.

Supplementary Table 9-5: Fully adjusted Cox Regression Model of mortality associated with CFS as continuous variable

	HR	Lower 95% C.I.	Upper 95% C.I.	P
CFS	**1.39**	**1.13**	**1.70**	**0.002**
Age	1.00	0.97	1.02	0.761
Gender				
Male		REFERENCE		
Female	0.87	0.56	1.36	0.550
Ethnicity				
White		REFERENCE		
South Asian	0.68	0.37	1.24	0.207
Black	0.94	0.51	1.74	0.845
Other	0.69	0.09	5.29	0.721
BMI	0.98	0.96	1.01	0.304
IMD Quintile				
1		REFERENCE		
2	0.94	0.52	1.70	0.830
3	1.15	0.64	2.06	0.647
4	0.86	0.37	1.98	0.728
5	0.79	0.32	1.95	0.616
Unknown	0.82	0.29	2.36	0.718
Charlson Index*	**1.17**	**1.04**	**1.32**	**0.010**
Previous admissions	1.03	0.93	1.13	0.624
Number Medications	1.00	0.93	1.06	0.898
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.47	0.75	2.89	0.264
Never Smoked	0.86	0.44	1.67	0.660
Albumin (g/L)	**0.94**	**0.90**	**0.98**	**0.004**
Walking Aid Use				
No		REFERENCE		
Yes	1.21	0.70	2.11	0.491
HD vintage	1.00	1.00	1.00	0.776
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	0.17	0.02	1.27	0.084

HR = Hazard Ratio. *=CKD omitted. **= Number of admissions in year prior to assessment.

Supplementary Table 9-6: Fully adjusted Cox Regression Model of mortality associated with CFS-MDT as continuous variable

	HR	Lower 95% C.I.	Upper 95% C.I.	P
CFS-MDT	**1.36**	**1.16**	**1.59**	**<0.001**
Age	1.00	0.97	1.02	0.802
Gender				
Male		REFERENCE		
Female	0.85	0.55	1.32	0.471
Ethnicity				
White		REFERENCE		
South Asian	0.68	0.37	1.25	0.213
Black	0.92	0.50	1.69	0.782
Other	1.00	0.13	7.68	0.996
BMI	0.99	0.96	1.01	0.327
IMD Quintile				
1		REFERENCE		
2	0.92	0.51	1.66	0.781
3	1.11	0.62	2.01	0.717
4	0.80	0.35	1.84	0.597
5	0.79	0.33	1.92	0.607
Unknown	0.79	0.27	2.26	0.655
Charlson Index*	**1.15**	**1.02**	**1.30**	**0.027**
Previous admissions	1.04	0.94	1.15	0.443
Number Medications	1.00	0.94	1.07	0.903
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.44	0.73	2.82	0.293
Never Smoked	0.82	0.43	1.58	0.554
Albumin (g/L)	0.95	0.91	1.00	0.036
Walking Aid Use				
No		REFERENCE		
Yes	1.25	0.72	2.16	0.435
HD vintage	1.00	1.00	1.00	0.850
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	0.22	0.03	1.64	0.139

HR = Hazard Ratio. *=CKD omitted. **= Number of admissions in year prior to assessment.

Supplementary Table 9-7: Fully adjusted Cox Regression Model of mortality/hospitalisation associated with CFS status - ordinal variable

	HR	Lower 95% C.I.	Upper 95% C.I.	P
CFS				
Robust		REFERENCE		
Vulnerable	1.22	0.85	1.75	0.281
Frail	**1.56**	**1.13**	**2.16**	**0.008**
Age	0.99	0.98	1.01	0.295
Gender				
Male		REFERENCE		
Female	0.93	0.74	1.18	0.549
Ethnicity				
White		REFERENCE		
South Asian	1.09	0.81	1.46	0.567
Black	1.00	0.72	1.40	0.991
Other	0.74	0.34	1.61	0.444
BMI	0.99	0.97	1.01	0.234
IMD Quintile				
1		REFERENCE		
2	1.01	0.74	1.38	0.967
3	0.75	0.53	1.05	0.091
4	0.91	0.59	1.39	0.653
5	0.63	0.39	1.03	0.067
Unknown	0.89	0.55	1.42	0.624
Charlson Index*	1.03	0.96	1.11	0.398
Previous admissions	**1.09**	**1.04**	**1.15**	**<0.001**
Number Medications	1.04	1.00	1.07	0.054
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.86	0.60	1.24	0.419
Never Smoked	0.86	0.61	1.22	0.397
Albumin (g/L)	**0.97**	**0.94**	**0.99**	**0.006**
Walking Aid Use				
No		REFERENCE		
Yes	1.12	0.85	1.48	0.425
HD vintage	1.00	1.00	1.00	0.201
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	0.93	0.63	1.36	0.695

HR = Hazard Ratio. *=CKD omitted. **= Number of admissions in year prior to assessment.

Supplementary Table 9-8: Fully adjusted Cox Regression Model of mortality/hospitalisation associated with CFS-MDT status - ordinal variable

	HR	Lower 95% C.I.	Upper 95% C.I.	P
CFS-MDT				
Robust		REFERENCE		
Vulnerable	1.08	0.79	1.48	0.634
Frail	1.35	0.99	1.85	0.058
Age	0.99	0.98	1.01	0.363
Gender				
Male		REFERENCE		
Female	0.94	0.74	1.19	0.608
Ethnicity				
White		REFERENCE		
South Asian	1.12	0.84	1.51	0.431
Black	1.04	0.75	1.46	0.797
Other	0.73	0.34	1.60	0.438
BMI	0.99	0.97	1.01	0.181
IMD Quintile				
1		REFERENCE		
2	1.00	0.73	1.37	0.993
3	0.74	0.53	1.03	0.078
4	0.91	0.59	1.39	0.653
5	0.61	0.38	1.00	0.050
Unknown	0.88	0.55	1.41	0.590
Charlson Index*	1.02	0.95	1.10	0.566
Previous admissions	**1.09**	**1.04**	**1.14**	**<0.001**
Number Medications	**1.04**	**1.00**	**1.08**	**0.030**
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.87	0.61	1.26	0.470
Never Smoked	0.87	0.61	1.23	0.429
Albumin (g/L)	**0.97**	**0.94**	**0.99**	**0.009**
Walking Aid Use				
No		REFERENCE		
Yes	1.24	0.95	1.61	0.113
HD vintage	1.00	1.00	1.00	0.215
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	0.96	0.65	1.42	0.851

HR = Hazard Ratio. *=CKD omitted. **= Number of admissions in year prior to assessment.

Supplementary Table 9-9: Fully adjusted Cox Regression Model of mortality/hospitalisation associated with CFS – continuous variable

	HR	Lower 95% C.I.	Upper 95% C.I.	P
CFS	**1.14**	**1.03**	**1.26**	**0.010**
Age	0.99	0.98	1.00	0.251
Gender				
Male		REFERENCE		
Female	0.92	0.73	1.17	0.501
Ethnicity				
White		REFERENCE		
South Asian	1.10	0.82	1.48	0.507
Black	1.02	0.73	1.42	0.910
Other	0.73	0.33	1.59	0.424
BMI	0.99	0.97	1.01	0.207
IMD Quintile				
1		REFERENCE		
2	1.04	0.76	1.42	0.805
3	0.77	0.55	1.07	0.121
4	0.94	0.61	1.45	0.787
5	0.64	0.39	1.05	0.078
Unknown	0.90	0.56	1.43	0.649
Charlson Index*	1.03	0.96	1.11	0.380
Previous admissions	**1.09**	**1.04**	**1.14**	**<0.001**
Number Medications	1.03	1.00	1.07	0.057
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.87	0.61	1.25	0.454
Never Smoked	0.86	0.61	1.22	0.403
Albumin (g/L)	**0.97**	**0.94**	**0.99**	**0.006**
Walking Aid Use				
No		REFERENCE		
Yes	1.12	0.85	1.48	0.422
HD vintage	1.00	1.00	1.00	0.214
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	0.93	0.64	1.36	0.711

HR = Hazard Ratio. *=CKD omitted. **= Number of admissions in year prior to assessment.

Supplementary Table 9-10: Fully adjusted Cox Regression Model of mortality/hospitalisation associated with CFS-MDT – continuous variable

	HR	Lower 95% C.I.	Upper 95% C.I.	P
CFS-MDT	**1.12**	**1.02**	**1.23**	**0.019**
Age	0.99	0.98	1.01	0.382
Gender				
Male		REFERENCE		
Female	0.93	0.74	1.18	0.552
Ethnicity				
White		REFERENCE		
South Asian	1.12	0.84	1.50	0.442
Black	1.04	0.74	1.45	0.829
Other	0.73	0.34	1.60	0.432
BMI	0.99	0.97	1.01	0.182
IMD Quintile				
1		REFERENCE		
2	1.01	0.74	1.39	0.934
3	0.76	0.54	1.06	0.105
4	0.92	0.60	1.40	0.690
5	0.65	0.40	1.06	0.084
Unknown	0.89	0.56	1.43	0.636
Charlson Index*	1.02	0.95	1.10	0.583
Previous admissions	**1.09**	**1.04**	**1.14**	**<0.001**
Number Medications	**1.04**	**1.00**	**1.07**	**0.039**
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.87	0.61	1.26	0.466
Never Smoked	0.86	0.61	1.21	0.382
Albumin (g/L)	**0.97**	**0.95**	**1.00**	**0.023**
Walking Aid Use				
No		REFERENCE		
Yes	1.20	0.92	1.57	0.174
HD vintage	1.00	1.00	1.00	0.226
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	1.00	0.68	1.48	0.999

HR = Hazard Ratio. *=CKD omitted. **= Number of admissions in year prior to assessment.

Supplementary Table 9-11: Fully adjusted negative binomial regression of hospital admissions associated with CFS – continuous variable

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
CFS	**1.14**	**1.04**	**1.25**	**0.006**
Age	**0.99**	**0.98**	**1.00**	**0.047**
Gender				
Male		REFERENCE		
Female	0.96	0.78	1.20	0.742
Ethnicity				
White		REFERENCE		
South Asian	0.79	0.59	1.05	0.109
Black	**0.65**	**0.47**	**0.90**	**0.008**
Other	0.85	0.41	1.76	0.667
BMI	0.99	0.98	1.01	0.267
IMD Quintile				
1		REFERENCE		
2	0.88	0.65	1.18	0.383
3	0.75	0.55	1.03	0.074
4	0.83	0.56	1.25	0.375
5	0.71	0.45	1.12	0.142
Unknown	1.19	0.78	1.82	0.408
Charlson Index*	**1.09**	**1.02**	**1.17**	**0.011**
Previous admissions	**1.09**	**1.04**	**1.15**	**<0.001**
Number Medications	1.03	1.00	1.06	0.087
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.02	0.71	1.45	0.933
Never Smoked	0.89	0.65	1.23	0.491
Albumin (g/L)	0.98	0.96	1.01	0.157
Walking Aid Use				
No		REFERENCE		
Yes	**1.37**	**1.06**	**1.78**	**0.017**
HD vintage	1.00	1.00	1.00	0.566
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	0.85	0.59	1.23	0.390
Constant	**0.01**	**0.00**	**0.02**	**<0.001**

IRR= Incidence Rate Ratio, obtained by negative binomial regression. *=CKD omitted. **= Number of admissions in year prior to assessment.

Supplementary Table 9-12: Fully adjusted negative binomial regression of hospital admissions associated with CFS-MDT – continuous variable

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
CFS-MDT	**1.10**	**1.02**	**1.19**	**0.020**
Age	**0.99**	**0.98**	**1.00**	**0.030**
Gender				
Male		REFERENCE		
Female	0.97	0.78	1.21	0.792
Ethnicity				
White		REFERENCE		
South Asian	0.79	0.59	1.07	0.124
Black	**0.65**	**0.47**	**0.89**	**0.008**
Other	0.93	0.45	1.92	0.844
BMI	0.99	0.98	1.01	0.347
IMD Quintile				
1		REFERENCE		
2	0.87	0.65	1.18	0.376
3	0.74	0.54	1.02	0.068
4	0.81	0.54	1.21	0.295
5	0.70	0.44	1.12	0.137
Unknown	1.17	0.76	1.78	0.478
Charlson Index*	**1.09**	**1.02**	**1.17**	**0.014**
Previous admissions	**1.09**	**1.04**	**1.14**	**0.001**
Number Medications	**1.03**	**1.00**	**1.07**	**0.046**
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.02	0.71	1.46	0.916
Never Smoked	0.90	0.65	1.25	0.538
Albumin (g/L)	0.99	0.97	1.01	0.501
Walking Aid Use				
No		REFERENCE		
Yes	**1.47**	**1.15**	**1.88**	**0.002**
HD vintage	1.00	1.00	1.00	0.419
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	0.89	0.62	1.29	0.532
Constant	**0.00**	**0.00**	**0.02**	**<0.001**

IRR= Incidence Rate Ratio, obtained by negative binomial regression. *=CKD omitted. **= Number of admissions in year prior to assessment.

Supplementary Table 9-13: Fully adjusted negative binomial regression of total nights in hospital associated with CFS – continuous variable

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
CFS	1.13	0.97	1.33	0.126
Age	**0.98**	**0.96**	**1.00**	**0.036**
Gender				
Male		REFERENCE		
Female	0.98	0.69	1.38	0.888
Ethnicity				
White		REFERENCE		
South Asian	0.74	0.44	1.23	0.243
Black	0.76	0.45	1.29	0.310
Other	0.54	0.17	1.71	0.298
BMI	0.99	0.96	1.01	0.251
IMD Quintile				
1		REFERENCE		
2	**0.59**	**0.36**	**0.97**	**0.036**
3	0.76	0.44	1.29	0.301
4	0.83	0.43	1.61	0.584
5	1.07	0.51	2.25	0.851
Unknown	1.14	0.57	2.28	0.714
Charlson Index*	1.11	0.99	1.25	0.086
Previous admissions	**1.13**	**1.03**	**1.22**	**0.007**
Number Medications	1.00	0.95	1.06	0.882
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	**1.98**	**1.10**	**3.57**	**0.023**
Never Smoked	1.29	0.76	2.19	0.353
Albumin (g/L)	0.96	0.92	0.99	0.019
Walking Aid Use				
No		REFERENCE		
	2.12	**1.37**	**3.28**	**0.001**
HD vintage	1.00	1.00	1.00	0.589
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	0.81	0.45	1.43	0.463
Constant	**0.14**	**0.02**	**0.92**	**0.040**

IRR= Incidence Rate Ratio, obtained by negative binomial regression. *=CKD omitted. **= Number of admissions in year prior to assessment.

Supplementary Table 9-14: Fully adjusted negative binomial regression of total nights in hospital associated with CFS-MDT – continuous variable

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
CFS-MDT	**1.22**	**1.08**	**1.38**	**0.001**
Age	**0.98**	**0.96**	**1.00**	**0.029**
Gender				
Male		REFERENCE		
Female	0.89	0.63	1.27	0.531
Ethnicity				
White		REFERENCE		
South Asian	0.77	0.47	1.28	0.314
Black	0.74	0.44	1.25	0.261
Other	0.63	0.20	1.96	0.423
BMI	0.99	0.97	1.02	0.493
IMD Quintile				
1		REFERENCE		
2	0.64	0.39	1.04	0.073
3	0.71	0.42	1.21	0.212
4	0.79	0.41	1.52	0.484
5	1.18	0.57	2.45	0.658
Unknown	1.07	0.53	2.13	0.855
Charlson Index*	1.08	0.97	1.22	0.170
Previous admissions	**1.12**	**1.03**	**1.22**	**0.008**
Number Medications	1.00	0.95	1.05	0.992
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	**1.84**	**1.03**	**3.30**	**0.039**
Never Smoked	1.21	0.71	2.06	0.478
Albumin (g/L)	0.98	0.95	1.02	0.355
Walking Aid Use				
No		REFERENCE		
Yes	**2.13**	**1.45**	**3.12**	**<0.001**
HD vintage	1.00	1.00	1.00	0.882
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	0.90	0.51	1.58	0.707
Constant	**0.05**	**0.01**	**0.39**	**0.004**

IRR= Incidence Rate Ratio, obtained by negative binomial regression. *=CKD omitted. **= Number of admissions in year prior to assessment.

Supplementary Table 9-15: Fully adjusted negative binomial regression admissions associated with CFS frailty status – ordinal variable

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
CFS				
Robust		REFERENCE		
Vulnerable	1.16	0.83	1.61	0.387
Frail	**1.59**	**1.20**	**2.13**	**0.002**
Age	**0.99**	**0.98**	**1.00**	**0.044**
Gender				
Male		REFERENCE		
Female	0.96	0.78	1.20	0.736
Ethnicity				
White		REFERENCE		
South Asian	0.78	0.58	1.05	0.098
Black	**0.64**	**0.46**	**0.88**	**0.006**
Other	0.84	0.41	1.75	0.648
BMI	0.99	0.98	1.01	0.270
IMD Quintile				
1		REFERENCE		
2	0.87	0.64	1.17	0.353
3	**0.73**	**0.53**	**1.00**	**0.047**
4	0.81	0.54	1.21	0.309
5	0.66	0.42	1.05	0.080
Unknown	1.21	0.80	1.84	0.371
Charlson Index*	**1.09**	**1.02**	**1.17**	**0.011**
Previous admissions	**1.09**	**1.04**	**1.15**	**<0.001**
Number Medications	1.03	0.99	1.06	0.117
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.02	0.71	1.46	0.913
Never Smoked	0.90	0.65	1.24	0.503
Albumin (g/L)	0.98	0.96	1.01	0.133
Walking Aid Use				
No		REFERENCE		
Yes	**1.36**	**1.06**	**1.76**	**0.017**
HD vintage	1.00	1.00	1.00	0.527
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	0.84	0.59	1.21	0.355
Constant	**0.01**	**0.00**	**0.02**	**<0.001**

IRR= Incidence Rate Ratio, obtained by negative binomial regression. *=CKD omitted. **= Number of admissions in year prior to assessment.

Supplementary Table 9-16: Fully adjusted negative binomial regression admissions associated with CFS-MDT frailty status – ordinal variable

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
CFS-MDT				
Robust		REFERENCE		
Vulnerable	1.27	0.94	1.71	0.121
Frail	**1.41**	**1.05**	**1.89**	**0.023**
Age	**0.99**	**0.98**	**1.00**	**0.030**
Gender				
Male		REFERENCE		
Female	0.97	0.78	1.21	0.816
Ethnicity				
White		REFERENCE		
South Asian	0.80	0.60	1.07	0.130
Black	**0.65**	**0.47**	**0.89**	**0.008**
Other	0.90	0.44	1.87	0.783
BMI	0.99	0.98	1.01	0.307
IMD Quintile				
1		REFERENCE		
2	0.85	0.63	1.15	0.303
3	0.73	0.53	1.00	0.050
4	0.80	0.53	1.19	0.266
5	0.69	0.43	1.10	0.115
Unknown	1.17	0.77	1.79	0.467
Charlson Index*	**1.09**	**1.02**	**1.17**	**0.013**
Previous admissions	**1.09**	**1.04**	**1.15**	**<0.001**
Number Medications	1.03	1.00	1.07	0.049
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.01	0.71	1.45	0.938
Never Smoked	0.90	0.65	1.25	0.543
Albumin (g/L)	0.99	0.97	1.01	0.371
Walking Aid Use				
No		REFERENCE		
Yes	**1.47**	**1.15**	**1.88**	**0.002**
HD vintage	1.00	1.00	1.00	0.463
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	0.89	0.61	1.28	0.525
Constant	**0.01**	**0.00**	**0.02**	**<0.001**

IRR= Incidence Rate Ratio, obtained by negative binomial regression. *=CKD omitted. **= Number of admissions in year prior to assessment.

Supplementary Table 9-17: Fully adjusted negative binomial regression of total nights in hospital associated with CFS frailty status – ordinal variable

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
CFS				
Robust		REFERENCE		
Vulnerable	1.19	0.69	2.04	0.533
Frail	1.59	0.98	2.59	0.062
Age	**0.98**	**0.96**	**1.00**	**0.032**
Gender				
Male		REFERENCE		
Female	0.96	0.68	1.38	0.844
Ethnicity				
White		REFERENCE		
South Asian	0.74	0.45	1.24	0.254
Black	0.75	0.44	1.27	0.291
Other	0.53	0.17	1.67	0.276
BMI	0.99	0.96	1.01	0.251
IMD Quintile				
1		REFERENCE		
2	**0.59**	**0.36**	**0.97**	**0.036**
3	0.73	0.43	1.25	0.255
4	0.79	0.41	1.54	0.497
5	0.98	0.47	2.08	0.967
Unknown	1.15	0.58	2.31	0.686
Charlson Index*	1.11	0.99	1.25	0.079
Previous admissions	**1.12**	**1.03**	**1.22**	**0.007**
Number Medications	1.00	0.95	1.06	0.997
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	**2.03**	**1.12**	**3.69**	**0.020**
Never Smoked	1.30	0.76	2.21	0.341
Albumin (g/L)	**0.96**	**0.92**	**0.99**	**0.013**
Walking Aid Use				
No				
Yes	**2.07**	**1.34**	**3.18**	**0.001**
HD vintage	1.00	1.00	1.00	0.555
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	0.79	0.45	1.40	0.426
Constant	0.22	0.03	1.41	0.110

IRR= Incidence Rate Ratio, obtained by negative binomial regression. *=CKD omitted. **= Number of admissions in year prior to assessment.

Supplementary Table 9-18: Fully adjusted negative binomial regression of total nights in hospital associated with CFS-MDT frailty status – ordinal variable

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
CFS-MDT				
Robust		REFERENCE		
Vulnerable	**1.65**	**1.01**	**2.69**	**0.045**
Frail	**1.91**	**1.19**	**3.07**	**0.008**
Age	**0.98**	**0.96**	**0.99**	**0.009**
Gender				
Male		REFERENCE		
Female	0.94	0.66	1.33	0.720
Ethnicity				
White		REFERENCE		
South Asian	0.77	0.47	1.29	0.326
Black	0.81	0.48	1.36	0.424
Other	0.54	0.17	1.69	0.289
BMI	0.98	0.96	1.01	0.220
IMD Quintile				
1		REFERENCE		
2	**0.60**	**0.37**	**0.99**	**0.044**
3	0.70	0.41	1.19	0.186
4	0.79	0.41	1.52	0.476
5	1.13	0.54	2.37	0.743
Unknown	1.08	0.54	2.17	0.833
Charlson Index*	1.10	0.98	1.23	0.122
Previous admissions	**1.13**	**1.04**	**1.23**	**0.005**
Number Medications	1.01	0.95	1.06	0.781
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	**1.89**	**1.05**	**3.40**	**0.033**
Never Smoked	1.28	0.75	2.17	0.370
Albumin (g/L)	0.97	0.94	1.01	0.117
Walking Aid Use				
No		REFERENCE		
Yes	**2.26**	**1.53**	**3.33**	**<0.001**
HD vintage	1.00	1.00	1.00	0.409
Transplant Listing Status				
Not Active/Not Listed		REFERENCE		
Active	0.88	0.50	1.57	0.676
Constant	**0.14**	**0.02**	**0.94**	**0.043**

IRR= Incidence Rate Ratio, obtained by negative binomial regression. *=CKD omitted. **= Number of admissions in year prior to assessment.

Chapter 10:

Depression is associated with frailty and lower quality of life in haemodialysis recipients, but not with mortality or hospitalisation.

Authors: Benjamin M Anderson, Muhammad Qasim, Gonzalo Correa, Felicity Evison, Suzy Gallier, Charles J Ferro, Thomas A Jackson, Adnan Sharif

10.1 Extent of Personal Contribution

I coordinated all study visits with participants and dialysis unit staff. I recruited participants, and collected all baseline data with the support of Dr Gonzalo Correa, Dr Muhammad Qasim, and Dr Adnan Sharif. All colleagues were supervised by me in their data collection, and I was responsible for maintaining training and personnel logs in the site file.

Ms Felicity Evison, and Ms Suzy Gallier were responsible for interrogation of EPR for IMD Quintile assessment and HES/OPCS/ONS data for mortality and hospitalisation follow-up. I performed all subsequent data cleaning, integrity, and analyses with guidance from Dr Adnan Sharif.

The first draft of the manuscript was written by myself and I was responsible for all edits and revisions. This chapter is based upon a manuscript accepted for publication in CKJ: Clinical Kidney Journal, for which I am first author.[328]

10.2 Abstract

10.2.1 Background

Frailty and depression are highly prevalent in haemodialysis recipients, exhibit a reciprocal relationship, and are associated with increased mortality, hospitalisation, and lower quality of life. Despite this, there has been little exploration of the relationship between depression and frailty upon patient outcomes. We aimed to explore the relationship between depression and frailty and their associations with mortality, hospitalisation, and quality of life (QOL).

10.2.2 Methods

We performed a prospective cohort study of prevalent haemodialysis recipients linked to national datasets for outcomes including mortality and hospitalisation. Depression was assessed using PHQ-9, frailty using Clinical Frailty Scale (CFS), and quality of life using EuroQol EQ-5D Summary Index.

10.2.3 Results

485 prevalent haemodialysis recipients were recruited, with 111 deaths and 1241 hospitalisations during follow-up. CFS was independently associated with mortality (HR 1.31; 95% C.I. 1.08, 1.59; P = 0.006), hospitalisation (IRR 1.13; 95% C.I. 1.03, 1.25; P = 0.010), and lower HRQOL (Coef. -0.401; 95% C.I. -0.511, -0.292; P<0.001). PHQ-9 score was independently associated with lower QOL (Coef. -0.042; 95% C.I. -0.063, -0.021; P<0.001), but not mortality (HR 1.00; 95% C.I. 0.96, 1.04; P = 0.901), or hospitalisation (IRR 0.99; 95% C.I. 0.97, 1.01; P =

0.351). In an adjusted model including CFS, moderate depression was associated with reduced hospitalisation (IRR 0.72; 95% C.I. 0.56, 0.93; P = 0.013).

10.2.4 Discussion

With addition of frailty, depression was associated with lower hospital admissions, but poorer quality of life. The relationship between frailty and depression, and their influence on outcomes is complex, requiring further study.

10.3 Introduction

We have seen that frailty is associated with hospitalisation and mortality in haemodialysis recipients, and that on the balance of ease of use alongside association with important outcomes, the CFS likely represents the optimal choice of frailty tool in this population. We now turn our attention to the interplay between frailty and depression.

Depression impacts upon quality of life in haemodialysis recipients,[193,194] but is generally under-recognised in haemodialysis populations.[195] The Patient Health Questionnaire-9 (PHQ-9) has been validated in dialysis recipients, with 92% sensitivity and 92% specificity for detection of depression.[196] Depression of at least moderate severity was present in 28% of participants of a large prospective cohort, and both moderate depression and continuous PHQ-9 scores have been associated with mortality.[197-199] In a systematic review and meta-analysis of published observational studies, depression was associated with increased mortality hazard for dialysis recipients.[200] A diagnosis of depression has also been associated with greater hospitalisation, but lower mortality within hospital admission episodes in retrospective cohorts.[201,202]

Frailty is also associated with poor quality of life for kidney patients, which begins early at a pre-dialysis stage as identified in Brazilian[234] and UK[235] cohorts. In haemodialysis patients, McAdams-DeMarco and colleagues noted self-rated fair/poor quality of life was more likely in frail haemodialysis recipients, and that frailty was associated with worsening quality of life over time.[236] A decline in quality of life in frail haemodialysis recipients was also observed in a small Canadian cohort.[237] Qualitative analysis by Hall and colleagues explored this further,

finding frail and non-frail older haemodialysis recipients held different perspectives of health-related quality of life (HRQOL) in semi-structured interviews.[231]

Despite the high prevalence of both frailty and depression, there has been little exploration of the relationship between the two in haemodialysis recipients. A systematic review of depression and frailty in non-dialysis older adults has suggested a reciprocal relationship between frailty and depression, with each being a risk factor for the other.[203] However, Sy and colleagues found prevalent depression was associated with incident frailty, but not vice versa in a prevalent United States (US) dialysis cohort.[204] US and European dialysis demographics and outcomes differ significantly,[205] therefore these relationships require further study in non-US haemodialysis populations. As a clear overlap exists between symptoms of frailty and depression, the relationship between them and their associations with patient-centred outcomes requires scrutiny. Therefore, the aims of this study were; i) to explore the relationship between frailty and depression, and ii) to assess the association of depression with mortality, hospitalisation, and quality of life in haemodialysis recipients.

10.4 Materials and Methods

10.4.1 Study design

FITNESS study design, eligibility, consent and baseline data acquisition are presented in detail in Chapters Chapter 2: and 2.2.

PHQ-9 scores were obtained by patient questionnaire with 9 questions each scored between 0-3 for frequency of depression symptoms, giving a total score of between 0-27[196]. The

Physical Activity Index (PAI) was derived from the GP Physical Activity Questionnaire (GPPAQ) via a validated formula.[268,269] Electronic Patient Records were interrogated for comorbidities, drug history, alongside dialysis vintage and adequacy, previous transplantation, and biochemical data. Self-reported change in health (henceforth "health change") was obtained by asking the question "How has your health changed in the last year?" with potential responses of "Better" "The Same" or "Worse". Determination of socio-economic deprivation was based upon the Index of Multiple Deprivation 2015 (IMD), a multiple deprivation model calculated at the local level area, with 1 representing the most deprived and 5 the least deprived area respectively.

The Clinical Frailty Scale was obtained by interpretation of ADL questionnaire responses, with possible responses of 1-9. A CFS of 1 represented very fit, and 8 severely frail. A CFS score of 9 was attributed to those who were terminally ill but not overtly frail.

10.4.2 Outcomes

Mortality data were obtained by electronic record linkage of all FITNESS study recruits to Office of National Statistics (ONS), a UK-wide repository of death certificate data. This ensures robust coverage of mortality data capture and comprehensive description of causality. Hospital Episode Statistics (HES), a database containing all secondary care episodes in any NHS hospital in England, provided robust national data for all hospitalisations. Hospital admissions were defined as any hospital episode lasting ≥1 night.

Health-related quality of life was assessed using Euroqol EQ-5D-3L. This was converted into the single-measure EQ-5D Summary Index via a standardised formula.[267] This results in a potential score of between 1 (if no HRQOL deficits identified) and -0.716 (if extreme deficit in every domain), and has been validated in UK populations.

10.4.3 Recruitment

Recruitment and power calculations are explored in detail in previous work from the FITNESS project.[263,272]

10.4.4 Statistics

Statistical analysis was performed using STATA 17 (StataCorp 2021, Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) and R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). Categorical data were presented as numbers and percentages, with continuous variables reported as medians and interquartile ranges (IQRs).

Survival analyses were performed by Cox's Proportional Hazards Model. The proportional hazard assumption was checked and satisfied by examination of plots of the log-negative-log of the within-group survivorship functions versus log time as well as comparing Kaplan-Meier (observed) with Cox (expected) survival curves with our study variables, alongside selected covariables for adjusted analyses (reported as Hazard Ratios [HR] with 95% Confidence Intervals [CI]). As kidney transplantation may materially affect mortality, these analyses were re-run using Fine and Gray subdistribution hazards model, with any kidney transplant as a competing event.

Incidence rate ratios were obtained for admissions data by negative binomial regression, death-censored and offset by length of follow-up. Negative binomial distribution was confirmed by interrogation of means and variances and visual interpretation of expected versus observed distribution plots.

All survival and admissions regressions were performed unadjusted and adjusted for an *a priori* list of covariables, based on a known or suspected relationship with dialysis-related mortality/admission (age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage, self-reported change in health, and kidney transplant wait-listing). Further adjusted models were performed using the aforementioned covariables plus the addition of CFS score.

Odds ratios of both frailty and moderate depression were obtained by logistic regression. Linear regressions were performed to explore the relationship between continuous frailty and PHQ-9 scores. Linearity was checked by comparison of observed values by linear and Lowess fit plots, and by plotting observed versus predicted residual values. These linear and logistic regressions were performed unadjusted and as a series of adjusted models based upon *a priori* covariables selected for known or suspected relationship with the outcome of interest. For depression, model 1 included frailty, age, ethnicity, gender. Model 2 added IMD quintile, social support and education level. Model 3 added admissions in the past year, Charlson index (CKD

excluded), cognitive impairment, current antidepressant use, total medication number, and haemodialysis vintage. Model 4 added self-reported pain, self-reported change in health and overall self-rated health (EQ-5D visual analogue scale/100). For frailty, Model 1 included depression, age, gender and ethnicity. Model 2 added education level, social support and IMD quintile. Model 3 added Charlson Index (CKD excluded), cognitive impairment, smoking status, self-rated change in health and overall health. Model 4 added use of walking aids, Physical Activity Index, slow timed walk and low grip strength.

The EQ-5D summary index is right-censored, with a maximum value of one. Therefore, it was transformed using the following equation $\frac{(x+0.594)}{1.594}$ to give a fractional score between 0 and 1. Fractional regressions for the transformed fractional EQ-5D summary index were performed unadjusted and subject to a separate set of *a priori* covariable models, based upon known or suspected relationship with HRQOL, covariables found to significantly associate with frailty and/or PHQ-9 scores were also added to reduce confounding. Models were constructed in a pre-determined stepwise manner. Model 1 included age, gender, ethnicity, education level, social support, IMD quintile, and employment status. Model 2 added to these haemodialysis vintage, Charlson comorbidity index (CKD omitted), haemoglobin, Kt/V, and current use of antidepressant medication. Model 3 added use of walking aids, slow walking (or inability to walk), and physical activity index. Model 4 added EQ-5D VAS, and self-rated health change.

Variables that demonstrated significance in the final multivariable models were tested for interaction with both CFS and PHQ-9 scores and an interaction term for the outcome of interest.

Missing values for IMD quintile were handled with a separate category. Otherwise, missing data were assumed missing at random and handled via listwise deletion as all other covariables had <1% data missing. A p value < 0.05 was considered significant in the statistical analysis.

10.5 Results

10.5.1 Study Cohort Demographics

Figure 4-1 shows the PRISMA study flow of participant recruitment to the FITNESS study, with 485 prevalent haemodialysis patients with baseline frailty assessments and data linkage. Follow up was 678 days (interquartile range: 531-812 days), with all participants receiving a minimum potential follow-up of 365 days from recruitment. Baseline demographics are described in detail elsewhere.[272] Table 10-1 highlights key demographics stratified by frailty status at study recruitment.

10.5.2 Depression Scores

The median PHQ-9 score was 5 (IQR 2-10), with 222 participants (46.3%) reporting minimal depression, 131 (27.3%) reporting mild depression, 76 (15.8%) reporting moderate depression, 38 (7.9%) reporting moderately-severe depression, and 13 (2.7%) reporting

severe depression. Overall, 127 participants (26.5%) reported at least a moderate level of depression.

10.5.3 A reciprocal relationship between frailty and depression

Figure 10-1 demonstrates that, on both univariable and each multivariable analysis, every increase in CFS score was associated with increased PHQ-9 scores. Table 10-2 demonstrates that on multivariable analysis, the following were associated with increasing PHQ-9 score; CFS, self-reported worse health, antidepressant use, and overall medication number. Increasing age and South Asian ethnicity (versus white) were associated with lower PHQ-9 scores.

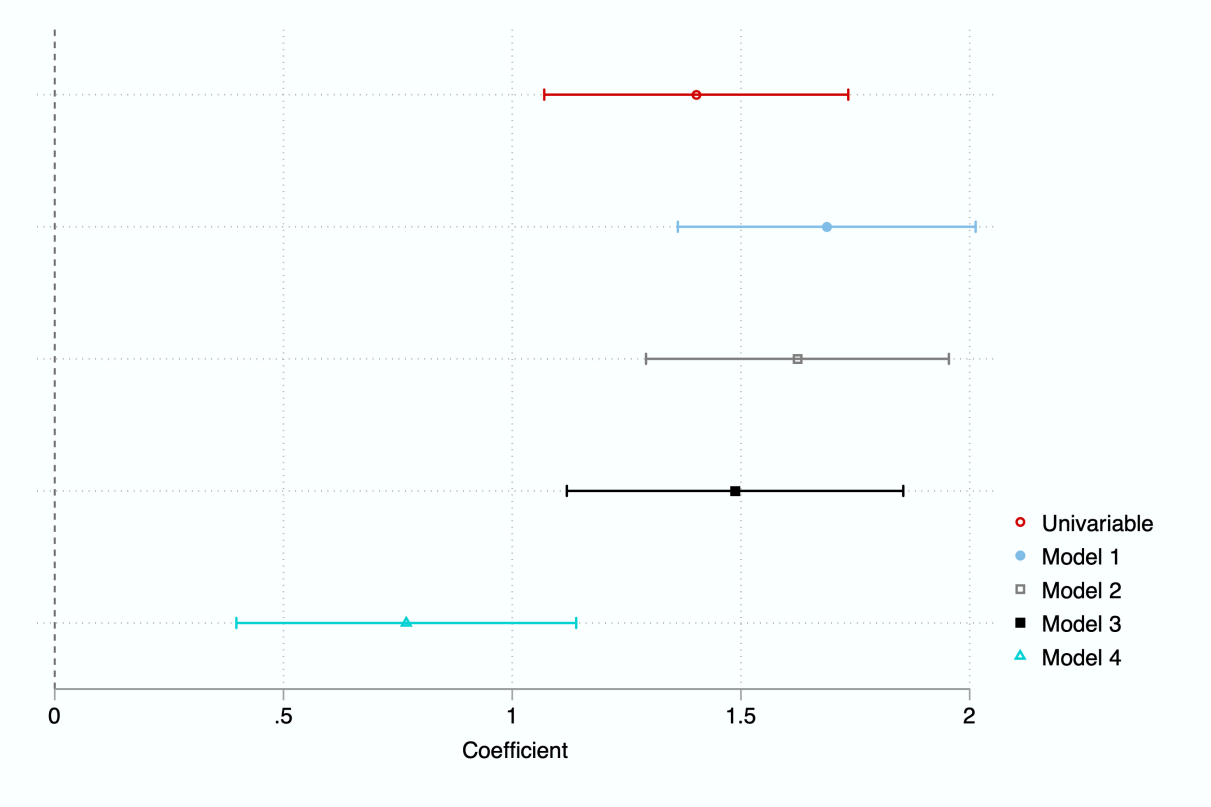


Figure 10-1: Change in PHQ-9 score with each one point increase in CFS. Simple and multiple linear regressions shown.

Figure 10-2 demonstrates that PHQ-9 score was associated with CFS score on all adjusted models. Table 10-3 highlights the fully adjusted model, with PHQ-9 score, female sex, Charlson index, walking aid use, and slow walking speed all associated with increasing CFS score. On the same model, self-rated health, increasing physical activity, and social support were associated with lower CFS scores.

10.5.4 Mortality and hospitalisation

Over a follow-up period comprising a total of 862.1 patient-years, we observed 111 (22.9%) deaths, 2,729 attendances to hospital, 1,241 hospital admissions of at least one night's duration (1.44 admissions per patient-year), and 10,175 total nights spent in hospital. Overall, 382 (78.8%) participants had at least one hospital admission during follow-up, with the median number of admissions was 2 (IQR: 0-4).

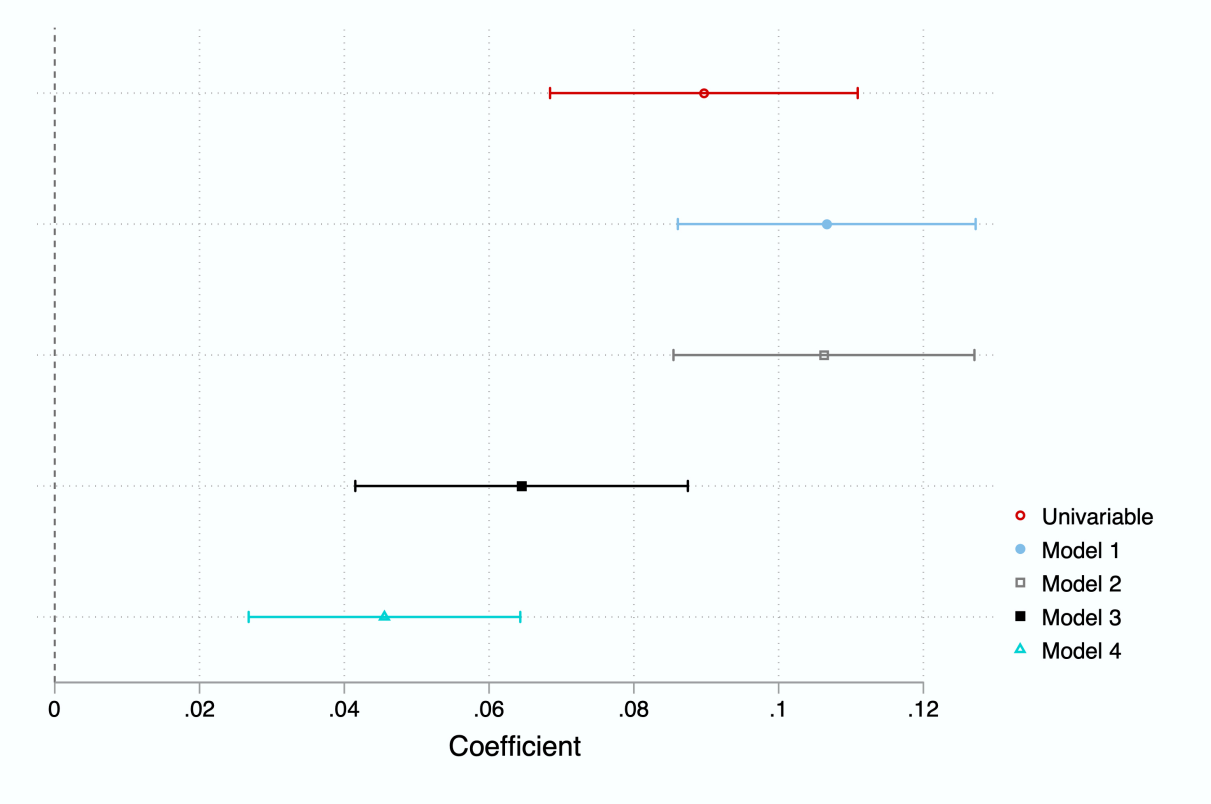


Figure 10-2: Change in CFS score associated with each one-point increase in PHQ-9 score. Simple and multiple linear regression results shown.

10.5.5 Depression and mortality

Neither PHQ-9 score nor moderate depression were associated with mortality, on either unadjusted or adjusted analyses, as shown in Table 10-4 and Table 10-5. A competing risks model with transplantation as the competing event showed similar results, as demonstrated in Table 10-6 and Table 10-7. Fully adjusted Cox regression models are shown in Supplementary Table 10-2 to Supplementary Table 10-5.

10.5.6 Depression and hospital admissions

Raw PHQ-9 score was associated with increased rates of hospitalisation on univariable analysis (IRR 1.02, 95% C.I. 1.00-1.04, P=0.028), but this was lost on multivariable analyses both with

CFS included (IRR 0.99, 95% C.I. 0.97-1.01, P=0.351) and excluded (IRR 1.00, 95% C.I. 0.98-1.02, P=0.973) from the model. Full model results are shown in Supplementary Table 10-6 and Supplementary Table 10-7.

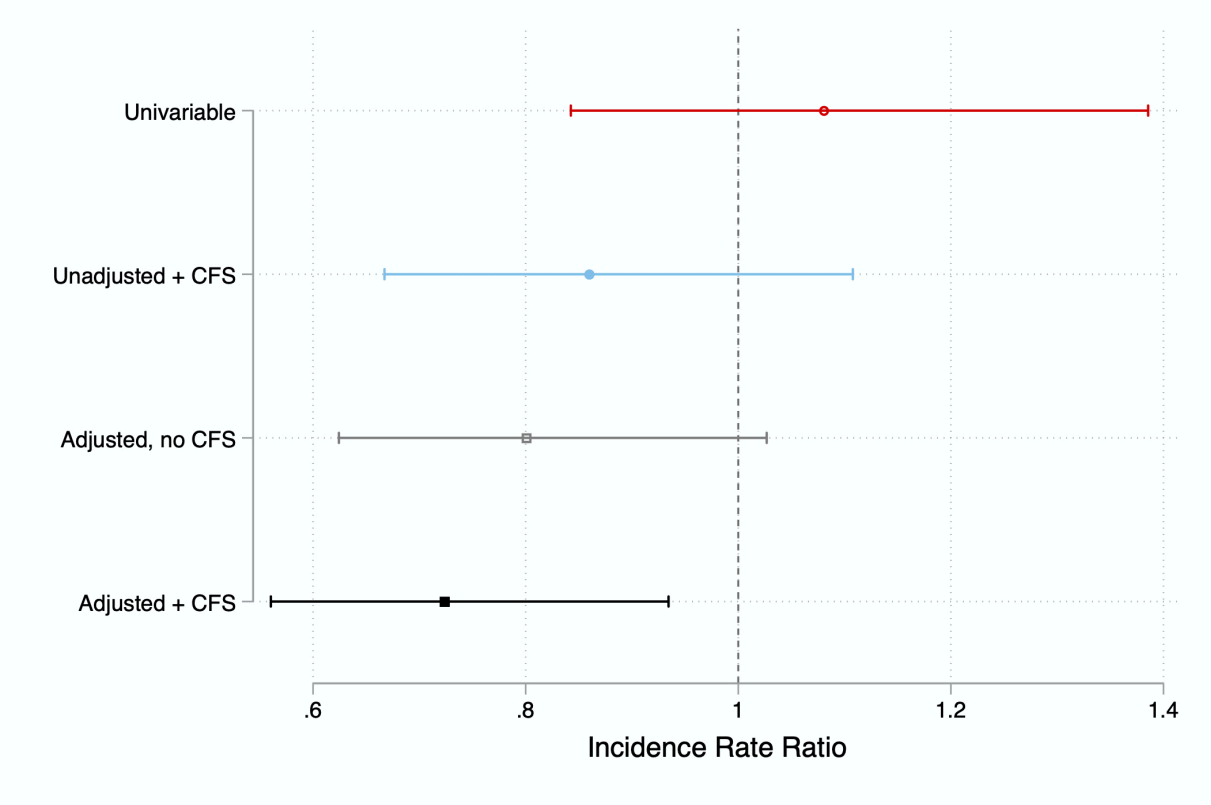


Figure 10-3: Incidence Rate Ratios of hospital admissions associated with at least moderate depression on univariable and multivariable analyses, both with and without the inclusion of CFS in the model

Figure 10-3 shows moderate depression was not associated with rates of hospital admissions in univariable or multivariable analyses where CFS was omitted. However, IRRs for admissions were significantly lower upon multivariable analysis with the addition of CFS into the model. Full model results are shown in Supplementary Table 10-8 and Supplementary Table 10-9.

10.5.7 Depression, Frailty and Quality of Life

Table 10-8 demonstrates that in the fully adjusted Model 4, the following were all independently associated with poorer quality of life; PHQ-9 score, CFS score, female gender, university education, lack of social support, haemodialysis vintage, slow walking speed, moderate activity, self-rated health, and cognitive impairment.

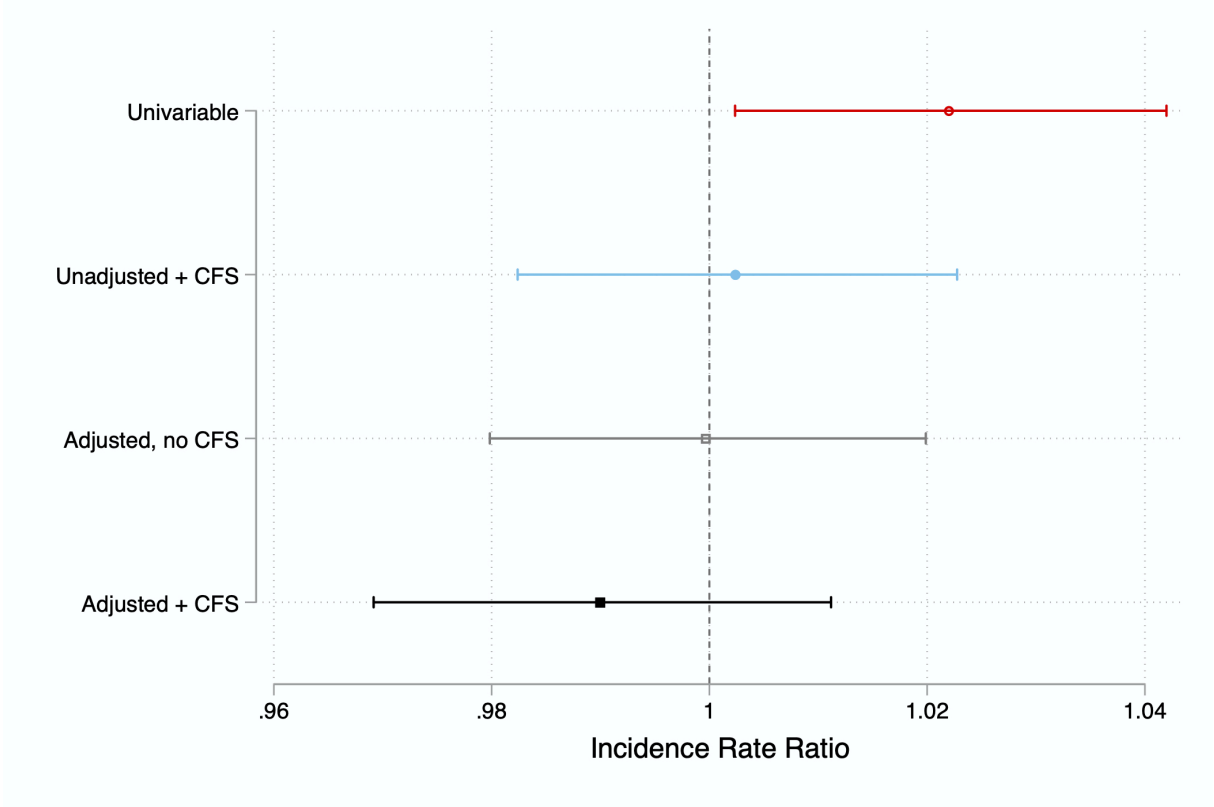


Figure 10-4: Incidence Rate Ratios of hospital admissions associated with continuous PHQ-9 scores on univariable and multivariable analyses, both with and without the inclusion of CFS in the model

10.6 Discussion

Frailty and depression are both associated with adverse outcomes in haemodialysis recipients, but there has been little investigation of the relationship between these important conditions and patient outcomes. To the best of our knowledge, this study is the first to demonstrate

that frailty and poor self-reported health over the past year are associated with increased PHQ-9 scores for haemodialysis patients, whereas self-reported physical activity is inversely associated with PHQ-9 score. We did not replicate findings of a significant association between depression and mortality, nor any association with hospital admissions on multivariable analyses. Our data highlights the complex association between frailty and depression in haemodialysis recipients, but does not support depression as an associate of mortality or hospitalisation. However, depression remains an important outcome in itself as evidenced by its association with lower quality of life.

Our data corroborate work suggesting a reciprocal relationship between depression and frailty. In a systematic review of frailty and depression in non-dialysis elderly people, a reciprocal and bi-directional relationship was observed between depression and frailty was observed.[203] By contrast, Sy and colleagues observed in a large US multicentre longitudinal haemodialysis cohort that depression was associated with incident frailty but not vice-versa.[204] However, the same cohort however demonstrate an association baseline frailty and baseline depression. Our cohort confirms this association even after adjustment for numerous *a priori* covariables, including many that may be considered surrogates for frailty and/or depression, suggesting a robust relationship between the two.

The lack of association between depression and mortality runs counter to work from other groups and warrants further discussion. In a large prospective cohort study, Sanglimbene and colleagues observed moderate depression by the Beck Depression Inventory (BDI) to be associated with all-cause mortality in haemodialysis. Chilcot and colleagues also observed an

association between moderate depression and mortality using both the BDI and PHQ-9.[198] In a meta-analysis, depression scores were associated with a modest mortality HR of 1.04,[200] though heterogeneity in study populations and depression measures limit interpretation of these results. The effect size seen in this meta-analysis was small, from a sample population of 8,267 participants, suggesting our lack of significant association between depression and mortality may represent an underpowered sample. A lack of appreciable effect size on mortality hazard in our cohort, however, undermines this hypothesis. Machado and colleagues, in an umbrella review of published systematic reviews and meta-analyses, observed nominally significant results to suggest an association between depression and all-cause mortality in the general population.[329] However, the evidence becomes weaker when focusing on studies using structured interviews and those adjusting for potential confounders. Therefore, a causal effect of depression on all-cause and cause-specific mortality remains unproven and is consistent with our data.

We can speculate depressed and frail haemodialysis recipients may be less inclined to seek medical attention for the sequelae of their frailty, or that healthcare providers may be more inclined to attribute their presenting complaints to co-morbid depression rather than organic disease. There was however no appreciable interaction effect between these two variables. Alternatively, serial measures of depression may be more sensitive at identifying patients at risk of adverse outcomes. Weisbord and colleagues have reported an associated increase in hospitalisation and mortality for haemodialysis recipients with moderate to severe depression upon serial prospective measures of depression.[199] To further illustrate the heterogenous nature of reported outcomes, a coded diagnosis of depression in retrospective registry studies

amongst haemodialysis recipients was associated with greater admission rates and length of stay in hospital,[202] but lower mortality risk during inpatient stay.[201] However, caution with such data interpretation is required as coding data has been shown to have limited accuracy when applied to comorbidities – rather than primary admission diagnoses – and thus limits the potential accuracy of their use in research.[315] Further work is warranted to better understand these important outcomes for haemodialysis patients.

The association between frailty, depression and HRQOL is less well described in haemodialysis recipients. Jafari and colleagues demonstrated frailty to be associated with lower EQ-5D scores in a small Canadian haemodialysis cohort.[237] McAdams-DeMarco and colleagues found an association between frailty and self-rated fair or poor health, though this might not be considered as a HRQOL measure *per se*.[236] Depression has also been associated with lower quality of life in haemodialysis recipients.[193,194] Our data demonstrates frailty and depression independently associate with poorer health-related quality of life, which has not been reported before. Furthermore, we have demonstrated sex, education, social support, haemodialysis vintage, walking speed, cognitive impairment and self-rated health all have independent associations with poorer HRQOL. Whilst these data only describe associations, rather than predictors of lower HRQOL, they suggest that the determinants of HRQOL may be complex and require detailed study.

FITNESS is amongst the first studies to examine the relationship between frailty and depression in a large prospective haemodialysis cohort. Strengths of this study include the large prospective cohort with robust data linkage for outcomes. The cohort is well described

with multiple areas of frailty, quality of life, comorbidity, cognition, depression, and musculoskeletal function accounted for in the analysis. Further strengths include the diversity of demographics, comorbidities and socio-economic backgrounds representative of the local population.[327] However, our data should be interpreted with caution in non-English populations, and validation of our findings elsewhere is required. Limitations also include the single baseline data collection for frailty and depression phenotyping; both are dynamic syndromes and repeated measures would offer greater detail and arguably accuracy.[199,313] Our CFS definition deviates slightly from the original validation sample,[27] in that no MDT discussion was held to determine frailty status after clinical interview. However, as argued in prior chapters, we may argue that our approach is largely concordant with guidance upon CFS use in clinical practice.[52] Use of the EQ-5D summary index for HRQOL is validated in UK populations, but its relationship with other HRQOL measures is uncertain. Finally, we report associations in these observational data rather than causation, and due caution should be maintained when applying these findings to the individual haemodialysis recipient in clinical practice.

To conclude, depression and frailty are intimately linked in haemodialysis recipients, and independently associate with poorer quality of life, but only frailty is associated with mortality and hospitalisation in this cohort. Our data highlights some of the complexity in assessing frailty and its effects in individuals and populations, including associations with other competing risks like depression. Further research is warranted in this area to understand the cause and effect of frailty, and its associated outcomes, among haemodialysis patients.

10.7 Tables

Table 10-1: Baseline Demographics of the FITNESS cohort stratified by frailty status

		Total Cohort	Not Frail	Frail
Frail		261 53.8%	- -	- -
Median Age		63 53-74	60 50-72	65 55-76
Median PHQ-9		5 2-10	3 1-7	7 3-6
Median MoCA		22 17-25	23 20-26	20 16-23
Median Albumin (g/L)		39 35-41	39 36-42	38 34-41
Median BMI		26.8 23.2-32.3	26 23.0-30.7	27.9 23.2-33.7
Median Charlson Score*		4 3-6	4 2-5	5 4-7
Median HD Vintage (months)		37 17-76	33 13-66	41 19.9-81.5
Median Kt/V		1.59 1.39-1.85	1.58 1.38-1.80	1.61 1.41-1.88
Median EQ Summary Index		0.779 0.516-1.00	1 0.779-1.00	0.62 0.189-0.796
Health Change	*Better*	94 19.4%	52 23.2%	42 16.1%
	The Same	174 35.9%	90 40.2%	84 32.2%
	Worse	217 44.7%	82 36.6%	135 51.7%
IMD Quintile	*1*	212 43.7%	96 42.9%	116 44.4%
	2	87 17.9%	43 19.2%	44 16.9%
	3	85 17.5%	38 17.0%	47 18.0%
	4	38 7.8%	20 8.9%	18 6.9%
	5	33 6.8%	14 6.3%	19 7.3%
	Unknown	30 6.2%	13 5.8%	17 6.5%
Ethnicity	*White*	281 57.9%	13 61.2%	144 55.2%
	South Asian	115 23.7%	44 19.6%	71 27.2%
	Black	76 15.7%	35 15.6%	41 15.7%
	Other	13 2.7%	8 3.6%	5 1.9%
Gender	*Male*	284 58.6%	148 66.1%	136 52.1%
Comorbidities	*Diabetes*	138 28.5%	43 19.2%	95 36.4%
	MI	98 20.2%	34 15.2%	64 24.5%
	CVA/TIA	57 11.8%	17 7.6%	40 15.3%
	Cancer	56 11.6%	30 13.4%	26 10.0%
	Heart Failure	52 10.7%	19 8.5%	33 12.6%
	PVD	47 9.7%	15 6.7%	32 12.3%

		Total Cohort	Not Frail	Frail
Primary renal disease	*Diabetic*	114 23.5%	33 14.7%	81 31.3%
	Hypertensive	39 8.0%	22 9.8%	17 6.5%
	Ischaemic	38 7.8%	14 6.3%	24 9.2%
	IgA	37 7.6%	20 8.9%	17 6.5%
	PKD	28 5.8%	17 7.6%	11 4.2%
	FSGS	24 5.0%	14 6.3%	10 3.8%
	Reflux	17 3.5%	7 3.1%	10 3.8%
	Obstructive	16 3.3%	10 4.5%	6 2.3%
	AAV	15 3.1%	11 4.9%	4 1.5%
	Interstitial Nephritis	10 2.1%	6 2.7%	4 1.5%
	Myeloma	10 2.1%	8 3.6%	2 0.8%
	Unknown	68 14.0%	31 13.8%	37 14.2%
Smoking Status	*Current*	68 14.1%	38 17.0%	30 11.5%
	Ex	132 27.3%	64 28.6%	68 26.2%
	Never	284 58.7%	122 54.5%	162 62.3%
Dialysis Access	*Line*	113 23.3%	47 21.0%	66 25.3%
Tx List Status	*Active*	58 12.0%	36 16.1%	22 8.4%
	Suspended	15 3.1%	9 4.0%	6 2.3%
	Not listed	412 85.0%	179 79.9%	233 89.3%
Employment Status	*Employed*	69 14.3%	61 27.2%	8 3.1%
	Unemployed	148 30.6%	58 25.9%	90 34.6%
	Retired	267 55.2%	105 46.9%	162 62.3%
Job Role	*Unskilled Manual*	181 39.3%	70 32.1%	111 45.7%
	Skilled Manual	101 21.9%	50 22.9%	51 21.0%
	Clerical	52 11.3%	28 12.8%	24 9.9%
	Managerial	46 10.0%	26 11.9%	20 8.2%
	Professional	81 17.6%	44 20.2%	37 15.2%
Education Level	*High School*	342 70.7%	146 65.2%	196 75.4%
	College/Sixth Form	92 19.0%	49 21.9%	43 16.5%
	University	50 10.3%	29 13.0%	21 8.1%

Table 10-2: Linear regression of change in PHQ-9 score associated with covariables in fully adjusted model 4

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
CFS Score	**0.768**	**0.397**	**1.14**	**<0.001**
Age	**-0.093**	**-0.137**	**-0.050**	**<0.001**
Ethnicity				
White		REFERENCE		
South Asian	**-1.54**	**-2.74**	**-0.344**	**0.012**
Black	-0.689	-1.96	0.578	0.286
Other	-0.007	-2.83	2.81	0.996
Gender				
Male		REFERENCE		
Female	0.527	-0.366	1.42	0.246
IMD Quintile				
1		REFERENCE		
2	-0.164	-1.37	1.05	0.790
3	-0.083	-1.31	1.14	0.894
4	-0.611	-2.27	1.05	0.471
5	-0.424	-2.18	1.34	0.636
Unknown	0.062	-1.88	2.00	0.950
Education Level				
High School		REFERENCE		
College/6th form	-0.919	-2.05	0.209	0.110
University	**-1.91**	**-3.39**	**-0.422**	**0.012**
Prior admissions	-0.008	-0.188	0.172	0.931
Charlson Index *	-0.079	-0.350	0.193	0.570
Cognitive Impairment				
No		REFERENCE		
Yes	-0.366	-1.49	0.753	0.521
Antidepressant Use				
No		REFERENCE		
Yes	**3.69**	**2.29**	**5.09**	**<0.001**
Number medications	0.075	-0.056	0.206	0.260
HD vintage	-0.001	-0.010	0.007	0.778
Self-rated pain				
None		REFERENCE		
Moderate	**1.63**	**0.664**	**2.60**	**0.001**
Extreme	**2.61**	**0.867**	**4.36**	**0.003**
Self-rated health change				
Better/The Same		REFERENCE		
Worse	**1.73**	**0.808**	**2.65**	**<0.001**
Self-rated health/100	**-0.056**	**-0.078**	**-0.034**	**<0.001**
Constant	**10.635**	**7.19**	**14.084**	**<0.001**

Bold text indicates P<0.05. *CKD omitted.

Table 10-3: Linear regression of change in CFS score associated with covariables in fully adjusted model 4

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Score	**0.046**	**0.027**	**0.064**	**<0.001**
Age	-0.008	-0.017	0.001	0.083
Gender				
Male		REFERENCE		
Female	**0.226**	**0.040**	**0.412**	**0.017**
Ethnicity				
White		REFERENCE		
South Asian	0.214	-0.037	0.466	0.095
Black	-0.012	-0.278	0.254	0.929
Other	0.257	-0.331	0.844	0.391
Education level				
High School		REFERENCE		
College/6th form	0.008	-0.224	0.240	0.945
University	-0.152	-0.468	0.163	0.344
IMD Quintile				
1		REFERENCE		
2	0.104	-0.147	0.354	0.416
3	0.015	-0.238	0.269	0.905
4	-0.301	-0.647	0.045	0.088
5	0.007	-0.362	0.376	0.969
Unknown	0.156	-0.240	0.551	0.439
Social Support				
No		REFERENCE		
Yes	**-0.698**	**-1.07**	**-0.332**	**<0.001**
Charlson Index*	**0.094**	**0.040**	**0.147**	**0.001**
Cognitive Impairment				
No		REFERENCE		
Yes	0.030	-0.201	0.261	0.798
Smoking status				
Current		REFERENCE		
Ex	0.277	-0.013	0.566	0.061
Never	0.172	-0.100	0.444	0.214
Self-rated health change				
Better/The Same		REFERENCE		
Worse	0.075	-0.117	0.267	0.441
Self-rated helath/100	**-0.006**	**-0.011**	**-0.002**	**0.006**
Walking aid use				
No		REFERENCE		
Yes	**0.532**	**0.307**	**0.758**	**<0.001**
Physical Activity Index				
Inactive		REFERENCE		
Moderately Inactive	**-0.384**	**-0.732**	**-0.035**	**0.031**
Moderately Active	**-1.07**	**-1.49**	**-0.641**	**<0.001**
Active	**-1.86**	**-2.30**	**-1.42**	**<0.001**
Slow walking speed**				
No		REFERENCE		
Yes	**0.712**	**0.482**	**0.941**	**<0.001**
Low grip strength**				
No		REFERENCE		
Yes	0.082	-0.119	0.283	0.424
Constant	**3.88**	**3.20**	**4.55**	**<0.001**

Table 10-4: Cox regression model of mortality hazard associated with PHQ-9 and CFS scores as continuous variables

CFS in Model?	Variable	HR	Lower 95% C.I.	Upper 95% C.I.	P
Without CFS	*Unadjusted*				
	PHQ-9 Score	1.02	0.99	1.05	0.220
With CFS	PHQ-9 Score	0.98	0.95	1.02	0.337
	CFS	**1.51**	**1.30**	**1.76**	**<0.001**
Without CFS	*Adjusted*				
	PHQ-9 Score	1.02	0.980	1.05	0.398
With CFS	PHQ-9 Score	1.00	0.96	1.04	0.901
	CFS	**1.31**	**1.08**	**1.59**	**0.006**

HR = hazard ratio. C.I. = confidence interval. Bold text indicates significance at P<0.05 level. Adjusted models included age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage, self-reported change in health, and kidney transplant wait-listing.

Table 10-5: Cox regression model of mortality hazard associated with moderate depression and CFS scores as a continuous variable

CFS in Model?	Variable	HR	Lower 95% C.I.	Upper 95% C.I.	P
Without CFS	*Unadjusted*				
	Mod Depression	1.16	0.77	1.75	0.472
With CFS	Mod Depression	0.79	0.52	1.22	0.296
	CFS	**1.51**	**1.30**	**1.75**	**<0.001**
Without CFS	*Adjusted*				
	Mod Depression	1.13	0.72	1.79	0.596
With CFS	Mod Depression	0.91	0.57	1.47	0.713
	CFS	**1.32**	**1.09**	**1.60**	**0.004**

HR = hazard ratio. C.I. = confidence interval. Bold text indicates significance at P<0.05 level. Adjusted models included age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage, self-reported change in health, and kidney transplant wait-listing.

Table 10-6: Fine and Gray model of mortality subhazard associated with PHQ-9 scores and CFS frailty as continuous variables

CFS in Model?	Variable	SHR	Lower 95% C.I.	Upper 95% C.I.	P
Without CFS	*Unadjusted*				
	PHQ-9 Score	1.02	0.99	1.05	0.155
With CFS	PHQ-9 Score	0.98	0.95	1.02	0.365
	CFS	**1.55**	**1.33**	**1.81**	**<0.001**
Without CFS	*Adjusted*				
	PHQ-9 Score	1.02	0.98	1.06	0.371
With CFS	PHQ-9 Score	1.00	0.96	1.04	0.939
	CFS	**1.34**	**1.12**	**1.61**	**0.002**

Obtained by Fine and Gray subdistribution hazards model with kidney transplantation as a competing event. SHR = subhazard ratio. C.I. = confidence interval. Bold text indicates significance at P<0.05 level. Adjusted models included age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage, self-reported change in health, and kidney transplant wait-listing.

Table 10-7: Fine and Gray model of mortality subhazard associated with at least moderate depression and CFS frailty as a continuous variable

CFS in Model?	Variable	SHR	Lower 95% C.I.	Upper 95% C.I.	P
Without CFS	*Unadjusted*				
	Mod Depression	1.20	0.80	1.80	0.378
With CFS	Mod Depression	0.80	0.53	1.22	0.307
	CFS	**1.54**	**1.34**	**1.79**	**<0.001**
Without CFS	*Adjusted*				
	Mod Depression	1.15	0.72	1.83	0.564
With CFS	Mod Depression	0.91	0.56	1.49	0.716
	CFS	**1.35**	**1.13**	**1.62**	**0.001**

Obtained by Fine and Gray subdistribution hazards model with kidney transplantation as a competing event. SHR = subhazard ratio. C.I. = confidence interval. Bold text indicates significance at P<0.05 level. Adjusted models included age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage, self-reported change in health, and kidney transplant wait-listing.

Table 10-8: Associates of Fractional EQ-5D Summary Index - fully adjusted model 4

	Coeffficient	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Score	**-0.042**	**-0.063**	**-0.021**	**<0.001**
CFS	**-0.401**	**-0.511**	**-0.292**	**<0.001**
Age	0.002	-0.013	0.016	0.829
Gender				
Male		REFERENCE		
Female	**-0.233**	**-0.442**	**-0.023**	**0.030**
Ethnicity				
White		REFERENCE		
South Asian	0.271	-0.031	0.573	0.078
Black	0.135	-0.191	0.462	0.416
Other	-0.487	-1.18	0.206	0.169
Education Level				
High School		REFERENCE		
College/6th form	-0.262	-0.553	0.029	0.078
University	**-0.379**	**-0.690**	**-0.067**	**0.017**
Social Support?				
Yes		REFERENCE		
No	**-0.486**	**-0.807**	**-0.165**	**0.003**
IMD Quintile				
1		REFERENCE		
2	-0.219	-0.511	0.072	0.141
3	0.024	-0.270	0.318	0.874
4	0.135	-0.264	0.534	0.508
5	0.243	-0.227	0.713	0.311
999	0.127	-0.398	0.652	0.636
Employment Status				
Employed		REFERENCE		
Unemployed	-0.021	-0.716	0.675	0.954
Retired	0.101	-0.512	0.714	0.747
HD vintage (months)	**-0.003**	**-0.005**	**-0.001**	**0.009**
Charlson Index*	-0.011	-0.070	0.047	0.706
Hb (g/L)	0.004	-0.005	0.013	0.361
Kt/V	0.242	-0.060	0.544	0.117
Antidepressant Use?				
No		REFERENCE		
Yes	-0.100	-0.435	0.235	0.558
Use of walking aids?				
No		REFERENCE		
Yes	-0.233	-0.484	0.017	0.068
Walking Speed				
Not Slow		REFERENCE		
Slow	**-0.435**	**-0.695**	**-0.175**	**0.001**
Physical Activity Index				
Inactive		REFERENCE		
Moderately Inactive	-0.070	-0.775	0.634	0.845
Moderately Active	**-0.861**	**-1.48**	**-0.246**	**0.006**
Active	-0.091	-0.964	0.783	0.838
Self-rated health/100	**0.012**	**0.007**	**0.017**	**<0.001**
Health Change in the past year				
Better/Same		REFERENCE		
Worse	-0.180	-0.396	0.036	0.102
Cognitive Impairment				
No		REFERENCE		
Yes	**-0.308**	**-0.571**	**-0.045**	**0.022**
Constant	**3.110**	**1.296**	**4.924**	**0.001**

10.8 Supplementary Materials

Supplementary Table 10-1: Stepwise addition of a priori covariables into regression models

Model 1	Model 2	Model 3	Model 4
		Depression	
Frailty	Frailty	Frailty	Frailty
Age	Age	Age	Age
Ethnicity	Ethnicity	Ethnicity	Ethnicity
Gender	Gender	Gender	Gender
	IMD Quintile	IMD Quintile	IMD Quintile
	Social Support	Social Support	Social Support
	Education Level	Education Level	Education Level
		Admissions in past year	Admissions in past year
		Charlson Comorbidity Index (CKD excluded)	Charlson Comorbidity Index (CKD excluded)
		Cognitive Impairment	Cognitive Impairment
		Current antidepressant use	Current antidepressant use
		Total medication number	Total medication number
		Haemodialysis vintage	Haemodialysis vintage
			Self-rated pain (EQ-5D)
			Health change in past year (Better, The Same, Worse)
			Health Today (EQ-5D VAS)
		Frailty	
Depression	Depression	Depression	Depression
Age	Age	Age	Age
Ethnicity	Ethnicity	Ethnicity	Ethnicity
Gender	Gender	Gender	Gender
	IMD Quintile	IMD Quintile	IMD Quintile
	Social Support	Social Support	Social Support
	Education Level	Education Level	Education Level
		Charlson Comorbidity Index (CKD excluded)	Charlson Comorbidity Index (CKD excluded)
		Cognitive Impairment	Cognitive Impairment
		Smoking Status	Smoking Status
		Health change in past year (Better, The Same, Worse)	Health change in past year (Better, The Same, Worse)
		Health today (EQ-5D VAS)	Health today (EQ-5D VAS)
			Walking aid use
			Physical Activity Index from GPPAQ
			Slow walking speed
			Low grip strength
		Fractional EQ-5D Summary Index	
Age	Age	Age	Age
Gender	Gender	Gender	Gender
Ethnicity	Ethnicity	Ethnicity	Ethnicity
Education Level	Education Level	Education Level	Education Level
Social Support (Yes/No)	Social Support (Yes/No)	Social Support (Yes/No)	Social Support (Yes/No)
IMD Quintile	IMD Quintile	IMD Quintile	IMD Quintile
Employment Status	Employment Status	Employment Status	Employment Status
	Haemodialysis Vintage	Haemodialysis Vintage	Haemodialysis Vintage
	Charlson Comorbidity Index (CKD excluded)	Charlson Comorbidity Index (CKD excluded)	Charlson Comorbidity Index (CKD excluded)
	Haemoglobin (g/dL)	Haemoglobin (g/dL)	Haemoglobin (g/dL)
	Kt/V	Kt/V	Kt/V
	Current antidepressant use	Current antidepressant use	Current antidepressant use
		Walking aid use	Walking aid use
		Physical Activity Index from GPPAQ	Physical Activity Index from GPPAQ
		Slow walking speed	Slow walking speed
			Health change in past year (Better, The Same, Worse)
			Health today (EQ-5D VAS)

Supplementary Table 10-2: Fully adjusted Cox regression of mortality associated with PHQ-9 Score. CFS omitted.

	HR	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Score	1.02	0.980	1.05	0.398
Age	0.994	0.973	1.02	0.598
Gender				
Male		REF		
Female	0.941	0.629	1.41	0.767
Ethnicity				
White		REF		
South Asian	0.583	0.321	1.06	0.076
Black	0.968	0.555	1.69	0.910
Other	0.568	0.076	4.24	0.581
BMI	0.995	0.968	1.02	0.705
IMD Quintile				
1		REF		
2	1.07	0.621	1.84	0.809
3	1.25	0.722	2.15	0.431
4	0.749	0.327	1.71	0.494
5	0.828	0.360	1.91	0.658
Unknown	0.967	0.377	2.48	0.945
Charlson Index*	**1.19**	**1.063**	**1.32**	**0.002**
Previous Admissions	1.07	0.977	1.16	0.154
Number of Medications	1.02	0.963	1.08	0.503
Smoking Status				
Current		REF		
Ex	1.28	0.691	2.38	0.429
Never	0.831	0.456	1.51	0.544
Albumin	**0.949**	**0.911**	**0.989**	**0.012**
Walking Aid Use				
No		REF		
Yes	**1.82**	**1.13**	**2.93**	**0.014**
HD vintage	1.00	0.998	1.01	0.315
Transplant Listing Status				
Not listed/Not active		REF		
Active	0.144	0.020	1.06	0.057

*CKD omitted. Bold text indicates significant at P<0.05 level

Supplementary Table 10-3: Fully adjusted Cox regression model of mortality associated with PHQ-9 Score. CFS included.

	HR	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Score	1.00	0.96	1.04	0.901
Age	0.99	0.97	1.02	0.604
Clinical Frailty Scale	**1.31**	**1.08**	**1.59**	**0.006**
Gender				
Male		REF		
Female	0.87	0.58	1.31	0.515
Ethnicity				
White		REF		
South Asian	**0.54**	**0.30**	**0.98**	**0.044**
Black	0.97	0.55	1.69	0.913
Other	0.52	0.07	3.86	0.519
BMI	0.99	0.96	1.02	0.539
IMD Quintile				
1		REF		
2	1.07	0.62	1.84	0.816
3	1.27	0.74	2.19	0.385
4	0.79	0.34	1.80	0.567
5	0.85	0.37	1.96	0.702
Unknown	1.02	0.40	2.62	0.970
Charlson Index*	**1.16**	**1.04**	**1.30**	**0.007**
Previous Admissions	1.07	0.98	1.17	0.146
Number of Medications	1.01	0.95	1.07	0.802
Smoking Status				
Current		REF		
Ex	1.27	0.68	2.35	0.451
Never	0.79	0.44	1.45	0.451
Albumin	**0.95**	**0.92**	**0.99**	**0.020**
Walking Aid Use				
No		REF		
Yes	1.41	0.85	2.35	0.186
HD vintage	1.00	1.00	1.00	0.419
Transplant Listing Status				
Not listed/Not active		REF		
Active	0.15	0.02	1.12	0.064

*CKD omitted. Bold text indicates significant at P<0.05 level

Supplementary Table 10-4: Fully adjusted Cox regression model of mortality associated with moderate depression. CFS omitted.

	HR	Lower 95% C.I.	Upper 95% C.I.	P
Moderate Depression				
No		REF		
Yes	1.13	0.72	1.79	0.596
Age	0.99	0.97	1.01	0.527
Gender				
Male	1.00			
Female	0.95	0.64	1.42	0.809
Ethnicity				
White		REF		
South Asian	0.57	0.32	1.04	0.066
Black	0.95	0.54	1.65	0.845
Other	0.54	0.07	4.06	0.553
BMI	0.99	0.97	1.02	0.679
IMD Quintile				
1		REF		
2	1.05	0.61	1.81	0.855
3	1.23	0.71	2.12	0.459
4	0.74	0.32	1.68	0.465
5	0.80	0.35	1.84	0.602
Unknown	0.96	0.37	2.47	0.933
Charlson Index*	**1.19**	**1.06**	**1.32**	**0.002**
Previous Admissions	1.06	0.98	1.16	0.163
Number of Medications	1.02	0.97	1.08	0.44
Smoking Status				
Current		REF		
Ex	1.29	0.69	2.39	0.424
Never	0.83	0.46	1.52	0.551
Albumin	**0.95**	**0.91**	**0.99**	**0.013**
Walking Aid Use				
No		REF		
Yes	**1.83**	**1.13**	**2.94**	**0.013**
HD vintage	1.00	1.00	1.01	0.312
Transplant Listing Status				
Not listed/Not active		REF		
Active	0.14	0.02	1.06	0.057

*CKD omitted. Bold text indicates significant at P<0.05 level

Supplementary Table 10-5: Fully adjusted Cox regression of mortality associated with moderate depression. CFS included.

	HR	Lower 95% C.I.	Upper 95% C.I.	P
Moderate Depression				
No		REF		
Yes	0.91	0.57	1.47	0.713
Age	0.99	0.97	1.02	0.568
Clinical Frailty Scale	**1.32**	**1.09**	**1.60**	**0.004**
Gender				
Male		REF		
Female	0.87	0.58	1.31	0.509
Ethnicity				
White		REF		
South Asian	**0.54**	**0.30**	**0.98**	**0.041**
Black	0.97	0.56	1.70	0.924
Other	0.52	0.07	3.93	0.530
BMI	0.99	0.96	1.02	0.541
IMD Quintile				
1		REF		
2	1.06	0.62	1.82	0.834
3	1.26	0.73	2.17	0.398
4	0.78	0.34	1.79	0.560
5	0.85	0.37	1.96	0.706
Unknown	1.02	0.40	2.63	0.964
Charlson Index*	**1.16**	**1.04**	**1.29**	**0.008**
Previous Admissions	1.07	0.98	1.17	0.145
Number of Medications	1.01	0.95	1.07	0.789
Smoking Status				
Current		REF		
Ex	1.28	0.69	2.37	0.440
Never	0.80	0.44	1.45	0.456
Albumin	**0.95**	**0.92**	**0.99**	**0.020**
Walking Aid Use				
No		REF		
Yes	1.42	0.85	2.36	0.182
HD vintage	1.00	1.00	1.00	0.437
Transplant Listing Status				
Not listed/Not active		REF		
Active	0.15	0.02	1.11	0.063

*CKD omitted. Bold text indicates significant at P<0.05 level

Supplementary Table 10-6: Incidence Rate Ratios of admissions associated with PHQ-9 scores. Adjusted model, CFS omitted

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Score	1.00	0.98	1.02	0.973
Age	**0.99**	**0.98**	**1.00**	**0.027**
Gender				
Male		REF		
Female	1.00	0.81	1.23	0.978
Ethnicity				
White		REF		
South Asian	0.83	0.62	1.10	0.196
Black	**0.69**	**0.50**	**0.94**	**0.020**
Other	0.86	0.44	1.67	0.651
BMI	1.00	0.98	1.01	0.723
IMD Quintile				
1		REF		
2	0.88	0.65	1.18	0.381
3	0.81	0.60	1.11	0.191
4	0.78	0.52	1.16	0.216
5	0.69	0.44	1.10	0.122
Unknown	1.24	0.82	1.88	0.306
Charlson Index*	**1.10**	**1.04**	**1.18**	**0.002**
Previous Admissions	**1.10**	**1.05**	**1.15**	**<0.001**
Number of Medications	1.03	1.00	1.06	0.097
Smoking Status				
Current		REF		
Ex	0.87	0.61	1.23	0.432
Never	0.80	0.58	1.10	0.164
Albumin	1.00	0.99	1.00	0.142
Walking Aid Use				
No		REF		
Yes	**1.74**	**1.39**	**2.19**	**<0.001**
HD vintage	1.00	1.00	1.00	0.926
Transplant Listing Status				
Not listed/Not active		REF		
Active	0.88	0.61	1.26	0.491

*CKD omitted. Bold text indicates significant at P<0.05 level

Supplementary Table 10-7: Incidence Rate Ratios of hospital admissions associated with PHQ-9 score. Adjusted model with CFS included.

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Score	0.99	0.97	1.01	0.351
Age	0.99	0.98	1.00	0.020
Clinical Frailty Scale	1.13	1.03	1.25	0.010
Gender				
Male		REF		
Female	0.97	0.78	1.19	0.749
Ethnicity				
White	1.00			
South Asian	0.79	0.59	1.05	0.102
Black	0.69	0.50	0.94	0.020
Other	0.81	0.42	1.59	0.548
BMI	1.00	0.98	1.01	0.664
IMD Quintile				
1		REF		
2	0.87	0.65	1.17	0.367
3	0.82	0.60	1.11	0.204
4	0.80	0.54	1.20	0.283
5	0.72	0.46	1.15	0.168
Unknown	1.27	0.84	1.91	0.262
Charlson Index*	1.09	1.02	1.16	0.007
Previous Admissions	1.10	1.05	1.15	0.000
Number of Medications	1.02	0.99	1.05	0.169
Smoking Status				
Current		REF		
Ex	0.85	0.60	1.21	0.369
Never	0.77	0.57	1.06	0.111
Albumin	1.00	0.99	1.00	0.185
Walking Aid Use				
No		REF		
Yes	1.52	1.19	1.95	0.001
HD vintage	1.00	1.00	1.00	0.927
Transplant Listing Status				
Not listed/Not active		REF		
Active	0.89	0.62	1.27	0.521

*CKD omitted. Bold text indicates significant at P<0.05 level

Supplementary Table 10-8: incidence Rate Ratios of hospital admissions associated with moderate depression. Adjusted model, CFS omitted

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
Moderate Depression				
No		REF		
Yes	0.80	0.62	1.03	0.080
Age	**0.99**	**0.97**	**1.00**	**0.010**
Gender				
Male		REF		
Female	1.01	0.81	1.24	0.954
Ethnicity				
White		REF		
South Asian	0.80	0.60	1.06	0.122
Black	**0.68**	**0.50**	**0.93**	**0.016**
Other	0.83	0.43	1.61	0.581
BMI	1.00	0.98	1.01	0.745
IMD Quintile				
1		REF		
2	0.86	0.64	1.15	0.313
3	0.80	0.59	1.09	0.154
4	0.78	0.52	1.16	0.220
5	0.67	0.42	1.06	0.087
Unknown	1.26	0.83	1.90	0.279
Charlson Index*	**1.10**	**1.03**	**1.18**	**0.003**
Previous Admissions	**1.10**	**1.05**	**1.15**	**<0.001**
Number of Medications	**1.03**	**1.00**	**1.06**	**0.042**
Smoking Status				
Current		REF		
Ex	0.88	0.62	1.24	0.459
Never	0.80	0.59	1.10	0.176
Albumin	1.00	0.99	1.00	0.141
Walking Aid Use				
No		REF		
Yes	**1.80**	**1.43**	**2.26**	**<0.001**
HD vintage	1.00	1.00	1.00	0.790
Transplant Listing Status				
Not listed/Not active		REF		
Active	0.86	0.60	1.24	0.428

*CKD omitted. Bold text indicates significant at P<0.05 level

Supplementary Table 10-9: Incidence Rate Ratios of hospital admissions associated with moderate depression. Adjusted model including CFS.

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
Moderate Depression				
No		REF		
Yes	**0.72**	**0.56**	**0.93**	**0.013**
Age	**0.99**	**0.98**	**1.00**	**0.010**
Clinical Frailty Scale	**1.15**	**1.05**	**1.26**	**0.003**
Gender				
Male		REF		
Female	0.96	0.78	1.19	0.737
Ethnicity				
White		REF		
South Asian	0.76	0.57	1.01	0.061
Black	**0.69**	**0.50**	**0.94**	**0.018**
Other	0.79	0.41	1.54	0.491
BMI	1.00	0.98	1.01	0.712
IMD Quintile				
1		REF		
2	0.87	0.65	1.16	0.330
3	0.81	0.59	1.09	0.167
4	0.81	0.54	1.21	0.306
5	0.71	0.45	1.12	0.139
Unknown	1.29	0.85	1.94	0.229
Charlson Index*	**1.09**	**1.02**	**1.16**	**0.010**
Previous Admissions	**1.10**	**1.05**	**1.15**	**<0.001**
Number of Medications	1.02	0.99	1.06	0.110
Smoking Status				
Current		REF		
Ex	0.86	0.61	1.22	0.402
Never	0.78	0.57	1.07	0.119
Albumin	1.00	0.99	1.00	0.180
Walking Aid Use				
No		REF		
Yes	**1.54**	**1.20**	**1.97**	**0.001**
HD vintage	1.00	1.00	1.00	0.770
Transplant Listing Status				
Not listed/Not active		REF		
Active	0.88	0.61	1.25	0.473

*CKD omitted. Bold text indicates significant at P<0.05 level

Chapter 11:

Somatic symptoms of depression lose association with mortality upon adjustment for frailty: analysis from the FITNESS haemodialysis cohort.

Authors: Benjamin M Anderson, Muhammad Qasim, Gonzalo Correa, Felicity Evison, Suzy Gallier, Charles J Ferro, Thomas A Jackson, Adnan Sharif

11.1 Extent of Personal Contribution

I coordinated all study visits with participants and dialysis unit staff. I recruited participants, and collected all baseline data with the support of Dr Gonzalo Correa, Dr Muhammad Qasim, and Dr Adnan Sharif. All colleagues were supervised by me in their data collection, and I was responsible for maintaining training and personnel logs in the site file.

Ms Felicity Evison, and Ms Suzy Gallier were responsible for interrogation of EPR for IMD Quintile assessment and HES/OPCS/ONS data for mortality and hospitalisation follow-up. I performed all subsequent data cleaning, integrity, and analyses with guidance from Dr Adnan Sharif.

The first draft of the manuscript was written by myself and I was responsible for all edits and revisions. This chapter is based upon a manuscript submitted for peer-review to Haemodialysis International on 27th July 2022, submission number HDI-22-0231.

11.2 Abstract

11.2.1 Introduction

The somatic symptom component of depression has been associated with increased hospitalisation and mortality, and poorer health-related quality of life (HRQOL). However, the relationship of subsets of depression symptoms with frailty, and their impact upon outcomes, is not known. This study aimed to; 1) explore the relationship between Clinical Frailty Scale (CFS) and components of depression, and; 2) assess the association between the components of depression with mortality, hospitalisation, and quality of life in haemodialysis recipients.

11.2.2 Methods

We conducted a prospective cohort study of prevalent (≥3 months) haemodialysis recipients, with deep bio-clinical phenotyping including CFS and PHQ-9 somatic (fatigue, poor appetite, poor sleep) and cognitive component scores. EuroQol EQ-5D Summary Index was used to assess HRQOL at baseline. Electronic linkage to English national administration datasets ensured robust follow-up data for hospitalisation and mortality events.

11.2.3 Findings

Both PHQ-9 somatic (β= 0.067; 95% C.I. 0.029 to 0.104; P<0.001) and cognitive (β=0.062; 95% C.I. 0.034 to 0.089; P<0.001) components were associated with increased CFS scores. Both somatic (β=-0.062; 95% C.I. -0.104 to -0.021; P<0.001) and cognitive (β=0.052; 95% C.I. -0.081 to -0.024; P<0.001) scores were associated with lower EQ-5D Summary Index scores on fractional regression. Somatic scores were associated with increased mortality on multivariable analyses (HR 1.08; 95% C.I. 1.00 to 1.17; P=0.038) but lost this association on

addition of CFS (HR1.06; 95% C.I. 0.977 to 1.14; P=0.173). The PHQ-9 cognitive component scores were not associated with mortality on any analyses. Neither component score was associated with hospitalisation on multivariable analyses.

11.2.4 Conclusions

Both somatic and cognitive component scores of PHQ-9 are associated with frailty and poorer HRQOL in haemodialysis recipients, but were not associated with mortality or hospitalisation when adjusted for frailty. The risk profile of depression somatic scores may be related to overlap with symptoms of frailty.

11.3 Introduction

We have seen that there is a reciprocal relationship between CFS frailty and depression, that both are independently linked to poorer HRQOL, but only frailty is associated with mortality. Work elsewhere has explored dividing depression scores into somatic and cognitive symptom components.[208] The somatic symptom subset of the Beck Depression Inventory (BDI) has been associated with mortality and hospitalisation in haemodialysis recipients in Dutch[209] and Jordanian[210] haemodialysis recipients. In the Dutch cohort, depression, somatic symptoms, and cognitive symptoms were all associated with lower quality of life.[209]

Frailty has been associated with poorer quality of life in Brazilian[234] and UK[235] non-dialysis CKD cohorts. McAdams-DeMarco and colleagues found that self-rated fair/poor quality of life was more likely in frail haemodialysis recipients, and that frailty was associated with worsening quality of life over time.[236] A decline in quality of life in frail haemodialysis recipients was also observed in a small Canadian cohort.[237]

Whilst there are reports of a reciprocal relationship between frailty and depression[203,204], reports we have corroborated in the previous chapter, no such exploration of the relationship between frailty versus the somatic and cognitive components of depression has taken place. This may be important as the somatic symptoms of depression – tiredness, poor sleep, and lack of appetite – show considerable overlap with those of frailty. Therefore, the aims of this study were to; 1) explore the relationship between frailty and components of depression, and; 2) assess the association between the components of depression with mortality, hospitalisation, and quality of life in haemodialysis recipients.

11.4 Materials and Methods

11.4.1 Study design

FITNESS study design, eligibility, power calculations, consent and baseline data acquisition are presented in detail in Chapters Chapter 2: and 2.2.

PHQ-9 scores were obtained by patient questionnaire with 9 questions each scored between 0-3 for frequency of depression symptoms, giving a total score of between 0-27[196]. PHQ-9 somatic component scores included questions 3 (Trouble falling or staying asleep, or sleeping too much), 4 (Feeling tired or having little energy), and 5 (Poor appetite or overeating). Cognitive component scores included questions 1 (Little interest or pleasure in doing things), 2 (Feeling down, depressed, or hopeless), 6 (Feeling bad about yourself – or that you are a failure or have let yourself or your family down), 7 (Trouble concentrating on things, such as reading the newspaper or watching television), 8 (Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual), and 9 (Thoughts that you would be better off dead or of hurting yourself in some way).[208]

The Clinical Frailty Scale was obtained by interpretation of ADL questionnaire responses, with possible responses of 1-9. A CFS of 1 represented very fit, and 8 severely frail. A CFS score of 9 was attributed to those who were terminally ill but not overtly frail.

11.4.2 Outcomes

Mortality and hospitalisation data were obtained from EPR as described in previous chapters. Health-related quality of life was assessed using EuroQol EQ-5D-3L. This was converted into the single-measure EQ-5D Summary Index via a standardised formula.[267] This formula returns a score of between 1 (if no HRQOL deficits identified) and -0.716 (if extreme deficit in every domain), and has been validated in UK populations.

11.4.3 Statistics

Statistical analysis was performed using STATA 17 (StataCorp 2021, Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) and R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). Categorical data was presented as numbers and percentages, with continuous variables reported as medians and interquartile ranges (IQRs).

Survival analyses were performed by generation of Kaplan-Meier curve estimates and time-to-event outcomes were analysed with the Cox's Proportional Hazards Model. The proportional hazard assumption was checked and satisfied by examination of plots of the log-negative-log of the within-group survivorship functions versus log time as well as comparing Kaplan-Meier (observed) with Cox (expected) survival curves with our study variables, alongside selected covariables for adjusted analyses (reported as Hazard Ratios [HR] with 95% Confidence Intervals [CI]).

Linear regressions were performed to explore the relationship between continuous frailty and PHQ-9 scores, and between these same scores and EQ-5D summary index. Linearity was

checked by comparison of observed values by linear and Lowess fit plots, and by plotting observed versus predicted residual values. These were performed unadjusted and as a series of adjusted models based upon *a priori* covariables selected for known or suspected relationship with the outcome of interest. For depression, model 1 included frailty, age, ethnicity, gender. Model 2 added IMD quintile, social support and education level. Model 3 added admissions in the past year, Charlson index (CKD excluded), cognitive impairment, current antidepressant use, total medication number, and haemodialysis vintage. Model 4 added self-reported pain, self-reported change in health and overall self-rated health. For frailty, Model A included depression, age, gender and ethnicity. Model B added education level, social support and IMD quintile. Model C added Charlson Index (CKD excluded), cognitive impairment, smoking status, self-rated change in health and overall health. Model D added use of walking aids, Physical Activity Index, slow timed walk and low grip strength.

Regressions for EQ-5D summary index were performed unadjusted and subject to a separate set of *a priori* covariable models, based upon known or suspected relationship with HRQOL, covariables found to significantly associate with frailty and/or PHQ-9 scores were also added to reduce confounding. Models were constructed in a pre-determined stepwise manner. Model 1 included age, gender, ethnicity, education level, social support, IMD quintile, and employment status. Model 2 added to these haemodialysis vintage, Charlson comorbidity index (CKD omitted), haemoglobin, Kt/V, and current use of antidepressant medication. Model 3 added use of walking aids, slow walking (or inability to walk), and physical activity index. Model 4 added EQ self-rated health today (continuous score from 0-100), and self-rated health change.

Incidence rate ratios were obtained for count data by negative binomial regression, death-censored and offset by length of follow-up. Negative binomial distribution was confirmed by interrogation of means and variances and visual interpretation of expected versus observed distribution plots. Zero-truncated negative binomial regressions were performed for nights per admission, as by definition these could not equal zero.

All Cox and negative binomial regressions were performed unadjusted and adjusted for an *a priori* list of covariables, based on a known or suspected relationship with dialysis-related mortality/admission (age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage, self-reported change in health, and kidney transplant wait-listing). Further adjusted models were performed using the aforementioned covariables plus the addition of CFS score. No transplant-listed participants died within 1-year of recruitment, so this covariable was omitted in the final logistic regression models for 1-year mortality.

Missing IMD Quintile data were handled via a dummy variable, all other covariables had <1% data missing, were assumed missing at random, and handled via listwise deletion. A P-value <0.05 was considered significant in the statistical analysis.

11.5 Results

11.5.1 Study Cohort Demographics

Figure 4-1 shows the PRISMA study flow of participant recruitment to the FITNESS study, with 485 prevalent haemodialysis patients with baseline frailty assessments and data linkage. Follow up was 678 days (interquartile range: 531-812 days), with minimum potential follow-up of 365 days from recruitment. Baseline demographics are described in detail elsewhere.[272] Table 11-1 shows key demographics stratified by frailty status at study recruitment.

11.5.2 PHQ-9 Somatic and Affective Scores

The median PHQ-9 somatic and cognitive scores were 3 (IQR 1, 6) and 1 (IQR 0, 5) respectively. Scores ranged from 0-9 for PHQ-9 somatic score and 0-18 for PHQ-9 cognitive score.

11.5.3 Relationship with Frailty

Figure 11-1 and Figure 11-2 show that both somatic and cognitive scores were positively associated with CFS score on simple and all multiple linear regression models. Full results of the final models for somatic and cognitive scores are shown in Table 11-2 and Table 11-3 respectively.

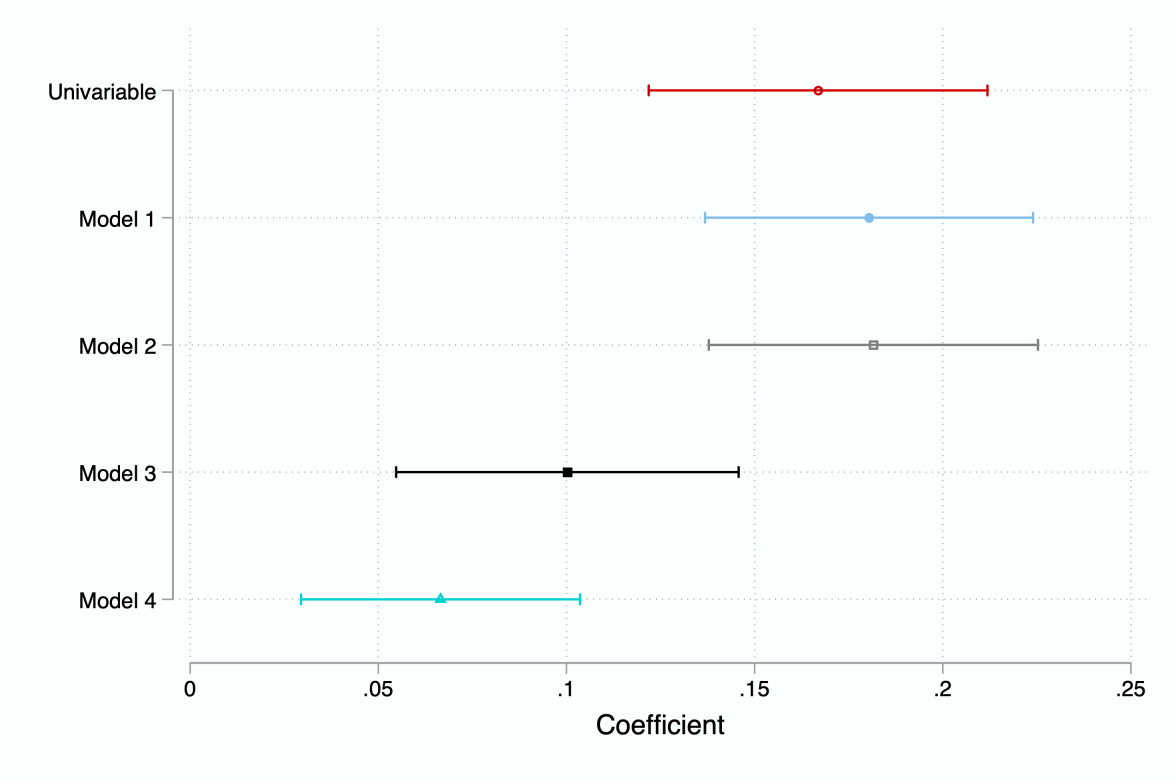


Figure 11-1: Change in CFS score associated with one-point increase in PHQ-9 somatic component score on simple and multiple linear regression models.

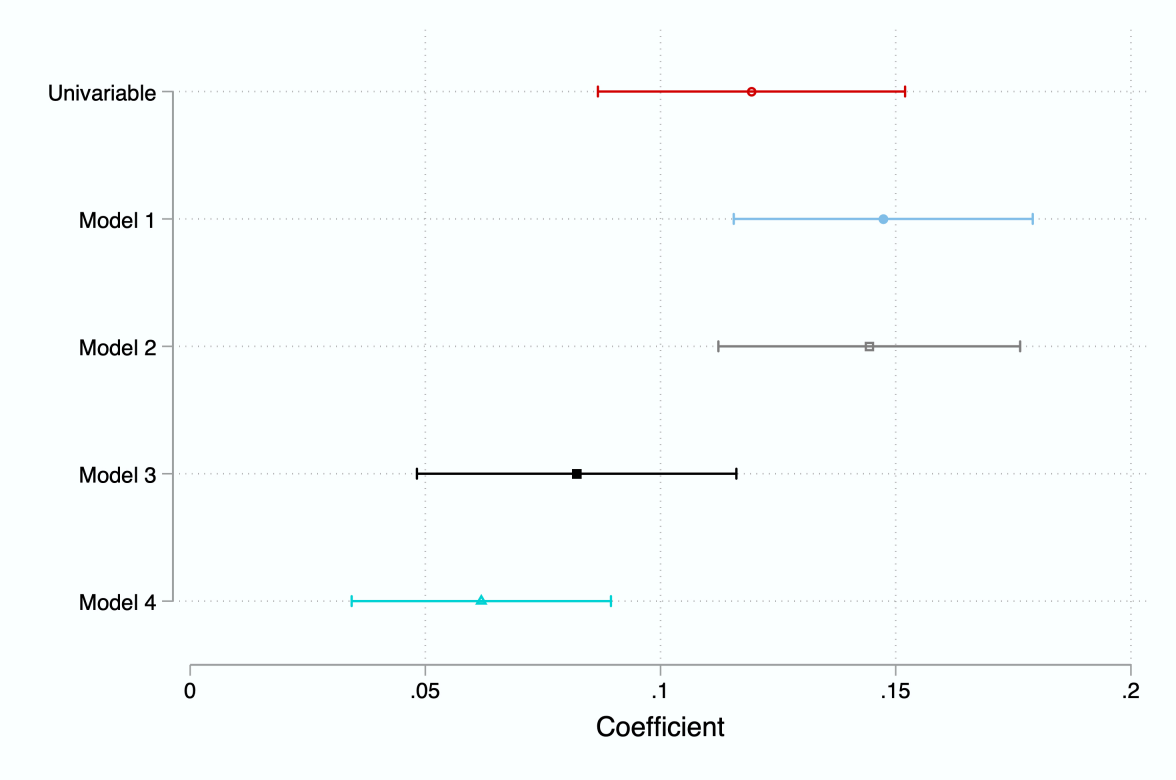


Figure 11-2: Change in CFS score associated with one-point increase in PHQ-9 cognitive component score on simple and multiple linear regression models.

11.5.4 Association with mortality

PHQ-9 somatic component was associated with mortality on univariable analysis (HR 1.10; 95% C.I. 1.02, 1.17; P=0.007), but cognitive component was not (HR 1.00; 95% C.I. 0.950, 1.05; P=0.977). Figure 11-3 shows that somatic component retained this association on multivariable analysis with CFS omitted but lost the significance on addition of CFS to the model. Affective component was not associated with mortality regardless of CFS inclusion. Full adjusted models are shown in Supplementary Table 11-1 to Supplementary Table 11-4. Adding kidney transplantation did not affect interpretation of results, as shown in Supplementary Table 11-5.

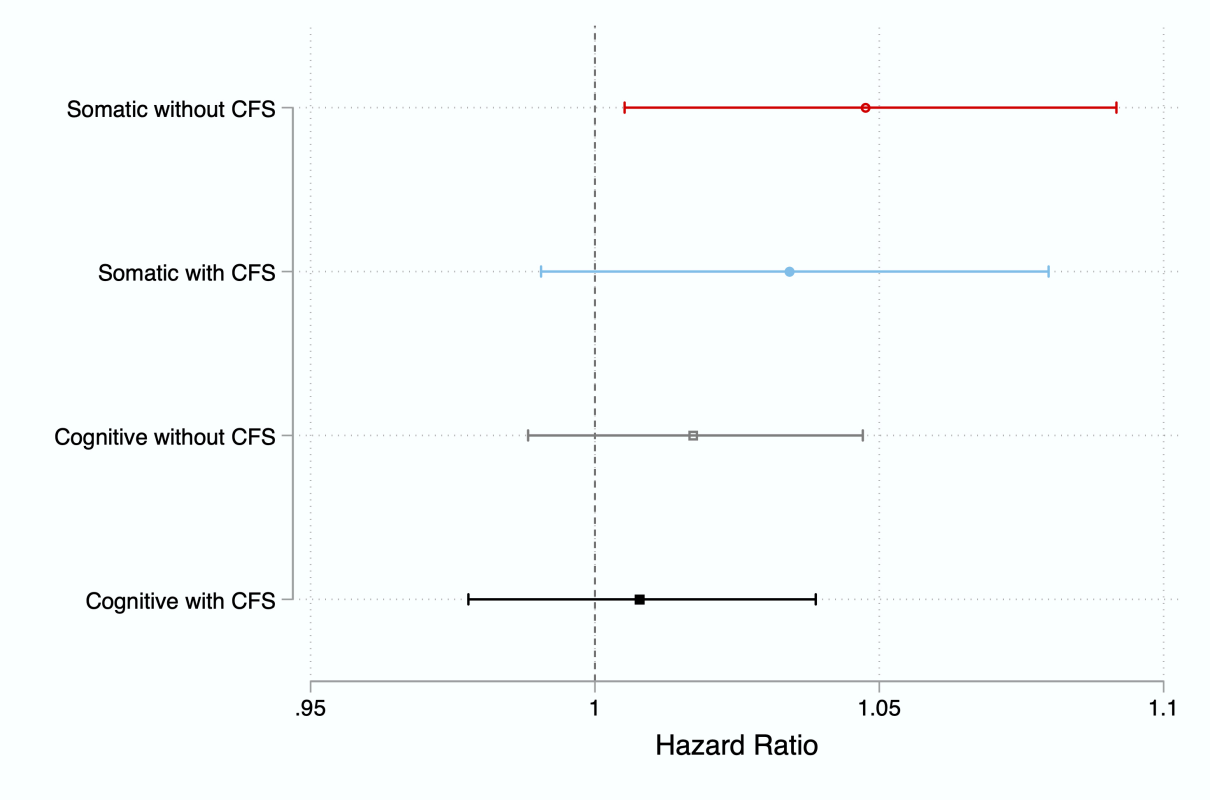


Figure 11-3: Hazard ratios for mortality associated with PHQ-9 somatic and cognitive component scores on multivariable linear regression both with and without inclusion of CFS in the model

11.5.5 Association with hospital admissions

PHQ-9 somatic score was associated with increased rates of hospital admissions on univariable analysis (IRR 1.05, 95% C.I. 1.01, 1.10, P=0.015), but not upon multivariable analysis (IRR 1.00, 95% C.I. 0.96, 1.04; P=0.993).

PHQ-9 cognitive scores were not associated with rates of hospital admissions on either univariable (IRR 1.02; 95% C.I. 1.00, 1.06; P=0.103), or multivariable analyses (IRR 0.98; 95% C.I. 0.95, 1.01; P=0.194). Fully adjusted model results for somatic and cognitive scores are shown in Table 11-4Table 11-5 respectively, and show that of the *a priori* covariables in these models, age, CFS, Charlson Index, number of previous admissions, and walking aid use were all associated with higher rates of admissions, whilst black ethnicity was associated with lower admission rates when included in both cognitive and somatic component score models. Supplementary Table 11-5: Fine and Gray subdistribution hazards model of mortality associated with PHQ-9 somatic and cognitive component scores, both with and without CFS included in model

Adjustment	CFS in model?	SHR	Lower 95% C.I.	Upper 95% C.I.	P
Somatic Component					
Unadjusted	No	**1.10**	**1.03**	**1.18**	**0.004**
	Yes	1.03	0.96	1.11	0.382
Adjusted	No	**1.09**	**1.01**	**1.18**	**0.036**
	Yes	1.06	0.97	1.15	0.181
Cognitive Component					
Unadjusted	No	1.00	0.95	1.05	0.949
	Yes	0.95	0.89	1.00	0.063
Adjusted	No	1.00	0.94	1.06	0.923
	Yes	0.97	0.91	1.03	0.308

CFS= Clinical Frailty Scale. SHR=subdistribution hazards ratio. C.I.=confidence interval. Obtained via Fine and Gray subdistribution hazards model with any kidney transplant as a competing event. Unadjusted and adjusted models shown. Adjusted models included age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass

index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage, self-reported change in health, and kidney transplant wait-listing. Bold text indicates significance at $P<0.05$ level.

Supplementary Table 11-6 and Supplementary Table 11-7 show that omission of CFS score from multivariable models did not significantly alter results.

11.5.6 Association with quality of life

Increases in both somatic and cognitive components of PHQ-9 were associated with lower EQ Summary Index scores on fractional regression, as shown in Figure 11-4 and Supplementary Table 11-8. Furthermore, Figure 11-4 shows increasing CFS scores were also associated with significant reductions in EQ Summary Index on all models, independent of somatic and cognitive component scores. Fully adjusted fractional regression model results are shown in Supplementary Table 11-9 and Supplementary Table 11-10.

11.6 Discussion

Both depression and frailty have been associated with mortality and hospitalisation in dialysis patients.[197-202] However, previous work in the FITNESS cohort has shown that depression was not significantly associated with either of these important negative outcomes (submitted for peer-review). The somatic and cognitive components of depression have also been associated with hospitalisation and mortality,[209,210] though their relationship with frailty has not been explored. Here we show that both the somatic and cognitive components of depression are associated with increasing frailty. Only somatic symptoms were associated with increased mortality and hospitalisation in univariable analyses but lost these associations on multivariable analyses. Both cognitive and somatic symptoms were associated with lower health related quality of life. Lack of association between somatic depression symptoms and

hospitalisation or mortality contradict reports elsewhere, but the association with poorer quality of life indicates that these symptoms remain important to haemodialysis recipients.

Work within the FITNESS cohort has shown that whilst PHQ-9 scores associate with frailty, they predict neither admissions nor mortality in prevalent haemodialysis recipients. Schouten and colleagues showed a differential risk profile between the somatic and cognitive components of the BDI. Somatic, but not cognitive, symptoms were associated with all-cause mortality, whereas both dimensions were associated with hospitalisation and poorer HRQOL.[209] Khalil *et al*. found a significant association between both somatic and cognitive component scores of the BDI with mortality and hospitalisation in a Jordanian haemodialysis cohort.[210]

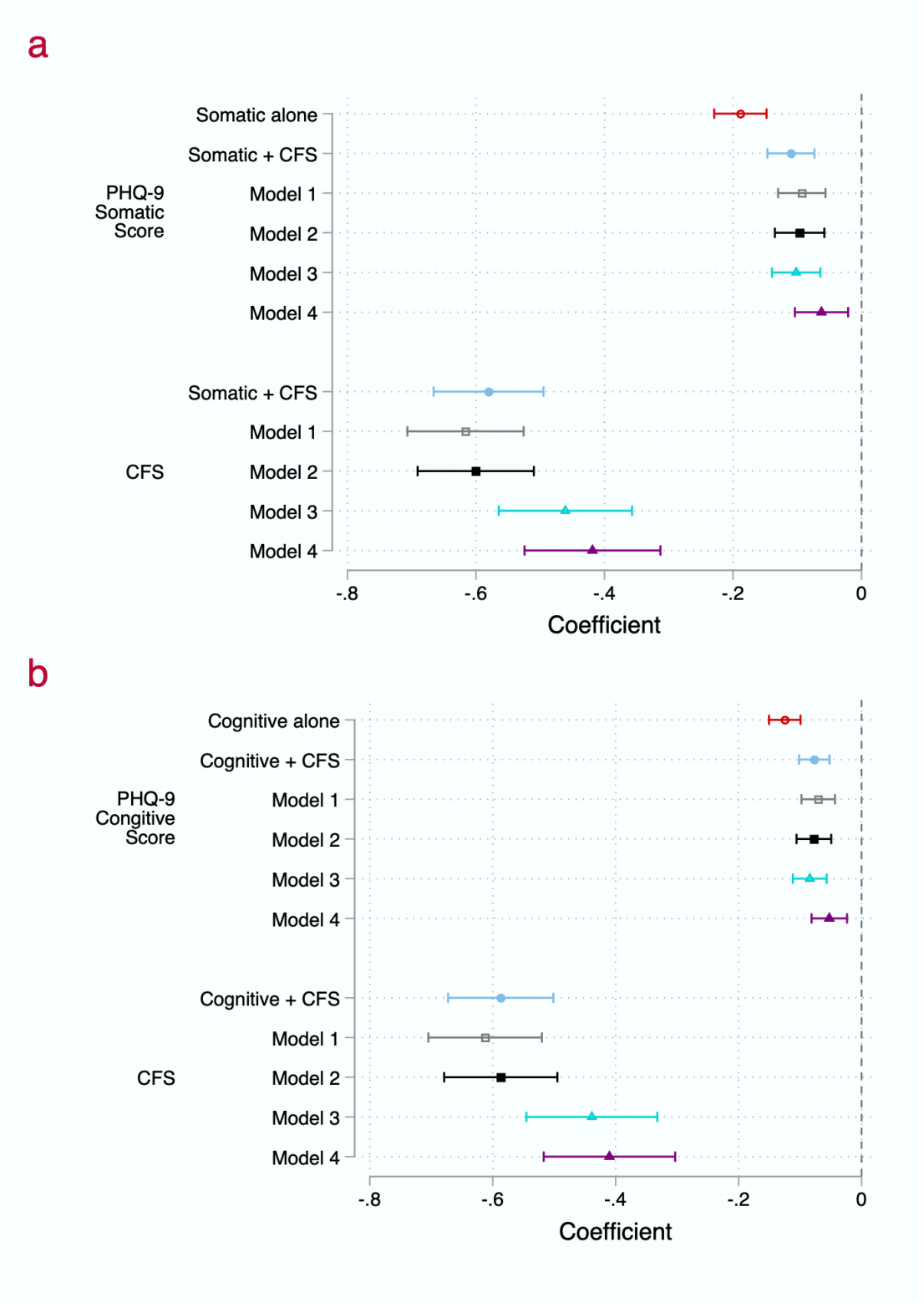


Figure 11-4: Associated change in Fractional EQ-5D Summary Index score with changes in CFS and PHQ-9 component scores on unadjusted and multivariable fractional regressions. a) Models including somatic component score. b) Models including cognitive component score

In the FITNESS cohort, however, the cognitive component did not associate with hospitalisation or mortality. Furthermore, whilst the somatic component did associate with mortality on multivariable analysis, it lost this association on addition of frailty into the model. We must exercise caution when comparing data across national and socio-cultural boundaries, obtained using different methodologies and heterogenous depression scores. However, neither the Dutch nor Jordanian cohorts included a frailty measure in their analyses. Given the overlap between symptoms of frailty and somatic depression symptoms, we may speculate that the somatic depressive symptoms may represent a surrogate marker for frailty in haemodialysis recipients. This may explain the loss of mortality association upon the addition of a *de facto* measure of frailty – and a more powerful associate with negative outcomes. These novel findings indicate some of the complexity inherent to frailty assessment in heavily comorbid populations such as haemodialysis.

FITNESS is amongst the first studies to examine the relationship between frailty and symptom subsets of depression in a large prospective haemodialysis cohort. Strengths of this study include the large prospective cohort with robust data linkage for outcomes. The cohort is well described with multiple areas of frailty, quality of life, comorbidity, cognition, depression, and musculoskeletal function accounted for in the analysis. Further strengths include the diversity of demographics, comorbidities and socio-economic backgrounds representative of the local population.[327] However, our data should be interpreted with caution in non-English populations, and validation of our findings elsewhere is required. Limitations also include the single baseline data collection for frailty and depression phenotyping; both are dynamic syndromes and repeated measures would offer greater detail

and arguably accuracy.[199,313] Our CFS definition deviates slightly from the original validation sample,[27] in that no MDT discussion was held to determine frailty status after clinical interview. However, we would argue that our approach is largely concordant with guidance upon CFS use in clinical practice.[52] Use of the EQ-5D summary index for HRQOL is validated in UK populations, but its relationship with other HRQOL measures is uncertain. Finally, we report associations rather than causation in these observational data, and due caution should be maintained when applying these findings to the individual haemodialysis recipient in clinical practice.

To conclude, both somatic and cognitive components of depression are associated with frailty and poorer HRQOL in haemodialysis recipients, but not associated with mortality or hospitalisation on fully adjusted models including frailty. These data may suggest that there is overlap between frailty and depression in their associations with negative patient outcomes. Further work is warranted to better understand and distinguish individual versus cumulative contributions from overlapping co-morbidities towards adverse outcomes in prevalent haemodialysis patients.

11.7 Tables

Table 11-1: Baseline demographics stratified by frailty status

		Total Cohort	Not Frail	Frail
Frail		261	-	-
		53.8%	-	-
Median Age		63	60	65
		53-74	50-72	55-76
Median PHQ-9 Somatic Score		3	2	4
		1-6	1-4	2-6
Median PHQ-9 Cognitive Score		1	1	3
		0-5	0-3	0-6
Median MoCA		22	23	20
		17-25	20-26	16-23
Median Albumin (g/L)		39	39	38
		35-41	36-42	34-41
Median BMI		26.8	26	27.9
		23.2-32.3	23.0-30.7	23.2-33.7
Median Charlson Score*		4	4	5
		3-6	2-5	4-7
Median HD Vintage (months)		37	33	41
		17-76	13-66	19.9-81.5
Median Kt/V		1.59	1.58	1.61
		1.39-1.85	1.38-1.80	1.41-1.88
Median EQ Summary Index		0.779	1	0.62
		0.516-1.00	0.779-1.00	0.189-0.796
Health Change	*Better*	94	52	42
		19.4%	23.2%	16.1%
	The Same	174	90	84
		35.9%	40.2%	32.2%
	Worse	217	82	135
		44.7%	36.6%	51.7%
IMD Quintile	*1*	212	96	116
		43.7%	42.9%	44.4%
	2	87	43	44
		17.9%	19.2%	16.9%
	3	85	38	47
		17.5%	17.0%	18.0%
	4	38	20	18
		7.8%	8.9%	6.9%
	5	33	14	19
		6.8%	6.3%	7.3%
	Unknown	30	13	17
		6.2%	5.8%	6.5%
Ethnicity	*White*	281	13	144

		57.9%	61.2%	55.2%
	South Asian	115	44	71
		23.7%	19.6%	27.2%
	Black	76	35	41
		15.7%	15.6%	15.7%
	Other	13	8	5
		2.7%	3.6%	1.9%
Gender	*Male*	284	148	136
		58.6%	66.1%	52.1%
Comorbidities	*Diabetes*	138	43	95
		28.5%	19.2%	36.4%
	MI	98	34	64
		20.2%	15.2%	24.5%
	CVA/TIA	57	17	40
		11.8%	7.6%	15.3%
	Cancer	56	30	26
		11.6%	13.4%	10.0%
	Heart Failure	52	19	33
		10.7%	8.5%	12.6%
	PVD	47	15	32
		9.7%	6.7%	12.3%
Primary renal disease	*Diabetic*	114	33	81
		23.5%	14.7%	31.3%
	Hypertensive	39	22	17
		8.0%	9.8%	6.5%
	Ischaemic	38	14	24
		7.8%	6.3%	9.2%
	IgA	37	20	17
		7.6%	8.9%	6.5%
	PKD	28	17	11
		5.8%	7.6%	4.2%
	FSGS	24	14	10
		5.0%	6.3%	3.8%
	Reflux	17	7	10
		3.5%	3.1%	3.8%
	Obstructive	16	10	6
		3.3%	4.5%	2.3%
	AAV	15	11	4
		3.1%	4.9%	1.5%
	Interstitial Nephritis	10	6	4
		2.1%	2.7%	1.5%
	Myeloma	10	8	2
		2.1%	3.6%	0.8%
	Unknown	68	31	37

		14.0%	13.8%	14.2%
Smoking Status	*Current*	68	38	30
		14.1%	17.0%	11.5%
	Ex	132	64	68
		27.3%	28.6%	26.2%
	Never	284	122	162
		58.7%	54.5%	62.3%
Dialysis Access	*Line*	113	47	66
		23.3%	21.0%	25.3%
Transplant List Status	*Active*	58	36	22
		12.0%	16.1%	8.4%
	Suspended	15	9	6
		3.1%	4.0%	2.3%
	Not listed	412	179	233
		85.0%	79.9%	89.3%
Employment Status	*Employed*	69	61	8
		14.3%	27.2%	3.1%
	Unemployed	148	58	90
		30.6%	25.9%	34.6%
	Retired	267	105	162
		55.2%	46.9%	62.3%
Job Role	*Unskilled Manual*	181	70	111
		39.3%	32.1%	45.7%
	Skilled Manual	101	50	51
		21.9%	22.9%	21.0%
	Clerical	52	28	24
		11.3%	12.8%	9.9%
	Managerial	46	26	20
		10.0%	11.9%	8.2%
	Professional	81	44	37
		17.6%	20.2%	15.2%
Education Level	*High School*	342	146	196
		70.7%	65.2%	75.4%
	College/Sixth Form	92	49	43
		19.0%	21.9%	16.5%
	University	50	29	21
		10.3%	13.0%	8.1%
Residence	*Own Home*	462	218	244
		95.9%	97.8%	94.2%
	Warden-Controlled	12	3	9

		2.5%	1.4%	3.5%
	Residential Home	5	2	3
		1.0%	0.9%	1.2%
	Nursing Home	3	0	3
		0.6%	0.0%	1.2%

*CKD omitted from Charlson Index

Table 11-2: Multiple linear regression of CFS score associated with PHQ-9 Somatic Score. Fully adjusted model 4.

	Coef.	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 somatic score	**0.067**	**0.029**	**0.104**	**<0.001**
Age	**-0.011**	**-0.020**	**-0.002**	**0.019**
Gender				
Male		REFERENCE		
Female	**0.224**	**0.037**	**0.412**	**0.019**
Ethnicity				
White		REFERENCE		
South Asian	0.181	-0.072	0.434	0.160
Black	-0.048	-0.314	0.218	0.724
Other	0.274	-0.320	0.868	0.365
Education Level				
High School		REFERENCE		
College/6th form	-0.009	-0.242	0.224	0.937
University	-0.211	-0.529	0.106	0.191
IMD Quintile				
1		REFERENCE		
2	0.109	-0.144	0.361	0.398
3	-0.002	-0.258	0.254	0.989
4	**-0.354**	**-0.703**	**-0.005**	**0.047**
5	-0.003	-0.376	0.370	0.987
Unknown	0.212	-0.182	0.606	0.291
Social Support				
Yes		REFERENCE		
No	**-0.687**	**-1.06**	**-0.316**	**<0.001**
Charlson Index*	**0.094**	**0.040**	**0.148**	**0.001**
Cognitive Impairment				
No		REFERENCE		
Yes	0.011	-0.220	0.243	0.923
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	**0.294**	**0.004**	**0.585**	**0.047**
Never Smoked	0.197	-0.076	0.469	0.157
Health Change				
Better/The Same		REFERENCE		
Worse	0.112	-0.080	0.305	0.252
EQ VAS Score	**-0.008**	**-0.013**	**-0.004**	**<0.001**
Walking Aid Use				
No		REFERENCE		
Yes	**0.517**	**0.291**	**0.743**	**<0.001**

Physical Activity Index				
Inactive		REFERENCE		
Moderately Inactive	**-0.408**	**-0.760**	**-0.056**	**0.023**
Moderately Active	**-1.07**	**-1.49**	**-0.648**	**<0.001**
Active	**-1.92**	**-2.36**	**-1.48**	**<0.001**
Walking Speed				
Not Slow		REFERENCE		
Slow	**0.721**	**0.491**	**0.951**	**<0.001**
Grip Strength				
Not Weak		REFERENCE		
Weak	0.075	-0.128	0.279	0.466
Constant	**4.22**	**3.59**	**4.85**	**<0.001**

*CKD omitted from Charlson Index

Table 11-3: Multiple linear regression of CFS score associated with PHQ-9 Cognitive Score. Fully adjusted model 4.

	Coef.	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Cognitive score	**0.062**	**0.034**	**0.089**	**<0.001**
Age	-0.008	-0.017	0.001	0.072
Gender				
Male		REFERENCE		
Female	**0.249**	**0.064**	**0.433**	**0.008**
Ethnicity				
White		REFERENCE		
South Asian	0.208	-0.044	0.459	0.105
Black	0.018	-0.247	0.284	0.891
Other	0.259	-0.330	0.848	0.388
Education Level				
High School		REFERENCE		
College/6th form	-0.002	-0.233	0.230	0.989
University	-0.172	-0.488	0.144	0.286
IMD Quintile				
1		REFERENCE		
2	0.094	-0.156	0.344	0.461
3	0.024	-0.230	0.278	0.854
4	-0.273	-0.621	0.075	0.124
5	0.004	-0.366	0.374	0.982
Unknown	0.221	-0.170	0.612	0.267
Social Support				
Yes		REFERENCE		
No	**-0.683**	**-1.05**	**-0.316**	**<0.001**
Charlson Index*	**0.095**	**0.041**	**0.148**	**0.001**
Cognitive Impairment				
No		REFERENCE		
Yes	-0.003	-0.233	0.226	0.977
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.279	-0.009	0.568	0.058
Never Smoked	0.151	-0.120	0.423	0.274
Health Change				
Better/The Same		REFERENCE		
Worse	0.114	-0.076	0.303	0.240
EQ VAS Score	**-0.007**	**-0.011**	**-0.002**	**0.004**
Walking Aid Use				
No		REFERENCE		
Yes	**0.565**	**0.341**	**0.790**	**<0.001**
Physical Activity Index				
Inactive		REFERENCE		
Moderately Inactive	**-0.391**	**-0.740**	**-0.042**	**0.028**
Moderately Active	**-1.03**	**-1.45**	**-0.610**	**<0.001**
Active	**-1.88**	**-2.32**	**-1.44**	**<0.001**
Walking Speed				
Not Slow		REFERENCE		
Slow	**0.690**	**0.461**	**0.918**	**<0.001**
Grip Strenght				

Not Weak		REFERENCE		
Weak	0.100	-0.101	0.300	0.330
Constant	**4.01**	**3.36**	**4.65**	**<0.001**

*CKD omitted from Charlson Index

Table 11-4: Incidence Rate Ratios of hospital admissions associated with PHQ-9 Somatic component score. Fully adjusted model including CFS

	HR	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Somatic Score	1.00	0.959	1.04	0.993
Age	**1.12**	**1.02**	**1.23**	**0.019**
CFS	**0.989**	**0.978**	**1.000**	**0.044**
Gender				
Male		REFERENCE		
Female	0.969	0.785	1.20	0.770
Ethnicity				
White		REFERENCE		
South Asian	0.826	0.622	1.10	0.188
Black	**0.687**	**0.504**	**0.937**	**0.018**
Other	0.848	0.436	1.65	0.628
BMI	0.998	0.983	1.01	0.757
IMD Quintile				
1		REFERENCE		
2	0.887	0.664	1.18	0.415
3	0.829	0.610	1.13	0.231
4	0.808	0.542	1.21	0.298
5	0.771	0.495	1.20	0.250
Unknown	1.25	0.830	1.87	0.289
Charlson Index	**1.09**	**1.03**	**1.17**	**0.006**
Previous Admissions	**1.10**	**1.05**	**1.16**	**<0.001**
Medication Number	1.02	0.989	1.05	0.208
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.842	0.598	1.18	0.324
Never Smoked	0.764	0.560	1.04	0.090
Albumin	0.998	0.994	1.00	0.155
Walking Aid Use				
No		REFERENCE		
Yes	**1.50**	**1.17**	**1.91**	**0.001**
HD vintage	1.000	0.998	1.00	0.968
Transplant Listed				
No		REFERENCE		
Yes	0.903	0.633	1.29	0.575
Constant	**0.003**	**0.001**	**0.007**	**<0.001**

*CKD omitted from Charlson Index

Table 11-5: Incidence Rate Ratios of hospital admissions associated with PHQ-9 cognitive component score. Fully adjusted model including CFS

	HR	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Cognitive Score	0.980	0.950	1.01	0.194
Age	**1.14**	**1.04**	**1.26**	**0.007**
CFS	**0.987**	**0.977**	**0.998**	**0.021**
Gender				
Male		REFERENCE		
Female	0.971	0.788	1.20	0.785
Ethnicity				
White		REFERENCE		
South Asian	0.802	0.604	1.06	0.126
Black	**0.670**	**0.490**	**0.914**	**0.012**
Other	0.822	0.423	1.60	0.564
BMI	0.997	0.983	1.01	0.701
IMD Quintile				
1		REFERENCE		
2	0.871	0.652	1.16	0.349
3	0.823	0.605	1.12	0.212
4	0.802	0.538	1.20	0.279
5	0.756	0.485	1.18	0.215
Unknown	1.26	0.838	1.89	0.268
Charlson Index	**1.09**	**1.02**	**1.16**	**0.007**
Previous Admissions	**1.10**	**1.05**	**1.16**	**<0.001**
Medication Number	1.02	0.992	1.05	0.146
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.840	0.598	1.18	0.318
Never Smoked	0.762	0.558	1.04	0.086
Albumin	0.998	0.994	1.00	0.158
Walking Aid Use				
No		REFERENCE		
Yes	**1.49**	**1.17**	**1.91**	**0.001**
HD vintage	1.00	0.998	1.00	0.944
Transplant Listed				
No		REFERENCE		
Yes	0.896	0.628	1.28	0.546
Constant	**0.003**	**0.001**	**0.008**	**<0.001**

*CKD omitted from Charlson Index

Supplementary Table 11-1: Fully adjusted Cox regression model of mortality associated with PHQ-9 Somatic Component Score. CFS omitted.

	HR	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Somatic Score	**1.08**	**1.00**	**1.17**	**0.038**
Age	0.997	0.975	1.018	0.755
Gender				
Male		REFERENCE		
Female	0.894	0.595	1.34	0.587
Ethnicity				
White		REFERENCE		
South Asian	0.586	0.325	1.06	0.076
Black	0.948	0.543	1.66	0.852
Other	0.553	0.074	4.11	0.563
BMI	0.995	0.969	1.02	0.739
IMD Quintile				
1		REFERENCE		
2	1.10	0.635	1.89	0.743
3	1.26	0.730	2.16	0.411
4	0.750	0.329	1.71	0.494
5	0.834	0.362	1.92	0.669
Unknown	0.945	0.369	2.42	0.907
Charlson Index	**1.18**	**1.06**	**1.32**	**0.002**
Previous Admissions	1.07	0.981	1.17	0.128
Medication Number	1.01	0.955	1.07	0.706
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.28	0.686	2.38	0.439
Never Smoked	0.851	0.467	1.55	0.599
Albumin	**0.944**	**0.907**	**0.983**	**0.006**
Walking Aid Use				
No		REFERENCE		
Yes	**1.73**	**1.07**	**2.78**	**0.024**
HD vintage	1.00	0.998	1.01	0.324
Transplant Listed				
No		REFERENCE		
Yes	0.150	0.020	1.11	0.063

*CKD omitted from Charlson Index

Supplementary Table 11-2: Fully adjusted Cox regression of mortality associated with PHQ-9 Somatic Component Score. CFS included.

	HR	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Somatic Score	1.06	0.977	1.14	0.173
Age	0.998	0.977	1.02	0.844
CFS	**1.26**	**1.05**	**1.53**	**0.015**
Gender				
Male		REFERENCE		
Female	0.838	0.557	1.26	0.397
Ethnicity				
White		REFERENCE		
South Asian	0.560	0.311	1.01	0.054
Black	0.968	0.554	1.69	0.908
Other	0.516	0.069	3.86	0.519
BMI	0.993	0.966	1.02	0.600
IMD Quintile				
1		REFERENCE		
2	1.11	0.645	1.92	0.698
3	1.29	0.753	2.22	0.352
4	0.811	0.355	1.85	0.619
5	0.868	0.376	2.01	0.741
Unknown	0.974	0.379	2.50	0.955
Charlson Index*	**1.16**	**1.04**	**1.29**	**0.007**
Previous Admissions	1.07	0.980	1.17	0.127
Medication Number	1.00	0.944	1.06	0.977
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.25	0.673	2.34	0.475
Never Smoked	0.809	0.443	1.48	0.491
Albumin	**0.948**	**0.910**	**0.987**	**0.009**
Walking Aid Use				
No		REFERENCE		
Yes	1.37	0.824	2.29	0.223
HD vintage	1.00	0.998	1.00	0.387
Transplant Listed				
No		REFERENCE		
Yes	0.158	0.021	1.16	0.070

*CKD omitted from Charlson Index

Supplementary Table 11-3: Fully adjusted Cox regression of mortality associated with PHQ-9 Affective Component Score. CFS omitted.

	HR	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Cognitive Score	0.996	0.941	1.05	0.877
Age	0.993	0.972	1.01	0.498
Gender				
Male		REFERENCE		
Female	0.952	0.637	1.42	0.812
Ethnicity				
White		REFERENCE		
South Asian	0.559	0.308	1.01	0.056
Black	0.926	0.528	1.62	0.788
Other	0.553	0.074	4.13	0.564
BMI	0.996	0.969	1.02	0.762
IMD Quintile				
1		REFERENCE		
2	1.02	0.593	1.76	0.936
3	1.21	0.698	2.09	0.499
4	0.730	0.319	1.67	0.457
5	0.760	0.331	1.74	0.517
Unknown	0.933	0.363	2.40	0.885
Charlson Index*	**1.18**	**1.06**	**1.32**	**0.003**
Previous Admissions	1.07	0.978	1.16	0.147
Medication Number	1.03	0.970	1.09	0.356
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.32	0.712	2.45	0.376
Never Smoked	0.854	0.467	1.56	0.608
Albumin	**0.947**	**0.909**	**0.986**	**0.008**
Walking Aid Use				
No		REFERENCE		
Yes	**1.81**	**1.13**	**2.91**	**0.014**
HD vintage	1.00	0.998	1.01	0.339
Transplant Listed				
No		REFERENCE		
Yes	0.145	0.020	1.07	0.059

*CKD omitted from Charlson Index

Supplementary Table 11-4: Fully adjusted Cox regression model of mortality associated with PHQ-9 Affective Component Score. CFS included.

	HR	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Cognitive Score	0.967	0.910	1.03	0.270
Age	0.993	0.972	1.01	0.503
CFS	**1.35**	**1.12**	**1.64**	**0.002**
Gender				
Male		REFERENCE		
Female	0.871	0.582	1.30	0.503
Ethnicity				
White		REFERENCE		
South Asian	**0.517**	**0.286**	**0.935**	**0.029**
Black	0.915	0.521	1.61	0.759
Other	0.492	0.066	3.69	0.490
BMI	0.992	0.965	1.02	0.555
IMD Quintile				
1		REFERENCE		
2	1.02	0.589	1.76	0.948
3	1.23	0.713	2.12	0.456
4	0.766	0.335	1.75	0.527
5	0.792	0.344	1.82	0.584
Unknown	0.987	0.384	2.54	0.979
Charlson Index	**1.16**	**1.04**	**1.29**	**0.010**
Previous Admissions	1.07	0.978	1.17	0.140
Medication Number	1.01	0.954	1.07	0.708
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.30	0.703	2.42	0.400
Never Smoked	0.825	0.450	1.51	0.533
Albumin	**0.951**	**0.913**	**0.989**	**0.013**
Walking Aid Use				
No		REFERENCE		
Yes	1.36	0.817	2.26	0.238
HD vintage	1.00	0.998	1.00	0.482
Transplant Listed				
No		REFERENCE		
Yes	0.154	0.021	1.14	0.067

Supplementary Table 11-5: Fine and Gray subdistribution hazards model of mortality associated with PHQ-9 somatic and cognitive component scores, both with and without CFS included in model

Adjustment	CFS in model?	SHR	Lower 95% C.I.	Upper 95% C.I.	P
Somatic Component					
Unadjusted	No	**1.10**	**1.03**	**1.18**	**0.004**
	Yes	1.03	0.96	1.11	0.382
Adjusted	No	**1.09**	**1.01**	**1.18**	**0.036**
	Yes	1.06	0.97	1.15	0.181
Cognitive Component					
Unadjusted	No	1.00	0.95	1.05	0.949
	Yes	0.95	0.89	1.00	0.063
Adjusted	No	1.00	0.94	1.06	0.923
	Yes	0.97	0.91	1.03	0.308

CFS= Clinical Frailty Scale. SHR=subdistribution hazards ratio. C.I.=confidence interval. Obtained via Fine and Gray subdistribution hazards model with any kidney transplant as a competing event. Unadjusted and adjusted models shown. Adjusted models included age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage, self-reported change in health, and kidney transplant wait-listing. Bold text indicates significance at $P<0.05$ level.

Supplementary Table 11-6: Incidence Rate Ratios of hospital admissions associated with PHQ-9 somatic component score. Adjusted model with CFS omitted.

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Somatic Score	1.01	0.97	1.05	0.559
Age	**0.99**	**0.98**	**1.00**	**0.043**
Gender				
Male		REFERENCE		
Female	0.997	0.808	1.23	0.978
Ethnicity				
White		REFERENCE		
South Asian	0.857	0.645	1.14	0.286
Black	**0.679**	**0.497**	**0.927**	**0.015**
Other	0.879	0.451	1.71	0.704
BMI	0.998	0.983	1.01	0.786
IMD Quintile				
1		REFERENCE		
2	0.882	0.660	1.18	0.400
3	0.820	0.602	1.12	0.207
4	0.777	0.520	1.16	0.219
5	0.735	0.471	1.15	0.175
Unknown	1.23	0.816	1.85	0.324
Charlson Index*	**1.10**	**1.04**	**1.18**	**0.002**
Previous Admissions	**1.10**	**1.05**	**1.16**	**<0.001**
Medication Number	1.02	0.994	1.06	0.117
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.855	0.606	1.21	0.374
Never Smoked	0.785	0.574	1.07	0.129
Albumin	0.997	0.994	1.00	0.118
Walking Aid Use				
No		REFERENCE		
Yes	**1.70**	**1.35**	**2.12**	**<0.001**
HD vintage	1.00	0.998	1.00	0.962
Transplant Listed				
No		REFERENCE		
Yes	0.893	0.624	1.28	0.537
Constant	**0.004**	**0.002**	**0.009**	**<0.001**

*CKD omitted from Charlson Index

Supplementary Table 11-7: Incidence Rate Ratios of hospital admissions associated with PHQ-9 cognitive component score. Adjusted model with CFS omitted.

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Cognitive Score	0.994	0.965	1.02	0.707
Age	**0.988**	**0.977**	**0.999**	**0.027**
Gender				
Male		REFERENCE		
Female	1.01	0.817	1.24	0.948
Ethnicity				
White		REFERENCE		
South Asian	0.841	0.634	1.12	0.231
Black	0.672	0.491	0.920	0.013
Other	0.862	0.442	1.68	0.662
BMI	0.998	0.983	1.01	0.778
IMD Quintile				
1		REFERENCE		
2	0.870	0.650	1.16	0.351
3	0.814	0.598	1.11	0.193
4	0.778	0.521	1.16	0.221
5	0.721	0.462	1.13	0.151
Unknown	1.23	0.816	1.85	0.322
Charlson Index*	**1.10**	**1.04**	**1.18**	**0.002**
Previous Admissions	**1.10**	**1.05**	**1.15**	**<0.001**
Medication Number	1.03	0.998	1.06	0.066
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.854	0.605	1.21	0.369
Never Smoked	0.784	0.573	1.07	0.127
Albumin	0.997	0.994	1.00	0.126
Walking Aid Use				
No		REFERENCE		
Yes	**1.72**	**1.37**	**2.16**	**<0.001**
HD vintage	1.000	0.998	1.00	0.927
Transplant Listed				
No		REFERENCE		
Yes	0.884	0.618	1.26	0.499
Constant	**0.005**	**0.002**	**0.010**	**<0.001**

*CKD omitted from Charlson Index

Supplementary Table 11-8: Fractional regression coefficients of somatic and cognitive component PHQ-9 scores upon EQ summary index

PHQ-9 Component	Fractional Regression Model	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
Somatic	Univariable	-0.110	-0.146	-0.073	<0.001
	1	-0.093	-0.130	-0.056	<0.001
	2	-0.096	-0.135	-0.058	<0.001
	3	-0.102	-0.139	-0.064	<0.001
	4	-0.062	-0.104	-0.021	0.003
Cognitive	Univariable	-0.077	-0.102	-0.052	<0.001
	1	-0.071	-0.098	-0.043	<0.001
	2	-0.078	-0.106	-0.049	<0.001
	3	-0.084	-0.112	-0.057	<0.001
	4	-0.052	-0.081	-0.024	<0.001

Model definitions: model 1 included frailty, age, ethnicity, gender. Model 2 added IMD quintile, social support and education level. Model 3 added admissions in the past year, Charlson index (CKD excluded), cognitive impairment, current antidepressant use, total medication number, and haemodialysis vintage. Model 4 added self-reported pain, self-reported change in health and overall self-rated health (EQ-5D visual analogue scale/100).

Supplementary Table 11-9: Fractional Regression of association of PHQ-9 Somatic Component scores with EQ Summary Index: Fully adjusted Model 4

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Somatic Score	**-0.062**	**-0.104**	**-0.021**	**0.003**
CFS	**-0.419**	**-0.524**	**-0.313**	**<0.001**
Age	0.003	-0.010	0.017	0.631
Gender				
Male		REFERENCE		
Female	**-0.220**	**-0.433**	**-0.007**	**0.043**
Ethnicity				
White		REFERENCE		
South Asian	**0.305**	**0.009**	**0.601**	**0.043**
Black	0.173	-0.149	0.496	0.292
Other	-0.498	-1.219	0.224	0.176
Education Level				
High School		REFERENCE		
College/6th form	-0.244	-0.537	0.048	0.102
University	**-0.339**	**-0.647**	**-0.031**	**0.031**
Social Support?				
Yes		REFERENCE		
No	**-0.507**	**-0.844**	**-0.169**	**0.003**
IMD Quintile				
1		REFERENCE		
2	-0.210	-0.506	0.087	0.166
3	0.043	-0.258	0.344	0.779
4	0.188	-0.213	0.590	0.358
5	0.283	-0.196	0.762	0.246
Unknown	0.184	-0.322	0.690	0.475
Employment Status				
Employed		REFERENCE		
Unemployed	-0.034	-0.711	0.642	0.921
Retired	0.133	-0.469	0.735	0.665
HD Vintage (months)	**-0.003**	**-0.005**	**-0.001**	**0.012**
Charlson Comorbidity Index*	-0.011	-0.068	0.047	0.717
Haemoglobin (g/L)	0.003	-0.007	0.012	0.585
Kt/V	0.155	-0.147	0.457	0.315
Antidepressant Use?				
No		REFERENCE		
Yes	-0.154	-0.501	0.193	0.384
Walking Aid Use?				
No		REFERENCE		

Yes	-0.170	-0.421	0.082	0.185
Slow walk speed?				
No		REFERENCE		
Yes	**-0.464**	**-0.730**	**-0.198**	**0.001**
Physical Activity Index				
Inactive		REFERENCE		
Moderately Inactive	-0.076	-0.751	0.598	0.825
Moderately Active	**-0.793**	**-1.397**	**-0.188**	**0.010**
Active	-0.084	-0.959	0.792	0.852
Self-reported health today (/100)**	**0.014**	**0.009**	**0.019**	**<0.001**
Self-reported health change***				
Better		REFERENCE		
The Same	0.134	-0.166	0.433	0.382
Worse	-0.100	-0.385	0.185	0.491
Cognitive Impairment				
No		REFERENCE		
Yes	**-0.305**	**-0.569**	**-0.040**	**0.024**
Constant	**3.080**	**1.275**	**4.885**	**0.001**

*CKD omitted. **from EQ-5D VAS. ***health change in past year, self-reported.

Supplementary Table 11-10: Fractional Regression of association of PHQ-9 Cognitive Component scores with EQ Summary Index: Fully adjusted Model 4

	Coefficient	Lower 95% C.I.	Upper 95% C.I.	P
PHQ-9 Cognitive Score	**-0.052**	**-0.081**	**-0.024**	**<0.001**
CFS	**-0.410**	**-0.517**	**-0.303**	**<0.001**
Age	0.003	-0.011	0.016	0.716
Gender				
Male		REFERENCE		
Female	**-0.254**	**-0.461**	**-0.046**	**0.017**
Ethnicity				
White		REFERENCE		
South Asian	0.270	-0.031	0.570	0.079
Black	0.146	-0.176	0.468	0.373
Other	-0.476	-1.238	0.286	0.221
Education Level				
High School		REFERENCE		
College/6th form	-0.272	-0.559	0.016	0.064
University	**-0.378**	**-0.694**	**-0.062**	**0.019**
Social Support?				
Yes		REFERENCE		
No	**-0.511**	**-0.836**	**-0.185**	**0.002**
IMD Quintile				
1		REFERENCE		
2	-0.186	-0.482	0.110	0.219
3	0.021	-0.270	0.312	0.889
4	0.125	-0.279	0.530	0.544
5	0.291	-0.179	0.761	0.225
Unknown	0.156	-0.346	0.658	0.543
Employment Status				
Employed		REFERENCE		
Unemployed	-0.042	-0.737	0.654	0.906
Retired	0.056	-0.568	0.680	0.861
HD Vintage (months)	**-0.003**	**-0.005**	**-0.001**	**0.008**
Charlson Comorbidity Index*	-0.012	-0.072	0.047	0.684
Haemoglobin (g/L)	0.005	-0.004	0.014	0.317
Kt/V	0.250	-0.049	0.549	0.101
Antidepressant Use?				
No		REFERENCE		
Yes	-0.132	-0.453	0.190	0.422
Walking Aid Use?				
No		REFERENCE		
Yes	-0.216	-0.465	0.032	0.088
Slow walk speed?				
No		REFERENCE		
Yes	**-0.444**	**-0.705**	**-0.184**	**0.001**
Physical Activity Index				
Inactive		REFERENCE		
Moderately Inactive	-0.076	-0.787	0.635	0.834
Moderately Active	**-0.805**	**-1.415**	**-0.194**	**0.010**

Active	-0.093	-0.978	0.791	0.836
Self-reported health today (/100)**	**0.013**	**0.007**	**0.018**	**<0.001**
Self-reported health change***				
Better		REFERENCE		
The Same	0.096	-0.206	0.398	0.533
Worse	-0.134	-0.419	0.152	0.359
Cognitive Impairment				
No		REFERENCE		
Yes	**-0.302**	**-0.567**	**-0.038**	**0.025**
Constant	**2.852**	**1.073**	**4.631**	**0.002**

*CKD omitted. **from EQ-5D VAS. ***health change in past year, self-reported.

Chapter 12:

Cognitive impairment, frailty and adverse outcomes among prevalent haemodialysis recipients

Authors: Benjamin M Anderson, Muhammad Qasim, Gonzalo Correa, Felicity Evison, Suzy Gallier, Charles J Ferro, Thomas A Jackson, Adnan Sharif

12.1 Extent of Personal Contribution

I coordinated all study visits with participants and dialysis unit staff. I recruited participants, and collected all baseline data with the support of Dr Gonzalo Correa, Dr Muhammad Qasim, and Dr Adnan Sharif. All colleagues were supervised by me in their data collection, and I was responsible for maintaining training and personnel logs in the site file.

Ms Felicity Evison, and Ms Suzy Gallier were responsible for interrogation of EPR for IMD Quintile assessment and HES/OPCS/ONS data for mortality and hospitalisation follow-up. I performed all subsequent data cleaning, integrity, and analyses with guidance from Dr Adnan Sharif.

The first draft of the manuscript was written by myself and I was responsible for all edits and revisions. This manuscript was originally submitted for peer-review to Kidney International Reports on 8th July 2022, submission reference KIR-07-22-0606. This was rejected after peer-review. Therefore this chapter is based upon that original manuscript and amendments made following reviewer comments from KI Reports. It has been now submitted to Kidney Medicine for consideration of peer-reviewed publication.

12.2 Abstract

12.2.1 Rationale and Objective

Frailty and cognitive impairment are common in haemodialysis recipients, and have been associated with high mortality. There is considerable heterogeneity in frailty reporting, with little comparison between commonly used frailty tools, and little exploration of the interplay between cognition and frailty. The aims were to explore the relationship between frailty scores and cognition and their associations with hospitalisation and mortality.

12.2.2 Study Design

Prospective cohort study

12.2.3 Setting and Population

Prevalent haemodialysis recipients liked to national datasets for hospitalisation and mortality.

12.2.4 Predictors

Montreal Cognitive Assessment (MoCA), Frailty Phenotype (FP), Frailty Index (FI), Edmonton Frailty Scale (EFS), and Clinical Frailty Scale (CFS) were performed at baseline.

12.2.5 Outcomes

Mortality, hospitalisation.

12.2.6 Analytical Approach

Cox Proportional Hazards model for mortality, censored for end of follow up. Negative binomial regression for admission rates, censored for death/end of follow-up.

12.2.7 Results

448 participants were recruited with valid MoCAs, followed up for a median of 685 days. There were 103 (23%) deaths and 1120 admissions of at least one night. Cognitive impairment was

identified in 346 (77.2%) participants. Increasing frailty by all definitions was associated with poorer cognition. Cognition was not associated with mortality (HR 0.993, 95% C.I. 0.952-1.03, P=0.406) or hospitalisation (IRR 1.01, 95% C.I. 0.985-1.04, P=0.391) on multivariable analyses. There were interactions between MoCA scores and increasing frailty by FI (P = 0.002) and CFS (P = 0.005); predicted admissions were highest when both MoCA and frailty scores were high, and when both scores were low.

12.2.8 Conclusion

Cognitive impairment is highly prevalent in this haemodialysis cohort. The interaction between cognition and frailty upon rates of admission suggests the MoCA offers value in identifying higher risk haemodialysis populations with both high and low degrees of frailty.

12.3 Introduction

Cognitive impairment is common in haemodialysis recipients,[211-213] and worsens in both incident and prevalent haemodialysis recipients.[211,214,215] Cognitive impairment among haemodialysis patients is associated with mortality,[216-220] but little is known about its association with hospitalisation. Many aetiological factors contribute to development of cognitive impairment, which are common in both general population and haemodialysis cohorts.[215,221,222] However, one common factor which is far more prevalent among haemodialysis patients is frailty.

A systematic review and meta-analysis identified a relationship between incident cognitive impairment and frailty in the general population,[330] but relatively little is known about the interplay between frailty and cognition in the setting of haemodialysis. FP frailty was associated with cognitive impairment in incident haemodialysis recipients,[223] and was associated with cognitive impairment by Montreal Cognitive Assessment (MoCA)[224] in prevalent Indian haemodialysis recipients over 75 years, though inferences may be limited by small numbers.[225]

There is an unmet need to explore the relationship between other definitions of frailty and cognitive impairment, and how they associate with adverse outcomes. Therefore, the aims of this study are to; i) explore and compare the relationship between cognitive impairment and frailty by FP, FI, EFS, and CFS; ii) ascertain the association of cognitive impairment with mortality and hospitalisation in haemodialysis recipients; iii) explore the interplay between frailty and cognition with respect to mortality and hospitalisation in haemodialysis.

12.4 Methods

FITNESS study design, eligibility, power calculations, consent and baseline data acquisition are presented in detail in Chapters Chapter 2: and 2.2.

12.4.1 Frailty score amendments

Cognitive impairment comprised a deficit in the FI, so this was omitted from for analyses of association with MoCA scores, giving a composite score of 31 deficits for this particular analysis. For association with MoCA scores, an amended EFS was used omitting the clock drawing element as this also formed part of the MoCA.

All frailty scores were treated as continuous variables for this analysis.

12.4.2 Montreal Cognitive Assessment

Study participants completed a MoCA prior to dialysis connection.[224] Scores on the MoCA range from zero to 30, with a score of <26 indicating cognitive impairment. The MoCA has been validated in abridged form for the visually impaired by omitting the executive function and naming sections.[265] This protocol was used for participants with visual impairment. A further protocol was used to perform MoCA without executive function only for participants with difficulties with manual dexterity. MoCA scores were treated both as raw scores and as a binary measure of cognitive impairment, defined as <26 for participants completing the full MoCA protocol, <21 for participants lacking dexterity, and <18 for visually impaired.

12.4.3 Outcomes

Mortality data were obtained by electronic record linkage of all FITNESS study recruits to Office of National Statistics (ONS), a UK-wide repository of death certificate data. This ensures robust coverage of mortality data capture and comprehensive description of causality. Electronic patient records, Hospital Episode Statistics (HES) were interrogated for hospitalisation. Admissions were defined as any hospital episode lasting ≥1 night.

12.4.4 Statistics

Statistical analysis was performed using STATA 17 (StataCorp 2021, Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Categorical data were presented as numbers and percentages, with continuous variables reported as medians and interquartile ranges (IQRs). T-tests for between age group MoCA comparisons were performed on square-transformed data to satisfy normal distribution, subsequently back-transformed for reporting.

Associations with MoCA scores were analysed using linear regression treating frailty as a continuous variable, having satisfied the linear assumption via visual comparison of observed versus Lowess fit lines on scatter plot and augmented component plus residual plots. Robust standard errors were specified to account for heteroscedasticity. Multicollinearity was excluded on all analyses by variance inflation factor <10.

Odds ratios for cognitive impairment were obtained by logistic regression. Linear and logistic regressions were performed on study variables and adjusted for *a priori* covariables selected

for known or suspected relationship with cognitive impairment: known dementia, PTH level, haemodialysis vintage, education level, diabetes status, haemoglobin, albumin, smoking status, PHQ-9 score, and previous cerebrovascular accident (CVA).[331]

Survival analyses were performed with the Fine and Gray Subdistribution Hazards Model, with any kidney transplant as a competing event. The proportional hazard assumption was checked and satisfied by examination of plots of the log-negative-log of the within-group survivorship functions versus log time as well as comparing Kaplan-Meier (observed) with Cox (expected) survival curves with our study variables, alongside selected covariables for adjusted analyses (reported as Hazard Ratios [HR] with 95% Confidence Intervals [CI]).

Incidence rate ratios were obtained for count data by Negative Binomial Regression, death-censored and offset by length of follow-up. Negative binomial distribution was confirmed by over-dispersed means and variances and visual interpretation of expected versus observed distribution plots.

Fine and Gray and negative binomial regressions were performed treating both frailty and MoCA as continuous variables for the main analyses. They included unadjusted analyses and adjusted for an *a priori* list of covariables, based on a known or suspected relationship with dialysis-related mortality/admission (age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications,

smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status).

All interaction analyses were performed on models adjusted for the aforementioned covariables. Contour plots of predicted outcome and marginal effect of MoCA upon predicted outcome were generated to explore interactions where these were statistically significant.

To avoid confounding from differing maximum scores, all analyses using MoCA scores as a continuous variable were performed only for participants who completed the full MoCA protocol. Missing IMD Quintile data were handled via a dummy variable. Other missing data were assumed missing at random and handled via listwise deletion as all other covariables had <1% data missing. P values < 0.05 were considered statistically significant.

12.5 Results

12.5.1 Study Cohort Demographics

Figure 12-1 shows the PRISMA study flow of participant recruitment to the FITNESS study, with 448 prevalent haemodialysis patients with baseline frailty and MoCA assessments and data linkage. Median follow up was 685 days (interquartile range: 543-812 days); all participants had a minimum potential follow-up of 365 days from recruitment. Baseline demographics of the FITNESS cohort are described in detail elsewhere.[272] Table 12-1 shows key demographics stratified by different frailty instruments at study recruitment.



Figure 12-1: PRISMA flow diagram of study recruitment and participation

12.5.2 Cognitive Impairment and Frailty

In total, 30 participants completed the visual impairment MoCA protocol, with a further 17 completing the poor dexterity protocol. The median MoCA score was 22 (IQR 19-25). Mean MoCA scores were significantly lower in those over 65-years ($\bar{x}$ = 21.1, 95% C.I. 20.5-21.7) versus those under 65-years ($\bar{x}$ = 23.2, 95% C.I. 22.7-23.8; P<0.001). Overall, 346 (77.2%) participants had some evidence of cognitive impairment.

Table 12-2 shows increasing frailty by each tool was associated with lower MoCA scores on both univariable and multivariable analyses. Fully adjusted models are shown in Supplementary Table 12-1 to Supplementary Table 12-4. Table 12-3 shows that each frailty score was associated with increased odds of cognitive impairment on univariable analysis, but these associations lost significance upon multivariable analyses.

12.5.3 Mortality and Hospitalisation

Total participant follow-up was 799.3 patient-years, during which there were 103 (23.0%) deaths, and 1120 admissions of at least one night. 326 (72.8%) participants had at least one hospital admission during follow-up. Figure 2 shows frequency of admissions within the FITNESS cohort.

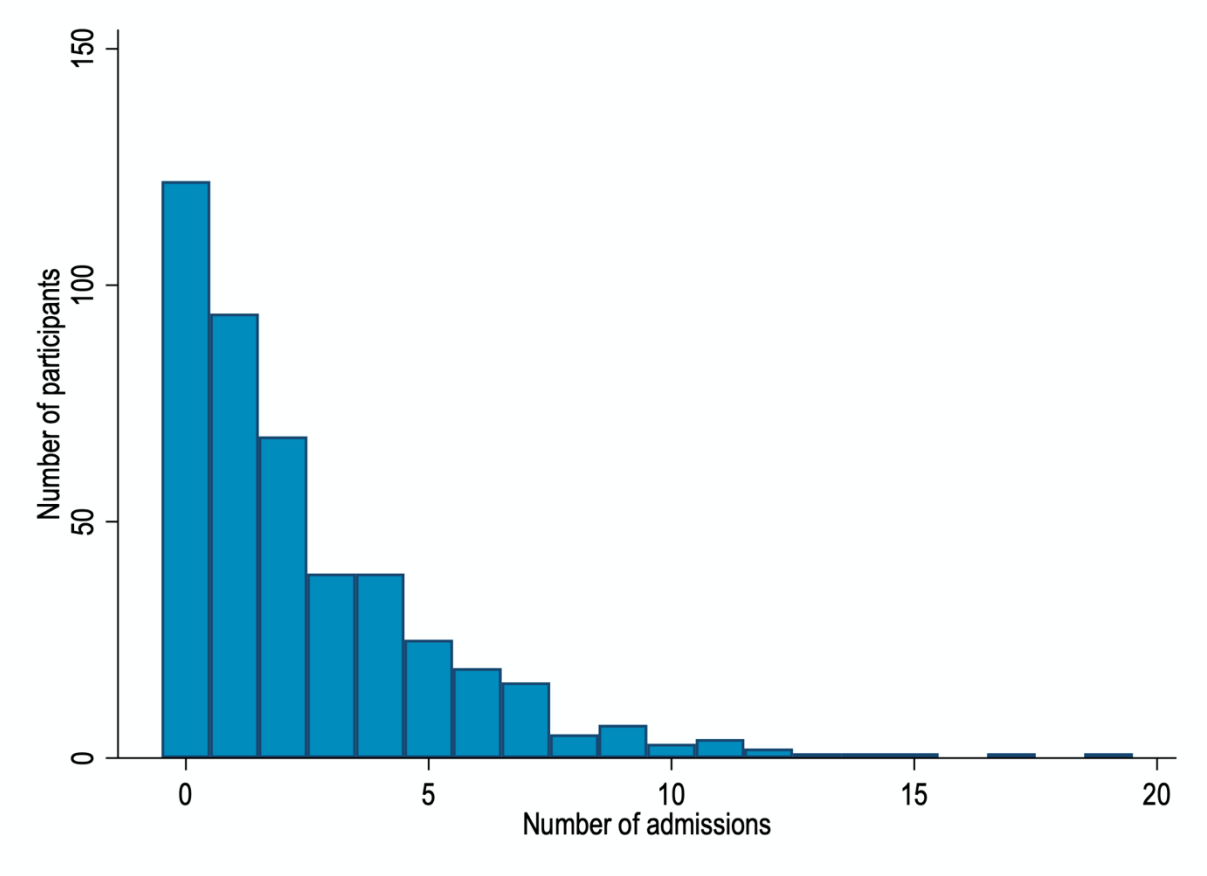


Figure 12-2: Frequency of hospital admissions ≥1 night during follow-up

12.5.4 Mortality and Cognition

Table 12-4 shows that MoCA scores were not associated with mortality on univariable or multivariable analyses. Cognitive impairment also did not associate with mortality on univariable or multivariable analyses as shown in Table 12-5. Full models are shown in

Supplementary Table 12-5 to Supplementary Table 12-14. No significant interactions between frailty and cognition were identified upon mortality.

12.5.5 Hospitalisation and Cognition

Table 12-6 demonstrates no association between MoCA score and rates of admission on univariable or multivariable analyses. Cognitive impairment also did not associate with rates of admission on univariable or multivariable analyses, as shown in Table 12-7.

There was a significant interaction between MoCA and frailty scores upon rates of admissions for the FI (P=0.002 for interaction) and CFS (P=0.005). There was no significant interaction between MoCA and FP or EFS scores. Figure 12-3 shows that predicted admissions were highest when both MoCA and frailty scores were high, and also when both scores were low. The marginal effects of both frailty and MoCA upon predicted admissions was highest at the extremes of cognition and frailty; each increase in either frailty or MoCA score reduced predicted admissions in less frail individuals, particularly at low MoCA scores. Conversely each increase in frailty or MoCA score increased predicted admissions in more frail participants, particularly at high MoCA scores. Fully adjusted final models are shown in Supplementary Table 12-15 to Supplementary Table 12-19.

12.6 Discussion

Cognitive impairment is common in haemodialysis recipients[211,212] and has been associated with mortality.[216-218] However, the interplay between frailty, cognitive impairment and outcomes among haemodialysis patients has not been fully explored and our analysis offers

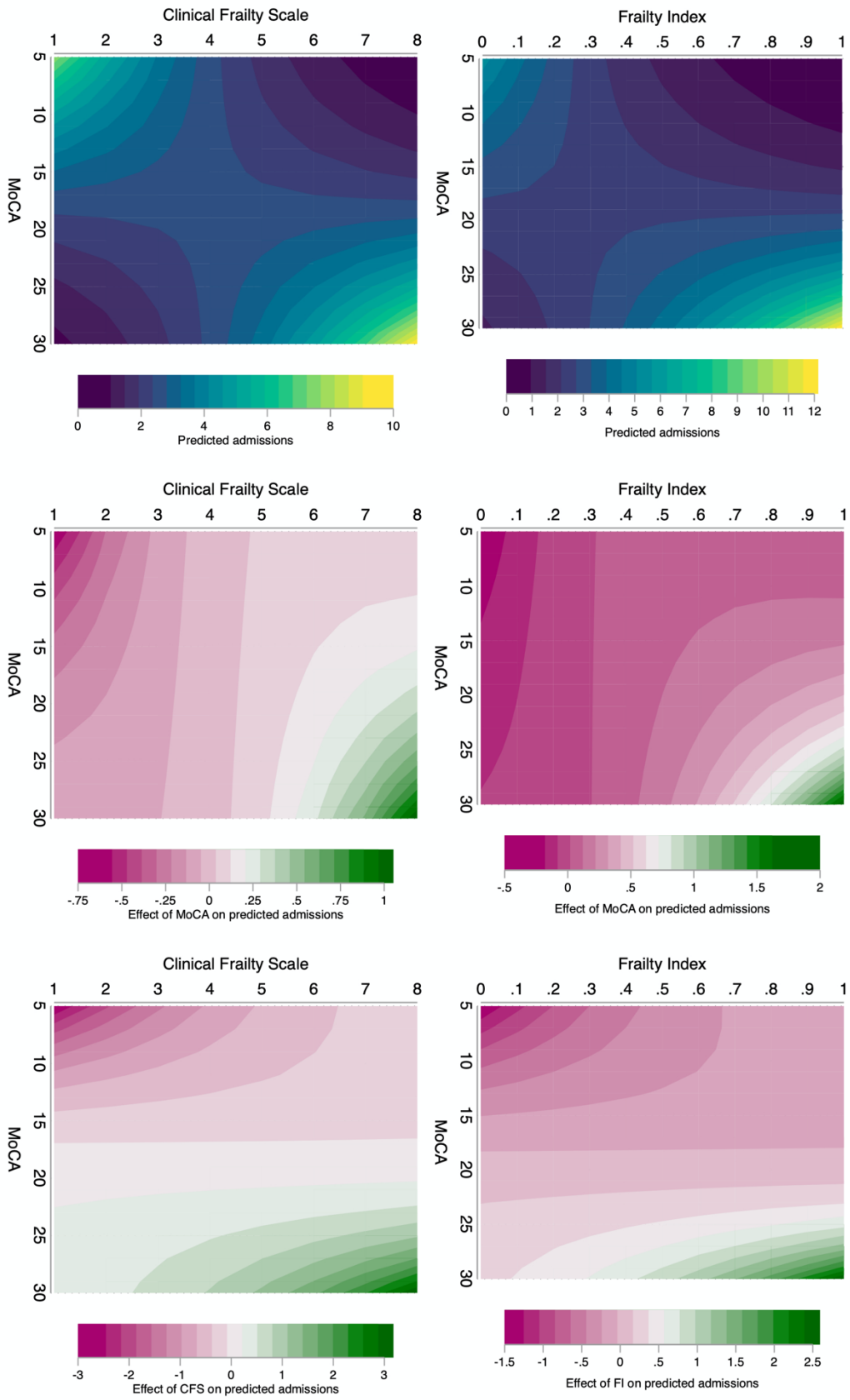


Figure 12-3: Interaction between MoCA and frailty scores on predicted rates of hospital admissions.

novel insights that have not been previously described. In this study, we report cognitive impairment is highly prevalent in a large single centre haemodialysis cohort of adults >18 years. Regardless of definition, increasing frailty is associated with lower MoCA scores and cognitive impairment in prevalent haemodialysis recipients, although the FP lost the latter association on multivariable analysis. Lower MoCA scores are not associated with either mortality or hospitalisation, although some frailty tools interact with MoCA upon rates of admission. Predicted admissions are highest where there was discordance between frailty and cognition; severe frailty with no cognitive impairment or vice versa. Predicted admissions were fewest in the absence of frailty or cognitive impairment, and perhaps surprisingly in the setting of severe frailty with severe cognitive impairment. The marginal effect of MoCA scores upon predicted admissions was greater where the discordance between frailty and cognitive impairment was highest. Finally, increases in frailty or MoCA scores augmented predicted admissions in severely frail participants without cognitive impairment but decreased predicted admissions in the not frail but severely cognitively impaired. To our knowledge, these are the first reported data to suggest such an interaction between cognition and frailty, which should stimulate further exploration and validation in other cohorts. Studies to assess frailty interventions should include cognition as an outcome of interest.

We did not identify an association between cognitive impairment and mortality. This may be partly explained by different definitions of cognitive impairment. Kurella and colleagues found that known or suspected dementia on clinical noting review was associated with increased mortality risk.[220] Hall *et al.* demonstrated that the lowest quintile on the SF-12 mental component summary was associated with an OR of 1.3 for mortality.[219] While both these

studies are larger than the FITNESS cohort, they are both limited by reliance upon proxy measures of cognitive impairment in exclusively elderly cohorts. However, in our analyses that were adjusted for age, we did not identify any interaction between age and MoCA on mortality or hospitalisation episodes. Therefore, age does not appear to satisfactorily explain the differential results. van Zwieten and colleagues have reported increased mortality in cognitive impairment on neurocognitive assessment.[218] Drew and colleagues also report that poorer executive function was associated with all-cause mortality.[217] Interestingly, Mini Mental State Examination scores were not associated with mortality,[217] which we may consider to be a similar cognitive screening tool to the MoCA. These latter two studies have the benefit of more detailed cognitive assessment and were performed on haemodialysis recipients of all adult ages. It can be speculated that this greater degree of granular data increases the sensitivity for mortality.

In our study, we describe for the first time that frailty is associated with poorer cognition in a prevalent haemodialysis recipient of all adults aged >18 years. Furthermore, we have demonstrated that – whilst cognition was not associated with mortality or hospitalisation in its own right – there appears to be an interaction between cognition and frailty upon predicted admissions. It is interesting that both the predicted admissions, and the marginal effect of MoCA scores upon those predicted admissions, were greater where the greatest discordance was observed between cognitive function and frailty. Potential explanations for these phenomena range from the simple to the more speculative. It is intuitive that those who are neither frail nor cognitively impaired are unlikely to require many admissions, relative to their peers. However, we may speculate that those experiencing both severe frailty and severe

cognitive impairment may be subject to considerable admission avoidance efforts by caregivers and medical providers. We may also posit that those with severe frailty but with good cognition may be more likely to seek medical attention for the sequelae of their frailty; it is striking that the marginal effect of each increase in MoCA scores is strongly positive upon predicted admissions in this group. Furthermore, severe cognitive impairment in the absence of functional impairment may present significant challenges to caregivers resulting in greater hospital admissions; increase in MoCA scores associated with fewer predicted admissions in this group.

FITNESS is to our knowledge the largest prospective cohort study to compare frequently used frailty tools in haemodialysis, the first to compare their associations with both mortality and hospitalisation, and the first to suggest that cognitive impairment may modulate the associations of frailty with admissions. Further strengths include diversity of demographics, comorbidities and socio-economic backgrounds representative of the local population.[327] However our data should be interpreted with caution in non-English populations, and validation of our findings elsewhere is required. A limitation of FITNESS is the single cross-sectional assessment, as frailty is a dynamic state, with year-by-year variability observed.[313] As a prevalent cohort – albeit with adjustment for dialysis vintage in analyses – our findings are not directly translatable to incident haemodialysis. There were small variations in application of frailty tool criteria from other studies. The CFS was derived after clinical interview, but omitting the multi-disciplinary discussion as in the original validation cohort.[27] However, our CFS closely represents real-world application of the tool in clinical practice.[52] Our FP included questionnaire responses

regarding energy expenditure, rather than a Minnesota Leisure Time Questionnaire, in keeping with work in another haemodialysis cohort.[270] Our EFS included a 4m walk in lieu of a timed up and go test; we would argue it also tests muscle function, but we cannot be certain this did not influence results. Our definition of cognitive impairment included participants who were either visually impaired or unable to write, with proportionate reductions in thresholds for cognitive impairment in each case. This is in keeping with previous work on MoCA adjustment for visual impairment, but such a strategy may influence results. In another limitation, some 95% confidence intervals crossed the point of no effect by small margins, raising the possibility of type II error. Finally, whilst these data describe associations, caution should be exercised when considering the applicability of these findings to the individual haemodialysis recipient in clinical practice.

To conclude, in a large prevalent haemodialysis cohort increasing frailty scores – however defined – were associated with lower MoCA scores, but not with increased odds of cognitive impairment. There appears to be an interaction between MoCA scores and frailty upon the association with hospitalisation, but MoCA is not independently associated with hospitalisation or mortality. The Montreal Cognitive Assessment may therefore offer added discriminative value in identifying higher risk haemodialysis populations with both high and low degrees of frailty. These results should stimulate further exploration of the interplay between frailty and cognitive impairment, particularly with regards to adverse outcomes.

12.7 Tables

Table 12-1: Baseline demographics of FITNESS study participants

Parameter		Total cohort	Participants identified as frail by:			
			FP	**FI**	**EFS**	**CFS**
Participants identified as frail (% of total cohort)		-	182 (40.6%)	281 (62.7%)	228 (50.9%)	234 (52.2%)
Median MoCA		22 (17-25)	20 (16-24)	20 (16-23)	20 (15-23)	20 (16-23)
Median Age		63 (53-74)	67 (56-77)	63 (53-75)	63 (53-74)	65 (54-76)
Self-Reported Health Change	Better	84 (18.8%)	23 (12.6%)	40 (14.2%)	40 (17.5%)	35 (15.0%)
	The Same	161 (35.9%)	55 (30.2%)	81 (28.8%)	63 (27.6%)	75 (32.1%)
	Worse	203 (45.3%)	104 (57.1%)	160 (56.9%)	125 (54.8%)	124 (53.0%)
IMD Quintile	*1*	187 (41.7%)	80 (44.0%)	125 (44.5%)	106 (46.5%)	96 (41.0%)
	2	83 (18.5%)	39 (21.4%)	49 (17.4%)	42 (18.4%)	42 (18.0%)
	3	83 (18.5%)	29 (15.9%)	52 (18.5%)	34 (14.9%)	47 (20.1%)
	4	37 (8.3%)	14 (7.7%)	22 (7.8%)	16 (7.0%)	17 (7.3%)
	5	32 (7.1%)	11 (6.0%)	19 (6.8%)	18 (7.9%)	18 (7.7%)
	Unknown	26 (5.8%)	9 (5.0%)	14 (5.0%)	12 (5.3%)	14 (6.0%)
Ethnicity	*White*	279 (62.3%)	120 (65.9%)	173 (61.6%)	132 (57.9%)	143 (61.1%)
	South Asian	84 (18.8%)	34 (18.7%)	58 (20.6%)	48 (21.1%)	48 (20.5%)
	Black	74 (16.5%)	25 (13.7%)	55 (15.7%)	45 (19.7)	39 (16.7%)
	Other	11 (2.46%)	3 (1.7%)	6 (2.1%)	3 (1.3%)	4 (1.7%)
Male		257 (57.4%)	94 (51.7%)	148 (52.7%)	119 (52.2%)	118 (50.4%)
Median Albumin		39 (35-42)	38 (33-41)	38 (34-41)	38 (34-41)	39 (35-41)
Median BMI		26.8 (23.1-32.3)	27 (22.7-32.9)	27.7 (23.1-33.1)	27.7 (23.1-33.6)	27.7 (23.2-33.7)
Cause of kidney failure*	*Diabetes*	96 (21.4%)	52 (28.6%)	71 (25.3%)	62 (27.2%)	66 (28.2%)
	Ischaemic	35 (7.8%)	16 (8.8%)	25 (8.9%)	18 (7.9%)	22 (9.4%)
	Hypertension	33 (7.4%)	11 (6.0%)	19 (6.8%)	18 (7.9%)	13 (5.6%)

	IgA	36 (8.0%)	12 (6.6%)	21 (7.5%)	19 (8.3%)	17 (7.3%)
	PKD	28 (6.3%)	7 (3.9%)	14 (5.0%)	11 (4.8%)	11 (4.7%)
	FSGS	22 (4.9%)	9 (5.0%)	11 3.9%)	12 (5.3%)	8 (3.4%)
	Reflux	17 (3.8%)	11 (6.0%)	12 (4.3%)	10 (4.4%)	10 (4.3%)
	Obstructive	16 (3.6%)	7 (3.9%)	8 (2.9%)	7 (3.1%)	6 (2.6%)
	AAV	15 (3.4%)	5 (2.8%)	6 (2.1%)	5 (2.2%)	4 (1.7%)
	Interstitial Nephritis	10 (2.2%)	4 (2.2%)	5 (1.8%)	3 (1.3%)	4 (1.7%)
	Myeloma	10 (2.2%)	2 (1.1%)	5 (1.8%)	3 (1.3%)	2 (0.9%)
	Other	41 (9.2%)	18 (9.9%)	29 (10.3%)	24 (10.5%)	24 (10.3%)
	Unknown	65 (14.5%)	21 (11.5%)	37 (13.2%)	25 (11.0%)	34 (14.5%)
Medical co-morbidities	*MI*	87 (19.4%)	45 (24.7%)	64 (22.8%)	55 (24.1%)	55 (23.5%)
	Heart failure	49 (10.9%)	23 (12.6%)	33 (11.7%)	30 (13.2%)	31 (13.3%)
	Stroke/TIA	55 (12.3%)	34(17.9%)	42 (15.0%)	34 (14.9%)	36 (16.2%)
	PVD	45 (10.0%)	25 (13.7%)	34 (12.1%)	25 (11.0%)	30 (12.8%)
	Cancer	55 (12.3%)	17 (9.3%)	33 (11.7%)	24 10.5%)	25 (10.7%)
	Diabetes	119 (26.6%)	59 (33.4%)	82 (29.2%)	63 32.0%)	78 (33.3%)
Smoking history	*Current*	67 (15.0%)	27 (14.9%)	40 (14.3%)	36 (15.9%)	29 (12.5%)
	Previous	128 (28.6%)	50 (27.6%)	77 (27.5%)	59 (26.0%)	66 (28.3%)
	Never	252 (56.4%)	104 (57.5%)	163 (58.2%)	132 (58.2%)	138 (59.2%)
Median Charlson Score**		4 (3-6)	5 (4-7)	5 (3-6)	5 (3-6)	5 (4-6)
Dialysis details	*Dialysis vintage (median in months)*	36 (17-76)	46 (22-93)	40 (18-79)	34 (16-75)	41 (20-79)
	Line	107 (23.9%)	50 (27.5%)	72 (25.6%)	63 (27.6%)	61 (26.1%)
	Kt/V	1.60 (1.39-1.86)	1.62 (1.41-1.9)	1.61 (1.42-1.88)	1.61 (1.37-1.87)	1.63 (1.42-1.89)
Transplant list status	*Active*	51 (11.4%)	11 (6.0%)	26 (9.3%)	20 (8.8%)	20 (8.6%)
	Suspended	15 (3.4%)	2 (1.1%)	9 (3.2%)	6 (2.6%)	6 (2.6%)
	Not listed	382 (85.3%)	169 (92.9%)	246 (87.5%)	202 (88.6%)	208 (88.9%)
	Employed	66 (14.8%)	5 (2.8%)	16 (5.7%)	13 (5.7%)	8 (3.4%)

% Employment Status	*Unemployed*	135 (30.2%)	61 (33.7%)	105 (37.5%)	91 (4.01%)	80 (34.3%)
	Retired	246 (55.0%)	115 (63.5%)	159 (56.8%)	123 (54.2%)	145 (62.2%)
% Job Role***	*Unskilled Manual*	158 (37.1%)	79 (45.9%)	113 (43.3%)	90 (42.7%)	93 (42.7%)
	Skilled Manual	95 (22.3%)	33 (19.2%)	54 (20.7%)	46 (21.8%)	47 (21.6%)
	Clerical	52 (12.2%)	24 (14.0%)	33 (12.6%)	27 (12.8%)	24 (11.0%)
	Managerial	44 (10.3%)	13 (7.6%)	20 (7.7%)	17 (8.1%)	19 (8.7%)
	Professional	77 (18.1%)	23 (13.4%)	41 (15.7%)	31 (14.7%)	35 (16.1%)
% Education Level	*High School*	310 (69.4%)	134 (74.0%)	206 (73.6%)	171 (75.3%)	172 (73.8%)
	College/Sixth Form	88 (19.7%)	37 (20.4%)	52 (18.6%)	39 (17.2%)	41 (17.6%)
	University	49 (11.0%)	10 (5.5%)	22 (7.9%)	17 (7.5%)	20 (8.6%)
Residence	*Own home*	425 (95.5%)	167 (92.3%)	262 (93.9%)	208 (92.4%)	217 (93.5%)
	Warden-Controlled Flat	12 (2.7%)	7 (3.9%)	10 (3.6%)	11 (4.9%)	9 (3.9%)
	Residential Home	5 (1.12%)	4 (2.2%)	4 (1.4%)	4 (1.8%)	3 (1.3%)
	Nursing Home	3 (0.67%)	3 (1.7%)	3 (1.1%)	2 (0.9%)	3 (1.3%)
% With Professional Carers****		32 (7.5%)	27 (15.7%)	31 (11.7%)	28 (12.1%)	32 (14.6%)

*Some participants had >1 cause of kidney failure listed. **Chronic kidney disease omitted from Charlson Score.
***Current job or previous job if unemployed/retired. ****For those living in own home.

Table 12-2: Linear regression of MoCA scores by frailty

	Coef	Lower 95% C.I.	Upper 95% C.I.	P
Univariable				
Frailty Phenotype	-0.893	-1.21	-0.573	<0.001
Frailty Index*	-0.629	-0.852	-0.406	<0.001
Edmonton Frailty Scale**	-0.368	-0.54	-0.195	<0.001
Clinical Frailty Scale	-0.959	-1.26	-0.653	<0.001
Multivariable				
Frailty Phenotype	-0.792	-1.12	-0.458	<0.001
Frailty Index*	-0.781	-1.05	-0.512	<0.001
Edmonton Frailty Scale**	-0.471	-0.665	-0.278	<0.001
Clinical Frailty Scale	-0.904	-1.24	-0.566	<0.001

Visually or dexterity impaired participants excluded. *Cognitive impairment excluded from FI for this analysis, FI scaled so coefficient correspond to 0.1 point rise in FI. **Clock-drawing excluded from EFS. Multivariable analysis adjusted for known dementia, PTH, HD vintage, education level, diabetes, haemoglobin, albumin, smoking status, PHQ-9 score, previous CVA.

Table 12-3: Logistic regression of cognitive impairment by frailty

	OR	Lower 95% C.I.	Upper 95% C.I.	P
Univariable				
Frailty Phenotype	**1.37**	**1.14**	**1.63**	**<0.001**
Frailty Index*	**1.21**	**1.07**	**1.38**	**0.004**
Edmonton Frailty Scale**	1.08	0.99	1.18	0.07
Clinical Frailty Scale	**1.37**	**1.15**	**1.63**	**<0.001**
Multivariable				
Frailty Phenotype	1.19	0.96	1.48	0.11
Frailty Index*	1.16	0.97	1.37	0.10
Edmonton Frailty Scale**	1.07	0.96	1.21	0.23
Clinical Frailty Scale	1.21	0.99	1.48	0.06

OR=Odds ratio for cognitive impairment. 95% C.I.=95% confidence interval. Bold text indicates significance at P<0.05 level. *Cognitive impairment excluded from FI for this analysis, FI scaled so coefficient correspond to 0.1 point rise in FI. **Clock-drawing excluded from EFS. Multivariable analysis adjusted for known dementia, PTH, HD vintage, education level, diabetes, haemoglobin, albumin, smoking status, PHQ-9 score, previous CVA.

Table 12-4: Subdistribution Hazard ratios for mortality according to continuous MoCA and frailty scores. Unadjusted and adjusted model results shown

Frailty tool in model	Variable	SHR	Lower 95% C.I.	Upper 95% C.I.	P
Unadjusted					
-	MoCA Only	0.99	0.94	1.03	0.58
Frailty Phenotype	MoCA	1.01	0.97	1.07	0.55
	FP	1.45	1.25	1.67	<0.001
Frailty Index	MoCA	1.02	0.97	1.07	0.47
	FI*	**1.26**	**1.14**	**1.39**	**<0.001**
Edmonton Frailty Scale	MoCA	1.02	0.97	1.07	0.39
	EFS	**1.17**	**1.09**	**1.25**	**<0.001**
Clinical Frailty Scale	MoCA	1.02	0.97	1.07	0.54
	CFS	**1.44**	**1.22**	**1.70**	**<0.001**
Adjusted					
-	MoCA Only	1.00	0.95	1.05	0.88
Frailty Phenotype	MoCA	1.01	0.96	1.07	0.76
	FP	1.22	1.50	1.00	0.05
Frailty Index	MoCA	1.01	0.96	1.08	0.62
	FI*	**1.21**	**0.06**	**1.37**	**0.005**
Edmonton Frailty Scale	MoCA	1.01	0.95	1.07	0.71
	EFS	1.08	0.98	1.19	0.13
Clinical Frailty Scale	MoCA	1.01	0.95	1.07	0.78
	CFS	**1.32**	**1.09**	**1.61**	**0.005**

Obtained by Fine and Gray Subdistribution Hazards analysis, kidney transplantation as competing event, and censored for end of follow-up. Bold text indicates significance at P<0.05 level. SHR= Subdistribution Hazard Ratio. 95% C.I. = 95% confidence interval.. *FI scaled so HRs correspond to 0.1 point rise in FI. Multivariable analysis adjusted for age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status

Table 12-5: Subdistribution hazards of mortality associated with cognitive impairment and increasing continuous frailty scores. Adjusted and unadjusted models shown.

Frailty tool in model	Variable	SHR	Lower 95% C.I.	Upper 95% C.I.	P
		Unadjusted			
-	Cog Imp	1.20	0.71	2.02	0.49
Frailty Phenotype	Cog Imp	1.00	0.59	1.69	0.99
	FP	**1.43**	**1.24**	**1.64**	**<0.001**
Frailty Index	Cog Imp	0.96	0.57	1.63	0.89
	FI*	**1.24**	**1.13**	**1.37**	**<0.001**
Edmonton Frailty Scale	Cog Imp	1.02	0.60	1.72	0.96
	EFS	**1.15**	**1.08**	**1.23**	**<0.001**
Clinical Frailty Scale	Cog Imp	0.99	0.59	1.66	0.98
	CFS	**1.42**	**1.21**	**1.67**	**<0.001**
		Adjusted			
-	Cog Imp	1.04	0.58	1.85	0.90
Frailty Phenotype	Cog Imp	0.94	0.52	1.69	0.83
	FP	1.22	0.99	1.49	0.06
Frailty Index	Cog Imp	0.92	0.52	1.65	0.79
	FI*	**1.20**	**1.06**	**1.37**	**0.005**
Edmonton Frailty Scale	Cog Imp	0.97	0.54	1.73	0.92
	EFS	**1.07**	**0.97**	**1.19**	**0.16**
Clinical Frailty Scale	Cog Imp	0.98	0.56	1.73	0.95
	CFS	**1.32**	**1.08**	**1.60**	**0.006**

Obtained by Fine and Gray Subdistribution Hazards analysis, kidney transplantation as competing event, and censored for end of follow-up. Bold text indicates significance at P<0.05 level. SHR= Subdistribution Hazard Ratio. 95% C.I. = 95% confidence interval.. *FI scaled so HRs correspond to 0.1 point rise in FI. Multivariable analysis adjusted for age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status

Table 12-6: Incidence rate ratios of hospital admissions by continuous MoCA and frailty scores on adjusted and unadjusted analyses.

		HR	Lower 95% C.I.	Upper 95% C.I.	P
Unadjusted					
-	MoCA Only	1.00	0.98	1.03	0.92
Frailty	MoCA	1.02	0.99	1.04	0.24
Phenotype	FP	**1.21**	**1.11**	**1.32**	**<0.001**
Frailty Index	MoCA	1.02	0.99	1.04	0.18
	FI*	**1.17**	**1.10**	**1.25**	**<0.001**
Edmonton	MoCA	1.03	1.00	1.06	0.05
Frailty Scale	EFS	**1.12**	**1.08**	**1.17**	**<0.001**
Clinical	MoCA	1.02	0.99	1.04	0.24
Frailty Scale	CFS	**1.26**	**1.16**	**1.38**	**<0.001**
Adjusted					
-	MoCA Only	1.01	0.99	1.04	0.39
Frailty	MoCA	1.01	0.99	1.04	0.34
Phenotype	FP	1.04	0.94	1.14	0.46
Frailty Index	MoCA	1.06	0.98	1.14	0.13
	FI*	1.02	0.99	1.04	0.25
Edmonton	MoCA	1.02	0.99	1.04	0.25
Frailty Scale	EFS	1.03	0.98	1.08	0.31
Clinical	MoCA	1.02	0.99	1.04	0.21
Frailty Scale	CFS	**1.15**	**1.04**	**1.26**	**0.006**

Obtained by negative binomial regression, offset for length of follow-up and censored for death. IRR=incidence rate ratio. CI= cognitive impairment. 95% C.I.=95% confidence intervals. Bold text indicates significance at P<0.05 level. *FI scaled so IRRs correspond to 0.1 point rise in FI. Multivariable analysis adjusted for age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status

Table 12-7: Incidence Rate Ratios of hospital admissions associated with cognitive impairment and increasing continuous frailty. Unadjusted and adjusted analyses shown.

Frailty tool in model	Variable	IRR	Lower 95% C.I.	Upper 95% C.I.	P
		Unadjusted			
-	Cog Imp	1.02	0.78	1.34	0.88
Frailty Phenotype	Cog Imp	0.92	0.71	1.21	0.56
	FP	**1.22**	**1.12**	**1.32**	**<0.001**
Frailty Index	Cog Imp	0.91	0.69	1.18	0.47
	FI*	**1.16**	**1.09**	**1.23**	**<0.001**
Edmonton Frailty Scale	Cog Imp	0.90	0.69	1.18	0.45
	EFS	**1.11**	**1.06**	**1.15**	**<0.001**
Clinical Frailty Scale	Cog Imp	0.94	0.72	1.22	0.64
	CFS	**1.24**	**1.15**	**1.35**	**<0.001**
		Adjusted			
-	Cog Imp	0.95	0.73	1.24	0.71
Frailty Phenotype	Cog Imp	0.94	0.72	1.23	0.66
	FP	1.05	0.96	1.15	0.32
Frailty Index	Cog Imp	0.93	0.71	1.21	0.59
	FI*	1.05	0.98	1.12	0.16
Edmonton Frailty Scale	Cog Imp	0.94	0.72	1.22	0.64
	EFS	1.01	0.97	1.06	0.53
Clinical Frailty Scale	Cog Imp	0.94	0.72	1.21	0.62
	CFS	**1.13**	**1.03**	**1.24**	**0.01**

Obtained by negative binomial regression, offset for length of follow-up and censored for death. IRR=incidence rate ratio. CI= cognitive impairment. 95% C.I.=95% confidence intervals. Bold text indicates significance at P<0.05 level. *FI scaled so IRRs correspond to 0.1 point rise in FI. Multivariable analysis adjusted for age, sex, ethnicity [grouped into white, south Asian, black and other ethnicities], body mass index, index of multiple deprivation, Charlson comorbidity index [CKD omitted], number of hospitalisation episodes, number of medications, smoking status, serum albumin, use of walking aids, dialysis vintage and kidney transplant wait-listing in addition to frailty status

12.8 Supplementary Materials

Supplementary Table 12-1: Multiple linear regression of MoCA score by frailty phenotype

	β	Lower 95% C.I.	Upper 95% C.I.	P
Frailty Phenotype	**-0.79**	**-1.12**	**-0.46**	**<0.001**
Dementia				
No		REFERENCE		
Yes	0.37	-1.42	2.16	0.685
PTH	0.00	-0.01	0.01	0.623
HD vintage	0.00	0.00	0.00	0.541
Education Level				
High School		REFERENCE		
College/6th form	**3.26**	**2.19**	**4.33**	**<0.001**
University	**4.35**	**3.15**	**5.56**	**<0.001**
Diabetes				
No		REFERENCE		
Yes	**-1.16**	**-2.12**	**-0.19**	**0.019**
Hb (g/L)	0.01	-0.02	0.05	0.510
Serum Albumin	0.00	0.00	0.00	0.859
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.44	-0.96	1.84	0.539
Never Smoked	-1.03	-2.37	0.30	0.129
PHQ-9 Score	**0.12**	**0.03**	**0.20**	**0.007**
Previous Stroke				
No		REFERENCE		
Yes	-0.67	-1.93	0.59	0.299
Constant	**21.0**	**16.8**	**25.2**	**<0.001**

PTH=parathyroid hormone. PHQ-9 = PHQ-9 depression score. Previous CVA = previous cerebrovascular accident or transient ischaemic attack. Bold text indicates significance at P<0.005 level.

Supplementary Table 12-2: Multiple linear regression of MoCA score by frailty index

	β	Lower 95% C.I.	Upper 95% C.I.	P
Frailty Index	**-0.78**	**-1.05**	**-0.51**	**<0.001**
Dementia				
No		REFERENCE		
Yes	-0.14	-2.01	1.73	0.883
PTH	0.00	-0.01	0.01	0.629
HD vintage	0.00	0.00	0.00	0.324
Education Level				
High School		REFERENCE		
College/6th form	**3.19**	**2.13**	**4.25**	**<0.001**
University	**4.39**	**3.16**	**5.62**	**<0.001**
Diabetes				
No		REFERENCE		
Yes	-0.91	-1.89	0.06	0.067
Hb (g/L)	0.01	-0.03	0.05	0.594
Serum Albumin	0.00	0.00	0.00	0.857
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.69	-0.69	2.06	0.327
Never Smoked	-0.79	-2.11	0.52	0.235
PHQ-9 Score	**0.20**	**0.10**	**0.30**	**<0.001**
Previous Stroke				
No		REFERENCE		
Yes	-0.55	-1.82	0.72	0.393
Constant	**21.3**	**17.1**	**25.5**	**<0.001**

*Frailty Index scaled such that **β** is for each 0.1 rise in FI. Cognitive impairment omitted from FI score for this analysis. PTH=parathyroid hormone. PHQ-9 = PHQ-9 depression score. Previous CVA = previous cerebrovascular accident or transient ischaemic attack. Bold text indicates significance at P<0.005 level.*

Supplementary Table 12-3: Multiple linear regression of MoCA score by Edmonton frailty scale

	β	Lower 95% C.I.	Upper 95% C.I.	P
Edmonton Frailty Scale	**-0.47**	**-0.66**	**-0.28**	**<0.001**
Dementia				
No		REFERENCE		
Yes	0.26	-1.54	2.07	0.774
PTH	0.00	-0.01	0.01	0.560
HD vintage	0.00	0.00	0.00	0.162
Education Level				
High School		REFERENCE		
College/6th form	**3.35**	**2.25**	**4.45**	**<0.001**
University	**4.54**	**3.33**	**5.76**	**<0.001**
Diabetes				
No		REFERENCE		
Yes	**-1.15**	**-2.13**	**-0.18**	**0.020**
Hb (g/L)	0.01	-0.02	0.05	0.551
Serum Albumin	0.00	0.00	0.01	0.451
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.21	-1.17	1.58	0.765
Never Smoked	-1.26	-2.55	0.04	0.058
PHQ-9 Score	**0.16**	**0.07**	**0.25**	**0.001**
Previous Stroke				
No		REFERENCE		
Yes	-0.84	-2.09	0.40	0.185
Constant	**22.7**	**18.6**	**26.9**	**<0.001**

PTH=parathyroid hormone. PHQ-9 = PHQ-9 depression score. Previous CVA = previous cerebrovascular accident or transient ischaemic attack. Bold text indicates significance at P<0.005 level. Clock drawing omitted from EFS score for this analysis

Supplementary Table 12-4: Multiple linear regression of MoCA score by Clinical Frailty Scale

	β	Lower 95% C.I.	Upper 95% C.I.	P
Clinical Frailty Scale	**-0.90**	**-1.24**	**-0.57**	**<0.001**
Dementia				
No		REFERENCE		
Yes	0.04	-1.77	1.85	0.964
PTH	0.00	-0.01	0.01	0.612
HD vintage	0.00	0.00	0.00	0.344
Education Level				
High School		REFERENCE		
College/6th form	**3.24**	**2.19**	**4.29**	**<0.001**
University	**4.33**	**3.12**	**5.55**	**<0.001**
Diabetes				
No		REFERENCE		
Yes	-0.95	-1.92	0.02	0.056
Hb (g/L)	0.02	-0.02	0.05	0.343
Serum Albumin	0.00	0.00	0.00	0.652
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.72	-0.69	2.13	0.317
Never Smoked	-0.83	-2.17	0.51	0.224
PHQ-9 Score	**0.13**	**0.04**	**0.21**	**0.005**
Previous Stroke				
No		REFERENCE		
Yes	-0.66	-1.86	0.55	0.284
Constant	**22.5**	**18.2**	**26.9**	**<0.001**

PTH=parathyroid hormone. PHQ-9 = PHQ-9 depression score. Previous CVA = previous cerebrovascular accident or transient ischaemic attack. Bold text indicates significance at P<0.005 level.

Supplementary Table 12-5: Fully adjusted Fine and Gray Subdistribution Hazards model of MoCA scores associated with mortality hazard

	SHR	Lower 95% C.I.	Upper 95% C.I.	P
MoCA	1.00	0.94	1.06	0.93
Age	1.00	0.97	1.03	0.98
Gender				
Male		REFERENCE		
Female	0.76	0.48	1.21	0.24
Ethnicity				
White		REFERENCE		
South Asian	0.61	0.30	1.24	0.18
Black	0.78	0.40	1.51	0.45
Other	1.10	0.12	10.61	0.93
BMI	0.99	0.95	1.03	0.59
IMD Quintile				
1		REFERENCE		
2	1.45	0.80	2.63	0.22
3	1.48	0.74	2.96	0.27
4	1.01	0.36	2.85	0.98
5	1.27	0.56	2.91	0.57
Unknown	0.94	0.30	2.92	0.92
Charlson Index*	1.12	0.99	1.27	0.06
Previous Admissions**	1.10	0.99	1.22	0.08
Number Medications	1.03	0.97	1.10	0.31
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.29	0.61	2.73	0.50
Never Smoked	0.81	0.39	1.72	0.59
Albumin	**0.94**	**0.89**	**0.99**	**0.02**
Walking Aid Use				
No		REFERENCE		
Yes	**1.83**	**1.06**	**3.16**	**0.03**
Haemodialysis Vintage	1.00	1.00	1.01	0.56
Transplant List Status				
Not Active		REFERENCE		
Active	**0.00**	**0.00**	**0.00**	**<0.001**

Obtained by Fine and Gray Subdistribution Hazards analysis, kidney transplantation as competing event, and censored for end of follow-up. Bold text indicates significance at P<0.05 level. SHR= Subdistribution Hazard Ratio. 95% C.I. = 95% confidence interval.

Supplementary Table 12-6: Fully adjusted Fine and Gray model of mortality associated with continuous MoCA and FP scores

	SHR	Lower 95% C.I.	Upper 95% C.I.	P
MoCA	1.01	0.96	1.07	0.76
Frailty Phenotype	1.22	1.50	1.00	0.05
Age	1.00	0.98	1.03	0.95
Gender				
Male		REFERENCE		
Female	0.74	0.46	1.18	0.21
Ethnicity				
White		REFERENCE		
South Asian	0.63	0.30	1.31	0.22
Black	0.84	0.42	1.66	0.61
Other	1.16	0.12	11.20	0.90
BMI	0.99	0.95	1.03	0.54
IMD Quintile				
1		REFERENCE		
2	1.50	0.82	2.73	0.19
3	1.53	0.75	3.12	0.24
4	0.98	0.36	2.68	0.96
5	1.35	0.58	3.13	0.48
Unknown	0.93	0.31	2.80	0.89
Charlson Index*	1.12	0.98	1.27	0.09
Previous Admissions**	1.09	0.98	1.21	0.12
Number Medications	1.02	0.96	1.09	0.53
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.34	0.62	2.87	0.46
Never Smoked	0.81	0.37	1.74	0.58
Albumin	**0.95**	**0.90**	**1.00**	**0.04**
Walking Aid Use				
No		REFERENCE		
Yes	1.47	0.80	2.68	0.21
Haemodialysis Vintage	1.00	1.00	1.01	0.60
Transplant List Status				
Not Active		REFERENCE		
Active	**0.00**	**0.00**	**0.00**	**<0.001**

Obtained by Fine and Gray Subdistribution Hazards analysis, kidney transplantation as competing event, and censored for end of follow-up. Bold text indicates significance at P<0.05 level. SHR= Subdistribution Hazard Ratio. 95% C.I. = 95% confidence interval.

Supplementary Table 12-7: Fully adjusted Fine and Gray model of mortality associated with continuous MoCA and FI scores.

	SHR	Lower 95% C.I.	Upper 95% C.I.	P
MoCA	1.01	0.96	1.08	0.62
Frailty Index*	**1.21**	**0.06**	**1.37**	**0.005**
Age	1.01	0.98	1.04	0.56
Gender				
Male		REFERENCE		
Female	0.73	0.46	1.15	0.17
Ethnicity				
White		REFERENCE		
South Asian	0.57	0.27	1.22	0.15
Black	0.90	0.45	1.80	0.78
Other	1.30	0.13	12.6	0.82
BMI	0.98	0.95	1.02	0.44
IMD Quintile				
1		REFERENCE		
2	1.54	0.85	2.81	0.16
3	1.63	0.81	3.28	0.17
4	1.03	0.38	2.76	0.96
5	1.40	0.60	3.25	0.43
Unknown	0.95	0.32	2.78	0.92
Charlson Index**	1.10	0.97	1.24	0.13
Previous Admissions***	1.10	0.99	1.22	0.08
Number Medications	1.01	0.95	1.08	0.67
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.22	0.57	2.63	0.60
Never Smoked	0.74	0.34	1.59	0.43
Albumin	**0.94**	**0.90**	**0.99**	**0.03**
Walking Aid Use				
No		REFERENCE		
Yes	1.38	0.76	2.50	0.29
Haemodialysis Vintage	1.00	1.00	1.01	0.53
Transplant List Status				
Not Active		REFERENCE		
Active	0.00	0.00	.	1.00

Obtained by Fine and Gray Subdistribution Hazards analysis, kidney transplantation as competing event, and censored for end of follow-up. Bold text indicates significance at P<0.05

level. SHR= Subdistribution Hazard Ratio. 95% C.I. = 95% confidence interval. SHR given for each 0.1 point rise in FI.

Supplementary Table 12-8: Fully adjusted Fine and Gray model of mortality associated with continuous MoCA and EFS scores.

	SHR	Lower 95% C.I.	Upper 95% C.I.	P
MoCA	1.01	0.95	1.07	0.71
Edmonton Frailty Scale	1.08	0.98	1.19	0.13
Age	1.00	0.98	1.03	0.82
Gender				
Male		REFERENCE		
Female	0.76	0.48	1.21	0.25
Ethnicity				
White		REFERENCE		
South Asian	0.62	0.30	1.30	0.21
Black	0.80	0.41	1.55	0.51
Other	1.28	0.13	12.76	0.83
BMI	0.99	0.95	1.03	0.53
IMD Quintile				
1		REFERENCE		
2	1.45	0.79	2.66	0.22
3	1.53	0.76	3.09	0.24
4	0.97	0.35	2.69	0.96
5	1.34	0.59	0.31	0.49
Unknown	0.94	0.31	2.84	0.91
Charlson Index*	1.11	0.99	1.26	0.08
Previous Admissions**	1.07	0.95	1.20	0.24
Number Medications	1.02	0.96	1.09	0.54
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.34	0.62	2.87	0.46
Never Smoked	0.81	0.38	1.74	0.59
Albumin	**0.94**	**0.90**	**1.00**	**0.03**
Walking Aid Use				
No		REFERENCE		
Yes	1.63	0.91	2.90	0.10
Haemodialysis Vintage	1.00	1.00	1.01	0.57
Transplant List Status				
Not Active		REFERENCE		
Active	**0.00**	**0.00**	**0.00**	**<0.001**

Obtained by Fine and Gray Subdistribution Hazards analysis, kidney transplantation as

competing event, and censored for end of follow-up. Bold text indicates significance at P<0.05 level. SHR= Subdistribution Hazard Ratio. 95% C.I. = 95% confidence interval.

Supplementary Table 12-9: Fully adjusted Fine and Gray model of mortality associated with continuous MoCA and CFS scores.

	SHR	Lower 95% C.I.	Upper 95% C.I.	P
MoCA	1.01	0.95	1.07	0.78
Clinical Frailty Scale	**1.32**	**1.09**	**1.61**	**0.005**
Age	1.00	0.98	1.03	0.71
Gender				
Male		REFERENCE		
Female	0.71	0.45	1.12	0.14
Ethnicity				
White		REFERENCE		
South Asian	0.58	0.28	1.21	0.15
Black	0.85	0.53	1.67	0.64
Other	1.40	0.14	13.51	0.77
BMI	0.99	0.95	1.03	0.50
IMD Quintile				
1		REFERENCE		
2	1.46	0.80	2.66	0.21
3	1.52	0.76	3.05	0.23
4	1.07	0.38	2.97	0.90
5	1.32	0.57	3.07	0.52
Unknown	0.91	0.30	2.73	0.86
Charlson Index*	1.10	0.98	1.23	0.11
Previous Admissions**	1.11	0.99	1.23	0.06
Number Medications	1.02	0.95	1.09	0.61
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	1.22	0.57	2.62	0.60
Never Smoked	0.77	0.36	1.66	0.51
Albumin	0.94	0.89	0.99	0.02
Walking Aid Use				
No		REFERENCE		
Yes	1.41	0.79	2.51	0.25
Haemodialysis Vintage	1.00	1.00	1.01	0.53
Transplant List Status				
Not Active		REFERENCE		
Active	0.00	.	.	.

Obtained by Fine and Gray Subdistribution Hazards analysis, kidney transplantation as

competing event, and censored for end of follow-up. Bold text indicates significance at P<0.05 level. SHR= Subdistribution Hazard Ratio. 95% C.I. = 95% confidence interval.

Supplementary Table 12-10: Fully adjusted Fine and Gray model of mortality associated with cognitive impairment

	SHR	Lower 95% C.I.	Upper 95% C.I.	P
Cognitive Impairment				
No		REFERENCE		
Yes	1.04	0.58	1.85	0.90
Age	1.00	0.97	1.03	0.98
Gender				
Male		REFERENCE		
Female	0.76	0.47	1.21	0.25
Ethnicity				
White		REFERENCE		
South Asian	0.61	0.30	1.24	0.17
Black	0.78	0.40	1.52	0.46
Other	1.10	0.11	10.58	0.94
BMI				
IMD Quintile		REFERENCE		
1	1.45	0.80	2.63	0.21
2	1.47	0.76	2.86	0.25
3	1.01	0.38	2.70	0.99
4	1.27	0.56	2.89	0.57
5	0.94	0.31	2.88	0.91
Unknown	0.99	0.95	1.03	0.59
Charlson Index*	1.12	0.99	1.27	0.06
Previous Admissions**	1.10	0.99	1.22	0.08
Number Medications	1.00	1.00	1.01	0.57
Smoking Status	1.03	0.97	1.10	0.31
Current Smoker				
Ex-Smoker		REFERENCE		
Never Smoked	1.29	0.61	2.74	0.50
Albumin	0.82	0.39	1.71	0.59
Walking Aid Use	0.94	0.89	0.99	0.02
No				
Yes		REFERENCE		
Haemodialysis Vintage	**1.84**	**1.07**	**3.15**	**0.03**
Transplant List Status				
Not Active		REFERENCE		
Active	**0.00**	**0.00**	**0.00**	**<0.001**

Obtained by Fine and Gray Subdistribution Hazards analysis, kidney transplantation as

competing event, and censored for end of follow-up. Bold text indicates significance at P<0.05 level. SHR= Subdistribution Hazard Ratio. 95% C.I. = 95% confidence interval.

Supplementary Table 12-11: Fully adjusted Fine and Gray model of mortality associated with cognitive impairment and continuous FP frailty

	SHR	Lower 95% C.I.	Upper 95% C.I.	P
Cognitive Impairment				
No		REFERENCE		
Yes	0.94	0.52	1.69	0.83
Frailty Phenotype	1.22	0.99	1.49	0.06
Age	1.00	0.97	1.03	0.97
Gender				
Male		REFERENCE		
Female	0.74	0.46	1.18	0.21
Ethnicity				
White		REFERENCE		
South Asian	0.62	0.30	1.29	0.20
Black	0.83	0.42	1.64	0.59
Other	1.17	0.12	11.29	0.89
BMI				
IMD Quintile		REFERENCE		
1	1.51	0.83	2.74	0.18
2	1.56	0.78	3.10	0.21
3	1.00	0.38	2.59	0.99
4	1.37	0.59	3.15	0.46
5	0.94	0.31	2.85	0.91
Unknown	0.99	0.95	1.03	0.54
Charlson Index*	1.12	0.98	1.27	0.09
Previous Admissions**	1.09	0.98	1.21	0.12
Number Medications	1.00	1.00	1.01	0.60
Smoking Status	1.02	0.95	1.09	0.54
Current Smoker				
Ex-Smoker		REFERENCE		
Never Smoked	1.35	0.63	2.90	0.44
Albumin	0.80	0.37	1.74	0.58
Walking Aid Use	0.95	0.90	1.00	0.05
No				
Yes		REFERENCE		
Haemodialysis Vintage	1.47	0.80	2.68	0.22
Transplant List Status				
Not Active		REFERENCE		
Active	**0.00**	**0.00**	**0.00**	**<0.001**

Obtained by Fine and Gray Subdistribution Hazards analysis, kidney transplantation as

competing event, and censored for end of follow-up. Bold text indicates significance at P<0.05 level. SHR= Subdistribution Hazard Ratio. 95% C.I. = 95% confidence interval.

Supplementary Table 12-12: Fully adjusted Fine and Gray model of mortality associated with cognitive impairment and continuous FI frailty

	SHR	Lower 95% C.I.	Upper 95% C.I.	P
Cognitive Impairment				
No		REFERENCE		
Yes	0.92	0.52	1.65	0.79
Frailty Index*	**1.20**	**1.06**	**1.37**	**0.005**
Age	1.01	0.98	1.04	0.59
Gender				
Male		REFERENCE		
Female	0.73	0.46	1.15	0.17
Ethnicity				
White		REFERENCE		
South Asian	0.56	0.27	1.19	0.13
Black	0.89	0.45	1.77	0.74
Other	1.29	0.13	12.49	0.83
BMI				
IMD Quintile		REFERENCE		
1	1.56	0.86	2.84	0.15
2	1.69	0.85	3.33	0.13
3	1.07	0.42	2.75	0.88
4	1.45	0.62	3.36	0.39
5	0.98	0.33	2.88	0.97
Unknown	0.99	0.95	1.03	0.47
Charlson Index**	1.10	0.97	1.24	0.14
Previous Admissions***	1.10	0.99	1.23	0.08
Number Medications	1.00	1.00	1.01	0.54
Smoking Status	1.01	0.95	1.08	0.69
Current Smoker				
Ex-Smoker		REFERENCE		
Never Smoked	1.23	0.57	2.64	0.60
Albumin	0.73	0.34	1.58	0.42
Walking Aid Use	**0.94**	**0.90**	**1.00**	**0.03**
No				
Yes		REFERENCE		
Haemodialysis Vintage	1.37	0.76	2.50	0.30
Transplant List Status				
Not Active		REFERENCE		
Active	**0.00**	**0.00**	**0.00**	**<0.001**

Obtained by Fine and Gray Subdistribution Hazards analysis, kidney transplantation as competing event, and censored for end of follow-up. Bold text indicates significance at P<0.05 level. SHR= Subdistribution Hazard Ratio. 95% C.I. = 95% confidence interval. *SHR given for each 0.1 point rise in FI. ** CKD omitted. *** Number of admissions in year prior to recruitment.

Supplementary Table 12-13: Fully adjusted Fine and Gray model of mortality associated with cognitive impairment and continuous EFS frailty

	SHR	Lower 95% C.I.	Upper 95% C.I.	P
Cognitive Impairment				
No		REFERENCE		
Yes	0.97	0.54	1.73	0.92
Edmonton Frailty Scale	1.07	0.97	1.19	0.16
Age	1.00	0.98	1.03	0.87
Gender				
Male		REFERENCE		
Female	0.76	0.48	1.21	0.25
Ethnicity				
White		REFERENCE		
South Asian	0.61	0.30	1.26	0.18
Black	0.78	0.40	1.54	0.48
Other	1.27	0.13	12.68	0.84
BMI				
IMD Quintile		REFERENCE		
1	1.47	0.80	2.68	0.21
2	1.56	0.79	3.08	0.21
3	1.01	0.38	2.63	0.99
4	1.36	0.59	3.11	0.47
5	0.95	0.31	2.88	0.93
Unknown	0.99	0.95	1.03	0.53
Charlson Index*	1.11	0.99	1.26	0.09
Previous Admissions**	1.07	0.96	1.21	0.22
Number Medications	1.00	1.00	1.01	0.57
Smoking Status	1.02	0.96	1.09	0.53
Current Smoker				
Ex-Smoker		REFERENCE		
Never Smoked	1.35	0.63	2.91	0.44
Albumin	0.81	0.38	1.73	0.59
Walking Aid Use	**0.94**	**0.90**	**0.99**	**0.03**
No				
Yes		REFERENCE		
Haemodialysis Vintage	1.63	0.91	2.91	0.10
Transplant List Status				
Not Active		REFERENCE		
Active	**0.00**	**0.00**	**0.00**	**<0.001**

Obtained by Fine and Gray Subdistribution Hazards analysis, kidney transplantation as competing event, and censored for end of follow-up. Bold text indicates significance at P<0.05 level. SHR= Subdistribution Hazard Ratio. 95% C.I. = 95% confidence interval. * CKD omitted. ** Number of admissions in year prior to recruitment.

Supplementary Table 12-14: Fully adjusted Fine and Gray model of mortality associated with cognitive impairment and continuous EFS frailty

	SHR	Lower 95% C.I.	Upper 95% C.I.	P
Cognitive Impairment				
No		REFERENCE		
Yes	0.98	0.56	1.73	0.95
Clinical Frailty Scale	**1.32**	**1.08**	**1.60**	**0.006**
Age	1.00	0.98	1.03	0.74
Gender				
Male		REFERENCE		
Female	0.71	0.45	1.12	0.14
Ethnicity				
White		REFERENCE		
South Asian	0.57	0.27	1.18	0.13
Black	0.84	0.42	1.65	0.60
Other	1.39	0.14	13.45	0.78
BMI				
IMD Quintile		REFERENCE		
1	1.48	0.82	2.68	0.20
2	1.55	0.79	3.02	0.20
3	1.09	0.41	2.87	0.86
4	1.34	0.58	3.11	0.50
5	0.92	0.31	2.76	0.88
Unknown	0.99	0.95	1.03	0.50
Charlson Index*	1.10	0.98	1.23	0.12
Previous Admissions**	1.11	1.00	1.23	0.06
Number Medications	1.00	1.00	1.01	0.53
Smoking Status	1.02	0.95	1.09	0.62
Current Smoker				
Ex-Smoker		REFERENCE		
Never Smoked	1.24	0.58	2.66	0.59
Albumin	0.77	0.36	1.65	0.51
Walking Aid Use	**0.94**	**0.89**	**0.99**	**0.02**
No				
Yes		REFERENCE		
Haemodialysis Vintage	1.40	0.79	2.51	0.25
Transplant List Status				
Not Active		REFERENCE		
Active	**0.00**	**0.00**	**0.00**	**<0.001**

Obtained by Fine and Gray Subdistribution Hazards analysis, kidney transplantation as competing event, and censored for end of follow-up. Bold text indicates significance at P<0.05 level. SHR= Subdistribution Hazard Ratio. 95% C.I. = 95% confidence interval. * CKD omitted. ** Number of admissions in year prior to recruitment.

Supplementary Table 12-15: Fully adjusted model of rates of admission associated with MoCA scores.

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
MoCA	1.01	0.99	1.04	0.39
Age	0.99	0.98	1.00	0.08
Gender				
Male		REFERENCE		
Female	0.99	0.79	1.24	0.92
Ethnicity				
White		REFERENCE		
South Asian	0.81	0.58	1.12	0.21
Black	0.75	0.53	1.05	0.09
Other	1.12	0.53	2.34	0.76
BMI	1.00	0.99	1.02	0.61
IMD Quintile				
1		REFERENCE		
2	0.77	0.56	1.06	0.11
3	0.81	0.58	1.12	0.20
4	0.80	0.52	1.22	0.29
5	0.78	0.49	1.26	0.31
Unknown	1.15	0.74	1.81	0.53
Charlson Index*	**1.10**	**1.03**	**1.18**	**0.005**
Previous Admissions**	**1.12**	**1.07**	**1.18**	**<0.001**
Number Medications	1.03	0.99	1.06	0.11
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.89	0.62	1.28	0.53
Never Smoked	0.81	0.58	1.12	0.20
Albumin	1.00	0.99	1.00	0.09
Walking Aid Use				
No		REFERENCE		
Yes	1.72	1.35	2.19	<0.001
Haemodialysis Vintage	1.00	1.00	1.00	0.52
Transplant List Status				
Not Active		REFERENCE		
Active	0.96	0.65	1.41	0.82
Constant	**0.00**	**0.00**	**0.01**	**<0.001**

*Obtained by negative binomial regression, censored for death/end of follow-up. Bold text indicates significance at P<0.05 level. IRR=Incidence Rate Ratio. 95% C.I. = 95% confidence interval. *CKD excluded. **Number of admissions in year prior to recruitment*

Supplementary Table 12-16: Fully adjusted model of rates of admission associated with MoCA scores. FP included in model

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
Frailty Phenotype	1.04	0.94	1.14	0.46
MoCA	1.01	0.99	1.04	0.34
Age	0.99	0.98	1.00	0.08
Gender				
Male		REFERENCE		
Female	0.98	0.78	1.23	0.87
Ethnicity				
White		REFERENCE		
South Asian	0.80	0.58	1.12	0.19
Black	0.76	0.54	1.07	0.11
Other	1.13	0.54	2.37	0.74
BMI	1.00	0.99	1.02	0.57
IMD Quintile				
1		REFERENCE		
2	0.78	0.57	1.07	0.12
3	0.81	0.58	1.13	0.21
4	0.79	0.52	1.21	0.29
5	0.80	0.50	1.29	0.37
Unknown	1.15	0.74	1.81	0.53
Charlson Index*	**1.10**	**1.03**	**1.18**	**0.005**
Previous Admissions**	**1.12**	**1.06**	**1.18**	**<0.001**
Number Medications	1.02	0.99	1.06	0.13
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.89	0.62	1.28	0.54
Never Smoked	0.81	0.58	1.12	0.20
Albumin	1.00	0.99	1.00	0.11
Walking Aid Use				
No		REFERENCE		
Yes	**1.63**	**1.24**	**2.16**	**0.001**
Haemodialysis Vintage	1.00	1.00	1.00	0.52
Transplant List Status				
Not Active		REFERENCE		
Active	0.96	0.65	1.41	0.83
Constant	**0.00**	**0.00**	**0.01**	**<0.001**

*Obtained by negative binomial regression, censored for death/end of follow-up. Bold text indicates significance at P<0.05 level. IRR=Incidence Rate Ratio. 95% C.I. = 95% confidence interval. *CKD excluded. **Number of admissions in year prior to recruitment*

Supplementary Table 12-17: Fully adjusted model of rates of admission associated with MoCA scores. FI included in model

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
Frailty Index*	1.06	0.98	1.14	0.13
MoCA	1.02	0.99	1.04	0.25
Age	0.99	0.98	1.00	0.15
Gender				
Male		REFERENCE		
Female	0.98	0.78	1.23	0.84
Ethnicity				
White		REFERENCE		
South Asian	0.80	0.58	1.11	0.19
Black	0.78	0.55	1.09	0.15
Other	1.14	0.54	2.37	0.73
BMI	1.00	0.99	1.02	0.65
IMD Quintile				
1		REFERENCE		
2	0.79	0.57	1.08	0.14
3	0.82	0.59	1.15	0.25
4	0.79	0.52	1.21	0.28
5	0.82	0.51	1.32	0.42
Unknown	1.16	0.74	1.81	0.52
Charlson Index**	**1.10**	**1.03**	**1.18**	**0.007**
Previous Admissions***	**1.12**	**1.07**	**1.18**	**<0.001**
Number Medications	1.02	0.99	1.05	0.20
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.88	0.61	1.26	0.48
Never Smoked	0.79	0.57	1.10	0.17
Albumin	1.00	0.99	1.00	0.10
Walking Aid Use				
No		REFERENCE		
Yes	**1.55**	**1.18**	**2.04**	**0.002**
Haemodialysis Vintage	1.00	1.00	1.00	0.46
Transplant List Status				
Not Active		REFERENCE		
Active	0.96	0.66	1.42	0.85
Constant	**0.00**	**0.00**	**0.01**	**<0.001**

*Obtained by negative binomial regression, censored for death/end of follow-up. Bold text indicates significance at P<0.05 level. IRR=Incidence Rate Ratio. 95% C.I. = 95% confidence interval. *FI scaled so IRRs relate to each 0.1 rise in FI. **CKD excluded. ***Number of admissions in year prior to recruitment*

Supplementary Table 12-18: Fully adjusted model of rates of admission associated with MoCA scores. EFS included in model

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
Edmonton Frailty Scale	1.03	0.98	1.08	0.31
MoCA	1.02	0.99	1.04	0.25
Age	0.99	0.98	1.00	0.11
Gender				
Male		REFERENCE		
Female	0.99	0.78	1.24	0.90
Ethnicity				
White		REFERENCE		
South Asian	0.81	0.59	1.13	0.22
Black	0.75	0.54	1.06	0.10
Other	1.17	0.56	2.46	0.68
BMI	1.00	0.99	1.02	0.61
IMD Quintile				
1		REFERENCE		
2	0.77	0.56	1.06	0.11
3	0.81	0.58	1.12	0.20
4	0.78	0.51	1.20	0.26
5	0.78	0.49	1.26	0.31
Unknown	1.15	0.73	1.80	0.54
Charlson Index*	**1.10**	**1.03**	**1.18**	**0.005**
Previous Admissions**	**1.11**	**1.05**	**1.17**	**<0.001**
Number Medications	1.02	0.99	1.06	0.17
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.89	0.62	1.28	0.53
Never Smoked	0.80	0.58	1.12	0.19
Albumin	1.00	0.99	1.00	0.12
Walking Aid Use				
No		REFERENCE		
Yes	**1.63**	**1.26**	**2.12**	**<0.001**
Haemodialysis Vintage	1.00	1.00	1.00	0.45
Transplant List Status				
Not Active		REFERENCE		
Active	0.96	0.65	1.41	0.83
Constant	**0.00**	**0.00**	**0.01**	**<0.001**

*Obtained by negative binomial regression, censored for death/end of follow-up. Bold text indicates significance at P<0.05 level. IRR=Incidence Rate Ratio. 95% C.I. = 95% confidence interval. *CKD excluded. **Number of admissions in year prior to recruitment*

Supplementary Table 12-19: Fully adjusted model of rates of admission associated with MoCA scores. CFS included in model

	IRR	Lower 95% C.I.	Upper 95% C.I.	P
Clinical Frailty Scale	**1.15**	**1.04**	**1.26**	**0.006**
MoCA	1.02	0.99	1.04	0.21
Age	0.99	0.98	1.00	0.13
Gender				
Male		REFERENCE		
Female	0.96	0.77	1.21	0.75
Ethnicity				
White		REFERENCE		
South Asian	0.80	0.57	1.10	0.17
Black	0.78	0.56	1.10	0.15
Other	1.10	0.53	2.29	0.79
BMI	1.00	0.99	1.02	0.62
IMD Quintile				
1		REFERENCE		
2	0.78	0.57	1.07	0.13
3	0.82	0.59	1.14	0.24
4	0.82	0.54	1.24	0.35
5	0.84	0.52	1.34	0.46
Unknown	1.14	0.73	1.78	0.56
Charlson Index*	**1.09**	**1.02**	**1.17**	**0.01**
Previous Admissions**	**1.13**	**1.07**	**1.19**	**<0.001**
Number Medications	1.02	0.99	1.05	0.26
Smoking Status				
Current Smoker		REFERENCE		
Ex-Smoker	0.86	0.60	1.23	0.41
Never Smoked	0.78	0.56	1.07	0.13
Albumin	1.00	0.99	1.00	0.11
Walking Aid Use				
No		REFERENCE		
Yes	**1.47**	**1.13**	**1.91**	**0.004**
Haemodialysis Vintage	1.00	1.00	1.00	0.37
Transplant List Status				
Not Active		REFERENCE		
Active	0.98	0.67	1.43	0.90
Constant	**0.00**	**0.00**	**0.00**	**<0.001**

*Obtained by negative binomial regression, censored for death/end of follow-up. Bold text indicates significance at P<0.05 level. IRR=Incidence Rate Ratio. 95% C.I. = 95% confidence interval. *CKD excluded. **Number of admissions in year prior to recruitment*

Chapter 13:
Multidisciplinary Intervention

13.1 Plans

The second stage of the FITNESS project – described in detail as "Work Package 2" in Chapter 2: – was due to be a multidisciplinary patient-centred intervention underpinned by behavioural change techniques (BCTs). This was due to include participant goals at its core, and the intervention as such was the use of BCTs to help the participants to work on these goals with expert dietetic and physiotherapy input. Here we will review the plans for Work Package 2, including selected methods pertaining directly to this phase of the study. We shall then appraise some of the challenges that ultimately precluded the timely progression of this RCT phase of the study, before considering some personal reflections upon what may be learned from the experience.

13.2 Work Package 2: Methods

The original plan for FITNESS was a prospective, single centre, open-label, cohort multiple randomised controlled (cm-RCT) study[264] which would be split into two elements. Work Package 1 is a cohort study of prevalent haemodialysis patients which aimed to identify the prevalence of frailty amongst this population and outcomes associated with frailty such as mortality, hospitalisation and quality of life. Patients from work package 1 who were identified as "Pre-Frail", as defined by the Frailty Index, would then be invited to participate in work package 2, which will compare the effect of active lifestyle intervention versus current standard of care upon frailty measurements and outcomes. As part of the cm-RCT design, eligible patients will be selected for invitation to participate in work-package 2 according to a stratified randomisation module. Invited participants will be randomised into active or passive intervention groups. The duration of the clinical intervention in work package 2 will be 6

months, with electronic data-linkage follow-up for 5 years after study participation to allow for continued capture of outcome measures.

13.2.1 Inclusion and Exclusion Criteria

13.2.1.1 Inclusion Criteria

- Aged 18 and over
- Received regular haemodialysis for at least 3 months' duration
- Able to provide informed consent
- Participant in Work Package 1
- Identified as pre-frail in Work Package 1
- Suitable English Proficiency: an ability to understand a medical consultation in English.

13.2.1.2 Exclusion Criteria

- Deemed unsuitable to complete study (clinician advice)
- Currently enrolled in another clinical intervention trial
- Receiving emergency inpatient care within 4-weeks of recruitment/assessment (patients admitted for routine procedures e.g. dialysis access will be eligible for inclusion)
- Planned live-donor kidney transplant during study period

13.2.2 Plan of Investigation

13.2.2.1 Study protocol

The FITNESS protocol has been designed and reported in line with SPIRIT guidelines, with SPIRIT checklist shown in Figure 13-2.[332]

13.2.2.2 Recruitment and Consent

Potential participants will be identified through their previous participation in work package 1. Patients scored as "pre-frail" will randomly selected to participate in work package 2. Patient information sheets will be given to the patients in advance of a discussion with the researcher either by post or in person. Individuals will be approached at their usual dialysis unit appointment for discussion and potential recruitment to the study. Potential participants will be given the opportunity to reflect on the information given both verbally and within the written information sheet. No fixed time is specified for the length or timing of this prior interview as it will be dependent upon the patient's understanding of their underlying disease and of the research project. As in work package 1, it is important that non-English speaking patients are given full opportunity to participate in this study and the same methods will be used. Written consent will be received from each patient entering the study. A study patient identifier will be allocated and recorded on the study recruitment log.

Work package 1 patients who meet eligibility criteria will be randomly selected for participation in work package 2 using REDCap™ (in random permuted blocks within strata to balance numbers and characteristics). Participants who have subsequently been approached and given consent to participate in work package 2 will be randomised once more using REDCap™ (in random permuted blocks within strata to balance numbers and characteristics)

into one of the following lifestyle intervention groups (n=25 for each intervention group, total 50 participants). As part of cm-RCT design, data from pre-frail work package 1 patients who were eligible, but not selected for participation in work package 2 will provide a further comparator group for analysis. As an open-label study, neither participants nor researchers will be blinded to group allocation.

1. Active Intervention Group: This group will receive interventions designed to address frailty and will consist of dietitian referral for dietetic advice and physiotherapist referral for a graded exercise programme. The participants will receive this in addition to their usual haemodialysis standard of care. To reduce potential bias, neither the physiotherapist nor the dietitian will have regular input with haemodialysis patients as part of their job plan. Each patient will have five face-to-face appointments with the dietitian and physiotherapist (lasting 45-60 minutes) at baseline, week 6, week 12, week 18 and week 24. Brief telephone reviews will be conducted in between appointments (approximately 2-3 weeks after each face-to-face appointment) to review progress and provide additional support during the active intervention period. Some appointments may be substituted with telephone support if preferred by the patient. Patients will have their diet reviewed by a dietitian and healthy eating advice will be given based upon guidelines issued by British Dietetic Association Guidelines,[333] which provide recommendations for minimum protein intake in dialysis patients. Patients will be advised to keep food and exercise diaries to monitor compliance with initiated changes and will be followed up by the research team prospectively (using face-to-face appointments and telephone reviews) to monitor progress and reinforce the advice (in addition to routine clinic visits). In addition, a graded

exercise program will be established by the physiotherapist to increase physical activity in line with both the patient's stated goals at initial assessment and their deficits identified upon frailty scoring.

The dietitian and physiotherapist will be supported by a Senior Lecturer and Consultant in Addiction Psychiatry who has expertise in behavioural change therapy. The dietitian and physiotherapist will be trained with motivational interviewing skills and the following psychological tools will be utilised to support the active intervention:

1. Cognitive Behavioural Therapy (CBT) intervention incorporating node-link mapping, which are simple to train and apply. We will utilise simple goal setting techniques, combined with relapse prevention strategies, and a simple visual representation system for presenting CBT-type interventions. Node-link mapping is more effective than standard consultations for improving the therapeutic alliance, increasing focus on key issues during the session, and improving outcomes. There is also evidence of efficacy in patients with poor reading skills or working in a language other than their first language (important for our patient demographics).[257]
2. Social Behaviour and Network Therapy (SBNT) is an intervention that draws in members of the family, social network and mutual self-help or peer support groups to help the patient set and achieve goals. It has been developed and tested by colleagues in Birmingham, with an evidence base in the context of liver transplantation.[259] A combination of these two techniques, together with

motivational interviewing[334] by the dietitian and physiotherapist after appropriate training, will facilitate supportive psychosocial interventions to change lifestyle behaviour.

2. Passive Control Group: This group will receive their usual standard of care from their treating dialysis centre, including usual dietitian input. However, there will be no psychosocial intervention or focused exercise and dietary monitoring programme. Follow up will be at routine clinic visits only where lifestyle modification advice will be reinforced as per usual clinical practise. Physiotherapy may be offered to these patients as per standard referral guidelines, but will not have the psychosocial underpinning of the intervention group.

Both groups will undergo a repeat frailty testing at recruitment to Work Package 2, during the mid-point (3-months +/- 2 weeks) and the end of study intervention (6-months +/-2 weeks) (see Figure 13-1 and Figure 13-2). This will include frailty assessment, ultrasonography and questionnaires identical to the baseline data collected at recruitment to Work Package 1, as detailed in Chapter 2. The aim is to assess if there is any change in frailty status, which will provide data to underpin a power calculation for a subsequent large-scale study. Additional pre-specified secondary outcomes will be collected as highlighted below in the protocol. Participants will also be invited to complete a series of questionnaires to ascertain the tolerability and suitability of the intervention trial, and to guide the delivery of the trial on a larger scale.

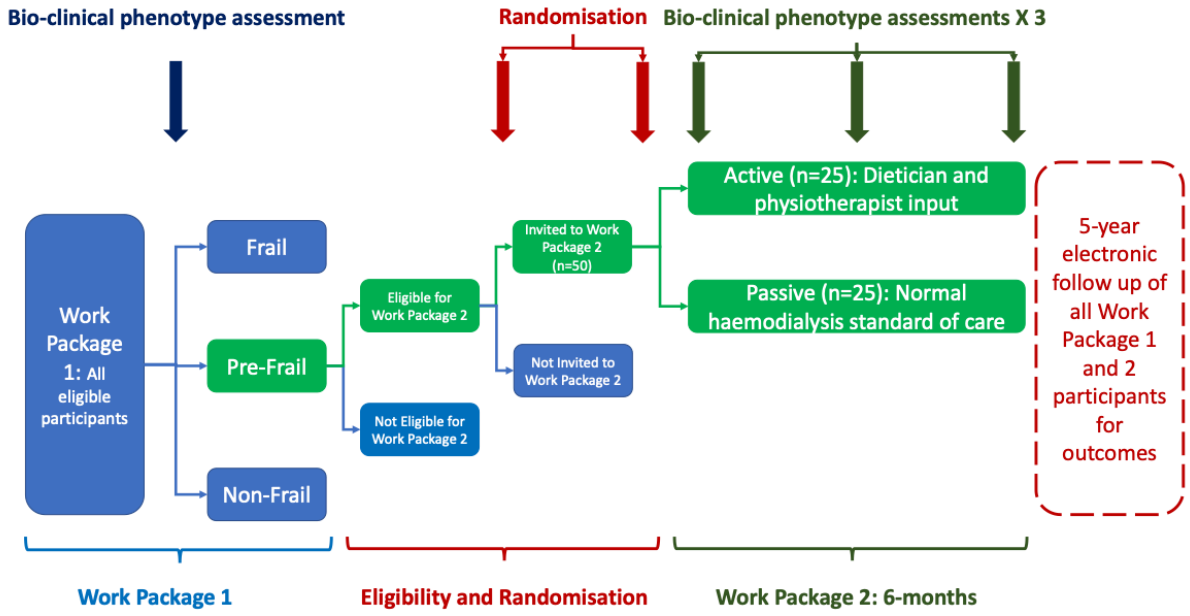


Figure 13-1: Flowchart of participants in FITNESS work packages 1 and 2, As part of cm-RCT methodology, all eligible participants will first be randomised for potential invitation to the study (n=50). Potential recruits will then be approached for involvement in work package 2, and after further valid consent, will then be randomised into active or passive groups.

13.2.3 Study outcomes

13.2.3.1 Primary endpoint

1. Feasibility and tolerability of the clinical intervention study (recruitment rates, loss to follow up, study withdrawal)

13.2.3.2 Secondary endpoints

1. Refinement to the multi-disciplinary intervention based upon views from participants and stakeholders (from post-study questionnaires).
2. Change in frailty status (based on Fried Frailty Phenotype, Clinical Frailty Scale)
3. Difference in clinical and biochemical outcomes

4. Quality of life score (EQ-5D-3L)
5. Receipt of kidney transplant
6. Vascular access failure
7. Long-term clinical outcomes (death, cardiac events, hospitalisation) to University Hospital Birmingham electronic patient records) and Hospital Episode Statistics

13.2.4 Data Handling

Data collected throughout the study will be entered onto a study specific data base REDCap™ (Research Electronic Data Capture)[271] with secure storage and full oversight from information governance. Any paper records which form part of the source data for the study will be retained securely at site.

Patients will be consented for electronic data capture of clinical parameters (e.g. biochemical data) from University Hospitals Birmingham EPR at 1-month, 3-months, 1-year, 3-years and 5-years post-recruitment (facilitated through informatics linkage utilising Hospital Patient Registration number). In addition, clinical outcomes (e.g. hospital admissions, medical events, surgical procedures, death etc.) will be electronically captured from Hospital Episodes Statistics for the same time points (facilitated through informatics data linkage utilising NHS number). This will allow long-term data capture of important clinical outcomes without direct patient involvement.

13.2.4.1 Tissue Collection

Blood samples will be taken from the 50 work package 2 participants, alongside 50 work package 1 participants each from the frail and non-frail groups. Plasma, serum, PBMCs and whole blood will be stored for future immunophenotyping.

13.2.4.2 Data Monitoring and Risk

There are no specific risks anticipated with this study. However, any study-related adverse events will be documented and reported to the steering committee. Should a participant report any thoughts of deliberate self-harm or suicide, or complete a PHQ-9 score of over 20 during the study, a discussion will be held with the patient asking whether they would like a referral to the patient's nephrologist or psychology services at the trust.

A serious adverse event (SAE) is defined by the HRA as an untoward occurrence that:

- Results in death;
- Is life-threatening;
- Requires hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital abnormality or birth defect; or
- Is otherwise considered medically significant by the investigator.

An SAE occurring to a research participant will be reported to the Research Ethics Committee (REC) where in the opinion of the Chief Investigator the event was:

Related: it resulted from the administration of any of the research procedures, and

Unexpected: the type of event is not listed in the protocol as an expected occurrence.

Any SAE will be reported to the REC within 15 days of the Chief Investigator becoming aware of the event. All other SAE's will need reporting as AE's on the case report form.

Exceptions to expedited reporting include hospitalisation for:

- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications.
- Treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

Patients will be asked if any adverse events have occurred when they attend for any trial related procedure.

Figure 2: SPIRIT Figure for Work Package 2

	Study Period										
	Enrolment	Allocation	Weeks Post-Allocation								
Timepoint (weeks)	**-2-->0**	**0**	**6**	**12**	**14**	**18**	**24**	**28**	**52**	**156**	**260**
Enrolment:											
Eligibility Screen/Randomised selection of participants	X										
Informed Consent	X										
Treatment Allocation/Randomisation		X									
Interventions:											
Active Group: Dietitian/Physiotherapist review with behavioural intervention		X	X	X		X	X				
Passive Group: Dialysis standard of care		◆	—	—	—	—	◆				
Blood sampling and storage: Both groups*		X						X			
Assessments:											
Baseline Demographics**		X									
Clinical Assessment***		X			X			X			
Patient Reported Outcomes****		X			X			X			
Electronic Data Capture of clinical outcomes*****									X	X	X

* Serum, plasma and PBMCs stored as outlined above.
**Extensive baseline data including cause of end-stage kidney disease, dialysis modality, dialysis duration, biochemical data, past medical history, medications, social history
***Frailty status, dialysis adequacy and biochemical data as per existing dialysis Quality Assurance processes
****Patient reported outcomes (physical activity and psychological well being as highlighted above)
***** Long-term clinical outcomes (patient survival, hospitalisation, cardiac events, transplantation) via electronic tagging to University Hospital Birmingham electronic patient records (via Patient Registration number) and national registries (via NHS number)

Figure 13-2: SPIRIT figure for work package 2. Taken from Anderson et al. Trials 2018

13.2.4.3 Participant Withdrawal

In the event of patients wishing to discontinue in the trial, the participant would be withdrawn from the study with the assurance that their usual care will continue unaffected. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected, or any other research procedures carried out on or

in relation to the participant. If the patient consented to have long term electronic tracking of their outcomes, this would be continued.

13.2.5 Statistics

Work package 2 is designed as a feasibility study so no specific power calculations have been made. However, one of the secondary outcomes is to use the data regarding effect sizes to determine the sample required for a larger multi-centre study based upon the feasibility of work package 2.

Statistical analyses will be performed using STATA 17 (StataCorp 2021, Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC)Normality of data will be assessed using the Kolmogorov-Smirnov tests. Paired sample *t*-test and Wilcoxon signed rank test, for parametric and non-parametric data respectively, will be used to compare the means of two variables from a single group. Comparison of data between groups will be made using unpaired student *t*-tests and the Mann-Whitney test for parametric and nonparametric data respectively. Categorical data will be analysed using Pearson's or Spearman's test as appropriate. A p value < 0.05 is considered significant in the statistical analysis.

13.3 Challenges

Setting up the intervention phase of FITNESS was beset with a number of challenges. The funding was available for a dietitian and physiotherapist to be trained by a consultant psychiatrist in BCTs. Furthermore, appropriate colleagues were identified to fill the dietetic and physiotherapist roles within Work Package 2. Unfortunately, we were unable to secure

the services of the physiotherapist due to problems “back-filling” the time they would spend out of clinical work. Discussions were ongoing with allied health professional (AHP) leaders within UHB about how to bridge this gap when the COVID-19 pandemic struck in early 2020. This understandably put a pause on all research activity whilst NHS trusts grappled with the resultant public health emergency. I indeed was recalled back to full-time clinical work for 3-months during this time.

13.4 Future Plans

By the time the emergency footing in hospitals was stood down, it was felt to be too late to proceed with the original plan of recruiting from within the FITNESS cohort as part of our cmRCT protocol. Given a significant proportion of the FITNESS cohort had died during the period between recruitment and the end of the first COVID wave, survivor bias was a real concern. Instead we plan to recruit a new group of participants for FITNESS Work Package 2, with a view to completing the intervention study. No timelines have yet been established for this, and clearly a substantial amendment will need to be filed with the Research Ethics Committee and UHB Research and Development in order for this to proceed.

13.5 Reflections

It is a real frustration that we were unable to proceed with the intervention phase of the study as planned. Much of my frustration is borne of the manner in which we were unable to secure the physiotherapy time in the first instance to run “Work Package 2” immediately after the cohort was established, as were our original plans. It became clear on speaking with AHP leaders in UHB that the difficulties we experienced were a consequence of the state of

physiotherapist numbers nationwide. Due to low numbers of available qualified physiotherapists, job offers were often going unfilled. Consequently, as we required – and were only funded for – 25% whole time equivalent (WTE) physiotherapy time, this was never likely to be "back-filled" to cover non-negotiable inpatient work. I was perhaps somewhat optimistic when the funding was approved that the biggest potential obstacle to FITNESS had been negotiated, and did not foresee the difficulties to come. It would be easy to consider this a bureaucratic failure within the UHB organisation, but this is not a satisfactory conclusion. Indeed, all managers and administrators we met with were very keen to help in any way they could, and expressed their own frustration that research work was being held up due to staffing issues. In truth, due to COVID-19 I do not think Work Package 2 would have been completed as planned regardless, and COVID was of course a situation entirely outside of my control. I do think often however about how we may have approached this issue differently, and whether there was a way in which the study could have proceeded as planned. In retrospect it seems naïve to have thought we would be able to secure a physiotherapist with 25% WTE funding. We spent time in the design phase of FITNESS to scope out potentially interested parties for these posts, but perhaps if we'd spoken with AHP leaders in the trust we may have been prewarned of the recruitment difficulties and considered alternatives earlier in the study design. The superficially simplest solution would perhaps have been to offer a 100% WTE physiotherapy post, in a full-time research role for one year. I'm sure this would have been an attractive proposition to AHP colleagues, but it would have been much more difficult to secure this level of funding for a feasibility study. Even with the level of funding we did eventually secure, we had several grant applications denied from varied organisations. I know in other renal departments in the UK there are teams of higher degree-

funded research AHP posts, but these are in centres with a proven track record of delivering multi-disciplinary renal research and these structures were several years in the making. On reflection, I consider this episode to be a salutary lesson in the probable outcomes when naïve idealism meets organisational *realpolitik*.

Chapter 14:
Conclusions

During the course of this thesis, we have explored the correlations and agreement between four commonly used frailty scores in haemodialysis recipients; the Frailty Phenotype, Frailty Index, Edmonton Frailty Scale and the Clinical Frailty Scale. We have also compared these frailty tools for their association with important sequelae such as mortality, hospitalisation, and health-related quality of life. We have also proposed a new model of frailty screening, based upon the concept of self-reported health change, which may help to risk stratify in this high-risk population. Furthermore, the interplay between frailty and its constituents has been explored in detail, including sarcopenia, cognitive impairment, and depression. We shall now tie these strands together, consider themes demonstrated throughout these data, and posit some conclusions based upon this body of work. We shall also consider the unanswered questions highlighted by our data, and consider the ways in which these may be addressed.

14.1 Consensus is required on the optimal frailty tool in haemodialysis populations

In Chapter 3:, we saw that whilst the correlations between frailty tools were adequate, agreement between them upon frailty status is poor. This represents a challenge to kidney caregivers, as we may not readily extrapolate inferences across populations applying different frailty assessments. We postulate that each frailty tool is measuring a different subset of the frailty syndrome. As such there may be an argument for a "horses for courses" approach, choosing a frailty tool depending on the clinical or research question. On the whole, whilst we can recognise – and have indeed indulged at times in the course of this thesis – the urge to choose individual frailty scores for certain analyses, we would caution against this approach becoming the norm. Firstly, agreement and correlation between these scores are inadequate for comparison across groups. Secondly, we have seen during the course of this thesis that

the associations of frailty with other important syndromes and sequelae are variable dependent upon the frailty tool. We therefore cannot know whether apparent disparities between cohorts in terms of frailty prevalence or associations were not simply due to frailty definition. We therefore risk missing the lessons of frailty for our patients in a sea of methodological noise.

The cause of frailty in haemodialysis is best served by achieving consensus on the optimal frailty score to achieve some measure of homogeneity of reporting. A parallel with Acute Kidney Injury (AKI) may be apposite here. AKI was another important but ill-defined syndrome until consensus KDIGO criteria were proposed and accepted.[335] Prior to this, a plethora of screening definitions were utilised, creating barriers to research and intervention.

The consensus frailty tool need not be perfect, indeed the KDIGO AKI criteria have been subject to much criticism.[336] However, any consensus tool, however imperfect, could unify reporting of frailty and lead to improved understanding. For this to be possible, the frailty tool must associate strongly with adverse outcomes, and be simple enough for widespread clinical use.

14.2 The Clinical Frailty Scale likely represents the best choice of frailty tool in haemodialysis cohorts, but caveats remain.

In Chapter 6:, we saw that increasing frailty was associated with mortality regardless of the tool used. However, in Chapter 8: we also learned that the significance of this association was lost for the EFS when self-reported health change was added to the model. This suggests that

the EFS may be a less suitable marker of risk in haemodialysis recipients than the other tools, which demonstrated more robust associations. Considering mortality alone, each of the FP, FI, and CFS would appear suitable choices for frailty assessment in haemodialysis populations.

We have also reported in 0 that association with metrics of hospital admission are somewhat more variable between frailty scores. The CFS was the only score to associated with increased rates of hospital admissions, but was also the only tool not associate with nights spent in hospital on multivariable analyses.

Taking all of this into account, it is difficult to definitively recommend any of these frailty scores over another. However, we have seen that treating frailty scores as continuous variables appears to be appropriate, and as such tools designed for such use such as the FI and CFS may be more suitable. We argue that the combination of ease of use, familiarity within the wider medical community, and the association with hospital admissions makes CFS the most appropriate choice in prevalent haemodialysis recipients.

14.3 Patient reported outcome measures may play a role in risk-stratification in frailty

The importance of frailty in haemodialysis recipients should now be beyond question. However, we must not overlook the service implications of a screening tool that identifies over half of a haemodialysis population as being high risk for adverse outcomes. In Chapter 3:, we argued that the utility of such a screen could be questionable, and this is particularly so in the era of ever-tightening monetary constraints in healthcare. We cannot expect Care of the Elderly colleagues to offer CGAs to half the haemodialysis population; nor can we

anticipate that nephrologists can commit to performing this service in house. Other considerations include funding for the truly multi-disciplinary approach the CGA requires, and the training and maintenance of the skills and attitudes required of non-geriatricians to perform this role in addition to other clinical commitments. We can therefore argue that there is a need to consider how to further stratify risk in this population, in order to target interventions to those in most need. In Chapter 8:, we considered how self-reported health change may modulate the association of increasing frailty with mortality, and associates independently with hospitalisation. We proposed a notional model of how this may be integrated into frailty assessment and intervention pathways in Figure 8-2, but we recognise that this model at present has some significant flaws. Principal among these is that no evidence-based frailty intervention currently exists for haemodialysis recipients, thus the final step of intervening upon frailty remains unproven. Furthermore, our model would only obviate the need for formal frailty assessment in <20% of our cohort, which may not be enough to render such an approach feasible in clinical practice. It may be that other PROMs are of utility in identifying risk within haemodialysis populations, but this is speculative. We argue however, that the kidney community must address these challenges as a matter of urgency; we believe there is great potential to improve the quantity and quality of haemodialysis recipients' lives with an evidence-based frailty identification and intervention pathway. Any steps to render this feasible within current budgetary and organisational constraints must therefore be entertained.

14.4 Sarcopenia in haemodialysis recipients may differ from non-CKD older adults

We saw in Chapter 4: that both LMM and sarcopenia are highly prevalent in haemodialysis recipients. Sarcopenia and LMM were variably associated with frailty, with the FP and EFS showing the most robust associations. This is unsurprising, given the greater proportion of musculoskeletal components to these score than in the CFS or FI. We hesitate to declare the lack of association on fully adjusted models with the FI or CFS with sarcopenia as a drawback of these tools; it is important to note that whilst sarcopenia is a contributor to frailty, it is not a frailty surrogate. Rather we feel it offers further evidence that the individual frailty tools assessed in FITNESS may be measuring different subtypes of frailty.

The male preponderance of sarcopenia in haemodialysis – as we demonstrated in Chapter Chapter 5: – is striking, as it contrasts sharply with the distribution observed in non-CKD older adults. We have speculated as to potential contributors to such apparent disparity, and it would appear logical that the underlying drivers of sarcopenia differ between general elderly and haemodialysis populations, but this must be the subject of further mechanistic work.

14.5 There is an unmet need for evidence-based frailty interventions in haemodialysis

We have shown that frailty is associated with negative outcomes including mortality, hospitalisation, and poorer quality of life in haemodialysis recipients. It is therefore tempting to call for widespread frailty screening in clinical practice, but this is a temptation we shall resist. Wilson and Jungner's principles of screening include:

1. *"The condition should be an important health problem.*

2. *There should be an accepted treatment for patients with recognized disease.*

3. *Facilities for diagnosis and treatment should be available.*

4. *There should be a recognizable latent or early symptomatic phase.*

5. *There should be a suitable test or examination.*

6. *The test should be acceptable to the population.*

7. *The natural history of the condition, including development from latent to declared disease, should be adequately understood.*

8. *There should be an agreed policy on whom to treat as patients.*

9. *The cost of case-finding (including a diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.*

10. *Case-finding should be a continuous process and not a "once and for all" project."*[337]

We hope that the FITNESS project has helped to address some of these principles, with perhaps the greatest input into points 1 and 5. However, the greatest unmet need for frail haemodialysis recipients remains the absence of an evidence-based intervention.

We have argued that a CGA for each frail haemodialysis recipient is not feasible, so alternative interventions must be sought. The second stage of the FITNESS project was a feasibility RCT

of a psychologically supported multidisciplinary intervention, underpinned by behavioural change techniques. It is a source of regret that we have thus far been unable to pursue this, as it has the potential to guide further large-scale frailty intervention studies. Furthermore, as a multidisciplinary patient-centred assessment and intervention approach, we feel it mimics many of the components of a CGA.

The World Health Organisation has reiterated the need for a screening program to have strong scientific basis, and to do more harm than good. They observed that too few screening programs adhere to these principles,[338] and in the absence of a proven frailty intervention, we fear this is the trap that frailty assessment in haemodialysis recipients risks falling into. Unless and until a frailty intervention of proven utility is widely available, the kidney community risks screening our patients for a condition we do not yet fully understand and cannot yet effectively treat.

It would be prudent for any frailty intervention trial to consider economic analyses of the costs and benefits in the trial design; we may speculate that an intervention that served to reduce hospitalisation burden in the haemodialysis community may prove cost-effective even if the initial staffing costs appear prohibitive.

To conclude, frailty is common in haemodialysis, and associated with poor outcomes, but different frailty screening tools may measure different subtypes of frailty. We propose the Clinical Frailty Scale as the current best tool for use in haemodialysis frailty assessment. There is an urgent need for an evidence based frailty intervention to improve patient outcomes.

Chapter 15: Appendices

15.1 Published abstracts, presentations, and publications from this work

15.1.1 Poster Communications

Anderson BM, Correa G, Jackson TA, Ferro CJ, Sharif A. Correlation between frailty scores in haemodialysis recipients: analysis from the Frailty Intervention Trial iN End-Stage patientS on haemodialysis (FITNESS) study. June 2019 ERA-EDTA Budapest.

Anderson BM, Correa G, Jackson TA, Ferro CJ, Sharif A. Frailty Intervention Trial iN End-Stage patientS on haemodialysis (FITNESS): An overview of study cohort and outcome measures to date. June 2019 ERA-EDTA Budapest.

Anderson BM, Qasim M, Ferro C, Jackson T, Sharif A. Frailty Intervention Trial in End-Stage Patients on Haemodialysis (FITNESS): Baseline Data and Next Steps. International Conference on Frailty and Sarcopenia Research. Toulouse 2020.

Anderson BM, Correa G, Qasim M, Ferro C, Sharif A. Frailty Predicts Mortality and Emergency Admissions in Prevalent Haemodialysis Recipients: A Comparison of Commonly Used Frailty Scores in a Large Prospective UK Haemodialysis Cohort. UK Kidney Week 2020 (virtual).

Anderson BM, Correa G, Qasim M, Jackson T, Sharif A. Frailty Index and Clinical Frailty Scale are superior to frailty phenotype and Edmonton Frailty Scale in mortality prediction: results from a large European haemodialysis cohort. ERA-EDTA Milan 2021.

15.1.2 Invited Oral Communications

Anderson BM, Sharif A. Comparison of frailty tools and association with mortality and hospitalisation: data from the FITNESS haemodialysis cohort. Royal Society of Medicine Geriatric Nephrology Symposium. **October 2021** (Virtual).

15.1.3 Publications

Anderson BM, Dutton M, Day E, Jackson TA, Ferro CJ, Sharif A. Frailty Intervention Trial iN End-Stage patientS on haemodialysis (FITNESS): study protocol for a randomised controlled trial. *Trials* 2018; 19(1): 457.[263]

Anderson BM, Qasim M, Correa G, Evison F, Gallier S, Ferro CJ, Jackson TA, Sharif A. Correlations, agreement and utility of frailty instruments in prevalent haemodialysis patients: baseline cohort data from the FITNESS study. *Clinical Kidney Journal* 2022; 15(1):145-152.[272]

15.1.4 Peer-reviewed articles in press

Anderson BM, Qasim M, Correa G, Evison F, Gallier S, Ferro CJ, Jackson TA, Sharif A. Depression is associated with frailty and lower quality of life in haemodialysis recipients, but not with mortality or hospitalization. *Clinical Kidney Journal* 2022; In Press.[328]

Anderson BM, Qasim M, Correa G, Evison F, Gallier S, Ferro CJ, Jackson TA, Sharif A. Self-reported health change in haemodialysis recipients modulates the effect of frailty upon mortality and hospital admissions: outcomes from a large prospective UK cohort. *Nephrology Dialysis Transplantation* 2022; In Press.[316]

Anderson BM, Qasim M, Correa G, Evison F, Gallier S, Ferro CJ, Jackson TA, Sharif A. Cognitive impairment, frailty and adverse outcomes among prevalent haemodialysis recipients: results from a large UK prospective-cohort study. *Kidney Medicine* 2022. In Press.

Anderson BM, Wilson DV, Qasim M, Correa G, Evison F, Gallier S, Ferro CJ, Jackson TA, Sharif A. Ultrasound quadriceps muscle thickness is variably associated with frailty in haemodialysis recipients. *BMC Nephrology* 2022. In Press.

15.2 Published abstracts, presentations, and publications indirectly related to this work

15.2.1 Publications

Tabinor M, **Anderson B**, Istanbuly O, Ul Hussain A, Shah R, Peracha J, Savage J, Atamaniuk L, Sagmeister M, Belcher J, Solis-Trapala I, Ferro C, Davies S. Is bioimpedance-defined lean tissue mass a risk factor for mortality and surrogates of frailty in chronic kidney disease? A systematic review and meta-analysis. *PROSPERO*. 2021.

15.3 Published abstracts, presentations, and publications not related to this work

15.3.1 Oral Communications

Anderson BM, Evison F, Gallier S, Ferro C, Sharif A. Major Adverse Cardiovascular Events (MACE) after kidney transplantation: A population cohort analysis of English transplant centres. UK Kidney Week 2020 (virtual).

Anderson BM, Evison F, Gallier S, Ferro C, Sharif A. Major Adverse Cardiovascular Events (MACE) after kidney transplantation: A population cohort analysis of English transplant centres. ERA-EDTA Milan 2021.

15.3.2 Publications

Anderson B, Khalil K, Evison F, Nath J, Sharif A. Hypoalbuminaemia at time of surgery is associated with an increased risk for overall graft loss after kidney transplantation. *Nephrology (Carlton)* 2018; 24**:** 841-848

Arshad A, **Anderson B,** Sharif, A. Comparison of organ donation and transplantation rates between opt-out and opt-in systems. *Kidney International* 2019;95(6): 1453-1460

Khalil K, Hodson J, **Anderson B**, Nath J, Sharif A. Repatriation of Patients to Referral Centers and Outcomes After Kidney Transplantation: A Single-center Analysis From the United Kingdom. *Transplant Direct* 2018 Vol. 4 Issue 11 Pages e399

Pisavadia B, Arshad A, Chappelow I, Nightingale P, **Anderson B,** Nath J, Sharif A. Ethnicity matching and outcomes after kidney transplantation in the United Kingdom. *PLOS ONE* 2018;13(4) Pages e0195038

Williams A, Richardson C, McCready J, **Anderson B**, Tahir S, Nath J, Sharif A. Black Ethnicity is Not a Risk Factor for Mortality or Graft Loss After Kidney Transplant in the United Kingdom. *Exp Clin Transplant* 2018; 16(6): 682-689

Anderson B, Qasim M, Evison F, Gallier S, Townend JN, Ferro CJ, Sharif A. A population cohort analysis of English transplant centers indicates major adverse cardiovascular events after kidney transplantation. *Kidney International*; in press 2022.

Anderson et al. Trials (2018) 19:457
https://doi.org/10.1186/s13063-018-2842-x

Trials

STUDY PROTOCOL Open Access

Frailty Intervention Trial iN End-Stage patientS on haemodialysis (FITNESS): study protocol for a randomised controlled trial

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Abstract

Background: Frailty is a state of low physiological reserve and multi-systemic dysregulation that leads to susceptibility to external stressors; it is associated with adverse outcomes. North American data suggest that haemodialysis recipients are more likely to be frail than the general population, although data on UK cohorts are lacking. Furthermore, with a multitude of assessment tools, it is difficult for the clinician to ascertain which is most suitable for this population. The FITNESS Study aims to measure the prevalence and outcomes associated with frailty in a large UK haemodialysis cohort to determine the optimum frailty tool as defined by predictive value for mortality/hospitalisation and to conduct a feasibility study exploring a multi-disciplinary clinical intervention to improve frailty among haemodialysis recipients.

Methods/design: The study will follow a cohort multiple randomised controlled trial design; the initial cohort study will identify participants to be invited into a subsequent open-label randomised controlled trial. Eligible patients will be identified and recruited from their usual haemodialysis session. They will be invited to complete tasks and questionnaires collecting data on sarcopenia, immunosenescence, mood, cognition, disability, and comorbidity. Fifty pre-frail participants with suitable English proficiency will be randomly selected from this cohort to participate in the randomised controlled trial phase of the study. Further stratified randomisation will occur to assign these 50 participants to active or passive groups. The active group will receive a psychologically supported, patient-centred, multi-disciplinary intervention into frailty, in what we believe to be a first within this patient group. The control group will receive usual haemodialysis standard of care. All participants will be followed up using electronic patient records for outcomes to include hospitalisation and mortality. Primary outcomes for this phase of the study will be feasibility and tolerability of the clinical intervention study.

Discussion: The study will collect data on multiple aspects of frailty allowing for a rich dataset for detailed analysis. We believe this will be the first study to explore a psychologically supported, patient-centred intervention in this patient group.

Trial registration: Clinicaltrials.gov, NCT03071107. Registered on 6 March 2017.

Background

Frailty is a state of low physiological reserve and multi-systemic dysregulation that leaves the individual susceptible to external stressors [1]. Sarcopenia, an age-related, involuntary loss of skeletal muscle mass and strength and/or function is often seen as part of the frailty syndrome [2, 3]. Immunosenescence is another component of frailty, characterised by age-related deterioration in immune function, and is thought to be modifiable through exercise [4]. Frailty is prevalent among patients receiving haemodialysis, ranging between 30% to as high as 78% dependent upon the diagnostic tool used, and is associated with significant adverse outcomes such as falls, hospitalisation, mortality, and loss of functional independence [5–17]. These studies were conducted in North American cohorts, primarily using the Fried Frailty Phenotype, and to date we have no information regarding the prevalence or outcomes associated with frailty in a UK cohort. Dialysis outcomes differ

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significantly between these populations [18], limiting the generalisability of US data to UK cohorts. Whilst there are a range of validated subjective and objective measurements for frailty, it is unclear which has the most utility to guide clinical practice.

While frailty is not a fixed physiological state, there is currently no evidence to support any intervention targeted to improve frailty within patients receiving haemodialysis. In the general elderly population, there is some evidence of the utility of a multi-disciplinary approach to intervene on frailty. For example, the FIT study utilised a multi-factorial inter-disciplinary intervention which reduced frailty among older people by 14.7% at 12 months [19]; however, there were no other outcomes measured, such as quality of life, mortality, or hospital admissions. The majority of frailty intervention studies performed in both general and dialysis populations do not use validated measures of frailty for either inclusion criteria or outcome measures, but show that functional outcomes (i.e. disability) can be improved with exercise [20–22]. For those patients proceeding to kidney transplantation, frailty at the time of transplantation has been associated with poorer post-transplant outcomes [23–26], although there have not been any published attempts at "prehab" in prospective transplant recipients. Therefore, whether such a strategy would lead to more haemodialysis patients being deemed suitable to benefit from transplantation remains to be seen.

We speculate that patient behaviours can be modified to impact upon frailty. To the best of our knowledge, there have not been any published attempts to intervene upon frailty using behavioural change. Meta-analysis and meta-regression have shown that behavioural change techniques (BCTs) congruent with control theory [27] are significantly more effective than those that are not [28–30]. These include node-link mapping (NLM), which incorporates visual representations of behavioural change, alongside potential aids and barriers to this change with strategies to overcome these [31]. NLM is a technique already successfully used in addiction psychiatry [32]. Social behaviour and network therapy (SBNT) seeks to identify the level of social support for an individual, and aims to include significant supportive others in setting and monitoring goals, and has been successfully used in alcohol abstinence after liver transplantation [33].

It is speculated that long-term changes in behaviour and activity are likely to be required to impact upon frailty and, as such, BCTs may have a role to play in frailty interventions.

Aims

This study aims to: 1) measure prevalence and outcomes associated with frailty in a large UK haemodialysis cohort; 2) determine the optimum frailty assessment tool for UK patients receiving haemodialysis, as defined by predictive value for mortality/hospitalisation; and 3) conduct a feasibility study exploring a multi-disciplinary clinical intervention to improve frailty status among patients receiving haemodialysis

Methods/design

This is a prospective, single centre, open-label, cohort multiple randomised controlled trial (cm-RCT) [34] which will be split into two elements. Work package 1 is a cohort study of prevalent haemodialysis patients which aims to identify the prevalence of frailty among this population and outcomes associated with frailty such as mortality, hospitalisation, and quality of life. Patients from work package 1 who are identified as "pre-frail", as defined by the Frailty Index, will then be invited to participate in work package 2 which will compare the effect of active lifestyle intervention versus current standard of care upon frailty measurements and outcomes. All haemodialysis patients who meet the inclusion/exclusion criteria will be invited to participate in work package 1. As part of the cm-RCT design, eligible patients will be selected for invitation to participate in work package 2 according to a stratified randomisation module. Invited participants will be randomised into active or passive intervention groups. The duration of the clinical intervention in work package 2 will be 6 months, with electronic data-linkage follow-up for 5 years after study participation to allow for continued capture of outcome measures.

Study setting

Patients will be recruited from a single nephrology centre located in Birmingham, UK. The centre consists of one in-hospital dialysis unit and 10 private-provider satellite units distributed around the region, and provides haemodialysis to 1000 patients. It is planned to recruit at least 602 patients from this population to work package 1 with 50 patients recruited to work package 2. Birmingham and the West Midlands is a diverse, multi-cultural population and, as such, we will aim to recruit proportionate numbers of black, Asian and minority ethnic (BAME) participants to the study to accurately represent the community our hospital serves.

Inclusion and exclusion criteria

Work package 1: inclusion criteria

The inclusion criteria for work package 1 are: 1) aged 18 years and over; 2) received regular haemodialysis of at least 3 months duration; and 3) able to provide informed consent.

Work package 1: exclusion criteria

The work package 1 exclusion criterion is having received inpatient care within 4 weeks of recruitment (unless for vascular access).

Work package 2: inclusion criteria

The inclusion criteria for work package 2 are: 1) aged 18 years and over; 2) received regular haemodialysis of at least 3 months duration; 3) able to provide informed consent; 4) a participant in work package 1; 5) identified as pre-frail in work package 1; and 6) suitable English proficiency, i.e. an ability to understand a medical consultation in English.

Work package 2: exclusion criteria

The exclusion criteria for work package 2 are: 1) deemed unsuitable to complete study (clinician advice); 2) currently enrolled in another clinical intervention trial; 3) receiving emergency inpatient care within 4 weeks of recruitment/assessment (patients admitted for routine procedures, e.g. dialysis access, will be eligible for inclusion); and 4) planned live donor kidney transplant during study period.

Work package 1

Study protocol

Potential participants will be identified through a review of all patients attending haemodialysis sessions, currently available from electronic patient records (EPRs) and from clinicians in charge of each haemodialysis unit. Patient information leaflets (PILs) will be given to the patients in advance of a discussion with the researcher either by post or in person. Individuals will be approached at their usual dialysis unit appointment for discussion and potential recruitment to the study. Potential participants will be given the opportunity to reflect on the information given both verbally and within the PIL. No fixed time is specified for the length or timing of this prior interview as it will be dependent upon the patient's understanding of their underlying disease and of the research project. It is important that non-English speaking patients are given full opportunity to be informed and recruited to the study, to accurately reflect the demographics of the haemodialysis population. In these instances, we will use any possibility to discuss the study with patients to aid participation and consent. This may include using family, friends, dialysis staff, or the investigator team who may be proficient in the patients preferred language (e.g. Urdu, Punjabi). Written consent will be received from each patient entering the study.

Baseline assessment

Prior to the patient being connected to the dialysis machine, the following assessments will take place: 1) timed walk over 4 m; 2) assessment of grip strength with a dynamometer; and 3) Montreal Cognitive Assessment (MoCA)

When the patient is dialysing, the following assessments will be performed: 1) quadriceps ultrasound assessment; 2) questionnaires will be given to participants in either paper or electronic format via a tablet device, according to patient preference, including the 3-level version of the EuroQol five dimensions (EQ-5D-3 L) and the Patient Health Questionnaire (PHQ)-9 (where a PHQ-9 score of 20 or over may indicate depression and a discussion will be held with the patient asking whether they would like a discussion with their nephrologist or a referral to the renal psychology service); and 3) a questionnaire related to each frailty instrument, demographic data, and social history (level of education, employment status, nature of employment, smoking, and alcohol history).

EPRs will be interrogated for data on comorbidities, dialysis parameters, previous transplantation, biochemical data, medication history, and social deprivation score.

The patient's nephrologist will be invited to complete a Clinical Frail Scale for individual participants within 1 month of the baseline clinical assessment.

Data handling

Data collected throughout the study will be entered onto a study-specific database REDCap™ (Research Electronic Data Capture) [35] with secure storage and full oversight from information governance. Any paper records which form part of the source data for the study will be retained securely at site.

Patients will be consented for electronic data capture of clinical parameters (e.g. biochemical data) from University Hospitals Birmingham EPR at 1 month, 3 months, 1 year, 3 years, and 5 years post-recruitment (facilitated through informatics linkage utilising Hospital Patient Registration number). In addition, clinical outcomes (e.g. hospital admissions, medical events, surgical procedures, death, etc.) will be electronically captured from Hospital Episodes Statistics for the same time points (facilitated through informatics data linkage utilising National Health Service (NHS) numbers). This will allow long-term data capture of important clinical outcomes without direct patient involvement.

Work package 2: plan of investigation

Study protocol

The FITNESS protocol has been designed and reported in line with SPIRIT guidelines, with an attached SPIRIT flow diagram (see Fig. 2 later) and checklist (Additional file 1) [36].

Recruitment and consent

Potential participants will be identified through their previous participation in work package 1. Patients scored as "pre-frail" will randomly be selected to participate in work package 2. Patient information sheets will be given to the patients in advance of a discussion with the researcher either by post or in person. Individuals will be approached at their usual dialysis unit appointment for discussion and potential recruitment to the study.

Potential participants will be given the opportunity to reflect on the information given both verbally and within the written information sheet. No fixed time is specified for the length or timing of this prior interview as it will be dependent upon the patient's understanding of their underlying disease and of the research project. A certain level of English proficiency will be necessary to participate in the intervention, however it is important that non-native English speaking patients are given full opportunity to participate in this study and the same methods will be used as in work package 1 to facilitate this. Written consent will be received from each patient entering the study. A study patient identifier will be allocated and recorded on the study recruitment log.

Work package 1 patients who meet eligibility criteria will be randomly selected for participation in work package 2 using REDCap™ (in random permuted blocks within strata to balance numbers and characteristics). Participants who have subsequently been approached and given consent to participate in work package 2 will be randomised once more using REDCap™ (in random permuted blocks within strata to balance numbers and characteristics) into one of the following lifestyle intervention groups ($n = 25$ for each intervention group for a total of 50 participants). As part of the cm-RCT design, data from pre-frail work package 1 patients who were eligible but not selected for participation in work package 2 will provide a further comparator group for analysis. As an open-label study, neither participants nor researchers will be blinded to group allocation.

Active intervention group

This group will receive interventions designed to address frailty and will consist of dietitian referral for dietetic advice and physiotherapist referral for a graded exercise programme. The participants will receive this in addition to their usual haemodialysis standard of care. To reduce potential bias, neither the physiotherapist nor the dietitian will have regular input with haemodialysis patients as part of their job plan. Each patient will have five face-to-face appointments with the dietitian and physiotherapist (lasting 45–60 min) at baseline, week 6, week 12, week 18, and week 24. Brief telephone reviews will be conducted between appointments (approximately2–3 weeks after each face-to-face appointment) to review progress and provide additional support during the active intervention period. Some appointments may be substituted with telephone support if preferred by the patient. Patients will have their diet reviewed by a dietitian and healthy eating advice will be given based upon guidelines issued by the British Dietetic Association [37], which provide recommendations for minimum protein intake in dialysis patients. Patients will be advised to keep food and exercise diaries to monitor compliance with initiated changes and will be followed up by the research team prospectively (using face-to-face appointments and telephone reviews) to monitor progress and reinforce the advice (in addition to routine clinic visits). In addition, a graded exercise programme will be established by the physiotherapist to increase physical activity in line with both the patient's stated goals at initial assessment and their deficits identified upon frailty scoring.

The dietitian and physiotherapist will be supported by a Senior Lecturer and Consultant in Addiction Psychiatry who has expertise in behavioural change therapy. The dietitian and physiotherapist will be trained with motivational interviewing skills and the following psychological tools will be utilised to support the active intervention.

Cognitive behavioural therapy (CBT) intervention incorporating NLM is simple to train and apply. We will utilise simple goal-setting techniques, combined with relapse prevention strategies, and a simple visual representation system for presenting CBT-type interventions. NLM is more effective than standard consultations for improving the therapeutic alliance, increasing focus on key issues during the session, and improving outcomes. There is also evidence of efficacy in patients with poor reading skills or working in a language other than their first language (important for our patient demographics) [31].

SBNT is an intervention that draws in members of the family, social network, and mutual self-help or peer support groups to help the patient set and achieve goals. It has been developed and tested by colleagues in Birmingham, with an evidence base in the context of liver transplantation [33]. A combination of these two techniques, together with motivational interviewing [38] by the dietitian and physiotherapist after appropriate training, will facilitate supportive psychosocial interventions to change lifestyle behaviour.

Passive control group

This group will receive their usual standard of care from their treating dialysis centre, including usual dietitian input. However, there will be no psychosocial intervention or focused exercise and dietary monitoring programme. Follow-up will be at routine clinic visits only, where lifestyle modification advice will be reinforced as per usual clinical practise. Physiotherapy may be offered to these patients as per standard referral guidelines but will not have the psychosocial underpinning of the intervention group.

Both groups will undergo a repeat frailty testing during the mid-point (3 months ± 2 weeks) and the end of study intervention (6 months ± 2 weeks) (see Figs. 1 and 2). The aim is to assess if there is any change in frailty status which will provide data to underpin a power calculation for a subsequent large-scale study. Additional pre-specified secondary outcomes will be collected as highlighted below in the protocol. Participants will also be invited to complete a series of questionnaires to ascertain the

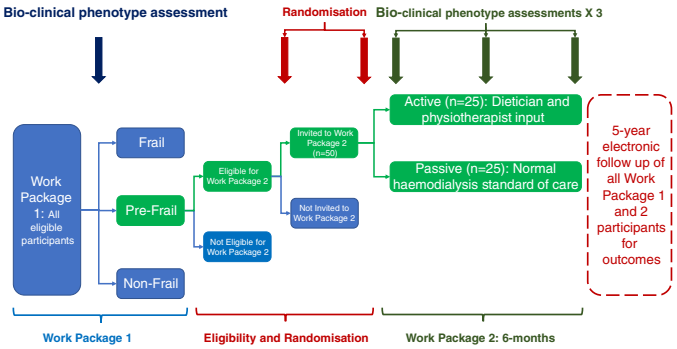


Fig. 1 Flowchart of participants in FITNESS work packages 1 and 2. As part of the cm-RCT methodology, all eligible participants will first be randomised for potential invitation to the study ($n = 50$). Potential recruits will then be approached for involvement in work package 2 and, after further valid consent, will then be randomised into active or passive groups

	Study Period										
	Enrolment	Allocation	Weeks Post-Allocation								
Timepoint (weeks)	-2-->0	0	6	12	14	18	24	28	52	156	260
Enrolment:											
Eligibility Screen/Randomised selection of participants	x										
Informed Consent	x										
Treatment Allocation/Randomisation		x									
Interventions:											
Active Group: Dietitian/Physiotherapist review with behavioural intervention		x	x	x		x	x				
Passive Group: Dialysis standard of care		◆	—	—	—	—	◆				
Blood sampling and storage: Both groups*		x						x			
Assessments:											
Baseline Demographics**		x									
Clinical Assessment***		x			x			x			
Patient Reported Outcomes****		x			x			x			
Electronic Data Capture of clinical outcomes*****									x	x	x

* Serum, plasma and PBMCs stored as outlined above.
**Extensive baseline data including cause of end-stage kidney disease, dialysis modality, dialysis duration, biochemical data, past medical history, medications, social history
***Frailty status, dialysis adequacy and biochemical data as per existing dialysis Quality Assurance processes
****Patient reported outcomes (physical activity and psychological well being as highlighted above)
***** Long-term clinical outcomes (patient survival, hospitalisation, cardiac events, transplantation) via electronic tagging to University Hospital Birmingham electronic patient records (via Patient Registration number) and national registries (via NHS number)

Fig. 2 Spirit figure for work package 2

tolerability and suitability of the intervention trial, and to guide the delivery of the trial on a larger scale.

Study outcomes

Primary endpoint

The primary endpoint is the feasibility and tolerability of the clinical intervention study (recruitment rates, loss to follow-up, and study withdrawal).

Secondary endpoints

Secondary endpoints include: 1) refinement of the multi-disciplinary intervention based upon views from participants and stakeholders (from post-study questionnaires); 2) change in frailty status (based on Fried Frailty Phenotype, Clinical Frailty Scale); 3) difference in clinical and biochemical outcomes; 4) quality of life score (EQ-5D-3 L); 5) receipt of kidney transplant; 6) vascular access failure; and 7) long-term clinical outcomes (death, cardiac events, hospitalisation) to University Hospital Birmingham electronic patient records and Hospital Episode Statistics

Data collection

Tissue collection

Blood samples will be taken from the 50 work package 2 participants, alongside 50 work package 1 participants each from the frail and non-frail groups. Plasma, serum, peripheral blood mononuclear cells (PBMCs) and whole blood will be stored for future immunophenotyping.

Electronic data capture

Electronic data capture will continue in work package 2 as previously described in work package 1.

Data monitoring and risk

There are no specific risks anticipated with this study. However, any study-related adverse events (AEs) will be documented and reported to the steering committee. Should a participant report any thoughts of deliberate self-harm or suicide, or complete a PHQ-9 score of over 20 during the study, a discussion will be held with the patient asking whether they would like a referral to the patient's nephrologist or psychology services at the trust.

A serious adverse event (SAE) is defined by the Health Research Authority as an untoward occurrence that: 1) results in death; 2) is life-threatening; 3) requires hospitalisation or prolongation of existing hospitalisation; 4) results in persistent or significant disability or incapacity; 5) consists of a congenital abnormality or birth defect; and 6) is otherwise considered medically significant by the investigator.

An SAE occurring to a research participant will be reported to the Research Ethics Committee (REC) where in the opinion of the Chief Investigator the event was: 1) related (it resulted from the administration of any of the research procedures); and unexpected (the type of event is not listed in the protocol as an expected occurrence).

Any SAE will be reported to the REC within 15 days of the Chief Investigator becoming aware of the event. All other SAEs will need reporting as AEs on the case report form.

Exceptions to expedited reporting include hospitalisation for: 1) treatment which was elective or pre-planned, or for a pre-existing condition not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications; and 2) treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

Patients will be asked if any adverse events have occurred when they attend for any trial-related procedure.

Participant withdrawal

In the event of patients wishing to discontinue in the trial, the participant would be withdrawn from the study with the assurance that their usual care will continue unaffected. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected, or any other research procedures carried out on or in relation to the participant. If the patient consented to have long-term electronic tracking of their outcomes, this would be continued.

Statistics

The principle parameters being examined in work package 1 are hospitalisation, mortality, and their association with frailty. Based upon US data [6], we have assumed an adjusted risk ratio of 2.24 for 1-year mortality and 1.56 for 1-year mortality and/or hospitalisation for frail versus non-frail patients receiving haemodialysis. We have assumed a baseline (non-frail) risk of 5% for 1-year mortality and a 40% risk of 1-year mortality/hospitalisation, powered to 0.8 and with a confidence interval of 0.95. We therefore calculate a sample size of 602 to be adequately powered to demonstrate a difference in 1-year mortality or 150 patients to be powered for 1-year mortality/hospitalisation.

Work package 2 is designed as a feasibility study so no specific power calculations have been made. However, one of the secondary outcomes is to use the data regarding effect sizes to determine the sample required for a larger multi-centre study based upon the feasibility of work package 2.

Statistical analysis will be performed using standard software (SPSS Version 25, Mac version, Chicago, USA). Normality of data will be assessed using the Kolmogorov-Smirnov tests. Paired sample t test and Wilcoxon signed rank test, for parametric and non-parametric data respectively, will be used to compare the means of two variables

from a single group. Comparison of data between groups will be made using unpaired student t tests and the Mann-Whitney test for parametric and non-parametric data, respectively. Categorical data will be analysed using Pearson's or Spearman's test as appropriate. A p value < 0.05 is considered significant in the statistical analysis.

Discussion

Frailty has been linked with adverse outcomes in North American haemodialysis cohorts [5–12, 17, 39, 40], but these data are not transferrable to UK patients since US dialysis populations have adverse outcomes compared with UK populations [18]. There is no agreement over the best frailty tool to assess patients, both within the general population and within haemodialysis cohorts. The Fried Frailty Phenotype [41] and Rockwood Frailty Index [42] are the most commonly cited instruments in geriatric and renal-specific literature, with the Clinical Frailty Scale also featuring in haemodialysis cohorts [12]. The Edmonton Frail Scale is recommended by the British Geriatric Society, but has yet to be validated in patients receiving haemodialysis [43]. We expect each of these instruments to show association with negative outcomes, but it is not yet known which of these provides the best predictive value in patients receiving haemodialysis. The cohort analysis embedded within this study will therefore seek to address this by comparing frailty instruments for their association with negative outcomes, whilst also addressing renal-specific outcomes such as transplantation or dialysis access failure. These data will allow renal practitioners to better understand which frailty tool is optimal for their population.

Multi-disciplinary intervention into frailty has shown promise [19], although a systematic review and meta-analysis was limited by the lack of validated measures of frailty as inclusion criteria and outcome measures in the published studies to date [22]. To our knowledge, there are no published data regarding frailty interventions within the UK haemodialysis population, although a US study showed self-reported disability could be reduced by such an intervention [20].

There is an urgent need for the development of interventions capable of enacting long-term change within patient groups. Our experience in Birmingham suggests that BCTs can modify behaviour with the potential to change clinical outcomes [33, 44]. Therefore, a patient-centred, frailty-specific BCT intervention may be beneficial for frail patients receiving haemodialysis and may improve clinical and patient-reported outcomes.

Work package 2 is an unblinded, randomised controlled study using a psychologically supported multi-disciplinary intervention into frailty compared with a control group which receives standard care. This will be used as a basis for exploring whether a large scale, multi-centre trial is feasible and warranted, while also providing data upon effect sizes to allow subsequent power calculation for such a study. We chose the "pre-frail" group as the focus of this intervention, firstly because they arguably have the most to gain—not progressing to frailty—and, secondly, because pre-frailty represents a much less heterogeneous group than frailty, the latter of which would include essentially functionally independent individuals with a few accumulated deficits along with bed-bound individuals and those approaching end-of-life. The pre-frail group therefore have an easily definable set of characteristics and have the ability to participate in, and benefit from, the proposed interventions.

One of the principle strengths of the study design is the breadth of data being collected. Researchers will collect data on multiple aspects of frailty from consenting patients to include aspects of sarcopenia (muscle mass, quality, and function), immunosenescence, functional status/disability, mood, cognitive status, and medical history. This rich dataset will allow detailed analysis of the heterogeneity or otherwise of frailty within the cohort. As work package 1 is a single time-point analysis with electronic follow-up thereafter, dropout should be minimal and large numbers of patients could be recruited to allow such detailed analysis to have real meaning to clinicians. Another strength lies in the cm-RCT design, whereby stratified random sampling will identify trial participants from consenting eligible cohort study participants. This approach has several benefits, including amelioration of potential attrition bias in the control group, long-term data follow-up for a large comparator group, and increased power for the study [34].

A weakness of the study is the single time-point assessment in work package 1, as frailty is known to change over time [45–47]. Nevertheless, objective frailty measurements still hold prognostic value [48].

This cohort randomised controlled trial will assess the prevalence and associations of frailty using validated measurement tools and test the utility of these instruments in predicting adverse outcomes. The study will also assess the feasibility of conducting a randomised controlled trial using an intervention designed to improve frailty.

Additional file

Additional file 1: SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol and related documents. (DOC 121 kb)

Abbreviations

AE: Adverse event; BAME: Black, Asian and minority ethnic; BCT: Behavioural change technique; CBT: Cognitive behavioural therapy; cm-RCT: Cohort multiple randomised controlled trial; EPR: Electronic patient record; MoCA: Montreal Cognitive Assessment; NHS: National Health Service; NLM: Node-link mapping; PHQ: Patient Health Questionnaire; PIL: Patient information leaflet; REC: Research Ethics Committee; REDCap: Research

Electronic Data Capture; SAE: Serious adverse event; SBNT: Social behaviour and network therapy

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Authors' contributions
BMA: study and protocol design, conduct, analysis, and dissemination of results. MD: protocol design. ED: design, training, and supervision of behavioural intervention. TAJ: study and protocol design, study supervision. CJF: study and protocol design, study supervision. AS: study and protocol design, conduct, supervision, analysis, and dissemination of results. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The FITNESS Study has been reviewed and received a favourable opinion from the South Birmingham Research Ethics Committee, reference 17/WM/0381.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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