

INTRODUCTION

- Adherence to prescribed therapy is a primary determinant of treatment success.^{1,2}
- Non-adherence may worsen therapeutic and economic outcomes, due to an increased risk of adverse clinical outcomes, increased frequency of physician consultations, higher rates of hospitalisation, and increased healthcare costs.^{1,3-5}
- Among patients with cardiovascular diseases (CVDs), approximately one-third are estimated to be affected by non-adherence to their medications.⁶
- Various approaches to improve CVD medication adherence (MA) and persistence have been studied,⁷ however there is a need for an up-to-date understanding of the evidence on health education programs, digital applications, and phone reminders for patients with hypertension or dyslipidaemia.

OBJECTIVE

To identify and synthesize evidence on the impact of non-pharmacological interventions on MA and persistence among patients with hypertension or dyslipidaemia.

METHODS

- We conducted a systematic literature review (SLR) of randomised controlled trials (RCTs) investigating ≥50 adult patients with hypertension or dyslipidaemia, published from July 2011 to July 2021. Eligible studies evaluated the effect of health education (HE), digital applications (DAPP), or phone reminders (PR) on MA or persistence.
- Data extracted included details of study, intervention characteristics, MA and persistence outcomes. We categorized intervention approaches according to definitions shown in **Table 1**, with reference to guidelines for reviews of complex interventions.⁸⁻¹⁰
- We synthesized data narratively using effect direction plots.¹¹ Quality assessment was performed for each study using the Cochrane Risk of Bias 2 tool.¹²

Table 1. Definitions of intervention categories applied in this review

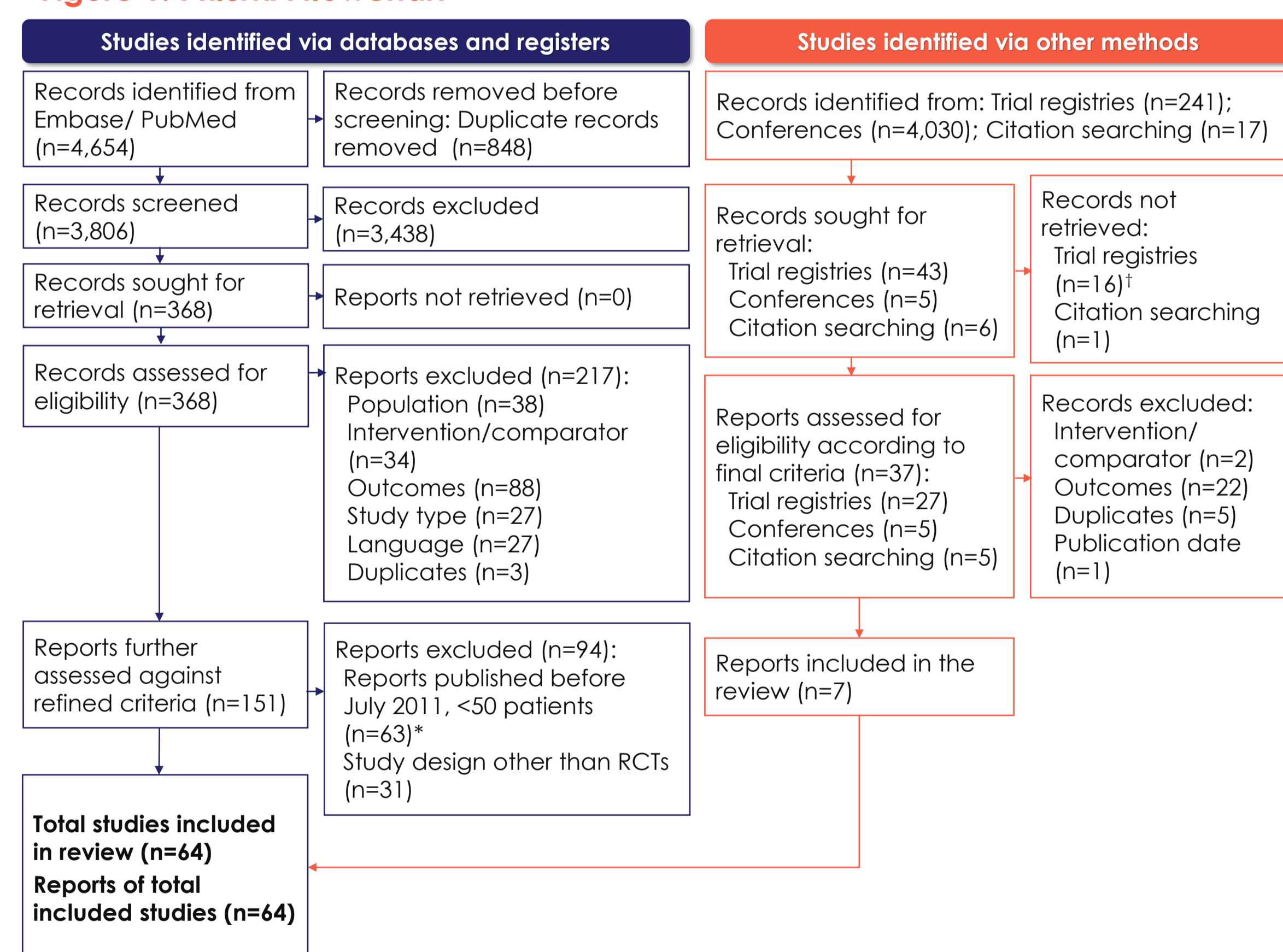
Item	Definition	Reference
Health education	Every intervention where a professional provided any kind of knowledge (e.g., medication information, disease state information, importance of adherence information), in any form (e.g., written, oral, in group, by telephone), to a patient with the aim of modifying patient's beliefs, attitudes or skills that facilitate adherence.	Wiecek <i>et al.</i> , 2019 ¹³
Digital application	App-based intervention delivered through a smartphone, tablet computer, or personal digital assistant to help, support, or give advice about medication adherence.	Armitage <i>et al.</i> , 2020 ⁴
Phone reminders	Telephone reminders / calls / SMS intended to remind patients to take their medication or refill their prescription	-

Blood pressure (BP) monitor device was defined as any intervention including monitoring device for recording of BP level features; Usual care was defined as standard of care or usual care considered as the usual care defined in the primary study¹³; Enhanced usual care was defined as standard of care or usual care, plus a short action implemented or given only at baseline and not intended to be the intervention being assessed

RESULTS

- Of 3,806 citations retrieved, a total of 64 studies were included in this SLR (52 RCTs and 12 cluster RCTs) (**Figure 1**).

Figure 1. PRISMA flowchart



RCT: randomised controlled trial; SLR: systematic literature review. *Studies published before July 2011 (n=50); studies with number of patients <50 (n=20) of which seven were published before 2011. †As per Clinicaltrials.gov. 16 studies had no results published. Note that studies identified by other methods (right hand column above) were searched and screened according to the final eligibility criteria.

- Most (68%) were published between 2016 to 2020, and most studies were conducted in the Asia-Pacific region (38%).
- Most studies (86%) had a sample size <600 patients (range: 52–25,388).
- Lengths of follow-up varied from 1 to 60 months.
- The most frequently assessed intervention category of interest was HE (62 studies). PR were assessed by 16 studies, and DAPP by 10 studies. Most studies (58%) evaluated single-modal interventions, and 27 studies assessed multi-modal interventions in which ≥2 intervention categories were implemented within the same intervention.
- All included studies investigated adherence. However, some studies (6%) used the word 'compliance' matching the definition for adherence. The most frequently used methods to assess MA were the Morisky Medication Adherence Scale (MMAS; 30 studies), followed by High Blood Pressure Compliance Scale (HBCS)/Hill-Bone Medication Adherence Scale (HBMAS; n=5), proportion of days covered (PDC; n=4), Medication Adherence Rating Scale (MARS; n=3), Medication Adherence Self-Efficacy Scale (MASSES; n=2), Medication Possession Ratio (MPR; n=2) and the Brief Medication Questionnaire (BMQ; n=2). The method used to assess MA was not specified in 16 studies.

DISCLOSURES

The study was funded by Servier. JBB, EI are employees of Servier; LZ, JL, MKB, and PA are employees of Amaris Consulting who received funding from Servier for the study; ZK is a paid consultant for Servier; APK received an honorarium for his support in the study protocol and results interpretation.

- Studies assessing HE in single-modal interventions largely found improvements in MA (83%) (**Figure 2**). All HE interventions that consisted of a single approach showed improvements in MA. Studies of interventions that consisted of ≥1 HE approach mostly found improvements in MA (72%) in the intervention arm.
- HE was included as part of a multi-modal intervention in 27 studies, of which 20 (74%) reported improvements in MA (**Figure 2**).
- Most studies (81%) assessing interventions that included PR reported improvements in MA (**Figure 2**).
- Studies evaluating interventions that included DAPPs found improved adherence in 8 of 10 studies (80%) (**Figure 2**).

Figure 2. Effect direction plot summarizing adherence and persistence outcomes in all studies

Intervention categories	Study	Study Design	Adherence	Persistence
HE (single component)	Al-Rubaey 2019	RCT	▲	
HE (single component)	Lu 2015	RCT	▲	
HE (single component)	Calvo 2021	RCT	▲ ₅	
HE (single component)	Delavar 2020	RCT	▲	
HE (single component)	Mattei da Silva 2020	RCT	▲	
HE (single component)	Maslakpak 2018	RCT	▲	
HE (single component)	Golshahi 2015	RCT	▲	
HE (single component)	Greer 2015	RCT	▲	
HE (single component)	Parra 2021	RCT	▲	
HE (single component)	Van der Laan 2018	RCT	▲ ₂	
HE (single component)	Varleta 2017	RCT	▲	
HE (single component)	Saleem 2015	RCT	▲	
HE (multicomponent)	Aghakhani 2019	RCT	▲	
HE (multicomponent)	Amer 2018	RCT	▲	
HE (multicomponent)	Obreli-Neto 2011	RCT	▲ ₂	
HE (multicomponent)	Torres-Robles 2021	CRCT	▲	
HE (multicomponent)	Onyinye 2021	RCT	▲	
HE (multicomponent)	Kolcu 2020	RCT	▲	
HE (multicomponent)	Zhang 2019	RCT	▲	
HE (multicomponent)	Kuhmer 2016	RCT	▲ ₂	
HE (multicomponent)	Friedberg 2015	RCT	▲ ₂	
HE (multicomponent)	Migneault 2012	RCT	▲	
HE (multicomponent)	Ashok Kumar 2011	RCT	▲	
HE (multicomponent)	Huang 2018	CRCT	▲	
HE (multicomponent)	Qvist 2020	RCT	▲ ₂	
HE (multicomponent)	Schoenthaler 2020	RCT	▲ ₂	
HE (multicomponent)	Abughosh 2019	RCT	▲ ₃	
HE (multicomponent)	Abughosh 2017	RCT	▲	▲
HE (multicomponent)	Sathvik 2013	RCT	▲ ₂	
HE (multicomponent)	Martin 2011	RCT	▲	
HE + PR	Shelini 2019	RCT	▲	
HE + PR	Byrne 2020	RCT	▲ ₃	
HE + PR	Buis 2017	RCT	▲	
HE + PR	Cicolini 2014	RCT	▲	
HE + PR	Bobrow 2016	RCT	▲ ₃	
HE + PR	Ramanath 2012	RCT	▲ ₂	
HE + PR	Varleta 2018	RCT	▲	
HE + PR	Párraga-Martínez 2018	RCT	▲	
HE + PR	Palileo 2014	RCT	▲	
HE + PR + DAPP	Márquez Contreras 2019	CRCT	▲	
HE + PR + DAPP	Manigault 2020	RCT	▲	
HE + PR + DAPP + BP monitor	Still 2020	RCT	▲	
HE + PR + BP monitor	Margolis 2013	CRCT	▲	
HE + PR + BP monitor	Stewart 2014	CRCT	▲ ₃	
HE + DAPP	Borzogi 2021	RCT	▲ ₂	
HE + DAPP	Sun 2020	RCT	▲	
HE + DAPP	Sartori 2020	RCT	▲	
HE + DAPP + BP monitor	Kim 2016	RCT	▲	
HE + DAPP + BP monitor	Gong 2020	RCT	▲	
HE + DAPP + Other	Du 2020	RCT	▲	▲
HE + BP monitor	Cuffee 2019	RCT	▲	
HE + BP monitor	Kim 2014	RCT	▲	
HE + BP monitor	Ogedegbe 2014	CRCT	▲	
HE + BP monitor	Ogedegbe 2012	RCT	▲	
HE + BP monitor + EMR	Lakshminarayan 2018	RCT	▲	
HE + BP monitor + Other	Wakefield 2012	RCT	▲	
HE + Other	Leiva 2014	RCT	▲	
HE + Other	Shen 2019	CRCT	▲	
HE + Other	Escortell-Mayor 2022	CRCT	▲	
HE + Other	Wei 2017	CRCT	▲	
HE + Other	Beune 2014	CRCT	▲ ₂	
HE + EMR platform	Persell 2018	CRCT	▲ ₂	
PR + electronic pill bottles	Mehta 2019	RCT	▲ ₂	
DAPP + PR + BP monitor	Chandler 2019	RCT	▲	

BP: blood pressure; DAPP: digital application; HE: health education; PR: phone reminders; RCT: randomised controlled trial; CRCT: cluster randomised controlled trial. Effect direction: upward arrow ▲ = positive health impact, downward arrow ▼ = negative health impact, sideways arrow ↔ = no change/mixed effects/conflicting findings. Sample size: Final sample size (individuals) in intervention group; large arrow ▲ >300; medium arrow ▲ 100-300; small arrow ▲ <100. Study quality: denoted by row colour: green = low risk of bias; amber = some concerns; red = high risk of bias.

- Statistical significance of change in MA in the intervention group vs the comparator group at the end of follow-up was assessed by 56 studies. Of these, 50% reported significant improvements favouring the intervention vs comparator, four had conflicting outcomes, and 24 reported non-significant differences. Across all studies assessing statistical significance, no negative trend was reported between the comparator arms.
- Two studies investigated persistence, both finding significant improvements using HE interventions.

CONCLUSIONS

- Most of the studies suggest that 'beyond the pill' approaches using HE, PR, or DAPPs have a positive effect on patient adherence.
- Heterogeneity in the design, conduct and reporting of the studies included in this review varied considerably, limiting the synthesis across studies.
- The evidence base was most established for interventions that included HE. Most of the studies with significant MA improvements included an HE component as part of the intervention.
- Numerically positive evidence was reported for patients using an intervention where a phone reminder was involved. However PR was always assessed in conjunction with other approach(es), and consequently the contribution of this approach is unclear.
- The benefit of digital applications on adherence remains to be clarified as all the studies using this approach included an HE or PR component, making the interpretation of the results complex.

REFERENCES

- Jimmy B, et al. *Oman Med J*. 2011;26(3):155-159.
- Osterberg L, et al. *NEJM*. 2005;353:487-97.
- Adherence to long-term therapies: evidence for action. Geneva, Switzerland: World Health Organization; 2003.
- Armitage LC, et al. *BMJ Open*. 2020;10:5.
- Demonceau J, et al. *Drugs*. 2013;73:545-62.
- Chang TE, et al. *Hypertension*. 2019;74:1324-32.
- Anderson LJ, et al. *Am J Health Syst Pharm*. 2020;77:138-47.
- Higgins JPT, et al. *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 2022.
- Guise J-M, et al. *J Clin Epidemiol*. 2014;67:1181-91.
- Guise J-M, et al. *Systematic Reviews of Complex Multicomponent Health Care Interventions*. 2014;11.
- Boon MH, et al. *Research Synthesis Methods*. 2021;12:29-33.
- Sterne JAC, et al. *BMJ*. 2019;366:14898.
- Wiecek E, et al. *PLoS One*. 2019;14:e0213432.