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Original Investigation

Association Between Depression and Mortality in Patients Receiving Long-term Dialysis: A Systematic Review and Meta-analysis

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Background: We aimed to systematically review and analyze the association between depression and mortality risk in adults with kidney failure treated by long-term dialysis.

Study Design: A systematic review and meta-analysis of observational studies.

Setting & Population: Patients receiving long-term dialysis.

Selection Criteria for Studies: Searching MEDLINE, EMBASE, and PsycINFO, we identified studies examining the relationship between depression, measured as depressive symptoms or clinical diagnosis, and mortality.

Predictor: Depression status as determined by physician diagnosis or self-reported scales.

Outcomes: Pooled adjusted HR and OR of depression for all-cause mortality.

Results: 15 of 31 included studies showed a significant association between depression and mortality, including 5 of 6 studies with more than 6,000 participants. A significant link was established between the presence of depressive symptoms and mortality (HR, 1.51; 95% CI, 1.35-1.69; $I^2 = 40\%$) based on 12 studies reporting depressive symptoms using depression scales (N = 21,055; mean age, 57.6 years). After adjusting for potential publication bias, the presence of depressive symptoms remained a significant predictor of mortality (HR, 1.45; 95% CI, 1.27-1.65). In addition, combining across 6 studies reporting per-unit change in depression score (n = 7,857) resulted in a significant effect (HR per unit change in score, 1.04; 95% CI, 1.01-1.06; $I^2 = 74\%$).

Limitations: Depression or depressive symptoms were documented only from medical charts or a single self-report assessment. Included studies were heterogeneous because of variations in measurement methods, design, and analysis.

Conclusions: There is considerable between-study heterogeneity in reports of depressive symptoms in dialysis patients, likely caused by high variability in the way depressive symptoms are measured. However, the overall significant independent effect of depressive symptoms on survival of dialysis patients warrants studying the underlying mechanisms of this relationship and the potential benefits of interventions to improve depression on the outcomes.

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INDEX WORDS: Maintenance dialysis; end-stage renal disease; depression; death; depressive symptoms; dysthymia.

During recent years, more attention has been paid to nonrenal symptoms of end-stage renal disease (ESRD).[1,2] It is estimated that up to 39.3% of patients with ESRD have depressive symptoms.[3,4] Several factors contribute to the development of depressive symptoms, such as loss of the primary role in the family, decreased physical function, medications, and dietary restrictions.[2,5,6] Depressive symptoms, accompanied by a high burden of physical symptoms, are associated with poor adherence to treatment and loss of well-being in patients with ESRD.[1,2] Accordingly, depression has been suggested to be linked with mortality.

Earlier studies linking depression with mortality risk in patients with ESRD were inconclusive, whereas recent large studies have demonstrated an independent association between depression and mortality.[7-10] Nonetheless, there is considerable variation in the reported findings, in part due to differences in study design, statistical methodology, and the method used to ascertain depression. The objective of this systematic review is to evaluate the association between depression, measured as either depressive symptoms using depression scales or

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clinical diagnosis, and mortality of patients on long-term dialysis therapy.

METHODS

Criteria for Selection of Studies

All observational studies published in either abstract or full form that included an assessment of the ability of depressive symptoms or clinical depression to predict mortality were included. Studies were included if they recruited adult participants 18 years or older who were receiving dialysis (hemodialysis and peritoneal dialysis modalities) as a long-term renal replacement therapy. Non-English articles were considered for inclusion provided that an abstract in English was available.

Depression was defined as documentation of clinical depression (major depression, minor depression, or dysthymia) or depressive symptoms since the initiation of dialysis therapy in any of the following ways: (1) a diagnosis of depression based on structured clinical interviews validated against the *Diagnostic and Statistical Manual of Mental Disorders* or the *International Classification of Diseases* criteria, (2) measurement of depressive symptoms using a depression scale, (3) measurement of depressive symptoms by subscales of other questionnaires if validated as an indicator of depressive symptoms, and (4) any clinical record of the diagnosis of depression during the period after initiation of long-term dialysis therapy.

The primary outcome of interest was all-cause mortality after the initiation of dialysis therapy. Studies with assessment of the outcome less than 3 months or more than 10 years after depression measurement were not included, based on the assumption that mortality occurring either very early or late after the screening is unlikely to be related to depression.

Identification of Studies

Search Strategy

Three online databases—MEDLINE (1948 to August 2012), EMBASE (1947 to August 2012), and PsycINFO (1806 to August 2012)—were searched using the text words "dialysis" OR "hemodialysis," "depression" OR "depressive," and "mortality" OR "survival" OR "death," as well as the vocabulary terms specific to each database. The OvidSP (Ovid Technologies Inc) was used to identify articles from the 3 indexing databases. No filters for language, publication status, or study design were applied (Item S1, available as online supplementary material). The search was performed using a specialist information manager–designed search strategy.

We also reviewed bibliographic information of pertinent review articles; proceedings of international conferences (World Congress of Nephrology, American Society of Nephrology Renal Week, and European Renal Association–European Dialysis and Transplant Association Congress; 2006 to August 2012); and dissertations (ProQuest; 1637-August 2012). Authors of abstracts were contacted for detailed data when possible.

Selection of Studies and Data Extraction

Search results were imported into EndNote X for Windows (Thomson Reuters), and duplications were excluded. Inclusive screening of titles was done by one author (F.F.) to exclude irrelevant records. Two authors (F.F. and N.A.) independently reviewed the refined list of records by screening titles and abstracts based on study design, participants, and the exposure and outcome of interest. Full texts of selected records were screened further. All full-text articles were assessed for eligibility by 2 authors (F.F. and N.A.), with discrepancies resolved through review by a third author (S.V.J.) and consensus. Two authors (F.F. and N.A.) independently extracted study characteristics and effect estimates. Double data entry into RevMan, version 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration), was applied by creating and comparing 2 separate RevMan files. In case of missing data, the investigators contacted the authors.

Assessment of Risk of Bias in Included Studies

Data quality was appraised independently by 3 authors (F.F., N.A., and S.V.J.). A modified version of the Newcastle-Ottawa Scale[11] for cohort studies was used for quality appraisal (Item S2). We considered the clinical structured interview of all participants for diagnosis of depression as the highest level of ascertainment of exposure, and identification of depressive symptoms using a depression scale applied to all participants as acceptable. Studies with documentation of depression or depressive symptoms without assessment in selected groups did not meet ascertainment of exposure quality standard. Clinically important determinants for mortality for the Newcastle-Ottawa Scale comparability tool included age, diabetes, and cardiac disease. Because the mechanism for a potential link between depression and mortality is unclear, the minimum time required for observation was unknown. Clinically, it was thought that depression-related mechanisms most likely are long term (with the rare exception of suicide and dialysis therapy withdrawal), and the authors therefore agreed that the study would be considered to have met quality appraisal criteria if they had at least 1 year of follow-up. A maximum lost-to-follow-up rate $<10\%$ was acceptable (Item S2). Studies that met the criteria for representativeness of the exposed cohort ($\geq$3 criteria for selection, $\geq$1 for comparability, and $\geq$2 in the outcome sections) were considered low risk of bias.

Assessment of Effect Size and Heterogeneity

For data presented as a dichotomous variable (presence or absence of clinical depression and depressive symptom scores above or below a cutoff point), crude and adjusted hazard ratios (HRs) and/or odds ratios (ORs) were extracted. Studies reporting data presented as a continuous variable had HRs and ORs for each unit change in scores extracted. When risk estimates were not reported, crude ORs were calculated with 95% confidence intervals (CIs), if possible. Standard errors of the risk estimates were calculated using standard methods.

Between-study heterogeneity was investigated by χ^2 test ($P < 0.1$), and I^2 statistic was used to quantify its impact.[12]

Quantitative Synthesis

Data Synthesis

Eligible studies for quantitative data synthesis were imported into RevMan, version 5.1. Meta-analysis was done to estimate a summary measure of the ORs and HRs. The included studies were grouped based on the effect size (OR and HR) and measurement method of depression (dichotomized or continuous depression score and diagnosis of depression based on prospective structured interviews or review of medical charts) for separate meta-analyses. Studies reporting more than one effect size were included in all applicable groups. The generic inverse variance weighting method (DerSimonian and Laird[13]) was used to test the overall effect for reports of crude and adjusted estimates. The random-effects model was used as a conservative approach to summarize the findings.

Assessment of Publication Bias

The funnel plot was used to visualize potential publication bias. We used the trim-and-fill method to adjust the calculated effect sizes for publication bias.[14] R statistical software, version 2.15.1 (R Foundation for Statistical Computing), was used.

Subgroup and Sensitivity Analysis

Subgroup analyses were planned a priori for the following possible sources of heterogeneity: (1) follow-up time (<1, 1-3, and >3 years), (2) time of measurement of depressive symptoms in relation to dialysis therapy initiation (incident vs prevalent or mixed prevalent and incident dialysis patients), (3) country (United States vs other countries), and (4) single versus repeated measurements of depression. We further investigated heterogeneity by performing univariable random-effects model metaregressions of the natural logarithm of adjusted effect size against these study characteristics. We implemented the model using the *metafor* library in the R statistical software package.[15] Sensitivity analyses were planned a priori, excluding studies with high risk of bias defined using the Newcastle-Ottawa Scale and studies with fewer than 100 participants.

RESULTS

Search Results

The search yielded 2,528 records, of which 63 were potentially relevant. The κ index for agreement between the 2 reviewers was 0.96. The selected reports were screened for eligibility for inclusion. Authors were contacted for additional information; attempts were successful in 7 cases with additional data provided by authors. Thirty-two studies were excluded, and 31 articles were included for qualitative synthesis (Fig 1).

Table 1 is a summary of 31 studies included in the review (N = 67,075; mean age, 60.4 years; male, 54.4%).[7,9,10,16-43] Eight studies were of samples smaller than 100, whereas 6 were of samples larger than 6,000 patients. Studies were of prospective (n = 25) or retrospective (n = 6) cohort design. Eighteen studies were limited to hemodialysis patients; 4, to peritoneal dialysis patients; and 9 included both. One study was limited to only men,[25] 1 predominantly included African Americans,[9] and 3 were limited to older dialysis patients.[16,23,27] In 7 studies, patients were incident dialysis patients at the start of follow-up, whereas the remaining studies included either prevalent or a mix of prevalent and incident dialysis patients. Follow-up duration was up to 1 year in 6 studies, longer than 1-3 years in 15, and longer than 3 years in 10.

Depression measurement was based on a screening scale in 23 studies, physician diagnosis records in medical charts in 6, and both in 2 studies. Eleven of the 25 studies of depression scales reported Beck Depression Inventory scores, with various cutoffs. The remaining 14 studies of this group used 8 different scales (Table 1). Three of the studies measured depressive symptoms more than once, of which 2 used a depression scale every 6 months for 1.5-2 years and applied time-varying survival analysis,[7,9] and the third study measured depressive symptoms twice and considered a persistent positive result as having depressive symptoms.[43] In the second group of 8 studies based on medical records of clinical depression (physician diagnosed), none of the studies assessed all patients systematically.

Table S1 summarizes the 32 excluded studies.[8,44-74] Nine studies were excluded because they did not determine depression using a disease-specific screening tool (Mental Health component of the 36-Item Short

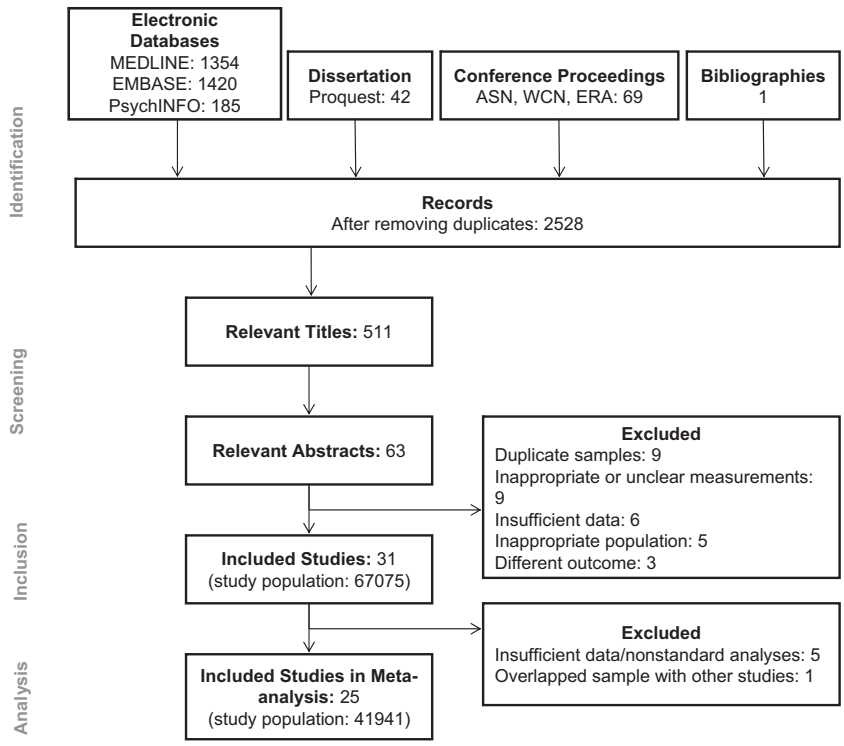

Figure 1. Flow diagram of search and selection of studies. Abbreviations: ASN, American Society of Nephrology; ERA, European Renal Association–European Dialysis and Transplant Association; WCN, World Congress of Nephrology.

Table 1. Characteristics of Included Studies

Study	Sample Characteristics	Measurement and Tool	Follow-up	Adjustment	Results
Balogun[16] (2011)	77 prevalent HD pts; age ≥ 65 y	Depressive symptoms, GDS-15 scores ≥ 5	3 y	Age, race, marital status	Adjusted HR, 1.91 (95% CI, 1.05-3.46)
Boulware[7] (2006)	917 incident HD & PD pts, age ≥ 18 y	Depressive symptoms, MHI-5 scores ≤ 52	2 y	Age, sex, race, marital status, education, coexistent illness, dialysis modality, antidepressant therapy, cardiovascular risk factors, BP, blood chemistry	Crude HR, 1.62 (95% CI, 1.07-2.44); adjusted HR, 2.22 (95% CI, 1.36-3.60)
Butt[17] (2007)	16,965 prevalent HD & PD pts, age ≥ 18 y	Clinical depression, medical records	4 y	HCV, HIV, drug use, CAD, stroke, DM, PVD, HBV, anemia	Significant, effect measure not reported
Chilcot[18] (2011)	223 incident HD pts, age > 18 y	Depressive score, BDI-II	16 mo	No	Crude HR, 1.01 (95% CI, 0.98-1.05) per 1-U ↑ score
Christensen[19] (1994)	78 incident HD patients, adults	Depression score, BDI	3.5 y	Age, serum urea nitrogen, family support	Not significant, effect measure not reported
Diefenthaeler[20] (2008)	40 incident HD pts, adults	Depressive symptoms, BDI scores ≥ 14	10.5 mo	Age, HTN, DM	Crude HR, 4.5 (95% CI, 1.1-17.7); adjusted HR, 6.5 (95% CI, 0.8-55.0)
Drayer[21] (2006)	62 incident & prevalent HD pts, age ≥ 18 y	Depressive symptoms, PHQ-9	2 y	Age, sex, race, comorbid conditions, albumin, Kt/V	Adjusted HR, 4.1 (95% CI, 1.2-13.8)
Einwohner[22] (2004)	66 prevalent PD pts, adults	Depression score, Zung SDS	3.5 y	Albumin, comorbid conditions (includes age & DM)	Crude HR, 1.06 (95% CI, 1.03-1.1) per 1-U ↑ score; adjusted HR, 1.05 (95% CI, 1.01-1.08) per 1-U ↑ score
Genestier[23] (2010)	112 incident PD pts, age ≥ 75 y	Clinical depression, medical records	18 mo	Charlson comorbidity, site, early referral, polymedication	Not significant, effect measure not reported
Griva[24] (2010)	145 prevalent HD & PD pts, age ≥ 18 y	Depressive symptoms, BDI-II scores ≥ 16	5 y	Age, employment, ESRD severity index, DM, CVD, vascular disease, SF-36, cognitive impairment	Crude HR, 2.53 (95% CI, 1.48-4.33); adjusted HR, 1.71 (95% CI, 0.96-3.06)
Hedayati[25] (2005)	1,588 prevalent HD pts, men; adults	Clinical depression, medical records	2 y	Age, DM, HTN, CHF, cardiac disease, liver disease, substance abuse	Adjusted OR, 0.98 (95% CI, 0.72-1.34)
Kimmel[9] (2000)	295 prevalent HD pts, 92% African American, age > 18 y	Categorized (standardized) depression score, BDI	3.5 y	Age, dialysis solution, severity coefficient, serum albumin, site	Crude HR, 1.24 (95% CI, 1.05-1.46); adjusted HR, 1.32 (95% CI, 1.13-1.55)
Kojima[26] (2010)	230 prevalent HD pts, age < 70 y	Depressive symptoms, BDI-II scores ≥ 14; depression score, BDI-II	5 y	Age, sex, SF-36, education, interdialytic weight gain, comorbidity, hematocrit, serum calcium, diastolic BP	For symptoms: adjusted HR, 2.36 (95% CI, 1.08-5.15); for score: adjusted HR, 1.05 (95% CI, 1.01-1.09) per 1-U ↑ score
Kutner[27] (1994)	287 prevalent HD pts, age ≥ 60 y	Depression score, CESD-20	3 y	Age, race, sex, education, ESRD cause, CVD, dialysis vintage, exercise, functional status	Not significant, effect measure not reported

(Continued)

Table 1 (Cont'd). Characteristics of Included Studies

Study	Sample Characteristics	Measurement and Tool	Follow-up	Adjustment	Results
Lacson[28] (2012)	6,415 incident HD pts, adults	Depressive symptoms & depression score, 2 items of SF-36	1 y	Age, race, sex, DM, SF-36, lab data	For symptoms: crude HR, 1.24 (95% CI, 1.28-1.43); adjusted HR, 1.32 (95% CI, 1.05-1.79); for 1-U ↑ score: crude HR, 1.09 (95% CI, 1.03-1.15); adjusted HR, 1.08 (95% CI, 1.01-1.14)
Lopes[30] (2002)	4,881 incident & prevalent HD pts, age > 17 y	Depressive symptoms, 2 items of SF-36; clinical depression, medical records	3 y	Demographics, lab data, comorbid conditions, dialysis vintage	For symptoms: crude HR, 1.39 (95% CI, 1.24-1.56); adjusted HR, 1.39 (95% CI, 1.23-1.57); for clinical depression: crude HR, 1.42 (95% CI, 1.27-1.60); adjusted HR, 1.23 (95% CI, 1.08-1.40)
Lopes[29] (2004)	6,987 incident & prevalent HD pts, age > 17 y	Depressive symptoms, CESD-10 scores ≥ 10; clinical depression, medical records	3 y	Age, sex, lab data, Kt/V, comorbid conditions, dialysis vintage, country	For symptoms: adjusted HR, 1.42 (95% CI, 1.29-1.57); for clinical depression: adjusted HR, 1.26 (95% CI, 1.1-1.43)
Mahajan[31] (2007)	52 prevalent PD pts, adults	Depressive symptoms, BDI scores > 11	2 y	No	Crude OR, 1.38 (95% CI, 0.24-7.94)
Miskulin[32,a] (2009)	7,685 prevalent HD pts, age > 17 y	Clinical depression, medical records	1.3 y	Age, race, sex, dialysis vintage	Adjusted HR, 1.24 (95% CI, 1.13-1.37)
Peng[33] (2010)	888 prevalent HD pts, age > 18 y	Depression score, BDI	7 y	Age, sex, lab data, DM, hepatitis C, SF-36	Crude HR, 1.02 (95% CI, 1.01-1.03) per 1-U ↑ score; adjusted HR, 1.00 (95% CI, 0.99-1.02) per 1-U ↑ score
Peterson[34] (1991)	57 incident & prevalent HD & PD pts, age > 22 y	Depression score, CDI	2 y	No	Crude HR, 1.11 (95% CI, 1.00-1.24) per 1-U ↑ score
Riezebos[10] (2010)	101 prevalent HD & PD pts, age ≥ 18 y	Depressive symptoms, HADS scores > 7	1 y	Age, sex, CVD, DM, dialysis vintage	Crude HR, 3.3 (95% CI, 1.2-9.6); adjusted HR, 5.0 (95% CI, 1.2-9.6)
Rosenthal Asher[35] (2012)	130 prevalent HD pts, age > 18 y	Depression score, BDI	5 y	Age, DM, dialysis vintage, hospitalizations	Adjusted HR, 1.05 (95% CI, 1.01-1.08) per 1-U ↑ score
Santos[36] (2012)	161 prevalent HD pts, age > 18 y	Depressive symptoms, CESD-10 ≥ 10	1 y	No	Crude OR, 2.26 (95% CI, 0.45-11.5)
Shulman[37] (1989)	64 prevalent HD pts, age ≥ 15 y	Depressive symptoms, BDI > 10	10 y	No	Significant, effect measure not reported
Simic Ogrizovic[38] (2009)	128 prevalent HD & PD pts, age > 18 y	Depression score, BDI	3 y	Age, lab data	Crude HR, 1.05 (95% CI, 1.02-1.08) per 1-U ↑ score; adjusted HR, 1.33 (95% CI, 1.00-1.06) per 1-U ↑ score
Soucie[39] (1996)	15,245 incident HD & PD pts, age > 15 y	Clinical depression, medical records	3 mo	Age, MI, activity impairment, race, sex, CHF, HTN, smoking	Crude OR, 0.79 (95% CI, 0.65-0.95); adjusted OR, 1.3 (95% CI, 1.0-1.6)

(Continued)

Table 1 (Cont'd). Characteristics of Included Studies

Study	Sample Characteristics	Measurement and Tool	Follow-up	Adjustment	Results
Szeto[40] (2008)	167 prevalent PD pts, age > 18 y	Depressive symptoms, HADS scores >7	1 y	No	Crude HR, 1.25 (95% CI, 0.58-2.70)
Takaki[41] (2005)	490 prevalent HD pts, age ≥ 18 y	Depression score, HADS	2.5 y	No	Crude HR, 1.48 (95% CI, 1.14-1.92) per 1-U ↑ score
Tsai[42] (2012)	2,312 incident HD & PD pts, age ≥ 20 y	Clinical depression, medical records	7 y	Age, sex, comorbid conditions	Crude OR, 1.01 (95% CI, 0.65-1.59)
Van den Beukel[43] (2010)	1,078 incident HD & PD pts, age ≥ 18 y	Depressive symptoms, MHI-5 ≤ 52	3.8 y	Age, sex, education, marital status, Davies comorbidity index, primary kidney disease, dialysis modality, lab data	Crude HR, 2.45 (95% CI, 1.87-3.20); adjusted HR, 1.83 (95% CI, 1.36-2.45)

Abbreviations and definitions: 1-U ↑, 1-unit increase; BDI, Beck Depression Inventory; BP, blood pressure; CAD, coronary artery disease; CDI, cognitive depression index; CESD, Center for Epidemiological Studies Depression Scale; CHF, congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; ESRD, end-stage renal disease; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; HBV, hepatitis B virus; HCV, hepatitis C virus; HD, hemodialysis; HIV, human immunodeficiency virus; HR, hazard ratio; HTN, hypertension; Kt/V, dialysis adequacy index; lab, laboratory; MHI, Mental Health Index; MI, myocardial infarction; OR, odds ratio; PD, peritoneal dialysis; PHQ, Patient Health Questionnaire; pts, patients; PVD, peripheral vascular disease; SDS, Self-rating Depression Scale; SF-36, 36-Item Short-Form Health Survey.

[a]This study includes the US data from the Dialysis Outcomes & Practice Patterns studies I, II, and III; therefore, because of the overlap with the data reported by Lopes et al,[29,30] was not included in calculation of overall rates and meta-analyses.

Form Health Survey [SF-36], n = 3; personality trait inventories, n = 4; single-item questionnaire, n = 1; and unspecified, n = 1). Six studies were excluded because of insufficient data. One study was not available in full text and 5 were abstract proceedings of conferences, all of which reported significant effect sizes, but data for adjustment for covariates were not available.

Qualitative Analyses

Risk of Bias in Included Studies

None of the 31 included studies provided structured clinical interviews of all participants. Seven studies were considered to be prone to a high risk of bias (Table S2). The main sources of bias were high or unreported rate of loss to follow-up and suboptimal method of ascertainment of the exposure.

Effects of Exposure

Depression was reported in 3 ways: (1) presence of depressive symptoms (based on scale cutoffs), (2) depression score (continuous data), and (3) documentation of physician diagnosis in medical charts. Fourteen studies (n = 21,146) reported the presence of depressive symptoms (point prevalence, 29.7%; range, 8.1%-65.4%). Physician-diagnosed depression was reported in 16.2% (range, 4.4%-27.7%) of 48,465 patients.

Fifteen of 31 studies found a relationship between depression and mortality after multivariable analysis (Table 1). The association was documented in 5 of 6 studies with sample sizes larger than 6,000[17,28-30,32] and all studies with repeated measurements of depression.[7,9,43]

Quantitative Synthesis

Of 31 studies included in the review, 25 provided data appropriate for quantitative data synthesis (13 reporting a significant association with mortality).[7,9,10,16,18,20-22,24-26,28-31,33-36,38-43] Of studies excluded from the meta-analysis, 4 did not find a statistically significant relationship between mortality and depression, whereas 2 did.

Presence of Depressive Symptoms

Fifteen studies reporting dichotomized results of depression scales were analyzed together. Combining across 9 reports of unadjusted HRs and 7 reports of ORs, the presence of depressive symptoms was a significant predictor of mortality (Table 2). Eight studies[7,9,10,20,24,28,30,43] reported HRs adjusted for covariates and crude HRs, and 4 studies[16,21,26,29] reported only adjusted HRs (12 studies; n = 21,055; mean age, 57.6 years; men, 53%). Based on these 12 studies, the presence of depressive symptoms significantly increased the risk of death by 51%

Table 2. Nonadjusted Effect Sizes of the Association of Depression and Mortality

Measurement	No. of Studies	Sample	Effect Size (95% CI)	*P*	I^2	Reference
Presence of depressive symptoms						
Crude HR	9	12,859	1.58 (1.33-1.88)	<0.001	79%	7, 9, 10, 20, 24, 28, 30, 40, 43
Crude OR[a]	7	559	2.33 (1.43-3.82)	<0.001	5%	10, 16, 20-22, 31, 36
Depressive score						
Crude HR	7	8,267	1.05 (1.02-1.08)	<0.001	76%	18, 22, 28, 33, 34, 38, 41
Physician diagnosis						
Crude HR	1	4,881	1.42 (1.27-1.59)	<0.001	NA	30
Crude OR	3	19,145	0.93 (0.73-1.18)	0.5	51%	5, 39, 42

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable; OR, odds ratio.
[a]OR is calculated for references 10, 16, and 20-22 based on data provided in the article.

(adjusted HR, 1.51; 95% CI, 1.35-1.69; $I^2 = 40\%$; Fig 2). The funnel plot (Fig 3) visualized the asymmetry, indicating the potential for publication bias, and the trim-and-fill method predicted that there were 5 hypothetically missing studies and imputed them. The adjusted meta-analysis after imputation gave an adjusted HR of 1.45 (95% CI, 1.27-1.65).

Depressive Score

Nine studies reported depression scores (continuous variable). The unadjusted HR for depressive scores showed a significant increase in mortality per unit of change (Table 2). Combining across 6 studies reporting adjusted analyses (n = 7,857; mean age, 61.3 years; men, 53%), depressive scores were associated significantly with mortality (adjusted HR, 1.04; 95% CI, 1.01-1.06; Fig 4). The effect size was based on heterogeneous results ($I^2 = 74\%$).

Physician-Diagnosed Depression

Five of the 7 studies reporting physician-diagnosed depression were included in the quantitative analysis. Two large studies reporting HRs showed a significant link between depression and mortality in univariable[30] and multivariable analysis.[29,30] The effect size for a diagnosis of depression was presented as OR in 3 studies, all of which failed to show a significant association (Table 2).[25,39,42] Meta-analysis was not possible due to the limited number of the studies.

Subgroups and Sensitivity Analysis

Subgroup and sensitivity analyses across different population and study quality groupings showed similar results across most of the analyses, suggesting a consistent relationship between depression and mortality (Tables 3 and 4). The subgroup of studies with repeated measurements of depression showed a higher risk of mortality for patients with depression (adjusted

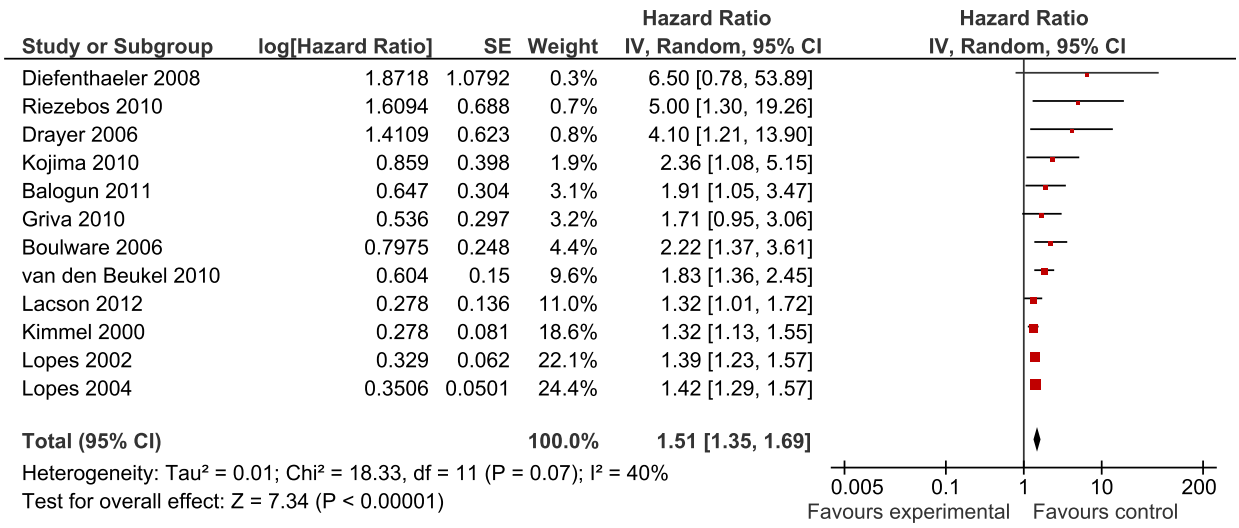

Figure 2. The association between the presence of depressive symptoms and mortality (adjusted risk estimates using hazard ratios). Abbreviations: CI, confidence interval; SE, standard error.

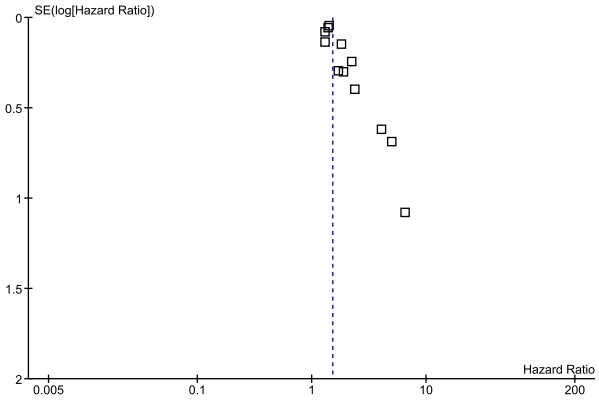

Figure 3. Funnel plot of studies reporting hazard ratios associated with the presence of depressive symptoms for mortality. Twelve studies are included, of which 5 on the right side of the vertical line are identified as outliers in the trim-and-fill analysis. Abbreviation: SE, standard error.

HR, 1.66; 95% CI, 1.22-2.25) than for those with a single application of depression scales at baseline.

We fitted a random-effects metaregression model for the association of the adjusted HR in the subgroup of studies reporting the presence of depressive symptoms with characteristics of the studies considered for subgroup analysis. Length of follow-up was not associated with the effect measure (slope = 0.001; 95% CI, −0.010 to 0.012; $P = 0.9$). Metaregression did not show a significant association between effect size and time of dialysis therapy initiation (incident vs prevalent patients; parameter, 0.087; 95% CI, −0.197 to 0.371; $P = 0.6$), country of origin of the study (United States vs non–United States; parameter, −0.025; 95% CI, −0.312 to 0.262; $P = 0.9$), and single versus repeated measurements of depression (parameter, 0.063; 95% CI, −0.224 to 0.349; $P = 0.7$).

DISCUSSION

Using meta-analytical techniques, we have shown an independent association between depression and increased mortality risk in the dialysis population. The magnitude of the increased risk was 1.5 times in the presence of depressive symptoms. This magnitude was slightly smaller when the risk of publication bias was incorporated using the trim-and-fill analysis. Studies with repeated measurements of depressive symptoms (longitudinal assessment) demonstrated a 1.66 times higher mortality risk with depressive symptoms.[7,9,43] These are seen regardless of the methods used to evaluate depression, characteristics of the population studied, and study design, suggesting that our findings are robust.

Our results cannot determine causality. However, our finding that there is increased mortality risk per unit of increase in depression scores (dose dependency) suggests a role for depression in the pathway of poor outcomes in dialysis patients. The subgroup of studies included in this meta-analysis have used different depression scales (reflected in the I^2 of 74%; Fig 4); thus, the quantified changes in effect size based on per-unit change in scores for depressive symptoms are not clinically meaningful. Nonetheless, our finding documents the relationship between severity of depressive symptoms and risk of death in dialysis patients. Katon[75] proposed a conceptual model of the interaction between depression and medical illnesses. According to this model, we hypothesize that depression and ESRD interact at 3 levels. First, depression can contribute to progression of chronic kidney disease to chronic kidney failure through parallel inflammatory pathways. Second, the lack of well-being associated with ESRD can lead to depression while simultaneously exacerbating the effect of ESRD on physical function, quality of life, and perceived burden of physical symptoms. Third, depression is linked with poorer outcomes of the disease through nonadherence to treatments and poor nutrition.[75] These theoretical interactions are supported by the observations that depression is associated with early initiation of dialysis therapy,[76,77] immune and inflammatory responses,[78-80] poor nutrition, nonadherence to treatment,[81,82] and

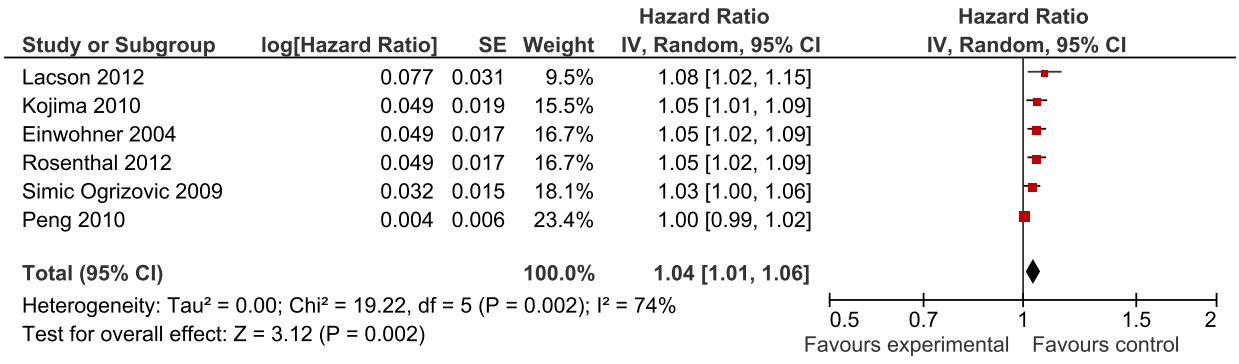

Figure 4. The association between depression scale score and mortality (adjusted risk estimates using hazard ratios per score). Abbreviations: CI, confidence interval; SE, standard error.

Table 3. Summary of Effect Sizes for Subgroups of Dialysis Patients

Subgroup	No. of Studies[a]	Sample	Adjusted HR (95% CI)	*P*	I^2	Reference
Presence of depressive symptoms[b]						
All studies	12	21,055	1.51 (1.35-1.69)	<0.001	40%	7, 9, 10, 16, 20, 21, 24, 26, 28-30, 43
Follow-up duration						
≤1 y	3	6,556	2.66 (0.85-8.25)	0.09	64%	10, 20, 28
>1-3 y	5	12,924	1.50 (1.30-1.72)	<0.001	44%	7, 16, 21, 29, 30
>3 y	4	1,575	1.59 (1.25-2.03)	<0.001	46%	9, 24, 26, 43
Dialysis initiation						
Incident patients	4	8,450	1.73 (1.27-2.35)	<0.001	51%	7, 20, 28, 43
Prevalent & incident patients	8	12,605	1.44 (1.30-1.60)	<0.001	31%	9, 10, 16, 21, 24, 26, 29, 30
Country of origin						
USA	5	7,593	1.57 (1.23-2.00)	<0.001	51%	7, 9, 16, 21, 28
Non-USA	5	1,594	1.95 (1.53-2.48)	<0.001	0%	10, 20, 24, 26, 43
Depression measurements						
Single measurement	9	18,938	1.48 (1.31-1.67)	<0.001	31%	10, 16, 20, 21, 24, 26, 28-30
Repeated measurements	3	2,117	1.66 (1.22-2.25)	0.001	70%	7, 9, 43
Depressive score						
All studies	6	7,857	1.04 (1.01-1.06)	0.002	74%	22, 26, 28, 33, 35, 38
Country of origin						
USA	3	6,611	1.05 (1.03-1.08)	<0.001	0%	22, 28, 35
Non-USA	3	1,246	1.02 (1.00-1.05)	0.09	73%	26, 33, 38

Abbreviations: CI, confidence interval; HR, hazard ratio; USA, United States of America.
[a]Restricted to those reporting adjusted HRs.
[b]Metaregression demonstrated no significant differences between subgroups.

higher risk of suicide and dialysis therapy discontinuation, suggesting biological plausibility.[83-85]

Depression has been associated with all-cause mortality in other medically unwell populations and in population-based studies, suggesting similarity with our findings in the dialysis population.[86-91] A community-level systematic review reported a 2-fold increased risk of dying in depressed individuals.[87] Pinquart and Duberstein[90] reviewed 43 studies of patients with cancer and reported a 22% higher risk of mortality for those with a depression diagnosis or depressive symptoms. Patients with ESRD may be at higher risk of depression-related mortality due to concomitant comorbid conditions. Non-ESRD patients with diabetes or cardiovascular disease, for example, have increased mortality if depressed (relative risks, 1.8 and 2.0, respectively).[92-94] However, our study found a relationship in patients with ESRD despite adjustment for these comorbid conditions. Given the accumulation of several factors related to depression and mortality in the setting of ESRD, the relationship between depression and patient outcome is deemed to be more complex.[95] Additionally, a large proportion of the ESRD population is 65 years and older, and it has been shown that elderly individuals have a 41% higher risk of mortality if they are depressed.[96]

We believe depression to be common but underrecognized in dialysis patients. Only one-third of

Table 4. Sensitivity Analyses of Adjusted Data for Effect Sizes of Association Between Depression and Mortality

Subgroup	No. of Studies	Sample	Adjusted HR (95% CI)	*P*	I^2	Reference
Presence of depressive symptoms						
Excluding 2 studies with high risk of bias[20,26]	10	20,785	1.48 (1.34-1.65)	<0.001	39%	7, 9, 10, 16, 21, 24, 28-30, 43
Excluding 4 studies with small sample size[10,16,20,21]	8	20,775	1.44 (1.32-1.57)	<0.001	25%	7, 9, 24, 26, 28-30, 43
Depressive score						
Excluding 1 study with high risk of bias[26]	5	7,627	1.04 (1.01-1.06)	0.007	76%	22, 28, 33, 35, 38
Excluding 1 study with small sample size[22]	5	7,791	1.04 (1.01-1.06)	0.008	75%	26, 28, 33, 35, 38

Abbreviations: CI, confidence interval; HR, hazard ratio.

those with a diagnosis of depression receive treatment.[29,97] Information about outcomes with pharmacologic and nonpharmacologic therapies for depression is limited to a few observational and clinical trials.[98-102] Systematic review of antidepressants for patients with chronic kidney disease demonstrated that the evidence for effectiveness of antidepressants is insufficient.[103,104] We propose the mortality risk reported by this systematic review provides sufficient incentive for further studies investigating the effectiveness of screening and therapy in the dialysis population.

We implemented strong and effective meta-analytical methods. However, our study is limited by the quality and heterogeneity of the studies included. None of the studies used structured clinical interview in the entire sample of dialysis patients, whereas many documented depression or depressive symptoms only from medical charts or a single self-report assessment. Studies relying on documentation of depression in medical charts lack ascertainment of the absence of depression in their nondepressed groups (ie, many patients on dialysis therapy are not evaluated and therefore a lack of clinical detection does not differentiate between not having been evaluated and not having depression). Our results also are limited by the heterogeneity caused by the variation in measurement methods, design, and analysis. Several steps were taken to limit the effects of this heterogeneity. We identified populations at most risk of heterogeneity. For example, many studies evaluated patients at only one time. We therefore analyzed studies with longitudinal measurement of depressive symptoms separately because we thought these studies were more likely to accurately identify patients with depression. Based on the Newcastle-Ottawa Scale for quality appraisal scores, a number of studies had a high risk of bias, whereas several studies had a limited duration of follow-up. We therefore isolated these factors and performed sensitivity analyses to better understand the effects of these limitations. In all cases, results were similar, suggesting a robust finding of increased mortality risk in those with depression. Appropriate meta-analysis of patients for whom the clinical diagnosis of depression was documented clinically was not feasible because of the small number of studies reporting adjusted effect sizes. Finally, we attempted to limit the impact of publication bias by an extensive search and using the trim-and-fill method.

In conclusion, the present systematic review and meta-analysis supports the independent association between depression and mortality risk in patients receiving maintenance dialysis. These data suggest further study evaluating whether screening or case finding strategies are effective and evaluating the effectiveness of treatments for depression in the dialysis population through well-designed clinical trials.

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SUPPLEMENTARY MATERIAL

Table S1: Excluded studies.

Table S2: Appraisal of included studies using the Newcastle-Ottawa Scale.

Item S1: Search strategy.

Item S2: Appraisal form (a modified Newcastle-Ottawa scale).

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2013.08.024) is available at www.ajkd.org

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