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Depression and Anxiety as Risk Factors for Morbidity and Mortality after Organ Transplantation: A Systematic Review and Meta-Analysis[1]

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Abstract

Background—Depression and anxiety are common mental health problems in transplant populations. There is mixed evidence concerning whether they increase morbidity and mortality risks post-transplant. If such associations exist, additional risk reduction strategies may be needed.

Methods—Four bibliographic databases were searched from 1981 through September, 2014 for studies prospectively examining whether depression or anxiety (determined with diagnostic evaluations or standardized symptom scales) affected risk for post-transplant mortality, graft loss, acute graft rejection, chronic rejection, cancer, infection, and rehospitalization.

Results—Twenty-seven studies (10 heart, total n=1,738; 6 liver, n=1,063; 5 kidney, n=49,515; 4 lung, n=584; 1 pancreas, n=80; 1 mixed recipient sample, n=205) were identified. In each, depression and/or anxiety were typically measured pre- or early post-transplant. Follow-up for outcomes was a median of 5.8 years (range:0.50–18.0). Depression increased the relative risk (RR) of mortality by 65% (RR=1.65, 95% CI:1.34,2.05; 20 studies). Meta-regression indicated that risk was stronger in studies that did (v. did not) control for potential confounders(p=.032). Risk was unaffected by type of transplant or other study characteristics. Depression increased death-censored graft loss risk (RR=1.65, CI:1.21,2.26, 3 studies). Depression was not associated with other morbidities (each morbidity assessed in 1–4 studies). Anxiety did not significantly increase mortality risk (RR=1.39, CI:0.85,2.27, 6 studies) or morbidity risks (assessed in single studies).

Conclusions—Depression increases risk for post-transplant mortality. Few studies considered morbidities; the depression-graft loss association suggests that linkages with morbidities deserve greater attention. Depression screening and treatment may be warranted, although whether these activities would reduce post-transplant mortality requires study.

Keywords

organ transplantation; depression; anxiety; mortality; graft loss; morbidities

Introduction

Organ transplantation promotes survival(1). It can foster improvements in other domains such as patient mental health and emotional well-being, and these too are recognized as salient outcomes during the transplantation process(2–6). Their importance as outcomes would alone justify the need for timely identification and treatment of common psychiatric conditions such as depression and anxiety in transplant patients. But it is possible that such mental health problems could have their own negative consequences, increasing both morbidity and mortality risks post-transplantation. Depressive and anxiety-related conditions each serve as risk factors for morbidities and mortality in community-based and nontransplant chronic disease populations(7–18). However, whether such associations occur in the context of transplantation is unclear.

On the one hand, one might argue that any impact of depression or anxiety on outcomes would be attenuated in transplant populations, given routine use of psychiatric evaluation protocols designed to screen out or identify transplant candidates requiring mental health intervention before transplantation (2,4,6,19–21). On the other hand, despite such protocols, prevalence rates of clinically significant depression and anxiety in transplant recipients remain substantially elevated over rates in the general population, and they equal or exceed rates in other chronic disease cohorts. For example, up to 63% of transplant recipients experience depression or anxiety during the first several years post-transplant(2,6,22–24), while rates during comparable time periods are 3–10% in the general population (9,25,26) and 10–40% in individuals with arthritis, cancers, heart disease, diabetes, kidney disease and lung disease(25–30). The elevated rates in transplant recipients may arise from stressors associated with the recovery and rehabilitation process, the need to follow a complex medical regimen, and adjustment to the prospect of new health threats including acute and chronic graft rejection, infections, and malignancies (2,6,19). In this context, it would be surprising if prevalent mental health problems such as depression and anxiety did not increase risk for poor outcomes in transplant populations, just as they do in other general population and patient groups(7–18).

To date, findings on whether either depression or anxiety predicts transplant-related outcomes appear mixed. For example, across different types of organ transplantation, some studies report that depression and/or anxiety occurring pre- or early post-transplant increases patients' risk for morbidities and mortality(31–35), with speculation that psychiatric distress results in behavioral problems (e.g., poorer medical adherence) and/or pathophysiological abnormalities that contribute to poor health outcomes. Other studies fail to find significant associations(36–38), or even report that greater depression or anxiety predicts more favorable post-transplant health outcomes(39,40), potentially due to behavioral factors (e.g., increased care-seeking among depressed individuals and/or increased symptom vigilance among anxious individuals, leading to quicker identification of transplant-related complications). It is also unclear whether depression is the more important risk factor, or whether anxiety plays an equally strong role(41). Reviews summarizing these effects have been narrative rather than systematic reviews. With few exceptions(4), they focus on narrow portions of the literature—considering, for example, only certain types of transplantation, or only reports published during brief time periods such as the 12–18 months before the review(22,23,41–46). The reviews note that differences across studies are difficult to reconcile due to variations in study methodology, including the timing and nature of assessments of predictors and outcomes, and the duration of follow-up. Other factors (e.g., type of transplantation, age group studied), may also affect observed associations, although their impact is unknown.

A clearer understanding of whether depression and/or anxiety affect risk for post-transplant morbidity and mortality, as well as factors moderating these associations' strength, could provide the foundation necessary for (a) identification of patients for whom mental health monitoring and care are particularly critical, and (b) clinical trials testing interventions to lessen any impact of depression and anxiety, thereby potentially reducing morbidities and mortality post-transplant. We thus conducted a systematic review and meta-analysis to achieve several goals. First, we sought to summarize and describe the literature across all

types of organ transplantation, and encompassing both adult and pediatric samples. Second, we aimed to determine how strongly depression and anxiety were each associated with post-transplant mortality and with common transplant-related morbidities. Third, we aimed to examine whether any observed associations varied depending on key study characteristics, including type of population evaluated (e.g., organ transplant type, age group), study methodology (e.g., approach to psychiatric assessment, follow-up duration), and study quality.

Methods

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(47).

Search Strategy and Study Selection

Following a protocol designed by the authors, eligible studies were sought from multiple sources (Figure 1). Table 1 lists inclusion/exclusion criteria; the search included publications through September, 2014. Pairs of authors (one of whom was M.A.D.) independently evaluated titles and abstracts of identified citations and, for those deemed potentially relevant by either member of the pair, full-text articles were retrieved.

Data Extraction

Pairs of authors (one of whom was M.A.D.) independently reviewed and extracted data from each study, and then met to reconcile any differences in data extracted.

Predictor-outcome associations—The primary information extracted pertained to prospective associations of depression and anxiety with any of 8 post-transplant outcomes listed in Table 1 (see inclusion criteria). Relative risks (RRs) and 95% Confidence IntervaIs (CIs), expressed in terms of risk for a poor post-transplant outcome as a function of a given psychiatric predictor, were extracted. We selected results from the full statistical model that adjusted for the largest number of potential confounders.

Assessment-related and other study characteristics—For each predictor (depression, anxiety), we recorded the assessment method used (standardized clinical interview v. standardized self-report symptom rating scale v. retrieval of medical records information on a clinical evaluation). We recorded whether the predictor was defined in terms of the presence/absence of caseness (i.e., individuals met criteria for diagnosable disorder or had a score exceeding a clinically-validated threshold establishing caseness on a symptom scale) or, alternatively, as degree of symptomatology along a continuous scale. We recorded whether the predictor was assessed pre- or post-transplant.

For transplant-related outcomes, we recorded their source (medical/registry records v. patient report). We extracted descriptive data about each study (e.g., publication date, type of transplantation).

To evaluate study methodologic quality and risk of bias(47,50,51), pairs of authors independently rated each study on 7 components of methodology using a validated scoring

system for each(52). We employed a consensus approach where any disagreements were resolved before assigning a final rating (see Appendix Table A1, footnote). The 7 components (each rated yes/no/cannot be determined) were whether (a) the sample was clearly described (e.g., including demographics, dates of transplant); (b) the patients approached for enrollment were representative of the study site's transplant population, (c) the sample enrolled was representative of those approached; (d) characteristics of patients lost to follow-up were clearly described; (e) outcome measures were clearly described; (f) all analyses adjusted for any differences in follow-up duration (censoring); and (g) all analyses of psychiatric variable-outcome variable associations adjusted for potential demographic and clinical confounders (i.e., factors that, if not controlled, could lead to erroneous conclusions about the true size of the associations)(52,53). A total quality score—a count of the components rated "yes" (score range, 0–7)—was computed for each study.

Statistical analysis

Descriptive statistics (e.g., percentages, means, standard deviations) were computed to characterize the studies in the systematic review. Among studies included in the meta-analysis, for each transplant-related outcome (e.g., mortality), we calculated the pooled estimate of the RR for the outcome given the presence (v. absence) of patient depression at baseline. We similarly calculated the RR given baseline anxiety. For studies examining depression (or anxiety) only as a continuous predictor, we separately calculated the pooled RR for the outcome in relation to incremental levels of depression symptomatology and the RR in relation to incremental anxiety symptomatology.

Across studies, the pooled RR is a weighted average that takes within-study variance into account. We generated it under a random effects model to allow generalizability beyond the retrieved studies(54). If the pooled RR was statistically significant, we evaluated the impact of publication bias, i.e., that studies finding predictor-outcome associations may have been more likely to be published. We did this by (a) examining Begg's funnel plot of study size by effect size and the accompanying Begg and Mazumdar rank correlation(54), and (b) calculating the "fail-safe N"(54,55), i.e., the number of missing studies obtaining null findings that would need to be added to the analysis so the pooled RR is no longer statistically significant.

When there was significant variability across studies in size of their individual RRs (based on the Q test for heterogeneity), we performed additional analyses. First, we performed a "leave-one-out" sensitivity analysis (wherein each study is individually removed from the analysis and the pooled RR is computed across remaining studies) to examine the pooled RR's stability and determine if any single study primarily accounted for its size(56). Next, we used random effects meta-regression(54,57) to determine whether RR variability across studies could be explained by 8 study characteristics: type of transplant, publication year, age group studied, maximum duration of follow-up, whether psychiatric status was assessed pre- or post-transplant, method used to assess psychiatric status, study methodologic quality, and whether the associations of outcomes with depression and anxiety were examined after controlling for potential confounders. (Although this latter variable was a component of the methodologic quality rating, we also examined it individually because of its potentially

critical role in influencing robustness and interpretation of any psychiatric status-outcome association.)

Results

Search results

As shown in Figure 1, 4,401 citations were identified, and 150 articles underwent full-text review. Of these articles, 33 were included in the systematic review(31–40,58–79), representing 27 studies of independent cohorts.

Description of studies

Table 2 summarizes descriptive information for the 27 studies; details for each investigation are in Table 3. The largest number of studies (n=10, 37%) focused on heart recipients. Studies were almost exclusively from North America or Europe. Across all studies, over 53,000 patients were included, contributing almost 164,000 person-years of observation. One registry-based report (with 47,899 kidney recipients)(32) greatly increased the volume of observations. Even so, Table 2 shows that studies of heart and liver transplantation each contributed over 1,000 patients. Fewer lung recipients have been studied. Most studies focused exclusively on adults. Two reports included transplant recipients of all ages; none focused solely on children. Follow-up duration was a median of almost 6 years across studies, ranging up to 18 years.

Table 2 shows that a majority of studies (59%) examined only depression as a risk factor, while 44% examined both depression and anxiety. (Among the latter, only two studies(60,75) attempted to determine independent effects of depression v. anxiety on outcome; none considered whether the occurrence of both conditions together had synergistic effects on outcomes.) In terms of assessment, in 74% of studies, depression and anxiety were measured via standardized diagnostic assessments (e.g., the Structured Clinical Interview for DSM-III or DSM-IV and/or psychometrically validated clinical scales)(see Table 3). Remaining studies utilized data extracted from mental health diagnostic evaluations in medical records.

Figure 2 shows the numbers of studies examining depression or anxiety in relation to each post-transplant outcome. Mortality was the most common outcome, examined in 24 studies in relation to depression and 10 studies in relation to anxiety. Morbidity outcomes were examined more rarely, with some areas (e.g., chronic graft rejection, cancer) receiving consideration in only 1–2 studies each. For most outcomes, studies of heart, liver, and lung recipients were most common. Exceptions were graft loss outcomes where kidney recipient studies predominated.

As shown in the last row of Table 2, the 27 studies varied in methodologic quality. Those with low quality scores (26% of studies) failed to meet quality standards in the majority of areas rated. (See Table 3 for each study’s total quality score; Appendix A provides individual ratings used to calculate total scores). The majority of studies received scores in the moderate to high quality range. Studies of liver recipients were most likely to receive high quality scores.

Meta-analysis

Twenty-three of the 27 studies provided sufficient quantitative information for meta-analysis.

Depression and risk for post-transplant mortality—Figure 3 shows the risk estimate from each of 20 studies that examined whether depression affected mortality risk: estimates ranged from an RR of 0.30, indicating a decreased mortality risk among patients with depression, to an RR of 2.83, indicating an almost threefold increased mortality risk. Across all studies, the pooled RR was 1.65 (CI:1.34,2.05), indicating a 65% greater mortality risk among patients with depression.

We found no evidence suggesting that publication bias accounted for the pooled RR's size, based on both a visual review of funnel plot evidence, and the finding that the plot's accompanying Begg and Mazumdar rank correlation was not significant ($\tau = -.20$, p=.218) (50). Furthermore, the fail-safe N was 251: this is the number of unpublished/unretrieved studies obtaining null findings that would need to be added to the analysis so that the pooled RR would become nonsignificant. The large fail-safe N suggests that the pooled RR is not an artifact of publication bias favoring reports of large, significant RRs.

As evident in Figure 3, the size of the risk estimates varied across the 20 studies; this heterogeneity was significant (Q=35.23, df=19, p=.013). "Leave-one-out" analysis showed that the pooled RR changed relatively little no matter which of the 20 studies was omitted (ranging from pooled RR=1.57, CI:1.25,1.96, to pooled RR=1.80, CI:1.50, 2.16), suggesting that no one study unduly influenced the results. We next examined whether study characteristics, such as type of transplant examined, accounted for the effect sizes' heterogeneity. We first considered the impact of each characteristic shown in Figure 4 individually (i.e., one predictor at a time in a meta-regression equation). We began this way because the total number of studies was not large enough to permit meta-regression with all characteristics included simultaneously(54,80). As shown in Figure 4 (third subsection), studies that included children found that depression more strongly increased mortality risk (RR=2.22) than did studies of adults only (RR=1.54); this difference was significant (Z=3.01, p=.003; univariate analysis). The depression-mortality association was also significantly stronger in studies that controlled for potential confounders than in studies that did not (Figure 4). There were no other significant differences. When the two significant characteristics from univariate analyses were included in a single meta-regression, study age group became nonsignificant (Z=1.62, p=.105; rightmost column of Figure), while the difference between studies that did v. did not control for potential confounders remained significant (Z=2.15, p=.032).

Anxiety and risk for post-transplant mortality—Figure 5 shows results for the 6 studies examining whether patient anxiety increased mortality risk. The pooled RR was 1.39, but was not statistically significant (CI:0.85,2.27). The studies' effect sizes did not show significant heterogeneity (Q=2.54, df=5, p=.771), precluding the need to examine differences by study characteristics.

Depression or anxiety as risk factors for post-transplant morbidities— Considering first depression as a risk factor, Figure 6a shows that, among the four studies examining overall graft loss (not censored for death), the pooled RR of 0.92 was not significant (CI:0.36,2.35). Despite significant heterogeneity across studies (Q=23.17, df=3, p<.001), there were too few studies to explore factors explaining the heterogeneity(50). Leave-one-out analysis showed that the pooled RR was consistently nonsignificant (range: pooled RR=0.63, CI:0.32,1.26 to RR=1.17, CI:0.44,3.06).

As shown in Figure 6b, among the three studies examining depression in relation to death-censored graft loss, the pooled RR of 1.65 was significant (CI:1.21,2.26). Concerning the potential for publication bias influencing these results, while there were too few studies to usefully examine the funnel plot, the fail-safe N of 50 suggests that the RR is robust to the discovery of many additional studies with null results. The studies did not show significant heterogeneity (Q=4.18, df=2, p=.124).

Two studies(36,60) examined depression in relation to acute graft rejection; neither found a significant association (RR=0.42, CI:0.08,2.14; RR=0.90, CI:0.48,1.69, respectively). The pooled RR of 0.81 was not significant (CI:0.45,1.47). There was no evidence of heterogeneity (Q=0.72, df=1, p=.395).

Remaining morbidities were examined relative to depression in only one study each, all with nonsignificant findings: depression did not increase heart recipients' risk of chronic graft rejection (RR=1.66, CI:0.57,4.86)(60) or cancer (RR=1.42, CI:0.57,3.54)(66), or liver recipients' risk of infection or rehospitalization (RR=1.29, CI:0.82,2.05; RR=1.19, CI: 0.81,1.75, respectively)(36).

With respect to anxiety and post-transplant morbidities, no studies examined overall graft loss or death-censored graft loss. Only single studies examined any of the other outcomes: anxiety did not significantly increase heart recipients' risk of acute rejection (RR=0.85, CI: 0.30,2.37)(60), chronic rejection (RR=1.50, CI:0.54,4.18)(60), or cancer (RR=1.40, CI: 0.49,4.01)(66).

Continuous measures of depressive and anxiety symptomatology, and risk for post-transplant mortality and morbidities—Among studies examining depression scale scores (with no imposed threshold defining clinically significant depression), we examined the pooled RR for mortality for each 1-point increment on the scale. Across 6 studies, the RR of 1.02 was not significant (CI:1.00,1.03)(Figure 7a). Studies' RRs did not show significant heterogeneity (Q=7.81, df=5, p=.167). Among 3 studies examining continuous anxiety scale scores, the pooled RR for mortality was 1.01 and was not significant (CI:0.99,1.03)(Figure 7b). There was no heterogeneity (Q=0.00, df=2, p=1.00). No studies examined continuous depression or anxiety scale scores in relation to post-transplant morbidities.

Discussion

We conducted the first systematic review with meta-analysis of a growing literature examining whether depression and anxiety increase morbidity and mortality risks after

transplantation. The review is timely given the continued challenge to identify modifiable risk factors in order to improve post-transplant outcomes. Most studies focused on depression, typically assessed pre- or early post-transplant, and its potential impact on post-transplant mortality risk. Few studies considered whether depression predicts transplant-related morbidities. Even fewer considered anxiety relative to either mortality or morbidity post-transplant.

We found that the presence of depression was associated with a 65% increased risk of post-transplant mortality. This effect size is well within the range of depression-mortality associations noted in community-based populations(8,9,11,12), and in cohorts with lung, heart or kidney disease(7,9–12,16,17,81–84), cancers(14,85), and diabetes(86). The risk effects found in these reports typically range between 20%-90%. In fact, in our meta-analysis, studies conducting the most stringent, rigorous analyses (by adjusting for potential confounders and thereby reducing the possibility of drawing erroneous conclusions about effect sizes)(50,52) found depression-mortality associations even stronger than those in other populations: depression more than doubled the risk of post-transplant mortality (RR=2.13).

In contrast, although anxiety appeared to bear a modest association with increased mortality risk post-transplant, this association was not significant. Anxiety has been found to increase mortality risk in other chronic disease populations(7,9,16–18). It is noteworthy, however, that we identified only six studies examining this relationship, and thus our estimate of the pooled effect size was less precise (wider CI) than the estimated effect for depression. In turn, although study methodologic quality was equivalent across investigations of depression and anxiety (see ratings, Table 3), the CIs around the estimates from individual studies examining anxiety tended to be slightly wider, indicating less precision, than those from studies examining depression (Figures 3 and 5). Given fewer and less precise estimates in the transplant literature, it remains premature to draw strong conclusions regarding anxiety's role in relation to mortality.

Given the larger pool of studies focused on depression and post-transplant mortality, we could examine whether depression's impact on risk varied depending on specific study characteristics. In addition to the difference noted above between studies that did vs. did not adjust for confounding factors, we found some evidence that depression more strongly predicted mortality in studies that included children than in those that did not. Although significant in univariate analysis, this effect was diminished in multivariable analysis. However, only two of 20 studies assessing mortality in the meta-analysis included children; none directly compared children to adults. Given evidence that psychosocial factors such as emotional well-being have heightened impact on health and behavioral outcomes after pediatric transplantation(87,88), establishing whether depression plays any role in pediatric samples should be a future research priority.

We found no evidence that the depression-mortality association's size was affected by other study-related characteristics, including type of organ transplant studied, era of study publication, method of determining depression caseness, timing of depression assessment (pre- v. post-transplant), and follow-up duration. The absence of significant differences based on assessment timing is particularly noteworthy because it suggests that any

occurrence of depression, whether pre- or post-transplant, has the potential to increase mortality risk. Depression is a readily treatable disorder and many pharmacologic and psychotherapeutic interventions exist(89,90). Although there is concern regarding the level of evidence and the safety of utilizing many interventions—particularly pharmacologic strategies—pre-transplant in individuals with severely compromised organ function(28,39,91,92), there is a large psychosomatic medicine practice-focused literature showing that pharmacologic and psychotherapeutic options can be utilized safely and effectively with transplant recipients who have stable organ function(6,23,44,93–96). Hence, ongoing screening (with treatment) for depression at routine post-transplant follow-up may be warranted, and has also been recommended pre-transplant(4,23,24,95), but with the caveat that we continue to lack the rigorous clinical trial evidence essential to assert that depression screening and treatment are effective. Moreover, any potential harms of screening also merit rigorous study.

But—if programs decide to undertake screening given the current state of the evidence—how best to screen for depression? We note that it was clinically significant depression—i.e., depression meeting diagnostic criteria or exceeding a threshold for caseness on a self-report scale—that increased mortality risk. In contrast, among studies considering depressive symptomatology along a continuum (assessed by scales, with no threshold imposed), there was no large or statistically significant association with mortality. This suggests that, rather than aiming to detect small and likely subclinical increments to symptomatology, screening efforts should focus identifying clinically significant depression, using validated assessment instruments with thresholds for caseness (e.g., Beck Depression Inventory-II(97), Patient Health Questionnaire-9(98)).

Our meta-analyses of post-transplant morbidity risks found that the largest numbers of studies considered graft loss in relation to depression. Risk for overall graft loss was not significantly increased by depression. However, death-censored graft loss allows for a more focused consideration of factors affecting graft function independent of patient mortality(48). Depression elevated risk for this outcome by 65%. All studies, however, focused on kidney recipients, who can receive dialysis or retransplantation after graft failure. Other organ recipients have no equivalent of dialysis and would require retransplantation. Retransplantation rates remain relatively low(1). Thus, although potentially important, it may be challenging to examine death-censored graft loss in relation to depression beyond kidney transplantation.

We found little evidence that risk for any other post-transplant morbidity was increased by either depression or anxiety. However, each outcome was examined in only 1–2 studies. Given that depression and anxiety are associated with increased risk for many morbidities in the general population (e.g., diabetes, cancers, cardiac events)(7,11,13,14,81–83), more extensive examination of associations with morbidities in transplant populations is needed.

Both behavioral and pathophysiological mechanisms may explain why depression would increase risk for post-transplant mortality and, at least in kidney recipients, death-censored graft loss. For example, depression can lead to poorer adherence to the post-transplant immunosuppressive medication regimen(99–102) which, in turn, can increase mortality and

graft loss(100,102,103). In multiple populations, depression is linked to poorer lifestyle behaviors including substance use, and inadequate diet and exercise(104–107). Depressed individuals frequently suffer from reduced social support and increased social isolation, both of which increase mortality risk(108–110). As noted above, depression increases risk for many medical conditions; these in turn contribute to mortality. Depression also appears to lead to reduced heart rate variability, and elevated levels of C-reactive protein and pro-inflammatory cytokines, each of which increase mortality risk in general population and advanced organ disease cohorts(111–115).

Such potential mechanisms have received little to no study in transplant populations, thus precluding consideration in our review. Other limitations of our review reflect the state of the research we synthesized: this literature provides little consideration of some patient subgroups (e.g., children); it focuses on all-cause rather than cause-specific mortality; and there is a dearth of work on post-transplant morbidities. There are other domains of outcomes that our review does not address, including patient-reported physical functional status, role function, and other components of quality of life.

We also could not examine combined effects of depression and anxiety for any evidence of synergistic effects on outcomes because no individual studies considered this issue. In addition, a potential criticism of our decision to employ meta-analysis is that meta-analysis combines results of studies that differ in their characteristics and it may ignore such differences(54,57). However, consistent with best practices for meta-analysis(50,54,56,80), we examined whether a variety of study characteristics moderated the size of the observed depression-mortality associations. In other instances (e.g., the anxiety-mortality association, the association of depression and death-censored graft loss), studies' effect sizes showed no evidence of heterogeneity, thus precluding a search for effect moderators. Nevertheless, we note that, overall, the relevant literature remains small, and there may be additional unmeasured factors that could influence the strength of observed risk factor-outcome associations. One such factor is receipt of mental health treatment. With one exception focused on depression treatment (72; discussed below), the studies we examined did not report whether patient outcomes differed as a function of psychiatric treatment. It is possible, for example, that anxiety bore a weaker, nonsignificant relationship to mortality in our meta-analysis because it was treated more aggressively than depression. However, studies examining psychiatric treatment in transplant populations suggest that anxiety is treated at similar rates or is even undertreated relative to depression (116–119). Finally, our review did not include "gray literature" (i.e., unpublished data and reports produced by government, academics, or industry that are not peer-reviewed or included in standard bibliographic databases)(50). However, whether the inclusion of gray literature leads to more accurate effect size estimates is unclear(50,120). Moreover, our results appear robust to publication bias.

Our review's limitations suggest issues important for future work. At the same time, our findings—particularly those showing a depression-post-transplant mortality association—provide an important foundation and justification for our recommendations of depression screening and focused treatment, not only pre- but post-transplant. We need not await an understanding of mechanisms by which depression increases mortality risk before

proceeding with risk-reduction activities. An observational study hints at the potential impact of such work within transplantation: Rogal et al.(72), in additional analyses of the DiMartini et al. cohort(31) included in the present meta-analysis, found that liver recipients who received adequate, evidence-based pharmacotherapy for early post-transplant depression had long-term survival equivalent to that of nondepressed recipients, while depressed recipients receiving inadequate or no treatment had poorer survival. Important next steps include randomized trials to determine if such effects are causal and robust. In the meantime, clinical attention to the mental health of transplant patients seems warranted, not only for maximizing quality of life but because of its potential to affect post-transplant survival.

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Abbreviations

RR	relative risk
CI	confidence interval
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
DSM-III	DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Fourth Edition

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Appendix

Table A1

Ratings of individual components of methodologic quality of studies included in the systematic review.*

Study (First author, year, related publications)	1. Patients in sample clearly described?	2. Patients approached representative of entire population?	3. Patients enrolled representative of entire population?	4. Characteristics of patients lost to follow-up described?	5. Is each outcome measure clearly described?	6. Do analyses adjust for different lengths of follow-up?	7. Adjustment for confounding in analyses of outcomes?	Total Score
Heart								
Maricle, 1989,[58] 1991[59]	N	?	?	Y	N	N	N	1
Dew, 1999[60]	Y	Y	Y	Y	Y	Y	N	6
Skotzko, 1999[38]	N	Y	Y	Y	Y	Y	N	5
Zipfel, 2002[61]	N	Y	?	Y	Y	Y	N	4
Grigioni, 2005,[62] Sirri, 2010[63]	N	?	?	Y	?	N	N	1
Owen, 2006[64]	N	Y	Y	Y	N	Y	N	4
Havik, 2007[33]	N	?	N	Y	Y	Y	Y	4
van de Beek, 2008[65]	Y	?	?	N	Y	Y	Y	4
Favaro, 2011[66]	Y	?	?	Y	Y	Y	N	4
Farmer, 2013[67]	Y	?	?	?	Y	Y	N	3
Liver								
Singh, 1997[68]	N	?	?	Y	Y	Y	N	3
Gedaly, 2008[69]	Y	Y	Y	Y	Y	Y	Y	7
Rowley, 2010[37]	Y	Y	Y	Y	Y	Y	N	6
Corruble, 2011[39],2011,[70] 2012[71]	Y	?	?	Y	Y	Y	N	4
DiMartini, 2011,[6 31] Rogal, 2013[72]	Y	Y	Y	N	N	Y	Y	5
Rogal, 2011[36]	Y	Y	Y	Y	Y	Y	Y	7
Kidney								
Burke, 2008[40]	N	?	?	N	N	Y	N	1
Dobbels, 2008[32]	N	Y	Y	N	Y	Y	Y	5
Novak, 2010[34] Molnar-Varga, 2011[73]	N	Y	Y	N	Y	Y	Y	5
Corruble, 2011[39]	Y	?	?	Y	Y	Y	N	4
Zelle, 2012[74]	Y	Y	?	N	Y	Y	Y	5

Study (First author, year, related publications)	1. Patients in sample clearly described?	2. Patients approached representative of entire population?	3. Patients enrolled representative of entire population?	4. Characteristics of patients lost to follow-up described?	5. Is each outcome measure clearly described?	6. Do analyses adjust for different lengths of follow-up?	7. Adjustment for confounding in analyses of outcomes?	Total Score
Lung								
Cohen, 1998[75]	N	?	?	N	?	Y	?	1
Vermeulen, 2008[76]	Y	Y	N	Y	Y	Y	N	5
Evon, 2010[77]	N	?	?	Y	Y	Y	Y	4
Smith,2014[35]	Y	Y	?	Y	Y	Y	Y	6
Other								
Popkin, 1993[78]	Y	Y	Y	Y	N	Y	N	5
Dobbels, 2009[79]	Y	Y	?	N	Y	N	N	3

*For items 1–4 and 6–7, Y = yes, N = no, ? = cannot be determined. For item 5, Y = yes, N = no, ? = mixed evidence across measures included in report. Total score is a count of items scored as yes (52). Interrater reliability (kappa) of item ratings prior to consensus discussions to reach final rating determinations averaged .78 across the 7 items (range, .63 to 1.00). (Benchmarks: kappas of .61–.80 indicate substantial agreement; kappas of .81 to 1.00 indicate near perfect to perfect agreement[121]). Disagreements were resolved by re-review of contents of articles and discussion to pinpoint specific evidence that most strongly supported assigning a specific rating. There were no cases in which the pair of authors rating a given study failed to resolve disagreements and reach final consensus.

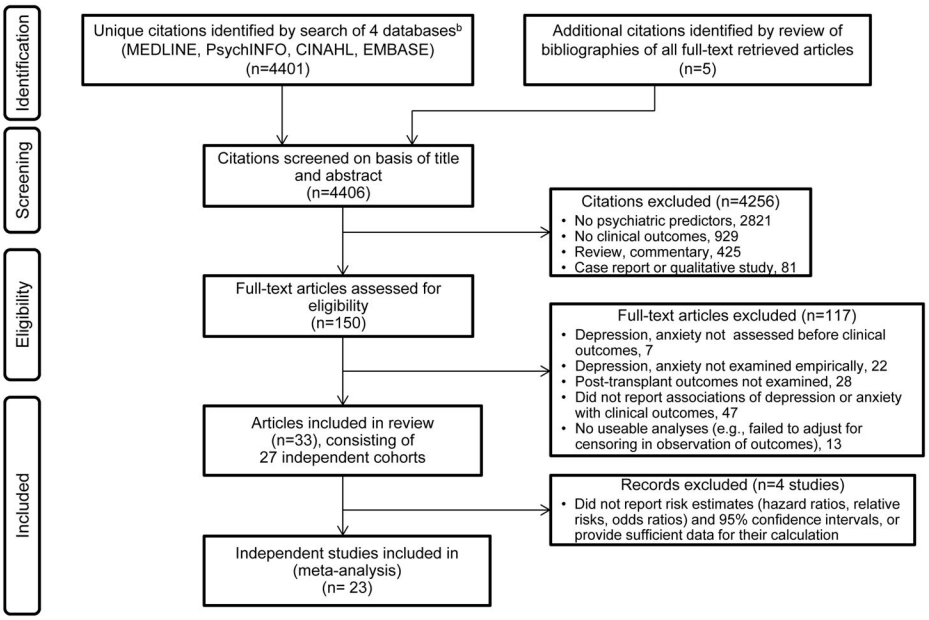

Figure 1.

PRISMA[a] flow diagram of study selection.

[a] Adapted from PRISMA guidelines (47).

[b] The search algorithm was (kidney transplant* or pancreas transplant* or heart transplant* or lung transplant* or heart-lung transplant* or liver transplant*) AND (psych* or mental or depress* or anxiety or mood) AND (survival or morbidity or mortality or cancer or rejection or infection or hospitalization or health), AND limit = 1981 – current (September, 2014) AND limit = human. Although an exclusion criterion to retrieved citations was that they were published in a language other than English, Spanish, French or German, none of the identified citations was excluded due to this criterion. See Table 1 for full list of inclusion/exclusion criteria.

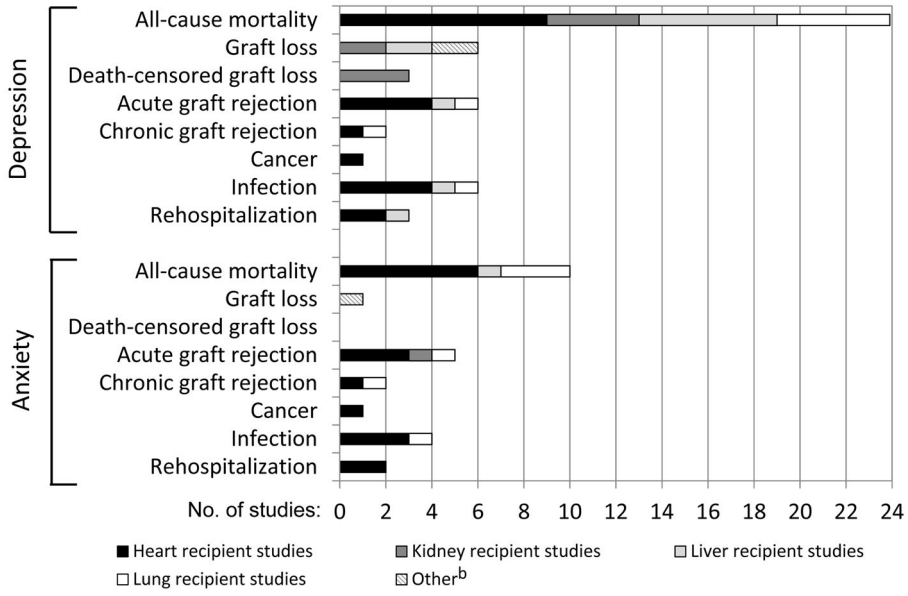

Figure 2.

Numbers of studies examining depression or anxiety in relation to each clinical outcome (across 27 studies in systematic review)[a]

[a] Post-transplant outcomes were determined in all studies from medical record or registry reviews, with the exception of Burke(40), in which the outcome was based on patient self-report.

[b] For depression, this category included one study of a mixed sample of heart recipients, liver recipients, and lung recipients, and one study of pancreas recipients. For anxiety, this category included the study of the mixed sample.

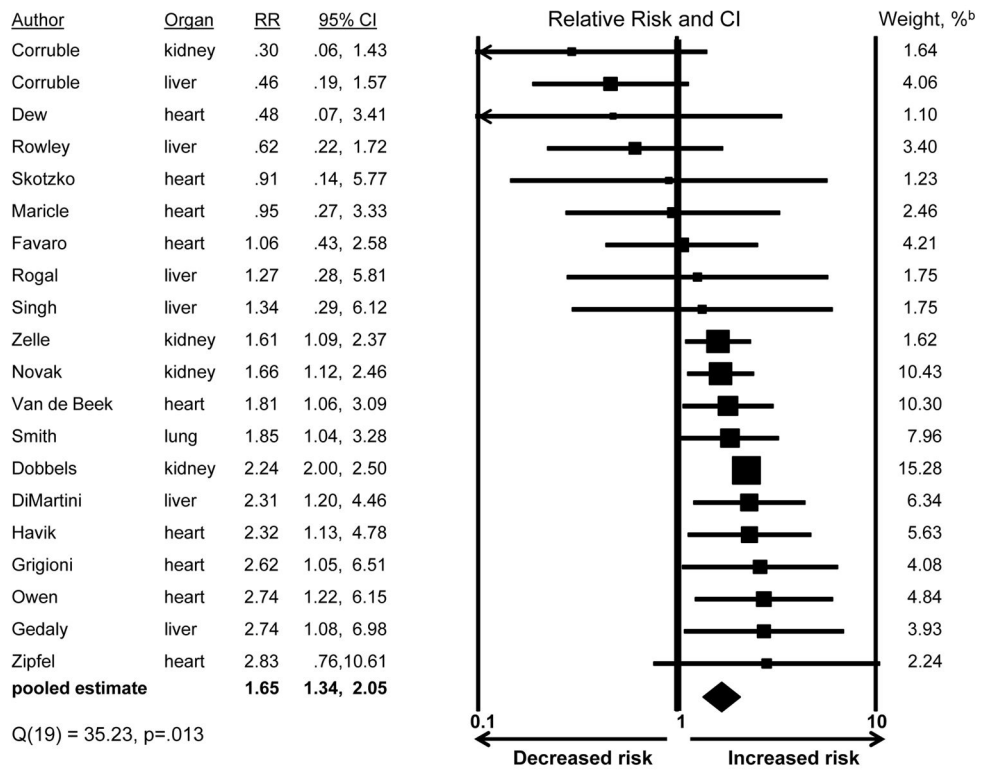

Figure 3.

Association of depression with post-transplant mortality[a]

[a] The studies classified patients according to depression status (present/absent). The presence of depression was defined as either diagnosable major depressive disorder or depression symptom levels exceeding an established threshold for caseness on a standardized symptom scale.

[b] Pooled estimate is weighted to take into account the precision of the effect within each study; larger weights are assigned to studies with greater precision.

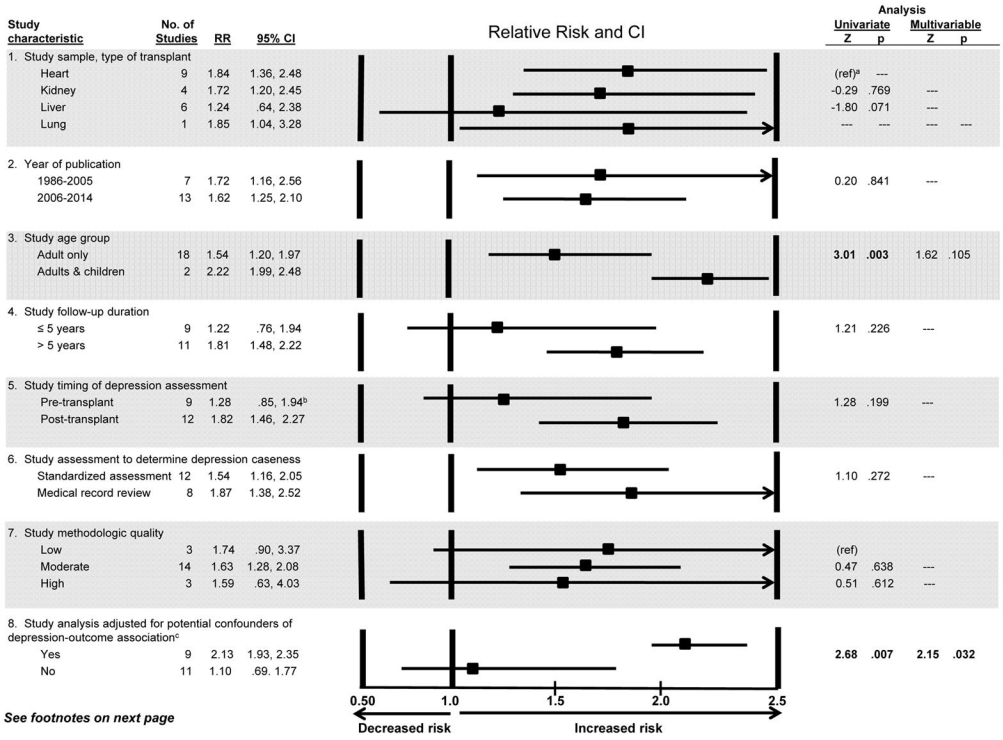

Figure 4.

Study characteristics potentially explaining variability in the size of the depression - post-transplant mortality association (relative risk): Meta-regression results

[a] Because there was only one lung recipient study and the relative risk was similar to heart recipient samples, the studies were combined to create a referent group of thoracic transplant recipients.

[b] Favaro et al.(66) examined pre- and post-transplant depression separately in relation to mortality. We report our analysis that includes both effect sizes (RRs) from this study. However, because the two effect sizes are not independent, we performed a sensitivity analysis by including only the effect based on pre-transplant depression, and then repeated the analysis including only the effect based on post-transplant depression. The separate results were indistinguishable from those reported here.

[c] Note that the comparison of studies that did vs. did not adjust for confounders was a between-studies comparison designed to test a question of effect modification, i.e., whether studies using more rigorous, stringent procedures (i.e., analyses that would reduce the possibility of drawing erroneous conclusions about the true size of the depression-mortality association) produced effect sizes that, on average, differed from those in studies that did not use such an analytic approach(50,52,80). At the same time, one might expect that within a given study, smaller effects would be observed after controlling for confounders compared to before such adjustment(80). Among the nine studies that reported controlling for confounders, 5 reported only results from multivariable models. Of the four studies that reported univariate results, followed by multivariable results, three observed that controlling for confounders did attenuate the size of the association of depression with mortality(33,34,74). The fourth study showed little difference in the size of depression-mortality associations between univariate and multivariable analyses(36).

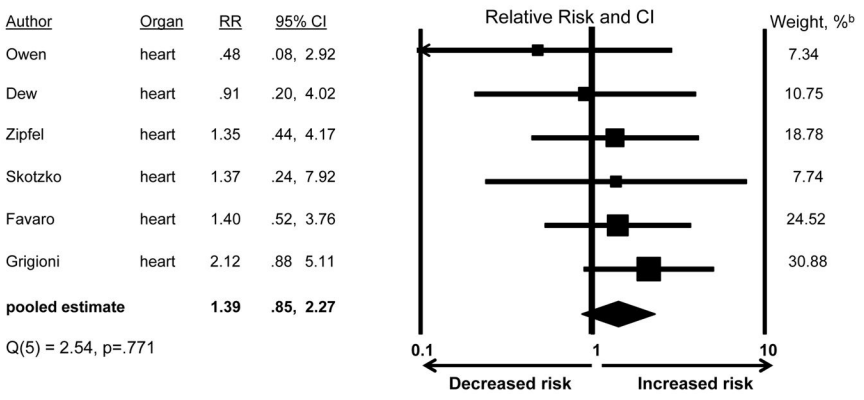

Figure 5.

Association of anxiety with post-transplant mortality[a]

[a] The studies classified patients according to anxiety status (present/absent). The presence of anxiety was defined as either any diagnosable anxiety disorder or anxiety symptom levels exceeding an established threshold for caseness on a standardized symptom scale.

[b] Pooled estimate is weighted to take into account the precision of the effect within each study; larger weights are assigned to studies with greater precision.

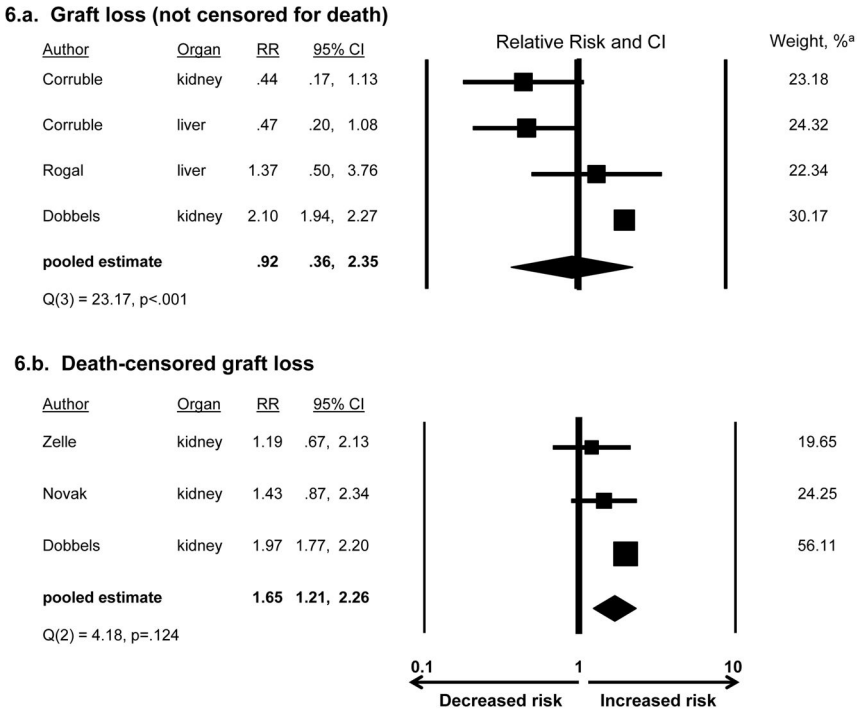

Figure 6.

Association of depression with post-transplant graft loss[a]

[a] See Figure 3 for definition of depression and explanation of weights

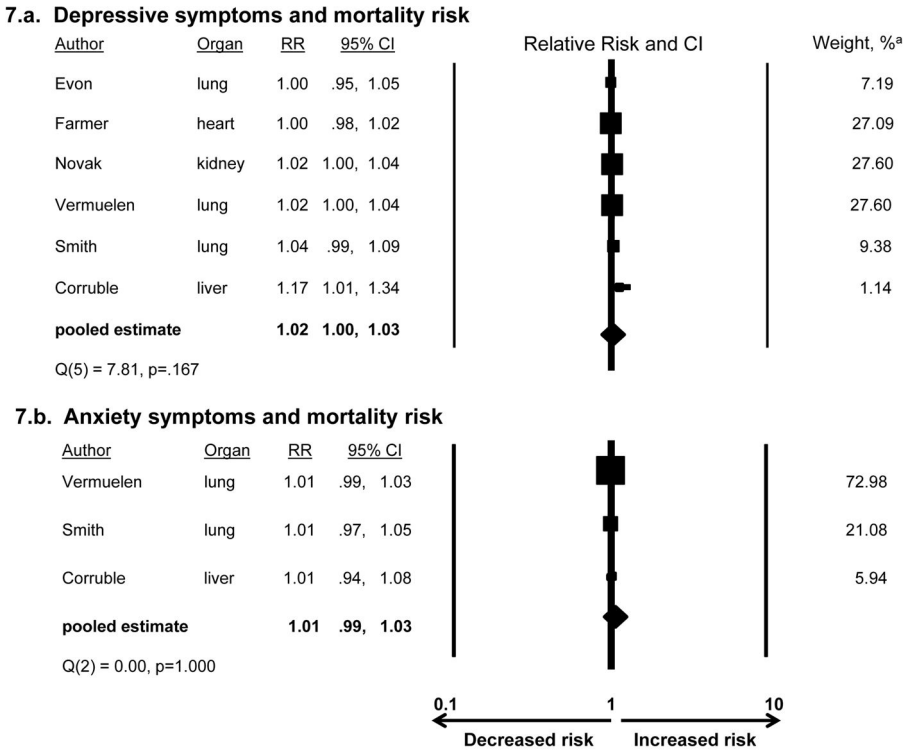

Figure 7.

Association of continuous measures of depression and anxiety symptoms and post-transplant mortality

[a] See Figure 3 for explanation of weights

Table 1

Inclusion and exclusion criteria for studies for the systematic review and meta-analysis.

Inclusion criteria	Exclusion criteria
For inclusion in both the systematic review and meta-analysis: • Study publication between 1981 (advent of cyclosporine and hence the modern era of transplantation) and September, 2014 inclusive. • Included solid organ transplant recipients. • Examined depression or anxiety in relation to any of 8 post-transplant outcomes: – All-cause mortality – Graft loss (graft failure resulting in return to dialysis [in kidney transplantation], retransplantation, or death with a functioning graft) (1,48) – Death-censored graft loss (graft failure resulting in return to dialysis [in kidney transplantation] or retransplantation; it excludes patient death with a functioning graft) (1,48) – Acute graft rejection – Chronic graft rejection – Cancer – Infection – Rehospitalization after the index hospitalization for transplant	For exclusion from both the systematic review and meta-analysis: • Publication in languages other than English, Spanish, French, or German. • Did not collect quantitative data (e.g., reviews, qualitative reports). • Data collected on depression and/or anxiety did not antedate the onset of transplant-related clinical outcomes. • No appropriate analyses were conducted (e.g., none of the analyses adjusted for censoring when examining risk of outcomes). • Despite performing at least some appropriate analyses, no findings concerning associations of either depression or anxiety with post-transplant outcome associations were reported. Among the final pool of studies in the systematic review, exclusion from the meta-analysis: • Did not report relative risk (RR) estimates for the associations of depression and/or anxiety with post-transplant outcomes (either hazard rates [HRs] if there was censoring during follow-up or relative risk ratios if there was no censoring) and 95% confidence intervals (CIs) AND • Did not provide sufficient information to allow RRs and CIs to be calculated (49).

Table 2

Descriptive information for 27 independent studies examining whether depression or anxiety affected risk for transplant-related mortality and morbidities.

		Type of Organ Transplantation				
Characteristic	**Total**	**Heart**	**Liver**	**Kidney**	**Lung**	**Other[a]**
Number of studies	27	10	6[b]	5[b]	4	2
Year of earliest relevant publication	1989	1989	1997	2008	1998	1993
Study location, % (n)						
North America	59.3 (16)	60.0 (6)	83.3 (5)	20.0 (1)	75.0 (3)	50.0 (1)
Europe	37.0 (10)	40.0 (4)	16.7 (1)	60.0 (3)	25.0 (1)	50.0 (1)
Other	3.7 (1)	0.0 (0)	0.0 (0)	20.0 (1)	0.0 (0)	0.0 (0)
Total number of countries represented	10	4	2	5	3	2
Age group studied, % (n)						
Adult only	92.6 (25)	90.0 (9)	100.0 (6)	80.0 (4)	100.0 (4)	100.0 (2)
Adult and child	7.4 (2)	10.0 (1)	0.0 (1)	20.0 (1)	0.0 (0)	0.0 (0)
Total number of patients studied	53,105	1,738	1,063	49,515	584	205
Sample size						
Median (IQR)	147 (103–201)	107 (101–188)	160 (125–224)	527 (105–24,389)	153 (84–201)	102 (80–102)
Absolute range	23–47,899	58–555	60–358	23–47,899	76–201	80–125
Total person years of observation	163,713	6,879	4,564	148,247	3,820	203
Duration of observation of follow-up, years						
Median (IQR)	5.8 (3.0–9.6)	5.4 (3.1–8.4)	7.4 (4.4–12.0)	3.0 (1.0–8.3)	10.8 (8.8–13.5)	2.6 (1.0–2.6)
Absolute range	0.5–18.0	1.0–18.0	2.7–13.0	0.5–8.7	8.5–14.0	1.0–4.3
Study focus on depression or anxiety as risk factors						
Depression only	51.9 (14)	30.0 (3)	83.3 (5)	80.0 (4)	25.0 (1)	50.0 (1)
Anxiety only	3.7 (1)	0.0 (0)	0.0 (0)	20.0 (1)	0.0 (0)	0.0 (0)
Both depression and anxiety	44.4 (12)	70.0 (7)	16.7 (1)	0.0 (0)	75.0 (3)	50.0 (1)

Characteristic	Total	Type of Organ Transplantation				
		Heart	Liver	Kidney	Lung	Other[a]
Study timing of assessment of depression and/or anxiety						
Pre-transplant	59.3 (16)	40.0 (4)	83.3 (5)	40.0 (2)	75.0 (3)	100.0 (2)
Post-transplant	33.3 (9)	50.0 (5)	16.7 (1)	60.0 (3)	0.0 (0)	0.0 (0)
Both pre- and post-transplant	7.4 (2)	10.0 (1)	0.0 (0)	0.0 (0)	25.0 (1)	0.0 (0)
Study assessment method for depression and/or anxiety						
Standardized clinical interview	11.1 (3)	20.0 (2)	0.0 (0)	0.0 (0)	0.0 (0)	50.0 (1)
Standardized self-report scale	55.6 (15)	30.0 (3)	50.0 (3)	80.0 (4)	100.0 (4)	50.0 (1)
Both standardized interview and scale	7.4 (2)	20.0 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Medical record review	25.9 (7)	30.0 (3)	50.0 (3)	20.0 (1)	0.0 (0)	0.0 (0)
Study quality evaluation, % (n)						
Low (score 1–3)	25.9 (7)	30.0 (3)	16.7 (1)	20.0 (1)	25.0 (1)	0.0 (0)
Moderate (4–5)	55.6 (15)	60.0 (6)	33.3 (2)	80.0 (4)	50.0 (2)	100.0 (2)
High (6–7)	18.5 (5)	10.0 (1)	50.0 (3)	0.0 (0)	25.0 (1)	0.0 (0)

[a] includes one study of pancreas recipients and one study with a mixed sample of recipients of different types of organ transplant recipients.

[b] One investigation reported on both a liver and a kidney recipient cohort(39). Because findings for each were provided separately, we considered this investigation as contributing two independent cohorts (i.e., two of the 27 cohorts in the systematic review).

Table 3

Characteristics of individual studies included in the systematic review.

Study first author, year, related publications	Country	Sample size	Baseline age	Male gender	Timing of baseline assessment	Post-tx followup duration	Psychiatric risk factor measures	Risk factor-outcome relationships examined[a]	Methodologic Quality[c]
Heart									
Maricle, 1989,[58] 1991[59]	U.S.A.	58	Adults	86.2%	Evaluation for tx	≥ 3 mo post-tx; M 2.1±1.1 y	DSM-III depressive disorder diagnoses in medical record of tx evaluation Depression and anxiety subscales, SCL-90, mean score[b]	Depression with Mortality Depression, anxiety with Acute rejection[b] Infection[b]	1
Dew, 1999[60]	U.S.A.	145	Aged ≥18, 46.9% < 50 y	84.1%	Across first year post-tx	2 y after baseline year	First year post-tx DSM-III-R depressive or anxiety disorders by SCID or CIDI Depression and anxiety subscales, SCL-90, score>1 SD of normative mean	Depression, anxiety with Mortality Acute rejection Chronic rejection	6
Skotzko, 1999[38]	U.S.A.	107	Adults	---	Evaluation for tx	Max 1 y post-tx	DSM-III-R depression and anxiety disorder diagnoses recorded in medical record of tx evaluation	Depression, anxiety with Mortality Acute rejection[b] Infection[b] Hospitalization[b]	5
Zipfel, 2002[61]	Germany	103	Adults aged ≥18	---	After listing for tx	M 4.4 y post-tx, max ~5 y	Zerssen Depression Scale, > median State subscale, STAI, score > median	Depression, anxiety with Mortality	4
Grigioni, 2005[62] Sirri, 2010[63]	Italy	95	Adults ≥ 18, M 56.0±10.1 y	83.2%	M 4.4±3.2 y post-tx, range 0.5–14.2	Max 6.2 y after baseline	Anxiety, Depression subscales, Kellner Symptom Questionnaire, score > median	Depression, anxiety with Mortality	1
Owen, 2006[64]	U.S.A.	108	Adults, M 53.3+12.9 y	73.1%	Evaluation for tx	M 2.7 y post-tx, range 1 day- 5.7 y	DSM depressive and anxiety disorder diagnoses recorded in medical record at tx evaluation	Depression, anxiety with Mortality Infection[b] Hospitalization[b]	4
Havik, 2007[33]	Norway	147	Adults, M 53.4±12.4 y, range 18–73	76.9%	M 5.6±3.9 y post-tx, range 1–16	M 6.0±0.3 after baseline	BDI, score ≥10	Depression with Mortality	4
van de Beek, 2008[65]	U.S.A.	313	Adults and children, median 52 y, IQR 38–59	---	Post-tx before hospital discharge	Median 5.5 y post tx, IQR 2.2–9.9, max 18 y	Diagnosis of depression recorded in medical record	Depression with Mortality	4
Favaro, 2011[66]	Italy	107	Adults, M 58.1±11.8 y, range 18–75	79.4%	M 3.4±1.4 y post-tx, range 1–5	M 7.8±0.5, y after baseline, range 7.2–8.9	DSM-IV post-tx current depression, PTSD diagnoses by SCID interview DSM-IV pre-tx life depression, PTSD diagnoses by SCID interview	Depression with Acute rejection[b] Depression, anxiety with Mortality Cancer	4

Study first author, year, related publications	Country	Sample size	Baseline age	Male gender	Timing of baseline assessment	Post-tx followup duration	Psychiatric risk factor measures	Risk factor-outcome relationships examined[a]	Methodologic Quality[c]
Farmer, 2013[67]	U.S.A.	555	Adults, M 59.4 y	79%	5–10 y post-tx	M 2.5 y after baseline, max 3.5 y	Cardiac Depression Scale, mean score	Depression with Mortality	3
Liver									
Singh, 1997[68]	U.S.A.	60	Adults	---	While on wait list for tx	Max 2.7 y post-tx	BDI-1, score >10	Depression with Mortality	3
Gedaly, 2008[69]	U.S.A.	147	Adults, median 52 y, range 26–69	89.4%	Pre-tx	Median 3.4 y post-tx, max 11.7	History of depression recorded in pre-tx medical record	Depression with Mortality	7
Rowley, 2010[37]	U.S.A.	358	Adults, M 50.2±9.7 y, range 18–73	62.3%	Evaluation for tx	Median 6.2 y post-tx, range 0–13	DSM-IV-TR depressive disorder diagnoses in medical record of transplant evaluation	Depression with Mortality	6
Corruble, 2011[39],2011,[70] 2012[71]	France	134 152 (overlaps with 134)	For n=134: Adults, ≥18, M 50.3±10.6 y For n=152: adults, ≥18	For n=134, 63.4%	While on wait list for tx	n=134: median 3.6 y post-tx, range =0.5–5.0 n=152: max 1.5 y post-tx	For n=134: BDI, short form, mean score State subscale, STAI, mean score For n=152: BDI, short form, score ≥4	Depression with Graft loss Depression, anxiety with Mortality	4
DiMartini, 2011[31] Rogal, 2013[72]	U.S.A.	167	Adults, M 50±8 y	84%	Across first year post-tx	9 y after baseline year	BDI-1, groups of patients with consistently low symptoms during year (scores<10), increasing symptoms, or consistently high symptoms (scores>15)	Depression with Mortality	5
Rogal, 2011[36]	U.S.A.	179	Adults, aged ≥18, M 52.1 y	71.5%	Evaluation for tx and while on wait list for tx	M 2.8 y post-tx, max 5.8 y	History of depression, antidepressant medication use in pre-tx medical record	Depression with Mortality Acute rejection Graft loss Infection Hospitalization	7
Kidney									
*Burke, 2008[40]	South Africa	23	Adults, M 29.7 y	52.2%	While on wait list for tx	All at 6 mo post-tx	State subscale, STAI, mean score[b]	Anxiety with Acute rejection[b]	1
Dobbels, 2008[32]	U.S.A.	47,899	Adults and children, 3% aged 0–17, 97% aged ≥18	60.0%	0–3 y post-tx	Max 3 yr post-tx	Medicare claim for ICD-9 diagnosis of depression not elsewhere classified recorded in United States Renal Data System database	Depression with Mortality Graft loss Graft loss (death censored)	5
Novak, 2010[34] Molnar-Varga, 2011[73]	Hungary	879	Adults, ≥18, M 49±13 y	58.4%	≥ 3 mo post-tx, median 4.5 y	Median 7.8 y after baseline	Center for Epidemiologic Studies Depression scale, mean score and score ≥18	Depression with Mortality Graft loss (death censored)	5
Corruble, 2011[39]	France	187	Adults, ≥18 y	---	While on tx wait list	Max 1.5 y post-tx	BDI, short form, score ≥4	Depression with Mortality Graft loss	4
Zelle, 2012[74]	The Netherlands	527	Adults, M 51 ±12 y	55.0%	Median 6.0 y post-tx, IQR 2.6–11.4	Median 7.0 y after baseline, IQR 6.2–7.5	Depression subscale, SCL-90, summed score ≥25	Depression with Mortality	5

Study first author, year, related publications	Country	Sample size	Baseline age	Male gender	Timing of baseline assessment	Post-tx followup duration	Psychiatric risk factor measures	Risk factor-outcome relationships examined[a]	Methodo-logic Quality[c]
								Graft loss (death censored)	
Lung									
*Cohen, 1998[75]	Canada	107	Adults, ≥23 y	---	Evaluation for tx	Max ~8.5 y post-tx	BDI, mean score[b] and score >13 State subscale, STAI, mean score[b]	Depression, anxiety with Mortality[b] Acute rejection[b] Chronic rejection[b] Infection[b]	1
Vermeulen, 2008[76]	The Netherlands	200	Adults, M 45 y, range 20–68	50.0%	While on tx wait list, assessment closest to tx (M 2.1 mo pre-tx)	Max ~14 y post-tx	ZDS, mean score State subscale, STAI, mean score	Depression, anxiety with Mortality	5
Evon, 2010[77]	U.S.A.	76	Adults, M 34.8 y	43.4%	Evaluation for tx	Max > 9 y post-tx	BDI, mean score	Depression with Mortality	4
Smith, 2014[35]	U.S.A.	201	Adults, M 49.1±13.2 y	38.8%	While on wait list for tx	M 9.2±1.5 y post-tx, range 4–12 y	BDI-II, mean score and score >13 State subscale, STAI, mean score	Depression, anxiety with Mortality	6
Other									
*Popkin, 1993[78] (pancreas)	U.S.A.	80	Adults, M 31.6 y	28.8%	Evaluation for tx	M 3.8 y post-tx, range 0–4.3 y	DSM-III depressive and anxiety disorder diagnoses from Diagnostic Interview Schedule conducted at tx evaluation[b]	Depression, anxiety with Graft loss[b]	5
*Dobbels, 2009[79] (heart, liver, or lung recipients)	Belgium	125	Adults, ≥18 y	---	While on wait list for tx	0.5–1 yr post-tx,	Depression, anxiety subscales, Hospital Anxiety and Depression Inventory, categorized into 4 levels of severity[b]	Depression with Graft loss[b]	3

*Study included in systematic review but not in the meta-analysis because insufficient information was provided in order to calculate any effect size measure.

[a]For each study, only risk factor-outcomes that were examined with appropriate analyses are listed (i.e., those that did not adjust for censoring in follow-up time, or provide sufficient data to perform such calculations, were excluded). Transplant outcomes were determined in all studies from medical record or registry reviews, with the exception of Burke(40), in which the outcome was based on patient self-report.

[b]Although appropriate analyses were performed to examine this variable, it could not be included in the meta-analysis because risk estimates and 95% CIs could not be determined from the information provided in the study.

[c]1=low, 7=high; see text for description of ratings.

Abbreviations: BDI, Beck Depression Inventory; CIDI, Composite International Diagnostic Instrument; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Disease; IQR, interquartile range; PTSD, post-traumatic stress disorder; SCID, Structured Clinical Interview for DSM; SCL-90, Symptom Check List 90; STAI, Spielberger State Trait Anxiety Inventory; tx, transplant; ZDS, Zung Depression Scale.