Negative Affect and Self-Agency's Association with Medication Adherence in Adult Organ Transplant Recipients:

A Meta-Analytic Study

by

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Abstract

Objective: In organ transplant, prevalence estimates of negative affect (e.g., depressive symptoms) are higher than in the general population and self-agency is required for successful medication regimen self-management. Nonetheless, the roles of these psychological factors for immunosuppressant adherence in the organ transplant population remain unclear.

Methods: Meta-analytic techniques were used to determine the associations between negative affect and self-agency with immunosuppressant adherence and to identify theoretically derived and methodological moderators of these associational effect sizes (ES).

Results: Across 50 studies and 46,106 adult organ recipients, the findings demonstrate that there is a small negative association between negative affect and adherence [mean weighted effect size: r= -.14, p= .00; 95% CI= -.175, -.096] and a small positive association between self-agency and adherence [ES: r= .17, p= .00; 95% CI= .094, .251]. Studies conducted outside of Europe and North America, assessing illness-specific negative affect and utilizing questionnaire adherence measures, and studies of better quality were associated with a larger effect size for the association between negative affect and adherence, and together they explained 54% of the heterogeneity in the effect sizes. For the association between self-agency and adherence, a higher percentage of females and medication-specific self-agency were associated with a larger effect size, explaining 34% of the heterogeneity in the effect sizes.

Conclusions: By elucidating overlooked trends in the existing literature for the associations between negative affect and self-agency with immunosuppressant adherence, the current meta-analyses clarify previously contradicting findings in organ transplant and demonstrate that higher negative affect and lower self-agency are each associated with poorer adherence to immunosuppressants in organ transplant. The findings also shed light on six factors contributing to the existing variability in effects and highlight the importance of careful consideration of study methodology in studies of adherence to immunosuppressants post organ transplant.

Keywords: Medication; Adherence; Organ Transplant; Negative Affect; Self-Agency; Meta-analysis

Dedication

I dedicate this work to :

My Dad and Mom
who have made many difficult sacrifices in life,
without which I would undoubtedly not be where I am today.

To my siblings, Diana, Daniel, and Simon,
who have been the greatest cheerleaders throughout my graduate career.

To my husband, Peter,
for his unfailing patience, support, sacrifice of many weekends, and unending belief in my abilities.

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Last but not least, thanks be to God.

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Glossary

Begg and Mazumdar's rank correlation test	A publication bias test used to assess whether there is an inverse correlation between study size and effect size (i.e., that smaller studies are more likely to be published when they have large effects). The correlation is a rank order correlation (Kendall Tau b) between treatment effect and the standard error (driven primarily by sample size).
Confidence Intervals	Confidence intervals contain a range of values for the summary effect size with 95% certainty.
Duval and Tweedie's trim and fill	A publication bias method, which allows imputing of the "missing studies" on the other side of the mean effect. It is an iterative process which removes the most extreme small studies from one side of the funnel plot, re-computing the effect size at each iteration until the funnel plot is symmetric about the new effect size. The algorithm then adds the original studies back into the analysis computing a mirror image of each, which serves to correct the variance.
Fail-safe N	The fail-safe N represents the number of "missing" studies with a null effect that would be need to be located and included for the cumulative effect size to become non-significant (i.e., $p > .05$).
Funnel Plot	Funnel plots are a visual representation of Fischer's Z (effect size) plotted against the standard error (an estimate of study sample size). In the funnel plot, larger studies appear on the top (smaller standard error) and cluster near the top of the mean effect size. Smaller studies appear at the bottom (larger standard error) and due to more sampling variation in effect size will be dispersed across a range of values, not just near the top of the mean effect size. In the absence of publication bias, it is expected that the studies will be distributed symmetrically about the combined effect size. In the presence of bias, it is expected that the bottom of the plot will show a higher concentration of studies on one side of the mean than the other (i.e., that smaller studies are more likely to be published if they have larger than average effects, which makes them more likely to meet the statistical significance criterion).
Prediction Interval	Prediction intervals estimate a range of values that the true effect size is expected to fall within for 95% of "exchangeable" studies that would be conducted in the future (IntHout et al., 2016).

Chapter 1.

Introduction

In Canada, there continues to be a growing demand for organ transplantation, which is the recommended treatment for organ failure. In 2018, 2849 solid organ transplants were performed (Canadian Institute for Health Information [CIHI], 2019). Of these, the majority were kidney transplants (59.9%) followed by liver (18.7%), lung (12.7%), heart (6.6%), and pancreas transplants (2%) (CIHI, 2019). Following transplantation, organ recipients must be prepared to follow a complex lifelong immunosuppressant regimen to preserve organ functioning and guard against rejection and loss (Pinsky et al., 2009; Takemoto et al., 2007). This is in addition to a treatment regimen that often additionally includes other medications needed for comorbid health conditions (e.g., antihypertensive agents for hypertension). Adherence is a dynamic process defined as "the extent to which . . . [taking medication], corresponds with agreed upon recommendations from a healthcare provider" (Fine et al., 2009; World Health Organization [WHO], 2003). Medication nonadherence is defined as a "deviation from the prescribed medication regimen sufficient to adversely influence its intended effect," and includes both a complete cessation of intake or nonconformity to the prescribed dosing and timing (Fine et al., 2009).

Despite the risks of organ rejection and loss, immunosuppressant nonadherence in organ transplant occurs commonly; the most recent aggregated estimates of the prevalence of immunosuppressant nonadherence are 35.6 (per 100 individuals per year) for kidney transplant, which is more than double that for heart transplant (14.5) and more than five times that for liver transplant (6.7) (Dew et al., 2007). Across all organ transplants, the estimated pooled immunosuppressant nonadherence prevalence is 22.6 (per 100 individuals per year), which is four times the rate of nonadherence observed for clinic appointment attendance (Dew et al., 2007). Therefore, although the majority of transplant recipients are adherent to their immunosuppressants, nonadherence to immunosuppressants remains a clinical challenge for patients and healthcare providers. Prevalence estimates of nonadherence to immunosuppressants vary owing to the wide variation in the methods of assessing adherence (Fine et al., 2009).

1.1. Methods of Assessing Immunosuppressant Adherence

The measurement of immunosuppressant adherence is challenging. Immunosuppressant medication adherence has been examined at both continuous and dichotomous levels, with a preference in research for measuring it on a continuum (Takemoto et al., 2007). There are also a variety of ways of assessing immunosuppressant adherence, classified as direct and indirect methods. Direct methods of measuring adherence are those that provide evidence of drug ingestion (e.g., measurement of blood drug levels), while indirect methods are those which provide some indication of drug taking behavior (e.g., self-report measures and electronic monitoring) (Osterberg et al., 2005). Importantly, each of these methods has its advantages and limitations, providing a unique vantage point, with no one method earning the title of gold standard for clinical use (Fine et al., 2009).

1.1.1. Direct Methods

Direct methods include direct observation, which is the most accurate and objective means of assessing adherence but is also impractical (Osterberg et al., 2005). More commonly used methods include measurement of drug levels or biological markers of the immunosuppressant medication in the blood and conducting urine assays (Osterberg et al., 2005). While these methods are simple to perform, their disadvantages include inconvenience to the patients and healthcare providers, applicability to a limited range of drugs, and accuracy considerations related to the half-life of the drugs (Chisholm, 2002; Osterberg et al., 2005). Urine assays only provide a qualitative indication of drug ingestion (Chisholm, 2002). Moreover, all of these methods are susceptible to the “white-coat adherence” effect, whereby adherence is improved by the patient in the days immediately preceding and subsequent to an appointment (Chisholm, 2002; Denhaerynck et al., 2005; Osterberg et al., 2005). As such, given that several factors can influence the precision of measuring immunosuppressant adherence through these methods, serum drug levels, urine assays, and biological markers are sometimes alternatively classified as indirect methods (Fine et al., 2009).

1.1.2. Indirect Methods

Indirect methods commonly include self-report, collateral report, rates of prescription refills, pill counts, electronic monitoring, chart review, measuring physiological markers and assessing a patient's clinical response (Denhaerynck et al., 2005; Osterberg et al., 2005). In clinical settings, self-report methods are the most useful given their simplicity, practicality, and cost-effectiveness (Osterberg et al., 2005). However, these methods are also dependent on the patient's accurate report, recall, and insight into adherence behavior (Osterberg et al., 2005). Notably, there exists a large variability across self-report measures and the domains of adherence that are assessed (e.g., taking adherence, timing adherence, dosing adherence as well as barriers to adherence). A systematic review by Dobbels and colleagues (2009) recommended only three out of twenty self-report measures as suitable for use with the transplant population when considering criteria of brevity, ease of scoring, and assessment of both timing and taking adherence. These included the BAASIS (Basel Assessment of Adherence Scale for Immunosuppressives), Medication Adherence Self-Report Inventory, and the Brief Antiretroviral Adherence Index (Dobbels et al., 2009). Unfortunately, none of these measures had established validity with transplant recipients, but, rather, were validated on the HIV population (Dobbels et al., 2009). As can be appreciated by the reader, this lack of standardization across self-report measures may make comparisons of adherence levels across samples and studies less clear. Collateral report is similar to and influenced by many of the same problems as self-report, but relies on a healthcare provider or family member to report on adherence behavior (Fine et al., 2009; Osterberg et al., 2005).

Rates of prescription refill and pill counts are simple to perform, though the process is time-consuming. Moreover, the validity of adherence data collected from these methods assumes that the immunosuppressant medication has actually been ingested (rather than discarded, shared, or hoarded) and that the patient visits pharmacies within a single network (Osterberg et al., 2005). Similarly, adherence during periods of patient hospitalization is unlikely to be captured. Owing to their precision and provision of a wealth of information on the timing and frequency of cap openings, electronic monitoring methods (e.g., Medication Event Monitoring System; [MEMS]) are considered the gold standard in drug trials (Fine et al., 2009). Commonly extracted data from electronic monitoring methods include taking adherence (% of prescribed doses taken), dosing adherence (% of days with correct dosing), timing adherence (% of doses taken within a 25% window of

the prescribed timing) and holidays (# of days without medication intake for 60 hours and 36 hours for once and twice daily immunosuppressants, respectively) (Osterberg et al., 2005; Schaffer-Keller et al., 2008). Nonetheless, more regular use of electronic monitoring methods is limited by their high cost, need for adequate staff and patient training, requirement of the patient's attendance to the clinic for the download of adherence data, the data validity's dependence on compliance to electronic monitoring rules (e.g., patients are instructed to only open the electronic bottle when the medication is to be ingested), and potential failure of technology (Osterberg et al., 2005). Utilizing chart review as a method of collecting medication adherence data is one of the least sensitive methods because clinicians are more likely to document major episodes of rejection or graft loss, which only serve as surrogates of nonadherence and do not necessarily capture less clinically significant incidents of nonadherence (Denhaerynck et al., 2005). Finally, assessing a patient's clinical response as an indicator of adherence is simple, but it is inaccurate given that factors other than immunosuppressant adherence can influence patient response (Osterberg et al., 2005).

1.1.3. Efforts at Improving the Assessment of Immunosuppressive Adherence

Given the variability in methods of assessing immunosuppressant medication adherence, the international Consensus Conference on nonadherence to immunosuppressant medications concluded that there does not exist a gold standard for the measurement of adherence in clinical practice, and further, that future studies need to determine the exact combination of individual methods that would result in the most accurate reading of adherence (Fine et al., 2009). Ultimately, the goal is the development of a standardized approach of measuring immunosuppressant adherence that is systematically employed across research and clinical settings (Fine et al., 2009). Existing research provides some direction on how adherence measurement can be improved. Schaffer-Keller et al. (2008) examined the diagnostic accuracy of individual measures of adherence, namely, 1) self-report, 2) immunosuppressant blood trough levels, and 3) collateral report, in comparison to electronic monitoring. Nonadherence according to electronic monitoring was defined as <98% taking adherence and/or one or more drug holidays. The researchers found low (albeit statistically significant) correlations between methods, and further that no single measure had both high sensitivity and specificity. Rather, a combination method that included self-report, collateral report, and blood assay

had the highest sensitivity (72.1%), though this composite also incorrectly identified a number of truly adherent individuals as being nonadherent (i.e., low specificity; 43%). Thus, the suggestion was that this combination of methods be used for screening and that further investigation be conducted when nonadherence is implicated (Schaffer-Keller et al., 2008).

Examination of individual methods' diagnostic prowess in detecting nonadherence as compared to electronic monitoring revealed that self-report had lower sensitivity (21%) than immunosuppressant drug assays (31-60% depending on the drug) and collateral reports by clinicians (57.9%) (Schaffer-Keller et al., 2008). This failure to detect nonadherent individuals who were identified through electronic monitoring may initially partly be explained by self-report's susceptibility to the social desirability effect, whereby recipients respond in a manner that is perceived as being more socially acceptable (i.e., report higher adherence); however, further examination of the predictive values of self-report methods suggests otherwise. The positive predictive value reveals that amongst those with a positive (i.e., "nonadherent") result on self-report only 20% are nonadherent according to electronic monitoring, which may be reflective of the two methods' low bivariate correlations (Schaffer-Keller et al., 2008). Moreover, specificity of self-report (90%) was higher than that of immunosuppressant drug assays (63-80%) and collateral reporting based on one (59%) or two reports (81%) (Schaffer-Keller et al., 2008). The negative predictive value reflects that amongst those with a negative screening (i.e., "adherent") on self-report, 90% are actually adherent on electronic monitoring. Therefore, "adherent" results on self-report may be more dependable than "nonadherent" findings, which provides at least some support against the prevailing assumption that adherence findings on self-report are overestimates. Supporting this, Butler et al. (2004a) found that in comparison to other methods (i.e., serum immunosuppressant levels, collateral reporting, self-report on paper), confidential reporting during an interview on whether doses were sometimes taken two hours later had the highest diagnostic accuracy for detecting both missed doses and erratic timing when electronic monitoring was used as a reference standard. Similarly, in Dew and colleagues' (2007) meta-analysis, self-report methods showed the highest nonadherence rates. Overall, these findings suggest that self-report measurements of adherence may approximate accuracies of electronic monitoring in confidential reporting conditions (though this is understandably not possible in clinical settings), when questions are specific (i.e., querying both timing and taking

adherence), and are carefully framed in a non-judgmental manner. In keeping with this, Kuypers (2020) recommends a combination method approach to facilitate detection of nonadherence clinically that consists of self-report immunosuppressant adherence measures followed by unstructured interview.

1.2. Negative Consequences of Nonadherence to Immunosuppressants in Organ Transplant

Although the exact level of nonadherence to immunosuppressants that is linked to poor outcomes has not been determined, owing to methodological differences in assessing adherence, drugs' varying "forgiveness" levels, and various other factors that may influence graft survival (e.g., matching) (Dew et al., 2018; Fine et al., 2009), there is an agreement that nothing short of full adherence should be the clinical target (De Geest et al., 1998; Pinsky et al., 2009; Takemoto et al., 2007). This is exemplified in heart transplant recipients, for whom research has demonstrated that even minor deviations from the regimen (i.e., <95% of the required doses) are associated with an increased risk of late acute rejection (De Geest et al., 1998). Similarly, in kidney recipients, even less than 95% of adherence has been demonstrated to increase the risk for graft rejection and loss (Nevins et al. 2009).

Nonadherence to immunosuppressant medications is no trivial issue given its ensuing negative impact on the transplant recipient's health, the healthcare system, and the economy. As mentioned above, it has been associated with poor graft outcomes, including acute rejection (De Geest et al., 1998; Mor et al., 1992; Morrissey et al., 2005; Takemoto et al., 2007), chronic rejection (Dickenmann et al., 2002; Takemoto et al., 2007), and graft failure and loss (Morrissey et al., 2005; Pinsky et al., 2009; Takemoto et al., 2007). Butler and colleagues' (2004b) meta-analysis demonstrated that kidney transplant recipients who were nonadherent to immunosuppressants were seven times more likely to experience graft failure compared to those who were adherent. In a prospective study on outcomes of subclinical noncompliance in kidney transplant recipients, those who were nonadherent one-year post transplant had a 3.2 greater risk of experiencing late acute rejection and of having higher serum creatinine (Vlaminck et al., 2004). Further, Denhaerynck and colleagues (2005) estimated that 20% of late acute rejections and 16% of graft losses were at least partly associated with nonadherence to immunosuppressants in kidney transplant recipients. Taken together these findings demonstrate that

nonadherence to immunosuppression significantly compromises the functioning and health of the transplanted organ and recipient, placing greater demand on clinicians and the healthcare system.

1.3. Reasons for Nonadherence

It is widely acknowledged that nonadherence to long-term therapy is a multi-faceted issue with no single factor being solely responsible (Sabate, 2003). To illustrate, in a relatively recent public meeting led by the Food and Drug Administration, transplant recipients identified five main immunosuppressant adherence-related challenges, including 1) distress related to the medications' side-effects and their long-term consequences (e.g., cancer); 2) forgetfulness; 3) coordinating medication and dietary requirements; 4) frequent dosing; and 5) burdens related to monitoring health indicators (e.g., vitals) and multiple clinic visits (Ettenger et al., 2018). A classification system of long term treatment adherence barriers (across various disease) has been put forth by the World Health Organization (WHO) and encompasses characteristics of the patient, his/her environment, and the disease in question (Table 1).

Table 1 World Health Organization's Classification of Adherence-related Barriers into Five Dimensions

Dimension	Examples of Specific Barriers
Socioeconomic	Age; Gender; Education; Race/Ethnicity; Income; Employment; Marital status; Social support; Living Situation; Distance from treatment center
Patient	Resources; Knowledge; Beliefs; Attitudes; Perceptions; Expectations; Perceived health
Therapy	Complexity of medical regimen; Duration of treatment; History of treatment
Disease/Condition	Symptom/Disease severity; Degree of disability; Rate of progression; Type of transplant; Comorbidities
Healthcare system/Provider	Developmental level of health services; Degree of reimbursement by health insurance plans; Medication distribution system; Level of knowledge and training for healthcare providers; System's provision of education to patients

Many risk factors, spanning the dimensional classification listed above, for nonadherence to immunosuppressants in organ transplant recipients have been identified (Fine et al., 2009). The resulting literature reveals some emerging trends for the relationships of such factors with immunosuppressant adherence. Dew and colleagues (2007) used meta-analytic techniques to summarize evidence for the association of age, gender, education, ethnicity, social support, and perceived health status with immunosuppressant nonadherence in adult organ transplant recipients. Of these, only non-white ethnicity, lower social support, and a worse perception of health were related to nonadherence (Dew et al., 2007), with the magnitudes of the effect sizes (ES) being at most small (r= .06, r= .10, and r= .15, respectively; Cohen, 1992). Of note, the association between non-white ethnicity and immunosuppressant nonadherence had a small fail-safe N (fail safe N=8), suggesting that this factor may likely be a proxy for other variables (e.g., insurance status). Importantly, these findings suggest that although nonadherence to immunosuppressants is contributed to by various factors, those of the demographic and socioeconomic domain (e.g., age, gender, education) appear to have little influence on nonadherence.

Based upon this research, there has been increasing research into risk factors belonging to other domains, including the role that psychological factors play in predicting

adherence (e.g., Demian, Shapiro, & Thornton, 2016; Gelb, Shapiro, & Thornton, 2010). Of these, variables belonging to two categories, (1) *negative affect* and (2) *self-agency,* have received considerable attention and are the focus of the current study. As outlined below, both of these factors are relevant to immunosuppressant adherence post-transplant and have the benefit of being common targets of evidence-based psychological interventions (e.g., cognitive behavioral therapies). Further, given that substantial existent literature that is now available, the current inconsistencies across findings can be meta-analytically clarified. In the coming section, *negative affect* and *self-agency* are operationally defined, a case for their relevance to immunosuppressant adherence in organ transplant is presented, and unresolved issues that this study aims to address are outlined.

1.4. Negative Affect

Negative emotions are a common experience for organ recipients as they navigate the uncertainty and stress associated with the evaluation process for transplant eligibility, anticipation of a suitable transplant while on the waitlist, surgery, rehabilitation, and adjustment to lifelong immunosuppression and its side effects. Moreover, recipients must adapt to living under the strain of being immunologically compromised and susceptible to infections (Corbett et al., 2013; Engle, 2001; Olbrisch et al., 2002).

Importantly, although transplantation has been found to lead to significant improvements in physical and overall quality of life for recipients, psychological quality of life is not as consistently improved given the encountered psychosocial difficulties following transplantation (Bravata et al., 1999; Dew et al., 1997). Throughout the transplantation process, recipients may struggle with thoughts and feelings related to loss of control, dependence, helplessness, and doubt about future plans and goals (Engle, 2001). Post transplantation, recipients may be expected to resume a normal life and responsibilities, which may further compound their stress (Engle, 2001). Related to this, transplant recipients speak of the difficulty in dealing with an “invisible disease” (Ettenger et al., 2018). Relational stress with family, friends, and employers is thus commonly encountered as roles are negotiated and expectations adjusted (Engle, 2001). Further, recipients live with fear of rejection of their transplanted organ and the potential consequences of being placed on the waitlist once again and/or the possibility of death while awaiting a suitable organ (Engle, 2001). Recipients have coined the term “post-

transplant stress disorder" to describe their constant fear of losing their transplant (Ettenger et al., 2018). Moreover, as previously mentioned, adjustment to the side effects of immunosuppressants (e.g., weight gain, increased hair growth, diabetes, fatigue, insomnia, cognitive side effects) may be difficult and is associated with distress and frustration (Engle, 2001; Ettenger et al., 2018).

Symptoms of depression are the most studied and common psychological difficulties organ recipients experience (Sher & Maldonado, 2019), with prevalence estimates of clinical levels of depression ranging from 17-25% (Chilcot et al., 2014; Dew et al., 1996; DiMartini et al., 2011) and exceeding those of the general population (National Institute of Mental Health, 2017; Patten et al. 2005). The emotional health of recipients has also been operationalized as alterations in the psychological quality of life, immunosuppressant side effect-related distress, distress, anxiety, stress, and the transplant's emotional impact. Clinically, these various indicators of negative affect commonly cooccur (e.g., depressive and anxiety symptoms; stress and immunosuppressant side effect related distress) and show strong associations with one another. For example, emotional/mental health quality of life is strongly correlated with depressive symptoms (r= -.74, p<.001) in kidney transplant recipients (Barotfi et al., 2006). Similarly, moderate to strong associations are observed between quality of life and both anxiety and depressive symptoms (r= .40 to .74) across both clinical and nonclinical samples (Bjelland et al., 2002). Thus, in the current study, *negative affect* (NA) in organ transplant is operationalized as encompassing these theoretically and empirically related indicators of negative emotion (i.e., depressive symptoms, anxiety symptoms, psychological quality of life, side-effect related distress, stress, and transplant's emotional impact).

1.4.1. Negative Affect's Association with Increased Morbidity and Mortality in Organ Transplant

A meta-analysis conducted several years ago demonstrated a 65% increased risk of mortality in depressed transplant recipients regardless of the type of organ transplant and the timing of depression onset (pre or post- transplant) (Dew et al., 2015). More specifically, in kidney transplant, there is a link between depressive levels and 5-year mortality (Corbett et al., 2013; Novak et al., 2010). Further, kidney transplant recipients with depression have a two-fold increase in graft failure, dialysis return, and death

(Dobbels et al., 2008). In liver transplant, post-transplant depression has been associated with abnormal liver functioning and increased mortality (10-year survival rate of 43% vs. 66% for those high and low on depression, respectively) (Corbett et al., 2013). In heart transplant, pre-transplant depression has been linked to increased complications, but not rejection (Corbett et al., 2013). Together, these findings demonstrate that increased NA, operationalized as depressive symptoms, is associated with an increased risk for poorer organ functioning, organ failure, and mortality.

Although the causal mechanisms linking increased NA and poor clinical outcomes have not been directly studied, proposed mechanisms include lifestyle factors associated with increased NA (e.g., lower physical activity and/or self-medication through drug use) as well as depression's relationship to cardiovascular illness and reduced social support (Chilcot et al., 2014; Dew et al., 2015). Importantly, one of the most commonly proposed mechanisms is through nonadherence to immunosuppressants (Chilcot et al., 2014; Dew et al., 2015). Nonadherence has been implicated as mediating the link between higher NA (both symptoms and diagnosis of depression) and worse clinical outcomes (e.g., graft failure) in organ transplant, including increased mortality (Corbett et al., 2013; Dew et al., 2015; DiMartini et al., 2011; Novak et al., 2010; Smith et al., 2018).

1.4.2. Negative Affect and Adherence

In a meta-analysis on the impact of depression on adherence to general treatment recommendations (e.g., appointment attendance), the authors found that individuals who were depressed were more than three times as likely to be nonadherent compared to those who were nondepressed (DiMatteo et al., 2000). The studies included a mixed medical group with only one study representing transplant (specifically, kidney) recipients (DiMatteo et al., 2000). Interestingly, anxiety did not demonstrate a statistically significant relationship with nonadherence, though it should be noted that none of the studies included in the anxiety and adherence analysis were of transplant recipients (Di Matteo et al., 2000). A more recent review on this topic by Grenard and colleagues demonstrated that patients with chronic diseases who also have depression were almost two times as likely to be nonadherent to medical treatment than those who were nondepressed (Grenard et al., 2011). Similar to DiMatteo et al.'s (2000) study, this review was limited to one study representing the transplant population and further to those studies conducted within the United States. The authors suggested various reasons for depression's potential

effect on nonadherence, including hopelessness and pessimism, decreased motivation, social isolation, and cognitive effects (e.g., decreased attention, memory, processing speed) (Di Matteo et al., 2000; Grenard et al., 2011). Previous research demonstrates that depression is associated with intentional rather than unintentional nonadherence (Griva et al., 2012). Each of these have been identified as correlates of nonadherence to long-term therapy (WHO, 2003) and immunosuppressant medications in organ transplant more specifically (Chisholm-Burns, Spivey, & Wilks, 2009; Griva, Davenport, Harrison, & Newman, 2012; Maikranz et al., 2007).

Research investigating the impact of NA on immunosuppressant medication adherence in organ transplant demonstrates inconsistencies in findings. Consistent with the above meta-analytic findings on the association between NA and nonadherence in other chronic illnesses, some research suggests that as NA increases, nonadherence to immunosuppressants does as well for organ transplant recipients (e.g., Brito et al., 2016; Cukor et al., 2009; O'Carroll et al., 2006). Importantly, NA is a multifaceted factor in transplant recipients that entails common elements shared across many psychological and medical disorders (e.g., depressive or anxiety symptoms) that may also interface with transplant-unique elements (e.g., worry over immunosuppressant side effects). Indeed, consistent with the contention that NA is a risk factor for nonadherence, recipients have identified the emotional distress related to immunosuppressant side effects as being amongst the primary reasons for nonadherence (Jamieson et al., 2016; Tong et al., 2011). In contrast, other findings report a lack of association between NA and adherence to immunosuppressants in organ transplant (e.g., Bosma et al., 2011; De Geest et al., 1998; Russell et al., 2010). This is also consistent with a meta-analytic study of chronic illness groups (not including transplant) where anxiety symptoms were not found to be predictive of adherence (DiMatteo, Lepper, & Croghan, 2000). Qualitative research also suggests that negative emotions (e.g., fear, worry of losing the transplant) can sometimes have an opposite effect, motivating recipients towards better adherence through feelings of indebtedness to the donor or gratitude to the healthcare team (Jamieson et al., 2016).

1.5. Self-Agency

Both self-efficacy and perceptions of personal control have been assessed in pre-transplant evaluations and identified by recipients as being important for successful self-management (Jamieson et al., 2016; Maldonado, 2019). Self-efficacy is a perceived

judgement on “how well one can execute courses of action” (Bandura, 1982, p. 122). Several studies have clarified the relationship between depression and nonadherence in various medical populations demonstrating it to be mediated by the degree of self-efficacy (Sacco et al., 2005; Schoenthaler, Ogedegbe, & Allegrante, 2009; Paterson, 2016). Perceived self-efficacy can be similar to or discordant with one’s true capabilities and has implications for decision-making on the tasks that are taken on or avoided, and the amount of time and effort devoted to these (Bandura, 1982).

A related factor, internal locus of control, refers to the belief that one is able to control the outcomes of one’s life (Rotter, 1966). Living with a transplant requires a high degree of self-management, defined as “the tasks [one] must undertake to live well with one or more chronic conditions” (Adams, Greiner, & Corrigan, 2004, p. 57). These include attendance at appointments, adherence to dietary restrictions and exercise recommendations, self-monitoring for signs of rejection, and adherence to the medication regimen. Research on self-efficacy and control in relation to self-management is motivated by cognitive theories, which commonly posit that one’s perceived degree of self-efficacy and/or of personal control influences the success and degree of engagement with health-related behavior (Ajzen, 1991; Bandura, 2001; Hale, Treharne, & Kitas, 2007). In organ transplant, self-efficacy and personal control are typically assessed by measures of general and/or task-specific self-efficacy, internal health locus of control, and perceptions of illness control. Previous meta-analytic research provides support for the convergent validity of self-efficacy and locus of control indicators (Judge et al., 2002). In this study, this overarching factor reflecting related beliefs about self-efficacy and personal control (Judge et al., 2002; Náfrádi, Nakamoto, & Schulz, 2017; Sherer et al., 1982) is referred to as *self-agency* (SA).

Table 2 Theories Motivating Research on Self-Agency and Adherence in Organ Transplant

Model	Description
Social Cognitive Theory (Bandura, 2001)	Considered to be the most comprehensive theory of behavior change, it posits that health-related behavior is influenced by the perception of control over the outcome, the degree of barriers, and the individual's confidence in carrying out the behavior.
Theory of Reasoned Action (TRA) and Theory of Planned Behavior (TPB) (Ajzen, 1991)	The TRA posits that the intention to perform the health-related behavior is the best predictor of performance of that action. TPB is a derivative of the TRA following the addition of the perception of ease of performing the behavior.
Common Sense Model (Hale, Treharne, & Kitas, 2007)	Illness representations are generated in response to a chronic illness including perceptions regarding the causes, duration, consequences and degree of controllability of the illness.

The relationship between SA and adherence to long-term treatment has been extensively studied in specific chronic illnesses (e.g., HIV) with meta-analytic techniques demonstrating lower self-efficacy to be an important predictor of nonadherence to antiretroviral therapy with a large effect size (Langebeek et al., 2014). In organ transplant, SA has been investigated as a risk factor for nonadherence to immunosuppressant medications, although not as extensively as NA has. Importantly, understanding the association of SA and immunosuppressant adherence in organ transplant has been hampered by inconsistent findings. Some studies report a positive association between SA and adherence (e.g., De Geest et al., 1995; Denhaerynck et al., 2018; Weng et al., 2017) consistent with meta-analytic findings in the HIV+ population (Langebeek et al., 2014). Other studies report a lack of association (e.g., Cukor et al., 2009; Russell et al., 2010; Scholz et al., 2012).

1.6. Potential Moderators of Associations of Negative Affect and Self-Agency with Immunosuppressant Adherence in Organ Transplant

In summary, evidence indicates that the effect of NA and SA on adherence to immunosuppressants in organ transplant remains unclear despite the dozens of studies addressing these questions. On the basis of existing literature, variables that could potentially clarify inconsistencies in the associations between NA and SA with

immunosuppressant adherence in organ transplant recipients were identified. These potential moderators can be categorized on the basis of the 1) operationalization of adherence measures; 2) operationalization of psychological factors (NA and SA); and 3) study/sample characteristics.

1.6.1. Medication Adherence Operationalization

Current findings on the relationship between NA and SA with immunosuppressant adherence are inconclusive perhaps reflecting the non-standardization of adherence measurement that ranges from self-report to electronic monitoring, and the low concordance amongst these methods (Fine et al., 2009; Osterberg et al., 2005; Schafer-Keller et al., 2008). The aim was to capture this inherent variability across adherence measures and to examine its impact on the association of NA and SA with immunosuppressant adherence. First, adherence measures were categorized according to whether adherence ratings were collected via *questionnaires* (self-report or collateral-report methods) or with other *quantitative* methods (e.g., electronic monitoring or serum concentrations).

In terms of questionnaire methods, these can vary by whether they only query execution (i.e., taking, timing, dosing adherence) through questions such as “Did you take your medications?,” or further probe barriers to adherence (e.g., forgetfulness, not feeling well) as previously identified in Dobbels et al.’s (2009) systematic review of commonly utilized self-report adherence measures. Given that the items related to barriers to adherence overlap with those on NA measures (e.g., factors such as forgetfulness are commonly queried as a potential barrier to immunosuppressant adherence and are also asked about in negative affect measures), coding for *barriers* was judged to be of value given the issue of common method bias (Podsakoff et al., 2003). Accordingly, it was hypothesized that adherence measures that query barriers would be more strongly associated with NA than adherence measures that only query execution. Finally, given the large variability in the psychometric properties of utilized adherence measures, we identified whether the adherence measure is e*stablished* or well-known (e.g., electronic monitoring, BAASIS questionnaire) or was rather non-established (e.g., generated by the researchers).

1.6.2. Psychological Factor (Negative Affect and Self-Agency) Operationalization

Elucidating between-study differences in the operational definitions of NA and SA and capturing their measurement nuances permits investigation into whether specific method differences contribute to differential relationships with immunosuppressant adherence. For example, SA has been conceptualized as being behavior-specific (e.g., medication self-efficacy) and also as a general indicator of one's efficaciousness across various tasks and behaviors (e.g., general self-efficacy; AbuSabha & Achterberg, 1997; Woodruff & Cashman, 1993). Research on immunosuppressant adherence in kidney recipients demonstrates that medication-specific self-efficacy loads higher on the construct of self-efficacy as compared to general measures of self-efficacy (Paterson et al., 2018). Together, this suggests that examining the relative impact of *medication-specific* versus general measures of SA on immunosuppressant adherence is essential.

Similarly, NA measures used in organ transplant research differ according to whether they query *illness-specific* emotional reactions (e.g., transplant-related stress) or more general emotional experiences (e.g., psychological quality of life, depressive symptoms, anxiety symptoms). NA measures can also be categorized according to whether they assess *symptoms of potentially diagnosable disorders* (e.g., depression; anxiety) or *other negative affect indicators* (e.g., psychological distress, psychological quality of life, transplant-related stress).

Further, similar to nonadherence measures, both NA and SA measures differ as to whether they are *established* or researcher-generated (e.g., single researcher-generated question querying whether recipients are stressed). By coding for each of these psychological factors' unique characteristics, we aimed to better elucidate their potential contribution to the existing variability in the associations between NA and SA with immunosuppressant adherence.

1.6.3. Study and Sample Characteristics

Other potential moderators examined have demonstrated prior associations with NA or SA and immunosuppressant adherence. For example, while female *gender* is a risk factor for increased depression and symptom distress in organ transplant recipients (Kugler et al., 2009; Sher & Maldonado, 2019) it has also been shown to be a correlate of

better immunosuppressant adherence in kidney transplant recipients (Demian et al., 2016; Denhaerynck et al., 2007). Further, variables that have demonstrated associations with reduced immunosuppressant adherence, including younger *age (*Denhaerynck et al., 2005), low *spousal support* (Dew et al., 2007), longer *time since transplantation* (Denhaerynck et al., 2005), and having a *kidney transplant* (Dew et al., 2007) were examined. Likely owing to healthcare system differences, one meta-analytic study demonstrated higher nonadherence levels in transplant recipients living in the United States compared to those in Europe (Denhaerynck et al., 2006; Dew et al., 2007). This suggested that *geographical location* would also be important to examine as a potential moderator for the association of the psychological variables (NA, SA) with immunosuppressant adherence.

1.7. Study Objectives and Hypotheses

As demonstrated by the above discussion, the role of psychological factors in portending immunosuppressant adherence is obscured across the single-sample organ transplant literature by inconsistencies in study methods, settings, and subsequent results. Meta-analytic approaches can clarify inconsistencies and elucidate overlooked trends in the literature. The very interstudy variation (e.g., differences in settings, approaches and samples) that is precluding decisive conclusions from being drawn from the literature can be systematically investigated with meta-analysis. Using meta-analysis, this work was designed to clarify: (1) the relationship between increased NA and reduced SA with immunosuppressant adherence in organ transplant recipients; and (2) the identifiable theoretically derived and methodological variables that moderate associations between NA and SA with immunosuppressant adherence. It was hypothesized that increased NA would be associated with worse immunosuppressant adherence and that increased SA would be associated with greater immunosuppressant adherence. As indicated, it was further hypothesized that there would be substantial heterogeneity in the effect sizes that would be moderated by interstudy variation in the measurement of immunosuppressant adherence and the psychological factors (NA and SA), as well as moderation arising from variation in study and sample characteristics.

Chapter 2. Method

2.1. Search Strategy and Study Selection

The study protocol was registered on PROSPERO (CRD42018085290). Established guidelines for conducting and reporting meta-analyses were followed (Moher et al., 2009). Studies were identified through a computerized search of CINAHL, MEDLINE, PsychInfo, and Web of Science databases with searches from 1960 (discovery of azathioprine use) until January 2018 and by manualized searches of the bibliographies of reviews on immunosuppressant adherence in organ transplantation. The librarian at Simon Fraser University was consulted and provided guidance on the search strategy utilized (e.g., key word selection; database choice). To capture the largest amount of relevant studies the key terms of *adherence, transplant, and immunosuppressant* and their proxies were utilized for the database search. Please refer to Figure 1 for a flowchart depicting the utilized search strategy and study selection process.

Studies were imported into Mendeley software and duplicates removed. Duplicate studies included those that were true duplicates and studies conducted by the same study group that reported on overlapping samples (Grenard et al., 2011). For the latter, as per previous meta-analytic work (e.g., Langebeek et al., 2014) we included only the more comprehensive study (i.e., largest sample) thereby eliminating the problem of effect size dependency, whereby effect sizes based on overlapping samples are statistically dependent. Effect size dependency can artificially reduce the variance and increase the occurrence of Type I errors (Borenstein et al., 2009; Cooper, 2009).

All studies were inspected to ensure they met the following criteria for inclusion: (a) study type: cross-sectional, longitudinal, case-control, randomized-control, cohort studies, or ecological; (b) study population: adult solid organ transplant recipients (kidney, liver, lung, heart, and/or pancreas) taking immunosuppressant medications (e.g., Azathioprine, Cyclosporine); and (c) provide a zero-order association between either of the psychological variables (NA or SA) and the outcome variable (medication adherence that was inclusive of immunosuppressant adherence). Studies were excluded if they (a) were reviews or case-studies; (b) included recipients of other transplant types (e.g., face, hand, bone marrow, etc.); or (c) were pediatric (<18 years of age). Amongst the grey literature, theses/dissertations were included as these were most likely to have been

subjected to peer-review and to present data on the coded variables of interest for the present meta-analyses (e.g., sample characteristics, detailed methods description) (Cooper et al., 2009).

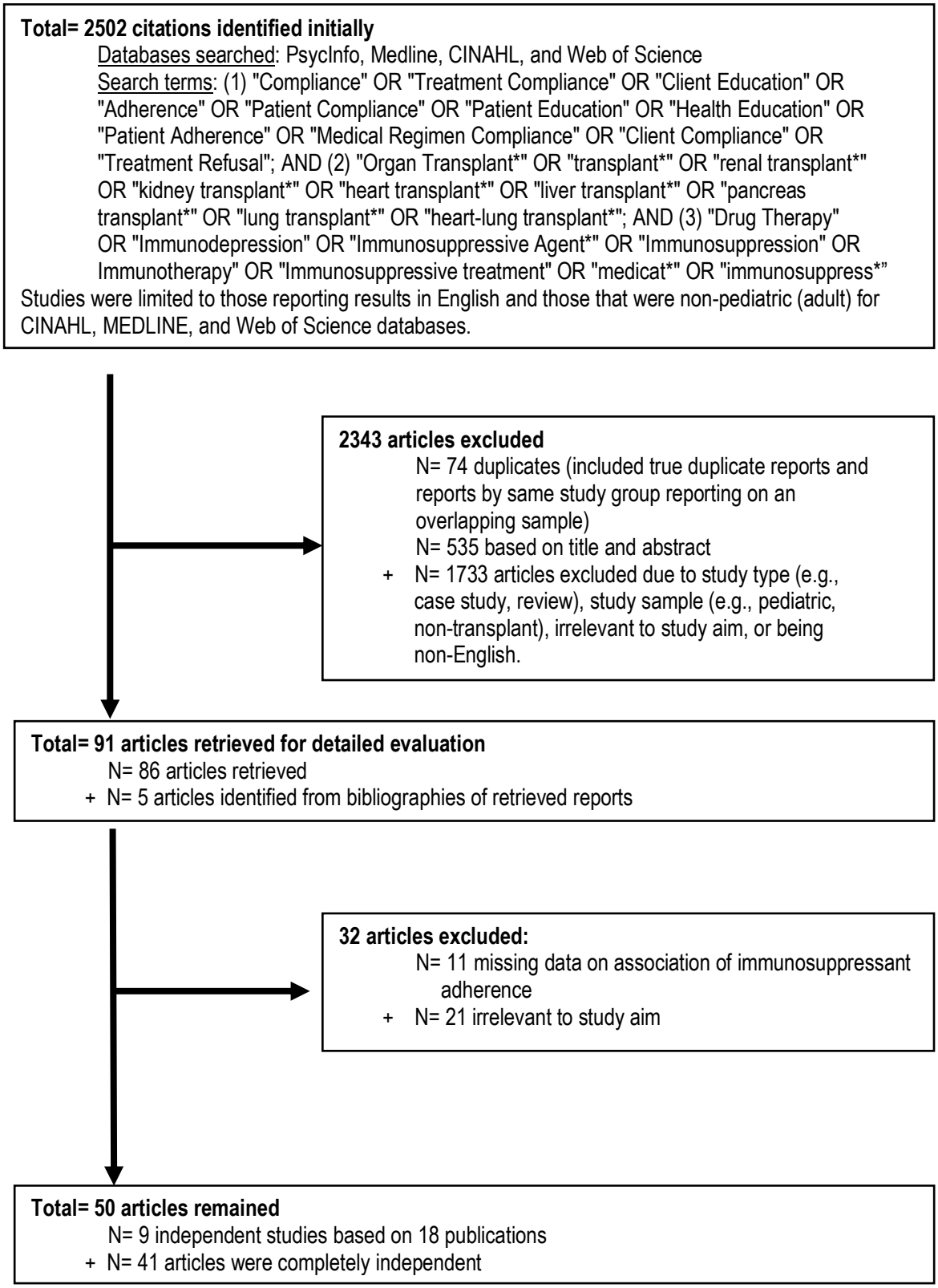


Figure 1 Flowchart of Utilized Search Strategy for the Meta-Analysis

2.2. Data Extraction and Coding

To mitigate against coding bias and ensure coding accuracy, half of the studies were coded by MD and reviewed by a colleague (TP) and the other half were coded by the colleague and reviewed by MD. Coded variables were as follows and are summarized in Tables 3-7.

2.2.1. Study and Sample Characteristics

Study and sample characteristics that were extracted and coded included sample size (*n*), age (mean/median, minimum, and maximum), gender composition, marital status, and geographical location. Transplant specific sample characteristics that were coded for included the organ transplant type (kidney, liver, heart, lung, or mixed sample) and recipients' time since transplantation. The latter reflected the average time since transplantation for the recipients when the adherence measurement was taken. In the case of longitudinal studies (operationally defined as studies that assessed the psychological and adherence variables at several timepoints), this reflected the average time since transplantation at the first point of adherence measurement.

Effect size data type (cross-sectional vs. prospective data) was also coded for. Cross-sectional data was that based on the concurrent measurement of the psychological and adherence variables (e.g., transplant recipients' negative affect and adherence behavior being concurrently assessed during a study clinic visit). Prospective data was that based on the measurement of the psychological variable prior to the adherence variable (e.g., psychological variable measured at baseline and adherence measured after 3 months).

Information that would allow for study quality rating was extracted. Study quality was assessed using the Downs and Black (1998) checklist (Appendix A), which addresses quality of reporting, validity and power as recommended by the STROBE statement for observational studies (von Elm et al., 2007). The checklist was shortened from 27 items to the 9 most relevant to the scope of the current meta-analysis. Study quality could theoretically range from 0 to 9, with higher numbers representing better study quality.

Table 3 Study and Sample Characteristics

Study	Meta-Analysis	Mean Age	Female %	Marital Status %	Organ Type	Time Since Tx (Mean years)	Location	Quality Score
Achille et al., 2006	NA	48	32	--	Kidney	1.58	North America	6.5
Annema et al., 2013	NA	56.4	48.4	79	Liver	9.9	Europe	6
Auamnoy 2000	SA	49	37	68.8	Kidney	--	North America	6.5
Belaiche et al., 2018	SA	54	38.8	71.6	Kidney	--	Europe	7.5
Bosma et al., 2011	Both	--	53.8	67.8	Lung	--	Europe	5.5
Brito et al., 2016	NA	44.1	38	70	Kidney	--	South America	8
Brocks et al., 2017	NA	59.7	21	--	Heart	--	Europe	6
Burkhalter et al., 2014	NA	59.7	37	--	Kidney	--	Europe	7
Butler et al., 2004	Both	48	34	71	Kidney	2.92	Europe	7
Chandler et al., 2017	NA	51	--	--	Kidney	--	North America	6.5
Chisholm et al., 2007	SA	51.6	41.4	44.3	Kidney	8.28	North America	5.5
Constantiner et al., 2013	NA	49.63	53.1	45.2	Kidney	5.8	North America	7
Couzi et al., 2013	NA	49.5	31.7	70.2	Kidney	0.25	Europe	6
Cukor et al., 2009	Both	44	41	--	Kidney	3.5	North America	6.5
De Geest et al., 1995	Both	46.19	43	78	Kidney	--	Europe	5.5
De Geest et al., 1998	Both	--	12.9	79.2	Heart	--	Europe	6
Delibasic et al., 2017	NA	--	28	58	Heart	1	North America	5.5
Denhaerynck et al., 2007	SA	53.6	43.4	77.5	Kidney	8.75	Europe	7.5
Denhaerynck et al., 2017	Both	53.6	27.27	68.85	Heart	3.4	Multi-Continents	7.5
Dew et al., 1996	Both	--	15.8	81	Heart	1	North America	5.5
Dobbels et al., 2009	NA	52.4	33.3	73	Mixed	1	Europe	5
Frazier et al., 1994	Both	42	42	56	Kidney	1.75	North America	4.5
Gelb et al., 2010	NA	50.07	47.6	--	Kidney	8	North America	7
Goetzmann et al., 2012	NA	54	33	100	Mixed	--	Europe	5
Griva et al., 2012	NA	49.7	40.4	68.8	Kidney	5.78	Europe	6
Hugon et al., 2004	SA	55.7	28.8	68.7	Mixed	7.3	Europe	8.5
Jindal et al., 2009	NA	--	40.4	--	Kidney	--	North America	6
Kim et al., 2016	NA	47	46.7	67.6	Kidney	2.96	Asia	8
Lee et al., 2015	NA	46.8	40.6	--	Kidney	--	Asia	5.5

Little et al., 2017	NA	--	60.9	77	Kidney	--	North America	6.5
Massey et al., 2013	SA	--	35.4	73.5	Kidney	0.125	Europe	6
Massey et al., 2015	NA	25.6	33.9	27.4	Kidney	--	Europe	7
O'Carroll et al., 2006	Both	55.8	48	--	Liver	5.82	Europe	5
Pabst et al., 2015	NA	53.15	35	--	Kidney	7.18	Europe	6
Paterson 2016	Both	53.9	40.3	69.7	Kidney	8.98	North America	7.5
Pisanti et al., 2016	NA	52.3	48	--	Kidney	--	Europe	6
Raiz et al., 1999	Both	50.3	47	68	Kidney	4.4	North America	4
Reber et al., 2016	NA	54.1	33.8	73	Kidney	5.5	Europe	9
Rosenberger et al., 2005	NA	47.1	41.9	--	Kidney	3.14	Europe	5.5
Russell et al., 2010	Both	60.38	38	51	Kidney	--	North America	7.5
Russell et al., 2013	Both	51.2	37	64	Kidney	5.7	North America	8
Sabbatini et al., 2014	NA	49.3	60.9	77	Kidney	7.9	Europe	6
Scholz et al., 2012	SA	54.32	33	100	Mixed	--	Europe	5.5
Shabany-Hamedan et al., 2014	NA	41.69	44.8	72.2	Kidney	5	Asia	6
Telles-Correia et al., 2012	Both	57.74	55	--	Liver	1	Europe	5.5
Teng et al., 2015	NA	44.9	39.4	39.4	Kidney	--	Asia	6.5
Wang et al., 2013	NA	51.4	9.6	95.7	Liver	4.6	Asia	8
Weng et al., 2005	Both	--	38.8	59.4	Kidney	1	North America	7
Weng et al., 2013	NA	--	40.1	66.3	Kidney	--	North America	8.5
Weng et al., 2017	SA	45.5	54.5	--	Kidney	7.4	Asia	6

Note: **Dashes indicate that data were not available for the variable. NA= Studies belonging to Negative Affect Meta-Analysis; SA= studies belonging to Self-Agency Meta-Analysis. For mean age, studies with a missing mean age either reported the median (n=5), reported means for sub-groups (n=1), or did not report age at all (n=3). Regarding the mean transplant time (years) variable, studies with a missing mean transplant time either reported median (n=8), reported mean for individual transplant groups (n=1), or did not report time at all (n=10).**

2.2.2. Psychological Factor (Negative Affect and Self-Agency) Characteristics

Negative Affect: Preliminary Analyses

To optimize our coding approach for NA, it was important to first examine a) whether recipients presented with clinical (i.e., potentially diagnosable) levels of depression and anxiety, and b) the difference of the adherence effect size based upon the NA indicator (depressive symptoms, anxiety symptoms, other indicator of NA). The rationale for initially examining the unique associations of depressive symptoms and anxiety symptoms with immunosuppressant adherence was that depression and anxiety are clinically different and because previous meta-analytic work by DiMatteo et al., 2000 had suggested potentially differential relationships. In terms of the former aim, of the studies reporting an adherence effect size for depression or anxiety (k=27), the majority utilized screening (k= 25) rather than diagnostic measures (k= 2, which utilized the Revised Clinical Interview Scale and ICD-10 Claims for Depression; see Table 4). For each study, the mean/median level of depression or anxiety of the sample was compared to established cut-off scores on the respective depression or anxiety screening measures (i.e., the score at or above which suggests the presence of clinically significant levels of depression and anxiety). Additionally, the percentage of the study sample that was clinically depressed or anxious was extracted or calculated using reported data (i.e., on the reported means and standard deviations of the depressive and anxiety variables of the sample). This preliminary analysis suggested that the majority of transplant recipients presented with symptoms of psychological distress rather than clinical levels of depression and/or anxiety (see Results).

Additionally, a number of studies provided adherence effect sizes derived from a) both depression and anxiety indicators, b) depression and another indicator of NA, or c) anxiety and another indicator of NA. The correlations of the adherence effect sizes for each of these NA measurement categories was examined and analyses revealed exceptionally strong effect size correlations across the various NA measurement categories (r= .82 - .99). Please refer to the Results for a presentation of findings that support meta-analytic aggregation of the effect sizes based on the various indicators of NA included in the present meta-analysis, with further analyses to assess potential moderation.

Negative Affect and Self-Agency

Coded variables included type of NA or SA indicator (e.g., depressive symptoms, medication self-efficacy) and the respectively utilized measures (e.g., BDI-II, Long-term Medication Behavior Self-Efficacy Scale (LTMBSE)). Additionally, the following factors were coded (a) whether *illness-specific reactions* were queried (e.g., Transplant Stress Questionnaire) or not (e.g., Hospital Anxiety Depression Scale) for NA; (b) whether the NA measures assessed depressive/anxiety symptoms (as these are symptoms of potentially diagnosable disorders) vs. other indicators of NA; (c) whether *medication-specificity* was assessed (e.g., LTMBSE) or not (e.g., Multidimensional Health Locus of Control Scale) for SA; (d) whether the measure was e*stablished* (well-known) or researcher-generated, (e) the measurement data type (continuous or non-continuous), and (f) whether the psychological factor (NA, SA) was measured pre- or post-transplant. Please refer to Tables 4 and 5 for a summary of coded variables relevant to the psychological factors (NA and SA).

Table 4 Negative Affect and Immunosuppressant Adherence Meta-analysis: Negative Affect-Specific Variables

Study	Negative Affect Indicators	Measure	Illness Specificity measured?	Researcher Generated or Non-established?	Measurement Data Type
Achille et al., 2006	*Composite effect size*: Psychological Distress + Stress + TX-Related Stress	Psychosocial Adjustment to Illness Scale; PSS; Frazier et al., 1995 TX-Stressor Scale	Yes	No	Continuous
Annema et al., 2013	*Composite effect size*: Depressive symptoms + Anxiety symptoms + Negative Affect	CES-D; STAI; PANAS	No	No	Continuous
Bosma et al., 2011	*Composite effect size*: Depressive symptoms + Anxiety symptoms	Zung Self-Rating Depression Scale; STAI	No	No	Non-continuous
Brito et al., 2016	Stress	LSSI	No	No	Non-continuous
Brocks et al., 2017	*Composite effect size*: Mental QOL + Depressive + Anxiety symptoms	Short Form-12; HADS	No	No	Continuous
Burkhalter et al., 2014	Depressive symptoms	DASS	No	No	Continuous
Butler et al., 2004	*Composite effect size*: Depressive symptoms + Illness Emotion	Revised Clinical Interview Schedule; IPQ	Yes	No	Continuous
Chandler et al., 2017	Perceived Stress	PSS	No	No	Continuous
Constantiner et al., 2013	Depressive symptoms	BDI-II	No	No	Continuous
Couzi et al., 2013	Depressive and anxiety symptoms	HADS-Global Score	No	No	Continuous
Cukor et al., 2009	Depressive symptoms	BDI-II	No	No	Continuous
De Geest et al., 1995	Symptom Distress	TX Symptom Frequency and Symptom Distress Scale	Yes	Yes	Continuous
De Geest et al., 1998	Depressive symptoms	BDI	No	No	Continuous
Delibasic et al., 2017	Depressive symptoms	BDI-II	No	No	Non-continuous

Denhaerynck et al., 2017	Depressive symptoms	DASS-21- Depression	No	No	Continuous
Dew et al., 1996	*Composite* effect size: Depressive + anxiety symptoms	Symptom Checklist-90	No	No	Non-continuous
Dobbels et al., 2009	Depressive symptoms	HADS	No	No	Continuous
Frazier et al., 1994	*Composite effect size*: Anxiety symptoms + Depressive symptoms + TX-Related Stress	BSI; BDI; Frazier et al., 1995 TX-Stressors Scale	Yes	Yes	Continuous
Gelb et al., 2010	Depressive symptoms	CES-D	No	No	Continuous
Goetzmann et al., 2012	Stress/Anxiety symptoms	Attitudes Towards Transplant Scale	Yes	Yes	Continuous
Griva et al., 2012	Depressive symptoms	BDI-II	No	No	Continuous
Jindal et al., 2009	Depressive diagnosis	Claims of Post-TX depression from ICD-9 Code	No	No	Non-continuous
Kim et al., 2016	Mental QOL	Short Form- 36	No	No	Continuous
Lee et al., 2015	*Composite effect size*: Symptom distress + Mental QOL	Modified TX Symptom Scale; Short Form-12	Yes	No	Continuous
Little et al., 2017	Depressive symptoms	BDI-II	No	No	Continuous
Massey et al., 2015	Negative Affect	PANAS	No	No	Continuous
O'Carrol et al., 2006	Emotional Effect of TX	BIPQ- Mood Subscale	Yes	No	Continuous
Pabst et al., 2015	*Composite effect size*: Depressive + anxiety symptoms	HADS	No	No	Continuous
Paterson 2016	Depressive Symptoms	CES-D	No	No	Continuous
Pisanti et al., 2016	*Composite effect size*: TX-related stress + Depression/anxiety	TX-Related Stressors Scale; Symptom Checklist	Yes	No	Continuous
Raiz et al., 1999	Mental QOL	SF-36	No	No	Continuous
Reber et al., 2016	*Composite effect size*: Depressive + anxiety symptoms	HADS	No	No	Continuous
Rosenberger et al., 2005	Symptom Distress	Researcher Generated Questionnaire/Interview	Yes	Yes	Continuous

Russell et al., 2010	Depressive symptoms	BDI	No	No	Continuous
Russell et al., 2013	Depressive symptoms	BDI	No	No	Continuous
Sabbatini et al., 2014	Anxiety symptoms	Single question to evaluate presence of anxiety	No	Yes	Non-continuous
Shabany-Hamedan et al., 2014	Psychological QOL	Quality of Life Scale	No	No	Continuous
Telles-Correia et al., 2012	*Composite effect size*: Emotional Effect of TX + Depressive symptoms + Anxiety symptoms	IPQ; HADS	Yes	No	Continuous
Teng et al., 2015	Symptom Distress	Symptom Experience of Immunosuppressive-Related Side Effects Scale (Modified from an original)	Yes	Yes	Continuous
Wang et al., 2013	Symptom Distress	Modified TX Symptom Occurrence & Symptom Distress Scale	Yes	No	Continuous
Weng et al., 2005	*Composite effect size*: Depressive symptoms + TX-related stress + QOL	CES-D; TX-Related Stress Scale; QOL Scale	Yes	No	Both
Weng et al., 2013	*Composite effect size*: Depressive and Anxiety symptoms + Perceived Stress	HADS; PSS	No	No	Continuous

Note: **BDI= Beck Depression Inventory; BIPQ= Brief Illness Perception Questionnaire; BSI= Brief Symptom Inventory; CES-D= Center for Epidemiologic Studies Depression Scale; DASS= Depression, Anxiety, & Stress Scale; HADS= Hospital Anxiety Depression Scale; IPQ= Illness Perception Questionnaire; LSSI= Lipp Stress Symptoms Inventory; PANAS= Positive and Negative Affect Schedule; PSS: Perceived Stress Scale; STAI=State Trait Anxiety Inventory; SF-36= Short Form-36; TX= Transplant.**

Table 5 Self-Agency and Immunosuppressant Adherence Meta-Analysis: Self-Agency-Specific Variables

Study	Self-Agency Indicator	Measure	Medication Specificity Measured?	Researcher Generated or Non-established?	Measurement Data Type
Auamnoy 2000	Medication SE	LTMBSES	Yes	No	Continuous
Belaiche et al., 2018	Control	TPB: Perceived Behavioral Control	Yes	No	Non-continuous
Bosma et al., 2011	Medication SE	LTMBSES	Yes	No	Non-continuous
Butler et al., 2004	Control	BIPQ: Control/cure subscale	No	No	Continuous
Chisholm et al., 2007	Perceived Behavioral Control	TPB: Perceived Behavioral Control	Yes	Yes	Continuous
Cukor et al., 2009	Internal LOC	MHLC	No	No	Continuous
De Geest et al., 1995	*Composite*: Self-Efficacy + Self-Care Agency	LTMBSES; ASA	Yes	Yes	Continuous
De Geest et al., 1998	Medication SE	LTMBSES	Yes	Yes	Continuous
Denhaerynck et al., 2007	Medication SE	LTMBSES	Yes	No	Continuous
Denhaerynck et al., 2017	Medication SE	LTMBSES	Yes	No	Continuous
Dew et al., 1996	Sense of mastery	Sense of Mastery Scale	No	No	Non-continuous
Frazier et al., 1994	Internal LOC	MHLC	No	No	Continuous
Hugon et al., 2004	Perceived Behavioral Control	TPB: Perceived Behavioral Control (2 items)	Yes	No	Continuous
Massey et al., 2013	Goal self-efficacy	Goal self-efficacy to taking medication	Yes	Yes	Continuous
O'Carroll et al., 2006	Personal Control	BIPQ: Personal Control scale	No	No	Continuous

Paterson 2016	*Composite* of five self-efficacy measures	GSE; Self-Efficacy Scale; NGSES; TX-ASES; MASES-Revised	Yes	No	Continuous
Raiz et al., 1999	Internal LOC	MHLC	No	No	Continuous
Russell et al., 2010	Medication SE	LTMBSES	Yes	No	Continuous
Russell et al., 2013	Medication SE	LTMBSES	Yes	No	Continuous
Scholz et al., 2012	Adherence Specific Self-Efficacy	Adherence Specific Self-Efficacy Scale	Yes	Yes	Continuous
Telles-Correia et al., 2012	Personal Control	Revised IPQ (Moss-Morris et al., 2002)	No	No	Continuous
Weng et al., 2005	Internal LOC	MHLC	No	No	Continuous
Weng et al., 2017	Medication SE	LTMBSES	Yes	Yes	Continuous

Note: **ASA= Appraisal of Self-Care Agency; BIPQ: Brief Illness Perception Questionnaire; GSE= General Self-Efficacy Scale; IPQ= Illness Perception Questionnaire; LTMBSES= Long-Term Medication Behavior Self-Efficacy Scale; MHLC= Multidimensional Health Locus of Control Scale; MASES= Medication Adherence Self-Efficacy Scale; NGSES= New General Self-Efficacy Scale; TPB= Theory of Planned Behavior Questionnaire; Tx-ASES= Transplant Adherence Self-Efficacy Scale.**

2.2.3. Adherence Characteristics

Based on the wide variation in immunosuppressant adherence measures utilized across studies, various variables were identified for coding. Adherence characteristics were coded according to measurement modality, which included self-report, collateral report, electronic monitoring, pharmacy data, blood serum levels, chart review, or a combination of any of the previous (e.g., self- and collateral report). Coding also reflected classification of these as questionnaire measures, quantitative measures, or composite-type (i.e., both questionnaire and quantitative adherence measures). Whether the measure queried adherence *barriers* (e.g., forgetfulness or not feeling well) was coded for, as well as if it is es*tablished* (i.e., well-known and commonly used) vs. generated by the study researchers. The measurement data type (continuous, non-continuous) and whether the adherence effect size was based on cross-sectional or prospective data was also coded for. Please refer to Tables 6 and 7 for a summary of coded variables relevant for adherence.

Table 6 Negative Affect and Immunosuppressant Adherence Meta-analysis: Adherence-Specific Variables

Study	Adherence Measurement Method	Measure	Questionnaire Measures?	Barriers Queried?	Researcher generated or Non-established?	Measurement Data Type
Achille et al., 2006	Self-Report	2 Questions adapted from Raiz et al., 1999	Yes	Yes	Yes	Non-continuous
Annema et al., 2013	Self-Report	TEQ	Yes	Yes	No	Continuous
Bosma et al., 2011	Electronic	Electronic pill bottle	No	No	No	Non-continuous
Brito et al., 2016	Self-Report	BAASIS	Yes	No	No	Non-continuous
Brocks et al., 2017	Self-Report	ITAS	Yes	Yes	No	Continuous
Burkhalter et al., 2014	Self-Report	VAS	Yes	No	Yes	Continuous
Butler et al., 2004	Electronic	Electronic pill bottle	No	No	No	Non-continuous
Chandler et al., 2017	Self-Report	MMAS	Yes	Yes	No	Non-continuous
Constantiner et al., 2013	Self-Report	ITAS	Yes	Yes	No	Continuous
Couzi et al., 2013	Self-Report	MAQ	Yes	Yes	No	Non-continuous
Cukor et al., 2009	Self-Report	ITAS	Yes	Yes	No	Continuous
De Geest et al., 1995	Self-Report	Researcher generated	Yes	No	Yes	Non-continuous
De Geest et al., 1998	Combination	Electronic pill bottle + Interview rating	Composite	No	Yes	Non-continuous
Delibasic et al., 2017	Medical Records	Medical Records	No	No	Yes	Non-continuous
Denhaerynck et al., 2017	Self-Report	BAASIS	Yes	No	No	Non-continuous
Dew et al., 1996	Combination	Self-report + Collateral Report	Yes	Yes	Yes	Non-continuous
Dobbels et al., 2009	Self-Report	Researcher generated	Yes	No	Yes	Non-continuous

Frazier et al., 1994	Self-Report	Researcher generated	Yes	Yes	Yes	Continuous
Gelb et al., 2010	Self-Report	TEQ	Yes	Yes	No	Continuous
Goetzmann et al., 2012	Self-Report	TEQ	Yes	Yes	No	Continuous
Griva et al., 2012	Self-Report	MARS	Yes	Yes	No	Continuous
Jindal et al., 2009	Combination	Self-report or Collateral Report	Yes	No	Yes	Non-continuous
Kim et al., 2016	Self-Report	TEQ	Yes	Yes	No	Continuous
Lee et al., 2015	Self-Report	MMAS-8	Yes	Yes	No	Non-continuous
Little et al., 2017	Self-Report	ITAS	Yes	Yes	No	Non-continuous
Massey et al., 2015	Self-Report	VAS	Yes	No	Yes	Continuous
O'Carrol et al., 2006	Self-Report	TEQ	Yes	Yes	No	Continuous
Pabst et al., 2015	Collateral	Physician-reported adherence	Yes	No	Yes	Non-continuous
Paterson 2016	Self-Report	TEQ	Yes	Yes	No	Continuous
Pisanti et al., 2016	Self-Report	TEQ	Yes	Yes	No	Continuous
Raiz et al., 1999	Self-Report	2 researcher generated questions	Yes	Yes	Yes	Continuous
Reber et al., 2016	Self-Report	BAASIS	Yes	No	No	Non-continuous
Rosenberger et al., 2005	Combination	Self-Report & Collateral Report	Yes	No	Yes	Non-continuous
Russell et al., 2010	Electronic	Electronic pill bottle	No	No	No	Continuous
Russell et al., 2013	Electronic	Electronic pill bottle	No	No	No	Continuous
Sabbatini et al., 2014	Self-Report	ITAS	Yes	Yes	No	Non-continuous
Shabany-Hamedan et al., 2014	Self-Report	ITAS	Yes	Yes	No	Non-continuous
Telles-Correia et al., 2012	Self-Report	MAQ	Yes	Yes	No	Continuous

Teng et al., 2015	Self-Report	Adherence with Immunosuppressive Medication Scale	Yes	No	Yes	Continuous
Wang et al., 2013	Self-Report	BAASIS	Yes	No	No	Non-continuous
Weng et al., 2005	Electronic	Electronic pill bottle	No	No	No	Non-continuous
Weng et al., 2013	Self-Report	ITAS	Yes	Yes	No	Non-continuous

Note: **BAASIS= Basel Assessment of Adherence to Immunosuppressive Medication Scale; Composite= effect size was based on a combination of questionnaire and quantitative adherence measures; ITAS= Immunosuppressive Therapy Adherence Scale; MARS= Medication Adherence Report Scale; MAQ= Medication Adherence Questionnaire; MMAS-8= Morisky Medication Adherence Scale; MMAS= Modified Medication Adherence Scale; TEQ= Transplant Effects Questionnaire; UNOS= United Network for Organ Sharing; VAS= Visual Analogue Scale.**

Table 7 Self-Agency and Immunosuppressant Adherence Meta-Analysis: Adherence-Specific Variables

Study	Type of Measure	Adherence Measure	Questionnaire Measures?	Barriers Queried?	Researcher Generated or Non-established?	Measurement Data Type
Auamnoy 2000	Self-Report	Researcher generated	Yes	Yes	Yes	Continuous
Belaiche et al., 2018	Biological	Coefficient of Variation	No	No	No	Non-continuous
Bosma et al., 2011	Electronic	Electronic pill bottle	No	No	No	Non-continuous
Butler et al., 2004	Electronic	Electronic pill bottle	No	No	No	Non-continuous
Chisholm et al., 2007	Pharmacy Data	Pharmacy refill records	No	No	No	Non-continuous
Cukor et al., 2009	Self-Report	ITAS	Yes	Yes	No	Continuous
De Geest et al., 1995	Self-Report	Researcher generated	Yes	No	Yes	Non-continuous
De Geest et al., 1998	Combination	Electronic pill bottle + Interview data	Composite	No	Yes	Non-continuous
Denhaerynck et al., 2007	Electronic	Electronic pill bottle	No	No	No	Non-continuous
Denhaerynck et al., 2017	Self-Report	BAASIS	Yes	No	No	Non-continuous
Dew et al., 1996	Combination	Self-report & Collateral Report	Yes	Yes	Yes	Non-continuous
Frazier et al., 1994	Self-Report	Researcher generated	Yes	Yes	Yes	Continuous
Hugon et al., 2004	Combination	Self-Report (Morisky-Green) + Serum IS Concentrations	Composite	Yes	No	Non-continuous
Massey et al., 2013	Self-Report	BAASIS	Yes	No	No	Non-continuous
O'Carroll et al., 2006	Self-Report	TEQ	Yes	Yes	No	Continuous
Paterson 2016	Self-Report	TEQ	Yes	Yes	No	Continuous
Raiz et al., 1999	Self-Report	2 Questions	Yes	Yes	Yes	Continuous
Russell et al., 2010	Electronic	Electronic pill bottle	No	No	No	Continuous

Russell et al., 2013	Electronic	Electronic pill bottle	No	No	No	Continuous
Scholz et al., 2012	Self-Report	TEQ	Yes	Yes	No	Continuous
Telles-Correia et al., 2012	Self-Report	MAQ	Yes	Yes	No	Continuous
Weng et al., 2005	Electronic	Electronic pill bottle	No	No	No	Non-continuous
Weng et al., 2017	Self-Report	Researcher Generated	Yes	Yes	Yes	Continuous

Note: **BAASIS= Basel Assessment of Adherence to Immunosuppressive Medication Scale; Composite= effect size was based on a combination of questionnaire and quantitative adherence measures; ITAS= Immunosuppressive Therapy Adherence Scale; MAQ= Medication Adherence Questionnaire; TEQ= Transplant Effects Questionnaire.**

2.3. Statistical Analysis

Analyses were conducted using Comprehensive Meta-Analysis (CMA) Software Version 3. For all studies, the Pearson product-moment correlation coefficient (PPMCC; *r)* was extracted or calculated using available statistics or data (e.g., x^2; means and SD). In studies reporting only the regression coefficient, we utilized the procedure suggested by Peterson and Brown (2005) to calculate the zero-order correlation. The PPMCC was selected as the effect size as it provides information on both the magnitude and direction of the association.

2.3.1. Unreported Effect Sizes

In cases where effect sizes for examined associations of interest were unreported (i.e., for statistically non-significant associations), authors were contacted to obtain the effect size. If authors were unreachable after attempts at contact, a conservative estimate effect size of r=0 was assigned (DiMatteo et al., 2000; Grenard et al., 2011; Pigott, 1994). This was done for five studies within the NA analysis and 4 within the SA analysis. Sensitivity analysis were conducted to determine the potential bias of this procedure on the aggregate ESs and ESs at the sub-group level.

2.3.2. Effect Size Dependency

When multiple effect sizes were available for a single study, steps had to be taken to deal with the issue of effect size dependency (Scammacca, Roberts, & Stuebing, 2014); effect sizes were either pooled or selection decisions made to maximize power (i.e., selecting the effect size based on the largest *n* and/or continuous measurement) as previously done in meta-analytic work in this field (Grenard et al., 2011). Specifically, when studies reported effect sizes for multiple adherence methods (e.g., *r* for depression with self-reported *and* electronic measurement), the effect size based on the largest *n* and/or continuous measurement was selected to maximize power. In these instances, the effect sizes were not pooled given the known low concordance between the different methods of adherence assessment (Schafer-Keller et al., 2008). This was applicable for three studies within the NA analysis. The omitted ES in these cases were non-significant, missing ES based on serum concentrations or pharmacy data.

When studies reported multiple effect sizes for the same adherence method (e.g., *r* for depression with self-reported adherence and *r* for psychological distress for self-reported adherence), the effect sizes were pooled by obtaining a single average estimate effect size for that study. In the case of longitudinal studies reporting effect sizes at multiple time points, the effect size at the first adherence measurement was selected as it was based on the largest *n* and would thus maximize statistical power (Grenard et al., 2011). Across both meta-analyses, there were only two longitudinal studies with multiple time point ES data that were subjected to this selection procedure. The reason the ES for these two longitudinal studies were not combined is that both of these studies showed considerable attrition in sample size over the study duration (15% for one and 26% for the other). As such, the decision to select the ES based on the timepoint with the largest sample size has the advantage of being most robust and generalizable.

2.3.3. Type of Meta-analytic Model

A random effects model was employed to estimate the mean weighted correlational effect size for each of the psychological variables (i.e., NA, SA) and immunosuppressant adherence. A random effects model was used instead of the fixed effects model because it is not assumed that the studies were drawn from the same population given differences in the participants' characteristics (e.g., type of transplant, location) and the methods (e.g., means of assessing adherence) employed (Borenstein et al., 2009). Confidence and prediction intervals (95%) were calculated. Confidence intervals contain a range of values for the summary effect size with 95% certainty. Prediction intervals estimate a range of values that the true effect size is expected to fall within for 95% of "exchangeable" studies that would be conducted in the future (IntHout et al., 2016). Sensitivity analyses (i.e., impact on mean effect size with each study removed) and examination of scatterplots for sub-group analyses were used to identify potential outliers. Heterogeneity analyses were conducted to ascertain the degree of heterogeneity present amongst the effect sizes by examining the *Q*-statistic.

2.3.4. Moderator Analyses: Subgroup and Meta-regression

Across all studies, a median for the sample size (*n)*, participant age (mean/minimum/maximum), female%, married%, and the time since transplant was calculated. This value served as a median split for sub-group analyses of these

quantitative variables. Moderators (i.e., variables affecting the association between NA and SA with adherence and therefore potentially accounting for the heterogeneity observed in the effect sizes) were examined through sub-group analyses by pooling within-group estimates of tau-squared and by examining sub-group effect sizes and the overall between-subgroups *(Q_b)* heterogeneity (Borenstein et al., 2009). Of note, the variables and "sub-groups" examined as potential moderators in sub-group analyses were theoretically and methodologically informed (e.g., type of adherence method) as detailed previously, but additionally needed to represent the variability in the existing data. For example, it was not possible to examine each type of organ transplant in sub-group analysis given that the majority of transplants were kidney, and therefore, the studies contributing effect sizes for each of other organ groups would be too small for meaningful comparisons.

Potential moderator variables identified as meeting an a-priori criterion of $p<.10$ for Q_b were included in meta-regression models. To preserve the integrity of the meta-analytic data, potential moderators included in the meta-regression were those based on the largest number of studies. Meta-regression techniques were used to examine the unique effect of each of these moderators on the association between NA and SA with immunosuppressant adherence whilst controlling for the other moderator variables (Borenstein et al., 2009). To assess for the possibility that the association between NA and SA with adherence is an artifact of publication bias (e.g., studies showing no relationship are not published), funnel plots were examined, the fail-safe N statistic calculated, and the Begg and Mazumdar Rank Correlation Test was conducted.

Chapter 3. Results

3.1. Preliminary Analyses: Meta-Analytic Aggregation of Negative Affect Indicators

3.1.1. Levels of Negative Affect

A total of *k*= 26 and *k*= 11 studies examined the association of depressive symptoms and anxiety symptoms, respectively, with immunosuppressant adherence. Comparison of the mean (or median) level of depressive and/or anxiety symptoms with established screening measures' cut-off scores indicated that the median percentage of the recipient sample presenting with clinical levels of depression (based on k=18 studies reporting this data) and anxiety (based on k=8 studies reporting this data) symptoms was 18.8% (range of 0-36.18%) and 27.87% (range of 17.9-59%), respectively. Note that these percentages do not establish diagnostic rates, given that diagnosis cannot be made on the sole basis of screening measures (American Psychiatric Association, 2013).

Moreover, of the studies reporting the mean/median level of depressive symptoms for their sample (k=12), none of these study "averages" met cut-off scores on depression screening measures (e.g., the Center for Epidemiologic Studies Depression Scale (CES-D), Beck Depression Inventory (BDI), Hospital Anxiety Depression Scale (HADS)-Depression Subscale). Similarly, of the studies examining an association between anxiety levels and adherence (k=11), all utilized self-report screening measures. Of note, these were all measures of general anxiety (i.e., everyday worry, fear), rather than a specific type of anxiety disorder (e.g., social anxiety disorder; specific phobia) and included the State Trait Anxiety Inventory (STAI), Hospital Anxiety Depression Scale (HADS)-Anxiety Subscale, Brief Symptom Inventory (BSI), and Symptom Checklist-90. None of the "averages" from the compiled participants in studies reporting data for the mean/median level of anxiety in their sample (k=5) met established criteria for clinical levels of anxiety.

If it is accepted that recipients with scores below established cut-off levels are true negative cases, then the majority of recipients in the samples did not suffer from clinical levels of depression and anxiety. Rather, the majority of transplant recipients presented with subclinical levels of psychological distress.

3.1.2. Effect Size Correlations

Seven studies reported effect sizes of adherence based on both depressive symptoms and anxiety symptoms. The correlation between the effect size of depressive symptoms with adherence and the effect size of anxiety symptoms with adherence across these studies was very strong r= .82 (p= .024). Four studies reported adherence effect sizes based on both depressive symptoms and another NA indicator; the correlation between these effect sizes was similarly exceptionally strong (r= .954; p <.05). Similarly, across the three studies reporting an effect size for anxiety symptoms and adherence as well as another indicator of NA and adherence, the correlation was strong (r= .990; p= .091). In sum, although the above data are based on a small subsample of studies that reported multiple differential NA-Adherence effect sizes, the within-study correlations between adherence effect sizes based on various NA indicators were strong, lending validity to their meta-analytic convergence.

3.1.3. Adherence Effect Sizes: Depressive Symptoms vs. Anxiety Symptom vs. Other Negative Affect Indicators

Examination of unique effect sizes (through separate meta-analyses) for studies examining the various NA indicators (depressive symptoms, anxiety symptoms, and other indicators of negative affect) as correlates of adherence reveals comparable effect sizes, small in the magnitude, that range from r= -.082 to r= -.182 with overlapping prediction intervals. Specifically, the 26 studies reporting on an effect size of depressive symptoms with adherence reveal a summary effect size of r= -.082 (p=.00) (Figure 2). This is comparable to the summary effect size observed for the 11 studies reporting an effect size of anxiety symptoms with adherence (r= -.092; p=.058) (Figure 3). Note that it was not possible to compare effect sizes for studies examining the effect size of anxiety symptoms and adherence vs. the effect size of depressive symptoms and adherence in sub-group analyses due to the issue of dependency of effect sizes arising from the fact that the majority of studies examined the association between both anxiety and depressive symptoms with adherence, whilst only one study examined anxiety solely in association with nonadherence. As such, the effect size of depressive symptoms with adherence was compared to the effect size of anxiety symptoms with adherence in separate meta-analyses as reported above. The summary effect size based on other indicators of negative affect (e.g., psychological distress, symptom distress) based on 22 studies was

r= -.182 (*p*= .00) (Figure 4). The purpose of this preliminary analysis was to obtain a broad indication of any potential major divergences in either magnitude or direction between the adherence effect sizes based on the various NA indicators (depressive symptoms, anxiety symptoms, other indicators of negative affect). Together, the results of the above analyses supported meta-analytic aggregation of adherence effect size based on the various NA indicators, with further analyses to assess potential moderation.

Study	Correlation	Lower limit	Upper limit	Z-Value	p-Value	N for Adherence Measure
Delibasic et al. 2017	-0.558	-0.766	-0.244	-3.239	0.001	43
Little et al. 2017	-0.382	-0.607	-0.100	-2.612	0.009	39
Cukor et al. 2009	-0.380	-0.540	-0.193	-3.837	0.000	95
Gelb et al. 2010	-0.270	-0.441	-0.081	-2.769	0.006	103
Reber et al. 2016	-0.246	-0.443	-0.027	-2.195	0.028	74
Paterson 2016	-0.210	-0.336	-0.077	-3.074	0.002	211
Pabst et al. 2015	-0.198	-0.315	-0.075	-3.124	0.002	238
Frazier et al. 1994	-0.170	-0.290	-0.045	-2.648	0.008	241
Constantiner et al. 2013	-0.143	-0.250	-0.032	-2.531	0.011	312
Annema et al. 2013	-0.120	-0.234	-0.003	-2.010	0.044	281
Dew et al. 1996	-0.089	-0.317	0.148	-0.737	0.461	86
Russell et al. 2010	-0.080	-0.394	0.251	-0.467	0.640	37
Jindal et al. 2009	-0.068	-0.084	-0.051	-7.938	0.000	32757
Weng et al. 2013	-0.036	-0.159	0.088	-0.568	0.570	252
Denhaerynck et al. 2017	-0.035	-0.089	0.018	-1.293	0.196	1340
Weng et al. 2005	-0.026	-0.181	0.131	-0.323	0.746	278
Burkhalter et al. 2014	-0.011	-0.075	0.053	-0.334	0.738	926
Bosma et al. 2011	0.000	-0.206	0.206	0.000	1.000	91
De Geest et al. 1998	0.000	-0.195	0.195	0.000	1.000	101
Butler et al. 2004	0.000	-0.159	0.159	0.000	1.000	58
Telles-Correia et al. 2012	0.000	-0.250	0.250	0.000	1.000	62
Brocks et al. 2017	0.000	-0.087	0.087	0.000	1.000	505
Dobbels et al. 2009	0.000	-0.165	0.165	0.000	1.000	141
Couzi et al. 2013	0.012	-0.105	0.128	0.193	0.847	279
Griva et al. 2012	0.050	-0.083	0.182	0.734	0.463	218
Russell et al. 2013	0.050	-0.130	0.226	0.544	0.587	121
	-0.082	-0.118	-0.046	-4.434	0.000	

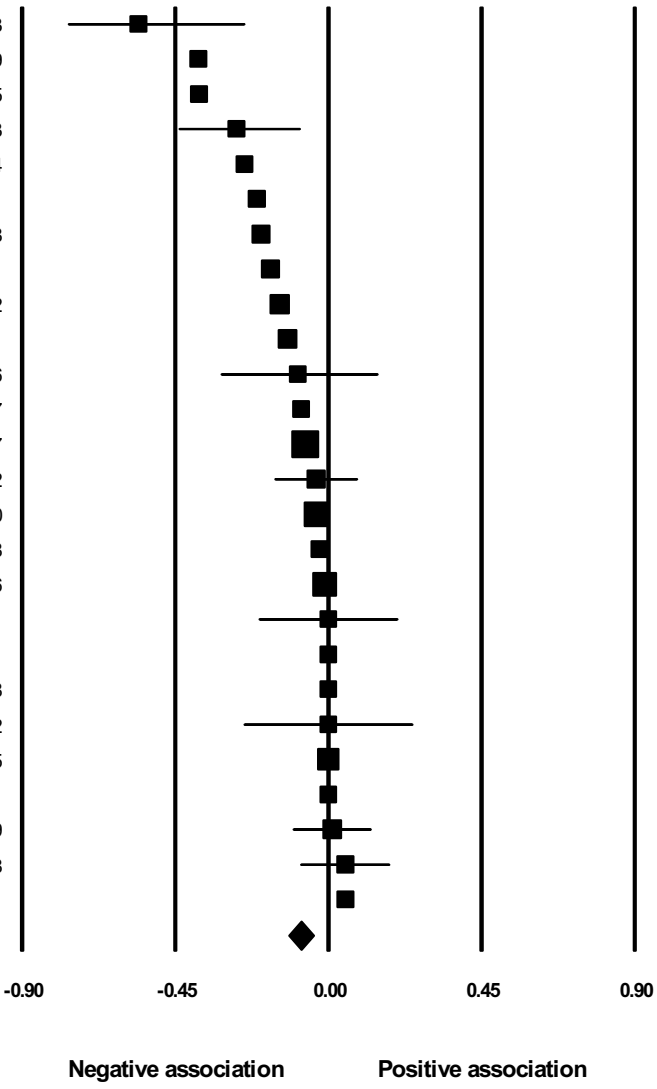


Figure 2 **Forest Plot: Association Between Depressive Symptoms and Immunosuppressant Adherence**

Note. **Q-value (homogeneity test statistic)= 60.04; *df*(Q)= 25; *p*-value= .00; I^2 (percentage of between-studies variability due to heterogeneity)= 58.36; Tau Squared= .00; Standard Error= .00; Variance= .00; Tau= .06; Prediction Interval (95%) *r*= -.20 to .04**

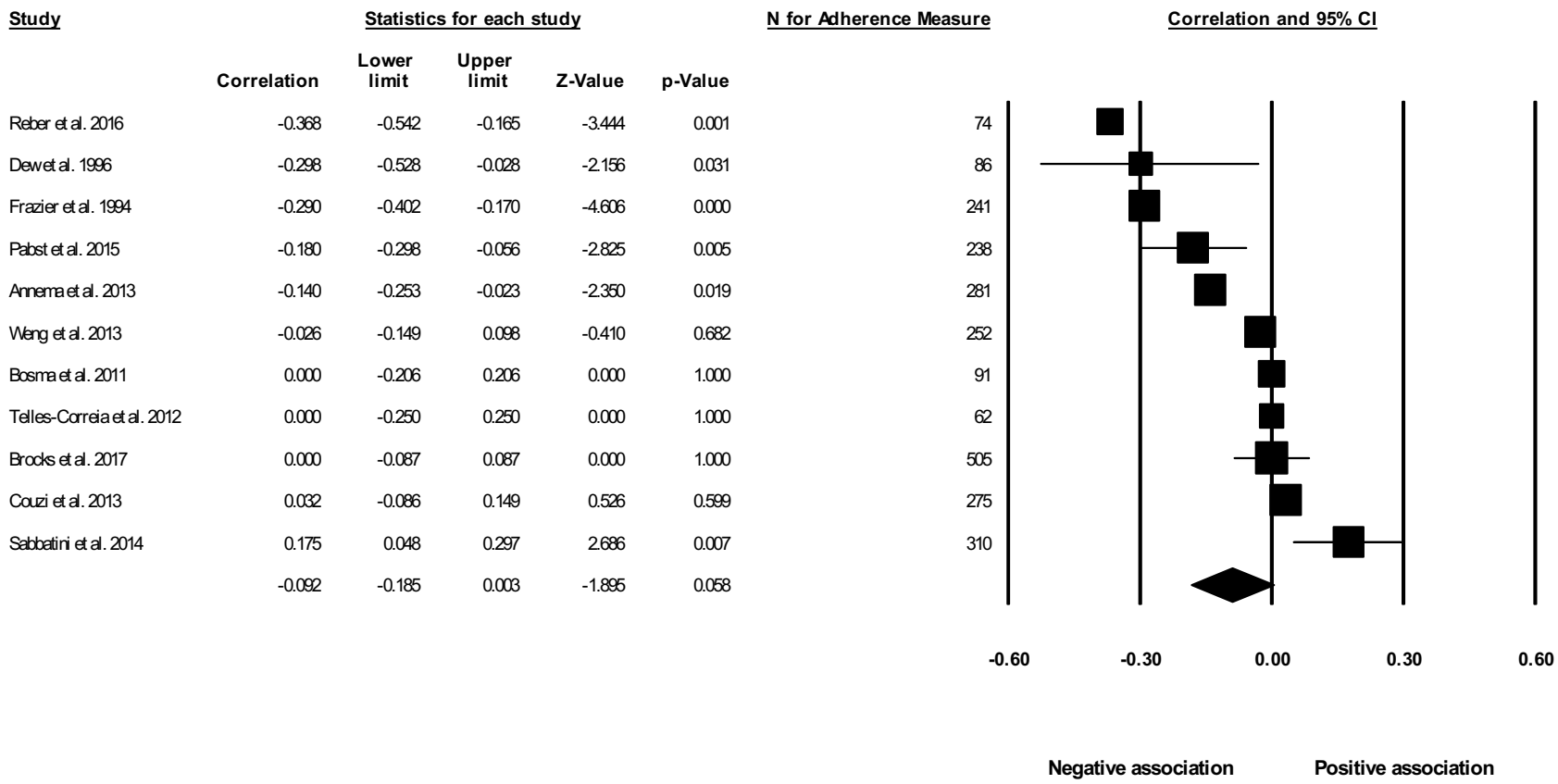
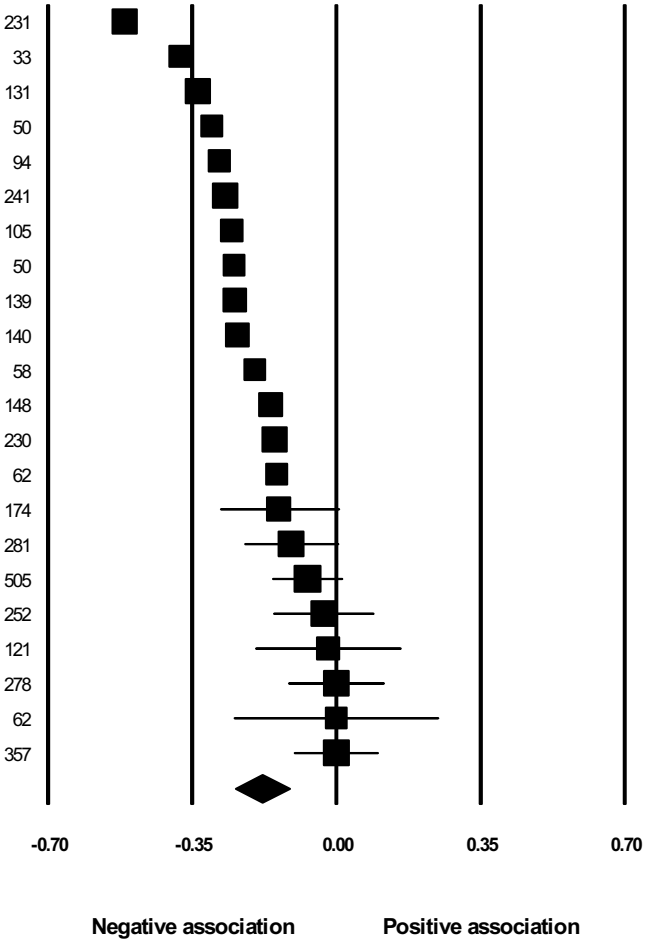


Figure 3 Forest Plot: Association Between Anxiety Symptoms and Immunosuppressant Adherence

Note. **Q-value= 48.14; *df*(Q)= 10; *p*-value= .00**
I^2 = 79.23; Tau Squared= .02; Standard Error= .01; Variance= .00; Tau= .14; Prediction Interval (95%) *r*= -.40 to .23

Figure 4 Forest Plot: Association Between Other Negative Affect Indicators and Immunosuppressant Adherence

Study	Correlation	Lower limit	Upper limit	Z-Value	p-Value	N for Adherence Measure
Teng et al. 2015	-0.514	-0.603	-0.412	-8.579	0.000	231
O'Carrol et al. 2006	-0.380	-0.640	-0.042	-2.191	0.028	33
Lee et al. 2015	-0.336	-0.444	-0.218	-5.370	0.000	131
Brito et al. 2016	-0.302	-0.548	-0.009	-2.016	0.044	50
Wang et al. 2013	-0.284	-0.460	-0.086	-2.786	0.005	94
Frazier et al. 1994	-0.270	-0.383	-0.149	-4.271	0.000	241
Kim et al. 2016	-0.254	-0.425	-0.066	-2.623	0.009	105
Achille et al. 2006	-0.248	-0.492	0.033	-1.736	0.082	50
Rosenberger et al. 2005	-0.246	-0.391	-0.089	-3.043	0.002	139
Chandler et al. 2017	-0.240	-0.387	-0.082	-2.941	0.003	140
Butler et al. 2004	-0.198	-0.426	0.054	-1.541	0.123	58
De Geest et al. 1995	-0.160	-0.310	-0.001	-1.971	0.049	148
Shabany-Hamedan et al. 2014	-0.150	-0.274	-0.021	-2.277	0.023	230
Massey et al. 2015	-0.145	-0.381	0.109	-1.122	0.262	62
Pisanti et al. 2016	-0.140	-0.283	0.009	-1.843	0.065	174
Annema et al. 2013	-0.110	-0.224	0.007	-1.842	0.066	281
Brocks et al. 2017	-0.070	-0.156	0.017	-1.571	0.116	505
Weng et al. 2013	-0.031	-0.154	0.093	-0.489	0.625	252
Goetzmann et al. 2012	-0.020	-0.198	0.159	-0.217	0.828	121
Weng et al. 2005	0.000	-0.118	0.118	0.000	1.000	278
Telles-Correia et al. 2012	0.000	-0.250	0.250	0.000	1.000	62
Raiz et al. 1999	0.000	-0.104	0.104	0.000	1.000	357
	-0.182	-0.247	-0.115	-5.282	0.000	



Note. **Q-value= 86.65; df(Q)= 21; p-value= .00**
I^2 = 75.77; Tau Squared= .02; Standard Error= .01; Variance= .00; Tau= .14; Prediction Interval (95%) r= -.44 to .11

3.2. Summary of Study Characteristics

A summary of study characteristics is presented in Table 8. A total of 50 unique studies were included, 15 of which contributed effect sizes to both the NA and the SA-adherence meta-analyses. Please refer to Appendix B for a bibliography of included studies.

Table 8 Study Characteristics

Characteristic	Negative Affect	Self-Agency
Number of studies	42	23
Year of Earliest Publication	1994	1994
Study Location (N, %)		
North America	16 (38.1)	10 (43.5)
Europe	19 (45.2)	11 (47.8)
Asia	5 (11.9)	1 (4.35)
*Other **	2 (4.8)	1 (4.35)
Total number of countries represented	18	15
Total number of patients studied	41,258	4,848
Sample size		
Median, Range	139.5 (33 – 32,757)	121 (33 – 1378)
Age, Mean (SD)	50.02 (6.50)	51.47 (4.91)
Median of Mean Age, Range	50.19 (25.6- 60.38)	52.6 (42 – 60.38)
Minimum Age range	18 – 55	18 – 55
Maximum Age range	30 – 90	66 – 80
Female Gender %, Mean (SD)	38.86 (11.29)	38.53 (10.56)
Median, Range	40.1 (9.6 – 60.9)	38.8 (12.9 – 55)
Marital Status %, Mean (SD)	68.06 (14.85)	69.39 (12.05)
Median, Range	69.7 (27.4 – 100)	68.85 (44.3 – 100)
Organ Type (N, %)		
Kidney	30 (71.43)	15 (65.2)
Liver	4 (9.52)	2 (8.69)
Heart	5 (11.90)	3 (13.04)
Lung	1 (2.38)	1 (4.35)
Mixed	2 (4.76)	2 (8.69)
Measurement Method		
Self-report	31	12
Collateral	1	0
Electronic	5	6
Serum Immunosuppressant Conc.	0	1
Pharmacy	0	1
Medical Record	1	0
Combination		
Self/collateral	3	1
Electronic/Self-report	1	1
IS concentration/Self-report	--	1
Time Since Transplant, Mean years (SD)	4.19 (2.76)	4. 46 (3.05)
Median, Range	3.95 (0.25- 9.9)	3.95 (0.125 – 8.98)
Study Quality, Mean (SD)	6.39 (1.10)	6.32 (1.17)
Median, Range	6 (4-9)	6 (4-8.5)

Note: *For Negative Affect, other includes multicontinental (Denhaerynck et al., 2017) and South America (Brito et al., 2016). For Self-Agency, other includes multicontinental (Denhaerynck et al., 2017).

3.3. Levels of Nonadherence

A wide range of immunosuppressant nonadherence rates was represented in both meta-analyses, with average estimates comparable to previously documented rates of nonadherence in the transplant recipient population (Dew et al., 2007). Utilizing study researchers' definitions of nonadherence, the calculated crude median nonadherence percentage for NA-Adherence meta-analysis was 31.75% (range 6.3% to 86%) based on 31 studies providing data on the level of nonadherence of their sample. Nonadherence levels were 32.5% for questionnaire methods and 26.6% for other quantitative methods. For the SA-Adherence meta-analysis, the median nonadherence percentage was 26.3% (range of 7.7% to 86%) based on 16 studies. Nonadherence levels derived from questionnaires (28.2%) were comparable to those derived from other quantitative measures (26.3%).

3.4. Negative Affect and Immunosuppressant Adherence Meta-Analysis

The meta-analysis on the relationship between NA and adherence was based on a total of 42 studies, dating back to 1994, with a median *n* of 139.50 and total of 41,258 organ recipients. Eighteen countries were represented, and the majority of organ transplants are kidney (71.43%). Organ recipients were on average 50.02 years, 38.90% female, and 4.19 years post-transplant. Study quality ranged from 4 to 9, with a mean score of 6.39. The majority of studies utilized self-report measures to assess adherence. Overall, the average correlation between NA and immunosuppressant adherence was small in magnitude and negative in direction as expected (ES_r= -.136, 95% CI= -.175, -.096), indicating that as NA increases medication adherence decreases (see Figure 5 for forest plot). The prediction interval is *r*= -.34 to *r*= .08, which suggests that in most populations the correlation between negative affect and adherence will fall within this range. There was evidence of heterogeneity in the effect sizes across the studies (I^2= 77.78), suggesting that approximately 78% of the variance in the observed effects is due to variance in true effects. The remaining 22% is attributed to sampling error and is likely to disappear if the sample sizes were large enough.

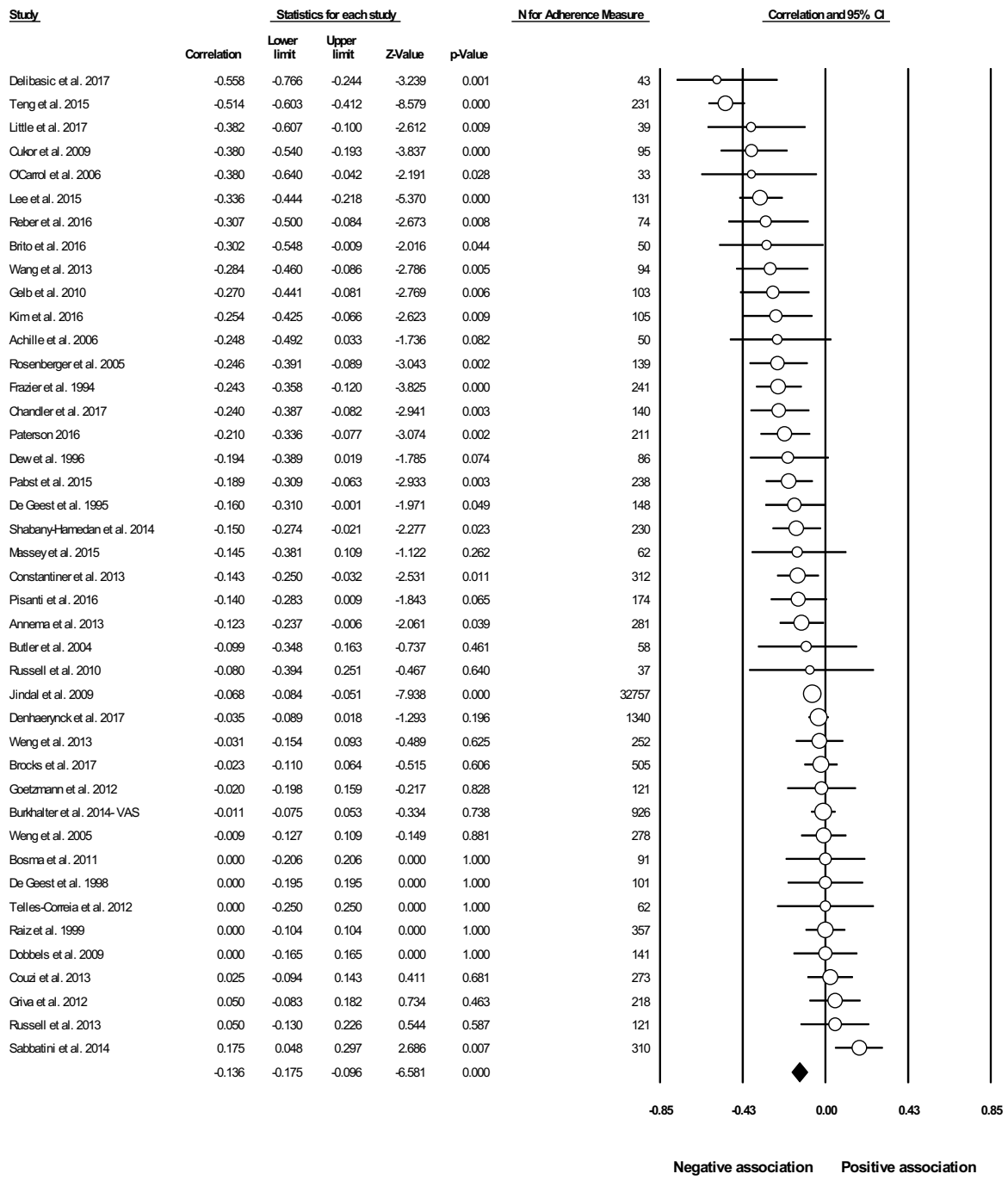


Figure 5 Association between Negative Affect and Immunosuppressant Adherence in Organ Transplant

Note. **Q-value (homogeneity test statistic)= 184.49; *df*(Q)= 41; *p*-value= .00; I^2 (percentage of between-studies variability due to heterogeneity)= 77.78; Tau Squared= .01; Standard Error= .01; Variance= .00; Tau=.10; Prediction Interval (95%) *r*= -.34 to .08.**

3.5. Self-Agency and Immunosuppressant Adherence Meta-Analysis

A total of 23 studies, dating back to 1994, with a median *n* of 121 and total of 4,848 organ recipients were included in the meta-analysis on SA and adherence. There were 15 countries represented, and the majority of organ transplants were also kidney (65.20%). Organ recipients were on average 51.47 years, 38.53% female, and 4.46 years post-transplant. Study quality ranged from 4.5 to 8.5, with a mean quality score of 6.32. The average correlation between SA and adherence was small in magnitude and positive in direction (ES_r= .173, 95% CI= .094, .251), indicating that as SA increases so does immunosuppressant adherence (see Figure 6 for forest plot). Moreover, the prediction interval suggests that in most populations the correlation between self-agency and adherence will fall somewhere between *r*= -.19 to *r*=.50. There was evidence of heterogeneity in the effect sizes across the studies (I^2= 91.24), suggesting that approximately 91% of the variance is due to variance in true effects; the remaining 9% is attributed to sampling error and is likely to disappear if the sample sizes were large enough. Removal of Chisholm et al., 2007 from the analysis, identified as an outlier on the basis of its relatively higher effect size (*r*=.76 and relative weight of 3.79), resulted in an average effect size of *r*= .143 (95% CI=.070, .214; *p*<.001; I^2=88.87%).

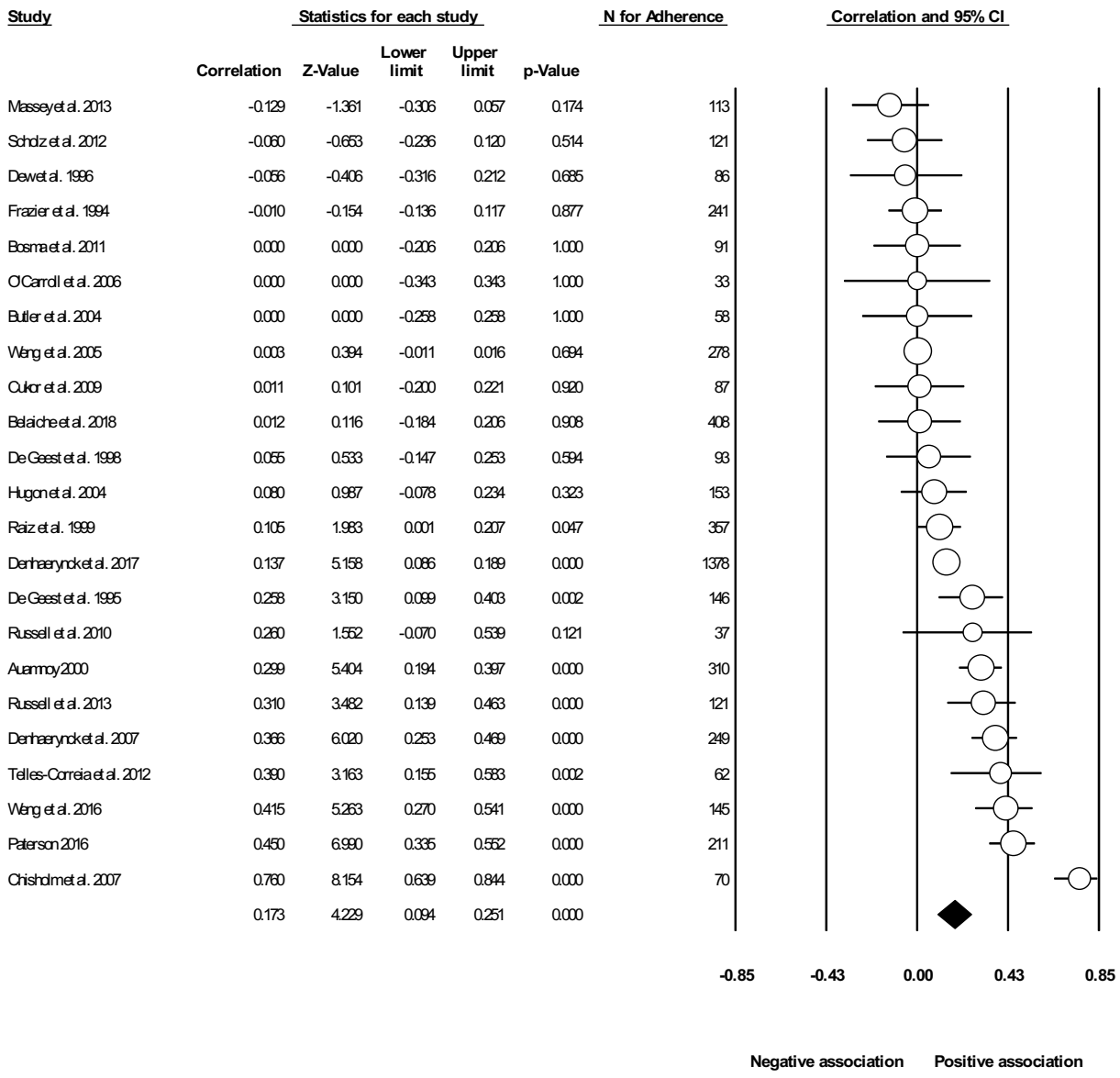


Figure 6 **Association between Self-Agency and Immunosuppressant Adherence in Organ Transplant**

Note. **Q-value (homogeneity test statistic)= 251.11; *df*(Q)= 22; *p*-value= .00; I^2 (percentage of between-studies variability due to heterogeneity)= 91.24; Tau Squared= .03; Standard Error=.02; Variance= .00; Tau= .17; Prediction Interval (95%) *r*= -.19 to .50.**

3.6. Moderator Analyses

3.6.1. Negative Affect and Immunosuppressant Adherence

Subgroup Analyses

Subgroup analyses revealed a total of seven potential moderators (meeting the a-priori criterion of $p<.10$) of the association of NA with immunosuppressant adherence. Four of these moderators were study and sample-specific variables: sample size, geographical location, study quality, and study data type (cross-sectional vs. prospective). Specifically, studies with a smaller sample size (i.e., $n< 139.5$; $r= -.203$, $p= .00$) showed a significantly stronger effect size ($Q_b= 7.261$; $p= .007$) compared to those with a larger sample size (i.e., $n> 139.5$; $r= -.095$, $p= .00$). Studies conducted outside of Europe and North America ($r= -.319$; $p= .00$) demonstrated a significantly stronger association ($Q_b= 17.678$; $p=.00$) than those conducted in either Europe or North America ($r= -.104$; $p= .00$). Studies with better study quality ($r= -.184$; $p= .00$) showed a stronger association ($Q_b= 3.720$; $p= .054$) than those of relatively lower study quality ($r= -.100$, $p= .00$). Studies reporting cross-sectional data ($r= -.153$; $p= .00$) were associated with stronger effect sizes ($Q_b= 3.167$; $p=.08$) compared to those whose data was prospective ($r= -.055$; $p= .278$).

Moreover, two NA-specific variables emerged as potential moderators in sub-group analyses: illness-specificity of NA and whether the NA indicator was based on a measure of a potentially diagnosable disorder (i.e., depressive or anxiety symptoms) vs. other indicators of NA. More specifically, ES based on illness-specific NA ($r= -.215$; $p= .00$) were stronger ($Q_b= 7.882$; $p= .005$) than those based on an NA indicator that was non-illness specific (e.g., depressive symptoms or psychological quality of life; $r= -.100$; $p= .00$). Effect sizes that were based on potentially diagnosable disorders (namely, depressive or anxiety symptoms; $r= -.094$; $p= .00$) were also significantly smaller ($Q_b= 9.006$; $p=.003$) than those based on other types of NA indicators (e.g., symptom distress; $r= -.231$; $p= .00$). Finally, questionnaire-type adherence measures ($r= -.147$; $p= .00$), in comparison to quantitative, showed stronger effect sizes ($Q_b= 3.647$; $p=.056$) than quantitative-type adherence measures ($r= -.015$; $p= .82$). Please refer to Table 9 for a presentation of findings related to variables examined in the sub-group analyses.

Table 9 Sub-group Analyses: Negative Affect and Immunosuppressant Adherence in Organ Transplant

Variable	*k*	*n*	*r*	95% CI	*p*-value	Heterogeneity (*Q; p*)
Study and Sample Variables						
Sample size	42					**Q_b= 7.261; *p*=.007**
<139.5	21	1695	-.203	-.264 to -.140	.00	Q_w= 42.662; *p*=.002
>139.5	21	39563	-.095	-.142 to -.047	.00	Q_w = 111.744; *p*=.00
Mean Age	34					Q_b= 2.608; *p*= .106
<50.19	17	2756	-.188	-.258 to -.116	.00	Q_w= 103.125; *p*=.00
>50.19	17	4855	-.105	-.176 to -.033	.00	Q_w= 36.396; *p*= .00
Min Age	35					Q_b= .006; *p*=.936
18	21	1634	-.129	-.190 to -.067	.00	Q_w= 118.781; *p*=.00
>18	14	6050	-.133	-.216 to -.048	.00	Q_w= 20.25; *p*= .09
Max Age	20					Q_b= 1.619; *p*= .203
<74.5	10	1238	-.204	-.297 to -.108	.00	Q_w= 39.674; *p*= .00
>74.5	10	2199	-.119	-.209 to -.027	.01	Q_w= 24.579; *p*=.003
Female	41					Q_b= .390; *p*= .532
40.1%	21	5081	-.121	-.184 to -.058	.00	Q_w= 95.753; *p*= .00
>40.1%	20	36037	-.149	-.210 to -.087	.00	Q_w= 84.570; *p*= .00
Marital Status	29					Q_b= .009; *p*= .923
<69.70	14	3688	-.127	-.212 to -.039	.0005	Q_w= 86.59; *p*= .00
>=69.70	15	2217	-.121	-.205 to -.026	.0007	Q_w= 42.039; *p*=.00
Geographical Location	41					**Q_b= 17.678; *p*=.00**
Euro-American	35	39077	-.104	-.143 to -.064	.00	Q_w= 98.166; *p*=.00
Other	6	841	-.319	-.403 to -.229	.00	Q_w= 20.880; *p*= .001
Geographical Location						**Q_b= 16.003; *p*= .00**
Asia	5	791	-.320	-.409 to -.225	.00	Q_w= 20.852; *p*=.00
Other	36	39127	-.107	-.146 to -.067	.00	Q_w= 100.574; *p*=.00
Geographical Location						Q_b= .189; *p*=.664
North America	16	35122	-.153	-.214 to -.092	.00	Q_w= 52.024; *p*=.00
Other	25	4796	-.133	-.201 to -.064	.00	Q_w= 127.155; *p*=.00
Organ	41					Q_b= .771; *p*= .380
Kidney	30	38360	-.151	-.200 to -.102	.00	Q_w= 160.224; *p*=.00
Other	11	2777	-.107	-.192 to -.019	.02	Q_w= 22.500; *p*=.013
Mean Years since TX	25					Q_b= .066; p=.797
<3.95	12	2868	-.131	-.212 to -.049	.00	Q_w= 35.564; *p*=.00
>3.95	13	2582	-.117	-.192 to -.040	.00	Q_w= 47.153; *p*=.00
Study Quality	42					**Q_b= 3.720; *p*=.054**
<=6	22	36680	-.100	-.157 to -.042	.00	Q_w= 76.133; *p*=.00
>6	20	4578	-.184	-.245 to -.120	.00	Q_w= 102.164; *p*=.00
Type of Study Data	42					**Q_b= 3.167; *p*=.08**
Cross-sectional data	33	40298	-.153	-.196 to -.108	.00	Q_w=169.411; *p*=.00
Prospective data	9	960	-.055	-.153 to .044	.278	Q_w=13.087; *p*=.11

Variable	*k*	*n*	*r*	95% CI	*p*-value	Heterogeneity (*Q; p*)
Negative Affect Measure Specific Variables						
Researcher-Generated	42					Q_b= 1.011; *p*=.315
Yes	6	1190	-.181	-.277 to -.083	.00	Q_w= 68.538; *p*= .00
No	36	40068	-.126	-.169 to -.083	.00	Q_w= 101.945; *p*=.00
Negative Affect	42					**Q_b= 7.882; *p*=.005**
Illness-specific	13	1760	-.215	-.281 to -.147	.00	Q_w= 55.571; *p*= .000
Non-illness specific	29	39498	-.100	-.143 to -.056	.00	Q_w= 86.338; *p*= .000
Negative Affect Measure	34					**Q_b= 9.006; *p*=.003**
Depressive or Anxiety Sx	20	37516	-.094	-.150 to -.038	.00	Q_w= 69.671; *p*=.00
Other indicator of NA	14	1891	-.231	-.288 to -.158	.00	Q_w= 57.577; *p*=.00
Measurement Data Type	41					Q_b= .563; *p*=.453
Continuous	35	7643	-.151	-.201 to -.100	.00	Q_w= 146.819; *p*=.00
Non-Continuous	6	33337	-.098	-.226 to .034	.14	Q_w= 26.363; *p*=.00
Measurement Time						Q_b= .051; *p*=.822
Pre-Transplant	3	246	-.115	-.293 to .070	.22	Q_w= 9.251; *p*=.010
Post-Transplant	39	41012	-.137	-.178 to -.096	.00	Q_w= 175.227; *p*=.00
Adherence Method Specific Variables						
Adherence	40					**Q_b= 3.647; *p*=.056**
Questionnaires	35	40529	-.147	-.189 to -.104	.00	Q_w= 171.803; *p*=.000
Quantitative methods	5	585	-.015	-.144 to .114	.82	Q_w= 1.039; *p*=.904
Barriers	42					Q_b= .013; *p*=.911
Yes	23	4329	-.135	-.191 to -.079	.00	Q_w= 85.098; *p*=.00
No	19	36929	-.140	-.203 to -.076	.00	Q_w= 95.022; *p*=.00
Researcher-Generated	42					Q_b= .857; *p*=.355
Yes	14	35520	-.167	-.241 to -.092	.00	Q_w= 90.219; *p*=.00
No	28	5738	-.124	-.178 to -.069	.00	Q_w= 93.927; *p*=.00
Exclusively Assessed Immunosuppressant Adherence	42					Q_b= .592; p=.442
Yes	33	7081	-.149	-.199 to -.098	.00	Q_w= 148.676; p=. 00
No	9	34177	-.106	-.201 to -.010	.03	Q_w= 29.165; p= .00
Measurement Data Type	42					Q_b= .088; *p*=.766
Continuous	19	4195	-.144	-.205 to -.082	.00	Q_w= 97.941; *p*=.00
Non-Continuous	23	37063	-.131	-.188 to -.074	.00	Q_w= 81.958; *p*=.00

***Note*: Variables with a dotted border --- emerged as significant moderators in sub-group analyses based on an a-priori criterion of *p*<.10 for Q_b.*k*= number of studies per sub-group; *n*= total sample size per subgroup; *r*= mean weighted effect size. Q_b= overall between-subgroups heterogeneity statistic; Q_w= overall within-subgroups heterogeneity statistic; Sx= symptoms.**

Meta-Regression

Further, meta-regression revealed a total of four moderators for the association between NA and adherence. Specifically, studies conducted outside of Europe and North America (z= 2.46, *p*= .014), of better quality (z= -2.76, *p*= .006), with ES based on illness-specific NA (z= -2.56, *p*= .016), and utilizing questionnaire adherence measures (z= -2.07, *p*= .039) were each associated with a significantly larger effect size for the association of NA with adherence, even after controlling for the effects of the other variables. The model was significant (Q= 43.76; *p* <.001) and explained 54% of the heterogeneity in effect sizes (Table 10). Note that the NA variable reflecting depressive/anxiety symptoms vs. other NA indicators was not included in the meta-regression to maintain the integrity of the data (given that a smaller number of studies contributed to this analysis; *k*= 34).

Table 10 Meta-regression Analysis for Negative Affect and Immunosuppressant Adherence

Covariate	Coefficient	Standard Error	95% CI	z-value	*p*-value*
Intercept	-.0582	.1182	-.2898 to .1735	-0.49	.6226
N Median Split: >139.5	.0726	.0416	-.0088 to .1540	1.75	.0808
Euro-American: Y	.1343	.0545	.0274 to .2412	2.46	.0138
Illness Specific NA: Y	-.1071	.0419	-.1892 to -.0250	-2.56	.0106
Questionnaire (Adherence): Y	-.1827	.0884	-.3560 to -.0094	-2.07	.0388
Quality: >6	-.1085	.0393	-.1856 to -.0315	-2.76	.0058
Type of Study Data: Cross-Sectional	.0299	.0726	-.1122 to .1722	.41	.6795

Note: **Dotted variables represent significant unique moderators for the association between NA and adherence. Y= Yes. Test of Model: Q= 43.76; df=6; *p*=.00.**
Goodness of fit: T^2=.0055; T=.0738; I^2 = 57.42%; Q= 75.16; df=32; *p*=.00.
Total between-study variance: T^2=.0118; T= .1085; I^2= 78.03%; Q= 172.98; df= 38; *p*=.00. N=39.
Proportion of total between-study variance explained by model: 54%
***p*-value is 2-sided.**

3.6.2. Self-Agency and Immunosuppressant Adherence

Subgroup Analyses

Subgroup analyses revealed a total of three potential moderators (meeting the a-priori criterion of *p*<.10) of the association of SA with adherence: gender, time since transplant, and the type of SA. Specifically, studies with a larger female percentage

(>38.8%; r= .273; p= .00) were associated with stronger effect sizes (Q_b= 7.136; p=.008) than those with a relatively smaller female percentage make-up (r= .080; p= .120). Studies whose recipients' transplant vintage was older (r=. 337; p= .00) showed a stronger effect size (Q_b= 14.20; p= .00) than those with relatively younger transplants (r= .042; p= .466). Finally, studies whose ES was based on medication-specific SA (r= .230; p= .00) demonstrated stronger effect sizes (Q_b= 4.702; p= .030) than those assessing non-medication-specific SA indicators (r= .055; p= .411). Please refer to Table 11 for a presentation of findings related to variables examined in the sub-group analyses.

Table 11 Sub-group Analyses: Self-Agency and Immunosuppressant Adherence in Organ Transplant

Variable	*k*	*n*	*r*	95% CI	*p*-value	Heterogeneity (*Q; p*)
Study and Sample Variables						
Sample size	23					Q_b= .360; *p*=.548
<=121	12	972	.146	.024 to .264	.019	Q_w=77.996; .*p*=.00
>121	11	3876	.196	.085 to .302	.001	Q_w=163.831; *p*=.00
Mean Age	18					Q_b= .428; *p*=.513
<52.6	9	1535	.258	.121 to .385	.000	Q_w= 74.769; *p*=.00
>52.6	9	2652	.193	.050 to .329	.008	Q_w= 47.460; *p*=.00
Min Age	15					Q_b= .343; *p*=.558
<19	7	2788	.239	.085 to .381	.003	Q_w= 47.895; *p*=.00
>=19	8	679	.174	.012 to .327	.035	Q_w= 69.172; *p*=.00
Max Age	12					Q_b= .177; *p*=.674
<=75	7	746	.172	-.041 to .370	.113	Q_w= 28.084; *p*=.00
>75	5	775	.241	-.010 to .462	.059	Q_w= 65.761; *p*= .00
Female	23					**Q_b= 7.136; *p*=.008**
<=38.8%	12	3156	.080	-.021 to .179	.120	Q_w= 67.809; *p*=.00
>38.8%	11	1692	.273	.172 to .368	.000	Q_w= 95.583; *p*=.00
Marital Status	19					Q_b= .700; *p*=.403
<68.9	10	3036	.195	.081 to .303	.001	Q_w= 131.023; *p*=.00
>68.9	9	1485	.123	-.003 to .246	.056	Q_w= 56.670; *p*=.00
Organ	21					Q_b= 1.269; *p*=.260
Kidney	15	2831	.222	.109 to .330	.000	Q_w= 224.020; *p*=.00
Other	6	1743	.096	-.098 to .282	.333	Q_w= 9.097; *p*=.105
Mean Years since TX	16					**Q_b= 14.20; *p*=.00**
< 3.95	8	2303	.042	-.071 to .154	.466	Q_w= 35.945; *p*=.00
>3.95	8	1339	.337	.232 to .433	.000	Q_w= 67.547; *p*=.00
Study Quality	23					Q_b=.059; *p*=.81
<=6	12	1558	.163	.045 to .277	.007	Q_w=92.069; *p*=.00
>6	11	3290	.184	.066 to .297	.002	Q_w=141.138; *p*=.00
Type of Study Data	23					Q_b= .007; *p*=.934
Cross-sectional data	15	3831	.176	.069 to .279	.001	Q_w=118.918; *p*=.00
Prospective data	8	1017	.168	.017 to .312	.029	Q_w=59.013; *p*=.00
Self-Agency Measure Specific Variables						
Researcher-Generated	23					Q_b=.148; *p*=.701
Yes	5	543	.203	.029 to .366	.023	Q_w= 64.332; *p*=.00
No	18	4305	.165	.074 to .254	.000	Q_w= 177.102; *p*=.00
Self-Agency	23					**Q_b=4.702; *p*=.030**
Medication Specific	15	3646	.230	.140 to .316	.000	Q_w=118.136; *p*=.00
Non-medication Specific	8	1202	.055	-.077 to .185	.411	Q_w=13.688; *p*=.057
Measurement Data Type	23					Q_b= 2.681; *p*=.102
Continuous	20	4263	.198	.112 to .280	.000	Q_w= 250.554; *p*=.00
Non-continuous	3	585	-.012	-.246 to .223	.919	Q_w= 0.165; *p*=.921

Variable	*k*	*n*	*r*	95% CI	*p*-value	Heterogeneity (*Q; p*)
Adherence Method Specific Variables						
Adherence	21					Q_b= .677; *p*=.411
Questionnaires	13	3290	.153	.030 to .271	.015	Q_w= 73.825; *p*=.00
Quantitative methods	8	1312	.235	.078 to .380	.004	Q_w= 114.116; *p*=.00
Barriers	23					Q_b= .044; *p*=.835
Yes	11	1806	.164	.047 to .277	.006	Q_w= 62.432; *p*=.00
No	12	3042	.181	.070 to .288	.001	Q_w= 145.814; *p*=.00
Researcher-Generated	23					Q_b=.020; *p*=.887
Yes	7	1378	.165	.020 to .303	.025	Q_w=30.667; *p*=.00
No	16	3470	.177	.079 to .272	.000	Q_w=192.072; *p*=.00
Exclusively Assessed Immunosuppressant Adherence	23					Q_b= .555; p= .456
Yes	19	4102	.188	.097 to .275	.00	Q_w= 239.854; p= .00
No	4	746	.104	-.098 to .299	.313	Q_w= 9.619; p= .022
Measurement Data Type	23					Q_b=.744; *p*=.388
Continuous	11	1725	.209	.096 to .316	.000	Q_w=58.885; *p*=.00
Non-continuous	12	3123	.142	.034 to .246	.010	Q_w=133.968; *p*=.00

***Note*: Variables with a dotted border --- emerged as significant moderators in sub-group analyses based on an a-priori criterion of $p<.10$ for Q_b. *k*= number of studies per sub-group; *n*= total sample size per subgroup; *r*= mean weighted effect size. Q_b= overall between-subgroups heterogeneity statistic; Q_w= overall within-subgroups heterogeneity statistic. The following sub-group effect size comparisons are not presented given a small number of studies representing sub-groups: Geographical Location (Euro-American; k=21 vs. Non-Euro-American; k=1), Measurement Time of Self-Agency Variable (Pre-transplant; k=1 vs. Post-transplant k=22).**

Meta-Regression

In meta-regression analysis, studies with a larger female percentage (>38.8%) (z=3.34; *p*=.001) and whose ES was based on medication-specific SA (z= 3.00; *p*=.003) were associated with a significantly larger effect size, even after controlling for the effects of the other variables. The model was significant (Q=16.84; *p*<.001) and explained 34% of the heterogeneity in effect sizes. Excluding Chisholm et al., 2007 did not change the unique moderators though the resultant explained variance increased to 46% (Table 12). Note that the years since transplant variable was not included in the meta-regression to preserve the integrity of the data (given that a smaller number of studies contributed to this analysis; *k*= 16).

Table 12 Meta-regression Analysis for Self-Agency and Immunosuppressant Adherence

Covariate	Coefficient	Standard Error	95% CI	z-value	*p*-value*
Intercept	-.0943	.0761	-.2434 to .0548	-1.24	.2150
%Female Median Split: >38.8	.2421	.0724	.1002 to .3839	3.34	.0008
Medication Specific SA: Y	.2304	.0769	.0797 to .3810	3.00	.0027

Note: **Y= Yes; C= Continuous level of measurement.**
Test of Model: Q= 16.84; df=2; p=.0002.
Goodness of fit: T2=.0201; T=.1418; I2=78.56%; Q=93.27; df=20; p=.00.
Total between-study variance: T2= .0303; T=.1740; I2= 91.24%; Q= 251.10; df= 22; p=.00. N= 23.
Proportion of total between-study variance explained by model: 34%
***p*-value is 2-sided.**

3.7. Publication Bias Analyses

Funnel plots were inspected and demonstrated approximate symmetry, though this was more apparent for the NA-Adherence meta-analysis than the SA-Adherence meta-analysis (Figure 7 and 8). The fail-safe Ns (*NA*=1526 studies; *SA*=625 studies) indicated that a large number of "missing" studies with a null effect would need to be located and included for the effect of NA and SA on immunosuppressant adherence to become non-significant, suggesting that the average ESs are highly robust to the discovery of additional studies. For the SA analysis, there was a non-significant correlation between standard error and effect size (τ_b=-.107; p=.24) further supporting a lack of publication bias. In contrast, there was a significant negative correlation between standard error and effect size (τ_b=-.294; p= .003) for the NA analyses, though meta-regression demonstrated that sample size did not significantly moderate the effect size. Further examination through Duval and Tweedie's Trim-and-Fill method, however, reveals no difference between the trim-and-fill estimator and the obtained effect size. This suggests that the NA-Adherence effect size is likely larger in smaller studies for reasons other than publication bias (i.e., "small study effect") (Borenstein et al., 2009).

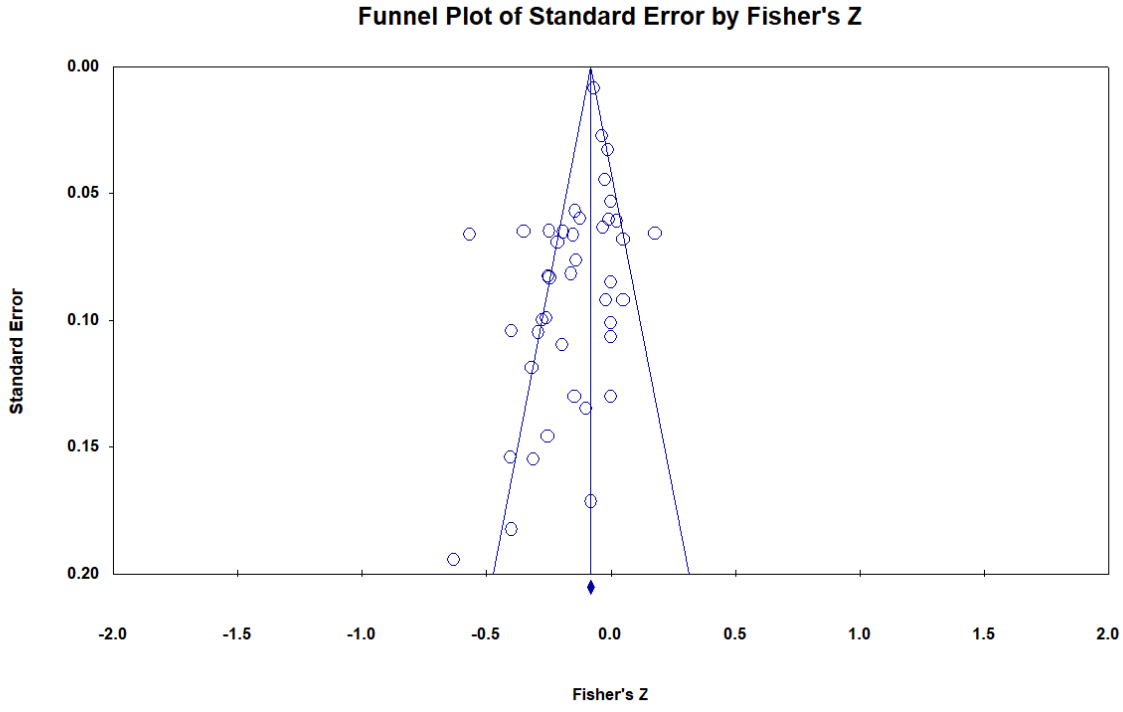


Figure 7 **Funnel Plot for the Association of Negative Affect and Immunosuppressant Adherence**

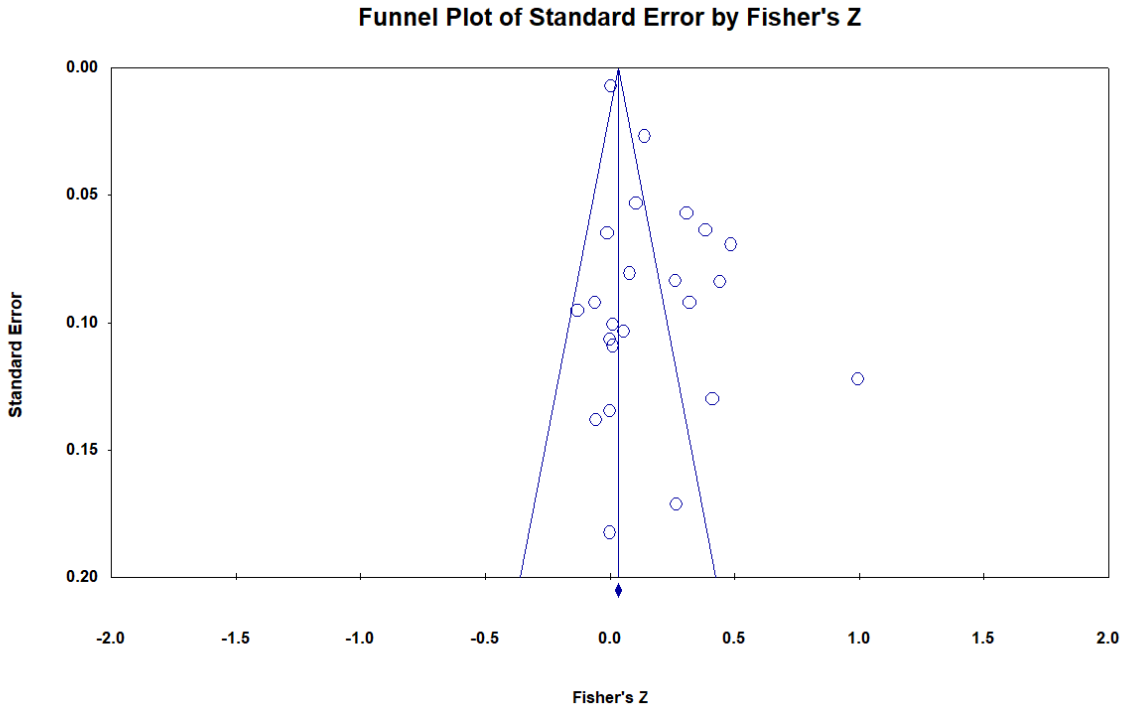


Figure 8 **Funnel Plot for the Association of Self-Agency and Immunosuppressant Adherence**

Chapter 4. Discussion

To our knowledge, this is the first meta-analytic work to investigate the associations between NA and SA with adherence to immunosuppressants in organ transplant. Across 50 studies and 46,106 recipients, the findings demonstrate that increased NA is associated with worse immunosuppressant adherence (average ES: *r*= -.14), while higher SA is associated with better immunosuppressant adherence (average ES: *r*= .17). The current study expands upon previous literature that had clarified the association of six variables' associations with immunosuppressant adherence (Dew et al., 2007) by examining the associations of two potentially modifiable variables—NA and SA—with immunosuppressant adherence. Moreover, the present study identifies a total of six clinical and methodology-specific variables (across both meta-analyses) that uniquely moderate the associations with immunosuppressant adherence in organ transplant. These factors are instrumental in guiding future research and clinical interventions to address nonadherence.

4.1. Negative Affect and Immunosuppressant Adherence

While NA was on average associated with immunosuppressant adherence, meta-regression revealed that the following characteristics were related to the largest NA and adherence associations (adjusted for other variables in the model): illness-specificity of NA, questionnaire adherence measures, location outside of Europe and North America, and higher quality studies, together explaining 54% of the effect size heterogeneity. The relatively larger association between illness/transplant-related NA and immunosuppressant adherence may involve an increased "potency" or "inescapability" of transplant-related NA. Specifically, in comparison to non-illness specific NA (e.g., depressive or anxiety symptoms), there is a relative lack of available treatments to relieve transplant-related symptoms and/or side-effects. In this way, it is possible that nonadherence is one of few coping behaviors aimed at escaping or mitigating the underlying causes of illness-specific NA (i.e., immunosuppressant side effects). This finding is of high clinical relevance given that it suggests that illness-specific negative affect, such as symptom and side-effect-related distress, is more problematic for nonadherence than are general indicators of negative affect (e.g., depression, anxiety, quality of life). To be sure, recipients identify the need to address immunosuppressant

side effects as a top research priority (Gallego et al., 2018). Together, this suggests that interventions that specifically target illness-specific NA are apt to be of clinical importance in managing nonadherence.

Of note, the present data pattern suggested that the majority of the transplant samples presented with subclinical levels of psychological distress (the median percentage of recipients who were clinically depressed or anxious— largely identified based on their meeting of cut-off scores on screening measures— was 18.8% and 27.87%, respectively). As such, it is possible that at higher severity levels of either depression and/or anxiety, recipients may show stronger associations with non-adherence; however, this was not the psychological presentation of the transplant recipients across studies included in this meta-analysis. Overall, our analyses supported an inclusive symptom-based analytic approach to distress by revealing convergence of the NA effect sizes, further supporting their meta-analytic aggregation. Divergences of effect sizes were apparent for adherence estimates based on depressive/anxiety symptoms, which were smaller in magnitude compared to the adherence effect size based on other indicators of NA. This finding may be partly explained by the latter's inclusion of illness-specific NA.

When adherence was measured via quantitative methods, the association between NA and adherence was negligible, which is a stark contrast to its measurement through questionnaire (self- or collateral report) measures. Susceptibility to common-method bias helps explain this finding, which refers to a systematic effect exerting an influence on the observed correlation between NA and adherence due to "common methods" (Podsakoff et al., 2003). Specifically, stronger associations may stem from construct overlap, given that self-report adherence measures have embedded within them specific items that are also captured by NA measures (e.g., forgetfulness, interfering negative emotion). Of note, however, and contrary to what was predicted, there was no difference between the effect size of adherence methods that queried barriers and those that did not. Nonetheless, it is possible that the degree to which such factors are endorsed as barriers to adherence may be reflective of recipients' NA, and thus this factor could benefit from further investigation in future research. Likewise, scale formats (e.g., Likert type scales) common to both measures of NA and self-reported adherence may inflate observed relationships, as can a common source of the rater (Podsakoff et al. 2003).

Of equal importance is research suggesting that method variance, such as context factors, can also deflate observed relationships (Podsakoff et al., 2003). Research utilizing questionnaire measures of adherence typically utilizes a small temporal window between administration of NA and adherence measures, maintaining similar contextual effects (e.g., state of mind). In contrast, in research utilizing quantitative adherence measures, adherence measurements are often obtained at a different time than are NA ratings. Such context effects are likely to be weakening the association of NA and adherence as measured by quantitative methods. Importantly, identification of the type of adherence measure (questionnaire vs. quantitative) as a moderator of the association between NA and adherence reinforces the importance of existing endeavors (Fine et al., 2009) aimed at developing a "gold standard" adherence measure. Given each adherence measure's unique advantages and limitations (Dew et al., 2007; Osterberg et al., 2005), a gold standard adherence measure is likely to include a combination of methods (e.g., self-report, collateral report, and assays) as previously done to maximize diagnostic accuracy (Schafer-Keller et al., 2008). The use of combination adherence methods is expected to both minimize the influence of method biases, as discussed above, and be more sensitive to capturing existing associations with important psychological factors such as NA.

In comparison to studies conducted in Europe and North America, those conducted elsewhere demonstrated a stronger association of NA with adherence. Of note, all of the countries in the Europe and North America grouping are classified as having a high gross domestic product (GDP), whereas those in the "other" category are a combination of high and low GDP countries and included primarily Asian countries (k=2 from China; k=2 from Korea; k=1 from Iran; and k=1 South America) (United Nations, 2017). Related to this, a weaker link between emotion and perceived health in high-GDP countries has been documented and is hypothesized to be related to the availability of medical interventions weakening the impact of emotion on health in wealthier countries (Pressman, Gallagher, & Lopez, 2013). As perceived health has been identified as a risk factor for nonadherence in organ transplant in prior meta-analytic work (Dew et al., 2007), the weaker association between NA and adherence in the Euro-American studies can be understood. Consistent with this finding, Langebeek and colleagues (2014) also found a stronger association between depressive symptoms and adherence in low and medium developed countries, compared to those that were more developed. Another explanation comes from the field of cultural health psychology. Studies demonstrating a stronger

association of NA with adherence were conducted in countries from collectivist cultures, which were primarily Asian. Asian cultures, particularly Chinese, tend to operate via a holistic model of health where physical and psychological health are inextricably tied to one another (Chen and Swartzman, 2001). Specific emphasis is placed on organ dysfunction, which may lead to fear, insomnia, forgetfulness, worry and sadness (Chen and Swartzman, 2001). Such a close link between these cultures' emotional wellbeing and physical health could help explain the stronger association between NA and management of transplantation through immunosuppressant adherence. Asian culture also places an emphasis on emotional suppression, and psychological distress may remain untreated due to underutilization of mental health services and associated stigma (Chen and Swartzman, 2001). To the extent that psychological distress is shunned and unmanaged, its effect on nonadherence may be more potent. Overall, these findings suggest that the literature on the relationship between NA and adherence in non-European/American cultures should be considered separately from that of Euro-American cultures given several unique characteristics inherent to non-Euro-American cultures.

4.2. Self-Agency and Immunosuppressant Adherence

Equally important and novel findings emerged from our analysis of SA and immunosuppressant adherence, whereby a higher female percentage and medication-specific SA were identified as unique moderators in meta-regression, accounting for 34% of the heterogeneity in effect sizes. In contrast to general measures of SA which showed a negligible association with adherence, a significant association was observed for medication-specific self-efficacy and adherence. Previous research from our lab has demonstrated that medication specific self-efficacy loads higher on the construct of self-efficacy than do general measures of self-efficacy in kidney transplant recipients (Paterson et al., 2018). Although the relative contribution of general vs. medication-specific self-efficacy on adherence was not examined by the researchers of that study, they hypothesized that medication-specific self-efficacy may be better predictive of adherence in kidney transplant in comparison to general measures of self-efficacy (Paterson et al., 2018). The present findings lend support to that prediction, extending it to other organ recipient groups, and suggest that a general sense of SA is not nearly as impactful as medication-specific SA for immunosuppressant adherence. As such, healthcare providers may find it worthwhile to elicit and address patient beliefs related to medication-specific

self-agency. Moreover, interventions aimed at increasing medication-specific SA may show promise in improving adherence.

The association of SA with adherence was significantly stronger with increased female percentage in studies and was on average negligible in samples with less female representation. This is perhaps suggestive that the association between SA and immunosuppressant adherence is stronger in females compared to males. It may also, however, be a function of a potentially restricted range in adherence levels. Although previous meta-analytic work across organ transplants is unsupportive of this (Dew et al., 2007), previous single-study findings suggest better medication adherence for females kidney transplant recipients (Denhaerynck et al., 2007; Demian et al., 2016). Statistically, a decreased percentage of females in study samples may potentially be restricting the range of adherence scores, which may in turn decrease the effect size magnitude (Goodwin and Leech, 2006).

4.3. Generalizability and Limitations

The present study demonstrates that, on average, there is a small and negative association between negative affect and immunosuppressant adherence. Additionally, on average, the association of self-agency and immunosuppressant adherence is small and positive in direction. These average associations were demonstrated across a large number of studies focusing exclusively on immunosuppressant adherence within the organ transplant population (i.e., 42 for negative affect and 23 for self-agency), which in comparison to previous meta-analyses (e.g., Dew et al. 2007; Di Matteo et al. 2000; Grenard et al. 2011) is comprehensive. Moreover, the use of robust statistical methods that are most suitable for the large variability across included studies (i.e., random effects meta-analyses) as well as smaller sub-group sizes (i.e., pooling of within-group estimates of tau-squared; Borenstein et al. 2009) lends validity to the conclusions drawn from our findings. Although the averaged effect sizes are small in magnitude (Cohen, 1992), predictive interval ranges suggest that that in some populations, the association may be as high as medium (r= .50) in magnitude for self-agency and approach r= -.34 for negative affect.

Importantly, however, a close examination of the prediction interval ranges for each of the NA (r= -.34 to .08*)* and SA (r= -.19 to.50) associations with immunosuppressant

adherence demonstrates that the ES overlaps with *r*= 0 and crosses into the opposite direction. This suggests that future similar studies *may* also be expected to show negligible associations, or associations that are opposite in direction to the averaged ES, of either NA and SA with immunosuppressant adherence. Specifically, in the case of the association of NA with immunosuppressant adherence, the association may at times be negligible or a small positive (as NA increases immunosuppressant adherence increases as well). The predictive interval of the association of SA with immunosuppressant adherence demonstrates that the association may at times be negative (as SA increases adherence to immunosuppressants decreases). Moderators identified in this meta-analysis provide insight into factors that would be expected to be associated with larger effect sizes. The containment of null and opposite effects within the prediction intervals is not a unique finding to the present meta-analysis. Previous investigation into this issue demonstrated that this occurs commonly; specifically, approximately three-fourth of statistically significant meta-analyses with demonstrated heterogeneity (I^2 >0) had a prediction interval containing the null effect. Moreover, one-fifth had a prediction interval that contained the opposite effect (Inthout et al., 2016). Our findings further highlight the importance of going beyond the report of confidence intervals (an index of precision of the summary effect size) to additionally reporting the prediction intervals (an index of dispersion of the effect size of individual studies).

Limitations of our study include assigning a conservative effect size of *r*= 0 for missing, non-significant effects. This is a common practice utilized by other meta-analyses in the field (e.g., DiMatteo et al., 2000; Grenard et al., 2011) and was applied to five and four studies within the NA and SA analyses, respectively. Importantly, however, sensitivity analyses on the impact of these particular studies revealed negligible change in the overall effect sizes (Δ of r= .016 for NA-Adherence meta-analysis and Δ of r= .025 for SA-Adherence meta-analysis). Similarly, sensitivity analysis conducted at the sub-group level did not demonstrate a bias associated with this procedure. On the other hand, the utilization of multiple measures of NA, SA, or adherence within a single study and hence the contribution of several adherence effect sizes by a single study was the rule rather than the exception. As such, common procedures related to dealing with multiple effect sizes (i.e., *a*-priori selection decisions based on maximizing statistical power, or aggregation of effect sizes) were utilized to eliminate the problem of effect size dependency. This meant that in some cases, not all study-reported effect sizes were

included in the analysis and/or that distinct types of NA, SA, or adherence moderators may have remained undetected in the present meta-analyses.

Other limitations are grounded in the characteristics of the included studies, particularly the correlational nature of research, which does not allow inferences on a causal relationship between the psychological factors and adherence. As such, it is possible that increased NA and lower SA each lead to lower adherence, or vice versa (i.e., poorer adherence leaves recipients feeling less efficacious or empowered and more distressed). Our rationale for focusing on zero-order correlations was that effect sizes based on partial correlations of the psychological factors and adherence would not be comparable across studies as studies. This selection decision was similarly utilized by previous meta-analytic work in the field (e.g., DiMatteo et al., 2000), and reflects the fact that individual studies vary in the confounds that are controlled for depending on their objectives and hypotheses. The implication is that the effect size magnitudes from partial correlation studies would reflect the covariates modelled by the investigators. This would introduce further heterogeneity and distort the association of the psychological factors with immunosuppressant adherence via the specific covariates included and their associations to adherence. As a first step, the present study's objective was to clarify the associations of NA and SA with adherence. However, future research and systematic reviews should focus on the utility of these psychological factors in predicting nonadherence as this would clarify the role of these factors in truly identifying recipients who are nonadherent (i.e., those meeting a defined threshold of not taking immunosuppressants as prescribed).

Additionally, it should be noted that the majority of studies assessing adherence via questionnaire methods were directly examining adherence to immunosuppressants through immunosuppressant medication-specific measures (e.g., Immunosuppressive Therapy Adherence Scales; Transplant Effects Questionnaire- Adherence Subscale, Basel Assessment of Adherence Scale for Immunosuppressives; electronic monitoring of immunosuppressant). However, there were 9 studies within the NA analysis and 4 studies within the SA analysis whose questionnaire measures queried adherence to the post-transplantation medication regimen generally (e.g., Medication Adherence Questionnaire), which in addition to immunosuppressant medications would have included other common medications that transplant recipients often take (e.g., antihypertensive agents). Subgroup analysis of the effect sizes based on the immunosuppressant medication-specific adherence measures vs. medication adherence measures did not

reveal significant differences in the effect sizes for either the NA (Q= .59; *p*= .44; Table 9) or the SA analysis (Q= .56; *p*= .46; Table 11), suggesting that this variable is unlikely to be contributing to the existing heterogeneity in the effect sizes. Importantly, none of these studies examined medication adherence that was exclusive of immunosuppressants. In terms of generalizability, our findings do not generalize to studies exclusively examining adherence to adjunct medications (e.g., antidepressants, antihypertensive agents, etc.).

Further, all of the included studies excluded recipients with poor organ functioning, which limits generalizability to recipients with good graft functioning. While this may be expected to restrict the range of nonadherence observed in the present sample and therefore decrease the magnitude of observed associations (Goodwin and Leech, 2006), our attempt at characterizing nonadherence levels of the present transplant sample demonstrated a wide range of nonadherence, and further, that nonadherence levels were comparable to previously documented rates (Dew et al., 2007). Admittedly, the accuracy of these levels suffers from, and is greatly confounded by, the variability of adherence methods utilized by researchers; however, we attempted to characterize these levels according to the adherence method used (questionnaire vs. other quantitative methods). Moreover, although studies were limited to those published in English, they were representative of up to 18 countries. Finally, it is possible that a few relevant published studies were missed due to our selection of search terms and databases.

4.4. Summary and Conclusions

In summary, the current meta-analyses extend our understanding of correlates of immunosuppressant adherence by providing novel conclusions regarding the magnitude and direction of the association of two psychological factors, NA and SA, with adherence to immunosuppressants in adult organ recipients following transplantation. Importantly, our findings elucidate factors contributing to the existing variability in adherence research and highlight the importance of careful consideration of aspects of methodology, including the types of measures used for the predictors (NA and SA) as well as for adherence, and the resulting implications. Future research can now shift to clarifying the role of NA and SA in predicting nonadherence and in considering these psychological variables as targets for intervention studies aimed at improving adherence to immunosuppressant medications. Clinically, the current findings suggest that transplant recipients experiencing NA (and especially illness-specific NA, such as distress from medication side effects)

and/or lower levels of medication-specific SA may also present with lower levels of adherence to immunosuppressants. Hence, an important initial clinical application of these findings may involve monitoring and supporting this subgroup of transplant recipients in managing their medication regimen. Similarly, recipients presenting with lower levels of adherence to immunosuppressants apt to have their NA and self-agency beliefs assessed and monitored.

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Appendix A.

Quality Assessment Tool for Non-Randomized Studies: Downs and Black Checklist (1998)

The checklist was shortened from 27 items to the 9 most relevant to the scope of the meta-analysis. Score each item as Yes (1); Partially (0.5) or No (0).

REPORTING

1. Are the objectives/hypothesis of the study clearly described?
2. Is the sample clearly described? This should address both:

Demographic information:	*Clinically relevant information:*
-age (mean)	-transplant type
-age range (min-max)	-min time since transplantation for inclusion
-gender composition	-average/median time since transplantation
-marital status	
-location of recruitment (e.g., hospital name)	

- Answer "yes" if all of the above (8/8) are provided.
- Answer "*partially*" if 5-7 of the above are provided.
- Answer "*no*" if a maximum 4/8 of the above are provided.

3. Was the source of the predictor variables (negative affect, self-agency) and adherence variables clearly described?
   - Measures must be clearly described. Variations of existing measures should be clearly described.
   - If not all of the above information is provided thoroughly, answer "partially."

4. Are the main findings of the study clearly described?
   - Relationship between either negative affect or self-agency with non-adherence. Effect size should be explicitly stated or calculable (i.e., even if finding is non-significant, an effect size should be provided).
   - If study reports multiple associations (e.g., self-agency with several adherence measures) and provides effect size for only some, but not other associations, answer "*partially*."

5. Does the study provide either estimates of the random variability in the data or frequency information (%/counts) for all of the variables of interest *(adherence, self-agency, and negative affect)*?
   - In non-normally distributed data, the inter-quartile range of results should be reported.
   - In normally distributed data, the standard error, standard deviation, or confidence intervals should be reported.
   - If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.
   - Answer "*partially*" if estimates are not provided for all variables studied in the study (self-agency/negative affect, adherence).

6. Have actual probability values been reported (e.g., 0.035 rather than < .05) for the associations of interest (i.e., of either self-agency or negative affect with non-adherence) except where the probability values are less than .001?
    - Answer "*partially*" if exact probabilities are not provided for all associations of interest.

VALIDITY

7. Were the predictor measures (negative affect, self-agency) used accurate (valid & reliable)?
    - Studies referring to other work that demonstrates the measures as accurate should be answered yes.
    - Predictor measure is considered valid/reliable if it is an established measure with existing reliability & validity information (not researcher-generated).
    - If it is translated from an existing tool into another language, psychometric properties must be reported.

8. Were the adherence measures used accurate (valid & reliable)?
    - Studies referring to other work that demonstrates the measures as accurate should be answered yes.
    - Adherence measure is considered valid/reliable if it is an established measure with existing reliability & validity information (not researcher-generated).
    - If it is translated from an existing tool into another language, psychometric properties must be reported.

POWER

9. Is there any explanation for how study size was arrived at, or mention of power?

Appendix B.

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