NEAR EAST UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF CLINICAL PHARMACY

TEST PERFORMANCE OF SELF-REPORT ADHERENCE TOOLS IN PATIENTS WITH HYPERTENSION: A SYSTEMATIC REVIEW AND A META-ANALYSIS

PhD THESIS

Mohammed AL ALAILI

Nicosia
September, 2022

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Approval

We certify that we have read the thesis submitted by Mohammed Al Alaili titled **"Test performance of self-report adherence tools in patients with hypertension: A systematic review and a meta-analysis"** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of PhD of Clinical Pharmacy.

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Declaration

I hereby declare that all information, documents, analysis and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of Institute of Graduate Studies, Near East University. I also declare that as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

Mohammed Al Alaili

18/1/2023

Acknowledgments

Abstract

Test Performance of Self-Report Adherence Tools in Patients with Hypertension: A Systematic Review and a Meta-Analysis

Al Alaili, Mohammed

Supervisor: Prof. Dr. Bilgen Basgut

PhD, Department of Clinical Pharmacy

January, 2023, 102 pages

Adherence has proved to have a positive influence on achieving plausible treatment outcomes. Self-report questionnaires are widely used in evaluating adherence, creating thus a high-powered research field. This review aims to provide an update of scales used in hypertension, which are compared and analyzed against reliability and validity.

PubMed, Web of Science and Cochrane Library were searched in May 2022 to identify studies. We extracted the study characteristics and evaluated their quality. A random-effects model with subgroup analysis was used to calculate estimates and heterogeneity parameters as well as regressions, funnel and forest plots. A bivariate model was selected to conduct validity analyses and draw Receiver Operating Characteristic (ROC) curves.

55 articles were identified and classified into 22 different reliable and validated tools. Pooled analyses predicted an overall good Cronbach's alpha of 0.76 (95%CI:0.67-0.83), a good ICC of 0.8 (95%CI:0.72-0.86) and an excellent correlation coefficient of 0.91 (95%CI:0.86-0.95), which all showed high heterogeneity and slight detection of asymmetry. Regression analyses showed that only time and the number of items/scale type influenced significantly retest and alpha, respectively. Overall validity showed acceptable sensitivity of 0.65 (95%CI:0.53-0.75) and specificity of 0.57 (95%CI:0.47-0.67) with a good Area Under Curve (AUC) of 0.637. Upon comparison, four tools showed superiority over Morisky's scale.

Adherence is a multi-dimensional phenomenon, which deems scales to be highly variable or complex; thus, complicating the selection process. Adherence to Refills and Medications Scale (ARMS) is the most promising free non-inferior alternative to Morisky, the most used scale.

Key Words: scales, cronbach's alpha, validity, stability, hypertension

Abstract

Test Performance of Self-Report Adherence Tools in Patients with Hypertension: A Systematic Review and a Meta-Analysis

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Adherence self-report scales are many, thus rendering scale selection a complex process. This review aspires to optimize this process for healthcare providers, especially when dealing with patients with hypertension. After reliability and validity analyses, five scales showed superiority regardless of the lack of gold standards.

Key Words: scales, cronbach's alpha, validity, stability, hypertension

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List of Abbreviations

ARMS= Adherence to Refills and Medication Scale

BMQ= Belief (or Brief) about Medication Questionnaire

BP= Blood Pressure

CFA= Confirmational Factor Analysis

CHPS=Compliance of Hypertensive Patients Scale

CYHBPIQ= Check Your High Blood Pressure IQ

EFA= Exploratory Factor Analysis

FATS= Facilitators of and Barriers to Adherence to Hypertension Treatment Scale

HTA= Hypertensive Treatment Adherence

ICC= Intra class Correlation Coefficient

LMAS=Lebanese Medication Adherence Scale

MAI=Medication Adherence Inventory

MAQ= Medication Adherence Questionnaire

MARS= Medication Adherence Reason or Reprot Scale

MASES=Medication Adherence Self-Efficacy Scale

MASRI= Medication Adherence Self-Report Inventory

MEMS= Medication Event Monitoring System

MMAS = Morisky Medication Adherence Scale

MML= Marginal Maximum Likelihood

MOS= Medical Outcome Study

MTQ=Medication-Taking Questionnaire

MUAH=Maastricht Utrecht Adherence in Hypertension

NPV= Negative Predictive Value

PAM= Patient Activation Measure

PCA= Principal Component Analysis

PDC= Proportion of Days Covered

PPV= Positive Predictive Value

PSM=Perceived Sensitivity to Medicines

QATSH=Questionnaire on Adherence to Systemic Hypertension

TAQPH=Treatment Adherence Questionnaire for Patients with Hypertension

TASHP=Therapeutic Adherence Scale for Hypertensive Patients

CHAPTER I
Introduction

The patient is the center of interest of health care providers where treatment outcomes optimization is their ultimate goal(Reynolds, 2009; Świątoniowska et al., 2020).

Statement of the Problem

Patients' non-adherence to drug therapy, as defined by WHO(Sabate, 2001), has been recognized as a significant culprit of treatment failure in 50%–60% of those suffering from non-communicable diseases, especially those with chronic diseases.

The measurement of adherence can be burdensome since acceptable parameters need to be carefully evaluated and individualized. Yet, myriad of tools are still available. However, they must be valid, reliable and precise for them to be adopted as standard references for research and practice(Bright, 2017; Lam & Fresco, 2015). Adherence can be measured objectively or subjectively, yet the latter is much more practical due to its low cost and rapid results despite its limitations(Pinto & Pereira, 2017). The main subjective methods are the self-reporting scales or questionnaires that vary in scope, scoring system, patient classification, strength, consistency and validity(Zullig et al., 2017).

“It is important to note that the research on validating and using existing self-report adherence tools is relatively robust and offers an exciting avenue for future research”(Nguyen et al., 2014). In this article, we are interested in studying such scales in hypertension, a prevalent disease that is highly studied regarding adherence. The suboptimal multifactorial non-adherence is a well-recognized contributing factor to

poor blood pressure control(Burnier & Egan, 2019; Peacock & Krousel-Wood, 2017; Villalva et al., 2017). Earlier reviews had concluded that none of the scales could be considered a gold standard(Pareja-Martínez et al., 2020; Perez-Escamilla et al., 2015).

Purpose of the Study

The current systematic review aims to review and update available scales, analyse and compare the evidence, provide evidence-based recommendations, guide care providers, highlight gaps for future research investigations and spare the use of licensed scales, if a free equivalent is proven to be applicable.

Significance of the Study

This review is the first to investigate, extensively, different psychometric properties for different adherence scales in hypertension.

Limitations

Meta-analysis has limitations, where causes can be exemplified as apples to oranges and garbage in garbage out comparisons. These limitations are most applicable to meta-analysis but can be found also in other analyses. (Cooper et al., 2009).

From the 1970's to the present, and based on what precedes, critics have invalidated this methodology. However, Glass defended this by stating, "Of course it mixes apples and oranges; in the study of fruit nothing else is sensible; comparing apples and oranges is the only endeavor worthy of true scientists; comparing apples to apples is trivia"(Glass, 2000)

In meta-analysis, effect size is analysed after being combined from sets of several studies. Since usually data groups are too diverse to be included, the outcome is skewed

results which aggravate the notion of garbage in garbage out. Inclusionary and exclusionary criteria is an approach to manage mixing data that is very dissimilar(Littell et al., 2009). In this case, critics will question the uprightness of the meta analysis. Attributed to that, Lipsey and Wilson (2001) advocate to only include research that is well-formulated(Lipsey & Wilson, 2001); however, no specific guidelines dictates quality research. Robust procedures help in filtering and narrowing which studies are to be chosen.

The gray literature that is hard to reach, since it is unpublished and may be standing in the 'drawer' of a researcher due to non-significant results, is another problem which is called "file drawer". Unpublished data can be superior or as important as published research but may not be published due to several causes (i.e. the results being non-significant). However, meta-analysis must include these to decide effect sizes for research to consider and manage for publication bias(Cooper et al., 2009).

When joining different *p*-values of published studies, overestimated bias into the effect sizes is obtained(Lipsey & Wilson, 2001), whereas when conducting any study it is preferred to reduce this effect as much as possible. Including gray or fugitive literature is one way(Kulinskaya et al., 2008). Additionally, systematic reviews may be prone to other types of bias: publication bias corresponds to the preference of only positive trials being published by journals or preference of studies investigating positive results ($p<0.05$).

CHAPTER II

Literature Review

Theoretical Framework

Adherence

The U.S. Food and Drug Administration (FDA) states, “Medication adherence, or taking medications correctly, is generally defined as the extent to which patients take medication as prescribed by their doctors. This involves factors such as getting prescriptions filled, remembering to take medication on time, and understanding the directions”. Non-adherence to medicines is classified as one of the biggest medication related issues. “WHO states that non-adherence to medications is a worldwide problem of striking magnitude.” Low medication adherence can lead to bad health consequences such as aggravating diseases/conditions or even patient death. Researches proved that there was a link between lack of or insufficient adherences to medications prescribed for chronic diseases with health facilities referrals/utilization. Furthermore, poor medication adherence also has an influence to increase health care cost. “There are 33%-69% of drug-related hospital admissions in US because of poor medication adherence, along with a cost of about $100 billion a year”

Adherence Tools

PSM. “The 5 items are slight modifications of the comments made by patients when prescribed medication during regularly scheduled and patient-requested physician visits. Study included patients receiving treatment for HIV infection and high blood

pressure, people taking a travel vaccination, and undergraduate students. Criterion-related validity was proved through associations between the PSM and negative beliefs about medicines (Beliefs about Medicines Questionnaire), anxiety and depression (Hospital Anxiety and Depression Scale). Predictive validity was assessed by examining associations between the PSM and medication adherence and symptom following vaccination. Test–retest reliability was high and been assessed 2 times in an undergraduate sample, 2 weeks apart. Cronbach's alpha was in the very good- excellent range. The results advocate its use as a research tool in studies of the use and effects of medicines."

TASHP. "Systematic random sampling was used to recruit 366 patients with hypertension in China. The psychometric tests of the TASHP included: construct validity (CFA) which produced 4 factors, criteria-related validity and a satisfactory internal reliability and split-half reliability. The TASHP is a validated and reliable instrument to measure the adherence to hypertension treatment in Chinese hypertensive patients. The cut-off score of 109 points can be considered as an effective measure to classify the level of adherence into satisfactory and low adherence behaviors."

QATHAS. "The process of developing this instrument involved theoretical, empirical and analytical procedures. The instrument underwent semantic and conceptual analysis by experts. The empirical procedure involved the application of the instrument to 1,000 users with systemic arterial hypertension treated at a referral center. The analytical phase validated the instrument through psychometric analysis and statistical procedures. The Item Response Theory model used in the analysis was the Samejima Gradual Response model. Twelve of the 23 items of the original instrument were calibrated and remained in the final version. Cronbach's alpha coefficient (α) was 0.81. The instrument was more suitable for measuring low adherence to hypertension treatment than high."

HTA. “After item generation using a qualitative study and literature review, the psychometric properties of the scale were evaluated using face (acceptable), content (acceptable), construct (6 subscales), and criterion validity and reliability (good alpha and excellent stability). Subscales included medication adherence and monitoring, adherence to safe diets, avoiding unsafe diets, self-medication, activity, and smoking. At the cut-off point of 86, the scale had significant sensitivity and specificity. All of the psychometric properties of the HTA-scale achieved the standard level and were sufficient to recommend this scale for patients with HTN.”

ARMS. “Polish translated version of the 12-items ARMS (ARMS-P) that identifies levels of adherence in the hypertensive population evaluating its psychometrics. The cross-sectional study included 279 hospitalized patients. Questionnaire comprises two subscales: adherence to taking medications (eight items) and adherence to refilling prescriptions (four items) demonstrating good psychometric properties that enable its use for assessing adherence in chronically ill patients, including in particular, patients with hypertension.”

MUAH. “Interviews to patients were recorded and reviewed by two investigators. An exploratory factor analysis was performed to 41 items filled by 255 patients and showed 4 factor solution labeled: positive attitude towards health care and medication (I), lack of discipline (II), aversion towards medication (III) and active coping with health problems (IV). Convergent validity was assessed by evaluating the association between sum scores on the identified subscales and three other adherence measures: (1) the Brief Medication Questionnaire (BMQ), (2) pharmacy refill records and (3) electronic monitoring. The MUAH-questionnaire has excellent psychometric properties and may be useful to identify factors that impede or facilitate adherence. However, it is not clear to what extent the questionnaire measures actual adherence, so validation of the MUAH-questionnaire in other studies is needed.”

MTQ. “Three-phase study describes its development and psychometric properties to measure the purposeful action domain (reasons individuals decide to accept medication treatment) in the medication adherence model for hypertension. Firstly, items were evaluated for content validity and clarity. Secondly, item analysis (12 items), internal consistency, and exploratory factor analysis (2 subscales) were performed. Thirdly, temporal stability and construct validity were evaluated. It appears to have good psychometric characteristics that represent the decision-making process for adherence in medication treatment for hypertension.”

MOS. “To determine recall of and adherence to physicians' recommendations among patients with chronic medical conditions and to measure the correspondence between self-reported adherence and disease activity. A total of 1751 patients with diabetes mellitus, hypertension, and heart disease were identified. Main outcome measures included recall of 15 disease-specific recommendations, self-reported general and specific adherence, and correlations between adherence and clinical measures of disease activity and control. The majority of chronically ill patients failed to recall elements of potentially important medical advice and did not always adhere to advice that was recalled. Additional research is needed to also determine which life-style changes are truly beneficial for these patients.”

MAI. “Purposive sampling (277 patients) was conducted at the cardiovascular clinics of two teaching hospitals and was guided by the self-regulation model. Predictors of adherence to prescribed medications in the hierarchical logistic regressions were treatment control, risk factors and psychological attribution. Factors that affect the patients’ adherence to prescribed medications and self-management recommendations differ greatly. Understanding patients’ lay views on hypertension allows health professionals providing effective care for better adherence to therapeutic regimens.”

MARS. “Using a cross-sectional study design, a 10-item version of the Medication Adherence Report Scale was piloted in two samples. Following principal components analysis, five items were retained to form MARS-5. The MARS-5 demonstrated acceptable reliability and validity. It shows promise as an effective self-report tool for measuring patients' reports of their medication use across a range of health conditions.”

LMAS. “A cross-sectional study including 405 patients was performed in outpatient cardiology clinics in Lebanon. Blood pressure was measured, a questionnaire filled, and sodium intake estimated by a urine test. Scale showed good internal consistency with 4 factors. It predicted hypertension control unlike MMAS-8. Stress and smoking predicted non-adherence.”

CHPS. “This scale was developed to incorporate other indicators of compliance also, such as intention, responsibility and collaboration. Data were collected from a convenience sample of 103 patients, in five health care centers. Dimensionality was explored using principal component analysis (5 subscales: lifestyle, intention, attitude, responsibility and smoking) and a good internal consistency that was estimated according to a standard item analysis approach and Theta coefficient. Validity was assessed using face validity, content validity and criterion-related validity (through the use of concurrent validity). This scale forms a useful starting point in the development of a reliable and valid tool to assess compliance of hypertensive patients, based on several indicators.”

FATS. “Focus groups consisted of 20 African American women from a total of 70. Internal consistency reliability, of the 18-item scale, estimated using Cronbach’s was good. FATS was significantly associated with the Hill-Bone High Blood Pressure Compliance Scale, the Enhancing Recovery From Coronary Heart Disease Social

Support Inventory, the and CAGE (cut down on your drinking, annoyed by being criticized for your drinking, guilty about drinking, and eye-opener drink in the morning) alcohol screening instrument. Further study in other samples of AA women is needed to confirm that the FATS adequately assesses facilitators of adherence to regimens for HBP."

New concepts by Lene Juel Kjeldsen et al. "2,914 medication users received questionnaires by mail. Two factor analyses were conducted based on responses to questions. Main outcome measures Medication-taking behavior and self-efficacy (beliefs about ability and capacity to accomplish a task), respectively. The adherence behavior measures included two concepts of intentional non-adherence (associated with aspects of self-regulation and effect concerns, respectively) and one measure of nonintentional non-adherence. Associations between the new concepts of non-adherence measurement and characteristics of non-adherers remain to be established and would be a subject for further studies."

Extent and Reasons by Corrine et al. "Cross-sectional survey involving the new measure and comparison measures to establish convergent, discriminant, and predictive validity (with BP). The new measure was re-administered 2–21 days later. Comparison measures included self-reported medication self-efficacy, beliefs about medications, impression management, conscientiousness, habit strength, and an existing non-adherence measure. Three items assessing the extent of non-adherence produced reliable scores. Intraclass correlations were 0.58 for the extent score and ranged from 0.07 to 0.64 for the reasons. The dual conceptualization of medication nonadherence allowed a stronger evaluation of the reliability and validity than was previously possible with measures that confounded these 2 constructs."

TAQPH. “A multi-phase psychometric questionnaire development method was used to develop the instrument. The 28 item pool was generated using literature review and focus group. Content validity was evaluated by expert panel. Then, the field testing was conducted by a convenience sampling of 278 hypertensive patients. Exploratory and confirmatory factor analyses (6 dimensions) were used to test construct validity. Finally, a very good internal consistency and test–retest reliability were assessed. The Persian version showed excellent reliabilities. The scale score was correlated with Morisky Medication Adherence Scale (MMAS).”

BMQ. “Beliefs about medicines is divided into general (8 items) and specific (10 items). The general describes the overuse and harms while the specific scale assesses necessity and concerns. The BMQ was adapted to Polish according to widely accepted guidelines (translation, back translation and checking readability). A total of 311 cardiovascular in- and outpatients as well as medical students taking chronic medication were surveyed to assess data-to-model fit and internal consistency of the measure. The criterion related validity was determined with the use of Polish version of the Adherence to Refills and Medications Scale. Confirmatory and exploratory factor analyses were used, as well as general linear modeling. Insignificant correlations were found with inpatients. Medical students may conceptualize beliefs about medicines in a different way; as a result, a modified version of BMQ-General for medically-educated people, was proposed. Conclusion The BMQ-PL exhibits satisfactory proof of validity to be used among cardiovascular patients. ICC was excellent with the Malaysian version. Discriminant validity revealed that BMQ Specific-Necessity score was significantly inversely correlated with the systolic blood pressure level.”

MAReasonS. “In this cross-sectional study, the 15-item MAR-Scale was administered to 665 Malaysian patients with hypertension The construct validity was examined in two phases (translation, a content validity checked by an expert panel, a face validity checked via a small preliminary test among patients with hypertension, and

exploratory factor analysis (EFA), internal consistency reliability calculations and confirmatory factor analysis (CFA)). EFA Consisted of five existing factors that were previously identified (i.e. issues with medication management, multiple medications, belief in medication, medication availability, and the patient's forgetfulness and convenience), while CFA extracted four factors (medication availability issues were not extracted). The final modified MAR-Scale model, which had 11 items and a four-factor structure, provided good evidence of convergent and discriminant validities and a good internal consistency of the items in the construct. In the Chinese version, exploratory factor analysis revealed six domains, including belief, self-perception, forgetfulness, management, availability, and miscellaneous issues. Criterion-related validity was assessed with the visual analog scale and two global items. Forgetfulness, belief issues, and self-perception issues were the most common non-adherence reasons."

MASES. "Self-efficacy, a known predictor of a wide range of health behaviors. A medication adherence self-efficacy scale was developed and evaluated in ambulatory hypertensive African-American patients in two sequential phases. Using qualitative techniques, responses were recorded verbatim, coded, and sorted into nine categories of barriers and facilitators of medication adherence. Concepts from categories were formatted into an initial 43-item self-efficacy questionnaire. Twenty-six items were retained for the final self-efficacy scale based on item-to-total correlation coefficient and clinical relevance of individual items. Confirmatory (CFA), exploratory (EFA) factor analyses, and classical test theory (CTT) analyses suggested that MASES is unidimensional and internally reliable. Item response theory (IRT) analyses led to a revised 13-item version of the scale. Clinicians and researchers can use this scale to identify situations in which patients have low self-efficacy in adhering to prescribed medications. MASES-Turkish consisted with original instrument. Patients with uncontrolled hypertension had lower self-efficacy scores compared to those with normal blood pressure. The Persian version of MASES was also assessed to be valid and reliable."

Hill Bone. "It assesses patient behaviors for three important behavioral domains of high blood pressure treatment: 1) reduced sodium intake; 2) appointment keeping; and 3) medication taking. This scale is comprised of 14 items in three subscales. The content validity of the scale was assessed by a relevant literature review and an expert panel, which focused on cultural sensitivity and appropriateness of the instrument for low literacy. Internal consistency reliability and predictive validity of the scale were evaluated. High compliance scale scores predicted significantly lower levels of blood pressure and blood pressure control. Moreover, high compliance scale scores at the baseline were significantly associated with blood pressure control at both baseline and at follow up in the two independent samples. This brief instrument provides a simple method for clinicians in various settings to use to assess patients' self-reported compliance levels and to plan appropriate intervention. The nine item subscale alone was tested to be a reliable tool. In Africans, a modified scale consisting of only 10 items demonstrated reasonable internal consistency and a significant predictive validity in that noncompliance predicted higher diastolic blood pressures and medication noncompliance tended to predict higher systolic blood pressures; however, appointment-making and dietary salt-intake subscales were not internally consistent. For the Turkish scale, factor analysis revealed a three-factor structure representing unintentional medication non-adherence; intentional medication non-adherence; and salt intake adherence. It can be forced into 2 structures. Internal consistency was good to very good. In primary care sample, Hill Bone scale showed unacceptable prediction and insufficient consistency. In a Korean sample, one factor subscale of 8-items is revealed to be valid and reliable. A 3 factor scale was tested to be suitable in Polish population. The modified Namibian version (3 constructs of 12 items) of the Hill-Bone scale is reliable and valid for assessing adherence to anti-hypertensives in Namibia where there is sub-optimal adherence to antihypertensive therapy among primary health cares. The Chinese version's EFA revealed a four-component structure representing two of medication taking; appointment keeping and reduced sodium intake with very good internal consistency rendering the use of this screening tool for the assessment of adherence to hypertension treatment is recommended. The translated Nepali version of the HBCTS demonstrated acceptable reliability and validity to measure adherence to

antihypertensive therapy among hypertensive patients in clinical and community settings in Nepal since exploratory factor analysis revealed a three-component structure; however, the loading of components into medication adherence, reduced salt intake and appointment keeping constructs were not identical to the original tool. It showed also a very good reliability. The success of hypertension therapy is dependent on the healthcare systems and healthcare professionals in supplying enough medication, support of friends/family, and maintaining scheduled follow-ups. A combination of interventions using low-cost mobile technology led by healthcare professionals could be endorsed. To fully practice universal access to medication, public and private hospitals in Namibia should collaborate."

MMAS-4. "The 4 items in the scale address barriers to medication-taking and permit the health care provider to reinforce positive adherence behaviors. Data on patient adherence to the medical regimen were collected at the end of an educational program along with blood pressure measurements throughout a 3-year follow-up period. It demonstrated both concurrent and predictive validity with regard to blood pressure control at 2 years and 5 years, respectively. However, it did not show a satisfactory reliability. The French version's specificity was around 100% allowing the physician to determine whether the lack of hypertension control is due to a drug-taking behavior problem, and to apply strategies enhancing compliance. However, because the sensitivity of this measurement is poor (25% average), it should not be used to rule out non-compliance. In primary care sample, it showed low acceptability and insufficient consistency. The underlying conceptual framework of medication adherence therefore needs to be rethought."

MMAS-8. "The authors assessed various psychosocial determinants of adherence, such as knowledge, social support, satisfaction with care, and complexity of the medical regimen. The 8-item medication adherence scale (7 yes/no items and one Likert scoring) was reliable and significantly associated with blood pressure control.

Using a cut point of <6, sensitivity was 93% and specificity was 53%. It can be used primarily with low-income, minority patients with hypertension and might function as a screening tool in outpatient settings with other patient groups. This scale was modified in a study to contain 7 items only. Sensitivities and specificities varied through the various translated versions of this scale (e.g. Urdu, French, Korean, Spanish, Brazilian, Persian, Polish,.). This scale showed a good test-retest reliability. Different versions adopted different thresholds and thus deduced different patient categorizations. The scale construct validity ranged from being unidimensional or made up of 2 or 3 constructs. For instance, the French version endorsed 8 as a threshold for high adherence, showed a moderate consistency and only revealed one dimension, same as the Turkish version. Korean version revealed 2 dimensions while another Korean study showed 3 constructs. Factors affecting adherence ranged differently reflecting to diverse populations, age and low income. The MMAS-8 may be routinely used to support communication about the medication-taking behavior in hypertensive patients."

Content of Scales

The adherence scales can be classified into five groups based on the details they seek to obtain(Vrijens et al., 2012). Group 1 scales tackle only information about medication taking behavior, where majority of those adherence scales estimate the number of doses taken while others explore the number of times patients are not adhering to refilling their prescription schedule. In addition to seeking information on medication-taking behavior as Group 1 scales, Group 2 cover also barriers to adherence. Majorly, they explore forgetfulness as an adherence barrier. They state some of its common cases such as when working or travelling. Other situations are physical barriers, such as sight problems, skilfulness issues and difficulty in swallowing. Contrary to Group 1, Group 3 scales just search for barriers to adherence. However, Group 4 scales are interested exclusively in beliefs related with adherence. Those scales include items about beliefs that are necessary, harmful and unnatural. At last, group 5

scales search for both barriers and beliefs linked with adherence. Most items in all scales spot angles of adherence that are compliant with the stratification provided by Vrijens et al.

Many scales identify non-adherence through cut-offs. That's said, many had categorized adherence by computing the total score and thus distinguishing the patients into two sets: adherent and non-adherent. Few scales segregated more between different ranks of patient's medication adherence (e.g. MAQ, MMAS, Brief Medication Questionnaire and Visual Analogue Scale) and hardly any scales had tested the sensitivity and specificity of their threshold against an objective measure of adherence.

Assessing of Reliability

Inter-rater or inter-observer reliability. A degree of consistency between two or more independent raters of the identical scale. Generally tested in a pilot study in two methods turning on the amount of assessment of the construct.

Test-retest reliability. It is a quantification of consistency between two estimations of the matching construct given to the identical population at two separate times. If the computations stayed the same on average, then the measure is reliable. "It is important to note that the time interval between the two tests is critical. In general, the longer the time gap, the more the chance that the two observations may change during this time (due to random error), and the lower will be the test-retest reliability. Heise argued that observed stability coefficients are a function of the intrinsic retest reliability of the instrument and the decay of true stability; if three time points are observed, reliability can be estimated as $(r_{12} * r_{23}) / r_{13,}$ which is sensitive mainly to macro-state changes that endure for a period of weeks or months"(Heise, 1969). A plausible clarification for the relationship between consistency and test-retest reliability is the psychological condition of the patient that may vary through the course of the test administration. Micro-state variability is when items bring respondent's various

perspectives of the self-concept into centre of attention. Multiple regressions can remove this micro-state component rendering coefficient alpha unrelated to the validity criteria.

Split-half reliability. It quantifies the reliability between two halves of a scale. As the instrument becomes longer (more items are added), random errors are reduced and thus it is more likely that the two halves of the construct will be identical. As a result, this method can amplify the consistency of lengthy tools.

Internal consistency reliability. It is an amount of consistency between dissimilar items of the same measure. In other words, if respondents rated an administered multiple-item construct measure in the same way, this can be an inference for internal consistency. This reliability can be evaluated in respect of average inter-item correlation, average item-to-total correlation, or very often, Cronbach's alpha which is originated by Lee Cronbach in 1951. Influencers in scale size in reliability evaluation can be computed utilizing the following equation(Cronbach, 1951):

$$\alpha = \frac{K}{K-1}\left(1 - \frac{\sum_{i=1}^{K}\sigma_{Y_i}^2}{\sigma_X^2}\right)$$

"In which K is the number of items in the measure, σ_X^2 is the variance (square of standard deviation) of the observed total scores, and $\sigma_{Y_i}^2$ is the observed variance for item I". Consequenlty, the standardized Cronbach's alpha can be computed using a simpler formula:

$$\alpha_{\text{standardized}} = \frac{K\bar{r}}{(1+(K-1)\bar{r})}$$

"where K is the number of items, $\bar{r}$ is the average inter-item correlation, i.e., the mean of K (K -1)/2 coefficients in the upper triangular (or lower triangular) correlation matrix".

Assessing of Validity

Appraising group 1 and group 2 scales is by determining the connection between them against an objective measure of adherence (i.e. MEMS for example and clinical outcomes) while questionnaires in groups 3–5 are more likely to depend on different perspectives to validation.

Content validity is regularly estimated through a group of subject experts. A scope of approaches is used for construct validity. Item analysis versus scales validated to reveal certain types of health beliefs and factor analyses of responses to additional scales or semi-structured interviews are two examples.

The results of criterion validity of each study can be drawn as a sensitivity and specificity point in a summary ROC (SROC) curve which will mark its location; the distribution of the points; and any link between sensitivity and specificity clearly visible across multiple studies(Takwoingi et al., 2015). The suggested analytical approaches for test performance all allow for the negative relation between sensitivity and specificity between studies due to the presence of different thresholds among different included studies (even patients groups can induce threshold-like variations) and various interpretations of the results. Moreover, since misleading results can be obtained through simple univariate analytic ways which pool sensitivity and specificity apart and thus obviating the possible threshold effect, an SROC curve approach was created by Moses et al to consider potential heterogeneity. However, it predicts that the difference is just related to the threshold effect and coincidence yet does not permit for heterogeneity. On the other hand, parameters of test accuracy are dynamic and not steady properties. They are influenced by several factors as: population, setting, traits and conduct of the test, and description of the target case; hence, heterogeneity is familiar in such studies.

Special hierarchical models have been established for Diagnostic Test Accuracy (DTA) meta-analysis that deem for the negative correlation in coupled measures across studies and heterogeneity(Takwoingi et al., 2015). Attributing to their name, they include statistical distributions at two ranks; within-study variability in sensitivity and

specificity is taken into consideration at the bottom level, and between-study variability at the top level. Two examples are the bivariate and the hierarchical summary receiver operating characteristic (HSROC) models which are utilized for meta-analysis when a sole sensitivity and specificity pair is present for every individual study. “The bivariate model highlights the estimation of a summary point (summary sensitivity and specificity) at a common threshold which is useful if studies used a standard threshold”; in contrast, the focus of the HSROC model is on evaluating an SROC curve across various thresholds which would be beneficial if studies adopted a diverse of thresholds. “Ideally, we would like to know which threshold on the curve gives the best performance, but the position of individual thresholds cannot be identified”; fortunately, these both models have been proved to have statistical characteristics in common, so the choice of which one to endorse must be guided by the research question yet is usually influenced by the identity of the present information (mixed thresholds) and its influence on the interpretation of summary conclusions, software efficiency and proficiency of the team. Attributing to their common statistical features, and when there is only a single test, SROC curves can be calculated from bivariate models and mean operating points from HSROC models, so the selection of model is academic. In comparisons of more than one test or comparisons of subgroups, the selection of model is pivotal. Bivariate meta-analysis of likelihood ratios and predictive values have been noted to face additional challenges.

Popular Scales in Practice

Group of questionnaires have been validated versus clinical measures, yet they do not estimate directly the medication-taking behaviour (for instance, MEMS). Some cases involve the Barroso 30-day Adherence Question and the Hill-Bone Compliance Scales.

Other tools revolve more on evaluating medication-taking behavior, as the MAQ, which is a short four-item group 3 scale that has been well-studied versus objective

measures of adherence. The minimum prerequisite to use a scale as an alternative option to an objective measure is the evidence of an important correlation between this scale and an appropriate objective measure in respondents with the same condition.

Beliefs about Medicines Questionnaire (BMQ) finds out if patients believe that their medicine is necessary. Also, pinpoints if the patients have any concerns about their medications.

Related Research

Previous review is comparing MMAS-4 and MMAS-8.(X. Tan et al., 2014). Morisky scales (4 and 8) have advantages over other self-report instruments; however, Morisky scales have drawbacks as they only identify few reasons associated with non-adherence and do not assess medication adherence (not explanatory tool). In addition, "the measurement of adherence by the Morisky scale and its modification still cannot be quantified very well and this might limit their application. Nina van de Steeg et al. showed that MMAS-4 was not valid for patients taking antihypertensive medications in Germany". It showed poor psychometric properties. The validity parameters (sensitivity and specificity) were 81% and 44%, respectively. Cronbach's alpha is equal to 0.6 which is below the acceptable threshold (0.7). Developing MMAS-8 resolved some of these issues.

Previous recent meta-analysis is tackling MMAS-8 accuracy in many subgroups/conditions/diseases.(Moon et al., 2017). 28 studies were analyzed regarding the reliability and validity of MMAS-8. The pooled Cronbach's α estimate ranged between 0.67 (95% Confidence Interval(CI), 0.65 to 0.69) and 0.77 (95% CI, 0.72 to 0.83) for different disease subgroups. With respect to test-retest, the pooled ICC was 0.85 on average. For a threshold of 6, the pooled sensitivity and specificity ranged between 0.43 (95% CI, 0.33 to 0.53) and 0.73 (95% CI, 0.68 to 0.78). "The MMAS-8 had acceptable internal consistency and reproducibility in a few diseases like type 2 diabetes. Using the cut-off value of 6, criterion validity was not enough good to validly screen a patient with nonadherence to medication."

Previous reviews showed that no scale was considered a gold standard(Pareja-Martínez et al., 2020; Perez-Escamilla et al., 2015). 17 various questionnaires (from 39 extracted articles) for measuring adherence to antihypertensive treatment were obtained (while in 2015, only 12 scales were extracted, where only 6 were validated and ranged between 4 to 28 items). Those tools were validated in 15 different countries and the number of items in the questionnaires ranged from three to 33. “Hill-Bone compliance to high blood pressure therapy scale, Morisky-Green-Levine test and an 8-item Self-Reported Medication Adherence Measurement were the most widely validated questionnaires”. Validity was tested more than reliability. Several questionnaires do not give information about content validity, while construct validity and concurrent validity are analyzed in majority of the questionnaires but give highly inconsistent results. However, known-groups validity was rarely analyzed. Almost all of the questionnaires provided Cronbach’s alpha information with acceptable results, but temporal stability was not analyzed that much. In conclusion, “none of the questionnaires included in the review demonstrates fulfillment of all of the validity tests (content validity, construct validity and criterion-related validity) and reliability tests (homogeneity and temporal stability) in an acceptable manner”. Hence, none can be considered a Gold Standard.

CHAPTER III
Methodology

This systematic review was done in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and reported in a protocol. It was registered in the International prospective register of systematic reviews (PROSPERO) Registry under the following number: CRD42022335608

Population

Adherence tools tested in patients with hypertesnion in any population and any age (above 18 years old) where chronically ill, frail or psychotic patients are usually aided or replaced by a caregiver or parent to fill the adherence scales.

Outcome

Tools should be tested for reliability and validity (at least one psychometric for each) to be included in the review. Where applicable, cronbach's alpha, ICC, correlation coefficients, sensitivity and specificity are the outcomes chosen to be further analyzed with their 95% confidence interval.

Search strategy

PubMed, Web of Science and Cochrane Library were searched in May 2022 with three sets of keywords: 'medication adherence, medication non-adherence, medication compliance or medication non-compliance; hypertension; and scale, tool or instrument'. Initially, articles were screened by abstracts and titles after removing duplications that were handled using Mendeley, a reference management software. Then, if an article tested adherence using a self-report scale, screening was continued for tools in the full

text and references were checked for inclusion criteria eligibility. The final remaining articles were categorized into tools (with their corresponding translated versions that were written in English) and were included in the review.

Research Design

Ultimately, the article should be in English, tackle hypertensive patients only, be a full-text article without grey literature, be a fully developed self-reporting tool (tested for at least one parameter for each of reliability and validity) and be a manuscript without lacking the full availability of psychometrics' details.

Data extraction

The corresponding data from the involved articles were produced using a pre-designed test-piloted electronic spreadsheet developed for this study. Data accuracy was checked by a second author and any disputes were settled by a third author. To facilitate viewing and interpreting these results, informative diagrams were created for the main outcomes. Extracted data included mainly the author and tool name, publication year, country and setting, population characteristics, scale type, number of items included, scale dimension covered, reliability parameters (internal consistency and test–retest) and validity parameters (face, content, criterion and construct).

Quality Assessment

QUADAS-2 Tool

Following the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2)(Whiting et al., 2011), the general quality of studies was determined. Patient selection, index test, reference standard and flow and timing were the four sections of

QUADAS-2 evaluation, which were assessed in terms of bias risk and three of them were tested concerning applicability(Schueler et al., 2012). Whenever a domain was non-applicable (e.g. criterion validity was not tested against a reference), it was omitted and the domain score was retotalled to give the result in the form of a percentage and even out results between domains; thus, facilitating the comparison.

COSMIN Tool

Owing to the high abundance of Cronbach's alphas extracted in this review, quality assessment is carried out for chosen alphas in an attempt to concise results and thus clarify and empower outcomes (i.e. sensitivity analyses). Generally, only the overall Cronbach's alpha (if calculated in the study) was included if its corresponding details were stated or could be extracted (e.g. sample size). The quality of Cronbach's alpha was assessed with the COSMIN (Consensus-based Standards for the selection of health status Measurement Instruments) checklist in the corresponding section of internal consistency (box 4)(Prinsen et al., 2018). This box uses various points to evaluate the study design (here modified to cover sample size; patients: item ratio of at least 10:1) and the statistical procedures (i.e. dimensionality) to estimate the way of assessing reliability. Each item has four modifiable answer choices: very good, adequate, doubtful or inadequate. To get the overall quality coefficient of the study, the worst item score was counted.

Methods of Analyses

The low-risk rated coefficients were selected for all further analyses. For normal distribution of the values in all analyses, Cronbach's alphas were transformed to Hakstein-Whalen coefficients(Rodriguez & Maeda, 2006); final results were then back-transformed to alpha according to the formulas cited, which also enable confidence intervals and variance calculations. For test–retest parameters, all intra-class coefficients (ICC which ranges between 0 and 1) and coefficient correlations(Thumburu

et al., 2015) (both Pearson and Spearman that range between -1 and 1) were extracted and analysed separately after being transformed to fisher's z coefficient for normal distribution of the values. Consequently, results were back-transformed and reported.

Random Effects (RE) Model Meta-Analysis

Random-effects meta-analysis, a more conservative model, is utilized to calculate weighted mean estimates across studies and 95% CIs(Brockwell & Gordon, 2001). The summary effect generated from the RE model estimates the mean of all the true effects. When the mean of these effects is 0.0 for a difference and 1.0 for the ratio, the null hypothesis of the summary is acheived. “The RE model measures the mean of the distribution and thereby requires consideration of two sources of variance: 1) within study error, and 2) variation in the true effects across studies. Both sources of variance are minimized by adjusting weight of each study”.

Heterogeneity Assessment

I^2, tau^2 and H^2 are computed to assess between and within studies heterogeneity respectively(Higgins et al., 2003; Mittlböck & Heinzl, 2006).

Statistical heterogeneity is present when there is diversity in the true treatment or risk factor sequels as a result of clinical variability and/or technical/operational variability.

Heterogeneity can be detected and assessed by statistical means. One of the familiar ways to assess heterogeneity is with Cochran’s chi-square test which is also known as the *Q*-statistic for heterogeneity. “Q is defined as

$$Q = \sum_{i=1}^{k} Wi(Yi - M)^2$$

Where

- Wi is the weight of the study
- Yi is the effect size
- M is the effect of study
- K is the number of studies."

Q is a standardized measure where it is not affected by the metric of the effect size index, but simply by the degree of freedom (*df*)

$df = k$ - 1, in which *k* is the number of studies.

Therefore, the high diversity owed to variations in the true effects between studies is calculated as Q-df. This evaluates the null hypothesis where total involved studies have the identical effect on the population. The *Q*-statistic has a weak power especially in the abundance of little information and an exaggerated strength of identifying clinically insignificant heterogeneity when there are numerous studies.

To overcome this disadvantage, I squared (I^2) statistics can be used to quantify inconsistencies between studies. According to Higgins, "I^2 statistics explained that the percentage of variability in the effect estimates is due to heterogeneity rather than chance(Higgins & Thompson, 2002). It is computed as

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

That is the ratio of excess dispersion to total dispersion.
The I^2 value ranges between 0% (indicate no observed heterogeneity) and a maximum of 100% (larger values indicate increasing heterogeneity)". Up till now, I^2 can be interpreted as follows:

- 0% to 40%: unimportant;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Notable heterogeneity is typically considered if I^2 is 50% or greater. It should be considered along with observed effects to give researchers an actual meaning of the true effects. I^2 is not a parameter of absolute heterogeneity and it does not give data on the dispersion of true effects. It cannot dependably tell us which of two meta-analyses presents more heterogeneity in true effects.

In the presence of statistically significant heterogeneity, one analytical method is to incorporate it into a RE model(Riley et al., 2011), but this does not solve heterogeneity. On contrary, it permits for variations in the treatment effect from one study to another as it predicts that there is a dispersion of true effect sizes; thus, the RE model uses the tau-squared (T^2) statistics to approximate between study variance from the observed effects.

Robust Variation Estimation

Then, when applicable, a robust variance estimation was calculated to check the difference in effect when coefficients from common samples were adjusted(Tipton, 2013).

Forest Plots and Sub-Groupings

Forest plots were drawn to visualize the analysis with sub-grouping to clarify and arrange results. Subgrouping helps explore heterogeneity sources(Borenstein & Higgins, 2013).

Sensitivity Analysis and Regressions

High-risk rated coefficients were excluded while doubtful rated alphas were included for sensitivity analysis(Pichery, 2014). Moderator regression is done by mixed-effect models with suspicious anticipated factors (scale type, age group, retesting time and number of items).

Criterion Validity

For criterion validity analyses, a study was included if it reported a 2 x 2 confusion matrix against a reference or if true positive (TP), true-negative (TN), false-positive (FP) and false-negative (FN) calculations were possible. Diagnostic odd ratios (DOR) with their 95% confidence intervals were also calculated and subsequent estimates were calculated using the Mantel–Haenszel (MH) method(Fontaine, 2005). Thresholds were kept as reported for each study, except for a few that did not have a specified cut-off, so we considered the mean average of the reported data as their threshold. Age, the number of items, subgrouping of tools and availability of at least one risk with QUADAS-2 were used as regressors. As for analyses with hierarchical models(Macaskill et al., 2010; Trikalinos et al., 2012), the bivariate and the hierarchical summary receiver operating characteristic (HSROC) models are equivalent in the absence of covariates, yet the bivariate model shows the effect on sensitivity and specificity rather than on accuracy in the presence of covariates(Harbord et al., 2007). So, in our study, summary estimates, area under curve (AUC) and summary receiver operating characteristic (SROC) curves were obtained through the bivariate model. Whenever the estimated SROC curves had the same shape, the relative diagnostic odd ratios (RDOR) were calculated to check and compare the relative test accuracy of two screening tools.

Publication Bias Assessment

Publication bias is not succeeding to encompass all related trials since they are not published and thus, not accessible. Publication bias is thought to affect around 25%-40% of published meta-analyses(Egger et al., 1997; Sterne et al., 2000). "Publication bias is considered highly likely when funnel plots(Sterne et al., 2011), drawn out of summary effect size (such as Cronbach's alpha coefficient) on the x-axis and measurement errors (standard error or inverse of standard error) on the y-axis, are graphed as skewed or asymmetric". Such bias was visualized with a contour-enhanced funnel plot and asymmetry was tested with ranks, egger's test and 'trim and fill'.

The regression method(Sterne et al., 2000) has more ability to identify diversities when equated to rank correlation tests. However, regression tests have disadvantgaes of false positives in certain situations as treatments with huge effects, studies of same sample sizes or trials with a few frequency of events.

"Egger's regression test is done when funnel plot asymmetry is present and it tests that the Y intercept from a regression line equals zero. It regresses the standard normal deviate (effect size divided by standard error) with the precision (reciprocal of standard error) as the predictor variable."

Trim and fill analysis(Duval & Tweedie, 2000) is a method that involves removing farthest points/trials from the funnel plot, re-computing the effect estimate and then obtaining a modified effect estimate in the presence of a symmetrical plot. Nonetheless, this analysis can underrate the true effect in the case of large between-study heterogeneity where publication bias is absent. Furthermore, this technique depends on the supposition that an asymmetric funnel plot is totally due to publication bias(Peters et al., 2007), whereas other affectors to the asymmetric funnel plot are available such as internal validity issues in smaller studies.

Statistical Analyses

We performed all analyses and figures using ‘metafor’ and ‘mada’ packages in R studio (4.1.1) and Microsoft Excel spreadsheet (2016). The level of significance was defined as $\alpha = 0.05$. Confidence intervals were calculated within R.

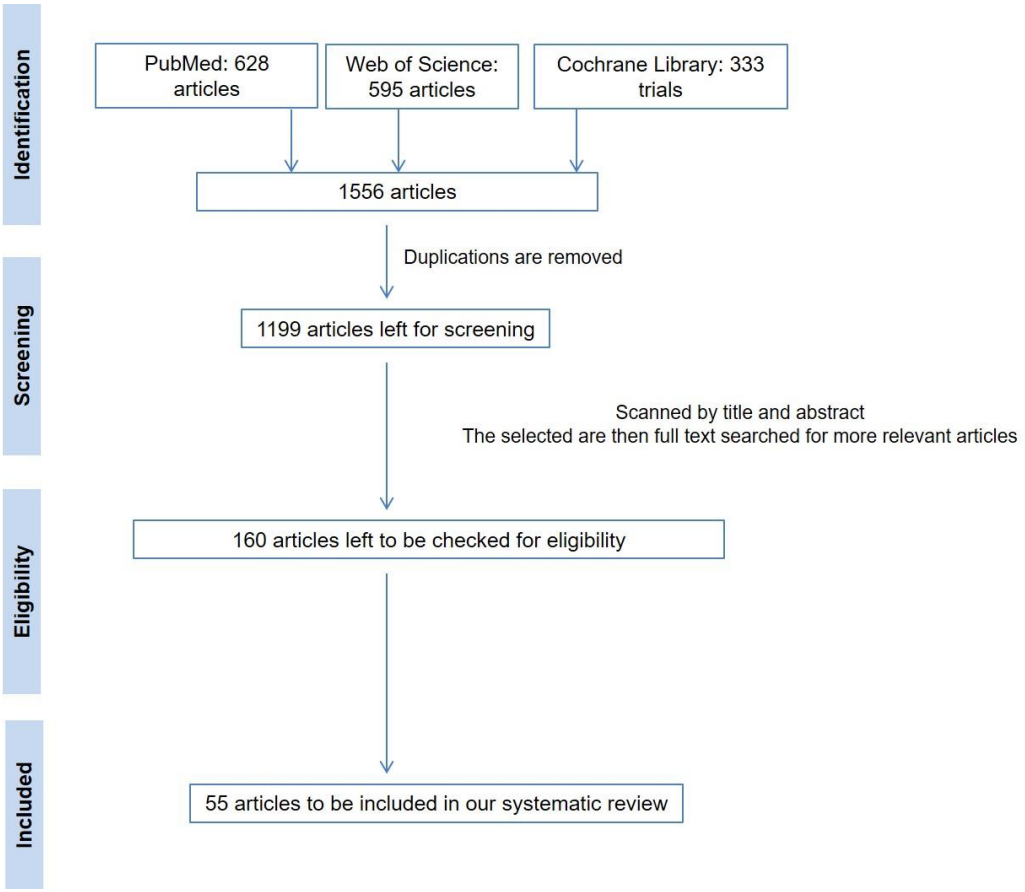
CHAPTER IV

Findings

Study Flow Chart

The included articles were double-checked for relevancy and the results were finalized with 55 articles (Figure 1). These articles were screened and classified into 22 main tools.

Figure 1- Review Flow Chart



Characteristics of Studies in the Review

All details of extracted studies can be found in the Appendix section.(Ahn & Ham, 2016; Al-Noumani & Al Omari, 2022; Bharmal et al., 2009; Bou Serhal et al., 2018; Cabral et al., 2018; Chan et al., 2020; P. F. Chen et al., 2020; S. L. Chen et al., 2009; de Oliveira-Filho et al., 2014; Dehghan et al., 2015, 2016, 2020b; Fernandez et al., 2008; Fongwa et al., 2015; Gozum & Hacihasanoglu, 2009; Grégoire et al., 1992; Hacihasanoglu et al., 2012; Hacıhasanoğlu Aşılar et al., 2014; He et al., 2016; Horne et al., 2013; Jankowska-Polanska et al., 2016; Johnson & Rogers, 2006; Karademir et al., 2009; Karbownik et al., 2020; J.-H. H. Kim et al., 2014; M. T. Kim et al., 2000; Kjeldsen et al., 2011; Korb-Savoldelli et al., 2012; Koschack et al., 2010; Kravitz et al., 1993; Krousel-Wood et al., 2005; Lahdenperä et al., 2003; Lambert et al., 2006; Ma et al., 2012; Moharamzad et al., 2015; D E Morisky et al., 1986; Donald E Morisky et al., 2008; Nashilongo et al., 2017; Ogedegbe et al., 2003; Okello et al., 2018; Pacheco Rodrigues et al., 2014; Pareja Martínez et al., 2015; Saffari et al., 2015a; Saleem et al., 2012; Shima et al., 2015; Shin & Kim, 2013; Song et al., 2011; C. S. Tan et al., 2018; Uchmanowicz et al., 2016; Voils et al., 2012; Wetzels et al., 2006)

Figures 2 and 3 show a brief collective synopsis of the main features of the obtained studies. Regarding the tools (Figure 2), most of them ranged between 4 and 14 items, with 8 owing the highest frequency (Figure 2A). 73% of tools used Likert scoring (Figure 2B) and were majorly covering attitudes, barriers and beliefs (Figure 2C)—TASHP, ARMS, MARS, LMAS and Morisky scales covered attitudes and barriers while beliefs were mainly covered in BMQ scale. Moreover, about half the studies were piloted (55%) and all tools had their Cronbach's alpha calculated (Figure 2D). Only one study tested split half reliability, 33% (18 studies) calculated test–retest reliability (Figure 2D) and none tested inter-rater reliability. Additionally, 78% (42 studies) were construct validated via factorial analyses (Figure 2E); 49% (26 studies) were criterion validated against an objective measure (Figure 2E) while 50% and 67% of tools were content and face validated, respectively (Figure 2E). The average time for scale completion was 30 min although several studies did not mention it. Concerning the general study variables (Figure 3), 44% of studies involved patients under 60 years old.

The majority of articles (60%) were published between 2006 and 2015. In addition, around one-third of the studies were executed in the United States (Figure 3A) with hospitals or clinics being the major setting of studies (Figure 3B).

Figure 2- Tools Characteristics Overview. (A) Frequency of scales' number of items; (B) type of included scales; (C) frequency of included scales' scope; (D) percentage of tested reliability parameters; (E) percentage of tested validity parameters

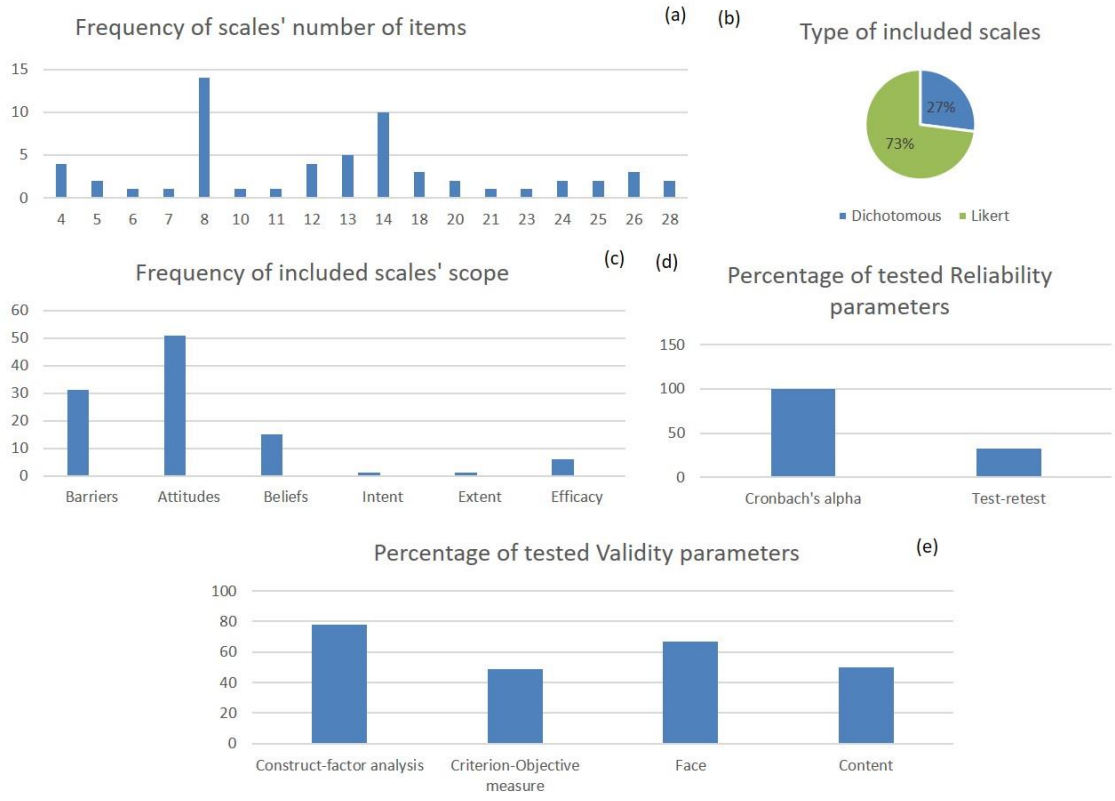
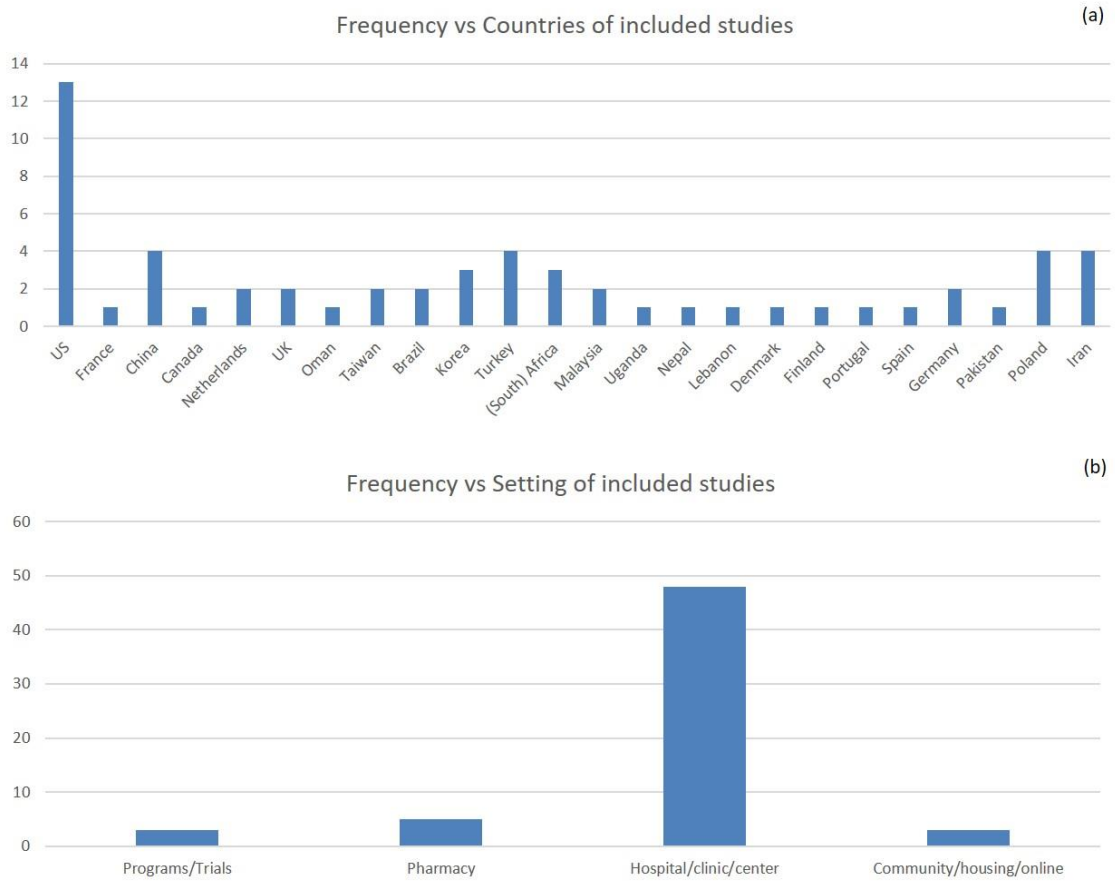


Figure 3- Study Characteristics Overview. (A) Frequency versus countries of included scales; (B) Frequency versus setting of included scales



Risk of Bias and Quality Assessment

Risk assessment results were shown in Figure 4. The overwhelming majority were high-quality studies. The existence of unclear risk was significantly present due to the high variability of study designs of included tools, whereas high risk or low-quality

studies were absent in the patient applicability concern aspect but detected (19%) in terms of bias (mainly due to lack of randomization) and flow and timing of the study (13%).

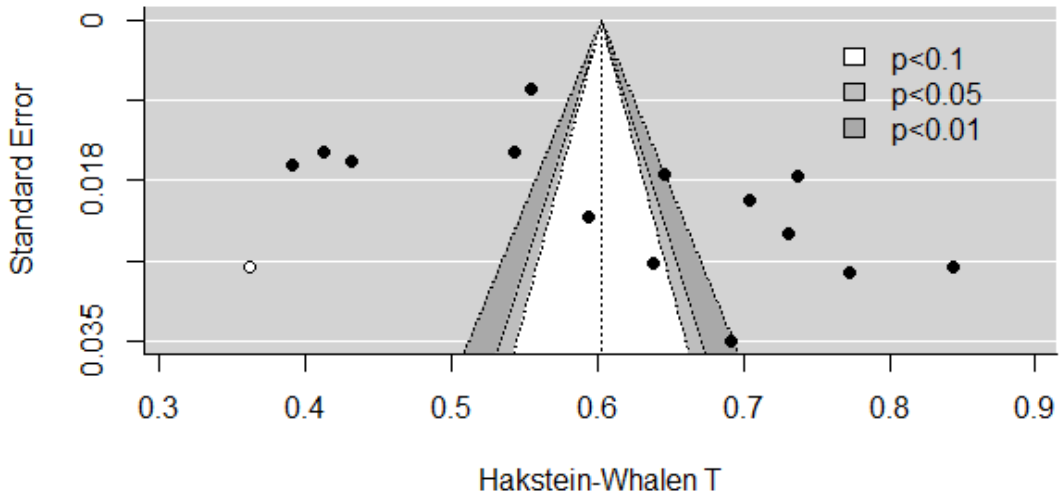
Fifty-one Cronbach coefficients were assessed with COSMIN: 27 were rated as inadequate (high risk); 10 were doubtful and 14 were rated as low risk (very good) alphas

Figure 4- QUADAS-2 Risk of Bias Assessment Results (%)

Evaluation of Publication Bias

Figure 5 shows the contour-enhanced funnel plot, revealing asymmetry with the trim and fill for the very good qualified coefficients. This was confirmed by the egger's regression test (z = 2.7, p = 0.006), trim and fill test (one missing study [SD = 2.5] on the left side) and ranks test (Kendall's tau = 0.45, p = 0.02). For ICC, slight asymmetry was confirmed with the egger's regression test (z = 1.8, p = 0.06) and ranks correlation test (tau = 0.3, p = 0.07) but not with the trim and fill test (zero missing studies). For correlation coefficients, asymmetry was not detected with any test.

Figure 5- Funnel Plot of High-Quality Cronbach's Alphas



Reliability

Meta-Regressions and Sensitivity Analysis

When doubtful alphas were included in the analysis, all tests confirmed publication bias (ranks correlation p = 0.03; egger's regression p = 0.0007 and two

studies were missing to the left with the trim and fill test). Moreover, when applying a regression model to these alphas against moderators, it showed that the scale type and the number of items were the factors influencing the results ($p < 0.0001$) but not the age ($p = 0.21$) nor the quality of alphas ($p = 0.33$). However, all factors resulted in high heterogeneity ($I2 > 95\%$, $p < 0.0001$). Likewise, the same results were derived when only high quality alphas were included ($p = 0.02$ and $p = 0.005$ for moderators of scale type and the number of items, respectively). For ICC, time was the only significant moderator ($p = 0.0008$), where only the 3-month interval showed a lack of heterogeneity (but insignificant with $p = 0.5$). On the contrary, none was a significant moderator for correlation coefficients (even for the type of correlation, $p = 0.47$). Robust variance estimation analysis did not change any of the resulting estimated coefficients calculated by the random effects models.

Forest Plots of the Meta-Analyses of Reliability Parameters

The alpha, after back-transformation, was equal to 0.76(95%CI: 0.66–0.8) even when doubtful alphas were included. The back-transformed estimated ICC and correlation coefficient were 0.8 (95%CI: 0.72–0.86) and 0.91(95%CI: 0.86–0.95), respectively, and both scored high heterogeneity ($I2 = 93\%$ and 78%, respectively). Thereby, to clarify visualization and enhance interpretation of the heterogeneity cause, three forest plots (Figures 6–8), displaying subgroupings, were drawn for all three coefficients. Again, heterogeneity was still detected significantly in most subgroups.

Figure 6- Forest Plot Showing Random Effect Model Analysis with a Subgroup Analysis for High-Quality Cronbach's Alpha.

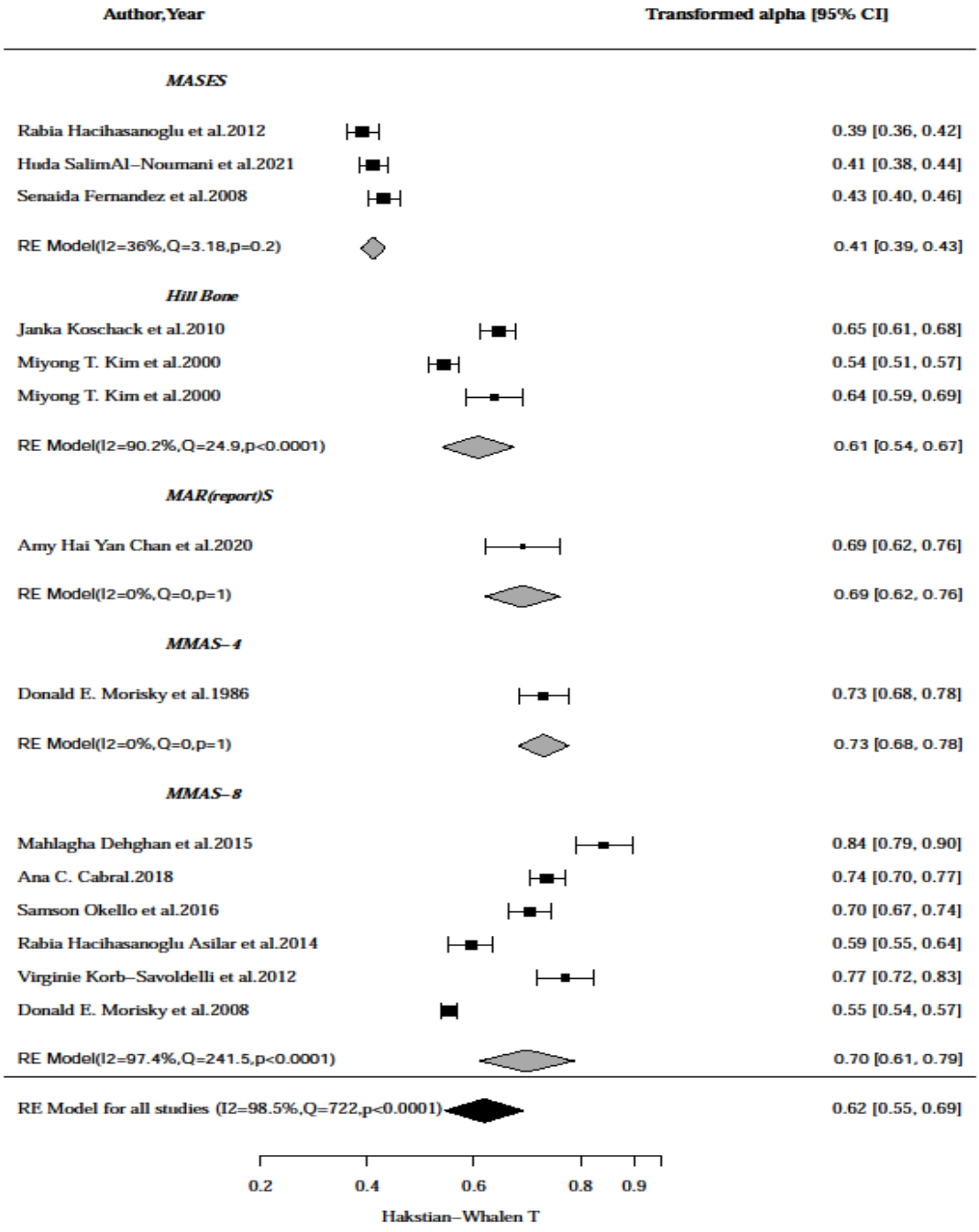


Figure 7- Forest Plot Showing Random Effect Model Analysis with a Subgroup Analysis for ICC.

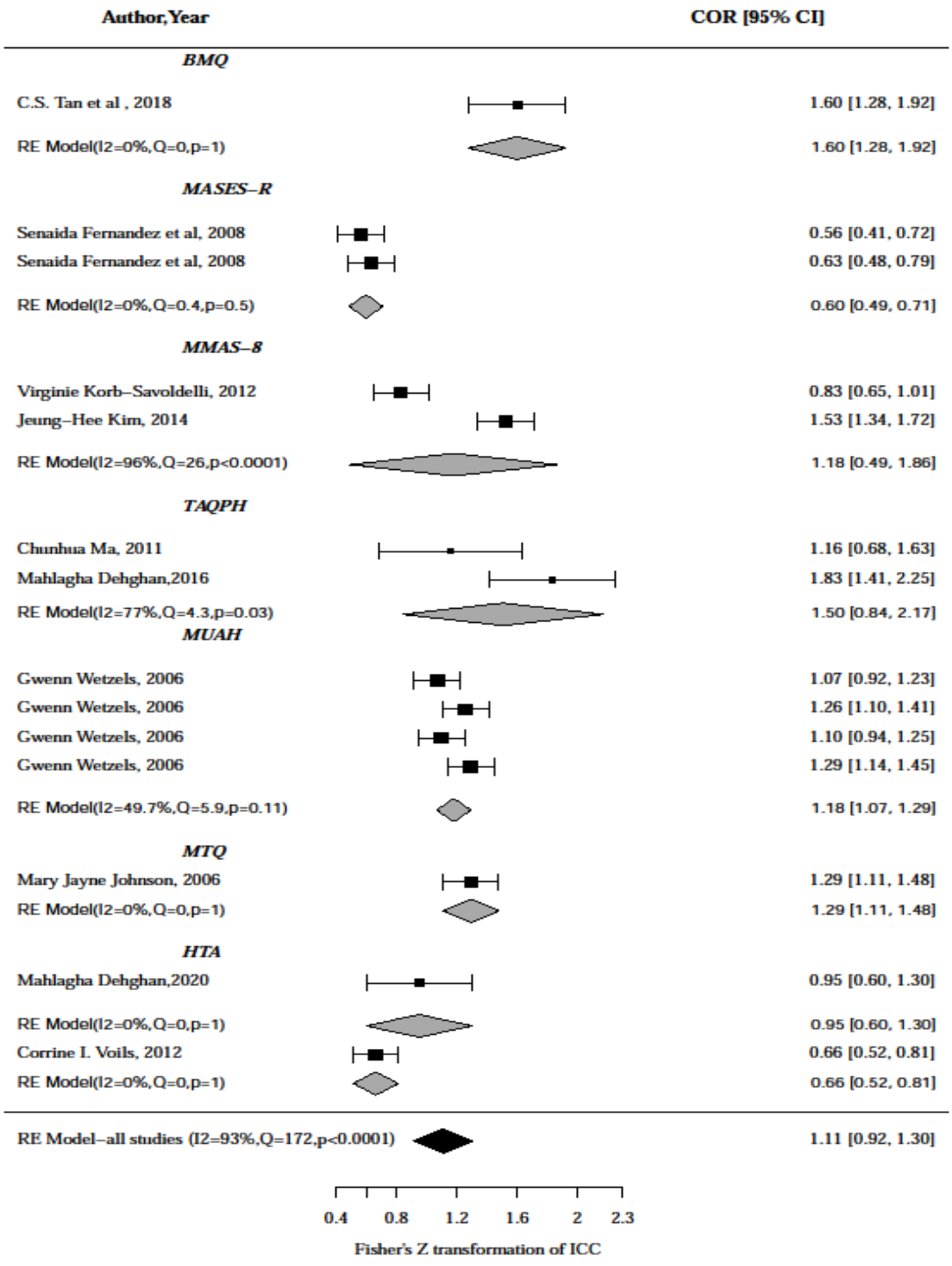
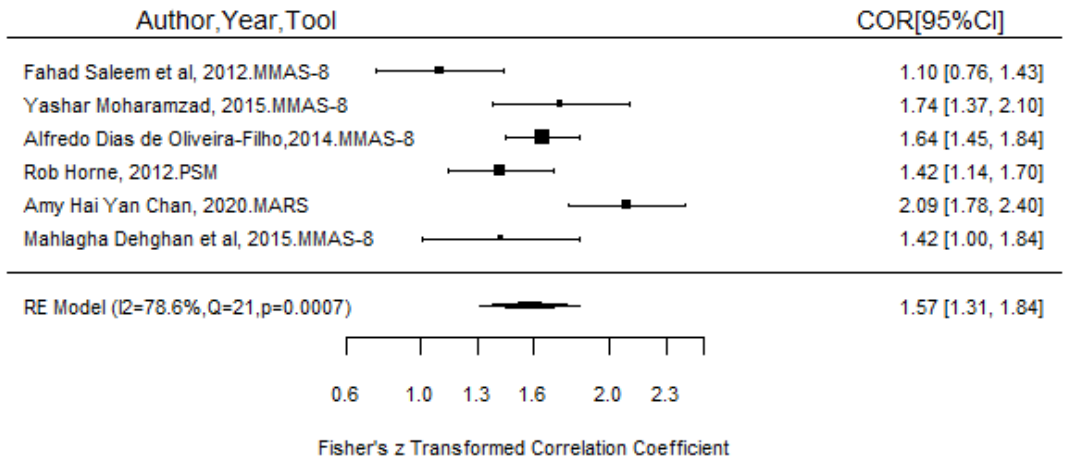


Figure 8- Forest Plot Showing Random Effect Model Analysis for Correlation Coefficients.



Validity

Meta-Analysis of Criterion Validity Parameters

Criterion validity was assessed in 21 extracted studies of 10 tools (HTA(Dehghan et al., 2020a), ARMS(Lomper et al., 2018), LMAS(Bou Serhal et al., 2018), TASHP(He et al., 2016), MASES(Gozum & Hacihasanoglu, 2009; Saffari et al., 2015b), Hill Bone(M. T. Kim et al., 2000; Koschack et al., 2010), MMAS-4(Grégoire et al., 1992; Koschack et al., 2010; D E Morisky et al., 1986), MMAS-8(Jankowska-Polanska et al., 2016; J.-H. H. Kim et al., 2014; Moharamzad et al., 2015; Donald E Morisky et al., 2008; Okello et al., 2018; Pareja Martínez et al., 2015; Saleem et al., 2012; Shin & Kim, 2013) and MARS (report(Chan et al., 2020) and reasons scales(P. F. Chen et al., 2020))), and adherence was compared against blood pressure control: an objective gold standard. Exploratory univariate analyses with forest plots showed the

expected presence of heterogeneity among sensitivities and specificities. The summary estimates (points and confidence region) and curve for all tools are shown in Figure 9 (sensitivity = 0.65 (95%CI:0.53–0.75), specificity = 0.57 (95%CI:0.47–0.67), AUC = 0.63 and beta = -0.25). Since we are comparing different tools with different thresholds, summary estimates are not completely reliable. Alternatively, the focus in such indirect comparisons is on the HSROC parameters calculated from the bivariate model (the AUC and the beta parameter that corresponds to the curve shape). The negative correlation (threshold effect) between sensitivity and specificity was confirmed in this model. The general estimated AUC was 0.65, which is good (>0.5) but not optimal since an AUC closer to "one" infers a more accurate test(Hajian-Tilaki, 2013). It is important to highlight that none of the regressors affected the results.

Additionally, Morisky's scale (MMAS-8) is the most studied tool(Pirri et al., 2020) (nine related articles/versions were extracted in our confusion matrix) and the most frequently used by clinicians. Therefore, its subgroup estimates were calculated (sensitivity = 0.69, specificity = 0.52, AUC = 0.637) and used along with its SROC curve, as a relative comparator for the remaining tools (or estimated subgroups of the same tool). Plausible comparison results are the curves with acceptable shapes, AUC >0.5 and coinciding or superior to that of MMAS-8. Figure 10 shows four tools that only met the previous criteria. TASHP (Figure 10A), LMAS (Figure 10B) and MARS (Figure 10C) curves were slightly superior to the curve of MMAS-8 (AUC = 0.69, 0.66 and 0.67, respectively) while the ARMS (Figure 10D) curve showed clear high superiority over the curve of MMAS-8 (AUC = 0.84). Since curves showed the same shape and comparison was quantitatively difficult, RDORs were computed after calculating the DOR estimate of the nine studies of MMAS-8 (DOR = 2.27, 95%CI: 1.96–2.6). According to RDOR values, three tools were slightly more accurate than MMAS-8 scoring 1.52 (95% CI: 1.1–2.1), 1.25 (95% CI: 0.86–1.8) and 1.37 (95% CI: 0.52–3.6) for TASHP (Figure 10A), LMAS (Figure 10B) and MARS (Figure 10C), respectively, while ARMS (Figure 10D) scored a much higher RDOR of 5.19 (95% CI: 3.1–8.8).

Figure 9- SROC Curve of Included Adherence Tools

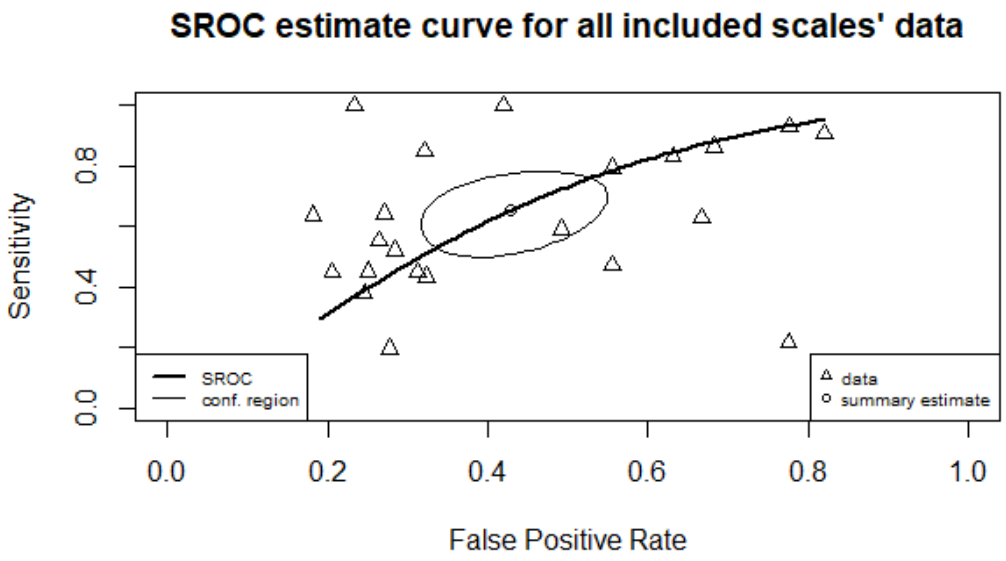
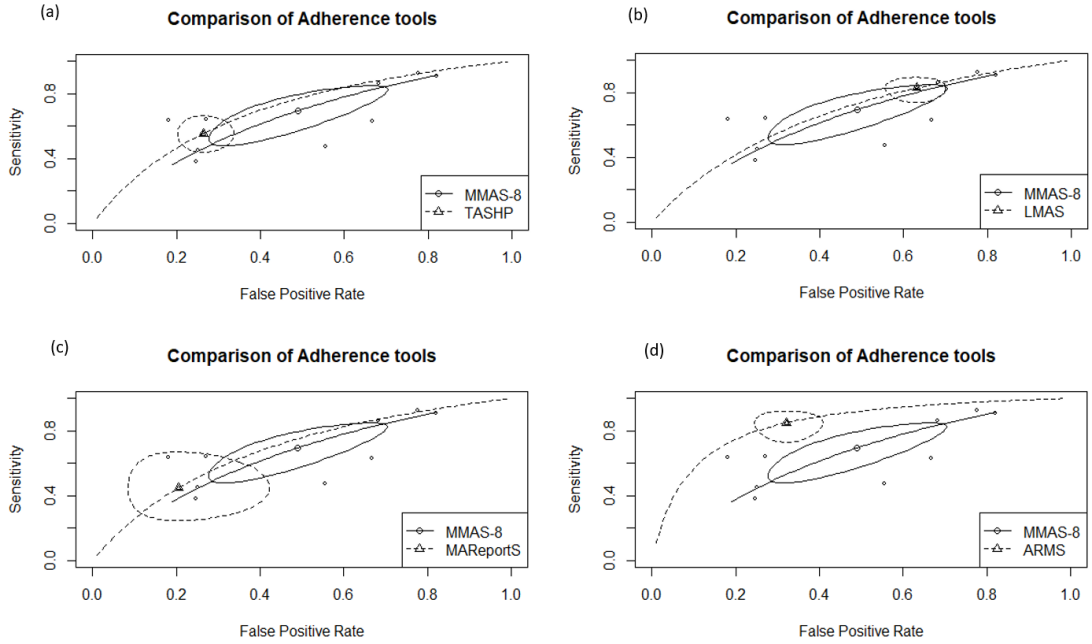


Figure 10-(A–D) Relative Comparison of SROC Curves of Four tools to MMAS-8 Curve



CHAPTER V

Discussion and Recommendations

This systematic review is a thorough highlight of reliable and validated adherence scales used by clinicians in hypertension. To our knowledge, it is the first review regarding the aim, inclusiveness and analyses involved in addressing the different aspects of diagnostic scales. Additionally, this study complements, explains and confirms previous reviews(Pareja-Martínez et al., 2020; Perez-Escamilla et al., 2015) in which no scale was considered a gold standard; simply because estimated parameters were not in the excellent range (except for correlation coefficient) and not all parameters were well studied in all tools.

Furthermore, this review provides an informative overview by displaying the qualitative analysis of the extracted tools in simplified graphs. Minor variabilities existed between tools and thus were not summarized in the figures but could still be deduced from the extraction table. Few tools were developed with the item test theory, while most adopted the classical test theory. Instrument administration methods varied between clinicians, patients or caregivers—MAR (report)S, ARMS, LMAS and TASHP tools were self-completed while the majority of Morisky scales were administered via an interview with a health practitioner. The method of piloting, content and face validity testing were different among tools, where not all tools calculated the content validity index nor tested literacy or reading level. Most cut-offs adopted and theoretically linked in some other cases were corresponding to 80% of the prescribed doses.

Construct validity was tested majorly via factorial analysis. The remaining studies either had not tested for construct validity or did it via objective measure (one study), against other scales (four studies) or via item/subscale correlations (two studies). Regarding criterion validity, around half the studies tested it objectively by measuring blood pressure control. The rest who tested for this aspect used other objective measures (i.e. MEMS, one study) or comparisons and correlations with other scales (eight studies).

The overall estimate of the meta-analyses of Cronbach's alpha (acceptable)(George & Mallery, 2003) and test–retest coefficients (good to excellent)(Koo & Li, 2016) revealed that tools yield reproducible results, which accredit and justify, alongside being affordable, the ongoing preference for utilizing scales, subjective measuring tools over objective ones. The asymmetry was slightly detected or considered absent depending on the adopted significance level (i.e. $p < 0.1$ or 0.05) with alphas and ICCs and was absent with correlation coefficients; thus, affirming the reliability and stability of scales. In addition, our review model and results were considered dependable since sensitivity, robust variance estimation and several critical regression analyses had a null influence, where results were just confirming the expected influencers for alpha (scale length and type) and ICC (time). A time interval of 3 months (as retest moderator) with zero heterogeneity could be attributed to the nature of hypertension being a chronic disease. However, further investigations should reveal the cause of many of the heterogeneities presented. Noting that our analysis included only overall Cronbach's alpha of tools, however, in many cases, subscales alone could be sufficient in clinical applications. In light of this, and due to their low count presented in our extracted studies, the stability coefficients of subscales were included for test–retest analysis. Although MASES showed the highest alpha and ICC (lowest transformed coefficients) and the least and insignificant heterogeneity ($I 2 = 36\%$, $p = 0.2$) inferring this tool is the most robust tool to be adopted concerning reliability and stability, it did not show satisfactory results with validity analyses against MMAS-8.

The strength point in the analysis of criterion validity parameters is that all studies were compared to an excellent standard as a reference. The 21 study estimates showed a curve of a beta parameter of -0.25, which was slightly different (lower) from that of the nine studies of the MMAS-8 subgroup (beta = 0.01). All psychometrics for MMAS-8 were consistent with the results of the hypertension subgroup of a recent meta-analysis tackling MMAS-8 accuracy although ours included a few different studies with different thresholds (thresholds kept as reported in their original study)(Moon et al., 2017). Calculating 2 x 2 matrices of some tools, through endorsing our threshold, might have induced bias and invalidated our results and conclusions, but these tools (along with some tools with the pre-reported threshold as MMAS-4) were

already obviated from relative comparisons due to their inferior model parameters and SROC curves against MMAS-8. MMAS-4 showed an inferior validity (worse curve shape and lower AUC) to MMAS-8, and that result cleared up a previous review(X. Tan et al., 2014) and a comparison study(Pedersini & Vietri, 2014). Only four tools: ARMS, TASHP, LMAS (inspired also by MMAS-8) and MARS were shown to be the candidate reciprocates for MMAS-8 (all their RDORs are close to 1 except for ARMS it is close to 5). MARS's confidence interval crossed graphically underneath the AUC of 0.5, which might have decreased the validity of such a tool and lessened its little superiority over MMAS. However, it was included in pooled analyses with MMAS and showed approximate resemblance concerning internal consistency and test–retest correlation coefficients. Most of LMAS's confidence interval superposed with that of MMAS, which equated these two tools regarding validity. Nevertheless, this tool was not included (same for TASHP) in any previous reliability parameter analyses with MMAS. ARMS showed the highest superiority over MMAS concerning validity; however, it was not eligible for our reliability and stability analyses even though it owes a very high overall alpha (0.9), thus lessening its potential to be endorsed as a reference.

All previous tools ranged along a different number of items and scale dimension coverage compared to MMAS-8, as MARS is shorter than MMAS-8 and LMAS while ARMS and TASHP are longer. This is pivotal, especially when considering customized clinical applications and time for scale administration. In addition, unpaid tools must be considered a valuable extra point to ensure the wider applicability, practicality and cost-effectiveness of these scales. Therefore, even if one study represented each of these tools versus nine studies for MMAS-8, this gave hope in regards to implementing them more in the clinical field. Hence, this might trigger future researchers to focus on testing them further, as they could be a safe free replacement to a previously well-studied and frequently used scale(Li-Wan-Po & Peterson, 2021).

Nevertheless, there is always more room for improvement in the future, where most tools in this review covered mainly three dimensions of adherence when a six-phase concept has been proposed(Gearing et al., 2011). Future improvements may also focus on increasing criterion validation, inter-rater and test–retest reliability testing of

tools, as these will increase the robustness of tools allowing them the potential to be endorsed as references. Moreover, the focus may be employed on further testing in different countries (other than the United States) and on translating various tools into different populations, which may improve validity estimates, such as AUC, or at least confirm and accredit our results. Furthermore, adopting and validating tools (if possible) in different diseases such as HIV—also a highly studied disease in which adherence is critical in such populations—can extrapolate and generalize our study results.

Finally, searching databases with restrictions such as the English language is considered a limitation. However, most translated tools are written in English and eventually extracted here, hence obviating any drawbacks.

CHAPTER VI

Conclusion

Selecting an optimal self-report scale might be challenging for health care providers since, at least, they vary between being self-sufficient or being a supplementary tool. However, despite the differences in their development, psychometrics and many various factors considered for customized applications, the bottom line for a more credible endorsement is having a reliable, stable and validated tool. ARMS— the most promising tool, TASHP, LMAS and MARS are free non-inferior credible alternatives to the Morisky scale, the most utilized and studied scale regardless of the lack of gold standards.

The immense analyses in this review—highlighting the variables, differences and gaps of tools exhibited—enable future investigations to increase the robustness of tools in many other diseases or conditions to catch up with this dynamic field of search and to trigger further diagnostic accuracy studies.

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APPENDICES

Appendix A

Table 1

Data Extraction Details for Study Characteristics

Tool / Author name	Year	Country / Setting	Population / Sample size
TASHP-Wei He et al	2015	China-health centers	366 pt, 51%males, age≈67yrs
PSM- Rob Horne et al	2012	mainly UK-studies collected	T: 1166pt, depends on sample general:>50% men,age≈35yrs
QATSH-Malvina Rodrigues et al	2014	Brazil-referral center	1000 pt
HTA-Mahlagha Dehghan et al	2020	Iran-university hospital	300pt,50.2%females,age≈60yrs
ARMS-Katarzyna Lomper et al	2018	Poland-hospital	T=290pt,66%females,age≈66yrs
MUAH-Gwenn Wetzels et al	2006	Netherlands-clinic/pharmacy	255 pt, 50%men, age≈60yrs
MTQ-Mary Jayne Johnson et al	2006	US-hospital/programs	T:236 pt, age≈62 yrs,65%females

Table 1 (continued)

MAI- Shiah-Lian Chen et al	2009	Taiwan-teaching hospitals	277 pt, 60%males, age≈66yrs
Razatul Shima et al	2015	Malaysia-primary care/clinic	665pt,56%males,age≈52yrs
(Malay version- MAR(reason)S			
Pin-Fang Chenet et al	2020	Taiwan-hospital/pharmacy	538pt,55%males,53%<65yrs
ChMAR(reason)-Scale (chinese version)			
LMAS-R. Bou Serhal et al	2018	Lebanon-outpatient clincis	405 pt, age≈65yrs, 52%females
Lene Juel Kjeldsen et al	2011	Denmark- pharmacies	1426 pt, 50% male,age≈64yrs
FATS-Marie N. Fongwa et al	2015	US- clinic	147,54yrs **african/american** females
Corrine I. Voils et al	2012	US-center	202 pt, 86%men, age≈64yrs
CHPS-Tiina S. Lahdenpera et al	2003	Finland-health centers	103 pt, 59%females, age≈54yrs

Table 1 (continued)

TAQPH	2011	China-hospitals	278pt, age≈59-68yrs,42%males
Chunhua Ma et al			
Mahlagha Dehghan et al	2016	Iran-hospitals	330pt, age≈57yrs,65%males
(persion version)			

MOS			
Richard L. Kravitz et al	1993	US	1751pt
MASES			
Gbenga Ogedegbe et al	2003	US-primary care practice	T:178pt,age≈57yrs,66%females (all african american)
Senaida Fernandez et al	2008	US-primary care practice	168pt,86%females,age≈54yrs
MASES-R: (revised- validation)			
Sebahat Gozum et al	2009	Turkey-primary care unit	140pt,51%males,age≈61yrs
MASES-T: (turkish version)			
Rabia Hacıhasanoğlu et al	2012	Turkey-health center	150pt,58%females,age≈62yrs
MASES-SF: (turkish Short Form)			
Mohsen Saffari et al	2015	Iran-health centers	184pt,55%males,age≈62yrs
(persian version)			
Mases-R - Huda Salim Al-Noumani et al	2021	Oman	199pt

Table 1 (continued)

(arabic version)			
Hill Bone			
Miyong T. Kim et al	2000	US-community (from 2 studies)	T: 480pt,51%males,age≈54yrs (all african american)
Marie Krousel-Wood et al	2005	US-outpatient clinic	239pt,51%males,age≈69yrs
Estelle Victoria Lambert et al	2006	South Africa-primary care	98pt,≈50%males,age≈52yrs

(african version)			
Melek Karademir et al	2009	Turkey-primary care center	200pt,70%females,58%≥61yrs
(turkish version)			
Janka Koschack et al	2010	Germany-primary care	353pt,51%males,age≈64yrs
(german version)			
Youngshin Song et al	2011	US-community based	T: 525pt,67%females,age≈66yrs
(HBMA-K -Korean subscale)			(all korean american pt)
Marie N. Fongwa et al	2015	US-clinic	70 females, age≈54yrs
Izabella Uchmanowicz et al	2016	Poland-medical center	117pt,55% females, age≈61yrs
(polish version)			
M. M. Nashilongo et al	2017	South Africa-primary care	120pt,age≈47yrs,56%females
(namibian version)		(in namibia)	
Rajina Shakya et al	2022	Nepal-health centers	282pt,52.5%males,age≈58yrs
(Nepalese version)			
Olivia Nakwafila et al	2022	Namibia-health facilities	400pt,age≈49yrs,67%females

Table 1 (continued)

Jingjing Pan et al	2020	China-hospital	234pt,47%females,92%>50yrs
(chinese version)			
BMQ			
C.S. Tan et al	2018	Malaysia-booths/programs	238pt,61%females,age≈57yrs
(malay version)			
Michał Karbownik et al	2020	Poland-in/outpatients	T:311pt,T:71%females,T≈53yrs
(BMQ-PL - polish version)			

MAR(report)**S**			
Amy Hai Yan Chan et al	2020	UK-hospital/clinic	T:428pt,52%males,age≈55yrs
MMAS-4			
Donald E. Morisky et al	1986	US-teaching hospital/clinic	T:400pt, 70%females,age≈54yrs (91%black)
Jean-Pierre Gregoire et al (french version)	1992	Canada-family clinic unit	109pt,66%females,age≈64yrs
Janka Koschack et al (german version)	2010	Germany-primary care	353pt,51%males,age≈64yrs
Chunhua Ma et al	2011	China-hospitals	278pt,age≈60yrs,58%females
MMAS-8			
Donald E. Morisky et al	2008	US-teaching hospital	1367pt,age≈53yrs,41%males (77%black)
Murtuza Bharmal et al	2009	US-online	396pt,50%males,age≈55yrs
Virginie Korb-Savoldelli et al (french version)	2012	France-hospital	199pt,age≈56yrs,57%males
Fahad Saleem et al (urdu version)	2012	Pakistan-hospital	110pt,age≈40yrs,72%males
Dong-Soo Shin et al (korean version)	2013	Korea-primary health care	92pt,79%females,age≈73yrs

Table 1 (continued)

Jeung-Hee Kim et al (MMAS-K- korean version)	2014	Korea-teaching hospital/clinic	373pt,55%males,age≈57yrs
Alfredo de Oliveira-Filho et al (portuguese version)	2014	Brazil-health system unit	937pt,72%females,age≈57yrs
Rabia Hacıhasanoğlu Aşılar et al (turkish version- MMAS TR)	2014	Turkey-centers	196pt,61%females,age≈62yrs
Yashar Moharamzad et al (persian version)	2015	Iran-multicenter (clinic,university hospital,pharmacy)	200pt,age≈60yrs,42%males
Samson Okello et al (MMAS-U-Runyankore/Rukiga version)	2016	Uganda - hospital/clinic	329pt,age≈55yrs,69%females

Table 1 (continued)

Yang Heui Ahn et al (modified morisky)	2016	Korea-offices/beneficiary	289pt,77%females,age≈69yrs
Ana C. Cabral (portuguese version)	2018	Portugal-hospital/pharmacy	472pt,52%females,age≈68yrs
Elisa PAREJA MARTÍNEZ et al (spanish version)	2015	Spain-pharmacy	100pt,57%females,age≈65yrs
Mahlagha Dehghan et al (persion version)	2015	Iran-hospitals	250pt,65%males,age≈56yrs
Beata Jankowska-Polanska et al	2016	Poland- university/clinic	110pt,age≈61yrs,55%females

(polish version)

Appendix B

Table 2

Data Extraction Details for Tools Chaaracteristics

Tool / Author name	No. of items	Piloted?	Type of scale		Coverage/Dimension
			Dichotomous	Likert	
TASHP-Wei He et al	25	no		X	attitudes
PSM- Rob Horne et al	5	no		X	Beliefs
QATSH-Malvina Rodrigues et al	12 of 23	no		X	attitudes
HTA-Mahlagha Dehghan et al	23	yes-30 pt		X	attitudes
ARMS-Katarzyna Lomper et al	12	yes-20pt		X	attitudes and barriers
MUAH-Gwenn Wetzels et al	25 of 44	yes-7 pt		X	attitudes and beliefs
MTQ-Mary Jayne Johnson et al	12 of 20	yes		X	beliefs

Table 2 (continued)

MAI- Shiah-Lian Chen et al	13	no		X	barrier and attitudes

Razatul Shima et al	11 of 15	yes	X	barriers,beliefs and attitudes
(Malay version- MAR(reason)S				
Pin-Fang Chenet et al	24+2 global items	yes	X	barriers,belliefs and attitudes
ChMAR(reason)-Scale (chinese version)				
LMAS-R. Bou Serhal et al	14 of 16	no	X	attitudes and barriers
Lene Juel Kjeldsen et al	13 item scale 20 item scale	yes	X	barriers,attitudes and beliefs
FATS-Marie N. Fongwa et al	18	yes-20 pt	X	barriers
Corrine I. Voils et al	24 of 28	no	X	(extent): barriers,beliefs and attitudes

Table 2 (continued)

CHPS-Tiina S. Lahdenpera et al	21	yes-12 pt	X	intent,attitudes,beliefs
TAQPH Chunhua Ma et al Mahlagha Dehghan et al (persion version)	28 of 167	no	X	attitudes
MOS		X	X	attitudes

Richard L. Kravitz et al	T: 20 - 2 sections & 15 related to recommendations			
MASES				
Gbenga Ogedegbe et al	26 of 43-9 sections	yes	X	self-efficacy:barriers,beliefs and attitudes
Senaida Fernandez et al	13			
MASES-R: (revised- validation)				
Sebahat Gozum et al	26	yes-20pt		
MASES-T: (turkish version)				
Rabia Hacıhasanoğlu et al	13			
MASES-SF: (turkish Short Form)				
Mohsen Saffari et al	26	yes-20pt		
(persian version)				

Table 2 (continued)

Mases-R - Huda Salim Al-Noumani et al	13			
(arabic version)				
Hill Bone				
Miyong T. Kim et al	14 of 25-3domains	yes-7 pt	X	attitudes
Marie Krousel-Wood et al				

Estelle Victoria Lambert et al (african version)	10	yes		
Melek Karademir et al (turkish version)	14	yes-30 pt		
Janka Koschack et al (german version)	14			
Youngshin Song et al (HBMA-K -Korean subscale)	8 of 9 (SF scale,since too reliable factor vs BP)			
Marie N. Fongwa et al	14			
Izabella Uchmanowicz et al (polish version)	14	yes-30 pt		
M. M. Nashilongo et al (namibian version)	12 of 14	yes		

Table 2 (continued)

Rajina Shakya et al (Nepalese version)	14			
Olivia Nakwafila et al	14			
Jingjing Pan et al (chinese version)	14	yes-30 pt		
BMQ				
C.S. Tan et al (malay version)	18	yes-20 pt	X	Beliefs

Michał Karbownik et al	18	yes-14pt			
(BMQ-PL - polish version)					
MAR(report)**S**					
Amy Hai Yan Chan et al	5 of 10	it is pilot		X	attitudes, barriers
		228 pt			
MMAS-4					
Donald E. Morisky et al	4 of 5	no	X		attitudes,barriers
Jean-Pierre Gregoire et al	4				
(french version)					
Janka Koschack et al					

Table 2 (continued)

(german version)					
Chunhua Ma et al					
MMAS-8					
Donald E. Morisky et al	8		X	X	attitudes,barrier
Murtuza Bharmal et al	7				
Virginie Korb-Savoldelli et al		yes-10pt			
(french version)					
Fahad Saleem et al		yes-25pt			

(urdu version)		
Dong-Soo Shin et al		yes
(korean version)		
Jeung-Hee Kim et al		yes-30pt
(MMAS-K- korean version)		
Alfredo de Oliveira-Filho et al		yes-20pt
(portuguese version)		
Rabia Hacıhasanoğlu Aşılar et al		yes-30 pt
(turkish version- MMAS TR)		
Yashar Moharamzad et al	8	yes

Table 2 (continued)

(persian version)		
Samson Okello et al		yes-10pt
(MMAS-U-Runyankore/Rukiga version)		
Yang Heui Ahn et al	6	
(modified morisky)		
Ana C. Cabral		yes-20pt
(portuguese version)		
Elisa PAREJA MARTÍNEZ et al	8	it is pilot
(spanish version)		

Mahlagha Dehghan et al	8		
(persion version)			
Beata Jankowska-Polanska et al	8	yes-25pt	
(polish version)			

Appendix C

Table 3

Data Extraction Details for Tools Reliability and Validity

	Reliability				Validity			
Tool / Author name	**Internal consistency**		**Test-retest**				**Construct**	**Criterion**
	(Cronbach's α)	**Split half**	**ICC**	**others**	**Content**	**Face**	**(converge/discriminant)**	**(concurrent/predictive)**
TASHP-Wei He et al	Overall = 0.83	4 scales:			no	no	CFA confirmed 4 structures	against Blood pressure
	.862 (in original-chinese)	0.89,0.85,						sensitivity=0.554
		0.73,0.73						specificity=0.736

PSM- Rob Horne et al	0.79-0.94		Pearson r=	no	no	vs BMQ,predictive by:
	range to all samples		0.89,time=			symptom reports & MASRI
			2 weeks			
QATSH-Malvina Rodrigues et al	0.81			yes	yes	Factorial analysis & MML method & Samejima model
HTA-Mahlagha Dehghan et al	0.76	0.74, time=		yes	yes	PFA- 6 factors vs BP
		2 weeks				ROC curve
ARMS-Katarzyna Lomper et al	0.954			yes	yes	CFA : 2 subscales vs BP, sensitivity=78.2%
						specificity=80.2%
MUAH-Gwenn Wetzels et al	0.63-0.80	range:		no	yes	EFA-4 factors
	range of subscales	0.79-0.86				vs BMQ, refill records &
		time=1m o				MEMS

Table 3(continued)

MTQ-Mary Jayne Johnson et al	0.80-0.88	range:	correlation	yes	yes	EFA and CFA-2 factors of 3
		0.79-0.86	range:			vs HBM, LBQ and BP log
		time=	t_{rr} = .80-.81			
		1 week				
MAI- Shiah-Lian Chen et al	0.89			no	no	factor analysis-3 subscales vs diastolic BP
						vs symptoms of side effects
Razatul Shima et al	T: 0.78	range:.51 -.9		yes	yes	EFA and CFA- 4 factors
(Malay version- MAR(reason)S		time: ---				
Pin-Fang Chenet et al	range:0.649-0.852			yes	yes	EFA-6 domains vs VAS & global items

ChMAR(reason)-Scale (chinese version)						
LMAS-R. Bou Serhal et al	0.48-0.695		no	no	EFA & PCA- 4 factors	vs MMAS-8 and BP
	range of subscales					82.9%sensitive,36.9%specific
Lene Juel Kjeldsen et al	13item range:		no	yes	EFA	
	0.68-0.92				13item into 4 factors	
	20item range:				20 item into 2 factors	
	0.84-0.98					
FATS-Marie N. Fongwa et al	0.78		yes	yes	EFA- 4 factors	vs Hill bone scale,
						CYHBPIQ and others
Corrine I. Voils et al	0.84 (0.80-0.87)	0.58 for	yes	yes	CFA - vs BMQ , MASES	vs BP measure
	for extent subscale	"extent"			morisky and others	
		0.07-0.64				
		range for				

Table 3(continued)

		"reasons"				
		time=				
		2-21 days				
CHPS-Tiina S. Lahdenpera et al	theta coefficient for		yes	yes	PCA- 5 subscales	vs BP,BMI and patient's own
	total scale=0.8					adherence scoring
TAQPH	0.86	0.82,time =	yes	yes	PCA/EFA & CFA- 6factors of 12	vs morisky and general
Chunhua Ma et al		10-14 days				self-efficacy scale
Mahlagha Dehghan et al	0.8	0.95,time =		yes	PCA, EFA and CFA	vs BP

(persion version)		2 weeks				
MOS						
Richard L. Kravitz et al	general=0.78				vs clinical indexes/parameters	
	3 specific subscales:					
	0.69,0.5,0.53					
MASES						
Gbenga Ogedegbe et al	43-item=0.96		range of k:	yes	yes EFA-5 factors	vs controlled BP
	26-item=0.95		0.07-1;time			
			is several days			
Senaida Fernandez et al	26 item=0.91	26item=.56			EFA and CFA-unidimensional	vs MMAS-4 & MEMS
MASES-R: (revised- validation)	13 item+retest=	13item=.51				
	0.92-0.90	time=3mo				

Table 3(continued)

Sebahat Gozum et al	0.92			yes	yes PCA	
MASES-T: (turkish version)					known group validity vs BP	
Rabia Hacıhasanoğlu et al	0.94				yes EFA and CFA	
MASES-SF: (turkish Short Form)					vs BP	
Mohsen Saffari et al	0.91		range of k:	yes	yes EFA & CFA-unidimensional	
(persian version)			0.28-1		vs BP	
			time= ---			
Mases-R - Huda Salim Al-Noumani et al	0.93				1 factor	vs Morisky scale

(arabic version)					
Hill Bone					
Miyong T. Kim et al	2 studies=0.74,0.84	yes	yes	PCA vs BP	vs BP
Marie Krousel-Wood et al	0.43 9 item subscale=.68			factor analysis- 1-2 factors	
Estelle Victoria Lambert et al	0.79		yes	item-total correlations	vs BP
(african version)	14-item: 0.77				
Melek Karademir et al	0.72	yes	yes	PCA- 3 factors	
(turkish version)					
Janka Koschack et al	0.73		yes	PCA- 3 components	vs BP
(german version)				vs morisky scale (vs 9-item= SF)	
Youngshin Song et al	9-item=0.77		yes	EFA- 1 factor	vs BP, beliefs & knowledge
(HBMA-K -Korean subscale)	8-item=0.88				

Table 3(continued)

Marie N. Fongwa et al	0.7			vs correlation with scales of BP check & social support	
Izabella Uchmanowicz et al	0.8; ICC=0.851	yes	yes	PCA-3 factors	vs BP
(polish version)	&9item subscale:.78				
M. M. Nashilongo et al	0.695			PCA-3 subscales of 4	
(namibian version)					
Rajina Shakya et al	0.84	yes	yes	PCA/EFA - 3 subscales	
(Nepalese version)					

Olivia Nakwafila et al	0.78				PCA- 3 subscales	
Jingjing Pan et al	0.85			yes	EFA-4 factors	
(chinese version)						
BMQ						
C.S. Tan et al	T: 0.86	T: 0.922	yes	yes	subscales correlations	
(malay version)		time=2			vs BP	
		weeks				
Michał Karbownik et al	range:0.42-0.82		yes	yes	CFA and EFA	vs ARMS
(BMQ-PL - polish version)	ω=0.9-0.91					
MAR(report)**S**						
Amy Hai Yan Chan et al	samples' alphas:	r=0.97			PCA- 3 factors for 10 items	vs BP
	0.67,0.68,0.84,0.89	time=			vs BMQ	
		2 weeks				

Table 3(continued)

MMAS-4						
Donald E. Morisky et al	0.61		yes	no	PCA- 1 construct	vs BP
						81%sensitive,44%specific
Jean-Pierre Gregoire et al	0.54					vs BP
(french version)						sensitivity/specificity are done
Janka Koschack et al	0.25			yes	vs Hill bone scale	vs BP
(german version)						
Chunhua Ma et al	0.61					
MMAS-8						
Donald E. Morisky et al	0.83		yes		CFA- 1 factor	vs MMAS-4 & BP :

							93%sensitive,53%specific
						vs coping,knowledge & others	
Murtuza Bharmal et al	0.82			yes			91%sensitive,50%specific
Virginie Korb-Savoldelli et al	0.54	0.68		yes	PCA and CFA- one dimension		
(french version)		time=1mo					
Fahad Saleem et al	0.701		0.8	yes	yes	vs MMAS-4	46.15%sensitive,60%specific
(urdu version)			time=1mo				PPV=45%,NPV=61.11%
							vs BP
Dong-Soo Shin et al	0.71				yes	EFA- 2 dimensions	vs BP
(korean version)						vs MMAS-4	52.5%sensitive,69.2%specific
Jeung-Hee Kim et al	0.56	0.91		yes	yes	vs MMAS-4	vs BP

Table 3(continued)

(MMAS-K- korean version)		time=				EFA/ CFA- 3 dimensions	64.3%sensitive,72.9%specific
		2 weeks					
							vs BP;
Alfredo de Oliveira-Filho et al	0.682		0.928	yes	yes	vs BP	86.1%sensitive,31.2%
(portuguese version)			time=				specific,PPV:57.4%,NPV: 68.3%
			2 weeks				
Rabia Hacıhasanoğlu Aşılar et al	0.79				yes	factor analysis- 1 factor	vs BP
(turkish version- MMAS TR)							
Yashar Moharamzad et al	0.697		0.94	yes	yes	PCA and CFA- 2 factors	vs BP
(persian version)			time=			vs BP	92.8%sensitive,22.3%specific

		14 days					PPV=52.9%,NPV=76.7%
Samson Okello et al	0.65	k=0.36		yes	PCA-2 factors		
(MMAS-U-Runyankore/Rukiga version)		time=					
		2 weeks					
Yang Heui Ahn et al	0.59				correlation with knowledge,		
(modified morisky)					motivation and efficacy		
Ana C. Cabral	0.6		yes	yes	CFA- unidimensional	vs knowledge & adherence	
(portuguese version)					vs adherence scale (portuguese) & knowledge	scale	
Elisa PAREJA MARTÍNEZ et al	0.676				EFA showed 3	vs BP	
(spanish version)					factors		

Table 3(continued)

Mahlagha Dehghan et al	0.4	spearman=.89	no	yes	CFA- unidimensional	vs BP	
(persion version)		time=2weeks					
Beata Jankowska-Polanska et al	0.81	K=0.6 and r	no	yes	factorial analysis- 2 factors	vs BP	
(polish version)		time=1 mo					

Appendix D

Table 4

Validity Parameters Analyses Details

Author, year	Thresh old	TP	FP	FN	TN	Sensitivit y %	[95% CI]	Specificit y %	[95% CI]	Sample size
Wei He, 2016	109	62	67	50	**7**	55.4	46.1,64 .2	73.6	67.9,78 .7	366
R. Bou Serhal, 2018	38	**7**	**6**	24	97	82.9	75.9,88 .3	36.9	31.3,42 .9	404
Amy Hai Yan Chan, 2019	_	13	7	16	27	44.8	28.4,62 .5	79.4	63.2,89 .7	63
Pin-Fang Chen, 2020	1 never	**146**	49	**0**	**108**	44.7	39.5,50 .2	68.7	61.2,75 .5	483
Donald E. Morisky, 1986	0	94	31	87	78	52	44.7,59 .1	71.5	62.5,79 .2	290
Jean-Pierre Gregoire, 1992	0	65	15	17	12	79.2	69.3,86 .6	44.4	27.6,62 .7	109

Janka Koschack, 2010	0	32	81	42	170	43	32.6,54.6	68	61.7,73.2	325
Janka Koschack, 2010	9	26	159	94	46	37	15.2,29.9	63	17.3,28.6	325
Miyong T. Kim, 1999	51	10	110	41	286	19.6	11,32.5	72	67.6,76.4	447
Alfredo Dias de Oliveira-Filho, 2014	<8	505	234	81	109	86	83.1,88.7	31.7	27.1,36.9	929
Samson Okello, 2016	<6	106	174	11	38	90.5	83.9,94.7	18	13.3,23.6	329
Dong-Soo Shin, 2013	<6	18	13	22	39	45	30.7,60.2	75	61.8,84.8	92
Yashar Moharamzad, 2015	<8	90	80	7	23	92.8	85.8,96.5	22.3	15.4,31.3	200
Jeung-Hee Kim, 2014	<6	36	86	20	231	64	51.2,75.5	73	67.7,77.5	373
Fahad Saleem, 2012	<6	42	8	24	36	63.6	51.6,74.2	81.8	68,90.5	110
Donald E. Morisky, 2008	<6	295	144	486	442	37.8	34.4,41.2	75.4	71.8,78.7	1367
Elisa Pareja Martines, 2015	<8	26	25	29	20	47.2	0.34,0.6	44.5	30,58	100

Table 4(continued)

Beata Jankowska-Polanska, 2016	<8	56	14	33	7	62.9	0.52,0.72	33.3	17, 54	110
Mohsen Saffari, 2015	65.1	111	108	0	149	100		58		368
Sebahat Gozum, 2009	65.1	87	45	0	148	100		76.6		280
Katarzyna Lomper, 2018	15	73	62	13	131	84.8	75.8,90	67.8	61,74	279
Mahlagha Dehghan, 2020	86	106	59	74	61	59	51,65	51	42,59	300

Appendix E

Turnitin Similarity Report

TEZ

ORİJİNALLİK RAPORU

%19	%18	%11	%4
BENZERLİK ENDEKSİ	İNTERNET KAYNAKLARI	YAYINLAR	ÖĞRENCİ ÖDEVLERİ

BİRİNCİL KAYNAKLAR

1	theses.gla.ac.uk İnternet Kaynağı	%3
2	www.ncbi.nlm.nih.gov İnternet Kaynağı	%3
3	espace.library.uq.edu.au İnternet Kaynağı	%2
4	eprints.nottingham.ac.uk İnternet Kaynağı	%2
5	www.scribd.com İnternet Kaynağı	%1
6	ecommons.luc.edu İnternet Kaynağı	%1
7	www.researchgate.net İnternet Kaynağı	%1
8	docs.neu.edu.tr İnternet Kaynağı	%1
9	Nguyen, Thi-My-Uyen, Adam LA Caze, and Neil Cottrell. "What are validated self-report adherence scales really measuring?: a	<%1

	systematic review", British Journal of Clinical Pharmacology, 2013. Yayın	
10	papyrus.bib.umontreal.ca İnternet Kaynağı	<%1
11	www.frontiersin.org İnternet Kaynağı	<%1
12	scholarworks.iupui.edu İnternet Kaynağı	<%1
13	mdpi-res.com İnternet Kaynağı	<%1
14	systematicreviewsjournal.biomedcentral.com İnternet Kaynağı	<%1
15	Submitted to University of South Africa Öğrenci Ödevi	<%1
16	go.gale.com İnternet Kaynağı	<%1
17	polynoe.lib.uniwa.gr İnternet Kaynağı	<%1
18	B. Mahendran, B. Rossi, M. Coleman, S. Smolarek. "The use of Endo-SPONGE® in rectal anastomotic leaks: a systematic review", Techniques in Coloproctology, 2020 Yayın	<%1
19	www.nature.com İnternet Kaynağı	

		<%1
20	link.springer.com İnternet Kaynağı	<%1
21	open.library.ubc.ca İnternet Kaynağı	<%1
22	eprints.keele.ac.uk İnternet Kaynağı	<%1
23	Liu, Jie, and Hong-xin Zhang. "1790 G/A polymorphism, but not 1772 C/T polymorphism, is significantly associated with Cancers: An update study", Gene, 2013. Yayın	<%1
24	www.scielo.br İnternet Kaynağı	<%1
25	Yemisi Takwoingi, Boliang Guo, Richard D Riley, Jonathan J Deeks. "Performance of methods for meta-analysis of diagnostic test accuracy with few studies or sparse data", Statistical Methods in Medical Research, 2015 Yayın	<%1
26	ir.lib.uwo.ca İnternet Kaynağı	<%1
27	journal.waocp.org İnternet Kaynağı	<%1

28	pure-oai.bham.ac.uk İnternet Kaynağı	<%1
29	www.aetna.com İnternet Kaynağı	<%1
30	"Publication Bias in Meta_Analysis", Wiley, 2005 Yayın	<%1
31	Tyler Pitre, Johnny Su, Jasmine Mah, Wryan Helmeczi et al. "Higher versus lower dose corticosteroids for severe to critical COVID-19: A systematic review and dose-response meta-analysis", Research Square Platform LLC, 2022 Yayın	<%1
32	onlinelibrary.wiley.com İnternet Kaynağı	<%1
33	S. G Moreno, A. J Sutton, E. H Turner, K. R Abrams, N. J Cooper, T. M Palmer, A E Ades. "Novel methods to deal with publication biases: secondary analysis of antidepressant trials in the FDA trial registry database and related journal publications", BMJ, 2009 Yayın	<%1
34	annalsofintensivecare.springeropen.com İnternet Kaynağı	<%1
35	"Systematic Reviews in Health Research", Wiley, 2022 Yayın	<%1

36	McCrae, R. R., J. E. Kurtz, S. Yamagata, and A. Terracciano. "Internal Consistency, Retest Reliability, and Their Implications for Personality Scale Validity", Personality and Social Psychology Review, 2011. Yayın	<%1
37	Piotr Sorokowski, Maciej Karwowski, Michał Misiak, Michalina Konstancja Marczak et al. "Sex Differences in Human Olfaction: A Meta-Analysis", Frontiers in Psychology, 2019 Yayın	<%1

Alıntıları çıkart üzerinde
Bibliyografyayı Çıkart Kapat
Eşleşmeleri çıkar Kapat

Appendix F

CV

Education

Near East University	2018-2023
PhD in Clinical Pharmacy	
IELTS Exam	Dec 2016
GRE Test	Feb 2016
TOEFL Exam	Jan 2016
Beirut Arab University, Beirut	2010 - 2015
BS in Pharmacy (3.74 cGPA – Honor List)	

- Objective Structured Clinical Examination
- Marketing and Management
- Professional Pharmacy Practice (Hospital)
- Pharmaceutical Layout and Quality
- First Aid

Beirut Arab University, Debbieh	2009
BS in Biology (3.4 GPA)	
National Evangelical Institute for Boys & Girls, Saida	1994 - 2009
Lebanese Baccalaureate in Life Sciences	

Experience

▪ **Trainee –** Community Pharmacies	Summers 2010-2014
▪ **Full time pharmacist at Machmoushi pharmacy**	Sep 2015 – Dec 2015

- **Full time pharmacist at Megapharmacy** Feb 2016-Mar 2016

- **Pharmacist at Pharmacy Sabbagh** May 2016-Sep 2018

- **Private tutor** 2009-present

Skills

- **Languages** Excellent command of English & Arabic (writing/speaking/listening/reading)
  Fair command of French and Turkish (speaking/listening/reading/writing)