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Original Article

ORIGINAL ARTICLE

Associations between depressive symptoms and disease progression in older patients with chronic kidney disease: results of the EQUAL study

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ABSTRACT

Background. Depressive symptoms are associated with adverse clinical outcomes in patients with end-stage kidney disease; however, few small studies have examined this association in patients with earlier phases of chronic kidney disease (CKD). We studied associations between baseline depressive symptoms and clinical outcomes in older patients with advanced CKD and examined whether these associations differed depending on sex.

Methods. CKD patients (≥65 years; estimated glomerular filtration rate ≤20 mL/min/1.73 m^2) were included from a European multicentre prospective cohort between 2012 and 2019. Depressive symptoms were measured by the five-item Mental Health Inventory (cut-off ≤70; 0–100 scale). Cox proportional hazard analysis was used to study associations between depressive symptoms and time to dialysis initiation, all-cause mortality and these outcomes combined. A joint model was used to study the association between depressive symptoms and kidney function over time. Analyses were adjusted for potential baseline confounders.

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Results. Overall kidney function decline in 1326 patients was –0.12 mL/min/1.73 m^2/month. A total of 515 patients showed depressive symptoms. No significant association was found between depressive symptoms and kidney function over time (P = 0.08). Unlike women, men with depressive symptoms had an increased mortality rate compared with those without symptoms [adjusted hazard ratio 1.41 (95% confidence interval 1.03–1.93)]. Depressive symptoms were not significantly associated with a higher hazard of dialysis initiation, or with the combined outcome (i.e. dialysis initiation and all-cause mortality).
Conclusions. There was no significant association between depressive symptoms at baseline and decline in kidney function over time in older patients with advanced CKD. Depressive symptoms at baseline were associated with a higher mortality rate in men.

Keywords: chronic kidney disease, clinical outcome, clinical trial, depressive symptoms, epidemiology, joint model, nephrology care, prospective cohort study, survival analysis

INTRODUCTION

Depressive symptoms are common in patients with chronic kidney disease (CKD), with a prevalence of 23–29% among patients with end-stage kidney disease (ESKD) [1, 2]. Previous studies have shown that depressive symptoms are associated with adverse health outcomes in patients with ESKD. A meta-analysis found that patients with depressive symptoms have a 1.5 times higher risk of mortality [3] and several other studies found comparable results regarding other clinical outcomes (e.g. hospitalization) [4–9]. The effect of depressive symptoms has also been explored in patients with advanced CKD not receiving dialysis, but not as extensively as in patients with ESKD. Earlier studies in this population show that depressive symptoms are associated with a higher rate of adverse outcomes [10–12]. However, these studies were conducted in small cohorts, with heterogeneous results [10–12]. Additionally, literature suggests that associations between depressive symptoms and adverse outcomes are stronger in men than in women on dialysis [13, 14]. To the best of our knowledge, no studies have been conducted to investigate whether this relationship indeed differs depending on sex in patients with advanced CKD.

It is of great importance to identify modifiable factors, such as depressive symptoms, affecting decline in kidney function. If depressive symptoms affect decline in kidney function indeed, adequate treatment of depressive symptoms may be used to impede disease progression and delay dialysis initiation in CKD patients. This is especially important because, once dialysis is initiated, health-related quality of life (HRQOL) deteriorates [15] and patients are exposed to dialysis-related health risks [16]. Specifically in older patients, maintaining HRQOL, rather than prolonging life, is emphasized during the decision process of initiating dialysis or starting conservative management [17]. Thus, considering the association between depressive symptoms and HRQOL [18, 19], it is particularly important to focus on depressive symptoms and associated outcomes of older patients with advanced CKD.

Taken together, this study aims to investigate associations between depressive symptoms and adverse outcomes in older patients with advanced CKD during nephrology care. The adverse outcomes studied include disease progression towards ESKD (i.e. decline in kidney function and time to dialysis initiation) and all-cause mortality. Second, this study aims to investigate whether these relationships differ depending on sex. It was hypothesized that depressive symptoms would be associated with faster disease progression and higher mortality, and that these associations would be stronger in men than in women [10–14].

MATERIALS AND METHODS

Study cohort

Data were obtained from the European Quality (EQUAL) study, an ongoing prospective observational cohort study of older patients with advanced CKD. Patients have been included since 2012 and originate from Germany, Italy, Sweden, Poland, the UK and the Netherlands. Inclusion criteria were as follows: age ≥65 years and estimated glomerular filtration rate (eGFR) that had dropped below 20 mL/min/1.73 m^2 for the first time during the past 6 months. Patients were excluded if the eGFR drop had resulted from an acute event, or if patients had received renal replacement therapy in the past. Included patients were followed until kidney transplantation, death or refusal of further participation. Follow-up ended on 24 April 2019, or earlier when patients were discharged to primary care or when treatment moved to another nephrology clinic. During participation, patients received routine medical care according to national treatment guidelines [based on the Kidney Disease Outcomes Quality Initiative (KDOQI)/Kidney Disease:Improving Global Outcomes (KDIGO) guidelines] [20]. A full description of the EQUAL study is published elsewhere [21]. For all participating centres, approval was obtained from the medical ethical committee or a comparable institutional board. All included patients gave written informed consent. The study was carried out in accordance with the declaration of Helsinki. Reporting was executed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [22].

Data collection

Demographic and clinical data were collected at baseline and subsequent 6-monthly follow-up visits. Dates of death, transplantation and dialysis initiation were registered, as well as causes of death and reasons for end of follow-up. Clinical data were entered into a web-based clinical record form by physicians and research nurses. Data on lifestyle and HRQOL were patient reported. Depressive symptoms were assessed using the validated five-question Mental Health Inventory (MHI-5) in each country's local language and showed a high internal consistency (Cronbach $\alpha = 0.835$) [23, 24]. MHI-5 scores ranges from 0 to 100, with a higher score indicating a better mental health (i.e. fewer depressive symptoms; Supplementary Appendix 1). A score ≤70 was used as cut-off for presence of depressive symptoms. This cut-off value was validated in patients with ESKD, with a sensitivity of 77% and specificity of 72% [25, 26]. The MHI-5 is a subset of questions from the Short Form 36

Health Survey (SF-36), representing its 'mental health' domain. The SF-36 has been validated in a variety of European countries, including Italy, Germany, the Netherlands, Sweden and the UK [25]. Following official SF-36 guidelines, the mental health score was calculated when minimal three of five questions were answered [26]. All laboratory tests and physical examinations were performed according to standard protocols of local participating nephrology centres. Data from different centres were standardized and recalculated into one uniform unit. Data will be shared on reasonable request to the corresponding author.

Statistical analyses

We used descriptive statistics to compute baseline characteristics. Average decline in eGFR was calculated by means of linear mixed modeling (LMM) with continuous kidney function (eGFR) as dependent variable and time as random variable. eGFR was updated every 6 months. Cox proportional hazard analysis was used to study associations between the presence of depressive symptoms at baseline and time to events (i.e. start of dialysis, all-cause mortality and combined adverse outcome) [27]. Associations between depressive symptoms at baseline and additional eGFR decline were studied by a joint model, combining longitudinal data (i.e. kidney function measurements) and time-to-event data (i.e. survival data such as time to events like dialysis initiation and mortality) [28, 29]. Depressive symptoms were included as dichotomous (cut-off value: 70) and continuous variables (scale 0–100) in separate Cox models. The model was adjusted for potential baseline confounders [age, sex, ethnicity, educational level, primary kidney disease (PKD), Charlson Comorbidity Index (CCI), body mass index (BMI), smoking status, nutritional status (Subjective Global Assessment: SGA), plasma albumin and urea levels], and adjusted for baseline eGFR. Time zero was the date patients completed the MHI-5. Patients were censored following kidney transplantation, discharge from nephrology clinic to primary care, withdrawal from study, lost-to-follow-up or end of follow-up, whichever came first. When start of dialysis was the outcome of interest, patients who had died were censored as well.

LMM was used to study the association between depressive symptoms at baseline and the change of kidney function per month. The LMM adequately takes into account a variable number of follow-up measurements and includes all measurements of patients who have been included in this study [30]. As we followed patients until death or dialysis initiation, missing eGFR values may be introduced when patients dropped out of the study due to mortality or were censored due to dialysis initiation. As eGFR is related to these events, we applied joint models to study the association between presence of depressive symptoms at baseline and change in eGFR over time, adjusted for informative drop-out due to death or dialysis initiation. The joint model combines Cox regression analysis with LMM in which presence of depressive symptoms was included as a fixed independent variable, time as both a fixed and random variable, and eGFR as a dependent variable [31]. The LMM included an interaction term (depressive symptoms*time), indicating additional eGFR change in the presence of depressive symptoms. The model was adjusted for the same potential baseline confounders as the Cox model. The joint model links the LMM described above to the Cox model, which captures the risk of the combined event of either mortality or dialysis. In this manner, the joint model informs the longitudinal eGFR trajectory on missingness caused by either dialysis initiation or death, and accounts for missing eGFR measurements due to drop-out. The LMM estimates may then be interpreted as the longitudinal eGFR trajectory in the hypothetical situation that none of the patients died or started dialysis.

To investigate differences in the effect of depressive symptoms on outcomes between men and women, all analyses were stratified for sex. To prevent loss of power and biased estimates, missing data were treated as follows: LMMs take into account missing outcomes (in this case eGFR) by maximum likelihood estimation [32] and missing baseline confounders were handled by multiple imputation with 10 iterations [33]. The following variables were included in the imputation model: sex, age, ethnicity, smoking status, comorbidities (including diabetes mellitus, cardiac disease, peripheral vascular disease, malignancies and lung disease), BMI, SGA, baseline eGFR, PKD, educational level, marital status, plasma albumin and urea levels, psychiatric disease and CCI. All continuous variables met the assumption for multiple imputation (i.e. normal distribution), except for urea; therefore, urea was log transformed before imputation. All statistical analyses were performed using SPSS (version 25; IBM), except for joint model analysis, which was performed with R (version 4.0.2; package JMbayes).

RESULTS

Baseline characteristics

Data were available from 1708 patients. Out of those, 1326 patients (78%) completed at least three out of five mental health questions at baseline and were included. There were no clinically relevant differences in baseline characteristics between patients with and without missing values.

Table 1 describes baseline characteristics for all patients, also stratified by presence of depressive symptoms (mental health score $\leq$70). Depressive symptoms were reported by 515 patients (39%), with median [interquartile range (IQR)] score of 56 (46–64), which was 88 (80–92) in patients without depressive symptoms. Compared with patients without depressive symptoms, patients with depressive symptoms were more often women ($P < 0.001$) and had more comorbidity ($P = 0.002$). Patients with depressive symptoms had more often a history of psychiatric disease ($P < 0.001$), particularly depression. Mean baseline eGFR was 18.8 mL/min/1.73 m^2, with no difference between patients with and without depressive symptoms ($P = 0.2$). Overall eGFR decline in all patients was –0.12 mL/min/1.73 m^2/month (95% CI –0.14 to –0.10). Median number of eGFR measurements was 2 (IQR 1–4), and 930 (70.1%) patients had one or more follow-up measurements in addition to their baseline measurement. An overview of baseline eGFR and all outcomes (both decline in kidney function and adverse clinical outcomes) analysed per group (with and without depressive symptoms; men and women) is shown in Table 2.

Depressive symptoms and time to adverse events

Median follow-up time was 24 (IQR 12–38) months, with maximum 78 months. During follow-up, 379 patients (28.6%) started dialysis, 30 patients (2.3%) received a kidney transplantation and 272 patients (20.5%) died (Supplementary Figures S1 and S2). There were no relevant differences in causes of death between the groups with and without depressive symptoms (Supplementary Table S1) ($P = 0.7$). Reasons for end of follow-up were as follows: wanting to stop study participation ($N = 66$; 5.0%), treatment taken over by general practitioner or

non-EQUAL centre (N = 87; 6.5%) or other reasons (N = 45; 3.4%). A total of 826 patients (62.3%) survived until end of follow-up.

Adjusted and unadjusted hazard ratios (HRs) for the entire cohort and stratified by sex are presented in Tables 3 and 4. Depressive symptoms were not significantly associated with earlier dialysis initiation [adjusted HR 1.05 (95% CI 0.84–1.31)], higher mortality risk [adjusted HR 1.26 (95% CI 0.98–1.63)] or combined adverse outcome [adjusted HR 1.15 (95% CI 0.97–1.36)]. In men, presence of depressive symptoms at baseline was associated with a higher mortality [adjusted HR 1.41 (95% CI 1.03–1.93)]. This result was also found in men using depressive symptoms as continuous variable [adjusted HR per

Table 1. Baseline characteristics of all patients, and stratified by patients with and without depressive symptoms

	All patients (N = 1326)	No depressive symptoms (N = 811; 61%)	Depressive symptoms (N = 515; 39%)	P-value
Demographic data				
Male sex, N (%)	883 (66.6)	588 (72.5)	295 (57.3)	<0.001
Age	75.74 ± 6.72	75.60 ± 6.64	75.97 ± 6.84	0.339
Country, N (%)				<0.001
Germany	138 (10.4)	85 (10.5)	53 (10.3)	
Italy	311 (23.5)	140 (17.3)	171 (33.2)	
The Netherlands	201 (15.2)	133 (16.4)	68 (13.2)	
Poland	51 (3.8)	30 (3.7)	21 (4.1)	
Sweden	292 (22.0)	212 (26.1)	80 (15.5)	
UK	333 (25.1)	211 (26.0)	122 (23.7)	
Ethnicity, N (%)[a,b]				0.204
White	1282 (96.7)	787 (97.0)	495 (96.1)	
Black	12 (0.9)	4 (0.5)	8 (1.6)	
Asian	10 (0.8)	7 (0.9)	3 (0.6)	
Mixed	4 (0.3)	3 (0.4)	1 (0.2)	
Level of education, N (%)[a,c]				<0.001
No education	28 (2.1)	7 (0.9)	21 (4.1)	
Low education	363 (27.4)	190 (23.4)	173 (33.6)	
Intermediate education	660 (49.8)	432 (53.3)	228 (44.3)	
High education	181 (13.7)	129 (15.9)	52 (10.1)	
Marital status, N (%)[a]				0.080
Married or living with partner	834 (62.9)	533 (65.7)	301 (58.4)	
Divorced or separated	92 (6.9)	53 (6.5)	39 (7.6)	
Widowed or partner has died	313 (23.6)	175 (21.6)	138 (26.8)	
Never married/lived with partner	51 (3.8)	31 (3.8)	20 (3.9)	
Smoking status, N (%)[a,d]	853 (64.3)	550 (67.8)	303 (58.8)	0.004
Clinical data				
Primary kidney disease, N (%)[a,e]				<0.001
Glomerular disease	125 (9.4)	94 (11.6)	31 (6.0)	
Diabetes	266 (20.1)	148 (18.2)	118 (22.9)	
Hypertension	472 (35.6)	310 (38.2)	162 (31.5)	
Other causes of kidney failure[f]	244 (18.4)	140 (17.3)	104 (20.2)	
Comorbidity, N (%)				
Diabetes mellitus[a]	535 (40.3)	306 (37.7)	229 (44.5)	0.013
Cerebrovascular disease[a,g]	195 (14.7)	120 (14.8)	75 (14.6)	0.599
Cardiac disease[a,h]	582 (43.9)	340 (41.9)	242 (47.0)	0.951
Peripheral vascular disease[a]	218 (16.4)	123 (15.2)	95 (18.4)	0.093
Malignancy[a,i]	275 (20.7)	163 (20.1)	112 (21.7)	0.394
Lung disease[a,j]	202 (15.2)	112 (13.8)	90 (17.5)	0.067
BMI, kg/m^2 [a]	28.26 ± 5.32	28.09 ± 4.87	28.54 ± 5.96	0.148
Nutritional status (SGA score)[a,k]				
Severely malnourished (1–2)	10 (0.8)	3 (0.4)	7 (1.4)	<0.001
Moderately malnourished (3–5)	328 (24.7)	169 (20.8)	159 (30.9)	
Normal nutritional status (6–7)	851 (64.2)	564 (69.5)	287 (55.7)	
CCI[a,l]	7.12 ± 1.86	6.99 ± 1.80	7.32 ± 1.95	0.002
eGFR (1.73 mL/min/m^2)[a,m]	18.80 ± 5.44	18.95 ± 5.21	18.58 ± 5.78	0.231
Plasma albumin level (g/L)[a]	37.76 ± 5.71	37.84 ± 5.65	37.64 ± 5.81	0.558
Plasma urea level (mmol/L)[a]	19.15 (15.40–24.1)	18.90 (15.31–23.80)	19.72 (15.47–24.61)	0.093
Systolic blood pressure (mmHg)[a]	142 ± 21.9	144 ± 21.9	140 ± 21.7	<0.001
Diastolic blood pressure (mmHg)[a]	74 ± 11.3	75 ± 11.6	73 ± 10.7	0.001
Heart rate (beats/min)[a]	71 ± 12.6	71 ± 13.2	71 ± 11.5	0.786
Plasma creatinine level (μmol/L)[a]	127 ± 94.8	137 ± 89.3	127 ± 103.0	0.844
Use of ACE inhibitors, N (%)[n]	262 (19.8)	185 (22.8)	77 (15.0)	<0.001

Table 1. Continued

	All patients (*N* = 1326)	No depressive symptoms (*N* = 811; 61%)	Depressive symptoms (*N* = 515; 39%)	P-value
Psychological/psychiatric data				
Psychiatric history, *N* (%)[a]	97 (7.3)	35 (4.3)	62 (12.0)	<0.001
Depression	58 (4.4)	17 (2.1)	41 (8.0)	
Dementia	15 (1.1)	7 (0.9)	8 (1.6)	
Use of antidepressants[n]	79 (7.7)	29 (4.8)	50 (11.5)	<0.001
Mental health score[o]	80 (60–92)	88 (80–92)	56 (46–64)	<0.001

Continuous variables are displayed as means ± standard deviation for normally distributed variables, and as median (boundaries of interquartile range) for skewed variables. Dichotomous and categorical variables are displayed as number (percentage). ACE, angiotensin-converting enzyme.
[a]Complete data available with the exception of the following variables: ethnicity 1308 (98.6%), level of education 1232 (92.9%), marital status 1290 (97.3%), smoking status 1289 (97.2%), PKD 1107 (83.5%), diabetes mellitus 1297 (97.8%), cerebrovascular disease 1283 (96.8%), cardiac disease 1187 (89.5%), peripheral vascular disease 1269 (95.7%), malignancy 1275 (96.2%), lung disease 1276 (96.2%), BMI 1230 (92.8%), nutritional status 1189 (89.7%), CCI 1290 (97.3%), eGFR 1303 (98.3%), plasma albumin level 1183 (89.2%), plasma urea level 1267 (95.6%), systolic blood pressure 1291 (97.4%), diastolic blood pressure 1291 (97.4%), heart rate 1166 (87.9%), plasma creatinine level 1303 (98.3%) and psychiatric history 1285 (96.9%).
[b]Ethnicity was investigator-assessed.
[c]Low: primary education only; intermediate: secondary school or vocational education; high: higher professional education, or university education.
[d]Patient-reported, smoking is defined as: currently smoking or smoked in the past.
[e]Primary kidney disease (PKD) was registered by the treating nephrologist, according to the diagnosis codes of the European Renal Association (ERA) [34].
[f]Comprising renal vascular disease, systemic diseases affecting the kidney, familial/hereditary nephropathies and miscellaneous renal disorders.
[g]Comprising ischaemic cerebrovascular accident/transient ischaemic attack and haemorrhagic cerebrovascular accident.
[h]Comprising myocardial infarct, angina pectoris, heart failure and left ventricular hypertrophy.
[i]Any malignancy, except for basal cell carcinoma and squamous cell carcinoma of the skin.
[j]Comprising chronic obstructive pulmonary disease and asthma.
[k]Subjective global assessment—seven-point scale, subjectively assessing the patient's nutritional status [35]. A higher SGA score indicates a better nutritional status.
[l]Score summarizing patient's disease status, based on comorbidity and age. A higher CCI score indicates a higher rate of comorbidity, and therefore a worse health status [36].
[m]eGFR—estimated glomerular filtration rate, calculated with the MDRD formula.
[n]Data on use of medication were not available for patients originating from Sweden. Data were available for 1032 patients (77.9%).
[o]Mental health score indicates the score on the MHI-5 questionnaire, with a higher score indicating a better mental health (range 0–100).

Table 2. Baseline eGFR, overall kidney function decline and incidence of adverse clinical outcomes, presented per subgroup

	Entire cohort (*N* = 1326)		Men (*N* = 883)		Women (*N* = 443)	
Outcome	No depressive symptoms (*N* = 811)	Depressive symptoms (*N* = 515)	No depressive symptoms (*N* = 588)	Depressive symptoms (*N* = 295)	No depressive symptoms (*N* = 223)	Depressive symptoms (*N* = 220)
Baseline eGFR ± SD[a] (mL/min/1.73 m^2)	18.95 ± 5.21	18.58 ± 5.78	18.83 ± 5.21	18.27 ± 5.59	19.26 ± 5.21	18.98 ± 6.01
Overall kidney function decline (95% CI)[b] (mL/min/1.73 m^2/month)	–0.14 (–0.16 to –0.11)**	–0.09 (–0.12 to –0.06)**	–0.16 (–0.19 to –0.14)**	–0.11 (–0.15 to –0.07)**	–0.07 (–0.12 to –0.03)*	–0.07 (–0.12 to –0.02)*
Start of dialysis[c], *N* (%)	237 (29.2)	142 (27.6)	189 (32.1)	95 (32.2)	48 (21.5)	47 (21.4)
All-cause mortality[d], *N* (%)	151 (18.6)	121 (23.5)	109 (18.5)	75 (25.4)	42 (18.8)	46 (20.9)
Combined adverse outcome[e], *N* (%)	388 (47.8)	263 (51.1)	298 (50.7)	170 (57.6)	90 (40.4)	93 (42.3)

[a]Estimated GFR—estimated glomerular filtration rate at baseline, calculated with the MDRD formula.
[b]Overall decline in kidney function, calculated by Linear Mixed Modelling.
[c]Number of patients that started dialysis during follow-up.
[d]Number of patients that died during follow-up.
[e]Number of patients that either started dialysis or died during follow-up.
*$P < 0.05$, **$P < 0.01$.

10 points 1.09 (95% CI 1.01–1.17)]. In men, having more depressive symptoms was associated with faster progression towards a combined adverse outcome [adjusted HR per 10 points 1.05 (95% CI 1.00–1.10)]. The association between depressive symptoms at baseline and all-cause mortality in men was also present when the analysis was additionally adjusted for country (Supplementary Table S2). In women, depressive symptoms were not significantly associated with adverse outcomes.

Depressive symptoms and eGFR decline

We found no significant association between depressive symptoms and kidney function over time in the joint model analyses accounting for drop-out (Table 5). In Supplementary Table S3, results of the LMM are shown (i.e. unadjusted for drop-out). Results of the LMM showed a small but statistically significant association between the presence of depressive symptoms at baseline and adjusted eGFR change over time [adjusted additional eGFR over time 0.05 mL/min/1.73 m^2/month (95% CI 0.01–0.09)]. This

Table 3. Association of the presence of depressive symptoms at baseline with time to start of dialysis, all-cause mortality and a combined adverse outcome

Outcome	Entire cohort		Men		Women	
	Crude HR (95% CI) ($N = 1326$)	Adjusted HR[a] (95% CI) ($N = 1326$)	Crude HR (95% CI) ($N = 883$)	Adjusted HR[a] (95% CI) ($N = 883$)	Crude HR (95% CI) ($N = 443$)	Adjusted HR[a] (95% CI) ($N = 443$)
Start of dialysis	1.03 (0.84–1.27)	1.05 (0.84–1.31)	1.15 (0.90–1.47)	1.08 (0.83–1.40)	1.05 (0.70–1.56)	1.19 (0.75–1.88)
All-cause mortality	1.38 (1.08–1.75)**	1.26 (0.98–1.63)	1.59 (1.19–2.14)**	1.41 (1.03–1.93)*	1.15 (0.76–1.75)	1.01 (0.64–1.58)
Combined adverse outcome[b]	1.16 (0.96–1.36)	1.15 (0.97–1.36)	1.31 (1.08 –1.58)**	1.20 (0.98–1.47)	1.09 (0.82–1.46)	1.10 (0.80–1.51)

The HR (95% CI) indicates the increased rate of an event (start of dialysis, all-cause mortality and combined adverse outcome) for the presence of depressive symptoms at baseline (i.e. a score ≤70 on the mental health score).
[a]Adjusted for age, sex, ethnicity, level of education, PKD, CCI, BMI, smoking status, SGA, eGFR at baseline, and plasma albumin and urea levels.
[b]Combined adverse outcome: either start of dialysis or all-cause mortality.
*$P < 0.05$, **$P < 0.01$.

Table 4. Association of the mental health score at baseline with time to start of dialysis, all-cause mortality and a combined adverse outcome

Outcome	Entire cohort		Men		Women	
	Crude HR (95% CI) ($N = 1326$)	Adjusted HR[a] (95% CI) ($N = 1326$)	Crude HR (95% CI) ($N = 883$)	Adjusted HR[a] (95% CI) ($N = 883$)	Crude HR (95% CI) ($N = 443$)	Adjusted HR[a] (95% CI) ($N = 443$)
Start of dialysis	1.02 (0.97–1.07)	1.02 (0.97–1.08)	1.05 (0.99–1.11)	1.03 (0.97–1.10)	1.03 (0.94–1.14)	1.03 (0.93–1.14)
All-cause mortality	1.09 (1.03–1.16)**	1.05 (0.99–1.12)	1.14 (1.06–1.22)**	1.09 (1.01–1.17)*	1.04 (0.95–1.15)	0.98 (0.89–1.09)
Combined adverse outcome[b]	1.05 (1.01–1.09)**	1.04 (1.00–1.08)	1.09 (1.04–1.14)**	1.05 (1.00–1.10)*	1.04 (0.97–1.11)	1.01 (0.94–1.08)

The HR (95% CI) indicates the increased rate of an event (start of dialysis, all-cause mortality and combined adverse outcome) for every 10 points decrease on the mental health score.
[a]Adjusted for age, sex, ethnicity, level of education, PKD, CCI, BMI, smoking status, SGA, eGFR at baseline, and plasma albumin and urea levels.
[b]Combined adverse outcome: either start of dialysis or all-cause mortality.
*$P < 0.05$, **$P < 0.01$.

significant result was also found in men [adjusted additional eGFR over time 0.05 mL/min/1.73 m^2/month (95% CI 0.00–0.10)]. These results imply a slower decline in eGFR over time associated with the presence of depressive symptoms at baseline. When additionally adjusting for drop-out, similar effects were found but were not significant anymore, as shown by the joint model results [entire cohort: adjusted additional eGFR over time 0.05 mL/min/1.73 m^2/month (95% CI –0.02 to –0.11)].

DISCUSSION

This study aimed to investigate associations between depressive symptoms and clinical outcomes in an international multicentre cohort of older patients with advanced CKD. Our results showed an association between depressive symptoms at baseline and all-cause mortality in men, but not in women. However, neither in men nor in women did we find a significant association between depressive symptoms at baseline and dialysis initiation, or with kidney function decline.

Previous studies investigating associations between depressive symptoms and clinical outcomes in patients with CKD did find an association between depressive symptoms and kidney function decline [10, 37, 38]. Recently, the association between depressive symptoms and faster kidney function decline was found in healthy adults [39]. It is possible that the sample size in our study was not large enough to detect small differences in kidney function decline related to depression using a joint model. Also, the absence of an association between depressive symptoms and faster decline in kidney function in our study might be explained by the relatively low number of eGFR measurements per patient. Otherwise, it is possible that the association between depressive symptoms and kidney function decline is more pronounced in earlier CKD stages than in advanced CKD. Presumably, in later CKD stages, other health-related factors such as physical condition are likely to be more influential on kidney function decline. The LMM analysis showed a small but statistically significant association between depressive symptoms at baseline and a slower decline in kidney function. Results of the joint model were similar, but not significant. This discrepancy in results (i.e. significance in the LMM, but not in the joint model results) may have been caused by the reduced power when using the joint model, which is also reflected by the broader 95% CIs in the joint model results compared with the LMM results.

Previous single-centre studies with smaller cohorts (between 100 and 568 participants) found an association between depressive symptoms and earlier dialysis initiation [10–12]. Follow-up of these studies was shorter than in our study, with the exception of Tsai *et al.* with a study duration equal to ours (i.e. 4-year follow-up) [10]. Moreover, baseline eGFR was higher in these previous studies compared with our study, and varied between 20 and 36 mL/min/1.73 m^2. In contrast, we did not observe a significant association between depressive symptoms and earlier dialysis initiation [10–12]. Considering the multicentre international character of our study, dialysis initiation might have differed considerably between institutions, which might

Table 5. The association of depressive symptoms with kidney function during follow-up, adjusted for competing events

	Entire cohort		Men		Women	
	Crude additional eGFR over time (95% CI) (N = 1326)	Adjusted additional eGFR over time[c] (95% CI) (N = 1326)	Crude additional eGFR over time (95% CI) (N = 883)	Adjusted additional eGFR over time[c] (95% CI) (N = 883)	Crude additional eGFR over time (95% CI) (N = 443)	Adjusted additional eGFR over time[c] (95% CI) (N = 443)
Presence of depressive symptoms[a]	0.05 (−0.01 to 0.11)	0.05 (−0.02 to 0.11)	0.05 (−0.04 to 0.14)	0.05 (−0.04 to 0.14)	0.00 (−0.16 to 0.16)	0.00 (−0.15 to 0.16)
10 points decrease in mental health score[b]	−0.01 (−0.03 to 0.00)	−0.01 (−0.03 to 0.00)	−0.01 (−0.03 to 0.01)	−0.01 (−0.03 to 0.01)	0.00 (−0.04 to 0.03)	0.00 (−0.04 to 0.03)

The additional effect on kidney function (95% CI) in mL/min/1.73 m^2/month is given for [a]the presence of depressive symptoms at baseline (i.e. a score ≤70 on the mental health score), and [b]for every 10 points decrease in mental health score. [c]Adjusted for age, sex, ethnicity, level of education, PKD, CCI, BMI, smoking status, SGA, and plasma albumin and urea levels.
*$P < 0.05$, **$P < 0.01$.

have influenced our results [40]. As we did not find a significant effect of depressive symptoms on kidney function, the absence of an association between depressive symptoms and dialysis initiation is expected. Furthermore, similar to previous studies in CKD patients [10–12], we did not observe an association between depressive symptoms and mortality in our complete study population (although we did observe this association in men). However, in ESKD patients, a meta-analysis did show a significant association between depressive symptoms and mortality [3]. This inconsistency—presence of an association between depressive symptoms and mortality in ESKD patients, but not in CKD patients—might partly be explained by the higher baseline risk of mortality in patients with ESKD [41]. It should also be noted that the HRs found in our study can be considered comparable to the HR found in the meta-analysis [HR 1.51 (95% CI 1.35–1.69)], but our confidence intervals are slightly too wide to conclude that our effects are significant. Moreover, adjusting for confounding remains a challenge given the all-encompassing nature of depression and the various potential mechanisms for adverse outcomes. Our adjustment for a large number of confounders may have led to overadjustment, emphasizing the importance of also considering our unadjusted results that do align with the meta-analysis results.

Interestingly, we found an increased risk of mortality in men with depressive symptoms, but not in women. This sex-specific effect has—to the best of our knowledge—not been reported previously in patients with advanced CKD [10–12]. Nevertheless, these findings correspond with those in other populations, where studies found a stronger effect of depressive symptoms on mortality in older men compared with older women [13, 14], and with the finding of Kop *et al*. that the association between depressive symptoms and acute kidney injury is stronger in men than in women [38]. Although it is well known that sex affects expression of affective disorders, mechanisms underlying the interaction between sex and adverse clinical outcomes have not yet been elucidated. It was hypothesized that men do not seek treatment until their symptoms are more severe [13, 42]. Thus, supposedly, when depression is recognized in men, it is often a more severe depression.

Several mechanisms could explain the association between depression and adverse clinical outcomes, such as the higher mortality we observed in male patients. First, depression is associated with maladaptive coping styles [43], which have been shown to predict mortality [44]. As such, depressive symptoms are associated with decreased treatment compliance in ESKD patients [45, 46]. Furthermore, biological effects of depression, such as activation of the hypothalamic–pituitary–adrenal axis and increased autonomic nerve system activity might lead to increased systemic inflammation and higher risk of cardiovascular events [47–49]. Presumably, a combination of behavioral and biological factors related to depression collectively results in adverse health outcomes. Recently, a Mendelian randomization study showed an association between positive life affect and lower risk of CKD, and a negative association between depressive symptoms and eGFR [50]. This suggests a causal link between psychological characteristics and kidney function, despite non-significance in our results.

The strengths of this study include the multicentre design including patients in various countries, long follow-up duration and large sample of patients. Also, this is the first study using a joint model to account for informative drop-out in the association between depressive symptoms and adverse outcomes in CKD patients. However, our study also has limitations. First, 1326 out of 1708 patients (77.6%) answered at least three MHI-5

questions at baseline and were included, which might have led to selection bias. Second, missing data on baseline confounders might have led to biased results. However, we handled missing data with multiple imputation and maximum likelihood estimation to prevent a loss of power and biased estimates [33]. Moreover, no relevant differences were observed between patients with and without missing data, and results from analyses without imputation of missing data on confounders showed comparable results. Therefore, it is unlikely that our results were biased due to missing data. Third, ethnicity is an important factor in the relationship between depression and mortality, but our population consisted almost exclusively of Caucasian people (96.7%) [51]. A more heterogeneous population would have increased generalizability. Fourth, the observational design prevents the drawing of conclusions about causality. Although we adjusted for important baseline confounders, residual confounding is possible [34]. The similarity in the symptoms and aetiology of depression and CKD further complicates conclusions about causality [35]. However, as mentioned above, results of a Mendelian randomization suggest a causal association between positive life affect and lower CKD incidence [50]. Presumably, there is an interplay between disease progression and development of depressive symptoms. Fifth, we executed our analyses with eGFR estimated by both the Modification of Diet in Renal Disease (MDRD) formula and Chronic Kidney Disease Epidemiology Collaboration formula ensuring precise estimation of kidney function. However, accuracy of both formulas diminishes in patients with advanced age and severe CKD [36]. Finally, although our questionnaire was validated extensively, using other methods for assessing depressive symptoms (e.g. more extensive questionnaires like the Beck Depression Inventory) could potentially have resulted in greater robustness of our results [26].

This study demonstrates an association between depressive symptoms at baseline and higher mortality in men. Thus, it is possible that at least in men, antidepressant treatment might not only improve HRQOL [18, 19], but could potentially improve survival. One potential strategy to improve outcomes is cognitive behavioural therapy, which is effective in ESKD patients [52, 53]. Randomized controlled trials are needed to evaluate its effect in patients with advanced CKD. Another topic for future research is development of depressive symptoms during nephrology care in relation to adverse outcomes. The latter is important because Kimmel *et al.* found a stronger association between depressive symptoms and mortality when depression was treated as time-varying covariate instead of baseline predictor [6].

In conclusion, we found that depressive symptoms are associated with higher mortality in older men with advanced CKD. As the association between depressive symptoms and all-cause mortality was particularly observed in men, professionals should especially be aware of depressive symptoms in older male patients with CKD. Because this association could already be observed before ESKD, attention for and detection of depressive symptoms in men with earlier CKD stages is of great importance.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

Research idea and study design: F.W.D., Y.M., B.C.E.M.; data acquisition: K.J.J., F.J.C., M.E., F.W.D., C.W.; statistical analysis: B.C.E.M., N.C.C., Y.M.; data interpretation: all authors; supervision or mentorship: Y.M., F.W.D. Each author contributes important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

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APPENDIX

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