# Can Temporal Self-Regulation Theory and Its Constructs Predict Medication Adherence? A Systematic Review and Meta-Analysis

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# Author note

Acknowledgements: The authors would like to thank Marcus Campbell who assisted in the screening of articles, and the authors of the articles who responded to requests for additional information. The authors would also like to thank the Australian Government for providing support to Caitlin Liddelow through the Stipend Scholarship program for Higher Degree by Research students. Additionally, Mark Boyes is supported by the National Health and Medical Research Council, Australia (Investigator Grant 1173043).

# Funding details: N/A

Disclosure statement: No potential competing interest was reported by the authors

#### Abstract

The relationships between temporal self-regulation theory (TST) constructs (intention, behavioural prepotency and self-regulatory capacity) and medication adherence should be established before further applying the theory to adherence. Searches of PsychINFO, Medline, EMBASE, CINAHL and Web of Science were conducted in 2019 (updated November 2021). Studies had to be original quantitative research, assessed the relationship between one of the constructs and adherence in one illness, and used an adult population. Risk of bias was assessed using the NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Three meta-analyses were conducted using *R*. Moderation analyses were also conducted. A total of 57 articles (60 studies) with 13,995 participants were included, with 7 studies included in more than one analysis. Results identified significant correlations between intention (r = .369, [95% CI: .25, .48]), behavioural prepotency (r = .332, [95% CI: .18, .48]), self-regulatory capacity (r = .213, [95% CI: .10, .32]) and adherence. There was some evidence of publication bias and no significant moderators. No studies explored the interactions in the theory, so whilst the constructs adequately predict adherence, future research should apply the theory to adherence in a specific illness to assess these relationships. Pre-registered on Prospero: CRD42019141395.

Keywords: medication adherence; TST; intention; habit; cues; self-regulation

When medication regimens are adhered to, individuals are three times more likely to experience positive health outcomes compared to those who do not adhere correctly (DiMatteo et al., 2002). Similarly, adherence to prescription medication is associated with better recovery or management of disease, decrease in the presence of comorbid conditions, a decrease in the likelihood of experiencing adverse events, decreased risk of mortality, and a reduction in the total amount of money spent on health care (Chisholm-Burns & Spivey, 2012; Cutler et al., 2018). Yet, despite this, medication adherence remains a global health concern with an estimated 50% of people with a chronic disease, who live in high-income countries, do not adhere to their medication regimen (Brown & Bussell, 2011; Clyne et al., 2016; De Geest & Sabaté, 2003). It is estimated that approximately 4% of all hospital admissions in North America, Europe, Asia and Australia are the direct result of non-adherence to prescription medications (Mongkhon et al., 2018). As the population continues to age, non-adherence to prescription medications to treat the rising multimorbidity of disease (Ho et al., 2009; Yang et al., 2022).

One of the first steps to improving medication adherence is to facilitate changes in behaviour (Kleinsinger, 2018). The application of psychosocial models of behaviour to medication adherence has been one way in which attempts have been made to further understand adherence with the hopes of changing behaviour (see Lin et al., 2016; Phillips et al., 2013; Williams et al., 2009; Yue et al., 2015). However, these theories and the interventions based on them have reported differing findings and effects (Conn et al., 2016; Rivet Amico et al., 2018). One of the most commonly applied and extended models of behaviour is the theory of planned behaviour (Ajzen, 1991), especially in the context of adherence behaviours (Bane et al., 2006; Kopelowicz et al., 2015; McKinney et al., 2015). It proposes that intention is the strongest predictor of behaviour, however, the greatest criticism and discrepancy of the theory is its issues in actually predicting behaviour, which is commonly referred to as the 'intention-behaviour gap' (Armitage & Conner, 2001; Sheeran & Webb, 2016). This suggests that intention alone is a poor predictor of health behaviour. A 2015 meta-analysis by Rich et al. (2015) found that the theory of planned behaviour variables (intention and perceived behavioural control) were only capable of predicting approximately 9% of variance in adherence behaviours. In attempts to negate the lack of predictive ability of the theory of planned behaviour, many psychosocial variables have been added to the model to explore their potential in accounting for additional variance (e.g., de Bruin et al., 2012; Liddelow, Mullan, & Novoradovskaya, 2020; Rhodes & Dickau, 2012). These variables (e.g., habit strength, anticipated regret and planning) have all shown to predict behaviour over and above the theory of planned behaviour variables (Gardner et al., 2011; Sniehotta et al., 2014). While the addition of such variables adds to the models' predictive ability, many researchers were still concerned with the validity and utility of the theory and called for its retirement in health behaviour research and to instead focus on other theories of behaviour (Sniehotta et al., 2014).

A more recent theory of behaviour that is being applied to health behaviours is temporal self-regulation theory (TST; Hall & Fong, 2007). TST is a dual-process model that follows on from the theory of planned behaviour, and while still suggesting that intention is the most proximal predictor of behaviour, it includes both behavioural prepotency (the frequency and habitual/automatic nature of the behaviour) and self-regulatory capacity (the ability to regulate emotions, thoughts and behaviours) as direct predictors of behaviour but also as individual moderators of the intention-behaviour relationship (Hall & Fong, 2007). Behavioural prepotency is the automatic component of the theory that occurs with little thought and is typically measured by habit strength, cues and frequency of past behaviour. Self-regulatory capacity is quite broad in TST and encapsulates "…any state or trait like factor that influences an individual's capacity to effortfully regulate their own behaviour (e.g., executive function, energy level)" (Hall & Fong, 2007, p. 14). As the theory is fairly new (compared to other theories), its applicability to various behaviours is limited. However, it has been used to predict volunteering behaviour (Mullan et al., 2021), healthy and unhealthy snacking (Elliston et al., 2017; Evans et al., 2017), binge drinking and alcohol consumption (Black et al., 2017; Murray & Mullan, 2019), sugar-sweetened beverage consumption (Moran & Mullan, 2020), vitamin and supplement use (Allom et al., 2018), and hand-washing behaviours (Liddelow, Ferrier, et al., 2021).

The theory has only been applied to medication adherence once, in a 2021 study where cues (as a component of behaviour prepotency) was the only significant predictor when using two different self-report measures of behaviour (Liddelow, Mullan, et al., 2021). Intention and a component of self-regulatory capacity, self-control, were only significant when using one of the measures of adherence. Despite its limited application to adherence, the constructs of TST have been used independently with mixed findings, with some showing habit strength is associated with better medication adherence (Phillips et al., 2016) whereas others show is not associated (Liddelow, Mullan, & Novoradovskaya, 2020). Therefore, the purpose of this meta-analysis is to synthesise the literature, and independently assess the relationships between each of the constructs of TST and medication adherence.

This review will also assess the moderating impacts of methodological factors such as study design, length of follow-up, and the type of measure of adherence. The relationship between two constructs may be different when measured at the same time point compared to if they are measured weeks or months apart. Given TST is proposed as a model of future health behaviour, this is important to unpack, similarly, as adherence is a long-term behaviour there may be differences in the strength of relationships over time (Rich et al., 2015). Furthermore, measurement in medication adherence has long been an issue (Brown & Bussell, 2011; Lam & Fresco, 2015). Self-report measures of adherence tend to be subject to social desirability bias and over-estimating of adherence, as well as not always measuring behaviour but rather measuring attitudes, beliefs or barriers towards medication adherence (Nguyen et al., 2014). While objective measures of adherence such as Medication Event Monitoring Systems (MEMS<sup>®</sup>) and prescription refills are also limited in that they do not necessarily measure adherence but rather opening a medication bottle or refilling a prescription. Therefore, the way adherence is measured will be a moderator to not only assess its possible influence on the relationships but also to see which measures of adherence are the most commonly used.

### Aim and Hypotheses

The current meta-analysis aims to conduct three individual analyses to identify and evaluate the individual predictive ability of the constructs (intention, behavioural prepotency and self-regulatory capacity) of TST in medication adherence. A secondary aim of this metaanalysis, following the moderation hypotheses of TST, is to explore the strength of the interactions between the TST constructs in adherence. It was hypothesised that:

H1: All three TST constructs would be significantly positively associated with medication adherence

**H2:** Secondly it was hypothesised that as per the theory, behavioural prepotency and self-regulatory capacity would moderate the intention-adherence relationship such that the relationship between intention and adherence would strengthen as self-regulatory capacity strengthens, but the relationship would weaken as behavioural prepotency increases.

**H3:** Thirdly, the study design (cross-sectional or longitudinal) is hypothesised to moderate the individual associations between the TST constructs and adherence, such that studies using longitudinal designs will show weaker associations compared to studies with cross-sectional designs.

**H4:** With previous research highlighting a stronger relationship between self-report subjective measures and medication adherence (Nguyen et al., 2014), it was hypothesised that studies measuring adherence with subjective measures would have stronger associations between the TST constructs and medication adherence.

# Methods

A protocol for this review was pre-registered with Prospero (CRD42019141395) before the commencement of the search for studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were also followed (Liberati et al., 2009; Page et al., 2021) and a checklist is included in Supplementary Materials. The APA Journal Article Reporting Standards Quantitative (JARS-Quant; Appelbaum et al., 2018) which provides guidelines for quantitative articles, including meta-analysis, was also followed. All data associated with this review is also accessible on Open Science Framework (https://osf.io/w9ktx).

## **Search Strategy**

Electronic searches of the databases PsychINFO (1806-present), Medline (1950present), EMBASE (1974-present), CINAHL (1900-present) and Web of Science (1900present) were conducted in November 2019. An updated search of the same databases was conducted in November 2021. All variables of interest were searched in separate searches in each database. An example search strategy for each variable of interest can be seen in Table 1. No search limits, such as language or year of publication, were applied. A combination of text words and subject headings (e.g. MeSH terms) were used in the search strategy, with slight variations between databases. The use of truncation, phrases and wildcards was also used. An individual literature search in each database was conducted for each of the three predictors of interest (intention, habit, and self-regulation) to ensure no key articles were missed. Some of the text words used in the searches included: (intent\* OR intention\*), (habit\* OR cue\* OR automatic\*), (self-regulat\* OR "executive function" OR self-control) AND (medication OR medicine OR "drug therapy" OR pharmacotherapy\*) AND (adhere\* OR comply OR compliance OR non-adherence or nonadherence).

# **Eligibility Criteria**

Studies were eligible for inclusion in the review if they investigated the role, influence or predictive ability of at least one of the constructs of interest (intention, habit, cues, past behaviour, executive function, self-regulation, self-control or planning) in medication adherence in a chronic disease, with medication adherence the outcome measure. All measures of adherence (e.g. self-report, electronic monitoring and biological markers) were eligible for inclusion. Studies that (i) measured adherence to medical or psychological therapy, lifestyle or addiction treatment, given these are not medication related (ii) assessed adherence in acute illnesses or to short-term medications, (iii) involved animals, (iv) a sample population below 18 years of age and, (v) not containing quantitative data, were excluded.

# Table 1

Example Search Strategy for 'Intention' From PsychINFO (Ovid)

- 1. exp Intention/ or exp Behavioral Intention/
- 2. Drug Therapy/
- 3. exp Treatment Compliance/
- 4. (intent\* or intention\*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]
- (medication\* or medicine\* or drug therapy or pharmacotherap\*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]
- 6. (adhere\* or comply\* or compliance or non-adherence or nonadherence).mp.
   [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

1 or 4
 2 or 5
 3 or 6

10. 7 and 8 and 9

#### **Study Selection Process**

Upon completion of the database searches, all articles were downloaded into Endnote. Here, duplicates were identified and removed. Title and abstract screening were conducted simultaneously to identify eligible studies meeting the inclusion criteria. The primary reviewer screened 100% of the titles and abstracts, with a secondary reviewer screening a random 20% of the articles to ensure agreement and consistency. Following the title and abstract screening, the full texts of each article were sourced and reviewed by the primary reviewer. If some of the studies included in the full-text stage were conference abstracts and if author details were available, they were contacted to request the full-text associated with this abstract. Similarly, for articles with statistics unsuitable for the analysis or no correlation matrix, the corresponding author was contacted via email requesting additional information. If there was no response from the authors, the article was subsequently removed from the analysis.

#### **Data Extraction and Analytic Strategy**

The primary reviewer independently extracted the key data items from the included articles using a data extraction form in Excel, created for this review. Several study characteristics were extracted including publication details, sample demographics, study design, illness or medication of interest, the TST construct of interest that was measured, types of construct measure used, outcome measure/s of adherence and relevant statistical results.

Zero-order correlation coefficients were the chosen effect size for this meta-analysis due to the expectation that studies will control for different covariates. Similarly, it was deemed the most appropriate as many of the studies employed cross-sectional correlational research designs. If authors included statistics such as  $\beta$  (beta) or adjusted Odds Ratios (OR), authors were contacted to request the zero-order correlations. If no response was received, these studies were subsequently excluded from the analysis. The standard error of each correlation co-efficient was manually calculated using the formula:

# $SE = (1-r^2)/\sqrt{N}$

With studies that used more than one measure of a construct (e.g., studies that used multiple measures of self-regulatory capacity), a preferred measure was identified and their correlation with medication adherence was extracted. This means only one correlation coefficient with adherence was extracted for each construct in each study. Specifically for self-regulatory capacity, given its broad definition in TST, choosing preferred measures for executive function is one way we can create homogeneity in the analysis. The Trails Making Test (A and B), which measure executive function and memory, and the Wisconsin Card Sorting Test, which measures cognitive reasoning, were the two preferred measures of selfregulatory capacity/executive function. For studies that used two or more individual measures of medication adherence, the correlation coefficient between the preferred measure of the construct and the first reported medication adherence measure was extracted. For example, if a study used both a subjective and an objective measure of medication adherence (without creating a composite) if the first reported correlation coefficient between the construct and medication adherence was for the objective measure, this was the extracted coefficient for the study. Choosing preferred measures for medication adherence was deemed inappropriate given the inconsistencies and complexities in the literature related to the best measures of medication adherence, especially subjective/self-report measures (Anghel et al., 2019; Lam & Fresco, 2015). These are both deviations from the protocol where it was planned to extract all reported relevant correlation coefficients. However, to reduce dependability in the data and the results, the method of extraction was changed. In line with the protocol, if different samples were reported in the same study (e.g. older adults and younger adults), with different results, both samples were retained for analysis.

All meta-analytic results were calculated using a standard random-effects model in the Metafor package for R (Vietchtbauer, 2010), with the estimation based on the restricted maximum likelihood estimator. In the protocol, Comprehensive Meta-Analysis (CMA) software was proposed. However, the research team had access to *R* and this was chosen as the preferred software for this analysis. Given the aim of the meta-analysis was to assess the strength of bivariate relationships between TST constructs and medication adherence, rather than assess a model, multivariate analyses or metaSEM were not appropriate. A standard random-effects model was chosen as it assumes that effect sizes are different between studies (heterogeneity) and we expected this as the studies included were all exploring different illnesses or medications. In addition, a random-effects model also calculates the most precise estimation of the pooled effect size when there is heterogeneity between studies (Field, 2001). Excess heterogeneity was assessed using Cochrane's Q statistic and  $I^2$ , with  $I^2$  indicating the proportion of variance attributable to excess heterogeneity between studies and is not an absolute measure of excess heterogeneity. According to Higgins et al. (2003),  $I^2$  statistics of 25%, 50% and 75% are considered low, moderate and high values of heterogeneity, respectively. Publication bias was assessed using both Egger's test, if significant at p < .05, indicates that publication bias is considered influential (Egger et al., 1997), and sunset (power-enhanced) funnel plots, which show the statistical power of studies to detect an underlying true effect but with colour-coded power regions (Kossmeier et al., 2020). It plots effect sizes (Pearson's r) against their standard errors (SEs). The colours range from a dark

red, indicating a highly underpowered study, to dark green for appropriately powered studies. A fail-safe *n* test was originally proposed, but with the change of software, sunset (powerenhanced) funnel plots were the best alternative in *R*. Sensitivity analyses were conducted using 'remove-one' analyses to assess the individual influence of each study on the overall effect if it were removed.

Tests of moderation were also conducted in each meta-analysis for study design, length of follow-up for longitudinal studies, and type of medication adherence measure. For studies that used subjective (self-report) measures of medication adherence, these measures were further divided, and moderation by the type of subjective measure was tested along with the other types of measures listed above. Type of illness was originally proposed as a moderator in the protocol, however, due to low numbers of studies for specific illness groups, this was not feasible. Type of medication adherence measure was originally proposed to be grouped according to self-report, electronic, objective, bodily indicators, and chemical, however similar to above some categories comprised of a too small number of studies and thus the categories were broadened. Length of follow-up was not originally proposed as a moderator, however as the theory is designed as a prospective theory of behaviour the decision was made during data extraction to include this as a moderator as relationships over time can vary over different lengths of time (Rich et al., 2015). As side-effects associated with the medications or illnesses, and the regimen of the sample were rarely reported in studies, these moderation analyses could not be conducted as per the protocol.

## **Moderator Coding**

Studies were classified according to their study design, either 1 = cross-sectional or 2 = longitudinal. The length of follow-up for longitudinal studies was also assessed, with follow-up reported in months. Furthermore, studies were coded into three groups based on the type of medication adherence measure used: 1 = subjective, 2 = objective and 3 = composite

of both. Due to the aforementioned measurement issues in medication adherence, to identify the different types of subjective measures that are used to measure medication adherence, all studies that used subjective measures were coded into three groups: 1 = measures behaviour, 2 = measures attitudes/beliefs, and 3 = items made for study.

#### Results

#### **Study Selection**

From the initial electronic database searches, a total of k = 15,637 published and unpublished articles were identified across all three variables of interest. The updated electronic database search identified an additional k = 4,329 articles (total of k = 19,966articles). After duplicates were removed from both searches (k = 6,571), a total of k = 13,455articles remained for screening. Title and abstract screening were conducted simultaneously for each variable of interest, and k = 13,125 articles, from both searches, were excluded. There was an agreement rate of 92.7% (Cohens  $\kappa = 0.55$ ) between the two screeners at this stage. The remaining 293 articles from the initial search (k = 128 in intention, k = 74 in behavioural pre-potency, and k = 91 in self-regulatory capacity) and the k = 37 (k = 15 in intention, k = 6in behavioural pre-potency, and k = 16 in self-regulatory capacity) from the updated search were subjected to full-text screening. After full-text screening, k = 24 articles remained in intention, k = 11 remained in behavioural prepotency and k = 22 remained in self-regulatory capacity. If an article was identified in one of the searches but measured more than one of the variables of interest, it was subsequently also included in the other variables' quantitative synthesis. For example, the article by Vluggen et al. (2019) was initially identified in the intention searches, but because they also measured behavioural pre-potency, it was subsequently also included in the behavioural pre-potency analysis. Reasons for exclusion during full-text screening included duplicates or using the same dataset (e.g., Burns et al.,

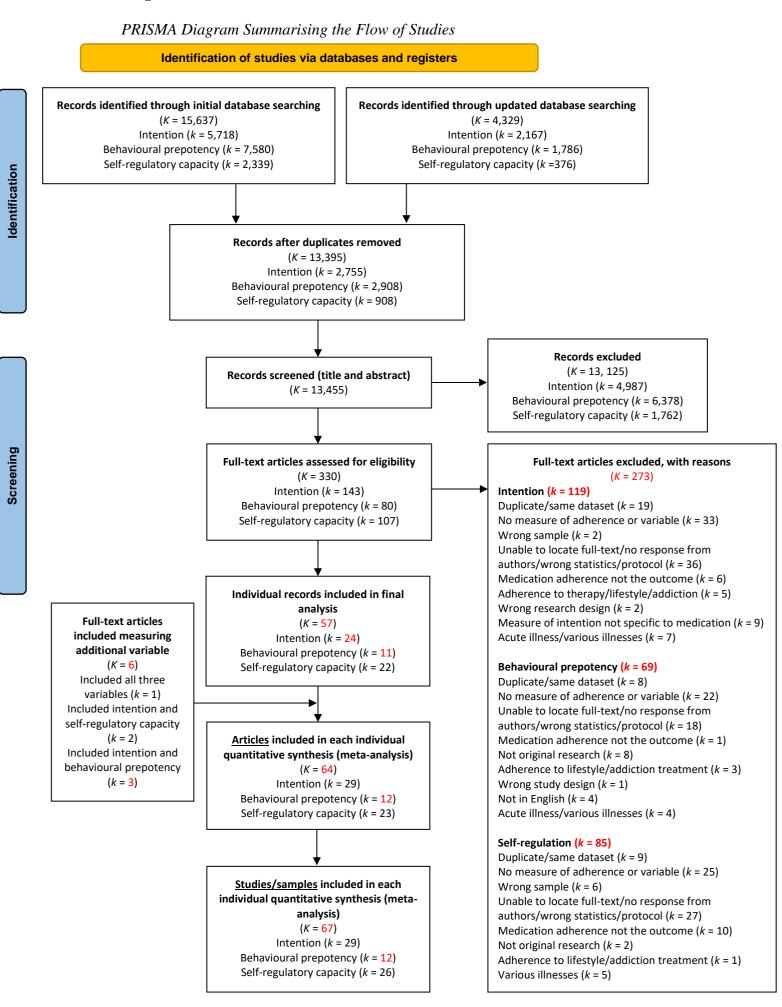
2019), wrong sample (e.g. adolescents or children) [e.g., Bai et al., 2015], medication adherence not the outcome (e.g., Kidd et al., 2016), adherence in various illnesses (e.g., Liddelow, Mullan, & Novoradovskaya, 2020), and non-empirical original research (e.g., Selnes, 2002). Six articles (Banas et al., 2017; Cook et al., 2015; de Bruin et al., 2012; Hoo et al., 2017, 2019; Vluggen et al., 2019) were identified as measuring more than one variable of interest and thus these studies were included in each of the respective analyses. A total of k =29 studies from k = 29 articles were included in the intention quantitative synthesis, k = 12studies from k = 12 articles in the behavioural prepotency quantitative synthesis and k = 26studies from k = 23 articles in the self-regulatory capacity quantitative synthesis. A total of k =6 articles were included in more than one of the quantitative syntheses.

Overall, k = 57 individual articles (k = 64 including articles included in more than one quantitative synthesis) with 60 different samples and 67 zero-order correlation coefficients (Ettenhofer et al. [2009] with two independent samples and Stilley et al. [2010] with three independent samples) were included in this meta-analysis. See Figure 1 which summarises the identification, screening, eligibility, and inclusion procedures. See Table 2 for a summary of the studies included in each meta-analysis.

# Description of Studies, Samples and Measures of Medication Adherence

Included studies were conducted between 1988 and 2020, with k = 55 published and k = 5 unpublished. The year 2012 had the most included studies (k = 7), followed by 2010, 2017 and 2019 with k = 5 studies each. Across the 60 samples, sample size ranged from 16 participants (Insel et al., 2008) to 1,433 participants (Molfenter et al., 2012), with a total of 13,995 participants and a mean sample size of 233.25 (SD = 250.58). The mean age across all samples was 52.67 years (SD = 12.93), ranging from an average of 20 years of age (Molloy et al., 2012) to 76 years (Kosilov et al., 2020). Females made up on average 48% of samples. Most of the studies (k = 32) contained samples from the Americas, followed by Europe and

the UK (k = 15). Regarding research design, k = 34 studies used cross-sectional designs and k = 26 used prospective or longitudinal designs with follow-up's ranging from four weeks (Casaletto et al., 2016; Hinkin et al., 2004; Phillips et al., 2013; Phillips et al., 2016) to two years (M = 23.12 weeks, SD = 24.17). Human immunodeficiency virus (HIV) or Acquired immunodeficiency syndrome (AIDS) was the most common illness of focus (k = 14), followed by cardiovascular diseases (k = 12).



Subjective (self-report) measures of medication adherence used in k = 40 studies, k = 17 studies used objective measures, and k = 3 used a composite measure. The most commonly used subjective measure of medication adherence was the Medication Adherence Report Scale (Horne & Weinman, 1999) which was used in k = 10 studies. However, the most commonly used measure of medication adherence overall was Medication Event Monitoring Caps (MEMS<sup>®</sup>), which was used in k = 15 studies. Other commonly used measures of adherence included the Morisky Medication Adherence Scale (MMAS-8<sup>©</sup>; Morisky et al., 2008), pharmacy refill records, and specific questions made for the study.

Table 2

Summary of Studies Included in The Meta-Analysis

Author and	Country	Illness of interest	Total	Mage years	% of	Study	Length of	Measure of variable	Measure	of medication adherence	Results
year			N	(SD) of sample	sample male	design	follow-up		Type of measure	Name	-
Intention Me	ta-Analysis										
Banas et al. (2017)	Tanzania	HIV /AIDS	158	43.75 (10.5)	30.7	L	5 months	Self-report 3 items made for study	0	Medication event monitoring system (MEMS®)	Intention was weakly negatively associated with adherence at 5 months ( $r = -0.070$ )
Belaiche et al. (2018)	France	Kidney Transplant	408	54	61.2	С	N/A	-	S	Compliance Evaluation Test (CET)	Intention was moderately negatively associated with adherence ( $r = -0.307$ )
Chisholm et al. (2007)	USA	Renal Transplant	158	51.0 (12.4)	60.1	С	N/A	Self-report 2 items made for study	0	Pharmacy refill data	Intention was moderately positively associated with adherence ( $r = 0.460, p$ <.01)
Cochran & Gitlin (1988)	USA	Bipolar Disorder	48	40.0	35.4	С	N/A	Self-report 1 item made for study	S	5 items adapted from Cochran (1984)	Intention was strongly positively associated with adherence ( $r = 0.880, p < .001$ )
Conner et al. (1998)	England	Mental Health Disorders, mainly depressive	61	-	-	L	9 weeks	Self-report 5 items made for study	S	Self-report by patient - % of time compliant	Intention was moderately positively associated with patient self-report adherence ( $r$ = 0.560, $p$ <.01)
Cook et al. (2015)	USA	Glaucoma	201	65.0 (11.2)	27.69	L	2 months	Intention subscale from the Adherence Attitude Inventory	0	MEMS®	Intention was weakly positively associated with MEMS adherence $(r = 0.270)$ .
de Bruin et al. (2012)	The Netherlands	HIV	56	48.9 (9.1)	88.0	L	3 months	Self-report 2 items made for study	СО	MEMS® and 1 self- report item	Intention was moderately positively associated with adherence ( $r = 0.550$ , $p$ <.001)

Fai et al. (2017)	USA	Type 2 Diabetes	115	50.97	-	С	N/A	-	S	Morisky Medication Adherence Scale (MMAS-8 <sup>©</sup> )	Intention was weakly positively associated with adherence ( $r = 0.290, p < .01$ )
Farmer et al. (2006)	England	Type 2 Diabetes	121	66.0	52.1	С	N/A	Self-report 2 items made for study	S	Medication Adherence Report Scale (MARS) – 5 items	Intention was weakly positively associated with adherence ( $r =$ 0.290, $p <$ .01)
Hagger et al. (2016)	Australia	Familial hypercholesterole mia	110	50.65 (13.81)	43.64	С	N/A	Self-report 1 item made for study	S	Self-report over previous 3 months	Intention was strongly positively associated with adherence ( $r = 0.635$ , $p < .001$ )
He et al. (2020)	China	Coronary Heart Disease	300	66.26 (10.22)	71.0	С	N/A	Self-report 4 items made for the study	S	Medication Adherence Report Scale (MARS) – 5 items	Intention was strongly positively associated with adherence ( $r = 0.690, p < .01$ )
Ho & Lee (2014)	Taiwan	Hypertension	604	-	-	С	N/A	Self-report (unsure number of items)	S	MMAS-8 <sup>©</sup>	Intention was moderately positively associated with adherence ( $r = 0.490, p$ <.001)
Holstad et al. (2006)	USA	HIV	120	36.5 (8.5)	60.0	С	N/A	Self-report 4 items from Antiretroviral Adherence Determination Questionnaire	S	Antiretroviral General Adherence Scale	Intention was weakly positively associated with adherence ( $r = 0.190$ , $p < .05$ )
Hoo et al. (2019)	England	Cystic Fibrosis	61	-	54.1	L	3 months	Self-report 1 item adapted from COM-B Self-Evaluation Questionnaire	0	Chipped nebulisers	Intention was weakly positively associated with adherence ( $r =$ 0.282, $p = .028$ )
Hoo et al. (2017)	England	Cystic Fibrosis	20	-	60.0	С	N/A	Self-report 2 items adapted from COM-B Self-Evaluation Questionnaire	0	I-neb (application) - % between total amount used against the agreed dosage	Intention was weakly negatively associated with adherence ( $r = -$ 0.093, $p = .695$ )

Jessop & Rutter (2003)	-	Asthma	330	57.2 (17.9)	33.3	С	N/A	Self-report 2 items made for study	S	Self-report 5 items made for study (over previous 3 months)	Intention was strongly positively associated with adherence ( $r =$ 0.610, $p$ <.001)
Lin et al. (2016)	Iran	Epilepsy	567	38.37 (6.71)	48.5	L	24 months	Self-report 5 items based on Ajzen (1991)	S	MARS – 5 items	Intention was strongly positively associated with adherence ( $r =$ 0.690)
McDonnell et al. (2001)	USA	Tuberculosis	62	46.5 (11.6)	-	С	N/A	4 items from Tuberculosis Adherence Determination Questionnaire	S	Tuberculosis General Adherence scale (over previous 4 weeks)	Intention was weakly positively associated with adherence ( $r =$ 0.290, $p < .005$
McKinney et al. (2015)	Malawi	HIV	358	-	0	С	N/A	Self-report 4 items based on Ajzen (1991)	S (but CO of two)	1. Two-day self-report recall of how many doses of medication patients took	Intention was very weakly positively associated with adherence ( $r = 0.010$ )
										2. One-month self- report recall by patient	
Molfenter et al. (2012)	USA	Cholesterol	1433	54.2 (9.79)	56.3	L	6 months	-	0	Past medication-refill behaviour using proportion of days covered (PDC)	Intention was moderately positively associated with adherence ( $r = 0.410$ )
Molloy et al. (2012)	Scotland	Oral Contraceptive Pill	130	20.46 (3.01)	-	С	N/A	Self-report 2 items made for study	S	MARS – 5 items (higher scores = non- adherence)	Intention was moderately negatively associated with adherence ( $r = -0.330$ , $p$ <.01)
Moore (1995)*	USA	Hypertension	100	66 (14.5)	23.0	С	N/A	Self-report 7 items made for study	S	Time since last medication (in hours)	Intention was weakly negatively associated with 'time since last medication' adherence ( $r$ = -0.260, $p < .01$ ).
Nelsen et al. (2013)	USA	HIV	244	51.8 (9.5)	92.0	С	N/A	Self-report 13 items previously validated by the authors	S	Self-reported adherence in the previous month using a Visual Analogue Scale - 90%	Intention was weakly positively associated with adherence ( $r = 0.250$ )

										or below was considered non- adherent	
Pakpour et al. (2014)	Iran	Coronary artery bypass surgery	223	59.21 (7.14)	76.2	L	12 months	Self-report 5 items adapted from previous research	S	MARS - 5 items	Intention was moderately positively associated with adherence ( $r = 0.340, p$ <.01)
Peleg et al. (2017)	Israel	Cardiovascular disease	106	55.71 (7.87)	100	L	6 months	Self-report 1 item made for study	S	MARS – 5 items	Intention was moderately positively associated with adherence ( $r = 0.470$ , $p$ <.001)
Putman (2004)	USA	Asthma	102	-	25.0	С	N/A	Asthma Behavioural Intention Instrument	S	Asthma Adherence Instrument	Intention was moderately positively associated with adherence ( $r = 0.350$ )
Quine et al. (2012)	England	Hypertension	934	69.0 (11.7)	42.0	L	2 months	Self-report 4 items made for study	S	Morisky Medication Adherence Scale 4 items (MMAS-4) and 1 additional item made for study	At follow-up, intention was weakly positively associated with adherence ( $r = 0.240, p$ <.001)
Scholz et al. (2012)	Switzerland	Organ Transplant	121	54.32 (13.32)	67.0	С	N/A	Self-report 4 items adapted from Chisholm et al. (2007)	S	Adherence subscale from the German version of the Transplant Effects Questionnaire (TxEQ- D)	Intention was moderately positively associated with adherence ( $r = 0.540$ )
Vluggen et al. (2019)	The Netherlands	Type 2 Diabetes	260	60.80 (6.80)	67.0	L	6 months	Self-report 2 items made for study	S	Probabilistic Medication Adherence Scale (ProMAS)	At follow-up, intention was weakly positively associated with adherence ( $r = 0.190, p$ <.01)
Author and year	Country	Illness of interest	Total N			Study design	Length of follow-up	Measure of variable	Measure o	f medication adherence	Results

				M <sub>age</sub> years (SD) of sample	% of sample male				Type of measure	Name	
Behavioural	Prepotency Mo	eta-Analysis		Ĩ							
Bolman et al. (2011)	USA	Asthma	139	31.5 (5.6)	29.5	С	N/A	SRHI – 12 items	S	MARS-5	Habit was strongly positively associated with adherence ( $r =$ 0.610, $p <$ .001)
Burns et al. (2019)	Canada	Type 2 Diabetes	790	64.05 (8.20)	50.8	С	N/A	SRBAI – 4 items	S	2 items made for study	Habit was weakly positively associated with adherence ( $r =$ 0.160, $p <$ .001)
Cook et al. (2015)*	USA	Glaucoma	201	65.0 (11.2)	27.69	L	2 months	Cues to action (within the Glaucoma Treatment Compliance Assessment Tool)	0	MEMS®	Cues to action was weakly negatively associated with MEMS adherence ( $r = -0.270$ )
Durand et al. (2018)	Ireland	Hypertension	2014	69.86 (10.69)	57.8	С	N/A	SRBAI – 4 items	S	MMAS-8©	Habit was moderately positively associated with MMAS-8 adherence ( $r = 0.350$ , p < .001)
Hoo et al. (2017)	England	Cystic Fibrosis	20	-	60.0	С	N/A	SRBAI – 4 items	0	I-neb (application) - % between total amount used against the agreed dosage	Habit was strongly positively associated with adherence ( $r = 0.640$ , $p = .002$ ).
Hoo et al. (2019)	England	Cystic Fibrosis	61	N/A	54.1	L	3 months	SRBAI – 4 items	0	Chipped nebulisers	Habit was strongly positively associated with adherence ( $r = 0.570$ , $p < .001$ ).
Ikechuwku et al. (2010)	Nigeria	Hypertension	756	56.5 (14.4)	63.8	С	N/A	Interview	S	"Pills taken over a specific period of time, divided by pills prescribed for that specific period of time" (3, 5, 7 days retrospective). Score	Habit was strongly positively associated with adherence ( $r = 0.600, p < .001$ ).

Attonito (2013)*	USA	HIV / AIDS	246	45.24 (7.04)	66.0	С	N/A	Executive function 1. The Colour Trails Test 2, Form A 2. The Category Test Short Form	S	Percentage of time ART medications were taken as prescribed over the course of a week	Executive function (composite measure) was positively weakly associated with adherence ( $r = 0.060$ )
Self-regulato	ry Capacity Me	ta-Analysis							measure		
Author and year	Country	Illness of interest	Total N	M <sub>age</sub> years (SD) of sample	% of sample male	Study design	Length of follow-up	Measure of variable	Type of	f medication adherence Name	Results
Vluggen et al. (2019)	The Netherlands	Type 2 Diabetes	260	60.80 (6.80)	67.0	L	6 months	Cues to Action – 11 items made for study	S	Probabilistic Medication Adherence Scale (ProMAS)	Cues were weakly negatively associated with adherence ( $r = -$ 0.180, $p < .01$ )
Wolkovich (2017)*	Israel	Multiple Sclerosis	96	41.9 (14.0)	29.2	L	6 months	SRHI – 12 items	S	Probabilistic Medication Adherence Scale (ProMAS)	Habit was weakly positively associated with adherence ( $r =$ 0.040, $p = .224$ )
Phillips et al. (2016)	USA	Type 2 diabetes	133	56.96 (12.04)	38.0	L	1 month	SRBAI – 4 items	S	MARS-5	Habit was moderately associated with MARS-5 adherence ( $r = 0.400$ , p < .001)
Phillips et al. (2013)	USA	Hypertension	71	67.90 (12.28)	37.0	L	1 month	SRHI and 4 items made for study	S	MARS-5	Habit was moderately positively associated with both MARS-5 adherence ( $r = 0.370$ , $p < .01$ )
Murphy et al. (2018)	Ireland	Oral Contraceptive Pill	245	22.41 (4.78)	0.0	С	N/A	SRBAI – 4 items	S	MARS-5	Habit was weakly positively associated with adherence ( $r =$ 0.240, $p$ <.001)
										was expressed as the average percentage of adherence across the three measurements	

Banas et al. (2017)	Tanzania	HIV /AIDS	158	43.75 years (10.5)	30.7	L	5 months	Self-regulation 4 items made for study	0	MEMS®	Self-regulation was weakly associated with adherence at 5 months ( $r$ = 0.190, $p$ <.05)
Bourdeau (2004)*	USA	Haemodialysis	82	59.7 (15.0)	55.0	L	3 months	Self-control Rosenbaum's Self- Control Schedule	S	1 item made for study	Self-control was weakly positively associated with adherence ( $r =$ 0.190, $p = .025$ )
Boyer et al. (2012)	France	Schizophrenia	169	36.6 (12.5)	73.4	С	N/A	Executive function measured by the Trail Making Test A	S	Medication Adherence Rating Scale (MARS) - 10	Executive function as measured by the trail making test A was weakly but positively associated with adherence ( $r = 0.050$ )
Casaletto et al. (2016)	USA	Bipolar disorder	50	47.1 (9.7)	88.0	L	1 month	Executive function (composite) 1. Wisconsin Card Sorting Task 2. Trail making Test B	0	MEMS®	Executive function (composite measure) was weakly positively associated with adherence ( $r = 0.240, p$ = .100)
Cholowski & Cantwell (2007)	Australia	Heart failure	51	72.3 (8.19)	-	С	N/A	Self-regulation 10 items made for study	S	Self-report during interview	Self-regulation was weakly positively associated with adherence ( $r = 0.170$ )
Contardo et al. (2009)	USA	HIV	99	44.5 (7.5)	58.8	L	4 weeks	Executive function 1. Trail Making Test A 2. Trail Making Test B	Ο	MEMS®	Executive function (composite measure) was weakly negatively associated with adherence ( $r = -0.110$ )
de Bruin, et al. (2012)	The Netherlands	HIV	56	48.9 (9.1)	88.0	L	3 months	Self-regulation 3 items made for study	СО	<ol> <li>MEMS®</li> <li>Self-report 1 item</li> </ol>	Self-regulation was strongly positively associated with adherence ( $r = 0.630$ , p < .001)
El-Missiry et al. (2015)	Egypt	Schizophrenia	137	32.3 (9.0)	70.6	L	6 months	Executive function	0	Brief Adherence Rating Scale (BARS)	Executive function was strongly positively

								Wisconsin Card Sorting Task (computer version)			associated with adherence ( $r = 0.500, p$ = .271)
Ettenhofer et al. (2009) A	USA	ΗIV	79	53.03 (4.46)	81.0	С	N/A	Executive function (composite) 1. Trail Making Test B 2. Stroop Colour-Word 3. Short Category Test 4. Wisconsin Card Sorting Task	CO	<ol> <li>MEMS®</li> <li>Number of doses of the MEMS-tracked medication missed</li> <li>Report of whether they missed a dose of their MEMS medication the previous day</li> <li>Medical Outcome Scale questionnaire</li> </ol>	Executive function (composite) was moderately positively associated with the composite adherence measure ( $r = 0.410$ , $p < .01$ ).
Ettenhofer et al. (2009) B	USA	HIV	352	40.49 (5.53)	80.4	С	N/A	Executive function (composite) 1. Trail Making Test B 2. Stroop Colour-Word 3. Short Category Test 4. Wisconsin Card Sorting Task	СО	<ol> <li>MEMS®</li> <li>Number of doses of the MEMS-tracked medication missed</li> <li>Report of whether they missed a dose of their MEMS medication the previous day</li> <li>Medical Outcome Scale questionnaire</li> </ol>	Executive function (composite) was weakly positively associated with the composite adherence measure ( $r = 0.020$ , $p = .730$ ).
Gelb et al. (2010)	Canada	Kidney transplant	103	50.07 (12.38)	52.7	С	N/A	Executive function measured by the Trail Making Test (A and B)	S	Immunosuppressant adherence subscale from the Transplant Effects Questionnaire (TxEQ)	Executive function as measured by the Trail Making task was weakly negatively associated with adherence ( $r = -0.160$ ).
Hinkin et al. (2002)	USA	HIV	137	44.1 (7.5)	82.0	С	N/A	Neuropsychological domain - measure contains 3 measures of executive function	0	MEMS®	The neuropsychological domain was moderately positively associated

											with adherence ( $r = 0.300, p = .030$ ).
Hinkin et al. (2004)	USA	ΗΙν	148	44.2 (7.7)	83.0	L	4 weeks	Executive function (composite) 1. Short Category Test 2. Trail Making Test B 3. Stroop Colour-Word	0	MEMS®	Poor executive function (composite measure) was strongly positively associated with poor adherence ( $r = 0.530$ ).
Hoo et al. (2017)	England	Cystic Fibrosis	20	-	60.0	С	N/A	Self-control Brief Self Control Scale (BSCS)	0	I-neb (application) - % between total amount used against the agreed dosage	Self-control was moderately positively associated with adherence ( $r = 0.440$ ).
Insel et al. (2008)	USA	Hypertension	16	70.19	56.25	L	2 months	Executive function as measured by the Wisconsin Card Sorting Task (categories completed)	0	MEMS®	Executive function was weakly positively associated with adherence ( $r = 0.190$ ).
Kosilov et al. (2019)	Russia	Overactive bladder	364	73.6 (8.1)	0.0	L	3 months	Executive function and working memory (composite) 1. Wisconsin Card Sorting test 2. Wechsler Memory Scale 3 3. California Verbal Learning Test	0	MEMS®	Executive function and working memory composite measure was moderately positively associated with adherence ( $r = 0.407$ , $p < .001$ ).
Kosilov et al. (2020)	Russia	Benign Prostatic Hyperplasia (BPH) and overactive bladder	395	76.10	100.0	L	3 months	Executive function (composite score) 1. Wisconsin Card Sorting Test 2. Wechsler Memory Scale 3 (subscales Mental Control, Digit Span Backward, and Letter Number Sequencing)	Ο	MEMS®	Executive function and working memory composite measure was moderately positively associated with adherence ( $r = 0.450$ , $p < .001$ ).
Kowalczyk (2012)*	USA	HIV	156	41.1 (8.7)	100.0	С	N/A	Executive function	S	Timeline Follow-Back	Executive function was weakly positively

								as measured by the Wisconsin card sorting task (categories completed)			associated with adherence ( $r = 0.084$ ).
O'Conor et al. (2019)	USA	COPD	388	68.0 (8.3)	41.7	L	12 months and 24 months	Executive function as measured by the Trail making Test A	S	MARS-10	Executive function as measured by the Trail Making Test A was weakly positively associated with adherence ( $r = 0.084$ ).
O'Conor et al. (2015)	USA	Asthma	425	67.4 (6.8)	16.5	С	N/A	Fluid abilities composite (processing speed, working memory, long- term memory, executive function, and global cognitive function) 1. Pattern Comparison 2. WMS Letter-Number Sequencing 3. WMS 2 story A 4. Trails Making Task A and B 5. Mini-Mental State Exam	S	MARS-10	Fluid ability was weakly positively associated with adherence ( <i>r</i> = 0.170, <i>p</i> <.001).
Stilley et al. (2010) A	USA	High cholesterol	157	46.2 (8.7)	54.1	L	6 months	Executive function (composite) 1. Trails Making Test B 2. Digit Span	0	MEMS®	Executive function was weakly negatively associated with adherence ( $r = -0.179$ ).
Stilley et al. (2010) B	USA	Diabetes/hyperten sion	354	63.7 (10.3)	40.5	L	24 days	Executive function Stroop Colour-Word Test	0	MEMS®	Executive function was very weakly positively associated with adherence ( $r = 0.001$ ).
Stilley et al. (2010) C	USA	Breast cancer	34	59.76 (4.66)	0.0	L	6 months	Executive function (composite) 1. Controlled Oral Word Association 2. Stroop Colour-Word	0	MEMS®	Executive function was moderately positively associated with adherence at 6 months ( $r$ = 0.384)

								3. Stockings of Cambridge			
Thames et al. (2011)	USA	HIV	51	48.2 (13.8)	76.9	С	N/A	Executive function (measures made into composite with all other neuropsychological measures) 1. Trail Making Test B 2. Wisconsin Card Sorting Task 3. Stroop Colour-Word	S	Percentage of antiretroviral medication doses taken over the last 30 days	Total neuropsychological functioning was weakly positively associated with adherence ( $r = 0.130$ , $p = .390$ )
Waldrop- Valverde et al. (2006)	USA	HIV	57	42.75 years (5.6)	3.5	С	1 week	Executive function (composite) 1. Colour Trails Test 1 and 2 2. Digit Span 3. Controlled Oral Word Association Test	S	Interviewer- administered questionnaire	Executive function was very weakly positively associated with adherence ( $r = 0.001$ ).

*Note.* \*indicates unpublished research, N = sample size, C = cross-sectional design, L = longitudinal design, S = subjective measure of

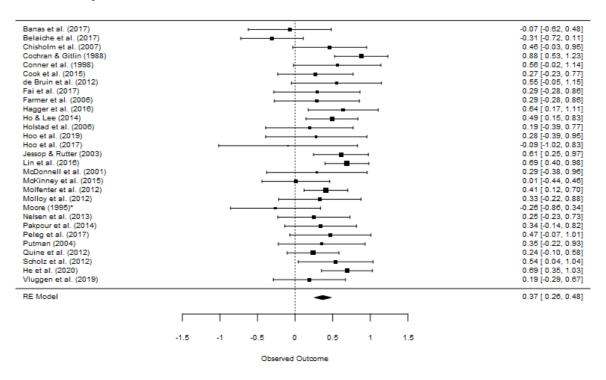
medication adherence, O = objective measure of medication adherence, CO = composite measure of medication adherence. A letter (i.e. B)

besides author name indicates a different sample within the same study.

#### **Intention Meta-Analysis**

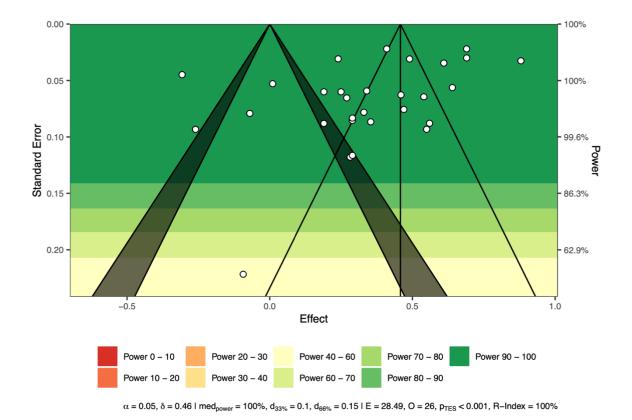
A total of k = 29 studies that include a measure of intention were included in the metaanalysis, with a total number of 7,172 participants ( $M_{age} = 52.46$  years). Studies were published between 1988 and 2020. The majority of studies were published (k = 28) and k = 18used a cross-sectional research design. The test of residual heterogeneity was significant Q(28) = 43.16, p = .034,  $I^2 = 38.67\%$ . The random-effects meta-analysis identified a significant moderate association between intention to adhere and medication adherence (Pooled r =0.369, 95% CI = 0.258, 0.480, p < .001). See Figure 2 for the forest plot of this association, outlying the independent observed outcomes of each included study, as well as the pooled outcome. Egger's test of publication bias was significant (p = .023) indicating publication bias was influential. The sunset-enhanced funnel plot also identified some publication bias due to its asymmetry. The median power of the included studies was 100%. See Figure 3 for the sunset-enhanced funnel plot. Sensitivity analysis showed that no individual study if it were removed, would have a significant effect on the overall pooled effect (see Supplementary Materials).

# Forest Plot of the Association Between Intention and Medication Adherence



Note. \*Unpublished research

Sunset-Enhanced Funnel Plot Showing Publication Bias and Power of the Included Studies in the Intention and Medication Adherence Meta-Analysis



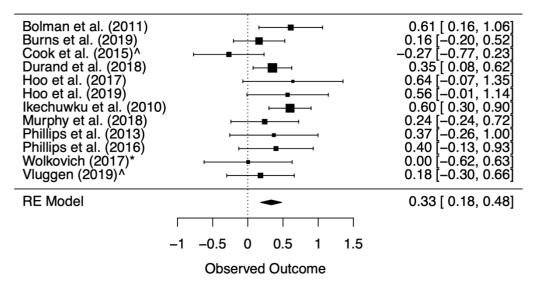
*Note.* The white circles represent the included studies (k = 29).  $\delta$  = true effect size; medpower = the median power of all studies; d33% = effect size needed for achieving 33% of median power; d66% = effect size needed for achieving 66% of median power; E = expected number of positive studies; O = observed number of positive studies; *p*TES = tests of excess significance (*p*-value); R-Index = expected replicability of findings.

#### **Behavioural Prepotency Meta-Analysis**

A total of k = 12 studies that measured habit strength (k = 10) or cues (k = 2) were included in the meta-analysis, with a total of 2,976 participants ( $M_{age} = 53.69$  years). All studies were conducted between 2010 – 2019, with k = 11 published. Study design was evenly split between cross-sectional (k = 6) and longitudinal (k = 6). The test of residual heterogeneity was non-significant Q(11) = 13.92, p = .237,  $I^2 = 23.15\%$ . The random-effects meta-analysis revealed a significant moderate association between behavioural prepotency and medication adherence (Pooled r = 0.332, 95% CI 0.183, 0.481, p < .001). See Figure 4 for the forest plot, outlying the independent observed outcomes of each included study, as well as the pooled outcome. Egger's test of publication bias was non-significant (p = .640), indicating publication bias was not influential. However, the sunset-enhanced funnel plot identified some publication bias due to its asymmetry. The median power of the included studies was 100%, all studies were above 80% power. See Figure 5 for the sunset-enhanced funnel plot. Sensitivity analysis showed that no individual study if it were removed, would have a significant effect on the overall pooled effect (see Supplementary Materials).

Forest Plot of the Association Between Behavioural Prepotency and Medication

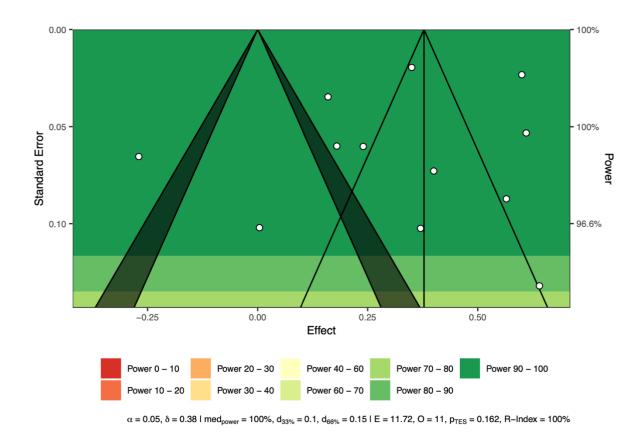
### Adherence



Note. ^Measure of behavioural prepotency was Cues to Action.

\* Unpublished research

Sunset-Enhanced Funnel Plot Showing Publication Bias and Power of the Included Studies in the Behavioural Prepotency and Medication Adherence Meta-Analysis



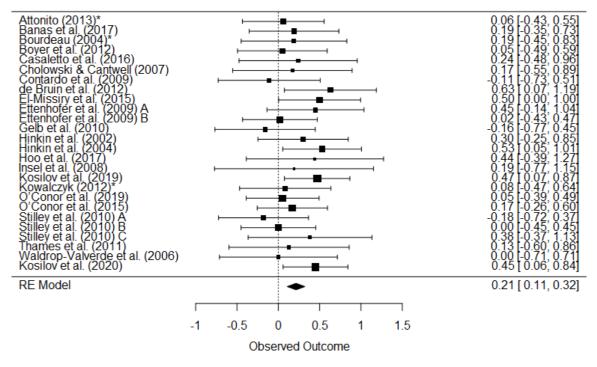
*Note*. The white circles represent the included studies (k = 29).  $\delta$  = true effect size; medpower = the median power of all studies; d33% = effect size needed for achieving 33% of median power; d66% = effect size needed for achieving 66% of median power; E = expected number of positive studies; O = observed number of positive studies; *p*TES = tests of excess significance (*p*-value); R-Index = expected replicability of findings.

#### **Self-Regulatory Capacity Meta-Analysis**

A total of k = 26 studies that measured self-regulation (k = 3), self-control (k = 2) or executive function (k = 21), were included in the meta-analysis. Combined, there were a total of 4,095 participants ( $M_{age} = 52.77$  years), and studies were conducted between. 2002 and 2020. The majority of studies were published (k = 23) and just over half used a longitudinal design (k = 14). Two studies had more than one sample (Ettenhofer et al., 2009; Stilley et al., 2010). The test of residual heterogeneity was non-significant Q (25) = 17.32, p = .870,  $I^2 =$ 0.00%. A random-effects meta-analysis revealed a significant weak association between selfregulatory capacity and medication adherence (Pooled r = 0.213, 95% CI 0.108, 0.321, p <.001). See Figure 6 for the forest plot of this association, outlying the independent observed outcomes of each included study, as well as the pooled outcome. Egger's test of publication bias was non-significant (p = .537), suggesting publication bias was not influential. However. the sunset-enhanced funnel plot identified some publication bias due to its asymmetry. The median power of the included studies was lower than the other two constructs at 85%. See Figure 7 for the sunset-enhanced funnel plot. Sensitivity analysis showed that no individual study if it were removed, would have a significant effect on the overall pooled effect (see Supplementary Materials).

Forest Plot of the Association Between Self-Regulatory Capacity and Medication

#### Adherence

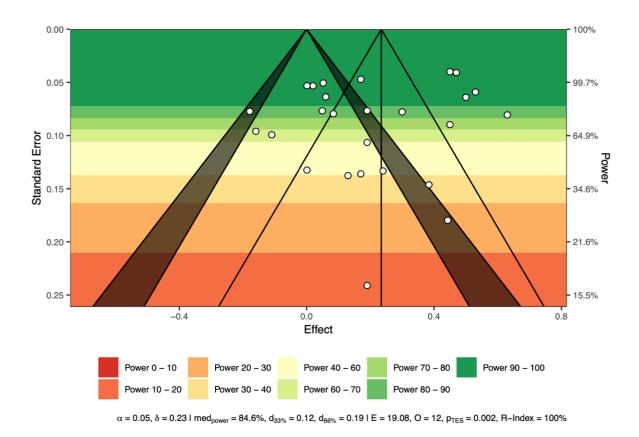


Note. \*Unpublished research

A letter (i.e. B) besides author name indicates a different sample within the same article.

# Figure 7

Sunset-Enhanced Funnel Plot Showing Publication Bias and Power of the Included Studies in the Self-regulatory Capacity and Medication Adherence Meta-Analysis



*Note*. The white circles represent the included studies (k = 29).  $\delta$  = true effect size; medpower = the median power of all studies; d33% = effect size needed for achieving 33% of median power; d66% = effect size needed for achieving 66% of median power; E = expected number of positive studies; O = observed number of positive studies; *p*TES = tests of excess significance (*p*-value); R-Index = expected replicability of findings.

# **Moderator Analysis and Meta-Regression**

Study design, length of follow-up, type of medication adherence measure and type of subjective medication adherence measure were all tested as moderators in each meta-analysis. In all three meta-analyses, no significant moderations were observed (see Table 3 for moderation and meta-regression results). This indicates that the strength of the association between the individual TST construct and medication adherence was neither strengthened nor weakened by study design, length of follow-up in longitudinal studies, or type of medication adherence measure.

# Table 3

# Moderator Analyses for the Associations Between the Three TST Constructs and Medication Adherence

	Intention				Behavioural Prepot	ency			Self-regulatory Capacity					
	B(95% CI)	р	Z	I <sup>2</sup>	B(95% CI)	Z	р	$I^2$	B(95% CI)	z	р	$I^2$		
Longitudinal <sup>a</sup>	0.01 (-0.23, 0.24)	.928	0.09	40.36%	-0.22 (-0.52, 0.07)	-1.49	.136	14.19%	0.15 (-0.07, 0.36)	1.34	.179	0.00%		
Length of Follow-Up	0.00 (-0.00, 0.01)	.053	1.93	0.00%	-0.02 (-0.04, 0.01)	-1.07	.286	0.00%	-0.00 (-0.00, 0.00)	-1.53	.124	0.00%		
<b>Subjective<sup>b</sup></b>	0.11 (-0.18, 0.41)	.444	0.76	40.86%	-0.10 (-0.43, 0.23)	-0.60	.545	24.43%	-0.14 (-0.37, 0.08)	-1.23	.217	0.00%		
<b>Composite</b> <sup>b</sup>	0.28 (-0.48, 1.04)	.468	0.73	40.86%	-	-	-	-	0.04 (-0.29, 0.38)	0.26	.797	0.00%		
Attitudes/beliefs <sup>c</sup>	-0.26 (-0.60, 0.07)	.121	-1.55	29.86%	-	-	-	-	-0.13 (-0.47, 0.22)	-0.72	.473	0.00%		
Made for study <sup>c</sup>	-	-	-	-	-	-	-	-	0.01 (-0.68, 0.69)	0.02	.981	0.00%		

Note.<sup>a</sup> in comparison with cross-sectional, <sup>b</sup> in comparison with objective measures, <sup>c</sup> in comparison with behavioural measures, -

indicates moderation could not be performed

## **Systematic Review of TST Relationships**

In line with TST, which proposes both behavioural prepotency and self-regulatory capacity moderate the relationship between intention and behaviour, the studies that measured one or more of the TST constructs was further examined. Of the 67 total studies included across the three meta-analyses, only one study by Hoo et al. (2017) measured all three constructs of TST. However, the study did not apply the theory, but rather explored the predictive ability of each construct independently. Two additional studies (Banas et al., 2017; de Bruin et al., 2012) included measures of intention and self-regulatory capacity, and three studies included measures of intention and behavioural prepotency (Cook et al., 2015; Hoo et al., 2019; Vluggen et al., 2019). These six studies also did not test or report any interactions between the variables of interest.

## **Risk of Bias Across Studies**

The study quality and risk of bias of each study were assessed using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. This tool provides 14 areas of quality that a study can be assessed on. Overall, k = 11 out of 60 (18.33%) studies assessed were deemed to be 'poor quality' or 'high risk of bias', k = 26 out of 60 (43.33%) were identified as being of 'fair quality' and the remaining k = 21 out of 60 (38.02%) were deemed to be of 'good quality'. The poor-quality ratings were mainly the result of having a cross-sectional design which limits the understanding of the predictive ability of the variables in adherence, not justifying the sample size or providing a description of power and not providing specific details about the sample. No studies were deemed too poor quality to warrant exclusion from the analysis. See Table 4 for a summary of whether each study included in the analysis met quality criteria and risk of bias safeguards.

# 41

# Table 4

Study Ouality and Risk of	of Bias of Each Stud	y Included in the Analysis

Author and Year	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 5	Criteria 6	Criteria 7	Criteria 8	Criteria 9	Criteria 10	Criteria 11	Criteria 12	Criteria 13	Criteria 14	Overall quality
Attonito (2013)	Y	Y	Y	Y	Y	Ν	N	NA	Y	Ν	Y	NA	NA	Ν	Good
Banas et al. (2017)	Y	Y	CD	Y	Ν	Y	Y	NA	Y	Ν	Y	NA	Y	Y	Good
Belaiche et al. (2017)	Y	Ν	CD	Y	Ν	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Poor
Bolman et al. (2011)	Y	Ν	Ν	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Y	Fair
Bourdeau (2004)	Y	Ν	Y	Y	Y	Y	Y	NA	Y	Ν	Y	NA	NR	Y	Good
Boyer et al. (2012)	Y	Y	CD	Y	Ν	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Fair
Burns et al. (2019)	Y	Y	NR	Y	Y	Ν	Ν	NA	Y	Ν	CD	NA	NA	Y	Fair
Casaletto et al. (2016)	Y	Ν	CD	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Fair
Chisholm et al. (2007)	Y	Y	Y	Y	Ν	Ν	Ν	NA	Y	Ν	Y	NA	NA	Y	Fair
Cholowski & Cantwell (2007)	Y	Y	CD	Y	Ν	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Fair
Cochran & Gitlin (1988)	Y	Ν	Ν	Y	Ν	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Poor
Conner et al. (1998)	Y	Ν	Y	Y	Y	Y	Y	NA	Y	Ν	Y	NA	CD	Ν	Good
Contardo et al. (2009)	Y	Ν	CD	Y	Ν	Y	Y	NA	Y	Ν	Y	NA	NR	Y	Good
Cook et al. (2015)	Y	Y	CD	Y	Y	Ν	CD	NA	Y	Ν	Y	NA	NR	Ν	Fair
de Bruin et al. (2012)	Y	Y	Y	Y	Y	Y	Y	NA	Y	Ν	Y	NA	Y	Y	Good
Durand et al. (2018)	Y	Ν	Y	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Fair
El-Missiry et al. (2015)	Y	Ν	CD	Y	Ν	Y	Y	NA	Y	Ν	Y	Y	Y	Ν	Good
Ettenhofer et al. (2009) A and B	Y	Ν	CD	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Y	Fair
Fai et al. (2017)	Y	Ν	CD	Y	Ν	Ν	Ν	NA	Ν	Ν	Ν	NA	NA	Ν	Poor
Farmer et al. (2006)	Y	Ν	Y	Y	Ν	Ν	Ν	NA	Ν	Ν	Y	NA	NA	Ν	Poor
Gelb et al. (2010)	Y	Y	Y	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Good

Hagger et al. (2016)	Y	Ν	Y	Y	Y	Ν	Ν	NA	Y	Ν	Ν	NA	NA	Ν	Poor
He et al. (2020)	Y	Y	Y	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Good
Hinkin et al. (2002)	Y	Ν	CD	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Y	Fair
Hinkin et al. (2004)	Y	Ν	CD	Y	Ν	Ν	Ν	NA	Y	Ν	Y	NA	CD	Ν	Fair
Ho & Lee (2014)*	Y	Ν	CD	CD	Ν	Ν	Ν	NA	NR	Ν	NR	NA	NA	Ν	Poor
Holstad et al. (2006)	Y	Ν	CD	Y	Ν	Ν	Ν	NA	Y	Ν	Y	NA	NA	Y	Fair
Hoo et al. (2017)	Y	Y	Y	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Good
Hoo et al. (2019)	Y	Ν	CD	CD	Y	Y	Y	NA	Y	Ν	Y	NA	CD	Ν	Fair
Ikechuwku et al. (2010)	Y	Y	CD	Y	Y	Ν	Ν	NA	Ν	Ν	Ν	NA	NA	Y	Poor
Insel et al. (2008)	Y	Ν	CD	Y	Ν	Y	Y	NA	Y	Ν	Y	NA	CD	Ν	Fair
Jessop & Rutter (2003)	Y	Ν	Ν	Y	Ν	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Poor
Kosilov et al. (2019)	Y	Y	CD	Y	Y	Y	Y	NA	Y	Ν	Ν	NA	Y	Ν	Good
Kosilov et al. (2020)	Y	Y	CD	Y	Ν	Ν	Y	NA	CD	Ν	Y	NA	CD	Y	Fair
Kowalczyk (2012)	Y	Ν	CD	Y	Y	Y	Y	NA	Y	Ν	Y	NA	Ν	Ν	Good
Lin et al. (2016)	Y	Y	Y	Y	Y	Y	Y	NA	Y	Ν	Y	NA	CD	Ν	Good
McDonnell et al. (2001)	Y	Y	NR	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Fair
McKinney et al. (2015)	Y	Y	Y	Y	Y	Ν	Ν	NA	Y	Ν	CD	NA	NA	Ν	Good
Molfenter et al. (2012)	Y	Y	Ν	Y	Y	Y	Y	NA	Y	Ν	Y	NA	NR	Y	Good
Molloy et al. (2012)	Y	Ν	NR	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Fair
Moore (1995)	Y	Ν	NR	Y	Y	Ν	Ν	NA	Y	Ν	Ν	NA	NA	Y	Poor
Murphy et al. (2018)	Y	Y	CD	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Fair
Nelsen et al. (2013)	Y	Y	Ν	Y	CD	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Fair
O'Conor et al. (2015)	Y	Y	Ν	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Y	Fair
O'Conor et al. (2019)	Y	Y	Ν	Y	Y	Y	Y	NA	Y	Ν	Y	NA	Ν	Y	Good
Pakpour et al. (2014)	Y	Y	Y	Y	Y	Y	Y	NA	Y	Ν	Y	NA	Y	Y	Good
Peleg et al. (2017)	Y	Y	Y	Y	Y	Y	Y	NA	Y	Ν	Y	NA	Y	Ν	Good

Phillips et al. (2013)	Y	Ν	Ν	Y	Y	Y	Y	NA	Y	Ν	Y	NA	Y	Ν	Good
Phillips et al. (2016)	Y	Ν	Ν	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Y	Fair
Putman (2004)	Y	Ν	Ν	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Fair
Quine et al. (2012)	Y	Ν	Y	Y	Y	Y	Y	NA	Y	Ν	Y	NA	Ν	Ν	Good
Scholz et al. (2012)	Y	Ν	Ν	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Y	Good
Stilley et al. (2010) A	Y	Ν	CD	CD	Ν	Y	Y	NA	Y	Ν	Y	NA	CD	Ν	Poor
Stilley et al. (2010) B	Y	Ν	CD	Y	Ν	Y	Y	NA	Y	Ν	Y	NA	CD	Ν	Fair
Stilley et al. (2010) C	Y	Ν	CD	Y	Ν	CD	CD	NA	Y	Ν	Y	NA	CD	Ν	Poor
Thames et al. (2011)	Y	Ν	CD	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Y	Fair
Vluggen et al. (2019)	Y	Y	Ν	Y	Y	CD	Y	NA	Y	Ν	Y	NA	Ν	Y	Good
Waldrop-Valverde et al. (2006)	Y	Ν	CD	Y	Y	Ν	Ν	NA	Y	Ν	Y	NA	NA	Ν	Poor
Wolkovich (2017)*	Y	Ν	CD	Y	Y	Y	Y	NA	Y	Ν	Y	NA	CD	CD	Fair

*Note.* \* no full text available; Y = quality criteria met; N = quality criteria not met; NA = quality criteria not applicable; NR = quality criteria not reported; CD = quality criteria cannot be determined.

Criteria 1 = Was the research question or objective in this paper clearly stated?; Criteria 2 = Was the study population clearly specified and defined?; Criteria 3 = Was the participation rate of eligible persons at least 50%?; Criteria 4 = Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?; Criteria 5: Was a sample size justification, power description, or variance and effect estimates provided?; Criteria 6 = For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?; Criteria 7 = Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?; Criteria 8 = For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome?; Criteria 10 = Was the exposure(s) assessed more than once over time?; Criteria 11 = Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; Criteria 13 = Was loss to follow-up after baseline 20% or less?; Criteria 14 = Were the outcome assessors blinded to the exposure status of participants?; Criteria 13 = Was loss to follow-up after baseline 20% or less?; Criteria 14 = Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)

#### Discussion

This is the first meta-analysis of studies that apply TST constructs to medication adherence across a range of illnesses. Three random-effects meta-analyses were conducted assessing the association between a TST construct (intention, behavioural prepotency or selfregulatory capacity) and medication adherence. No studies tested or reported on the interactions between the theory variables and adherence, and therefore this analysis could not be conducted.

# Intention

The findings of the current meta-analysis provide support for the continued use and application of TST to medication adherence, albeit with small effect sizes ranging from 0.213 (self-regulatory capacity) to 0.369 (intention) (Cohen, 1988). The findings showed all three associations were significant, which supports TST (Hall & Fong, 2007). Intention had the strongest association with medication adherence behaviour, which is consistent with the theory and a previous meta-analysis assessing the predictive ability of intention in adherence behaviours (Hall & Fong, 2007; Rich et al., 2015). While this finding is not unsurprising, what is interesting about this finding is that the strength of the association is considered moderate (r = .369), which is not expected given intention is considered the most pertinent predictor of behaviour in various theories of behaviour change (Ajzen, 1991; Hall & Fong, 2007), and in a previous meta-analysis by McEachan et al. (2011) intention also had the strongest association with future health behaviour. As we were unable to test the multivariate relationships between the TST variables and medication adherence, the association between intention and adherence may be moderated by other variables such as habit strength (Hall & Fong, 2007), which is predicted by TST.

#### **Behavioural Prepotency**

Regarding behavioural prepotency, the identified association with medication adherence was also moderate (r = .332) (Cohen, 1988). This finding supports the tenets of TST as behavioural prepotency is hypothesised to significantly predict behaviour (Hall & Fong, 2007). This is insightful as it not only supports TST but there are currently no other meta-analyses that have assessed the pooled strength of the association between behavioural prepotency and medication adherence. However, a recent systematic review by Badawy et al. (2020) identified a strong association between habit strength and medication adherence in chronic disease in 11 studies. This finding is inconsistent with our current finding, even though nine of the studies included in the systematic review were included in our current meta-analysis. One possible reason for this was the inclusion of studies (k = 2) that measured the association between cues to action and adherence. However, given the small number of studies that measured cues to action, we were unable to assess whether the construct measured (e.g., habit strength or cues to action) moderated the behavioural prepotency adherence relationship in any way. While both reviews arrive at a similar conclusion, the Badawy et al. (2020) systematic review did not conduct any quantitative analysis. There are also no details outlining how the authors arrived at their conclusion that habit and adherence are strongly associated given our pooled moderate correlation of r = .369. Due to metaanalyses not evaluating or summarising the findings, but rather analysing them statistically (Ganeshkumar & Gopalakrishnan, 2013), we believe the conclusion we have arrived at is the strongest and least biased (Drucker et al., 2016). But more research is clearly needed to understand the complexity of habit strength in medication adherence.

Furthermore, given only two studies (Cook et al., 2015; Vluggen et al., 2019) assessed cues to action, the lack of research exploring the relationship between cues and medication adherence is concerning. Previous research studies, particularly qualitative studies, have shown the importance of cues such as physical/visual cues, and contextual cues in aiding in medication adherence (Liddelow, Mullan, Boyes, et al., 2020; Orr et al., 2007), but it seems as though the role and influence of cues is rarely quantitatively explored. Future research should consider conducting more quantitative research exploring cues in adherence as this may provide avenues for future research.

## **Self-regulatory Capacity**

Further support for the theory was identified in the significant relationship between self-regulatory capacity and medication adherence. However, it was the weakest association amongst the three constructs (r = .213) which suggests it may not be as important in medication adherence as intention or behavioural prepotency. However, the association identified between self-regulatory capacity and medication adherence may not be an accurate representation of the true association between the two variables. This result may also be due to the aforementioned broad definition of self-regulatory capacity proposed in the original TST paper. As there are many state and trait-like factors within this definition of self-regulatory capacity, the strength of its relationship with adherence is likely to not be as strong as it would be if the definition was tighter (e.g., trait self-regulation).

Similarly, of the five studies that measured self-control or self-regulation through self-report, only one study measured state-based (specific to medication) self-regulation whereas the others measured trait-based (general ability) self-regulation. All of the studies included in the intention and behavioural prepotency meta-analyses included state-based measures of intention, habit and cues and yielded stronger associations. It may be that because self-control and self-regulation were mostly measured as a trait ability, the association with adherence is weaker. Future research in this area should consider using measures that specifically measure a cognitive ability rather than overall executive function, as well as use state-based measures of self-regulatory capacity rather than trait-based to ensure more accurate and valid findings regarding the association between self-regulatory capacity and medication adherence.

## Moderators

The findings revealed there were no significant moderating variables in any of the three analyses. This suggests that neither the study design, length of follow-up, type of medication adherence measure or type of subjective medication adherence measure influenced the relationship between any of the TST constructs and medication adherence. This is inconsistent with our hypotheses and previous research which has shown differences in findings, specifically when using different measures (e.g., objective or subjective) of medication adherence (Lam & Fresco, 2015; Liddelow, Mullan, et al., 2021). It is important to note that given the previously identified measurement issues in medication adherence, the use of unstandardised measures makes narrative synthesis difficult and potential findings complex to understand. All future quantitative research in medication adherence should be making a conscious effort to use standardised measures of medication adherence behaviour to allow for the synthesis of findings in the future.

Furthermore, given TST was developed to predict future health behaviour (Hall & Fong, 2007), the finding of no differences in the relationships between the constructs and adherence based on study design or length of follow-up suggests the theory may be applicable, albeit suitable, both cross-sectionally and longitudinally, with any length of follow-up. Given only one study has applied the theory in adherence (Liddelow, Mullan, et al., 2021), but did not meet the inclusion criteria, future research should consider applying the theory, as a whole, to adherence over different lengths of time to see if there are any differences in relationships.

# **Practical Implications**

The findings of this meta-analysis provide support for the continued exploration and study of the three TST constructs in medication adherence. Although half of the studies were cross-sectional in nature, many of the studies were still longitudinal in nature with sufficient time between baseline and follow-up to see the predictive effects of the constructs on adherence. Nevertheless, future research using prospective designs is warranted given the strengths of this research design over purely cross-sectional designs (Setia, 2016). Findings showed that all three constructs were positively correlated with medication adherence, suggesting improvements in any one of the constructs could result in improvements in medication adherence, despite possibly larger improvements if intention is targeted. This lends itself to experimental research and interventions aimed at improving medication adherence to include components to increase intention, behavioural prepotency/habit strength or self-regulatory capacity. However, as the analysis of the interactions was unable to be conducted, it is unknown exactly how improvements in one construct may influence the strength of another.

## **Strengths and Limitations**

One of the main strengths of this meta-analysis is that multiple different databases were searched when locating studies. This was to ensure that all areas of health, medicine and psychology were accounted for. Similarly, the included articles were published between 1988 – 2020, therefore providing a comprehensive analysis and summary of the current literature. Another strength of this review is the number of countries and illnesses that were represented in the analysis. Studies were conducted in both high- and low-income countries and assessed adherence to a range of diseases. This increases the generalisability of the findings of the review. Thirdly, according to the risk of bias assessment, only a few studies were deemed 'poor quality/high risk of bias', suggesting the quality of the research in the area of medication adherence is relatively high. However, our review is not without its limitations.

Firstly, there was a small degree of publication bias in each of the meta-analyses, as shown by the sunset-enhanced funnel plots. This suggests that some research in this area may

48

be contributing to the 'file-drawer problem' whereby non-significant research is not published (Salkind, 2007), and thus the true effect of these constructs on adherence may not be known.

Secondly, many of the identified studies that were appropriate for inclusion did not contain the correct statistics for our meta-analysis. As a result, authors contact details were obtained and authors were contacted via email requesting these statistics. However, the response rate was poor with only 8 out of 37 (21.62% response rate) authors contacted responding to requests for additional information. As a result, many studies that would have made a meaningful contribution to the meta-analyses were forced to be excluded. Therefore, the findings of this meta-analysis need to be interpreted with caution as it is not an accurate representation of all the literature in this area.

Thirdly, although a protocol for this review was developed and published on the Prospero database, we had to make some deviations from the protocol to improve the review. Specifically, we had to change our whole data analysis plan to ensure we were correctly analysing the available data. Whilst we hoped to analyse the theory and its interactions between variables, no data was available to do this. Whilst all deviations from the protocol have been clearly stated, we believe these deviations have improved the quality of the review.

# Conclusion

The current meta-analysis is the first to synthesise the associations between TST constructs and medication adherence. The findings provide support for the theory as well as the influence of each construct in medication adherence. All three constructs (intention, behavioural prepotency and self-regulatory capacity) were weakly-to-moderately associated with medication adherence. Study design, length of follow-up, and type of medication adherence measure did not moderate any of the relationships. The interactions between TST constructs were unable to be assessed due to lack of research, and thus future research should

apply the theory to adherence to explore these interactions proposed by the theory. Future research should also consider experimental research that incorporates elements and techniques aimed at increasing one of the TST constructs, to thus possibly increase medication adherence.

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