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Original Article

ORIGINAL ARTICLE

Depression is associated with frailty and lower quality of life in haemodialysis recipients, but not with mortality or hospitalization

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ABSTRACT

Background. Frailty and depression are highly prevalent in haemodialysis recipients, exhibit a reciprocal relationship, and are associated with increased mortality and hospitalization, 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, hospitalization and quality of life.

Methods. We performed a prospective cohort study of prevalent haemodialysis recipients linked to national datasets for outcomes including mortality and hospitalization. Depression was assessed using the Patient Health Questionnaire-9 (PHQ-9), frailty using the Clinical Frailty Scale (CFS) and quality of life using the EuroQol 5-Dimension (EQ-5D) Summary Index.

Results. A total of 485 prevalent haemodialysis recipients were recruited, with 111 deaths and 1241 hospitalizations during follow-up. CFS was independently associated with mortality [hazard ratio (HR) 1.31; 95% confidence interval (CI) 1.08, 1.59; $P = .006$], hospitalization [incidence rate ratio (IRR) 1.13; 95% CI 1.03, 1.25; $P = .010$] and lower quality of life (Coef. −0.401; 95% CI −0.511, −0.292; $P < .001$). PHQ-9 score was independently associated with lower quality of life (Coef. −0.042; 95% CI −0.063, −0.021; $P < .001$), but not mortality (HR 1.00; 95% CI 0.96, 1.04; $P = .901$) or hospitalization (IRR 0.99; 95% CI 0.97, 1.01; $P = .351$). In an adjusted model including CFS, moderate depression was associated with reduced hospitalization (IRR 0.72; 95% CI 0.56, 0.93; $P = .013$).

Conclusions. With the 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.

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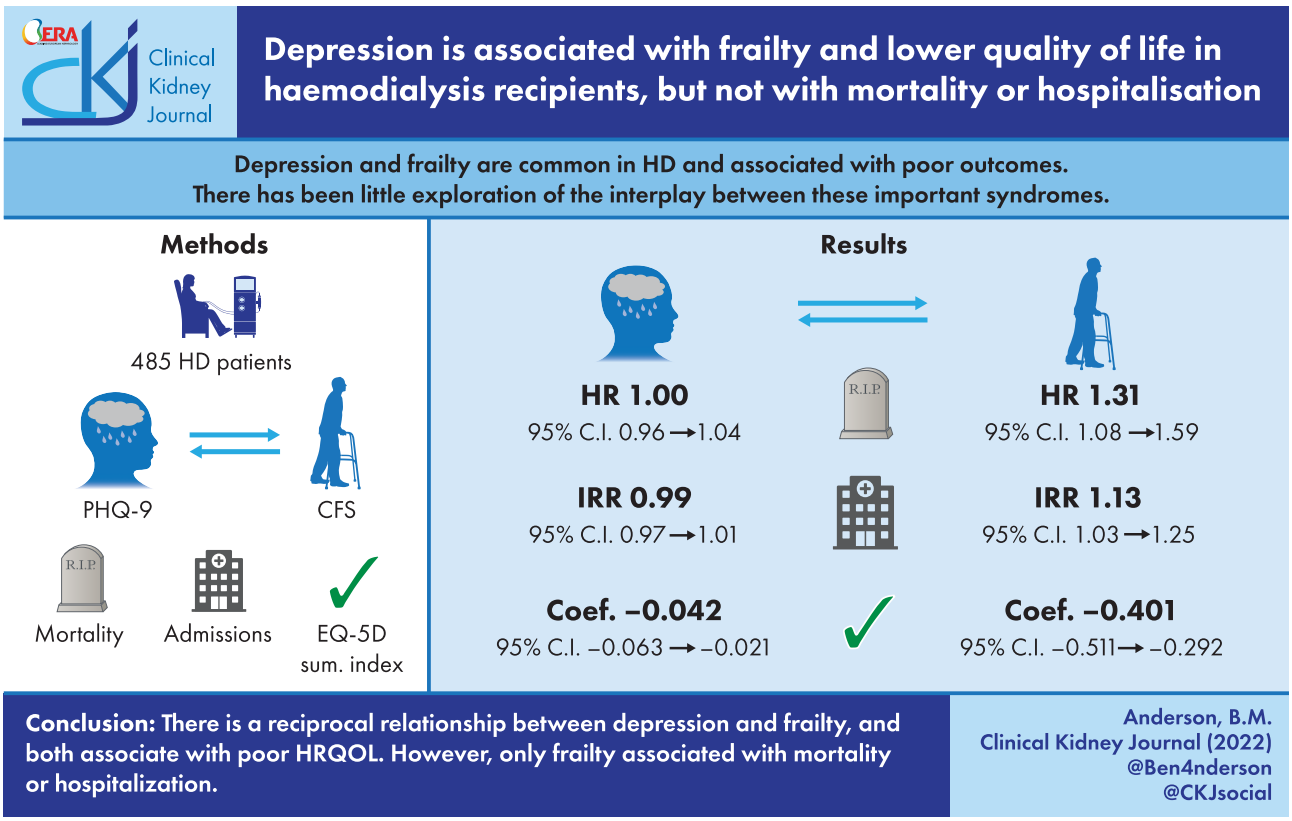
LAY SUMMARY

Depression and frailty are common in people who receive haemodialysis and are associated with negative outcomes including mortality, admission to hospital and poorer quality of life. Despite this, the relationship between depression and frailty and these important outcomes has not been studied. Here we show, in a large contemporary English haemodialysis population, that when frailty is taken into account, depression is associated with lower rates of hospitalization, but poorer quality of life. Depression was not associated with mortality. Frailty was associated with higher rates of admission, mortality and poorer quality of life. More work needs to be done to understand the complex relationship between frailty and depression in haemodialysis recipients.

GRAPHICAL ABSTRACT



Keywords: depression, frailty, haemodialysis, health-related quality of life, hospitalization, mortality

INTRODUCTION

Frailty is the syndrome of accelerated ageing, characterized by multi-system dysregulation, and vulnerability to stressors [1]. Agreement between frailty screening tools in haemodialysis recipients is poor, and we have previously argued that frailty screening must combine ease of use and predictive capability for adverse outcomes [2]. One commonly utilized definition is the Clinical Frailty Scale (CFS) [3], a simple global measure of frailty based upon activities of daily living after clinical interview. The CFS is being increasingly used in multiple settings [4, 5], and associates with mortality and hospitalization in haemodialysis [2, 6].

Frailty is also associated with poor quality of life for kidney patients, which begins early at a pre-dialysis stage [7, 8]. In haemodialysis patients, self-rated fair/poor quality of life was more likely in frail haemodialysis recipients, and frailty is associated with worsening quality of life over time [9, 10].

Depression also impacts upon quality of life [11, 12], but is under-recognized in haemodialysis populations [13]. The Patient Health Questionnaire-9 (PHQ-9) has 92% sensitivity and 92% specificity for detection of depression in haemodialysis recipients [14]. 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 [15–18]. A depression diagnosis has also been associated with greater hospitalization, but lower mortality within hospital admission episodes in retrospective cohorts [19, 20].

Despite 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 [21]. However, prevalent depression was associated with incident frailty, but not vice versa in a prevalent US dialysis cohort [22]. US and European dialysis demographics and outcomes differ significantly [23], 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, hospitalization and quality of life in haemodialysis recipients.

MATERIALS AND METHODS

Study design

The Frailty Intervention Trial iN End-Stage patientS on haemodialysis (FITNESS) study is a two-stage study that follows a cohort multiple randomized controlled trial (cmRCT) design [24]. 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). The first stage is a cross-sectional assessment and long-term follow up of study participants on maintenance haemodialysis. The full protocol for the FITNESS study has been described in detail elsewhere [25]. The study is reported in accordance with STROBE guidelines [26].

Study setting

Patients were recruited from a single nephrology centre located in Birmingham, UK, 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, before giving their consent to join the cohort study.

Eligibility criteria

Inclusion criteria included adults aged 18 years and over, anyone receiving regular haemodialysis for at least 3 months' duration and the ability to give informed consent. The only exclusion criterion was inpatient care within 4 weeks of recruitment unless for vascular access purposes (clotted or non-functional access, but excluding access infection), to avoid confounding of baseline data with frailty secondary to recent hospitalization.

Baseline assessment

Baseline assessments of all study participants took place before and during one of their usual dialysis sessions. To negate the potential effect of the long break from dialysis upon frailty measurements, we avoided the first haemodialysis session after the weekend interval. Where participants dialysed twice weekly, the dialysis session after the shortest interval was chosen for baseline assessment.

Study participants completed a number of investigations, which are detailed in our methodology paper [25]. Briefly, prior to connection to dialysis, participants underwent a timed 4-m walk from standing and bilateral hand-grip strength via dynamometer (Takei Grip D, Takei Scientific Instruments Co. Ltd, Japan), alongside a Montreal Cognitive Assessment (MoCA [27]). 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. PHQ-9 scores comprised nine questions each scored between 0 and 3 for frequency of depression symptoms, giving a total score of between 0 and 27. Moderate depression was defined as a PHQ-9 score of $\geq$10 [14]. The Physical Activity Index was derived from the GP Physical Activity Questionnaire via a validated formula [28, 29]. EPR were interrogated for comorbidities, drug history, dialysis vintage and adequacy, previous transplantation, and biochemical data. Determination of socioeconomic deprivation was based upon the Index of Multiple Deprivation 2015 (IMD), a multiple deprivation model calculated by local area, with 1 representing the most deprived and 5 the least deprived areas.

The CFS 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 score of 9 was attributed to those who were terminally ill but not overtly frail. A CFS of 5–8 inclusive was considered frail.

Outcomes

Mortality data were obtained by electronic record linkage of all FITNESS study recruits to Office of National Statistics, a UK-wide repository of death certificate data, with robust coverage of mortality data. Hospital Episode Statistics, a database containing all secondary care episodes in any NHS hospital in England, provided robust national data for all hospitalizations. Hospital admissions were defined as any hospital episode lasting one or more night.

Health-related quality of life (HRQOL) was assessed using Euroqol 5-Dimension 3-Level (EQ-5D-3L). This was converted into the single-measure EQ-5D Summary Index via a standardized formula [30]. 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.

Recruitment

Recruitment and power calculations are explored in detail in previous work from the FITNESS project [2, 25].

Statistics

Statistical analysis was performed using STATA 16 (StataCorp 2019, Stata Statistical Software: Release 16; StataCorp LLC, College Station, TX, USA) 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, censored for end of follow-up. 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.

Figure 1: PRISMA flowchart of study participation.

Incidence rate ratios (IRR) 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 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 hospitalization 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 these covariables plus CFS score.

Odds ratios (OR) 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.

The EQ-5D summary index is right-censored, with a maximum value of 1. Therefore, it was transformed using the following equation $\frac{(x + 0.594)}{1.594}$ to give a fractional score between 0 and 1, and fractional regressions were performed on these.

As each of frailty, depression and HRQOL have different potential associates, regression models were subject to adjustment for separate *a priori* covariables selected for known or suspected relationship with the outcome of interest. These models are detailed in Supplementary data, Table S1.

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. No such interactions were observed. Given recent evidence linking frailty to vascular access difficulty [31–33], sensitivity analyses were run on all final regression models with addition of vascular access type.

Missing values for IMD quintiles 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 <.05 was considered significant in the statistical analysis.

RESULTS

Study cohort demographics

Figure 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 (IQR 531–812 days), with all participants receiving a minimum potential follow-up of 365 days from recruitment. Baseline demographics are described in detail elsewhere [2]. Table 1 highlights key demographics stratified by frailty status at study recruitment.

Depression scores

The median PHQ-9 score was 5 (IQR 2–10), with 222 participants (46.3%) reporting minimal depression, 131 (27.3%) mild depression, 76 (15.8%) moderate depression, 38 (7.9%) moderately severe depression and 13 (2.7%) severe depression.

Correlation was weak between CFS and PHQ-9 scores (Rho = 0.361, $P < 0.001$). Figure 2 demonstrates that, on both univariable and each multivariable analysis, every increase in CFS score was associated with increased PHQ-9 scores. Table 2 shows full multivariable model results. Figure 3 demonstrates

Table 1: Baseline demographics of the FITNESS cohort stratified by frailty status.

		Total cohort	Not frail	Frail	P
Frail		261 (53.8)			
Median age (years)		63 (53–74)	60 (50–72)	65 (55–76)	.016
Median PHQ-9		5 (2–10)	3 (1–7)	7 (3–6)	<.001
Median MoCA		22 (17–25)	23 (20–26)	20 (16–23)	<.001
Median albumin (g/L)		39 (35–41)	39 (36–42)	38 (34–41)	.024
Median BMI (kg/m^2)		26.8 (23.2–32.3)	26 (23.0–30.7)	27.9 (23.2–33.7)	0.027
Median Charlson Score[a]		4 (3–6)	4 (2–5)	5 (4–7)	<.001
Median HD vintage (months)		37 (17–76)	33 (13–66)	41 (19.9–81.5)	.015
Median Kt/V		1.59 (1.39–1.85)	1.58 (1.38–1.80)	1.61 (1.41–1.88)	0.474
Median EQ-5D Summary Index		0.779 (0.516–1.00)	1 (0.779–1.00)	0.62 (0.189–0.796)	<.001
Health change	Better	94 (19.4)	52 (23.2)	42 (16.1)	.003
	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)	.921
	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)	.180
	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)	.002
Comorbidities	Diabetes	138 (28.5)	43 (19.2)	95 (36.4)	<.001
	MI	98 (20.2)	34 (15.2)	64 (24.5)	.011
	CVA/TIA	57 (11.8)	17 (7.6)	40 (15.3)	.008
	Cancer	56 (11.6)	30 (13.4)	26 (10.0)	.238
	Heart failure	52 (10.7)	19 (8.5)	33 (12.6)	.140
	PVD	47 (9.7)	15 (6.7)	32 (12.3)	.039
Primary renal disease	Diabetic	114 (23.5)	33 (14.7)	81 (31.3)	<.001
	Hypertensive	39 (8.0)	22 (9.8)	17 (6.5)	.182
	Ischaemic	38 (7.8)	14 (6.3)	24 (9.2)	.229
	IgA	37 (7.6)	20 (8.9)	17 (6.5)	.318
	PKD	28 (5.8)	17 (7.6)	11 (4.2)	.122
	FSGS	24 (5.0)	14 (6.3)	10 (3.8)	.221
	Reflux	17 (3.5)	7 (3.1)	10 (3.8)	.673
	Obstructive	16 (3.3)	10 (4.5)	6 (2.3)	.183
	AAV	15 (3.1)	11 (4.9)	4 (1.5)	.032
	Interstitial nephritis	10 (2.1)	6 (2.7)	4 (1.5)	.376
	Myeloma	10 (2.1)	8 (3.6)	2 (0.8)	.030
	Unknown	68 (14.0)	31 (13.8)	37 (14.2)	.915
Smoking status	Current	6814.1	38 (17.0)	30 (11.5)	
	Ex	132 (27.3)	64 (28.6)	68 (26.2)	.133
	Never	284 (58.7)	122 (54.5)	162 (62.3)	
Dialysis access	Line	113 (23.3)	47 (21.0)	66 (25.3)	.264
Tx list status	Active	58 (12.0)	36 (16.1)	22 (8.4)	.036
	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)	<.001
	Unemployed	148 (30.6)	58 (25.9)	90 (34.6)	
	Retired	267 (55.2)	105 (46.9)	162 (62.3)	
Job role[b]	Unskilled manual	181 (39.3)	70 (32.1)	111 (45.7)	.046
	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)	

Table 1: Continued.

		Total cohort	Not frail	Frail	*P*
Education level	High school	342 (70.7)	146 (65.2)	196 (75.4)	.042
	College/6th form	92 (19.0)	49 (21.9)	43 (16.5)	
	University	50 (10.3)	29 (13.0)	21 (8.1)	
Residence	Own home	462 (95.9)	218 (97.8)	244 (94.2)	.172
	Warden-controlled	12 (2.5)	3 (1.4)	9 (3.5)	
	Residential home	5 (1.0)	2 (0.9)	3 (1.2)	
	Nursing home	3 (0.6)	0 (0.0)	3 (1.2)	

Median (IQR) or *n* (%) shown.
[a]CKD omitted from Charlson Score.
[b]Or prior job role if unemployed/retired.
BMI: body mass index; HD: haemodialysis; CVA/TIA: cerebrovascular accident/transient ischaemic attack; PVD: peripheral vascular disease; PKD: polycystic kidney disease; FSGS: focal segmental glomerulosclerosis; AAV: ANCA-associated vasculitis.

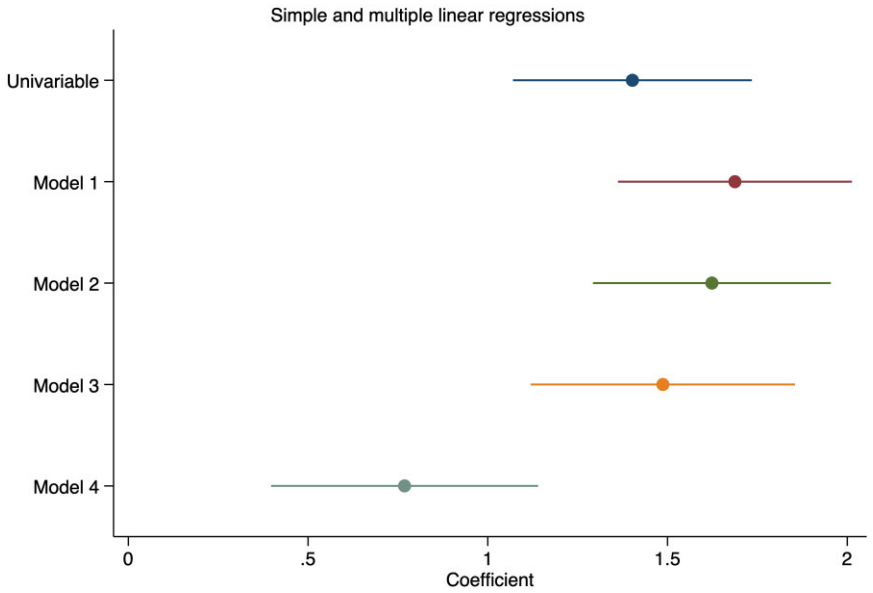


Figure 2: Change in PHQ-9 score with each 1-point increase in CFS.

that PHQ-9 score was associated with CFS score on all adjusted models; Table 3 highlights the fully adjusted model.

Mortality and hospitalization

Over a follow-up period comprising a total of 862.1 patient-years, we observed 111 (22.9%) deaths, 1241 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, and the median number of admissions was 2 (IQR 0–4).

Depression and mortality

PHQ-9 score was not associated with mortality, either on univariable [hazard ratio (HR) 1.02; 95% confidence interval (CI) 0.988, 1.05; $P = .220$] or multivariable analysis (HR 1.00; 95% CI 0.96–1.04; $P = .901$). Moderate depression was not associated with mortality on univariable (HR 1.16; 95% CI 0.771, 1.75; $P = .472$), or multivariable analyses (HR 0.91; 95% CI 0.57, 1.47; $P = .713$). Similar results were obtained upon Cox regression with omission of frailty from the adjusted analyses, as shown in Supplementary data, Tables S1–S4.

Depression and hospital admissions

PHQ-9 score was associated with increased rates of hospitalization on univariable analysis (IRR 1.02; 95% CI 1.00, 1.04; $P = .028$), but lost significance on multivariable analyses both with CFS (IRR 0.99; 95% CI 0.97, 1.01; $P = .351$) and without (IRR 1.00; 95% CI 0.98, 1.02; $P = .973$) in the model. Full models are shown in Supplementary data, Tables S5 and S6.

Figure 4 shows moderate depression was not associated with rates of hospital admissions in univariable or multivariable analyses where CFS was omitted. However, admissions were significantly lower upon multivariable analysis with the addition of CFS into the model. Full model results are shown in Supplementary data, Tables S7 and S8.

Depression, frailty and quality of life

Correlation was moderate between EQ Summary Index and both PHQ-9 (Rho = 0.448; $P < .001$), and CFS (Rho = 0.600; $P < .001$). Figure 5 highlights both CFS and PHQ-9 scores were associated with lower fractional EQ-5D summary index scores on all models—univariable and multivariable. The fully adjusted model is shown in Table 4.

Table 2: Linear regression of change in PHQ-9 score associated with covariables in fully adjusted Model 4.

	Coefficient	Lower 95% CI	Upper 95% CI	P
CFS score	**0.768**	**0.397**	**1.14**	**<.001**
Age	**−0.093**	**−0.137**	**−0.050**	**<.001**
Ethnicity				
White		REFERENCE		
South Asian	**−1.54**	**−2.74**	**−0.344**	**.012**
Black	−0.689	−1.96	0.578	.286
Other	−0.007	−2.83	2.81	.996
Gender				
Male		REFERENCE		
Female	0.527	−0.366	1.42	.246
IMD quintile				
1		REFERENCE		
2	−0.164	−1.37	1.05	.790
3	−0.083	−1.31	1.14	.894
4	−0.611	−2.27	1.05	.471
5	−0.424	−2.18	1.34	.636
Unknown	0.062	−1.88	2.00	.950
Education level				
High school		REFERENCE		
College/6th form	−0.919	−2.05	0.209	.110
University	**−1.91**	**−3.39**	**−0.422**	**.012**
Prior admissions	−0.008	−0.188	0.172	.931
Charlson Index[a]	−0.079	−0.350	0.193	.570
Cognitive impairment				
No		REFERENCE		
Yes	−0.366	−1.49	0.753	.521
Antidepressant use				
No		REFERENCE		
Yes	**3.69**	**2.29**	**5.09**	**<.001**
Number medications	0.075	−0.056	0.206	.260
HD vintage	−0.001	−0.010	0.007	.778
Self-rated pain				
None		REFERENCE		
Moderate	**1.63**	**0.664**	**2.60**	**.001**
Extreme	**2.61**	**0.867**	**4.36**	**.003**
Self-rated health change				
Better/The same		REFERENCE		
Worse	**1.73**	**0.808**	**2.65**	**<.001**
Self-rated health/100	**−0.056**	**−0.078**	**−0.034**	**<.001**
Constant	**10.6**	**7.19**	**14.1**	**<.001**

Coefficients derived from multiple linear regression. Bold text indicates significant at $P < .05$ level.
[a]CKD omitted from Charlson Index.

Sensitivity analyses

Addition of vascular access type to each regression model did not affect interpretation of the data, as shown in Supplementary data, Tables S10–S20.

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 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 an association between depression and mortality, or with hospital admissions on multivariable analyses. Our data highlight the complex association between frailty and depression in haemodialysis recipients, but do not support depression as an associate of mortality or hospitalization. Depression remains an important outcome 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 in non-dialysis elderly people, a bi-directional relationship was observed between depression and frailty [21]. 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 [22]. However, the same cohort demonstrated an association baseline frailty and baseline depression. Our cohort confirms this association even after

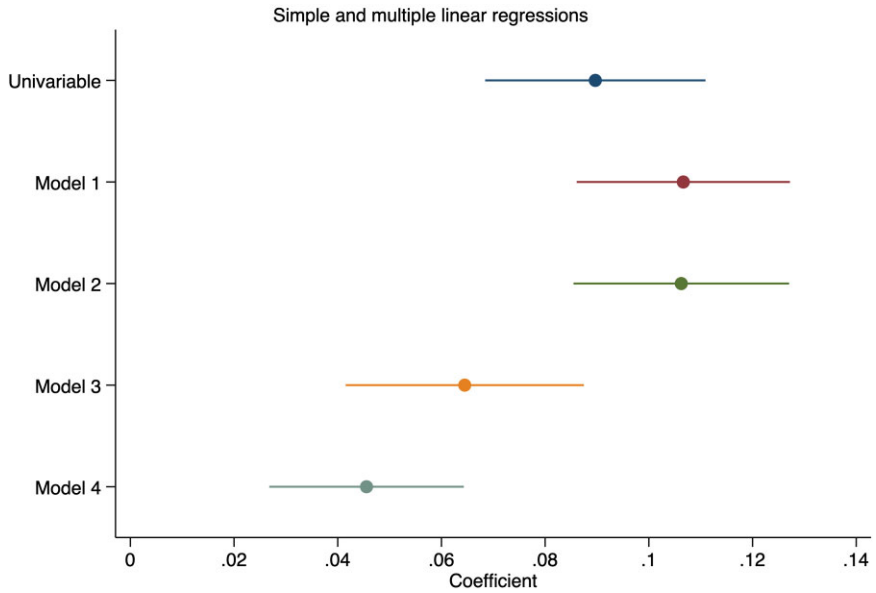


Figure 3: Increase in CFS associated with each 1-point increase in PHQ-9.

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 discussion. In a large prospective cohort study, Saglimbene and colleagues observed moderate depression by the Beck Depression Inventory (BDI) to be associated with all-cause mortality in haemodialysis [15]. Chilcot and colleagues also observed an association between moderate depression and mortality using both the BDI and PHQ-9 [16]. In a meta-analysis, depression scores were associated with a modest mortality HR of 1.04 [18], 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 8267 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 [34]. 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 likely to attribute their presenting complaints to comorbid 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 hospitalization and mortality for haemodialysis recipients with moderate to severe depression upon serial prospective measures of depression [17]. 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 [20], but lower mortality risk during inpatient stay [19]. Caution is required with interpretation, as coding data have been shown to have limited accuracy when applied to comorbidities—rather than primary admission diagnoses—and thus limit the potential utility in research [35]. 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 [10]. McAdams-DeMarco and colleagues found an association between frailty and self-rated fair or poor health, though this might not be considered as an HRQOL measure *per se* [9]. Depression has also been associated with lower quality of life in haemodialysis recipients [11, 12]. Our data demonstrate that frailty and depression independently associate with poorer HRQOL, 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 socioeconomic backgrounds representative of the local

Table 3: Linear regression of change in CFS score associated with covariables in fully adjusted Model 4.

	Coefficient	Lower 95% CI	Upper 95% CI	P
PHQ-9 score	**0.046**	**0.027**	**0.064**	**<.001**
Age	−0.008	−0.017	0.001	.083
Gender				
Male		REFERENCE		
Female	**0.226**	**0.040**	**0.412**	**.017**
Ethnicity				
White		REFERENCE		
South Asian	0.214	−0.037	0.466	.095
Black	−0.012	−0.278	0.254	.929
Other	0.257	−0.331	0.844	.391
Education level				
High school		REFERENCE		
College/6th form	0.008	−0.224	0.240	.945
University	−0.152	−0.468	0.163	.344
IMD quintile				
1		REFERENCE		
2	0.104	−0.147	0.354	.416
3	0.015	−0.238	0.269	.905
4	−0.301	−0.647	0.045	.088
5	0.007	−0.362	0.376	.969
Unknown	0.156	−0.240	0.551	.439
Social support				
No		REFERENCE		
Yes	**−0.698**	**−1.07**	**−0.332**	**<.001**
Charlson Index[a]	**0.094**	**0.040**	**0.147**	**.001**
Cognitive Impairment				
No		REFERENCE		
Yes	0.030	−0.201	0.261	.798
Smoking status				
Current		REFERENCE		
Ex	0.277	−0.013	0.566	.061
Never	0.172	−0.100	0.444	.214
Self-rated health change				
Better/The same		REFERENCE		
Worse	0.075	−0.117	0.267	.441
Self-rated health/100	**−0.006**	**−0.011**	**−0.002**	**.006**
Walking aid use				
No		REFERENCE		
Yes	**0.532**	**0.307**	**0.758**	**<.001**
Physical Activity Index				
Inactive		REFERENCE		
Moderately inactive	**−0.384**	**−0.732**	**−0.035**	**.031**
Moderately active	**−1.07**	**−1.49**	**−0.641**	**<.001**
Active	**−1.86**	**−2.30**	**−1.42**	**<.001**
Slow walking speed				
No		REFERENCE		
Yes	**0.712**	**0.482**	**0.941**	**<.001**
Low grip strength				
No		REFERENCE		
Yes	0.082	−0.119	0.283	.424
Constant	**3.88**	**3.20**	**4.55**	**<.001**

Coefficients derived from multiple linear regression. Bold text indicates significant at $P < 0.05$ level.
[a]CKD omitted from Charlson Index.

population [36]. However, our data should be interpreted with caution in non-English populations. Furthermore, as a single-centre analysis, 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 [17, 37]. Our dataset also lacked adjustment for a validated malnutrition score. Our CFS definition deviates slightly from the original validation sample [3], in that no multidisciplinary team discussion was held to determine frailty status after clinical interview. However, we would argue that our approach is analogous to CFS use in clinical practice [5]. 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

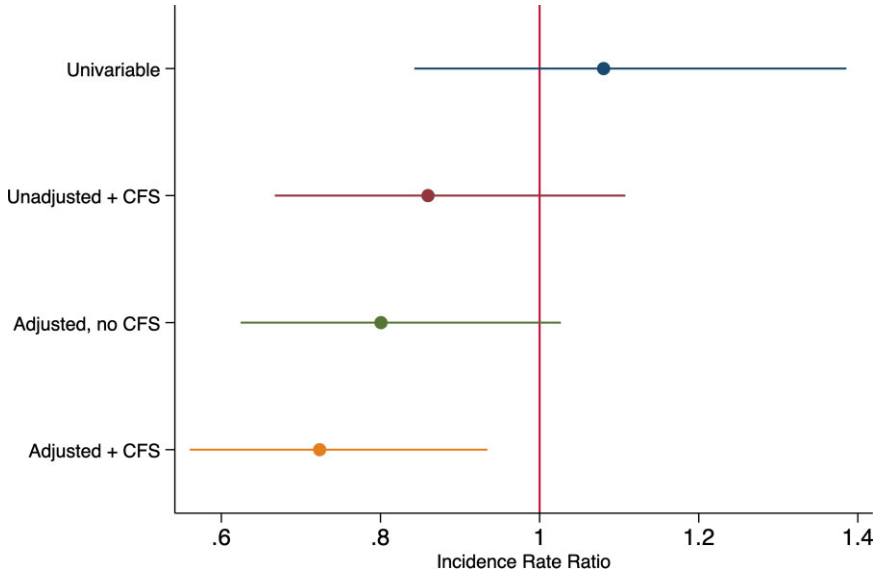


Figure 4: IRRs of hospital admissions associated with moderate depression.

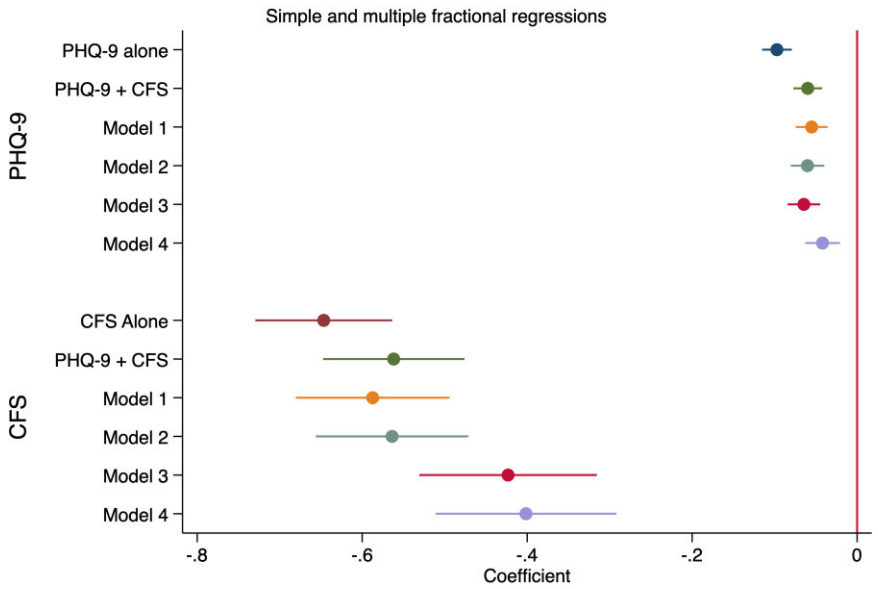


Figure 5: Change in fractional EQ Summary Index with increase in PHQ-9 and CFS scores.

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 hospitalization 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.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

Table 4: Associates of fractional EQ-5D Summary Index—fully adjusted Model 4.

	Coefficient	Lower 95% CI	Upper 95% CI	P
PHQ-9 score	**−0.042**	**−0.063**	**−0.021**	**<.001**
CFS	**−0.401**	**−0.511**	**−0.292**	**<.001**
Age	0.002	−0.013	0.016	.829
Gender				
Male		REFERENCE		
Female	**−0.233**	**−0.442**	**−0.023**	**.030**
Ethnicity				
White		REFERENCE		
South Asian	0.271	−0.031	0.573	.078
Black	0.135	−0.191	0.462	.416
Other	−0.487	−1.18	0.206	.169
Education level				
High School		REFERENCE		
College/6th form	−0.262	−0.553	0.029	.078
University	**−0.379**	**−0.690**	**−0.067**	**.017**
Social support				
Yes		REFERENCE		
No	**−0.486**	**−0.807**	**−0.165**	**.003**
IMD quintile				
1		REFERENCE		
2	−0.219	−0.511	0.072	.141
3	0.024	−0.270	0.318	.874
4	0.135	−0.264	0.534	.508
5	0.243	−0.227	0.713	.311
Unknown	0.127	−0.398	0.652	.636
Employment status				
Employed		REFERENCE		
Unemployed	−0.021	−0.716	0.675	.954
Retired	0.101	−0.512	0.714	.747
HD vintage (months)	**−0.003**	**−0.005**	**−0.001**	**.009**
Charlson Index[a]	−0.011	−0.070	0.047	.706
Hb (g/L)	0.004	−0.005	0.013	.361
Kt/V	0.242	−0.060	0.544	.117
Antidepressant use				
No		REFERENCE		
Yes	−0.100	−0.435	0.235	.558
Use of walking aids				
No		REFERENCE		
Yes	−0.233	−0.484	0.017	.068
Walking speed				
Not slow		REFERENCE		
Slow	**−0.435**	**−0.695**	**−0.175**	**.001**
Physical Activity Index				
Inactive		REFERENCE		
Moderately inactive	−0.070	−0.775	0.634	.845
Moderately active	**−0.861**	**−1.48**	**−0.246**	**.006**
Active	−0.091	−0.964	0.783	.838
Self-rated health/100	**0.012**	**0.007**	**0.017**	**<.001**
Health change in the past year				
Better/The same		REFERENCE		
Worse	−0.180	−0.396	0.036	.102
Cognitive impairment				
No		REFERENCE		
Yes	**−0.308**	**−0.571**	**−0.045**	**.022**
Constant	**3.110**	**1.296**	**4.924**	**.001**

CONFLICT OF INTEREST STATEMENT

The authors have no relevant conflicts of interest to declare. The results presented in this paper have not been published previously in whole or part, except in abstract format.

ETHICS COMMITTEE APPROVAL

The study protocol was subject to favourable opinion by the South Birmingham Research Ethics Committee (Ref: 17/WM/0 381) and institutional review board assessment

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