Ethnic differences in survival on dialysis in Europe

van den Beukel, T.O.

2013

5

Short-term versus long-term effects of depressive symptoms on mortality in patients on dialysis

S. van Dijk
T.O. van den Beukel
F.W. Dekker
S. le Cessie
A.A. Kaptein
A. Honig
C.E.H. Siegert
E.W. Boeschoten
R.T. Krediet
M. Verduijn

Psychosom Med 74:854-860, 2012

ABSTRACT

Objective Depressive symptoms seem to pose a risk factor for mortality among patients on dialysis. It is currently unknown whether the association is only short-lived and whether associations over time depend on specific causes of mortality.

Methods In a prospective nationwide cohort study, 1528 patients with end-stage renal disease starting on dialysis completed the Mental Health Inventory. Patients were observed up to five years or until the end of follow-up in April 2011. Cox regression analyses were used to calculate associations between depressive symptoms and short-term (0-6 months), medium-term (6-24 months), or long-term (24-60 months) cardiovascular and noncardiovascular mortality.

Results The adjusted hazard ratio (HR) was 1.43 (95% confidence interval [CI] 1.08-1.88) for cardiovascular mortality and 2.07 (95% CI 1.62-2.64) for noncardiovascular mortality. Depressive symptoms posed a strong risk factor for noncardiovascular mortality at the short-term (HR 2.82, 95% CI 1.58-5.05), medium-term (HR 2.08, 95% CI 1.40-3.09), and long-term (HR 1.84, 95% CI 1.26-2.69), whereas the association between depressive symptoms and cardiovascular mortality was not observed during the first 6 months of follow-up (HR 1.03, 95% CI 0.49-2.15).

Conclusion Depressive symptoms at the start of dialysis therapy are associated with short-, medium-, and long-term mortality. The cause-specific mortality risk over time may help clinicians to understand multifactorial causes of the association between depressive symptoms and survival.

INTRODUCTION

Depressive symptoms are highly prevalent in patients with end-stage renal disease (ESRD), and there is growing evidence that the presence of depressive symptoms poses a risk factor for mortality in these patients.[1-3] To understand the underlying mechanisms of depressive symptoms as a risk factor, more in-depth data about how depressive symptoms relate to mortality are needed. We currently do not know whether the effect of depressive symptoms on mortality is only short-lived or whether depressive symptoms at baseline also remain a predictor of poor survival at the long-term. There is a lack of knowledge about whether the effect of depressive symptoms on short-term mortality differs from its effect on long-term mortality because the time of follow-up in most studies was limited to 2 years. The few studies using time-varying methods, however, suggest that variations in the length of follow-up do influence the observed results.[4;5] Stronger effects of depressive symptoms on mortality were observed when the assessment of depressive symptoms was closer to the evaluation of medical outcomes, which may indicate that the effect of depression on mortality is only short-lived.

These findings regarding time-specific associations are important and need further clarification to understand the underlying mechanisms between depression and survival. It may provide information about the extent to whether the association can be explained by a poor somatic health that is accompanied by depressive symptoms or whether depressive symptoms result in a poor illness trajectory. If the effect of depressive symptoms on mortality is only short-lived indeed, this may suggest that the association between depressive symptoms and mortality is mainly caused by a poor somatic health. On the other hand, if depressive symptoms are especially associated with increased risk of mortality in the long-term, this may suggest that possible underlying processes unfold over time (e.g., by depressive symptoms influencing health behavior or via interactive effects on the immune system).

Besides comparing short- and long-term follow-up, it is important to distinguish between causes of mortality to explain the association between depressive symptoms and mortality. Traditionally, there has been considerable attention for depressive symptoms as a risk factor for cardiovascular mortality[6-8], whereas in patients with ESRD, noncardiovascular mortality may be affected by depression as well.[1;3;9]

In the current study, we measured depressive symptoms in a large cohort of incident patients on hemodialysis (HD) and peritoneal dialysis (PD) participating in a Dutch nationwide study, The Netherlands Co-operative Study on the Adequacy of Dialysis (NECOSAD). Investigating the effects of depressive symptoms in a sample of patients on dialysis is important because the potential detrimental effects of depressive symptoms at the start of dialysis on mortality are not well known. To the best of our knowledge, only two studies investigated whether depressive symptoms at the start of dialysis are associated with poor survival in patients on dialysis.[4;10] The aim of the current study was to investigate the short-, medium-, and long-term effects of depressive symptoms on cardiovascular and noncardiovascular mortality.

METHODS

Patients

Data were collected within the framework of NECOSAD, a prospective observational study among incident patients on HD and PD in 38 centers in the Netherlands between 1997 and 2007. Eligible patients were older than 18 years and had no history of renal replacement therapy. The study was approved by all local medical ethics committees, and all patients gave written informed consent before inclusion. The patients were observed from the start of dialysis until death or censoring (i.e., transfer to a nonparticipating dialysis center, withdrawal from the study, renal transplantation, recovery of kidney function, or end of the follow-up period in April 2011). To allow for stabilization of laboratory data and treatment modality, the baseline measures were taken at 3 months after the start of dialysis.

Measures

The following data were collected: sociodemographics, primary cause of kidney disease (using the European Renal Association-European Dialysis and Transplant Association coding system)[11], dialysis modality, residual glomerular filtration rate (rGFR; calculated as the mean of creatinine and urea clearance corrected for body surface area (in milliliters per minute per 1.73 m^2), body mass index, the Davies comorbidity index indicating the level of comorbidity (no, intermediate, severe)[12], the presence of diabetes mellitus, and the presence of cardiovascular disease (defined as having a history of myocardial infarction, angina pectoris, peripheral vascular disease, or cerebrovascular accident). Laboratory data comprised serum albumin level, hemoglobin, plasma calcium and phosphorus, intact parathyroid hormone

(iPTH), creatinine, and C-reactive protein (CRP) at baseline (i.e., at 3 months after starting dialysis).

Depressive symptoms were assessed at baseline using the Mental Health Inventory of the Kidney Disease-Specific Quality of Life Short Form, which has been validated as a reliable measure of detecting depressive symptoms in different populations.[13-16] The questionnaire includes five questions about how often during the past month patients had felt "downhearted and blue," "calm and peaceful," "happy," "nervous," and "so down in the dumps that nothing could cheer them up." Items were scored on a 6-point scale, varying from all of the time to none of the time. The reliability of the scale was good (Cronbach α = .82). The scores were summed and transformed to a scale ranging from 0 to 100. Depressive symptoms were assessed in a dichotomous manner using a cutoff of 52 (depressive symptoms present when the Mental health scores were $\leq$ 52). This cutoff showed a good specificity and sensitivity for detecting depressive symptoms in chronically ill patients (i.e., sensitivity of 83%, specificity of 65%)[17] and has been used previously in patients with ESRD.[4]

End points

Causes of death were classified according to the codes of the European Renal Association-European Dialysis and Transplant Association.[11] We defined cardiovascular mortality as death due to myocardial ischemia and infarction, hyperkalemia, hypokalemia, (hypertensive) cardiac failure, fluid overload, cerebrovascular accident, hemorrhage from ruptured vascular aneurysm, cardiac arrest, or mesenteric infarction and if the cause of death was coded as unknown. We designed all other causes of mortality as being noncardiovascular, that is, infection, malignancies, suicide or refusal of further treatment, cachexia, and miscellaneous.

Statistical analysis

To compare sociodemographic and medical characteristics between patients with and without depressive symptoms, 2-tailed *t* tests and X^2 tests were conducted. Cumulative mortality curves for overall survival were calculated with competing risk analysis, taking into account cause of mortality as a competing end point.[18]

Cox proportional hazard ratios (HRs) were calculated with 95% confidence intervals (95% CIs) to assess the overall association between depressive symptoms and all-cause mortality, cardiovascular mortality, and noncardiovascular mortality up to 5 years after baseline. We also checked whether the pattern of results remained similar if depressive symptoms were

analyzed as a continuous variable. To explore the association between depressive symptoms and specific causes of noncardiovascular mortality, we calculated HRs for mortality due to infection, malignancies, suicide or refusal of further treatment, and other noncardiovascular mortality separately.

To obtain a clear-cut comparison of the effects of depressive symptoms on short- and long-term mortality, HRs were calculated for three different periods after the assessment of depressive symptoms at baseline (i.e., at 3 months after starting dialysis): a) short-term mortality (0-6 months after baseline); b) medium-term mortality (6-24 months after baseline), and c) long-term mortality (24-60 months after baseline). As a consequence, medium- and long-term mortalities were conditional on having survived the previous period. Short-, medium-, and long-term effects of depressive symptoms at baseline were assessed for all-cause mortality, cardiovascular mortality, and noncardiovascular mortality. Time-dependent Cox regression analyses in which all three time periods were included were conducted to explore trends over time.

Both crude and adjusted analyses were conducted. On the basis of previous reports about depressive symptoms and mortality among patients with ESRD, we adjusted for age, sex, marital status, having children, ethnicity, educational level, being employed, dialysis modality, primary cause of renal disease, Davies comorbidity index, rGFR, body mass index, hemoglobin, iPTH, plasma phosphorus, serum albumin, and creatinine at baseline. All variables had less than 8.2% missing values, except for rGFR, which was missing for 16.5% of the patients. Missing values were imputed using standard multiple imputation methods (10 repetitions) in SPSS statistical software version 17.0 (SPSS, Chicago, IL), where missing data are imputed by multiple predictions based on the other known characteristics.[19;20] Because CRP was available for 716 (46.9%) of 1528 participants only, we did not include CRP in the mortality analyses. However, sensitivity analyses were conducted with imputed CRP as an additional covariate in all multivariate Cox regression analyses. Finally, sensitivity analyses were conducted to check whether results remained similar if all patients were excluded of whom the cause of death was unknown. All *p* values are reported 2 sided and were considered significant at a level less than 0.05.

Table 1. Characteristics of patients with and without depressive symptoms * at 3 months after starting dialysis treatment.

	Depressive symptoms not present (n = 1181)	**Depressive symptoms present (n = 347)**	***p***
Sociodemographic characteristics			
Age, years	59.1 (15.2)	62.3 (13.1)	<.001
Sex, % men	63.6	54.9	0.003
Education, % low	52.4	67.2	<.001
Married, % yes	72.8	69.0	0.166
Having children, % yes	77.5	80.5	0.239
Employed, % yes	23.8	12.3	<.001
Ethnicity, % white	94.1	90.5	0.020
Clinical			
Modality, % hemodialysis	62.4	67.2	0.100
BMI, kg/m²	24.7 (4.0)	25.0 (4.7)	0.394
Cause of ESRD, %			0.006
Diabetes Mellitus	13.3	19.7	
Glomerulonephritis	14.2	10.7	
Renal vascular disease	15.8	18.2	
Other	56.8	51.4	
Comorbidity			
Davies comorbidity, %			<.001
No	53.1	35.7	
Intermediate	40.1	50.4	
Severe	6.8	13.9	
Diabetes Mellitus, % yes	18.8	26.4	0.002
Cardiovascular disease, % yes	30.7	47.2	<.001
Laboratory			
Residual GFR, ml/min per 1.73m²	3.9 (2.8)	4.5 (4.1)	0.023
Albumin, g/dL	3.7 (5.1)	3.5 (5.3)	<.001
Hemoglobin, g/dL	11.3 (1.6)	11.0 (1.6)	0.005
Phosphorus, mmol/L	1.8 (0.5)	1.7 (0.5)	0.007
iPTH, pmol/L	24.2 (30.9)	19.3 (26.0)	0.004
Creatinine, umol/L	774.8 (243.1)	709.9 (250.1)	<.001
CRP, mg/L	11.0 (22.6)	16.9 (26.9)	0.014

Continuous variables are displayed as means (standard deviation) and statistical tests include 2-tailed *t* tests and X^2 tests.

BMI = body mass index; ESRD = end-stage renal disease; GFR = glomerular filtration rate; iPTH = intact parathyroid hormone; CRP = C-reactive protein.

* Depressive symptoms defined as a dichotomous variable (MHI $\leq$ 52 versus MHI > 52).

RESULTS

Questionnaire data were available for 1528 of 1956 patients who were registered as participants at baseline (78.1%). Patients who did complete the questionnaire were more often treated with PD (p=.003), were more often white (p<.001), had relatively often glomerulonephritis (p=.004), were more often married (p=.029), tended to be younger (p=.052), and had less often cardiovascular diseases (p=.002). For all other sociodemographic and comorbidity indicators, no differences were observed.

Of the 1528 patients who completed the baseline questionnaire, 22.7% reported depressive symptoms (i.e., mental health score $\leq$ 52). Patients with depressive symptoms were older, more often women, lower educated, more often nonemployed, and more often nonwhite (Table 1). Furthermore, compared with patients without depressive symptoms, patients with depressive symptoms comprised a group of patients with a higher level of comorbidity (Davies comorbidity index, diabetes mellitus, and cardiovascular diseases) and CRP; lower levels of serum albumin, creatinine, hemoglobin, iPTH, and phosphorus; and better renal functioning (rGFR).

Depressive symptoms and mortality

For 5 years after starting dialysis treatment, 671 patients were censored before reaching the end of the study period (435 patients were transplanted, 54 patients were transferred to a nonparticipating dialysis center or the center discontinued study participation, 159 patients withdrew from the study, and 23 patients had a recovery of renal function). Patients who were transplanted during follow-up experienced less depressive symptoms (p<.001), whereas the few patients who recovered reported more depressive symptoms at baseline (p=.017). No relation between depressive symptoms at baseline and either study withdrawal (p=.61) or switching between centers (p=.68) was observed. During follow-up, 590 (38.7%) deaths occurred, of which 274 (46.5%) related to a cardiovascular cause. Crude cumulative mortality during the 5-year follow-up for both cardiovascular and noncardiovascular reasons was greater in patients with depressive symptoms than in patients without depressive symptoms (Figure 1).

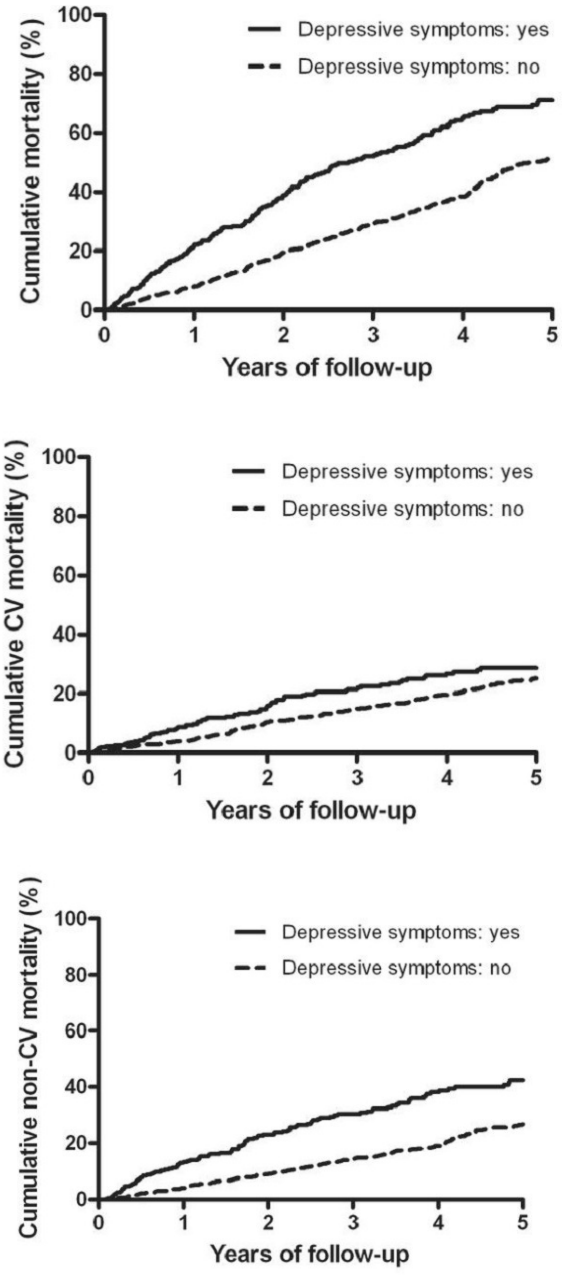

Figure 1. Crude cumulative all-cause, cardiovascular, and noncardiovascular mortality during a 5-year follow-up for patients with and without depressive symptoms.

Table 2 shows crude and adjusted HRs for depressive symptoms of all-cause, cardiovascular, and noncardiovascular mortality. Depressive symptoms were associated with a 1.5-fold increase for cardiovascular and a 2-fold increase for noncardiovascular mortality during the 5-year follow-up after adjustment for a wide range of demographic and clinical variables. Adjusting for laboratory measures (i.e., rGFR, hemoglobin, iPTH, plasma phosphorus, serum albumin, and creatinine) after stepwise adjustment for sociodemographic and clinical variables hardly attenuated the HRs (see Supplementary Table S1). Furthermore, we repeated all analyses with depressive symptoms as a continuous variable (reversed score). This did not change the overall pattern of results (cardiovascular mortality crude HR 1.012, 95% CI 1.006-1.019, adjusted HR 1.008, 95% CI 1.002-1.014; noncardiovascular mortality crude HR 1.023, 95% CI 1.017-1.029, adjusted HR 1.017, 95% CI 1.012-1.023).

To explore the association between depressive symptoms and specific causes of noncardiovascular mortality, HRs were calculated for death due to infection, malignancy, suicide or refusal of further treatment, and other noncardiovascular causes (Table 2). Depressive symptoms were related to all four categories of noncardiovascular causes, also after controlling for demographic and clinical variables.

Table 2. Association between depressive symptoms and overall mortality and mortality specified by cause at 5-year follow-up.

	Events,	Crude		Adjusted *	
	n	HR (95% CI)	*p*	HR (95% CI)	*p*
All-cause	590	2.04 (1.71-2.42)	<.001	1.75 (1.46-2.10)	<.001
Cardiovascular	274	1.68 (1.29-2.20)	<.001	1.43 (1.08-1.88)	.011
Noncardiovascular	316	2.38 (1.88-3.00)	<.001	2.07 (1.62-2.64)	<.001
Infection	80	1.98 (1.23-3.21)	.005	1.76 (1.07-2.90)	.025
Malignancy	46	3.06 (1.70-5.51)	<.001	2.84 (1.53-5.28)	.001
Suicide or refusal	62	2.15 (1.26-3.66)	.005	1.89 (1.08-3.30)	.026
Other	128	2.53 (1.76-3.64)	<.001	2.14 (1.46-3.12)	<.001

HR = hazard ratio; CI = confidence interval.

* Adjusted for age, sex, marital status, having children, ethnicity, educational level, being employed, dialysis modality, primary cause of renal disease, Davies comorbidity, glomerular filtration rate, body mass index, hemoglobin, intact parathyroid hormone, phosphorus, serum albumin, and creatinine.

Depressive symptoms and short-, medium-, and long-term mortality

In the short-term (0-6 months), medium-term (6-24 months), and long-term (24-60 months), 86 (36 cardiovascular, 50 noncardiovascular), 229 (116 cardiovascular, 113 noncardiovascular), and 275 (122 cardiovascular, 153 noncardiovascular) deaths occurred, respectively. Depressive symptoms at baseline were associated with short-, medium-, and long-term all-cause mortality, with adjusted HRs ranging from 1.61 till 1.93 (Table 3). The patterns of depressive symptom-related cardiovascular and noncardiovascular mortality differed (Table 3). The association between depressive symptoms and noncardiovascular mortality was present at the short, medium, and long terms. The HR for noncardiovascular mortality was most pronounced at the short-term, whereas short-term cardiovascular mortality was not elevated among patients with depressive symptoms. The varying risks associated with depressive symptoms over time were supported by a significant interaction between depressive symptoms and time for all-cause mortality (unadjusted HR 0.79, 95% CI 0.62-1.00) and noncardiovascular mortality (unadjusted HR 0.69, 95% CI 0.50-0.94) but not for cardiovascular mortality (unadjusted HR 0.95, 95% CI 0.65-1.39).

Table 3. Association between depressive symptoms and short-, medium-, and long-term mortality *.

	Short-term follow-up (0-6 months)		**Medium-term follow-up (6-24 months)**		**Long-term follow-up (24-60 months)**	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
All-cause crude	2.84 (1.86-4.35)	<.001	2.20 (1.67-2.88)	<.001	1.66 (1.26-2.19)	<.001
All-cause adjusted †	1.93 (1.24-3.03)	.004	1.77 (1.34-2.35)	<.001	1.61 (1.19-2.16)	.002
Cardiovascular crude	1.78 (0.89-3.57)	.102	1.85 (1.25-2.74)	.002	1.49 (0.97-2.28)	.070
Cardiovascular adjusted †	1.03 (0.49-2.15)	.942	1.51 (1.00-2.26)	.050	1.38 (0.89-2.15)	.156
Noncardiovascular crude	3.91 (2.24-6.80)	<.001	2.60 (1.78-3.80)	<.001	1.80 (1.25-2.60)	.002
Noncardiovascular adjusted†	2.82 (1.58-5.05)	<.001	2.08 (1.40-3.09)	<.001	1.84 (1.26-2.69)	.002

HR = hazard ratio; CI = confidence interval.

* Numbers of events during follow-up were as follows: short-term cardiovascular, n=36; noncardiovascular, n=50; medium-term cardiovascular, n=116; noncardiovascular, n=113; long-term cardiovascular, n=122; and noncardiovascular, n=153.

† Adjusted for age, sex, marital status, having children, ethnicity, educational level, being employed, dialysis modality, primary cause of renal disease, Davies comorbidity, glomerular filtration rate, body mass index, hemoglobin, intact parathyroid hormone, phosphorus, serum albumin, and creatinine.

Sensitivity analyses

CRP was included in all analyses as an additional covariate. This did not change the results (cardiovascular mortality adjusted HR 1.41, 95% CI 1.06-1.86, noncardiovascular mortality adjusted HR 2.03, 95% CI 1.59-2.59). Finally, all analyses were conducted, excluding patients of whom the cause of death was unknown. Also, for these sensitivity analyses, the data were not materially different (cardiovascular mortality crude HR 1.69, 95% CI 1.29-2.20, adjusted HR 1.41, 95% CI 1.07-1.86; noncardiovascular mortality crude HR 2.43, 95% CI 1.91-3.08, adjusted HR 2.12, 95% CI 1.65-2.72).

DISCUSSION

The current study provides further evidence about depressive symptoms being associated with poor survival among patients with ESRD. Importantly, during the 5-year follow-up, depressive symptoms 3 months after the initiation of dialysis were associated with a 1.5-fold increased cardiovascular mortality risk and a 2-fold increased noncardiovascular mortality risk, even after adjustment for a wide array of covariates. To the best of our knowledge, only two studies investigated the effect of depressive symptoms on mortality in incident patients on dialysis.[4;10] Consistent with our findings, Chilcot et al.[10] observed a significant association between baseline depressive symptoms and all-cause mortality. Because of a relatively small sample size (n=160), specific type of mortality was not considered in this study. In addition, Boulware et al.[4] observed an association between depressive symptoms and cardiovascular and all-cause mortality if time-varying analyses were applied. Interestingly, only noncardiovascular mortality was related to baseline depressive symptoms. Both studies reported mortality risk using a relatively short follow-up period and did not differentiate between short- and long-term mortalities.

In the current study, crude and adjusted associations between depressive symptoms at baseline and subsequent all-cause mortality were observed at short-term (0-6 months), medium-term (6-24 months), and long-term follow-up (24-60 months). Hence, in this large multicenter study of patients with ESRD, a simple assessment of patients' depressive symptoms at the start of HD or PD therapy seems to be a lasting marker of poor chances for survival. However, the patterns of results for short-, medium-, and long-term follow-up differed greatly if we considered either cardiovascular or noncardiovascular mortality: at the short-term, depressive symptoms at baseline seem to put patients especially at risk for

noncardiovascular mortality, whereas increased risks of cardiovascular mortality were not observed at short-term follow-up.

These findings are important for discovering the underlying mechanism between depressive symptoms and poor survival. Several possible explanations for the association can be provided. First, the effect may be attributed to so-called reversed causality. This means that disadvanced health resulted in increased depressed symptoms, instead of depressive symptoms resulting in a poor medical trajectory. In line with this, patients with depressive symptoms comprised a group of patients with higher prevalent comorbidity at baseline already, although contrary to what would be expected from the literature[21], renal function was better for patients with depressive symptoms. Because patient characteristics differed at baseline, we did carefully control for a large set of sociodemographic, medical, and laboratory characteristics, but this only slightly attenuated the effects we found. However, it is still possible that other comorbid disease characteristics could explain at least a part of the association between depressive symptoms and mortality. The observation that, after adjustment for a set of confounding factors, depressive symptoms did not seem to be a risk factor for cardiovascular mortality during the first 6 months is an indication that reversed causality may at least only partially explain the association between depressive symptoms and mortality.

Other suggested pathways consider the potentially bidirectional relation between depressive symptoms and immune system activity.[1;2;22] Evidence links depressive symptoms and proinflammatory cytokines[23-25], which also play a role in the pathogenesis of cardiovascular disease. Proinflammatory cytokines related not only to cardiovascular disease but also to the occurrence of infections. Interestingly, adjusting for serum albumin and also for CRP did not change the overall pattern of results, which may suggest that other factors contributed to the effect of depressive symptoms on mortality. Moreover, depressive symptoms seemed to pose a risk factor for all different causes of mortality. Additional explorative analyses did not reveal a specific noncardiovascular cause: The risk of infection-related mortality, cancer-related mortality, and suicide or refusal of further treatment all increased in patients with depressive symptoms. The nonspecific causes of mortality in combination with our results regarding the varying effects of depressive symptoms on short-, medium-, and long-term cardiovascular and noncardiovascular mortality suggest that future researchers should not limit their focus to a single biological pathway to explain the detrimental effects of depressive symptoms on mortality. Rather, multifactorial explanations

that involve a dynamic interplay between biological pathways and behavioral mediators should be considered.

Indeed, the potential impact of behavioral mediators in patients with ESRD and how these influence biological functioning has been underresearched to date.[2;26] Several studies show that depressive symptoms are related to poor health behavior such as detrimental life-style behaviors like smoking[27;28] and low levels of physical activity.[29] Depressive symptoms also predict low compliance with several aspects of therapy such as medication intake[30] and adhering to fluid restrictions,[31] which is a risk factor for mortality as well.[32;33] These factors should be incorporated to understand the underlying mechanisms between depressive symptoms and mortality.

The relation between depressive symptoms and negative health outcomes raises the question whether an adequate treatment of depressive symptoms is beneficial for patients with ESRD. Some encouraging results from trials providing cognitive behavioral therapy and antidepressants to target depression in HD patients suggest that modest improvements in well-being and quality of life might be expected from treatment.[34;35] This is important for clinical practice because, with an estimated prevalence of depression being between 20% and 30%[1], the burden of depressive symptoms among patients with ESRD is extensive. Clinicians should detect and treat depressive symptoms as early as possible. The current study shows that depressive symptoms at baseline are relatively strongly related to noncardiovascular mortality in the first 6 months, which underscores that it might be vital to detect depressive symptoms in an early phase. However, there is no evidence that screening and ameliorating depressive symptoms also positively influence the risk of mortality.[36;37]

Several limitations of the current study should be noted. First, not all participants of the NECOSAD study completed the questionnaires, which may influence the representativeness of the results of the whole population on dialysis. For example, responders seemed to experience cardiovascular diseases less often than did nonresponders. Second, although the 5-item Mental Health Inventory has been validated as a sound measure of depressive symptoms[13-17], the scale is not commonly used as a measure of depressive symptoms in patients with ESRD. A specific strength of the mental health scale is that it does not include somatic symptoms that can be attributed to both uremic symptoms of ESRD and depression. A practical advantage of the Mental Health Inventory is the brief format, which makes it feasible for recurrent assessments in standard care protocols.

CONCLUSION

The current study suggests that in the starting period of dialysis therapy already, depressive symptoms are a marker of subsequent mortality at the short, medium, and long terms. Furthermore, depressive symptoms seem to pose a strong risk factor for noncardiovascular mortality at the short-term, whereas cardiovascular mortality does not increase at the short-term yet. Hitherto, researchers have especially focused on cardiovascular pathways to understand the relation between depressive symptoms and mortality.[6-8] Our findings show that the association between depressive symptoms and specific causes of noncardiovascular mortality needs serious attention as well. Future studies should consider the effect of time and specific cause of mortality to unravel the underlying biological and psychological mechanisms.

ACKNOWLEDGEMENTS

We thank the patients and staff of all participating hospitals and dialysis centers and the staff of the NECOSAD trial office for their assistance in the collection and management of the data for this study. The contribution of Tessa O. van den Beukel was supported by a research fellowship of the European Renal Association-European Dialysis and Transplant Association (53-2009).

Supplementary Table 1. Association between depressive symptoms and mortality, specified by cause at 5-year follow-up with gradually more complex adjustment steps.

	Events, n	Crude HR (95% CI)	Step 1 Adjusted * HR (95% CI)	Step 2 – Adjusted † HR (95% CI)	Step 3 – Adjusted ‡ HR (95% CI)
All-cause	590	2.04 (1.71-2.42)	1.94 (1.63-2.32)	1.79 (1.49-2.14)	1.75 (1.46-2.10)
Cardiovascular	274	1.68 (1.29-2.20)	1.61 (1.23-2.12)	1.46 (1.11-1.92)	1.43 (1.08-1.88)
Noncardiovascular	316	2.38 (1.88-3.00)	2.25 (1.78-2.86)	2.10 (1.65-2.67)	2.07 (1.62-2.64)
Infection	80	1.98 (1.23-3.21)	1.85 (1.14-2.98)	1.83 (1.12-2.98)	1.76 (1.07-2.90)
Malignancy	46	3.06 (1.70-5.51)	3.25 (1.78-5.94)	2.94 (1.60-5.40)	2.84 (1.53-5.28)
Suicide or refusal	62	2.15 (1.26-3.66)	2.08 (1.21-3.59)	1.87 (1.08-3.24)	1.89 (1.08-3.30)
Other	128	2.53 (1.76-3.64)	2.30 (1.59-3.33)	2.14 (1.47-3.10)	2.14 (1.46-3.12)

HR = hazard ratio; CI = confidence interval.

* Adjusted for age, sex, marital status, having children, ethnicity, educational level, being employed.

† Additionally adjusted for dialysis modality, primary cause of renal disease, Davies comorbidity.

‡ Additionally adjusted for glomerular filtration rate, body mass index, hemoglobin, intact parathyroid hormone, phosphorus, serum albumin, and creatinine.

REFERENCES

1. Chilcot J, Wellsted D, Farrington K: Depression in end-stage renal disease: current advances and research. *Semin Dial* 23:74-82, 2010
2. Cukor D, Cohen SD, Peterson RA, Kimmel PL: Psychosocial aspects of chronic disease: ESRD as a paradigmatic illness. *J Am Soc Nephrol* 18:3042-3055, 2007
3. Finkelstein FO, Wuerth D, Finkelstein SH: An approach to addressing depression in patients with chronic kidney disease. *Blood Purif* 29:121-124, 2010
4. Boulware LE, Liu Y, Fink NE, Coresh J, Ford DE, Klag MJ, Powe NR: Temporal relation among depression symptoms, cardiovascular disease events, and mortality in end-stage renal disease: contribution of reverse causality. *Clin J Am Soc Nephrol* 1:496-504, 2006
5. Kimmel PL, Peterson RA, Weihs KL, Simmens SJ, Alleyne S, Cruz I, Veis JH: Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. *Kidney Int* 57:2093-2098, 2000
6. Grippo AJ, Johnson AK: Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. *Stress* 12:1-21, 2009
7. Mykletun A, Bjerkeset O, Dewey M, Prince M, Overland S, Stewart R: Anxiety, depression, and cause-specific mortality: the HUNT study. *Psychosom Med* 69:323-331, 2007
8. Schins A, Honig A, Crijns H, Baur L, Hamulyak K: Increased coronary events in depressed cardiovascular patients: 5-HT2A receptor as missing link? *Psychosom Med* 65:729-737, 2003
9. Riezebos RK, Nauta KJ, Honig A, Dekker FW, Siegert CE: The association of depressive symptoms with survival in a Dutch cohort of patients with end-stage renal disease. *Nephrol Dial Transplant* 25:231-236, 2010
10. Chilcot J, Davenport A, Wellsted D, Firth J, Farrington K: An association between depressive symptoms and survival in incident dialysis patients. *Nephrol Dial Transplant* 26:1628-1634, 2011
11. van Dijk PC, Jager KJ, de Charro F, Collart F, Cornet R, Dekker FW, Gronhagen-Riska C, Kramar R, Leivestad T, Simpson K, Briggs JD: Renal replacement therapy in Europe: the results of a collaborative effort by the ERA-EDTA registry and six national or regional registries. *Nephrol Dial Transplant* 16:1120-1129, 2001
12. Davies SJ, Russell L, Bryan J, Phillips L, Russell GI: Comorbidity, urea kinetics, and appetite in continuous ambulatory peritoneal dialysis patients: their interrelationship and prediction of survival. *Am J Kidney Dis* 26:353-361, 1995
13. Berwick DM, Murphy JM, Goldman PA, Ware JE, Jr., Barsky AJ, Weinstein MC: Performance of a five-item mental health screening test. *Med Care* 29:169-176, 1991

14. Cuijpers P, Smits N, Donker T, ten Have M, de Graaf R: Screening for mood and anxiety disorders with the five-item, the three-item, and the two-item Mental Health Inventory. *Psychiatry Res* 168:250-255, 2009
15. Friedman B, Heisel M, Delavan R: Validity of the SF-36 five-item Mental Health Index for major depression in functionally impaired, community-dwelling elderly patients. *J Am Geriatr Soc* 53:1978-1985, 2005
16. Rumpf HJ, Meyer C, Hapke U, John U: Screening for mental health: validity of the MHI-5 using DSM-IV Axis I psychiatric disorders as gold standard. *Psychiatry Res* 105:243-253, 2001
17. Holmes WC: A short, psychiatric, case-finding measure for HIV seropositive outpatients: performance characteristics of the 5-item mental health subscale of the SF-20 in a male, seropositive sample. *Med Care* 36:237-243, 1998
18. Verduijn M, Grootendorst DC, Dekker FW, Jager KJ, le Cessie S: The analysis of competing events like cause-specific mortality--beware of the Kaplan-Meier method. *Nephrol Dial Transplant* 26:56-61, 2011
19. Donders AR, van der Heijden GJ, Stijnen T, Moons KG: Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol* 59:1087-1091, 2006
20. van Buuren S, Boshuizen HC, Knook DL: Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med* 18:681-694, 1999
21. Fischer MJ, Xie D, Jordan N, Kop WJ, Krousel-Wood M, Kurella TM, Kusek JW, Ford V, Rosen LK, Strauss L, Teal VL, Yaffe K, Powe NR, Lash JP: Factors associated with depressive symptoms and use of antidepressant medications among participants in the Chronic Renal Insufficiency Cohort (CRIC) and Hispanic-CRIC Studies. *Am J Kidney Dis* 60:27-38, 2012
22. Khalil AA, Frazier SK: Depressive symptoms and dietary nonadherence in patients with end-stage renal disease receiving hemodialysis: a review of quantitative evidence. *Issues Ment Health Nurs* 31:324-330, 2010
23. Cyranowski JM, Marsland AL, Bromberger JT, Whiteside TL, Chang Y, Matthews KA: Depressive symptoms and production of proinflammatory cytokines by peripheral blood mononuclear cells stimulated in vitro. *Brain Behav Immun* 21:229-237, 2007
24. Dervisoglu E, Kir HM, Kalender B, Eraldemir C, Caglayan C: Depressive symptoms and proinflammatory cytokine levels in chronic renal failure patients. *Nephron Clin Pract* 108:c272-c277, 2008
25. Dogan E, Erkoc R, Eryonucu B, Sayarlioglu H, Agargun MY: Relation between depression, some laboratory parameters, and quality of life in hemodialysis patients. *Ren Fail* 27:695-699, 2005
26. Kaptein AA, van Dijk S, Broadbent E, Falzon L, Thong M, Dekker FW: Behavioural research in patients with end-stage renal disease: a review and research agenda. *Patient Educ Couns* 81:23-29, 2010

27. Osthus TB, Dammen T, Sandvik L, Bruun CM, Nordhus IH, Os I: Health-related quality of life and depression in dialysis patients: associations with current smoking. *Scand J Urol Nephrol* 44:46-55, 2010
28. Pasco JA, Williams LJ, Jacka FN, Ng F, Henry MJ, Nicholson GC, Kotowicz MA, Berk M: Tobacco smoking as a risk factor for major depressive disorder: population-based study. *Br J Psychiatry* 193:322-326, 2008
29. Roshanaei-Moghaddam B, Katon WJ, Russo J: The longitudinal effects of depression on physical activity. *Gen Hosp Psychiatry* 31:306-315, 2009
30. Cukor D, Rosenthal DS, Jindal RM, Brown CD, Kimmel PL: Depression is an important contributor to low medication adherence in hemodialyzed patients and transplant recipients. *Kidney Int* 75:1223-1229, 2009
31. Akman B, Uyar M, Afsar B, Sezer S, Ozdemir FN, Haberal M: Adherence, depression and quality of life in patients on a renal transplantation waiting list. *Transpl Int* 20:682-687, 2007
32. Denhaerynck K, Manhaeve D, Dobbels F, Garzoni D, Nolte C, De Geest S: Prevalence and consequences of nonadherence to hemodialysis regimens. *Am J Crit Care* 16:222-235, 2007
33. Saran R, Bragg-Gresham JL, Rayner HC, Goodkin DA, Keen ML, van Dijk PC, Kurokawa K, Piera L, Saito A, Fukuhara S, Young EW, Held PJ, Port FK: Nonadherence in hemodialysis: associations with mortality, hospitalization, and practice patterns in the DOPPS. *Kidney Int* 64:254-262, 2003
34. Cukor D: Use of CBT to treat depression among patients on hemodialysis. *Psychiatr Serv* 58:711-712, 2007
35. Wuerth D, Finkelstein SH, Finkelstein FO: The identification and treatment of depression in patients maintained on dialysis. *Semin Dial* 18:142-146, 2005
36. Meijer A, Roseman M, Milette K, Coyne JC, Stefanek ME, Ziegelstein RC, Arthurs E, Leavens A, Palmer SC, Stewart DE, de Jonge P, Thombs BD: Depression screening and patient outcomes in cancer: a systematic review. *PLoS One* 6:e27181, 2011
37. Thombs BD, de Jonge P, Coyne JC, Whooley MA, Frasure-Smith N, Mitchell AJ, Zuidersma M, Eze-Nliam C, Lima BB, Smith CG, Soderlund K, Ziegelstein RC: Depression screening and patient outcomes in cardiovascular care: a systematic review. *JAMA* 300:2161-2171, 2008