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Is social support associated with post-transplant medication adherence and outcomes? A Systematic Review and Meta-Analysis

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Abstract

Although social support is used to determine transplant eligibility, the relationship between social support, medication adherence, and survival among transplant recipients remains unclear. We estimated the relationship between social support and post-transplant medication adherence and outcomes using 10 electronic databases from inception to January 2016. Study quality was assessed and all review stages were conducted independently by 2 reviewers. Systematic review

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and meta-analysis were conducted. Thirty-two studies (9102 participants) met inclusion criteria: 21 assessed medication adherence (5197 participants), and 13 assessed clinical outcomes (3905 participants). Among high quality studies, neither social support nor marital status were predictive of medication adherence or post-transplant outcomes. Social support was not associated with medication adherence. It was associated with superior post-transplant outcomes, but the relationship was not significant among high quality studies. Compared to unmarried recipients, married recipients were more likely to adhere to medication post-transplant, but this relationship was not significant among high quality studies. Marital status was not significantly associated with transplant success. Social support is weakly and inconsistently associated with post-transplant adherence and outcomes. Larger prospective studies using consistent and validated measures are needed to justify the use of inadequate social support as a contraindication to transplantation.

Keywords

Social support; transplantation; evaluation criteria; systematic review; psychosocial; transplant outcomes; meta-analysis; disparities

Introduction

Transplantation is the optimal treatment for people with organ failure, and for many, represents the only life-saving therapy. In the United States, approximately 120,000 people await transplantation and waiting times for some organs can exceed 7 years [1]. In 2015 alone, 6287 people died on the waiting list [1]. Therefore, transplant clinicians increasingly must balance concerns for equity and efficiency (medical utility) when selecting candidates [2]. Clinical guidelines issued by the Centers for Medicare and Medicaid Services (CMS) and professional societies provide explicit recommendations for use of medical, demographic, psychological, and lifestyle factors to assist transplant centers in determining eligibility and balancing equity and efficiency [3–8]. However, vague CMS guidelines have raised concerns about potential ambiguity and lack of evidence for some waitlist criteria, including social support [9–12]. Lack of specificity regarding social support definitions and acceptable support thresholds has resulted in significant variation in transplant centers' approaches to using social support to determine eligibility. No guideline explicitly defines social support, however, it often is considered to be services, care, or encouragement provided by social network members, often spouses or partners, family, and friends [13, 14]. Consequently, patients may experience disparate access to the transplant waiting list [15–18].

Currently, inadequate social support is a contraindication to transplantation (Appendix 1) [3–7]. Consequently, patients who cannot demonstrate sufficient social support may be excluded or delayed from receiving life-saving treatment [13, 19, 20]. Persons of low socioeconomic status, racial and ethnic minorities, and those living in rural areas continue to face disproportionate difficulty in successfully completing transplant evaluations, the first step in the transplant process [9, 16–18, 21–26]. This may be partly due to greater difficulty meeting eligibility requirements, including social support [23, 27]. Using social support to determine eligibility could disproportionately impact vulnerable populations, who may face

greater difficulty demonstrating adequate social support because of strained support systems greater difficulty identifying caregivers who can take time away from work, and inability to self-finance home-based assistance [28, 29]. Given its potential for increasing inequality and federal regulations that mandate equity in access to the transplant waitlist [30, 31], it is important to understand how predictive social support is of post-transplant adherence and outcomes.

Lack of an established evidence base for using social support as an eligibility criterion distinguishes it from other evidence-based eligibility criteria, leaves it susceptible to personal bias, and illustrates the importance of synthesizing available data. While some studies have found that less social support is associated with worse transplant outcomes [32–37], others have concluded that this relationship is spurious [26, 38–40]. Although clinicians often cite the importance of social support for ensuring medication adherence post-transplant, the degree to which social support is predictive of adherence remains unclear [41]. Compared to other evidence-based criteria used to determine transplant eligibility, social support is controversial not only because of the variability and subjectivity of its assessment and the inconsistency in its measurement and use between centers [12], but because its relationship to post-transplant outcomes remains uncertain [42, 43]. Furthermore, social support is the only evaluation criterion that uses information about other people to determine an individual's transplant eligibility.

We attempt to resolve these discordant findings, and expand upon this meta-analysis to include more recent data, and specifically assess the importance of marital status which is often used in clinical assessments and clinical outcomes post-transplantation (graft survival, morbidity, and mortality). This study aims to estimate the impact of social support and marital status on (1) medication adherence and (2) clinical outcomes following solid organ transplantation.

Methods

We defined social support as services, care, or encouragement provided by social network members, including spouses or partners, family, and friends. We included measures of perceived support (patient's subjective perception of available support) and received support (objective assessment of informational, instrumental, tangible, emotional, and appraisal support received) [13, 14, 44–46]. Marital status was analyzed separately because it is frequently used in clinical practice as a primary measure of social support, and is considered among the more comparable social support measures [47]. To avoid confounding, we distinguished social support from psychiatric history, financial status, and socioeconomic status (although these are often all included in psychosocial evaluations for transplant eligibility), and restricted our analysis to include studies that have assessed the independent effect of social support on post-transplant outcomes.

Our outcomes were medication adherence and post-transplant clinical outcomes, including graft loss, mortality, and morbidity. In the case of multiple outcomes, we selected the most significant outcome for our primary analysis and performed sensitivity analyses using the

other measures. In studies using overlapping samples, we selected the largest or the one with longest follow-up.

We searched Pubmed, Ovid Medline, PsychINFO, Cochrane Library, and Google Scholar for English-language studies published before December 1, 2015. Search terms included *social support, organ transplantation, and non-adherence* (Appendix 2). We supplemented our search with reference mining of included articles.

Studies eligible for inclusion were those which involved adults (≥ 18 years) who underwent solid organ transplant and reported quantitative outcomes relating to at least one specific aim (i.e., medical adherence, post-transplant clinical outcomes). Due to the paucity of studies examining pre-transplant social support, we included studies that assessed social support preoperatively and postoperatively.

We required that studies report social support explicitly using validated instruments measuring social support, marital status, or measures of perceived and received support. As there is no standard measure for evaluating social support, all measures were considered (e.g., self-report, questionnaire, interviewer rating, and formal evaluation), with the exception of global psychosocial measures that conflate social support with psychological, psychiatric, financial, and other factors.

Two independent reviewers with expertise in social support assessments (KL, AD), transplantation (KL), and meta-analysis (MO, RB) assessed each study for inclusion (KL, AD) and extracted data (MO, RB) including country, follow-up time, method of recruitment, sample demographics, type of transplant, type of social support assessed (perceived vs. received; marital status, etc.), methods of assessment for social support, outcome assessed (medication adherence, clinical outcomes), and methods of outcome assessment. Discrepancies were reconciled through discussion leading to consensus.

Two reviewers (KL, AD) independently assessed the quality of included studies using a validated tool that has been used to assess the quality of observational studies and particularly in studies relating to transplantation [48, 49]. Reviewers evaluated risk of selection, non-response, and information biases, as well as potential confounding, on a 3-point scale, with designated a priori values, based on six study parameters: number of subjects, study design, statistical soundness, medical factors controlled, demographic factors controlled, and psychosocial measures (psychometric properties) (Table 3). Scores ≥ 15 were considered high quality, and scores below 14 were considered low quality. Discrepancies in quality assessments were resolved by discussion.

We first conducted a narrative systematic review, qualitatively categorizing the main factors by which studies differed. These included: type of support (perceived vs. received); support status (married/spouse vs. other support); study design (prospective, retrospective/cross-sectional); method of adherence assessment (electronic, multiple methods, self-report); organ type (kidney, liver, thoracic); and timing of social support assessment (pre vs post-transplant). We then qualitatively assessed the impact of marital status and social support on adherence and outcomes, using these groupings.

In a second step, we estimated the association between social support (marital status or measured social support) and adherence or clinical outcomes using a random-effects meta-analysis. We performed formal tests of heterogeneity by calculating the I^2 statistic [50]. Using the categories identified in the systematic review, we further explored potential heterogeneity by stratifying our analyses on variables potentially related to risk of bias (e.g. study design, study quality), and related to different types of support and outcomes, including transplanted organ (kidney, liver, pancreas, heart, lung), type of social support (perceived vs. received), and method of assessment (self-report, scale, clinical interview). All analyses were conducted using Comprehensive Meta-Analysis software (Biostat, Englewood, NJ).

If studies used multiple methods to evaluate social support, we selected the measure which was validated and most robust, and we included others in sensitivity analyses. If studies used multiple methods to evaluate adherence or clinical outcomes, we consulted experts in the appropriate transplant field (e.g. liver transplantation) to select the most relevant measure.

Results

The literature search identified 550 potential articles from electronic databases, and 45 additional studies were procured through bibliographic review. After removal of three duplicate publications, 547 remaining studies were screened during title and abstract review, 116 of which addressed the specific aims. After full-text screening, 32 studies met inclusion criteria: 21 studies assessed medication adherence and 13 studies assessed clinical outcomes (Figure 1).

Included studies were published between 1992 and 2015 and were conducted in seven countries. Studies included a number of different organ transplant types (with some including multiple organ types): 9 heart, 11 liver, 16 kidney, 8 lung, and 1 pancreas. Five studies included multiple organ types. There was wide variation in social support measures, follow-up time, and population characteristics. Included covariates and potential confounders were not consistent across studies. Studies used either marital status or a validated instrument to assess social support. In the absence of such measurements, social support was reported using modified instruments, semi-structured interview, or chart review with investigator rating (Table 1).

Eighteen (56%) of the included studies were of high quality (Table 3). Twelve (38%) of them were prospective studies. Twelve studies included over 200 participants, and 8 included fewer than 100 participants. Most studies controlled for at least two socio-demographic (age, gender, marital status, or education) and medical factors (diagnosis, type of transplant, or disease stage).

Medication Adherence

Marital Status—Twelve studies (2432 patients) examined the relationship between marital status and medication adherence for heart, liver, lung, and kidney recipients (sample size ranged from 37–544 recipients)[32, 36, 40, 51–59]. Marital status was generally extracted from medical records. Table 2 summarizes study characteristics and Table 3 reflects the

quality assessments. The heterogeneity across all twelve studies was minimal, with an I^2 value of 6%. Overall, married recipients experienced statistically significantly higher odds of medication adherence than their unmarried counterparts (OR =1.46 [CI 1.21, 1.77]) (Figure 2a).

However, evidence regarding the relationship between marital status and medication adherence varied based on study design and study quality (Table 4). In a sensitivity analysis assessing the impact of study design, there was no statistically significant association between marital status and medication adherence among prospective studies (3 studies; N=294; OR=1.24 (CI 0.75, 2.04), whereas a relatively strong and statistically significant association was observed among the 9 retrospective/cross-sectional studies (N= 2138) (OR= 1.51 [CI 1.22, 1.87]). Similarly, the association between marital status and medication adherence was not statistically significant among the six (N=1199) high quality homogenous ($I^2 = 0\%$) studies (OR= 1.20 [CI 0.92, 1.57]). The largest study which assessed the relationship between marital status and medication adherence among 444 liver transplant recipients using lab values, clinician notes, and the adapted version of the Medication Adherence Report Scale (MARS) found no significant association [56]. By contrast, three smaller retrospective studies of kidney recipients found a statistically significant relationship between unmarried recipients and lower medication adherence [40, 51, 53]. As the sensitivity analyses demonstrate, studies finding a significant effect for marital status tended to be retrospective, of lower quality, and mostly involved kidney transplant recipients (8 of 12 studies).

The relationship between marital status and medication adherence varied across organ transplant types (Table 4). The effect of social support on medication adherence was most pronounced in kidney transplant recipients (8 studies, N=1583), with odds of adherence in married participants in this group reaching 1.67 (CI 1.31, 2.13). Many of these were smaller studies, however, with sample sizes ranging from 37 to 252 kidney recipients, ranging in quality. We found that the association between marital status and medication adherence among liver transplant recipients (3 studies, N=696) was not statistically significant (OR= 1.13 [CI 0.85, 1.50]). Heterogeneity was low ($I^2 = 0\%$) for all subgroups. Although marital status was not predictive in one of the studies, other aspects of support (caregiver support and social connectedness) were associated with adherence.

Social Support (non-marital status)—A total of 16 studies (2765 patients) examined the relationship between social support (received or perceived) and medication adherence for heart, liver, and kidney recipients.[26, 32–36, 38–40, 53, 55–57, 60–62] Table 2 summarizes each study. Table 3 reflects the quality assessments. Overall, social support was not associated with post-transplant medication adherence (OR 1.05, CI 0.97, 1.14). There was more heterogeneity among these studies, likely due to inclusion of multiple types of support (perceived and received), and a large number of low quality studies ($I^2 = 66\%$) (Figure 2b). The relationship between social support and medication adherence did not show notable variability by organ transplant type, with the exception of liver transplants (Table 4). We found that liver transplant recipients with higher social support experienced 1.34 (CI 1.01, 1.77) higher odds of medication adherence. Another source of variation resulted from timing of the social support assessments. Among the 3 studies which assessed social support prior

to transplantation, social support was not associated with adherence (OR 1.00, CI 0.83, 1.19). However, among studies using only post-transplant assessments, the effect was larger (OR 1.11 CI 1.00, 1.24). There were no differences based on study design.

Nine high quality studies (N=1898) revealed a somewhat higher association between social support and medication adherence (OR 1.15, CI 1.00, 1.32) although the effect was not statistically significant, and there was notable heterogeneity ($I^2 = 76\%$). This may be due in part to the differences between the impact of perceived versus received support. The majority of studies measured perceived support. In studies which assessed patients using the subjective measure of perceived social support, patients who reported higher levels of social support showed statistically significantly higher odds of medication adherence (OR= 1.16 [CI 1.02, 1.32]).

One of the highest quality studies, a prospective study (n=304) of lung and heart recipients, found a statistically significant association between perceived family caregiver support and medication adherence, measured using recipient and caregiver surveys (OR 2.59; 95% CI, 1.20–5.58,), but reported no correlation with perceived support from friends [33]. Another study by the same authors (using the same measures of perceived support) did not find this association. This may be due to a younger population, a smaller sample size (n=101), transplant type (heart recipients), or differences in measurement of adherence. Four of the highest quality studies assessing perceived support did not find a statistically significant relationship between perceived support and adherence.

Clinical Outcomes

Thirteen studies (3905 patients) examined the association between clinical outcomes post-transplant and social support.[37–39, 63–72] Eight studies examined transplant success, seven assessed patient survival, and one assessed duration of graft function (with some studies reporting multiple outcomes, see Table 1). There was inconsistent evidence for a relationship between marital status and social support by outcome type. For studies that assessed numerous social support and outcome measures, we only included the significant findings in the meta-analytic models. We describe the findings in context, including non-significant findings, below.

Marital status—Five studies (N=3085) assessed the association between marital status and clinical outcomes [37, 39, 64–66]. Compared to unmarried recipients, married recipients experienced 1.25 higher odds of better post-transplant outcomes, but this was not statistically significant (95% CI 0.87, 1.79) (Figure 3a). These studies were heterogeneous ($I^2 = 72\%$). The association between marital status and clinical outcomes varied depending on study design and study quality (Table 4). Prospective and high quality studies (N=2745) found smaller associations (OR 1.08; CI 0.69, 1.69), while retrospective and low quality studies (N=340) found larger associations (OR 1.63; CI 0.88, 3.02), but none of these were statistically significant.

Of the two highest quality studies investigating marital status and survival, the larger, prospective multi-site study of 555 heart transplant recipients found a negative correlation between marital status and survival, suggesting that married recipients experienced lower 5-

to 10-year survival (Hazard Ratio, 2.96, $p=0.03$) [37]. Conversely, a study of 260 recipients of heart transplants found [64] that 5-year survival (excluding deaths within 60 days) was 84% for married patients and 69% for unmarried patients ($p<0.01$).

Social Support—Ten studies ($N=1455$) examined the association between social support (received or perceived) and clinical outcomes [37, 38, 63, 66–72]. Patients reporting higher social support experienced statistically significantly higher odds of superior post-transplant outcomes (OR 1.30 [CI 1.02, 1.66]) (Figure 3b), but the relationship was not significant when analysis was restricted to high quality studies (Table 4). There was no difference between estimates from prospective vs. retrospective studies. The impact of social support on post-transplant outcomes varied by organ transplant type. Social support was associated with 1.58 higher odds of better outcomes for heart recipients which was statistically significant (CI 1.13, 2.20), and 1.27 higher odds of better clinical outcomes for liver recipients, although this was not statistically significant (CI 0.83, 1.95).

Overall, social support was not consistently associated with improved survival. Three studies examined the relationship between perceived social support and survival, and only one found a positive correlation.[37, 69, 72] In the highest quality study ($n=555$), perceived social support (measured using the Social Support Index) was not significantly associated with survival, consistent with findings of another smaller study [37]. Conversely, a single prospective study of moderate quality found that, among 94 heart recipients, 92% of survivors as opposed to 71% of deceased had “good social support” as determined by psychologist and psychiatrist ($p=0.02$).[68]

All three studies examining the relationship between social support (or marital status) and acute rejection episodes found that social support was not associated with rejection.[39, 64, 68] One low quality retrospective study examining outcomes among pancreas recipients found mixed results between perceived social support and graft loss [66]. Among 80 pancreas recipients, authors found that low perceived support from a first degree relative, but not from a spouse or significant other, was significantly correlated with graft loss ($p<0.05$) [66]. Two studies found no significant relationship between social support (received, perceived, or marital status) and hospital length of stay or unexpected hospitalizations.[39, 72]

Discussion

Determining which patients to waitlist for transplantation involves complex decision-making by transplant teams, who must concurrently balance individual patient needs for life-saving treatment with the needs of the population to ensure good stewardship of donated organs. Transplant teams may also consider new CMS initiatives increasing oversight, reporting, and sanctions associated with poor outcomes, which may affect their risk tolerance. Ambiguous guidelines, broadly defined criteria and assessments, and insufficient evidence, can result in listing decisions made upon implicit judgments, undermining the National Organ Transplant Act (NOTA)’s goal of ensuring equity [28, 29].

Our analysis examined the evidence for using social support as a listing criterion. We found an inconsistent relationship between social support or marital status and medication adherence and clinical outcomes following transplantation. For the first time, our study estimates the independent impact of marital status and extends findings about the relationship between social support and medication adherence to clinical outcomes post-transplantation. Although social support is commonly thought to affect transplant outcomes primarily through adherence, we found that social support was not associated with medication adherence (OR 1.05, [CI 0.97, 1.14]). These results are consistent with a previous meta-analysis [41]. Among only high quality studies, social support was not significantly associated with post-transplant outcomes, however, greater social support was associated with superior post-transplant outcomes when all studies were included (OR 1.30 [CI 1.02, 1.66]). Overall, these findings suggest that although there is a statistically significant effect between social support and post-transplant outcomes, the effect does not hold among high quality studies. The relationship of social support to post-transplant outcome is an area where more high quality research is particularly needed, as few studies have examined it (n=10). Marital status was not significantly associated with post-transplant clinical outcomes post-transplantation, but was associated with medication adherence. Compared to unmarried recipients, married recipients experienced increased odds of being adherent to medication post-transplant (OR =1.46 [CI 1.21, 1.77]). Once again, however, the effect was not significant in high quality studies.

While marital status was significantly associated with better medication adherence, our study cannot establish a causal relationship between marital status and adherence, as several pathways and confounders may exist. First, this relationship was not observed in prospective studies or high quality studies, which found no effect for marital status on adherence. Consequently, study design and study quality may have an important effect on the strength and statistical significance of the associations between marital status and adherence reported among transplant recipients. High quality prospective trials are needed to establish a reliable estimate of this relationship.

Second, higher socioeconomic status, which is associated with adherence, is strongly correlated with marital status [73]. Third, although we estimated the overall effect of marital status, we had no indicators of relationship quality or the ways in which marital status contributed to social support. Future qualitative studies should explore this further. Finally, marital status, though potentially the most consistent indicator of social support, may be unstable among transplant recipients. Fear of rejection, new pathologies, adhering to a complex medication regimen, side effects such as weight gain, ascites, and sexual dysfunction, and high out of pocket costs of immunosuppression have been associated with marital strain post-transplantation [74]. As such, these results suggest that marital status and marital quality may be valuable to include in overall assessments of social support resources available to patients to assist with coping post-transplantation. However, there is insufficient evidence to support the use of either marital status or inadequate social support as absolute contraindications to transplantation.

Although we found little evidence to support using social support as a strict contraindication to transplantation, our findings suggest that social support may be protective for transplant

outcomes. Understanding how different types of support affect adherence and outcomes is important. For example, one of the highest quality studies, a prospective study of 304 heart and lung recipients, found that low perceived family caregiver support was associated with medication non-adherence (OR 2.59; 95% CI, 1.20–5.58, $p < 0.05$), but perceived support from friends was not associated with adherence [33]. By contrast, a study of only heart recipients by the same author [60] found that the association between poor caregiver support and medication adherence was not statistically significant, but was associated with difficulty in adhering to the overall regimen (including smoking cessation). A large retrospective study of liver recipients ($n=444$) found that low social support scores were associated with non-adherence, but this was not significant in multivariate models. [56]. Another study examined non-adherence during the preceding six months and found that social support *instability* was associated with non-adherence (OR 2.25, CI 1.09, 4.65), but that low social support *availability* was not [34]. While the inconsistent findings reflect that social support is not a direct explanatory variable, it may play an important indirect role as a mediator or moderator. Some studies examined which aspects of social support which may improve outcomes, including: social engagement, emotional support, improved coping, and instrumental support, among others. Better understanding the mechanisms by which social support is protective may help shape future interventions and inform waitlist criteria.

Understanding whether there is a critical time during which social support is necessary for ensuring good outcomes is also central to informing its use as an eligibility criterion. For example, some transplant centers view inadequate social support is an absolute contraindication, reflecting concerns about transportation primarily in the first year related to: the ability of patients to seek care at the first sign of rejection or illness, to adhere to follow-up visits.[75] This may be especially true of centers serving rural populations. Other centers cite a period of four to six weeks following surgery, reflecting concerns that patients with inadequate social support will be unable to meet the demands of complex and onerous tasks associated with post-operative care, resulting in acute complications. Still others suggest that people without long-term support may be less motivated or able to cope with medication side-effects and may be less inclined to commit to the behavioral changes needed to maintain their graft. Future studies should examine the timing, type, and outcomes of social support to inform eligibility criteria. Qualitative research is needed to gain a more comprehensive understanding of which factors of social support are most important for improving outcomes.

The small sample sizes for some organ types complicate the interpretation of our findings by differing types of organ transplant. For example, although marital status was significantly associated with medication adherence for kidney transplant recipients, the result was not significant for liver transplant recipients. Some of these effects may be due to the small number of studies for some organ transplants. For example, Table 4 shows the sensitivity analyses by organ transplant type, and illustrating that only 3 studies included data on liver transplant patients, but that among the 696 patients included in this analysis, the estimated effect was low (OR 1.13) and not significant. Selection bias may provide one potential explanation for differences in the effect of marital status for liver transplant recipients. Higher rates of divorce and unmarried persons among persons with substance abuse may disproportionately affect liver transplant recipients than recipients of other organs. The effect

of overall social support (disregarding marital status) is highest among liver transplant recipients (OR 1.34). Future studies should further examine differences by transplant type.

Our study is not without limitations. First, as social support cannot be randomly assigned, all studies were observational. Second, given the paucity of data, we included studies that evaluated social support before and after transplantation. Sensitivity analyses indicated that pre-post differences were not significant, although this should be examined further in future studies. Third, few studies examine the relationship between social support and long-term transplant outcomes. More long-term high prospective studies assessing social support before transplantation and following post-transplant outcomes are needed. Finally, it is important to acknowledge the heterogeneity of these studies, and, moreover, the complexity of the social support construct. The results of the meta-analysis may be challenging to interpret because of the variety of definitions and assessments, and as such it may be difficult to draw conclusions from the findings. Our results reflect a combination of expert review and meta-analysis. We approached this topic by first conducting a systematic review, qualitatively analyzing the relationship between social support or marital status, and adherence or outcomes. Our systematic review revealed sufficient similarities among the studies to merit conducting a meta-analysis in certain areas, while other measures (such as behavioral adherence and clinic follow-up) were too inconsistent to assess. The validity of the results of any meta-analysis is dependent upon the quality of the pooled studies. As previously discussed, the studies included in this review are not of high quality and are highly heterogeneous in their definitions of social support, outcome measures, and study designs. Consequently, our findings may not be completely generalizable and should be interpreted with caution.

Vulnerable populations continue to face considerable barriers to transplantation (2–5). Using social support as an eligibility criterion may restrict access for vulnerable populations, who may face greater difficulty demonstrating adequate support because of strained social support systems and inability to finance home-based supportive care. Persons of low socioeconomic status, racial and ethnic minorities, unmarried persons, older patients, and people with disabilities are more likely to have support systems strained by significant caregiving burdens and poor access to resources (18). Though the exact number of patients excluded due to social support is unknown, estimates of how many patients are excluded from the waitlist due to psychosocial factors range from 5.6% of all patients screened for transplantation, to 18.6% of liver transplant candidates at one center [76]. At this center, psychosocial factors were the most common reason for ineligibility among African-American candidates compared to white candidates [39]. Greater research illustrating how social support affects vulnerable populations is needed. More research should also examine the perceived legitimacy and perceived value of social support evaluation to transplant teams.

Although CMS guidelines require that social support be considered in transplant evaluations, lack of consistent definitions and high quality evidence supporting an association between social support and transplant success undercut uniformity and obscure transparency in the evaluation process. Procedures for evaluating social support vary widely between centers, as does the import of social support in listing decisions. While some centers designate lack of

social support as an absolute contraindication for transplantation, others require it only for certain organs, and still others consider social support only in conjunction with other factors. As such, more evidence is needed to determine how and why social support may be protective for transplant outcomes (if not medication adherence), and whether interventions can be tailored to help improve support among patients who have difficulty fulfilling this criterion. In a recent national survey of transplant clinicians, 86% of support the development of a more uniform approach to evaluating and considering social support in listing decisions (unpublished data, under review). Taken together, our findings support this sentiment: suggesting that use of social support should be revisited by the transplant community. CMS and UNOS should consider reevaluating how to incorporate social support in transplant evaluations in response to clinicians' desire for greater clarity and uniformity and the potential of disproportionate disadvantage for vulnerable populations.

Conclusions

Social support may be an unreliable predictor of post-transplant adherence and outcomes. Without greater evidence, professional societies may consider whether social support should be used to definitively exclude candidates from access to transplantation. Larger prospective studies using consistent and validated measures are needed to accurately assess the influence of social support on transplant outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Organ Procurement and Transplantation Network. 2016. [cited 2016 April 15]; Available from: <https://optn.transplant.hrsa.gov/data/>
2. UNOS Ethics Committee. Ethical Principles in the Allocation of Human Organs. United Network on Organ Sharing. 1992
3. Thapar M, Bonkovsky HL. Indications for liver transplant and AASLD guidelines. *Hepatology*. 2015; 61(1):408.
4. Shah PD, Orens JB. Guidelines for the selection of lung-transplant candidates. *Curr Opin Organ Transplant*. 2012; 17(5):467–473. [PubMed: 22941321]
5. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2015; 34(1):1–15. [PubMed: 25085497]
6. Phurrough, S., Salive, M., Harrison, S., Paserchia, L., Lofton, B. Decision Memorandum for Pancreas Transplants Decision Memo. Centers for Medicare and Medicaid Services; 2006.

7. Kasiske B, Cangro C, Hariharan S, Hricik D, Kerman R, Roth D, et al. The Evaluation of Renal Transplant Candidates: Clinical Practice Guidelines. The American Society of Transplantation. *Am J Transplant*. 2001; 2:5–95.
8. Services Department of Health and Human Services. , editor. Centers for Medicare and Medicaid Services. Interpretive Guidelines for the Organ Transplant Conditions of Participation (CoPs) 42 CFR. Baltimore, MD: Department of Health and Human Services; 2016.
9. Johansen KL, Zhang R, Huang Y, Patzer RE, Kutner NG. Association of race and insurance type with delayed assessment for kidney transplantation among patients initiating dialysis in the United States. *Clin J Am Soc Nephrol*. 2012; 7(9):1490–1497. [PubMed: 22837273]
10. Tong A, Hanson CS, Chapman JR, Halleck F, Budde K, Papachristou C, et al. The preferences and perspectives of nephrologists on patients' access to kidney transplantation: a systematic review. *Transplantation*. 2014; 98(7):682–691. [PubMed: 25119129]
11. Tong A, Howard K, Wong G, Cass A, Jan S, Irving M, et al. Nephrologists' perspectives on waitlisting and allocation of deceased donor kidneys for transplant. *Am J Kidney Dis*. 2011; 58(5):704–716. [PubMed: 21864961]
12. Batabyal P, Chapman JR, Wong G, Craig JC, Tong A. Clinical practice guidelines on wait-listing for kidney transplantation: consistent and equitable? *Transplantation*. 2012; 94(7):703–713. [PubMed: 22948443]
13. Dobbels F, De Geest S, Cleemput I, Fischler B, Kesteloot K, Vanhaecke J, et al. Psychosocial and behavioral selection criteria for solid organ transplantation. *Prog Transplant*. 2001; 11:121–132. [PubMed: 11871047]
14. Dew MA, Simmons RG, Roth LH, Schulberg HC, Thompson ME, Armitage JM, et al. Psychosocial predictors of vulnerability to distress in the year following heart transplantation. *Psychol Med*. 1994; 24:929–945. [PubMed: 7892361]
15. Ladin K, Rodrigue JR, Hanto DW. Framing disparities along the continuum of care from chronic kidney disease to transplantation: barriers and interventions. *Am J Transplant*. 2009; 9(4):669–674. [PubMed: 19344460]
16. Norris KC, Agodoa LY. Reducing disparities in assessment for kidney transplantation. *Clin J Am Soc Nephrol*. 2012; 7(9):1378–1381. [PubMed: 22904121]
17. Joshi S, Gaynor JJ, Bayers S, Guerra G, Eldefrawy A, Chediak Z, et al. Disparities among Blacks, Hispanics, and Whites in time from starting dialysis to kidney transplant waitlisting. *Transplantation*. 2013; 95(2):309–318. [PubMed: 23325005]
18. Patzer RE, Perryman JP, Schrager JD, Pastan S, Amaral S, Gazmararian JA, et al. The role of race and poverty on steps to kidney transplantation in the Southeastern United States. *Am J Transplant*. 2012; 12(2):358–368. [PubMed: 22233181]
19. Dew MA, Switzer GE, DiMartini A, Matukaitis J, Fitzgerald MG, Kormos RL. Psychosocial assessments and outcomes in organ transplantation. *Prog Transplant*. 2000; 10(4):239–259. [PubMed: 11232552]
20. Cupples S, Dew MA, Grady KL, De Geest S, Dobbels F, Lanuz D. Report of the Psychosocial Outcomes Workgroup of the Nursing and Social Sciences Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2006; 25(6):716–725. [PubMed: 16730578]
21. Goldfarb-Rumyantzev AS, Sandhu GS, Baird B, Barenbaum A, Yoon JH, Dimitri N, et al. Effect of education on racial disparities in access to kidney transplantation. *Clin Transplant*. 2012; 26(1):74–81. [PubMed: 21198857]
22. Schold JD, Gregg JA, Harman JS, Hall AG, Patton PR, Meier-Kriesche HU. Barriers to evaluation and wait listing for kidney transplantation. *Clin J Am Soc Nephrol*. 2011; 6(7):1760–1767. [PubMed: 21597030]
23. Axelrod DA, Guidinger MK, Finlayson S, Schaubel DE, Goodman DC, Chobanian M, et al. Rates of solid-organ wait-listing, transplantation, and survival among residents of rural and urban areas. *JAMA*. 2008; 299(2):202–207. [PubMed: 18182602]
24. Lehr CJ, Zaas DW. Candidacy for lung transplant and lung allocation. *Thoracic Surg Clinics*. 2015; 25(1):1–15.

25. Schold JD, Heaphy EL, Buccini LD, Poggio ED, Srinivas TR, Goldfarb DA, et al. Prominent impact of community risk factors on kidney transplant candidate processes and outcomes. *Am J Transplant.* 2013; 13(9):2374–2383.
26. Scholz U. Predicting intentions and adherence behavior in the context of organ transplantation: Gender differences of provided social support. *J Psychosomatic Res.* 2012; 72:214–219.
27. Browne T. The relationship between social networks and pathways to kidney transplant parity: evidence from black Americans in Chicago. *Soc Sci Med.* 2011; 73(5):663–667. [PubMed: 21803466]
28. Ladin K, Hanto DW. Understanding disparities in transplantation: do social networks provide the missing clue? *Am J Transplant.* 2010; 10(3):472–476. [PubMed: 20055801]
29. Moore G. Structural Determinants of Men's and Women's Personal Network. *Am Soc Rev.* 1990; 55(5):726–735.
30. National Organ Transplantation Act of 1984, Pub L. 98-507, 98 Stat. 2339-2348 (Oct. 19, 1984). In Washington, D.C.
31. Services Department of Health and Human Services. , editor. Final Rule (63 Federal Register 16295, at 16332). 1998. The "Final Rule" 42 CFR Part 121 Organ Procurement and Transplantation Network.
32. Chisholm-Burns MA, Spivey CA, Wilks SE. Social support and immunosuppressant therapy adherence among adult renal transplant recipients. *Clin Transplant.* 2010; 24(3):312–320. [PubMed: 19694770]
33. Dew MA, Dimartini AF, De Vito Dabbs A, Zomak R, De Geest S, Dobbels F, et al. Adherence to the medical regimen during the first two years after lung transplantation. *Transplantation.* 2008; 85(2):193–202. [PubMed: 18212623]
34. Rodrigue JR, Nelson DR, Hanto DW, Reed AI, Curry MP. Patient-reported immunosuppression nonadherence 6 to 24 months after liver transplant: association with pretransplant psychosocial factors and perceptions of health status change. *Prog Transplant.* 2013; 23(4):319–328. [PubMed: 24311395]
35. Pabst S, Bertram A, Zimmermann T, Schiffer M, de Zwaan M. Physician reported adherence to immunosuppressants in renal transplant patients: Prevalence, agreement, and correlates. *J Psychosom Res.* 2015; 79(5):364–371. [PubMed: 26526310]
36. Prihodova L, Nagyova I, Rosenberger J, Majernikova M, Roland R, Groothoff JW, et al. Adherence in patients in the first year after kidney transplantation and its impact on graft loss and mortality: a cross-sectional and prospective study. *J Adv Nurs.* 2014; 70(12):2871–2883. [PubMed: 24853863]
37. Farmer SA, Grady KL, Wang E, McGee EC Jr, Cotts WG, McCarthy PM. Demographic, psychosocial, and behavioral factors associated with survival after heart transplantation. *The Annals of thoracic surgery.* 2013; 95(3):876–883. [PubMed: 23374446]
38. Kiley DJ, Lam CS, Pollak R. A Study of Treatment Compliance Following Kidney Transplantation. *Transplantation.* 1993; 55(1):51–56. [PubMed: 8420064]
39. Dobbels F, Vanhaecke J, Dupont L, Nevens F, Verleden G, Pirenne J, et al. Pretransplant predictors of posttransplant adherence and clinical outcome: an evidence base for pretransplant psychosocial screening. *Transplantation.* 2009; 87(10):1497–1504. [PubMed: 19461486]
40. Frazier P, Davis-Ali S, Dahl K. Correlates of noncompliance among renal transplant recipients. *Clin Transplant.* 1994; 8:550–557. [PubMed: 7865918]
41. Dew MA, DiMartini AF, De Vito Dabbs A, Myaskovsky L, Steel J, Unruh M, et al. Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. *Transplantation.* 2007; 83(7):858–873. [PubMed: 17460556]
42. Olbrisch ME, Levenson JL. Psychosocial Assessment of Organ Transplant Candidates. *Psychosomatics.* 1995; 36(3):236–243. [PubMed: 7638310]
43. Corley M, Westerberg N, Elswick R, Connell D, Neil J, Sneed G, et al. Rationing Organs Using Psychosocial and Lifestyle Criteria. *Res Nurs Health.* 1998; 21:327–337. [PubMed: 9679809]
44. Chen W, Chen C, Lee P, Wang W. Quality of Life, Symptom Distress, and Social Support Among Renal Transplant Recipients in Southern Taiwan: A Correlational Study. *J Nurs Res.* 2007; 15(4): 319–327. [PubMed: 18080976]

45. Langford C, Bowsher J, Maloney J, Lillis P. Social support: a conceptual analysis. *J Adv Nurs*. 1997; 25:95–100. [PubMed: 9004016]
46. House JS, Landis KR, Umberson D. Social Relationships and Health. *Science*. 1988; 241(4865): 540–545. [PubMed: 3399889]
47. Lindsey, AM., Yates, BC. Social Support: Conceptualization and Measurement Instruments. In: Frank-Stromborg, M., Olsen, SJ., editors. *Instruments for Clinical Health-care Research*. Third. Sudbury, MA: Jones and Bartlett Publishers; 2004.
48. Bland CJ, Meurer LN, Maldonado G. A Systematic Approach to Conducting a Non-statistical Meta-analysis of Research Literature. *Acad Med*. 1995; 70(7):642–653. [PubMed: 7612129]
49. Hoodin F, Weber S. A Systematic Review of Psychosocial Factors Affecting Survival After Bone Marrow Transplantation. *Psychosomatics*. 2003; 44:181–195. [PubMed: 12724499]
50. Higgins J, Thompson S, Deeks J, Altman D. Measuring inconsistency in meta-analyses. *BMJ*. 2003; 327(7414):557–560. [PubMed: 12958120]
51. De Geest S, Borgermans L, Gemoets H, Abraham I, Vlamincx H, Evers G, et al. Incidence, Determinants, and Consequences of Subclinical Noncompliance with Immunosuppressive Therapy in Renal Transplant Recipients. *Transplantation*. 1995; 59(3):340–347. [PubMed: 7871562]
52. Chisholm-Burns M, Pinsky B, Parker G, Johnson P, Arcona S, Buzinec P, et al. Factors related to immunosuppressant medication adherence in renal transplant recipients. *Clin Transplant*. 2012; 26(5):706–713. [PubMed: 22324912]
53. Weng F, Chandwani S, Kurtya K, Zacker C, Chisholm-Burns MA, Demissie K. Prevalence and correlates of medication non-adherence among kidney transplant recipients more than 6 months post-transplant: a cross-sectional study. *BMC Nephrol*. 2013; 14(261)
54. Hugon A, Roustit M, Lehmann A, Saint-Raymond C, Borrel E, Hilleret MN, et al. Influence of intention to adhere, beliefs and satisfaction about medicines on adherence in solid organ transplant recipients. *Transplantation*. 2014; 98(2):222–228. [PubMed: 24926826]
55. Lamba S, Nagurka R, Desai KK, Chun SJ, Holland B, Koneru B. Self-reported non-adherence to immune-suppressant therapy in liver transplant recipients: demographic, interpersonal, and intrapersonal factors. *Clin Transplant*. 2012; 26(2):328–335. [PubMed: 21955028]
56. Lieber SR, Volk ML. Non-adherence and graft failure in adult liver transplant recipients. *Dig Dis Sci*. 2013; 58(3):824–834. [PubMed: 23053889]
57. Russell CL, Cetingok M, Hamburger KQ, Owens S, Thompson D, Hathaway D, et al. Medication adherence in older renal transplant recipients. *Clin Nurs Res*. 2010; 19(2):95–112. [PubMed: 20185804]
58. Stillely CS, DiMartini A, Tarter R, de Vera M, Sereika SM, Dew MA, et al. Liver Transplant Recipients: Individual, Social, and Environmental Resources. *Prog Transplant*. 2010; 20(1):68–74. [PubMed: 20397349]
59. Massey EK, Tielen M, Laging M, Beck DK, Khemai R, van Gelder T, et al. The role of goal cognitions, illness perceptions and treatment beliefs in self-reported adherence after kidney transplantation: a cohort study. *J Psychosomat Res*. 2013; 75(3):229–234.
60. Dew MA, Roth LH, Thompson D. Medical compliance and its predictors in the first year after heart transplantation. *J Heart Lung Transplant*. 1996; 15(6):631–645. [PubMed: 8794030]
61. Rosenberger J, Geckova AM, van Dijk JP, Nagyova I, Roland R, van den Heuvel WJ, et al. Prevalence and characteristics of noncompliant behaviour and its risk factors in kidney transplant recipients. *Transplant Int*. 2005; 18(9):1072–1078.
62. Russell CL, Ashbaugh C, Peace L, Cetingok M, Hamburger KQ, Owens S, et al. Time-in-a-bottle (TIAB): a longitudinal, correlational study of patterns, potential predictors, and outcomes of immunosuppressive medication adherence in adult kidney transplant recipients. *Clin Transplant*. 2013; 27(5):E580–590. [PubMed: 24093614]
63. Smith PJ, Blumenthal JA, Trulock EP, Freedland KE, Carney RM, Davis RD, et al. Psychosocial Predictors of Mortality Following Lung Transplantation. *Am J Transplant*. 2015:1–7.
64. Tam V, Arnaoutakis GJ, George TJ, Russell SD, Merlo CA, Conte JV, et al. Marital status improves survival after orthotopic heart transplantation. *J Heart Lung Transplant*. 2011; 30(12):1389–1394. [PubMed: 21907593]

65. Naiman N, Baird BC, Isaacs RB, Koford JK, Habib AN, Wang BJ, et al. Role of pre-transplant marital status in renal transplant outcome. *Clin Transplant*. 2007; 21(1):38–46. [PubMed: 17302590]
66. Popkin MK, Callies AL, Colon EA, Lentz RD, Sutherland DE. Psychiatric diagnosis and the surgical outcome of pancreas transplantation in patients with type I diabetes mellitus. *Psychosomatics*. 1993; 34(3):251. [PubMed: 8493307]
67. Bunzel B, Wollenek G. Heart transplantation: Are there predictors for clinical success of surgery? *Thorac Cardiovasc Surg*. 1994; 42:103–107. [PubMed: 8016823]
68. Chacko RC, Harper RG, Gotto J, Young J. Psychiatric Interview and Psychometric Predictors of Cardiac Transplant Survival. *Am J Psychiatr*. 1996; 153(12):1607–1612. [PubMed: 8942458]
69. Goetzmann L, Klaghofer R, Wagner-Huber R, Halter J, Boehler A, Muellhaupt B, et al. Psychosocial vulnerability predicts psychosocial outcome after an organ transplant: results of a prospective study with lung, liver, and bone-marrow patients. *J Psychosom Res*. 2007; 62(1):93–100. [PubMed: 17188126]
70. Goetzmann L, Scheuer E, Naef R, Vetsch E, Buddeberg C, Russi E, et al. Psychosocial Situation and Physical Health in 50 Patients > 1 Year After Lung Transplantation. *CHEST*. 2005; 127:166–170. [PubMed: 15653979]
71. Stilley CS, DiMartini A, de Vera M. Individual and environmental correlates and predictors of early adherence and outcomes after liver transplantation. *Prog Transplant*. 2010; 20(1):58. [PubMed: 20397348]
72. Telles-Correia D, Barbosa A, Mega I, Barroso E, Monteiro E. Psychiatric and psychosocial predictors of medical outcome after liver transplantation: a prospective, single-center study. *Transplant Proc*. 2011; 43(1):155–157. [PubMed: 21335175]
73. Tamborini CR. The Never-Married in Old Age: Projections and Concerns for the Near Future. *Soc Sec Bulletin*. 2007; 67(2):25–40.
74. Luk W. The HRQoL of renal transplant patients. *J Clin Nur*. 2004; 13(2):201–209.
75. Personal communication: authors with a purposive sample of national transplant centers. Available by request from authors. 2016
76. Kemmer N, Alsina A, Neff GW. Social determinants of orthotopic liver transplantation candidacy: role of patient-related factors. *Transplant Proc*. 2011; 43(10):3769–3772. [PubMed: 22172844]

Figure 1.
Flow chart of literature search

(a)

Marital Status vs. Adherence

(b)

Social Support vs. Adherence **Figure 2.**

Forest Plots depicting relationship between marital status, social support and medication adherence

(a)

Marital Status vs. Clinical Outcomes **Social Support vs. Clinical Outcomes**

(b)

Figure 3.

Forest Plots depicting relationship between marital status, social support and clinical outcomes

Table 1

Description of Outcome Measures

Adherence Outcomes				
Author, year	Adherence type	Outcome measure name	Outcome measure type	Outcome measure definition
Chisholm-Burns, et al., 2009	Medication	Immunosuppressant Therapy Adherence Scale (ITAS)	Likert scale, self-report	Scale range 0–12; 0=low adherence and 12 = high adherence.
Chisholm-Burns, et al., 2012	Medication	Immunosuppressant Therapy Adherence Scale (ITAS)	Likert scale, self-report	Scale range 0–12; 0=low adherence and 12 = high adherence.
De Geest, et al., 1995	Medication	None	Interview	After interview, raters reached consensus and assigned patients to dichotomous groups (adherent or non-adherent [NA]). NA= Patient reported skipping medication >2-3 times in last year
Dew, et al., 1996	1) Medication 2) Clinic follow-up 3) Behavioral	Health Habits Survey (Adapted version of a validated scale)	Interview	For each category of adherence, respondents were asked about their frequency of non-compliance, then responses were dichotomized based on a “minimal level acceptable” defined a priori by the investigators, and then responses across the three categories were compared and combined
Dew, et al., 2008	1) Medication 2) Clinic follow-up 3) Behavioral	Health Habits Survey (was validated by the time this was published)	Interview	For each category of adherence, respondents were asked about their frequency of non-compliance, then responses were dichotomized based on a “minimal level acceptable” defined a priori by the investigators, and then responses across the three categories were compared and combined
Dobbels, et al., 2009	1) Medication	None	Self-report	Patients answering “never” (Single item: “In the last 14 days, how often did you not take a dose of your medication?”) were considered to be adherent. Any response other than “never” indicated non-adherence with medication taking
Frazier, et al., 1994	1) Medication 2) Clinic follow-up	1) None (Adapted version of a validated scale) 2) None	1) Self-report 2) Self-report	1) Frequency responses of missing medication for various reasons are summed for a composite score, with lower scores indicating lower adherence. 2) Frequency responses of failure to adhere to any aspect of clinic follow-up are summed for a composite score, with lower scores indicating lower adherence
Hugon, et al., 2014	Medication	None (Adapted version of a validated scale)	Self-report and blood trough levels of study med	Unclear
Kiley, et al., 1993	1) Medication 2) Clinic follow-up Behavioral	1) None 2) None 3) None	Clinician report(s)	1) Blood trough level of cyclosporine >30 ng/mL 2) Percentage of missed clinic visits <20% 3) Weight gain percentage <20% Four groups identified via discriminant analysis: overall adherent (diet and medication), NA with diet, NA with medication, and overall NA.

Adherence Outcomes				
Author, year	Adherence type	Outcome measure name	Outcome measure type	Outcome measure definition
Lamba, et al., 2012	Medication	None	Self-report	Respondents classified as NA if they answered "yes" to: "Have you missed or not taken doses of your transplant medications [in the last three months]?" and/or "if you have missed any dose of medications, what has been the frequency in the past three months?"
Lieber, et al., 2013	1) Medication 2) Clinic follow-up	1) Modified Multidimensional Adherence Questionnaire (MAQ) 2) Modified Medication Adherence Report Scale (MARS)	1) Self-report; blood trough levels of study med 2) Self-report	3 methods: Biochemical measure and clinician report; chart evidence (reported dichotomously, as absence or presence); and self-report using adapted MARS and MAQ (higher scores indicate lower adherence) to evaluate adherence-related attitudes and behaviors.
Massey, et al., 2013	Medication	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Likert scale, self-report	NA= Participant responded "yes" to any item on the BAASIS questionnaire (includes dimensions related to taking the medication itself, the timing of the dose, drug holidays, and dose reduction).
Pabst, et al., 2015	Medication	Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS)	Likert scale, self-report	Adherence was determined both with physician rating (scale 1–5, 1= very good adherence, 5= very poor) and the BAASIS questionnaire. If the physician classified a patient as less than "good", the patient was classified as NA
Prihodova, et al., 2014	Medication	None	Interview and self-report	In order to be classified as "Adherent" patient had to have "excellent" ratings on both clinician interview and self-report
Rodrigue, et al., 2013	Medication	None	Interview	Three definitions of self-reported NA (within 6 months): 1) Missed-dose adherent or NA; 2) altered-dose adherent or NA; 3) immunosuppression medication holidays. Patients were NA if they fell within 1 category
Rosenberger, et al., 2005	Medication	None	Self-report and Clinician rating	Patients and clinicians assessed adherence on a 5-point scale (1=modified treatment <1 time in last month; 5=always modified the treatment). Clinicians also based rating on study med blood level variations, Patients were considered adherent if they rated themselves as "excellent", and if this rating was in accordance with that of the clinician.
Russell, et al., 2010	Medication	None	Medication Event Monitoring System (MEMS)	Percentage of time participants were adherent was measured with MEMS cap and verified with MEMS journal.
Russell, et al., 2013	Medication	None	Medication Event Monitoring System (MEMS)	Percentage of time participants were adherent was measured with MEMS cap and verified with MEMS journal.
Scholz, et al., 2012	Medication	Transplant Effects Questionnaire (TxEQ-D) (German version of a validated scale)	Likert scale, self-report	5 items relating to adherence (1=definitely agree, 5=definitely disagree). Higher average score indicates higher adherence. Additionally, participants filled out a survey relating to their intentions to adhere.

Adherence Outcomes				
Author, year	Adherence type	Outcome measure name	Outcome measure type	Outcome measure definition
Stilley, et al., 2010	1) Medication 2) Clinic follow-up	None (Adapted version of a validated scale)	Self-report, MEMS, and Clinician report	1) Self-report and electronic pill bottle monitoring with medication diaries. 2) Percentage of scheduled appointments kept NA= Any deviation
Weng, et al., 2013	Medication	Immunosuppressant Therapy Adherence Scale (ITAS)	Likert scale, self-report	Scale range 0-12; 0=low adherence and 12 = high adherence.
Clinical Outcomes (Transplant success, Patient survival, Infection)				
Author, year	Clinical outcome type	Outcome measure name	Outcome measure type	Outcome measure definition
Bunzel, et al., 1994	Transplant success	None	Clinician report	"Results of surgery" score: Patients categorized as: "excellent," "good result," "moderate result," or "unsatisfactory result" with regard to postop complications; rejections; adverse effects of medication; hospital length of stay; ventricular function; cardiac rhythm; clinical performance
Chacko, et al., 1996	Patient survival	None	1) Clinician report of survival 2) Care index 3) Clinician report of rejection chart review	1) Measured in days lived since transplant 2) Ratio of total hospital and outpatient visit days after transplant to number of days of survival 3) Number of episodes of rejection or infection, and time from transplant until rejection, gathered from
Dobbels, et al., 2009	Transplant success	None	1) Graft loss 2) Clinician report of transplant rejection 3) Hospital length of stay	1) Composite score of patient death, re-transplantation, and chronic rejection, defined between six and 12 months post-TX. 2) Defined as moderate or severe (grade over II biopsies for all TX groups). 3) Number of unscheduled hospitalizations and hospitalized days, determined via chart review.
Farmer, et al., 2013	Patient survival	None	Clinician report of survival	Clinical data collected every six months from medical records
Goetzmann, et al., 2005	Transplant success	None	FEV ₁ (Forced Expiratory Volume)	Lung function (FEV ₁) was measured by spirometry. The term "chronic rejection" was used to describe the condition of bronchiolitis obliterans syndrome according to the criteria defined by the International Society of Heart and Lung Transplantation
Goetzmann, et al., 2007	Patient survival	None	Clinician report of survival	Participants who were alive 12 months post-transplant were classified as "survivors"
Kiley, 1993	Transplant success	None	Graft loss	Retrospective review of participants who continued to have a functioning graft versus those whose graft failed at least 18 months post-transplant
Naiman, et al., 2007	1) Transplant success 2) Patient survival	None	Clinician report	1. Time between the study transplant and the date of return to dialysis or re-transplant. 2. Time between the study transplant and recipient survival.
Popkin, et al., 1993	Graft loss	None	Clinician report of transplant success	Transplant success was measured as the duration of the full function of the graft, measured in weeks

Adherence Outcomes				
Author, year	Adherence type	Outcome measure name	Outcome measure type	Outcome measure definition
Smith, et al., 2015	Patient survival	None	Clinician report of survival	Survival was calculated from the time of 6-month assessment to the date of either death or last contact
Stilley, et al., 2010	Transplant success	None	Clinician report of liver function	Liver enzyme level: aspartate aminotransferase (high= >40 IU/mL), alanine aminotransferase (high= >40 IU/mL), γ -glutamyl transpeptidase, and total bilirubin (high= >65 IU/mL)
Tam, et al., 2011	1) Transplant success 2) Patient survival	None	1) Clinician report of transplant rejection 2) Public record	1) Time to first episode of drug-treated rejection information collected from biopsy notes 2) 5-year survival retrieved from electronic Index database and cross-referenced using the Social Security Death
Telles-Correia, et al., 2011	1) Transplant success 2) Patient survival	None	1) Hospital length of stay 2) Clinician report of survival	1) Length of inpatient stay after transplant, with shorter length of stay implying a better transplant outcome 2) Method not described

Table 2

Study Characteristics

Adherence Outcomes					
Author, year	N Patients	Mean Age (SD or range)	Study Design	Time since Transplantation (SD) (months)	Transplant Type (organ)
Chisholm-Burns, et al., 2009	81	48.9 (NR)	Multicenter Cross-sectional	Mean: 87.3 (56.2)	Kidney
Chisholm-Burns, et al., 2012	512	52.4 (10.7)	Multicenter Cross-sectional	Mean: 109 (89.18)	Kidney
De Geest, et al., 1995	148	46.2 (12.4)	Single-center Cross-sectional	1 year post-transplant	Kidney
Dew, et al., 1996	101	NR (84% were <50 years old)	Single-center Prospective Observational	6 weeks post-transplant at baseline; 12 months post-transplant at end of study	Heart
Dew, et al., 2008	304	NR	Single-center Prospective Observational	2 months post-transplant at baseline; 24 months post-transplant at end of study	Lung (N=178) Heart (N=126)
Dobbels, et al., 2009	141	52.4 (11.5)	Multicenter Prospective Observational	Pre-transplant at baseline; 12 months post-transplant at end of study	Lung (N= 52) Heart (N= 28) Liver (N= 61)
Frazier, et al., 1994	241	42 (13.7)	Single-center Cross-sectional	Range: 3–46 months post-transplant	Kidney
Hugon, et al., 2014	153	55.7 (13)	Multicenter Retrospective Cohort	Mean: 87.6 (6)	Lung (N= 33) Heart (N= 43) Liver (N= 42) Kidney (N= 44) *
Kiley, et al., 1993	105	42 (11.4)	Single-center Retrospective Cohort	Range: 18–55 months post-transplant	Kidney
Lamba, et al., 2012	281	53 (18–73)	Single-center Cross-sectional	1 year post-transplant	Liver
Lieber, et al., 2013	444	NR	Single-center Retrospective Cohort	Range: 6–18 months post-transplant	Liver
Massey, et al., 2013	113	53 (19–75)	Single-center Prospective Observational	6 weeks post-transplant	Kidney
Pabst, et al., 2015	238	53.2 (13.7)	Single-center Cross-sectional	1 year post-transplant	Kidney
Prithodova, et al., 2014	325	48.1 (12.8)	Single-center Prospective Observational	Mean: 7.74 (4.21)	Kidney
Rodrigue, et al., 2013	236	53 (11)	Multicenter Cross-sectional	Range: 6–24 months post-transplant	Liver
Rosenberger, et al., 2005	161	47.7 (11.7)	Multicenter Cross-sectional	Mean: 37.7 (27.3)	Kidney
Russell, et al., 2010	37	60.4 (4.5)	Single-center Longitudinal Observational	NR	Kidney
Russell, et al., 2013	121	NR	Multicenter Longitudinal Observational	NR	Kidney
Scholz, et al., 2012	121	54.3 (13.3)	Single-center Cross-sectional	6 months post-transplant	Lung (N= 42) Heart (N= 19) Liver (N= 29) Kidney (N= 31)

Adherence Outcomes					
Author, year	N Patients	Mean Age (SD or range)	Study Design	Time since Transplantation (SD) (months)	Transplant Type (organ)
Stille, et al., 2010	109	55.3 (9.8)	Single-center Prospective Observational	Range: 1–3 months post-transplant at baseline; 6 month follow up	Liver
Weng, et al., 2013	252	54.7 (NR)	Single-center Cross-sectional	Median: 34.8 (IQR: 16.8, 69.6)	Kidney
Clinical Outcomes					
Author, year	N Patients	Mean Age (SD)	Study Design	Time since Transplantation (mo)	Transplant Type (organ)
Bunzel, et al., 1994	50	NR	Single-center Prospective Observational	Pre-transplant at baseline; 12 months post-transplant at end of study	Heart
Chacko, et al., 1996	94	53 (11)	Single-center Prospective Observational	Mean 5.25 months pre-transplant; Range of post-transplant follow up: 9–56 months	Heart
Dobbels, et al., 2009	141	52.4 (11.5)	Multicenter Prospective Observational	Pre-transplant at baseline; 12 months post-transplant at end of study	Lung (N= 52) Heart (N= 28) Liver (N= 61)
Farner, et al., 2013	555	59.4 (9.84)	Multicenter Prospective Observational	Range: 60–120 months post-transplant	Heart
Goetzmann, et al., 2005	53	42.9 (13.6)	Single-center Cross-sectional	Mean: 50.4 (26.4)	Lung
Goetzmann, et al., 2007	76	44.8 (NR)	Single-center Prospective Observational	Pre-transplant at baseline; 12 months post-transplant at end of study	Lung (N= 22) Liver (N= 26) Bone Marrow (N= 28)
Kiley, 1993	105	42	Single-center Retrospective Cohort	Mean 34.6 (9.9)	Kidney
Naiman, et al., 2007	2061	46.1 (12.4)	Multicenter Cross-sectional	NR	Kidney
Popkin, et al., 1993	80	NR	Single-center Retrospective Cohort	Pre-transplant at baseline; 6 month follow-up	Pancreas
Smith, et al., 2015	132	49.8 (13.1)	Multicenter Retrospective Cohort	Pre-transplant at baseline; 6 month follow-up	Lung
Stille, et al., 2010	109	55.3 (9.8)	Single-center Prospective Observational	Range: 1–3 months post-transplant at baseline; 6 month follow up	Liver
Tam, et al., 2011	260	49 (12)	Single-center Retrospective Cohort	Pre-transplant at baseline; Mean of 68 (52) months post-transplant follow-up	Heart
Telles-Correia, et al., 2011	84	NR	Single-center Prospective Observational	Pre-transplant at baseline; 12 months post-transplant at end of study	Liver

* In Hugon, et al., 2013, nine patients had two transplanted organs (heart-kidney, n=4; heart-lung, n=2; liver-kidney, n=3)

N= Number of patients; SD= Standard Deviation; NR= Not reported

Quality Assessment for Studies of the Relationship Between Social Support and Adherence Or Outcomes After Solid Organ Transplantation in Adult Subjects^a

Study Parameter								
Type of Study and Reference	Number of Subjects	Study Design	Statistical Soundness	Medical Factors Controlled	Demographic Factors Controlled	Mean Ratings for All Behavioral Measures	Total	
Adherence								
1. Chisholm-Burns, et al., 2009	3	1	1	2 _b	3 _{e, f, g, h}	3	13	
2. Chisholm-Burns, et al., 2012	2	1	3	1	2 _f	3	12	
3. De Geest, et al., 1995	3	1	1	2 _b	3 _{f, g}	2	12	
4. Dew, et al., 2008	3	3	3	3 _{b, c}	3 _{f, h}	2	17	
5. Dew, et al., 1996	3	3	3	3 _{a, b, c}	3 _{e, f, h}	2	17	
6. Dobbels, et al., 2009*	3	3	3	3 _{b, c}	3 _{e, f, g, h}	2	17	
7. Frazier, et al., 1994	3	1	1	2 _b	3 _{e, f, g}	2	12	
8. Hugon, et al., 2014	3	2	3	3 _{b, c, d}	3 _{e, f, g, h}	2	16	
9. Kiley, et al., 1993	3	2	1	2 _b	2 _f	1	11	
10. Lamba, et al., 2012	3	1	2	2 _b	3 _{e, g, h}	2	13	
11. Lieber, et al., 2013	3	2	1	3 _{b, c}	3 _{e, f, g, h}	3	15	
12. Massey, et al., 2013	3	3	1	3 _{b, c}	3 _{e, f, g, h}	3	16	
13. Pabst, et al., 2015	3	1	3	3 _{a, b, c, d}	3 _{e, f}	3	16	
14. Prihodova, et al., 2014	3	1	3	3 _{b, c}	3 _{e, f, g, h}	2	15	
15. Rodrigue, et al., 2013	3	2	3	3 _{b, c}	3 _{e, f, g, h}	2	16	
16. Rosenberger, et al., 2005	3	1	3	3 _{a, b, c, d}	3 _{e, f, h}	2	15	
17. Russell, et al., 2013	3	3	1	2 _b	3 _{e, f, g, h}	2	14	
18. Russell, et al., 2010	1	2	2	3 _{b, c}	3 _{e, f, g}	2	13	
19. Scholz, et al., 2012	3	1	2	2 _b	2 _f	2	12	
20. Stille, et al., 2010*	3	3	2	2 _b	3 _{e, g, h}	2	15	

Study Parameter							Total
Type of Study and Reference	Number of Subjects	Study Design	Statistical Soundness	Medical Factors Controlled	Demographic Factors Controlled	Mean Ratings for All Behavioral Measures	
21. Weng, et al., 2013	3	1	3	3 _{a,b,c}	3 _{e,f,g,h}	3	16
Outcomes							
1. Bunzel, et al., 1994	2	3	1	3 _{b,c}	1	3	13
2. Chacko, et al., 1996	2	3	1	3 _{a,b,c}	3 _{e,f}	3	15
3. Dobbels, et al., 2009 [*]	3	3	3	3 _{b,c}	3 _{e,f,g,h}	2	17
4. Farmer, et al., 2013	3	3	3	3 _{a,b}	3 _{e,f,g,h}	3	18
5. Goetzmann, et al., 2005	2	1	2	2 _{b,c}	3 _{e,f,g,h}	3	13
6. Goetzmann, et al., 2007	2	3	3	1	1	3	13
7. Kiley, 1993	3	1	1	3 _{b,c}	1	3	12
8. Nairman, et al., 2007	3	2	3	3 _{a,b,c}	3 _{e,f,g}	2	16
9. Popkin, et al., 1993	2	2	1	3 _{a,b,c}	3 _{e,f,g}	1	12
10. Smith, et al., 2015	3	3	3	3 _{a,b,c}	3 _{e,f,h}	2	17
11. Stille, et al., 2010 [*]	3	3	1	2 _b	3 _{e,g,h}	3	15
12. Tam, et al., 2011	3	2	3	3 _{a,b,c}	3 _{e,f,g}	2	16
13. Telles-Correia, et al., 2011	2	3	3	2 _b	3 _{e,f,h}	3	16

^{*} Included in both outcomes and adherence.

^a System for rating methodological quality of studies. Parameters rated on a scale of 1 to 3, with a higher score indicating higher quality. Subscripts represent specific factors controlled (a=diagnosis, b=type of transplant, c=disease stage, d=risk estimate, e=age, f=gender, g=marital status, and h=educational level).

Table 4

Sensitivity Analyses Results

Variable	Total Trials	Number of Participants	Odds Ratio (95% CI)	I ² (%)
Marital Status vs. Adherence				
All Studies	12	2432	1.46 (1.21, 1.77)	6
Study Quality				
High	6	1199	1.20 (0.92, 1.57)	0
Low	6	1233	1.70 (1.33, 2.18)	0
Study Design				
Prospective	3	294	1.24 (0.75, 2.04)	0
Retrospective/Cross-sectional	9	2138	1.51 (1.22, 1.87)	20
Organ Transplant Type				
Kidney	8	1583	1.67 (1.31, 2.13)	0
Liver	3	696	1.13 (0.85, 1.50)	0
Mixed	1	153	2.73 (1.07, 6.97)	Not Applicable
Method of Adherence Assessment				
Electronic	1	37	1.67 (0.49, 5.72)	Not Applicable
Multiple Methods	4	834	1.15 (0.85, 1.55)	28
Self-report	7	1561	1.67 (1.32, 2.10)	0
Social Support vs. Adherence				
All Studies	16	2765	1.05 (0.97, 1.14)	66
Study Quality				
High	9	1898	1.15 (1.00, 1.32)	76
Low	7	867	1.05 (0.86, 1.27)	47
Study Design				
Prospective	5	654	1.07 (0.91, 1.25)	66
Retrospective/Cross-sectional	11	2111	1.09 (0.97, 1.23)	68
Organ Transplant Type				
Heart	1	86	1.18 (0.97, 1.44)	Not Applicable
Kidney	9	1360	1.00 (0.95, 1.05)	64
Liver	3	788	1.34 (1.01, 1.77)	56
Mixed	3	531	0.97 (0.95, 1.00)	76
Social Support Type				
Perceived	13	2283	1.16 (1.02, 1.32)	65
Received	3	482	0.99 (0.86, 1.14)	72
Method of Adherence Assessment				
Electronic	2	158	1.19 (0.67, 2.12)	0
Multiple Methods	5	1112	1.31 (1.02, 1.69)	77
Self-report	9	1495	0.98 (0.96, 1.00)	63
Timing of Social Support Assessment				

Variable	Total Trials	Number of Participants	Odds Ratio (95% CI)	I ² (%)
Pre-transplant	3	679	1.00 (0.83, 1.19)	64
Post-transplant	13	2086	1.11 (1.00, 1.24)	67
Marital Status vs. Clinical Outcomes				
Pre-transplant	3	679	1.00 (0.83, 1.19)	64
Post-transplant	13	2086	1.11 (1.00, 1.24)	67
All Studies	5	3085	1.25 (0.87, 1.79)	72
Study Quality				
High	3	2745	1.08 (0.69, 1.69)	81
Low	2	340	1.63 (0.88, 3.02)	0
Study Design				
Prospective	3	2745	1.08 (0.69, 1.69)	81
Retrospective/Cross-sectional	2	340	1.63 (0.88, 3.02)	0
Organ Transplant Type				
Heart	2	815	1.07 (0.51, 2.24)	87
Kidney	1	2065	1.17 (1.00, 1.37)	Not Applicable
Pancreas	1	80	1.73 (0.76, 3.92)	Not Applicable
Mixed	1	125	4.88 (1.10, 21.67)	Not Applicable
Social Support vs. Clinical Outcomes				
All Studies	10	1455	1.30 (1.02, 1.66)	25
Study Quality				
High	5	1075	1.31 (0.96, 1.79)	56
Low	5	380	1.28 (0.84, 2.04)	0
Study Design				
Prospective	7	1220	1.32 (0.98, 1.77)	31
Retrospective/Cross-sectional	3	235	1.24 (0.72, 2.15)	38
Organ Transplant Type				
Heart	3	699	1.58 (1.13, 2.20)	1
Kidney	1	105	1.00 (0.49, 2.02)	Not Applicable
Liver	2	294	1.27 (0.83, 1.95)	60
Lung	2	182	0.77 (0.44, 1.37)	0
Pancreas	1	80	2.28 (0.99, 5.24)	Not Applicable
Mixed	1	95	0.97 (0.26, 3.63)	Not Applicable
Social Support Type				
Perceived	9	1405	1.28 (0.99, 1.66)	31
Received	1	50	1.75 (0.61, 4.99)	Not Applicable
Timing of Social Support Assessment				
Pre-transplant	6	1024	1.58 (1.26, 1.99)	0
Post-transplant	4	431	0.86 (0.61, 1.22)	0