MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

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Systematic review on determinants of therapeutic adherence in individuals from 50 to 69 years of age

ÁREA CIENTÍFICA DE MEDICINA GERAL E FAMILIAR

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ABRIL/2022

SYSTEMATIC REVIEW ON DETERMINANTS OF THERAPEUTIC ADHERENCE IN INDIVIDUALS FROM 50 TO 69 YEARS OF AGE

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ABSTRACT

Introduction: Improving patients' adherence, according to the World Health Organization (WHO), may have a greater effect on health than any other improvement in therapy. Adherence can be defined as the implementation of an agreement between patient and physician in relation to the proposed therapeutic regimen. Poor adherence is associated with adverse outcomes, as it decreases treatment effectiveness, allows disease progression and increases urgent care visits, hospitalizations, socio-economic burden, overall higher morbidity and mortality. According to statistical demographical future projections, middle-aged patients will become, if they are not already, the predominant age group that use healthcare services. Therefore, it is crucial to identify specific barriers for each patient that can compromise adherence, while developing interventions and adopting appropriate methods to minimize them.

Objectives: We conducted a systematic review in order to identify which are the main determinants for therapeutic adherence and non-therapeutic adherence among patients in the age group of 50-69 years found in literature, with the goal of enabling physicians to predict which patients are at a higher or lower risk of non-adhesion to any therapeutic modality.

Methods: PubMed, Web of Science, SciELO and portuguese "Index das Revistas Médicas Portuguesas" (IRMP) databases, were searched from January 1st 2021 through January 21st 2022. Studies were included according to the criteria of the PICOS methodology: (P) population of individuals in age group from 50 to 69 years of age (middle-aged patients), (I) intervention for evaluation of the impact of multiple determinants of therapeutic adherence, (C) comparison between intervention and standard care or compliant and non-compliant groups, (O) outcomes were related to the review question, (S) study designs included experimental and observational studies. Registered in PROSPERO under number CRD42022301210.

Results: 26 articles were included which met the eligibility criteria, with a total of 17,309 patients who participated. Patient's age ranged from a mean of 37.5 (IQR 25-50.75) to 71.4 (±SD 5.6). Out of the 16 experimental studies, only 2 of them did not reach statistically significant improvement of adherence. After qualitative analysis, the main determinants increasing adherence were knowledge, educational level and older age. Determinants decreasing adherence were treatment complexity, polypharmacy, comorbidity, single civil status, rural or urban marginal residency and alcohol consumption.

Conclusion: The combination of different tools to measure adherence operating together can emerge as the closest method to patient's real adherence. The behavioural, digital and

remaining interventions to improve treatment adherence were efficient and feasible, revealing to be a potentially valuable adjunct in primary healthcare.

Keywords: therapeutic adherence, medication adherence, patient compliance, determinants, middle aged, systematic review.

RESUMO

Introdução: Melhorar a adesão terapêutica pode ter benefício na saúde superior a qualquer intervenção clínica, de acordo com a Organização Mundial da Saúde (OMS). Adesão pode ser definida como o cumprimento do acordo entre médico e doente, em relação ao plano terapêutico proposto. A fraca adesão está associada a efeitos adversos, como a diminuição da eficácia do tratamento, resultando num agravamento da situação clínica e no aumento ao recurso a serviços de urgência e número de internamentos. Por conseguinte, amplificam-se os custos socio-económicos e a morbimortalidade. Segundo as projeções demográficas estatísticas, doentes de meia-idade vão se tornar, caso já não o sejam, na faixa etária mais prevalente a utilizar os serviços de saúde. Deste modo, é fundamental identificar as barreiras específicas de cada doente que comprometam a sua adesão e adotar medidas apropriadas para as minimizar.

Objetivos: É objetivo desta revisão sistemática a identificação dos principais determinantes de adesão e não adesão terapêutica como forma de prever quem está em maior risco de não adesão a qualquer modalidade terapêutica entre os 50 e os 69 anos de idade.

Métodos: Os artigos foram obtidos através de pesquisa entre 1 de janeiro de 2021 e 21 de janeiro de 2022, nas bases de dados: PubMed, Web of Science, SciELO e Index das Revistas Médicas Portuguesas. Incluíram-se estudos de acordo com os critérios PICOS: (P) indivíduos no grupo etário entre os 50 e os 69 anos de idade, (I) intervenção para avaliação do impacto dos determinantes sobre a adesão terapêutica, (C) comparação entre intervenção e controlo com *standard care* ou grupos aderentes com não aderentes, (O) *outcomes* estão relacionados com a questão da revisão, (S) tipos de estudo incluídos foram experimentais e observacionais. Registada na PROSPERO com o número CRD42022301210.

Resultados: 26 artigos que cumpriram os critérios de elegibilidade foram incluídos, com participação total de 17,309 doentes. A média de idades oscilou entre 37.5 (IQR 25-50.75) e 71.4 (±SD 5.6). Apenas 2 do total de 16 estudos experimentais não apresentaram melhoria estatisticamente significativa da adesão. Os principais determinantes na análise qualitativa que aumentaram a adesão foram o grau de conhecimento, o nível de educação e a idade avançada. Os determinantes que diminuíram a adesão foram a complexidade do tratamento, polifarmacoterapia, comorbilidade, estado civil solteiro(a), residência rural ou urbana marginal e etilismo.

Conclusão: A combinação de diferentes métodos de avaliação pode ser a estratégia que se aproxime mais do valor autêntico da adesão. As intervenções comportamentais, digitais e as restantes incluídas demonstraram eficácia e viabilidade, pelo que o seu uso na prática clínica como instrumento complementar é de grande potencial.

***Palavras-chave*:** adesão terapêutica, adesão medicamentosa, complacência do paciente, determinantes, meia-idade, revisão sistemática

1. INTRODUCTION

Therapeutic adherence has over the years, increasingly become a theme of clinical concern and debate,[1-4] with the World Health Organization (WHO) claiming that improving patients' adherence may have a greater effect on health than any other improvement in therapy.[5] Adherence is defined by WHO and researchers as "the extent or degree to which a person's behaviour, whether it is taking medication, following a diet or carrying out lifestyle changes, corresponds with the agreed recommendations from a health care provider".[6-9] It is the implementation of the agreement between patient and physician in relation to the proposed therapeutic regimen.[6] The Organization emphasizes that non-adherence to long-term therapies is "a worldwide problem of impressive magnitudes", further revealing that the mean adherence rate in developed countries is 50%, while in developing countries the rates are even lower.[5-7]

Poor medication and lifestyle changes adherence is associated with adverse outcomes, as it decreases treatment effectiveness and leads to significant socio-economic burden on the healthcare system with higher costs of care.[3,7,10] In fact, the detriment of the patient's clinical situation, leads to medication waste and further prescription or change of therapy, disease progression,[1,11] increases urgent care visits and hospitalizations, overall higher morbidity and mortality with premature deaths and decreased control of chronic diseases,[13] which also results in significant treatment costs.[12] The undesirable burden further increases when indirect damage is also taken into consideration, such as the association of therapeutic non-adherence with reduced functional abilities with the loss of productivity, not to mention the negative impact on patient's quality of life.[1,11]

Any modifiable risk factor that can increase or decrease adherence is called a determinant.[4] Determinants can be classified into five different interacting dimensions: patient-related (e.g., health literacy), socioeconomic factors (e.g., treatment cost), disease-related (e.g., comorbidity), healthcare team and system-related (e.g., doctor-patient relationship) and treatment-related factors (e.g., side-effects).[4,8,10,14]

Population aging is a powerful and transforming demographic force. The considerable development of healthcare has made life expectancy increase without precedents.[15] In fact, in about five years, the number of people over the age of 65 will surpass children under the age of 5.[15,16] Statistical analysis of the population by age bracket from UN projections[16,17] and demographic data from WHO[15] show that, regarding the current total population, most individuals are between 25 to 64 years old and these numbers will increase even more by 2040, 2060 and subsequent years. Furthermore, the 65+ age group is projected to surpass the under 15 age group shortly after 2060's. Nowadays, the average mean age in developed countries, such as Japan, Germany or Italy is already within the middle-aged group and it will only naturally increase.[16,17] Middle-aged adults, older than 50 years of age, represent a central age group of clinical care, especially when it comes to chronic diseases and their management, often with comorbidity and polypharmacy.[18-20] This is particularly relevant because middle-aged and also elderly patients represent the main age groups that use healthcare services, especially in developed countries.[21] If we add this fact to the statistical demographical projections for the future, we can only expect that middle age patients will become, if not already, the predominant age group in clinical practice, thus with the highest socio-economic burden.

Currently, still amid the COVID-19 pandemic, it is crucial to rethink strategies to overcome the patient non-adherence problem with new care models,[7] while identifying specific barriers for each patient and adopting appropriate methods to minimize them.[4,11] In a time of increasing medical mistrust[22] and rapid spread of false health information,[23] a multidisciplinary approach with healthcare workers and all involved in patient's medication or lifestyle recommendations must be implemented[8,11] with the outmost understanding of individuals' adherence determinants.[4]

In the light of the aforementioned, this is a relevant study for medical knowledge, as it intends to identify which are the main determinants for therapeutic adherence and non-therapeutic adherence among patients in the age group of 50-69 years. It is compelling for its unique research and its future vision in improving patient care, as it attempts to aid physicians to clinically predict which patients are at a higher or lower risk of non-adhesion to any therapeutic modality.

2. METHODS

We conducted a systematic review in order to identify which are the main determinants for therapeutic adherence and non-therapeutic adherence among patients in the age group of 50-69 years found in literature, with the goal of enabling physicians to predict which patients are at a higher or lower risk of non-adhesion to any therapeutic modality. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used.[24]

2.1 Data sources and search strategy

The present review was registered in the PROSPERO international registry of systematic reviews platform under the number CRD42022301210. Systematic reviews are registered in this online database to help avoid duplication and decrease chances of reporting bias by allowing comparison of the finished review with what was established in the protocol. The search was performed using PubMed, Web of Science, SciELO and portuguese "Index das Revistas Médicas Portuguesas" (IRMP) databases. The publication date included for the review spanned from the 1st of January of 2021 to the 21st of January of 2022. All study citations from the different databases, excluding IRMP, were exported to Mendeley Reference Manager, which then were imported to Covidence, where bibliographic references and the review process was managed. Covidence is an online tool that streamlines parts of the systematic review process. However, the version free of charge of this powerful online software only allows 500 studies to be included. Therefore, a comprehensive search strategy with Medical Subject Headings (MeSH) and free-text terms (Table 1) were both used to ensure study heterogeneity from each database to make up the total of 500 articles.

2.2 Eligibility criteria

The PICOS methodology was used, which was an acronym for **P**opulation of individuals in the age group from 50 to 69 years of age (middle-aged patients), **I**ntervention for evaluation of the impact of multiple determinants of therapeutic adherence, **C**omparison between intervention and standard care groups or between compliant and non-compliant groups, **O**utcomes were related to the review question and **S**tudy designs included experimental and observational studies, such as prospective and retrospective cohorts, case-control and cross-sectional studies. The review question was the following:

What are the main determinants of therapeutical adherence and non-therapeutical adherence in individuals from the age group 50-69 years old and is it possible to predict a patient's likelihood for therapeutical adherence? These are our 2 main questions which we will attempt

to answer throughout the review. PICOS served as the starting point for the search strategy. As for the inclusion criteria, studies were eligible for inclusion if they satisfied the following conditions: (1) examined the clinical and adherence measurement on different determinants for therapeutical adherence; (2) middle-aged patient age group; (3) indexed in databases published in English, Spanish, French or Portuguese languages; (4) experimental and observational, including prospective and retrospective cohorts, case-control and cross-sectional studies; and (5) full text availability. The following studies were excluded: duplicated; did not state clearly the methodology and did not answer the study question; publication date not incorporated in those mentioned (Table 1); wrong study designs; underpowered studies with significant limitations or studies with payment requirement for full-text review.
Both pharmacological and non-pharmacological modalities were included for the evaluation of therapeutic adherence.

2.3 Study selection

The search in the databases was carried out by the main researcher (CB), who subsequently exported the abstracts of the articles found to Covidence. Titles and abstracts of all studies identified by the initial searches were independently screened by two review authors (CB and DV), where the eligibility criteria were applied. The ones that met the inclusion criteria were retrieved and those with any exclusion criteria were excluded. Those that were unclear were retrieved for further assessment, through complete reading in full-text review. Studies clearly irrelevant, and those whose abstract failed to give input about the aim of this search were excluded. Retrieved articles were classified as included or excluded, based on the reason for exclusion. Disagreements were solved by consensus. If doubt persisted, a third author would be asked to decide. Full-text review screening was performed by the main researcher (CB). To ensure transparency, the process of selection is summarised using a PRISMA flow diagram shown in Figure 1.

2.4 Quality assessment

Risk of bias was assessed by two independent investigators applying the risk-of-bias tools to each included study (CB and DV). For randomized controlled trials (RCTs), quality assessment adapted from Cochrane's Collaboration Tool (RoB 2.0) was used, which included the following five domains: risk of bias from (1) the randomization process, (2) due to deviations from the intended interventions (effect of assignment and adhering to intervention), (3) due to missing outcome data, (4) measurement of the outcome, (5) selection of the reported result as well as an overall risk-of-bias judgment. This tool included algorithms with signalling questions within each domain that typically covered the following options: yes, probably yes, no, probably

no, not applicable and no information. Each domain was judged as high, low or moderate risk (some concerns). Overall risk of bias depended on the assessment of the individual domains.[25]

As for cross-sectional, cohort and quasi-experimental studies, the JBI (Joanna Briggs Institute) critical appraisal checklists for analytical cross-sectional, cohort and quasi-experimental studies were used, respectively. It encompasses a checklist with several questions in order to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis,[26] finishing with overall judgement according to the percentage of affirmative answers. A consensus meeting was then held to resolve discrepancies and to arrive at a final risk of bias assessment summary.

2.5 Data synthesis and analysis

We performed descriptive analyses of the data and summarized the findings from these studies, with emphasis on statistical results reported in randomized controlled trials (RCTs) and observational studies. The qualitative analysis involved textual descriptions of population, intervention characteristics, adherence measurement, adherence and clinical outcomes, and differences between groups, when these results were available, for all studies included in this systematic review.

Table 1. Search strategy.

Database	Search method, MeSH and free-text terms
PubMed	("Treatment Adherence and Compliance"[Mesh]) AND "Middle Aged"[Mesh] Add. filter(s): Publication date - 1 year Article type – RCT
Web of Science	(“Treatment Adherence” OR “Therapeutic Adherence and Compliance” AND “Middle Aged”) Add. filter(s): Publication date – 01/01/2021 to 21/01/2022 (DD/MM/YYYY) Open access
SciELO	(Therapeutical Adherence) OR (Patient adherence) Add. filter(s): Publication date – 2021 and 2022
IRMP	Treatment Adherence Add. filter(s): Publication date – 1 year *not exported to Mendeley Reference Manager or imported to Covidence

RCT: Randomized Controlled Trial.

3. RESULTS

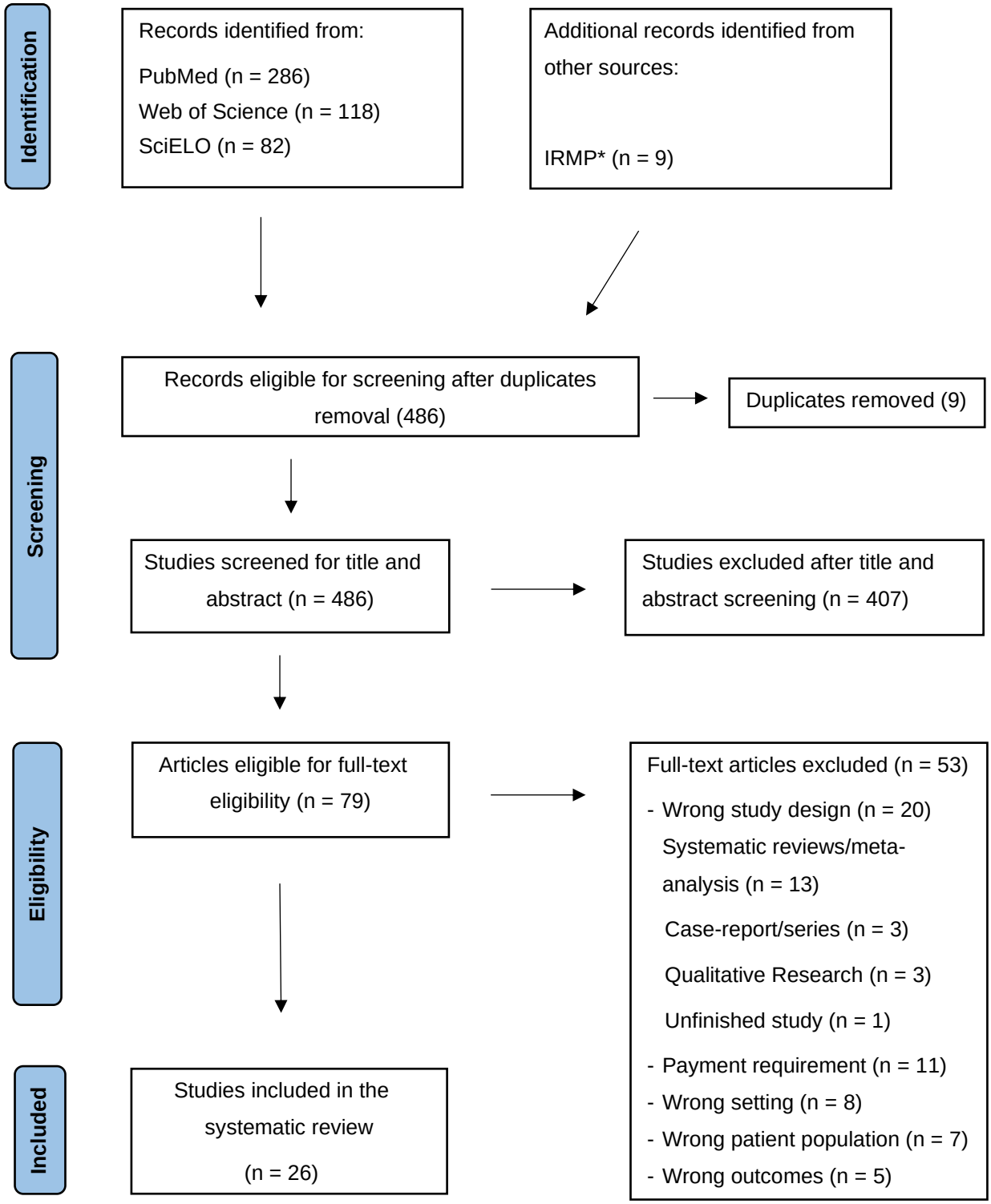

Figure 1. PRISMA flow diagram of literature search, screening process and study inclusion.

Abbreviations: IRMP, *Index das Revistas Médicas Portuguesas*

*Not imported to Covidence, due to the absence of reference exportation.

3.1 Study selection and characteristics

The comprehensive literature search with MeSH keywords and free-text terms resulted in a total of 486 articles after duplicates were removed, according to the eligibility criteria. The study inclusion process is demonstrated in a PRISMA flow diagram (Fig.1), which shows that after abstract and title screening and full-text review, the final number of articles that met all the inclusion criteria for this systematic review were 26. It also highlights the reasons for exclusion of articles after full-text review. The qualitative analysis of the eligible studies provided are shown in Table 2, which assessed: Author/Year/Country; Study Design; Sample Size and Mean Age; Intervention Characteristics; Adherence Measurement; adherence and clinical outcomes with difference between groups, statistical analysis with p-values, percentages and confidence intervals, when available, in the column of Results.

3.2 Summary of Results

This systematic review, as mentioned, included 26 articles which met the eligibility criteria, with a total of 17,309 patients who participated, and sample size varied from 32 to 6327. Patient's age ranged from a mean of 37.5 (IQR 25-50.75) to 71.4 (±SD 5.6). A total of 7 studies were conducted in Brazil, 3 in South Korea, 2 in the USA, 2 in the UK, and one from each of the following countries: Peru, Argentina, Canada, Sweden, Netherlands, Poland, Switzerland, Spain, Portugal, Ethiopia, India and Australia. As for the study design, out of the 26, 13 were randomized controlled trials, 9 cross-sectional studies, 2 quasi-experimental and 2 cohort studies.

Self-reported adherence with the completion of questionnaires or interviews was present in 22 studies, with at least one of the adherence measurement methods used. The most common self-reported forms were the four-item Morisky Green Levine Medication Adherence Scale, also known as the four-item Morisky Medication Adherence Scale (MMAS-4), in 4 studies and the more recent 8-item version (MMAS-8) also in another 4 studies. Other diagnostic adherence assessment instruments used: discontinuation of drug without refills, refill adherence evaluation, reviews of prescriptions or objective pill counts, used in a total of 5 studies in which 2 of them used the proportion of days covered (PDC) algorithm; objective and biochemical method for detection of drug/metabolites in urine samples was performed in 2 studies. Some other less frequent strategies, only seen in 1 study each, and generally in combination with another adherence method were: continuity of the family member in follow-up period; utilization of the ventilatory device for more than 4 hours a day, at least 70% of days under prescription, used as the only method of measurement; weight and abdominal circumference control, the practice of physical activity and alcohol consumption, in which these two latter ones were self-reported; calculation of percentage of doses taken (PDT) and

percentage of days on which the prescribed dose was taken correctly (PDTc), used as the only method of measurement; adherence evaluated with validated clinical outcomes using laboratory results and clinical records, and also adherence data from applications.

The qualitative analysis addressed different study designs, in which 16 had an experimental character, where the aim was mainly at whether an intervention was effective or ineffective, and the remaining 10 studies had an observational character, which evaluated which clinical characteristics were associated significantly with adherence and non-adherence. The following summary of results will show inside round brackets the frequency of studies. From the experimental studies, the intervention led to: significant association with adherence and mentioned clinical outcomes (8); significant association with adherence but without mention of clinical outcomes (4); significant association with adherence but not with clinical outcomes (2); significant association was seen with clinical outcomes but not with adherence (1);[27] no significant association with neither adherence nor clinical outcomes (1).[43] Among the interventions, the majority of them were based on behavioural and motivational (10) strategies, and also on eHealth programmes, whether through the use of smartphone digital apps as medication reminders, adaptive and interactive text-messaging schemes, medication and drug refill tracking apps, phone-based counselling and clinical assessments, access to informational websites and electronic medical records with medication review or gamified interactions to reward adherence (9). Of the aforementioned interventions, logically, some of them were used in combination or separately. Less common interventions included free of charge access to essential medicines (1), guidelines-based practice for hypertension (1), one pill (triple component single pill combination) vs. two pill groups (1) and the use of a medication reminder device (1).

In the 10 observational studies, the factors that significantly increased adherence or clinical outcomes control (blood pressure, glycaemia, HbA1c, LDL-cholesterol,…) were: knowledge level (2), educational level (2), older age (2), higher income, employment, unemployed patients (in comparison with active ones), low socioeconomic status, hospitalization history, patients from urban areas, married civil status, taking 4 or less medications, symptomatic patients with fatigue and palpitations, having medical insurance, treatment at specialist inpatient hypertension clinics and hospital wards (in comparison to patients treated by general practitioners), aspirin taking, using BiPAP instead of CPAP, room sharing, severe disease course in comparison to mild, limited alcohol consumption, smoking, comorbidity such as diabetes mellitus, use of other medication to treat other chronic diseases and the duration of treatment for hypertension. On the other hand, the factors that were significantly associated with lower or non-adherence or poorer clinical outcomes were: treatment complexity (3), number of drugs (polypharmacy) (2), single civil status (2), comorbidity (2), such as depression or chronic spine conditions, patients from rural or urban marginal areas (2), alcohol

consumption (2), low knowledge levels, lower income, higher income, low educational degree, symptomatic patients with dyspnea, chest pain, weakness or fatigue, duration of treatment, self-medication, smoking, low level of physical activity, patients that desire more information, younger age, age ≥ 70 years, male gender, female gender, use of private outpatient clinic, public healthcare system use, less than 4 total prescribed drugs, use of calcium channel blockers, use of β-blockers, aspirin monotherapy, starting therapy with clopidogrel and patients with hyperlipidaemia. The factors mentioned are all that were able to reach statistical significance in the included studies. Some of them appear as both adherence and non-adherence factors, while others are related to a specific disease. Therefore, a few examples highlight contradiction and even controversy, which will be later explored in the discussion of this systematic review.

3.3 Risk of bias assessment of the included studies

The quality assessment of randomized controlled trials (Table 3) was performed and adapted from Cochrane's Collaboration Tool (RoB 2.0). Overall risk-of-bias judgment shows that: 5 studies were low risk, 6 had some concerns and 2 were high risk. As for the cross-sectional, cohort and quasi-experimental studies included, JBI (Joanna Briggs Institute) critical appraisal checklist was used for quality assessment. Overall judgement was performed according to the percentage of affirmative answers. For the cross-sectional studies (Table 4): 5 studies were low risk, 3 were moderate risk and only 1 was high risk. For the cohort and quasi-experimental studies (Table 5): 2 were low risk and 2 were moderate risk.

Table 2. Summary of study characteristics (qualitative analysis).

Author (year)[reference] Country Study Design	Sample size Mean age	Intervention Characteristics	Adherence Measurement	Results
Andreae *et al.* (2021)[27] USA Cluster RCT	473 patients 57 (±SD 11)	Intervention: six-month, 11-session peer-delivered behavioral diabetes self-care program guided by social cognitive theory and the lived experience of illness (storytelling) over the phone and videos Control: self-paced general health program	Self-reported using a modified version of an adherence scale Medication adherence score range 0–3; higher score = worse adherence	All unadjusted outcome changes favoured the intervention arm, with no significant differences. ICC for medication adherence was p = 0.055 (95% CI -0.018, 0.145), thus not statistically significant. Study arms did not differ in A1c (p = 0.41), BP (p = 0.44), and LDL-C (p = 0.20) outcomes. Medication use self-efficacy was significant (p = 0.01).
Baptista *et al.* (2021)[28] Brazil Quasi-Experimental	133 individuals 45 years or over (70.0%)	Intervention: telephone based motivational interviews to family members of psychoactive substance users Control: Randomized family members received psychoeducation on psychoactive substances (not available later)	Continuity of the family member in the six-month follow-up, by making eight pre-scheduled calls and BAS	The use of alcohol showed statistical significance when associated with low follow-up adherence of family members (p = 0.05). Depression was the most frequent mental disorder of co-dependents (53.4%). 77.4% decreased their co-dependency when comparing the scores of the first and last call, despite the low adherence to the treatment.
Bruggmann *et al.* (2021)[29] Switzerland RCT	60 patients 59 (IQR 49-69)	Intervention: access to the web-based video and a short interview with the pharmacist, who gave each patient a medication card which contained all medications prescribed, connected to the e-learning website Control: usual care	Self-report questionnaire ARMS. Medication adherence score range 12-48; higher score = worse adherence	ARMS mean scores did not differ at 1 and 6 months (p = 0.99 and p = 0.33, respectively). ARMS mean score was significantly lower in the intervention group than in the control group at 3 months (12.54, 95% CI 12.08-13.00 vs 13.75, 95% CI 12.74-14.76; p = 0.03). Mean knowledge scores did not differ at 1, 3 or 6 months (all p>0.05).
Dessie *et al.* (2021)[30] Ethiopia Cluster RCT	186 patients Control: 50 (IQR 30-60) Treatment: 37.5 (IQR 25-50.75)	Intervention: self-care education based on social cognitive theory and on HF management comprising of intensive four-day training and one-day follow-up sessions offered every four months over the one-year project period Control: usual care administered to HF patients	Heart failure self-care adherence score MOS-SAS (eight-item scale) Score range 0-40; higher score = greater adherence	Intervention group had higher adherence scores than those in the control group, after baseline (p = 0.024). Being in the treatment group and multiple sessions' attendance (p < 0.001), so adherence increased with each round of education. Factors associated with increased adherence: taking aspirin (p < 0.05) and having hospitalization history (p < 0.05). Factors associated with reduced adherence: being single (p < 0.05).

Table 2. (continued)

Author (year)[reference] Country Study Design	Sample size Mean age	Intervention Characteristics	Adherence Measurement	Results
Farías-Vílchez *et al.* (2021)[31] Peru Cross-sectional	236 patients 50-59 years (47.5%) and 60-80 (29.2%)	Patients underwent analysis through the instruments: Form with sociodemographic data, Morisky Green-8 adherence scale and DKQ.24, in the attempt of establishing an association between medication adherence with knowledge or any sociodemographic data	Morisky Green-8 self - reported questionnaire. Score range 0-8; higher score = greater adherence	Inadequate knowledge predominated (68.2%). Knowledge, educational level and urban origin were statistically significant with adherence to treatment (all $p < 0.05$). Inadequate knowledge of diabetes, low degree of education and patients from rural or urban marginal areas predisposes higher risk of low adherence.
Guimarães *et al.* (2021)[32] Brazil Cross-sectional	253 patients 65.0 (±SD 13.3)	Patient's adherence to antihypertensive treatment, biosocial and laboratory data, habits and lifestyle, anthropometric measurements and body composition were collected. Later were subject to bivariate analysis of comparison between patients with controlled and uncontrolled blood pressure	MMAS-4 – self-reported questionnaire Score range 0-4: 0 - adherent. ≥1 – non-adherent	Adherence was not associated with any of the variables studied. For blood pressure control, the variables that were associated: positively, married marital status (OR 2.3; CI 1.34–4.28), and negatively the use of calcium channel blockers (OR 0.4; CI 0.19 – 0.92) and number of prescribed antihypertensive drugs (OR 0.78; CI 0.66–0.92).
Kassavou *et al.* (2021)[33] United Kingdom RCT	101 patients Intervention: 65 (±SD 10.6) Control: 67.1 (±SD 11)	Intervention: PAM consisted of a 3-month behavioural intervention and highly tailored text messaging programme or a smartphone app digital intervention Control: usual care	Objective validated medication adherence, using biochemical testing of urine samples and Self-reported medication adherence	Objective medication adherence was improved by an average 20% (95% CI 3–36) daily prescribed doses in the intervention vs. control. SBP was reduced by 9.16 mmHg (95% CI 5.69–12.64) and the DBP by 4.85 mmHg (95% CI 1.06–8.68) in the intervention vs. control. The improvements in biochemically validated medication adherence were associated with mean reductions of 10 mmHg (95% CI 7.35–13.12) in SBP in the intervention, and with mean reductions of 1 mmHg (95% CI 0.08–2.08) in the control.
Kim *et al.* (2021)[14] South Korea Retrospective cohort	4621 patients 66.4 (±SD 12.3)	Prevalence of discontinuation of APT was measured at 6,12,18 and 24 months. Comparison was made between antiplatelet continuers (≥ 12 months) and discontinuers (< 12 months) to evaluate the factors associated with premature discontinuation of APT	Discontinuation, or non-adherence – APT discontinued without refills throughout the rest of the observation period	35.5% discontinued APT at 12 months and 58.5% within 24 months. Factors associated with premature discontinuation within 12 months with 95% CI: aspirin monotherapy (2.17–3.25); CCI score ≥ 6 (1.31–1.98); starting with clopidogrel monotherapy (1.15–1.72); rural residency (1.14–1.62), < 4 total prescribed drugs (1.05–1.47), lower income (1.03–1.40 for middle income class and 1.02–1.45 for lower income class), and ages ≥70 years (1.00–1.31).
Li *et al.* (2021)[34] Australia RCT	124 patients 59.5 years	Intervention: Perx smartphone application that contained customised reminders and gamified interactions to reward verified medication adherence Control: standard care	Assessed with objective pill counts and validated with clinical outcomes at months 1,2,3,6,9 and 12	Medication adherence was higher in intervention group at month 2 ($p = 0.025$), 3 ($p = 0.046$) and at final month 12 ($p = 0.044$). The probability of HbA1c ≤6.5% was greater in the Perx group at months 9 and 12, and cholesterol (total and LDL-C) was lower in the Perx group at month 3. The intervention was particularly effective for those with obesity, taking medications for diabetes and taking ≤4 medications, all of which had $p < 0.05$.

Table 2. (continued)

Author (year)[reference] Country Study Design	Sample size Mean age	Intervention characteristics	Adherence Measurement	Results
Lima *et al.* (2021)[13] Brazil Cross-sectional	331 patients 41-50 (29.0%) 51-60 (42.9%) >60 (13.9%)	Patients had 2 questionnaires to fill out: - sociodemographic and labour characteristics, medical data and use of medications - self-reported adherence questionnaire	Self-reported medication adherence questionnaire. Score range 0-5; higher score = greater adherence	Medication adherence was statistically associated and lower in workers with weakness/fatigue (p = 0.05), dyspnea (p = 0.002), chest pain (p = 0.04), chronic spine conditions (p = 0.05) and depression (p = 0.03). Sociodemographic and labour characteristics, polypharmacy and type of medication were not associated with adherence (p>0.050).
Lima *et al.* (2022)[6] Brazil Cross-sectional	120 patients 70.1 (±SD 13.8)	Patients were subject to the following instruments through interview: - sociodemographic and clinical characterization (explanatory variables) - Brazilian version of MAT scale (outcome variable)	Measurement of Adherence to Treatment (MAT) scale. Score range 1-6; higher score = greater adherence	NOAC adherence was statistically in favour of inactive patients vs. active (p = 0.049) and patients with higher family income (p = 0.019). Significant and negative correlation with duration of NOAC use (p = 0.006), male sex (p = 0.048) and use of private outpatient clinic when compared to patients in public clinic (p = 0.025).
Llorca *et al.* (2021)[35] Spain Cross-sectional	6327 patients 64.7 (±SD 15.9)	Patients had a survey designed with five main sections: - sociodemographic data - clinical data (diseases and medication) - adherence assessment (main variable) - information about the disease - lifestyle and healthy habits	MMAS-4 – self-reported questionnaire. Patient is considered non-adherent with 1 negative answer out of 4 questions	Non-adherence was 48.4% (95%CI: 47.2-49.7%). The variables that reached significance with non-adherence: difficulty in taking medication (p < 0.001), self-medication (p < 0.001), desire for more information (p < 0.001), smoking (p = 0.025), a lower level of physical activity (p = 0.006), younger age (p = 0.001) and needing 2 to 3 (p = 0.015) and ≥4 (p < 0.001) chronic treatments.
Martins *et al.* (2021)[36] Portugal Cross-sectional	744 patients 64 (IQR 18)	Patient's data was collected with electronic clinical files: - sociodemographic, labour and medical characteristics with OSA severity classification - type of ventilatory device, use and difficulties - lifestyle and healthy habits - adherence to ventilatory therapy (main variable) - estimated costs related to non-adherence	Adherence to ventilatory therapy was defined by the utilization of the device for more than 4 hours a day, at least 70% of days under prescription	Good adherence was seen in 63.4% (95%CI: 60.5–67.4%). Variables associated with best adherence were older age (p = 0.014), using BIPAP versus CPAP (p = 0.046), primary economic sector vs tertiary sector (p = 0.014), room sharing (p = 0.002) and severe vs. mild OSA (p = 0.044). Intolerance, problems with the mask, nasal obstruction and xerostomia were mostly noted by non-adherents (p < 0.001).
Nascimento *et al.* (2021)[37] Brazil Cross-sectional	421 patients 59.9 (±SD 11)	Patients were evaluated with the following instruments: - sociodemographic data - clinical characteristics - adherence to non-pharmacological therapies as recommended by the 7th Brazilian Guideline on Arterial Hypertension	Non-pharmacological adherence assessed with weight and AC control, the practice of physical activity and alcohol consumption	Higher adherence: age (patients older than 65 years of age showed better adherence), limited alcohol consumption, smoking, comorbidity such as diabetes mellitus and use of medication to treat other chronic diseases and the duration of treatment for AH. Non-adherence: female sex, income and paid work and the use of β-blockers. All with p < 0.05.

Table 2. (continued)

Author (year)[reference] Country Study Design	Sample size Mean age	Intervention characteristics	Adherence Measurement	Results
Östbring *et al.* (2021)[38] Sweden RCT	316 patients Intervention: 68.3 (±SD 8.9) Control: 68.6 (±SD 8.6)	Intervention: standard care plus individualized follow-up program that included medication review and motivational interviewing (MIMeRiC) Control: standard care	Assessed through 2 methods: - self-reported adherence to cholesterol-lowering drug regimens (MMAS-8) - refill adherence and PDC	The intervention did not improve the clinical outcomes for LDL-C (p = 0.263), BP (p = 0.865) and quality of life (p = 0.485). More intervention than control patients were adherent to cholesterol-lowering drugs (p = 0.033), aspirin (p = 0.036) and had lower concern scores than patients in the control group (p = 0.035).
Padilha *et al.* (2021)[8] Brazil Cross-sectional	198 patients 65.8 (±SD11.4)	Patients had 3 questionnaires to fill out: - Morisky Green test, to assess pharmacological adherence (dependent variable) - variables subdivided in the 5 WHO proposed dimensions, that can interfere with patient adherence - knowledge about CAD	MMAS-4 – self-reported questionnaire Patient is considered non-adherent with 1 affirmative answer out of 4 questions	Most patients were non-compliant (57.1%). Fatigue (p = 0.01), palpitations (p = 0.042) and medical insurance (p = 0.035) were associated with adherence. Lack of adherence was associated with treatment complexity (p = 0.042), alcohol consumption (p = 0.012) and public health care system use (p = 0.048).
Persaud *et al.* (2021)[39] Canada RCT	786 patients Intervention: 51.0 (±SD 14.2) Control: 50.4 (±SD 14.3)	Intervention: free access to 128 essential medicines including antibiotics, analgesics, antipsychotics, antiretrovirals, glucose-lowering medicines, and antihypertensives Control: usual access to medicines	Through patient report and reviews of prescriptions in medical records at 24 months. Non-adherence if <80% of doses taken	Free distribution of essential medicines substantially increased adherence in comparison to the usual access group (p = 0.004). However, there was no statistically significant differences for the clinical outcomes, such as control of diabetes (p = 0.302), SBP (p = 0.210) or LDL-C (p = 0.130).
Sohn *et al.* (2021)[40] South Korea Prospective cohort	600 patients 58.6(±SD13.4)	Treatment patterns were used to examine whether physicians followed GBP. Therefore, this study compared clinical and patient-reported outcomes between GBP and non-GBP groups, and between adherent and non-adherent groups.	Self-reported adherence MMAS-8, an 8-item scale with three levels of adherence (high, medium, low)	A higher BP control rate was present in patients who were on GBP and also showed better results than those on GBP, but not adherent, or non-GBP patients (p < 0.001). The adherence percentage was 36.7% at baseline, increasing to 49.2% at 6 months (p < 0.001). The same outcomes were found for treatment satisfaction and QoL (p < 0.05).
Sung *et al*. (2021)[41] South Korea RCT	145 patients 56.0 (±SD15.3)	Intervention: one-pill (triple-component SPC, olmesartan/amlodipine/hydrochlorothiazide) Control: two-pill (dual-component SPC + one free pill: olmesartan/hydrochlorothiazide + amlodipine) Both for HTN treatment and maintained for 12 weeks	Measured through MEMS, calculating PDT and PDTc. For example: PDT = Number of doses taken / Number of prescribed doses × 100%	The SPC group had significantly higher PDT and PDTc, so better adherence than the two-pill group (p = 0.04). BPs, both at home and in clinic, tended to decrease more in the single-pill group than the two-pill group, but that difference was not statistically significant (all p >0.4). Home SBP at the end of the follow-up period was significantly lower in the SPC group than in the two-pill group (p = 0.04).

Table 2. (continued)

Author (year)[reference] Country Study Design	Sample size Mean age	Intervention characteristics	Adherence Measurement	Results
Thompson *et al.* (2021)[42] United Kingdom RCT	200 patients 66.0 (±SD 9.0)	After initial contact, patients had weekly telephone clinic assessments for 6 weeks and then randomised to: Intervention: PCI Control: placebo	- self-reported with questionnaire - direct assessment with HPLC MS for detection in urine samples	Self-reported adherence was >96% for all drugs in both groups and direct measurement was >90% for almost all drugs, at pre-randomization and follow-up. There were no differences at pre-randomization or at follow-up between PCI and placebo and no differences between self-reported and direct adherence, owing to near-perfect adherence levels by both measures.
Turakhia *et al*. (2021)[43] USA RCT	139 patients 65.02 (±SD9.6)	Intervention: medication and refill tracking phone app, daily app-based reminders, adaptive text messaging and phone-based counselling for severe non-adherence Control: usual care	MMAS-8, adherence data from applications and estimated based on refill pill counts using a validated PDC algorithm	PDC had no statistically significant difference between groups (p=0.62). There was no difference in secondary outcomes of the proportion with PDC ≥ 80% (p = 0.62), medication persistence (p = 0.12), or change in MMAS-8 (p = 0.76). Only hyperlipidaemia was associated with non-adherence (p = 0.01).
Valsaraj *et al.* (2021)[44] India RCT	67 patients Intervention: 43–65 (67%) Control 43-65 (66%)	Intervention 10 individual sessions conducted on a weekly basis of cognitive behaviour therapy (CBT) Control: Usual care with non-directive counselling	Haemodialysis adherence method with 5 subscales: Laboratory and clinical data, dialysis, fluid, diet and drug adherence	At 6 months, there was a significant reduction in IDWG in the CBT group (p = 0.001), SBP (p = 0.001) and DBP (p = 0.001) vs. control. There was an increase in haemoglobin (p = 0.001), dialysis, fluid and drug adherence scores (all p = 0.001) in the CBT group at 6 months compared to the control group.
Vieira *et al.* (2021)[5] Brazil Quasi-Experimental	32 patients 71.4 (±SD 5.6)	Intervention: patients used a medication reminder device (Supermed) Comparison was made between different measurement periods: pre-intervention, intervention day and post-intervention, with the outcomes (SBP, DBP, medication adherence and satisfaction survey.	MMAS-4 – self-reported questionnaire Score range 0-4; higher score = greater adherence	Adherence improved between pre and post-intervention (p < 0.001). Mean SBP and DBP differences between intervention day and post-intervention were 18.5mmHg (p < 0.0001) and 4.3mmHg (p < 0.007), respectively, and the differences between mean SBP and DBP between pre-intervention and post-intervention were 21.6mmHg (p < 0.001) and 4.7mmHg (p < 0.001), respectively.
Vluggen *et al.* (2021)[45] Netherlands RCT	478 patients 60.2 (±SD 6.78)	Intervention: eHealth program, My Diabetes Profile (MDP), on treatment behavior adherence in patients with T2DM for 6 months Control: usual care as part of a waiting-list	ProMAS self-reported questionnaire. Score range 0-18; higher score = greater adherence	Overall treatment adherence improved significantly in the intervention group compared with the control group (p = 0.03). A significant decrease was observed only in caloric intake from unhealthy snacks in comparison with the control group (p = 0.002). For adherence to PA (p = 0.27), OHAs (p = 0.08), and insulin therapy (p = 0.10), no significant changes were observed.

Table 2. (continued)

Author (year)[reference] Country Study Design	Sample size Mean age	Intervention characteristics	Adherence Measurement	Results
Garmendia *et al.* (2021)[46] Argentina RCT	90 patients 63 (±SD 9)	Intervention: Instructions of control group + access to free of charge smartphone digital app acting as medication reminder (MyTherapy®) Control: Written instructions of prescribed pharmacological treatment	Self-reported adherence MMAS-8, an 8-item scale 8 – totally adherent 6 or 7 – partially adherent <6 – less adherent	At 90 days, 67.4% (31/46) of patients using the smartphone application were adherent compared with 20.5% (9/44) of patients in the control group ($p < 0.001$). The intervention group had significantly higher MMAS-8 scores compared to the control group ($p < 0.001$). There were no differences between groups at baseline characteristics in relation to the previous medication, except for ACEI/ARB2 ($p = 0.049$).
Paczkowska *et al*. (2021)[47] Poland Cross-sectional	488 patients 63.7 (±SD13)	Patients were evaluated through questionnaire: - Sociodemographic data - 20 clinical questions: level of knowledge regarding therapeutic options, prevention, risk factors for HTN and complications of HTN - 5 questions regarding treatment adherence	Self-reported adherence questionnaire, with 5 questions (regular use of AHd, BP monitoring, PA, weight control and dietary sodium chloride restriction)	Patients with higher level of education, at specialist AH clinics and hospital wards had better knowledge on AH ($p = 0.0034$ and $p = 0.01$). Knowledge level depends on patient's education, source of income, and medical care site (all $p < 0.05$). Level of patient knowledge on AH had a significant effect on its improved treatment, with lower values of SBP and DBP ($p < 0.0001$). Patients with good knowledge were significantly (all $p < 0.0001$) more adherent to all 5 TA questions compared to patients with average or poor knowledge.

Abbreviations: USA, United States of America; RCT, randomized controlled trial; SD, standard deviation; CI, confidence interval; BP, blood pressure; ICC, intraclass correlation coefficient; LDL-C, low-density lipoprotein cholesterol; BAS, Behavioral Adherence Scale; IQR, interquartile range; ARMS, Adherence to Refills and Medication Scale; HF, heart failure; MOS-SAS, Medical Outcomes Study-Specific Adherence Scale; DKQ.24, Diabetes Knowledge Questionnaire with 24 questions; MGLMAS, Morisky Green Levine Medication Adherence Scale; OR, odds ratio; PAM, Program on Adherence to Medication; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; APT, anti-platelet therapy; CCI, Charlson comorbidity index; NOAC, new oral anticoagulants; BIPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; AC, abdominal circumference; AH, arterial hypertension; MIMeRiC, Motivational Interviewing and Medication Review in Coronary heart disease; MMAS-8, Morisky 8-item adherence scale; PDC, proportion of days covered; MMAS-4, Morisky 4-item adherence scale; GBP, guideline-based practice; QoL, quality of life; SPC, single-pill combination; MEMS, medication event monitoring system; PDT, percentage of doses taken; PDTc, percentage of days on which the prescribed dose was taken correctly; HPLC MS, high performance liquid chromatography-tandem mass spectrometry; PCI, percutaneous coronary intervention; IDWG, interdialytic weight gain; T2DM, type-2 diabetes mellitus; ProMAS, Probabilistic Medication Adherence Scale; PA, physical activity; OHAs, oral hypoglycemic agents; ACEI, angiotensin-converting-enzyme inhibitors; ARB2, angiotensin II receptor blockers; AHd, antihypertensive drug; TA, treatment adherence.

Table 3. Quality assessment of Randomized Controlled Trials with Cochrane's Collaboration Tool (RoB 2.0).

Study	D1	D2	D3	D4	D5	Overall
Andreae *et al.* (2021)[27]	+	−	+	+	+	−
Bruggmann *et al.* (2021)[29]	−	✕	+	+	+	✕
Dessie *et al.* (2021)[30]	+	+	+	+	+	+
Kassavou *et al.* (2021)[33]	+	+	+	+	+	+
Li *et al.* (2021)[34]	+	+	+	+	+	+
Östbring *et al.* (2021)[38]	−	+	−	+	+	−
Persaud *et al.* (2021)[39]	+	−	+	+	−	−
Sung *et al*. (2021)[41]	+	+	−	+	−	−
Thompson *et al.* (2021)[42]	+	+	+	+	−	−

Domains

D1: Risk of bias arising from the randomization process

D2: Risk of bias due to deviations from the intended interventions

D3: Risk of bias due to missing outcome data

D4: Risk of bias in measurement of the outcome

D5: Risk of bias in selection of the reported result

Judgement of risk of bias

✕ High

− Some concerns

\+ Low

Table 3. (continued)

Study	D1	D2	D3	D4	D5	Overall
Turakhia et al. (2021)[43]	+	−	+	×	−	×
Valsaraj *et al.* (2021)[44]	+	+	+	+	+	+
Vluggen *et al.* (2021)[45]	+	+	+	+	+	+
Garmendia *et al.* (2021)[46]	−	−	+	+	+	−

Domains

D1: Risk of bias arising from the randomization process

D2: Risk of bias due to deviations from the intended interventions

D3: Risk of bias due to missing outcome data

D4: Risk of bias in measurement of the outcome

D5: Risk of bias in selection of the reported result

Judgement of risk of bias

× High

− Some concerns

+ Low

Table 4. JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	%yes/risk
Farías-Vílchez *et al.* (2021)[31]	✓	✓	✓	✓	--	--	✓	✓	75.0% / Low
Guimarães *et al.* (2021)[32]	✓	✓	✓	✓	✓	✓	✓	✓	100% / Low
Lima *et al.* (2021)[13]	--	✓	✓	--	--	--	✓	✓	50.0% / High
Lima *et al.* (2022)[6]	✓	✓	--	✓	?	✓	--	✓	62.5% / Moderate
Llorca *et al.* (2021)[35]	✓	✓	✓	✓	✓	✓	✓	✓	100% / Low
Martins *et al.* (2021)[36]	✓	✓	✓	✓	?	✓	✓	✓	87.5% / Low
Nascimento *et al.* (2021)[37]	✓	✓	--	✓	--	--	✓	✓	62.5% / Moderate
Padilha *et al.* (2021)[8]	✓	✓	✓	✓	--	--	--	✓	62.5% / Moderate
Paczkowska *et al*. (2021)[47]	✓	✓	✓	--	✓	✓	✓	✓	87.5% / Low

Q1) Were the criteria for inclusion in the sample clearly defined?; Q2) Were the study subjects and the setting described in detail?; Q3) Was the exposure measured in a valid and reliable way?; Q4) Were objective, standard criteria used for measurement of the condition?; Q5) Were confounding factors identified?; Q6) Were strategies to deal with confounding factors stated?; Q7) Were the outcomes measured in a valid and reliable way?; Q8) Was appropriate statistical analysis used?

✓ - Yes
-- - No
? - Unclear
NA - Not applicable

Table 5. JBI Critical Appraisal Checklist for Cohort and Quasi-Experimental Studies (non-randomized experimental studies)

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	%yes/risk
Baptista *et al.* (2021)[28]	✓	✓	✓	--	✓	--	✓	✓	✓	**NA**	**NA**	77. (7)% / Moderate
Kim *et al.* (2021)[14]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100% / Low
Sohn *et al.* (2021)[40]	✓	✓	✓	**?**	✓	✓	✓	✓	--	--	✓	72. (72)% / Moderate
Vieira *et al.* (2021)[5]	✓	✓	✓	--	✓	✓	✓	✓	✓	**NA**	**NA**	88.(8)% / Low

Cohort checklist - Q1) Were the two groups similar and recruited from the same population?; Q2) Were the exposures measured similarly to assign people to both exposed and unexposed groups?; Q3) Was the exposure measured in a valid and reliable way?; Q4) Were confounding factors identified?; Q5) Were strategies to deal with confounding factors stated?; Q6) Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?; Q7) Were the outcomes measured in a valid and reliable way?; Q8) Was the follow up time reported and sufficient to be long enough for outcomes to occur?; Q9) Was follow up complete, and if not, were the reasons to loss to follow up described and explored?; Q10) Were strategies to address incomplete follow up utilized?; Q11) Was appropriate statistical analysis used?

Quasi-experimental checklist - Q1) Is it clear in the study what is the 'cause' and what is the 'effect' (i.e., there is no confusion about which variable comes first)?; Q2) Were the participants included in any comparisons similar?; Q3) Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?; Q4) Was there a control group?; Q5) Were there multiple measurements of the outcome both pre and post the intervention/exposure?; Q6) Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?; Q7) Were the outcomes of participants included in any comparisons measured in the same way?; Q8) Were outcomes measured in a reliable way?; Q9) Was appropriate statistical analysis used?

✓ - Yes
-- - No
? - Unclear
NA - Not applicable

4. DISCUSSION

This systematic review accounted for a widespread range of nationalities, addressing each global continent. This is likely the result of our search method, in which the MeSH keywords, free-text terms used and the inclusion of Portuguese, Spanish and French languages, besides English, in the 4 different databases were able to collect studies from countries across the world. 9 out of the 26 selected studies, approximately 34.6%, were conducted in South America, 3 out of 26 in North America, approximately 11.5%, 8 out of 26 in Europe, approximately 30.8%, only 1 out of 26 in Africa and also in Oceania, approximately 3.8% each, and 4 out of 26 coming from Asia, approximately 15,4%. The high number of articles coming from South America and Europe is probably due to an increased keyword accuracy of SciELO database with more studies accounting for the eligibility criteria, such as the aforementioned. Studies were included if the sample mean age (or its standard deviation or interquartile range) was within the patient age group of 50-69 years old.

A total of 22 of the included studies used self-reported methods as one of the adherence measurement tools. The completion of questionnaires, forms or interviews is a widely applied instrument and is considered the most applicable strategy in clinical practice due to its practicality and low cost.[32] Two of the most frequent self-reported adherence tools were the four-item Morisky Medication Adherence Scale (MMAS-4) and the more recent 8-item version (MMAS-8). These methods have proven to be valuable, simple, economic and feasible diagnostic tools to address medication non-adherence and compliance.[48,49] MMAS-8 was developed as an extension of the questionnaire that deepens the interpretation of adherence behaviours and shows better psychometric elements for outcome evaluation and minimizes several biases,[50] when compared to MMAS-4, with sensitivity and specificity of 93% and 53% for non-adherence.[43] However, there are limitations in the use of self-reported measurement of adherence, as it can underestimate or, more frequently, overestimate the result.[32,40] Subjective assessment is vulnerable to the possibility of reporter bias,[9] social desirability bias,[8,27,30] the Hawthorne Effect[43] and behaviour overestimation,[45] making available data error-prone. Another method that is commonly used by physicians and present in 5 of the included studies is refill adherence evaluation with reviews of prescriptions or objective pill counts, which also has similar limitations because of its partially subjective nature, making available data possibly unreliable.[42] A patient can refill his prescription, but this does not guarantee adherence. In contrast, and also a possible way to reduce such biases, as stated in other studies,[40,45] is the objective method that can precisely determine the treatment adherence of patients with the biochemical measurement of blood or urine samples to detect the presence or absence of the drug or its metabolites. As explained in some studies, it is an increasingly

available tool to be used as a direct, objective, specific and sensitive method to assess adherence.[33,42] Although, once again, it also has disadvantages of being costly, requiring significant technical expertise to develop and provides an estimate of adherence over a point period,[51] being at risk of the “white coat adherence” phenomenon, that occurs when the patient takes the drug before the measurement to avoid non-adherence detection.[42] Thus, we can conclude that each method of adherence evaluation has strengths and limitations and none is specific to an intervention or desired outcomes. As several studies suggest,[32,38,52] the combination of different measures operating together can emerge as the closest method to patients' real adherence.

The included studies differ not only in study design, but also in their primary, secondary outcomes and ultimately, study aim. For some of them, the aim was to evaluate the effectiveness of an intervention (for instance behavioural intervention or the feasibility of smartphone applications) to improve adherence, while others focused on establishing statistical association between adherence and several different factors, such as patient-related (e.g., comorbidity[14]) or health-service related (e.g., use of private outpatient clinic compared to public clinic[6]).

Our study focused on finding the main determinants of therapeutical adherence in the patient age group 50-69 years old and attempting to anticipate which patients should receive extra attention and interventions, in order to optimize adherence. In other words, what are the factors associated with therapeutical adherence and non-adherence, and which interventions proved to be efficient and feasible in clinical practice. Out of the 16 experimental studies, only 2 of them did not reach statistical improvement of adherence. This proves that the majority of the interventions, whether behavioural and motivational strategies or eHealth programmes, can improve overall pharmacological and non-pharmacological adherence, with the patient dynamically changing from a passive role into an active participant in the treatment process, acquiring accurate beliefs and increasing confidence in decision-making of medication use or lifestyle adoption self-efficacy. However, 7 out of 16 experimental studies either failed to reach significant association with clinical outcomes or they were not assessed. This is likely due to the fact that optimal adherence precedes the control of clinical outcomes, such as blood pressure, glycaemia or LDL-cholesterol levels. Therefore, as some of the studies mentioned, if adherence effects were sustained for a longer period, the intervention would also impact over the clinical outcomes.[33,38]

eHealth interventions are an attractive and rising modality, as more people have access to a variety of digital technologies, such as telehealth consultations and smartphone applications.[34,45] These offer a cost-effective, practical and helpful approach, with the ability to provide medication reminders, prescription refill notifications and automated adherence tracking,[42] especially important in the management of patients with chronic diseases.[30] Its

usefulness is particularly relevant in the midst of the COVID-19 pandemic, since the gap between healthcare visits, up to several months apart,[34] and necessary social distancing measures led to the adaption of healthcare services and physicians to conduct appointments and clinical reviews using telehealth and electronical schemes to ensure medication adherence sustainability.[42]

Other interventions such as the free access to essential medicines with improved adherence and reduced healthcare costs are findings that could support policy changes in countries planning to implement universal healthcare that includes access to medicines, mainly where medication cost is a significant non-adherence determinant.[39] The use of a single pill regimen, as already recommended by major guidelines, revealed to be a simple, easy, and feasible scheme to improve medication adherence, especially in patients with lower motivation.[41] Our included study provided a high level of supporting evidence for these recommendations.

As for behavioural and motivational strategies, person-centred consultations on medication use, specifically targeting medication beliefs,[38] can have a significant impact on compliance when used as an adjunct therapy for patients.[44] The behavioural interventions attempt in, more or less, adopting the patient-centred clinical model, to enhance patient adherence, which includes six dimensions: exploring both the disease and the illness experience, understanding the whole person, finding common ground, incorporating prevention and health promotion, being realistic and, thus, enhancing the doctor-patient relationship.[53,54]

The interventions also share the ultimate goal of increasing patient knowledge. It is relevant to identify patients with low levels of knowledge about their disease and enlighten them with interventions.[31] Higher levels of patient knowledge is associated with greater health literacy. A patient in the possession of adequate health literacy will more likely adopt responsible adherence behaviours.[37,55,56] Interventions aimed at health education and promotion should be prompted to improve the health literacy.[23] Ultimately, by increasing knowledge and health literacy, we increase therapeutic adherence. Same is identified with the educational level, since a low educational level is associated with poorer health literacy.[23]

Some factors can be explained, at greater or lower extent, with the Health Belief Model. Those were the factors increasing adherence: hospitalization history, symptomatic patients with fatigue and palpitations, severe disease course in comparison to mild, aspirin taking, comorbidity such as diabetes mellitus and use of other medication to treat other chronic diseases. Also, the factors decreasing adherence: less than 4 total prescribed drugs, aspirin monotherapy and starting therapy with clopidogrel. This theoretical model, which is specifically mentioned in some of the included studies,[8,14,41] demonstrates that, when patients believe they are ill, they are more likely to embrace healthy behaviours, including being more adherent to prescribed medications and lifestyle changes.[19] The more severe the clinical presentation, the

more concerned patients get and the more adherent they become. Also, patients with comorbidities, such as diabetes mellitus tend to produce more noticeable effects that motivate adherence, or maybe because regular clinical check-ups are required, so the benefits of adherence are tangibly noticed.[34] Taking less than 4 medications was also an adherence factor, while polypharmacy and treatment complexity was associated with non-adherence in 2 and 3 studies, respectively. The reasons for these determinants are forgetfulness, neglect,[8] confusion, and cognitive or pill burden associated with frequent and complex medication regimens,[32,34,35] and difficult incorporation in the patient's routine.[8] Also, polypharmacy increases the risk of drug interactions and adverse events, which can additionally compromise adherence.[13,57] Married civil status, as demonstrated in some studies,[32,58,59] can have a protective effect, attributed to behaviour changes and social support resulting from the union and the established family bond, a fundamental part of the health-disease process. This can explain why single civil status was associated with non-adherence. Alcohol consumption is related to low adherence and the reason can be due to the fear of possible undesirable effects of the association of medications with alcoholic beverages.[8] Patients from rural or urban marginal areas generally are repelled by various barriers when accessing health care services, for instance reduced number of health care institutions, fewer physicians, smaller opportunity to consult specialists, financial constraints, social isolation, longer distances to healthcare facilities and difficulties in transportation.[14,60,61] Comorbidity is an important obstacle to adherence, possibly due to poorer overall functional ability that makes optimal adherence challenging.[14,62] Some of the included studies mentioned older age to be both an adherence[36,37] and a non-adherence factor,[14] with one study also associating younger age to lower adherence levels.[35] On the one hand, impairment of cognitive and physical function, that undeniably increase with age,[14,63] are independent risk factors that increase non-adherence to medication.[64] On the other hand, once again in light of the Health Belief Model, because older patients generally have greater severity of illness than younger ones, they raise their awareness and concerns about their health status, culminating in improved adherence.[64]

Contradictory factors found in this systematic review (e.g., smoking increasing adherence) can be explained in light of the adherence measurement methods significant heterogeneity. Using the previously mentioned example, this study evaluated adherence according to weight and abdominal circumference control, where the effects of nicotine led to weight loss, generally due to an increased metabolic rate at rest and to the inhibition of appetite.[37] In the same study, the female gender is also associated with non-adherence, which can be explained by the higher distribution of adipose tissue and lower muscle mass of women, especially after menopause. This perfectly highlights how the determinants present in this review are dependent on the adherence instrument used. The variability is also explained by the presence of several other study parameters: some are disease-specific (e.g., room sharing)[36]; others are

healthcare and health system-specific (e.g., public vs. private care,[6,47] medical insurance)[8] which can be interpreted as evidence that determinants can also differ between countries and respective health systems; eligibility criteria, baseline characteristics, sample size, gender, sociodemographic and cultural status of the study may also fluctuate some results found (e.g., use of calcium-channel blockers[32] and β-blockers[37] associated with low adherence, employment vs. unemployment,[6,47] high vs. low socioeconomic level,[36] higher income vs. lower income).[6,14,37] On the one hand, higher income and socioeconomic level enables patients to buy their medication and have easier access to healthcare services, but also patients with low socioeconomic status can have greater adherence, probably because they are usually more receptive to medical counselling.[36] On the other hand, a lower income and socioeconomic level is associated with non-adherence, for the inverse reason mentioned previously, as patients struggle with their treatment purchase and access to healthcare services. Such determinants that can present simultaneously as adherence and non-adherence factors must be viewed with caution, as they should be seen as "study-specific".

These were all the determinants of adherence found within the projected 50-69 age group. The main strength of this systematic review is its compelling unique nature, as no other study in literature addressed the same design and objective.

4.1 Limitations

There are limitations to this systematic review. As discussed above, there was considerable heterogeneity in study designs, aims and outcomes in the qualitative analysis among studies, which makes clear comparisons difficult. The search strategy, which involved the free version of Covidence with only 500 studies allowed to be included. This might introduce selection bias, as the main researcher attempted to gather studies from the different databases, in order to attain the 500 articles. We did not measure the quality of evidence or study design against reported results, as it is not a meta-analysis. Lastly, quality assessment of the included studies was variable with a total of 6 randomized controlled trials judged to be with some concerns in at least one domain and 2 to be of high risk in at least one domain. Also, for the observational studies, 5 were evaluated as moderate risk while 1 was of high risk. The above-mentioned limitations highlight that the results interpretation and investigation should be made with caution.

5. CONCLUSION

There is no gold standard for the measurement of adherence, thus it is advised to combine different methods in order to obtain an authentic evaluation. The behavioural, digital and

remaining interventions to improve treatment adherence were efficient and feasible, revealing to be potentially beneficial adjuncts in primary care. The main determinants of adherence found in the qualitative analysis, for the individuals between 50 to 69 years of age, were knowledge and educational level, treatment complexity, polypharmacy, single civil status, comorbidity, rural or urban marginal residency, alcohol consumption and older age. For the ultimate goal of improving adherence, it is crucial to identify specific barriers for each patient population group that is more likely to be less adherent and adopt suitable strategies to overcome them.

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