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INDIVIDUAL INTERVENTIONS TO IMPROVE ADHERENCE TO PHARMACEUTICAL TREATMENT, DIET AND PHYSICAL ACTIVITY AMONG ADULTS WITH PRIMARY HYPERTENSION. A SYSTEMATIC REVIEW PROTOCOL.

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INDIVIDUAL INTERVENTIONS TO IMPROVE ADHERENCE TO PHARMACEUTICAL TREATMENT, DIET AND PHYSICAL ACTIVITY AMONG ADULTS WITH PRIMARY HYPERTENSION. A SYSTEMATIC REVIEW PROTOCOL.

Authors

1. Dora Inés Parra, Nursing School professor at Universidad Industrial de Santander, Bucaramanga, Colombia. Clinical and Community Nursing Doctoral student, Universidad de Valencia, Spain. e-mail: doiparra@uis.edu.co

2. María Isabel Trapero Gimeno, Nursing and Podology School professor at Universidad de Valencia, Spain. e-mail: isabel.trapero@uv.es.

3. Javier Mauricio Sánchez Rodríguez, Fundación Universitaria Sanitas professor. Bogotá, Colombia. e-mail: jmsanchezro@unisanitas.edu.co.

4. Lizeth Catherine Rodríguez Corredor, assistant physiotherapy professor at Fundación Universitaria de Ciencias de la Salud, FUCS, Bogotá, Colombia. e-mail: lizk263@hotmail.com.

5. Juliana Alexandra Hernández Vargas, epidemiologist at Colombian High Cost Diseases Fund, Bogotá, Colombia. e-mail: jhernandez@cuentadealtocosto.org.

6. Luis Alberto López Romero, epidemiologist, Fundación Cardiovascular de Colombia. e-mail: alberlop25@hotmail.com.

7. Fernando García López, epidemiologist, Centro Nacional de Epidemiología. Instituto de Salud Carlos III, Madrid, Spain. e-mail: fjgarcial@isciii.es.

8. Cristina Escudero-Gómez, documentalist, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain. e-mail: cescuderog@salud.madrid.org.

9. Silvia Juliana Trujillo Cáceres, epidemiologist at Colombian High-Cost Diseases Fund Account, Bogotá, Colombia. e-mail: strujillo@cuentadealtocosto.org

10. Pilar Serrano Gallardo, Nursing Department professor, School of Medicine at Universidad Autónoma de Madrid, España. e-mail: pilar.serrano@uam.es.

11. Lina María Vera Cala, Public Health Department professor at Universidad Industrial de Santander, Bucaramanga, Colombia. e-mail: limavera@uis.edu.co.

Correspondence author

Dora Inés Parra, associated professor, School of Nursing, Universidad Industrial de Santander; Bucaramanga, Colombia. Clinical and Community Nursing doctorate student, Universidad de Valencia, Spain.

Address: Calle 32 #32-70, Bucaramanga, Colombia, Postal code: 680002. Phone: +57 6345745 e-mail: doiparra@uis.edu.co.

Lina María Vera Cala, Public Health Department professor at the School of Health, Universidad Industrial de Santander, Bucaramanga, Colombia. e-mail: limavera@uis.edu.co.

ABSTRACT

Introduction. Hypertension is a chronic disease with 31% worldwide prevalence in adults. It has been associated with non-adherence to therapeutic regime with a negative impact on the prognosis of the disease and healthcare associated costs. The previous makes it necessary to identify effective interventions to improve adherence among this population. The objective of this protocol is to describe the methodology in a systematic review that will evaluate the effect of individual interventions to improve adherence to the prescribed pharmacologic treatment, diet and physical

activity in adults with primary hypertension.

Methods and analysis: Systematic search of randomized and non-randomized clinical trials will be conducted in six databases (PubMed/MEDLINE, BVS, CINAHL, Embase, Cochrane and Scopus). Studies in humans, published between 2009 and 2019, will be included, without language restrictions. The primary outcome will be a change in adherence measures to pharmacological treatment, diet and physical activity, evaluated through direct and indirect methods. Risk of bias, data synthesis, and analysis by subgroups will be evaluated by means of Review Manager, RevMan 5.3 and Stata 14, in case the criteria for meta-analysis are met.

Ethics and dissemination. Information to be analyzed is of a grouped nature, and given that it sources from published studies, no ethics committee approval is required. Results will be published in scientific journals, and through conferences, seminars, congresses, and symposiums. Copyrights will be respected by corresponding accrediting through the system of bibliographic references.

Key words: Hypertension, interventions, adherence, diet, exercise, adults

Register in PROSPERO (in process): identification number 147655 (7 December, 2019).

Strengths and limitations of this study

_The procedures of the study will be conducted in an independent and blinded manner by at least two reviewers.

_Bibliographic search will have no language restriction.

_Ample modality of individual interventions will be included, and adherence will be evaluated globally (pharmacological treatment, diet and physical activity).

_Variability in adherence measures can be associated with high heterogeneity, which may lead to conduct analysis by sub-groups and meta-regressions.

_The study will be conducted by an interdisciplinary group.

INTRODUCTION

Description of the condition

According to the guidelines of the European Societies of Cardiology and Hypertension (ESC/ESH) 2018, for diagnosis and treatment of hypertension the presence of hypertension is defined with values equal to or over 140 mmHg for arterial systolic pressure, or 90 mmHg for arterial diastolic pressure [1]. It is the most common chronic non-communicable disease, and it has been described as one of the main risk factors associated with cardiovascular morbimortality worldwide [2]. Its occurrence around the world stands at 31.0% (CI 95%: 30.0-32.2), and in low-to-middle-income countries, at 31.5% (CI 95%: 30.2-32.9), or 1, 04 billion adults [3]. As to incidence, a follow-up study in young adults, (median age 33), for over two decades estimated an incidence rate of 58.6 cases per 100,000 people (CI 95%: 52.8-64.9) [4]. According to the World Health Organization (WHO), hypertension in general increases risk of ischemic cardiopathy by three or four [5].

Additionally, prospective studies have shown hypertension to be one of the risk factors with the highest levels (31.0%) of contribution to incidence of cardiovascular events, followed by hypercholesterolemia (27.0%) and smoking (18.0%) [6]. Also, inadequate control of hypertension has been documented to be associated with 58.0% ischemic stroke, 50.0% hemorrhagic stroke, 55.0% ischemic cardiopathies, and 58.0% of other forms of cardiovascular disease [7]. Regarding disability-adjusted life years lost, hypertension is the main reason worldwide, rising from 95.9 million to 143.01 million between 1990 and 2015 [8].

Although efficacious drugs exist [9, 10] that actuate against the disease and prevent its complications, only half the individuals treated achieve proper control of hypertension (11], and many will abandon treatment without consulting with the doctor [9], a fact attributable largely to non-adherence and self-management [12].

Non-adherence to therapeutic regime is a worldwide phenomenon with grave repercussions that, according to the WHO is the consequence of multiple factors and is present in almost all patients with chronic diseases who show high rates of non-compliance [5, 13, 14]. As to hypertension patients, prevalence of adherence to pharmacologic treatment is variable, ranging between 24.1% and 92.7% [15], while for life-style-related aspects, non-compliance figures for physical exercise and diet stand at 68.8% and 30.9%, respectively [16]. The high prevalence of hypertension, non-adherence to therapeutic regime, and the costs arising from associated disabilities, call for search of interventions that will solve this problem efficaciously.

Description of the intervention

Adherence to therapeutic regime is defined as "the degree to which a person's behavior regarding medication intake, proper diet regime and modification of life habits fits the recommendations of their health care provider" [5], and they include both the pharmaceutical and non-pharmaceutical component.

The WHO acknowledges the need to implement effective strategies to achieve changes in health results, because despite advances in treatment of chronic diseases, and research into the problem of adherence, non-adherence remains the single most important reason for unreached hypertension control [17–19]. In this sense, the health team in charge of Primary Health Care (PHC) plays a key role in facing this problem [20, 21] through individual teaching that may be offered thru educational,

behavioral, and affective interventions, or a combination of the previous, (multifaceted) [22,23]. Although diverse studies [22–32] have shown their efficacy to improve adherence and hypertension control, a focus is required not only on the pharmacologic component, but also on life habits related to cardiovascular risk, like physical activity and diet [8, 22,31].

How the intervention might work

Different theoretical models exist to explain the phenomenon of non-adherence to therapeutic regime among chronic disease patients, like the theory of cognition and self-efficacy, and the models of belief in health, behavioral changes, motivation, and self-regulation [34-36]. Self-management has been highlighted recently; it offers chronic disease patients a series of supports to improve confidence, with a positive effect on adherence to therapeutic regime [12, 36–38].

Scientific evidence suggests that interventions developed by the health team to increase adherence to therapeutic regime in hypertension patients have focused mainly on the pharmacologic component, with an emphasis on not only pedagogic component with an individual focus, but also involving other dimensions like conduct and affective factors, or in some cases, combinations of the above mentioned aspects, and they are denominated multifaceted [10, 39, 40].

OBJECTIVES

This article describes the protocol for a systematic review that will evaluate the effects of individual interventions to improve adherence to recommendations of the health provider's team regarding medication treatment, diet and physical activity among adults with primary hypertension.

METHODS AND ANALYSIS

Eligibility criteria of the studies in this review

They were defined in accordance with the criteria included in the PICOt question.

Participants (P)

Adult people aged 18 or older, with primary hypertension diagnosis defined with systolic blood pressure (SAP) ≥140 mmHg or diastolic blood pressure (DAP) ≥90 mmHg, currently receiving PHC or that of a health provider's team, who are also undergoing hypertension treatment. Pregnant women, hospitalized people or with secondary hypertension will be excluded.

Primary hypertension is defined as that whose primary origin cause is unknown, and taken to be linked to genetics, diet, sedentary lifestyle and obesity [41, 42].

On the other hand, secondary hypertension is that resulting from diseases affecting other organs and systems [42, 43].

Types of interventions (I)

The different intervention types are specified next:

-Classification: Educational, behavioral, affective or multifaceted interventions oriented toward the individual will be included.

-Application scenario: outpatient or health provider patient.

-Methodology: in-person and non-in-person strategies.

-Personnel applying the intervention: interventions led by any health team member will be included.

-Objective: improve adherence to medication treatment, diet, and, or physical activity.

Comparison (C)

No comparator will be included, as the objective is to evaluate the effect of the different interventions, rather than of one in particular in any specific manner.

Types of outcome measures (O)

- Primary outcomes

The main result will be the difference of proportions or means in adherence to pharmacologic treatment, diet and physical activity [44-46] pre and post intervention. Measurements can be obtained through direct and indirect methods **(Example Table 1).**

Table 1. Direct and indirect methods reported in literature to evaluate adherence to therapeutic regime.

Pharmacologic treatment	Diet	Prescribed Physical Activity
Tablet Counting	Degree of adherence to diet DASH*	Accelerometry changes International Physical Activity Questionnaire (IPAQ)
Questionnaires (Morisky-Green, MARS, SMAQ)*	Anthropometric changes (IMC, ICC)*	
Electronic monitoring	Lipid profile changes	
Concentration of pharmaceutical or its metabolite in bodily fluids (blood, urine)		Strain test

Directly observed therapy		Six-minute-walk test

MARS (Medication Adherence Report Scale), SMAQ (Simplified Medication Adherence Questionnaire), DASH (Dietary Approaches to Stop Hypertension), BMI (Body Mass Index), WHI (Waist-Hip Index.).

-Secondary outcomes

- Percentage of participants with blood pressure control.
- Rate or proportion of morbimortality by major cardiovascular events (ischemic disease and stroke).
- Incremental rate of cost-effectiveness or cost-efficacy, cost-usefulness of interventions.

Self-reported outcomes such as quality of life and burden of disease.

Types of studies (t)

This review will include randomized and non-randomized clinical trials that have had a comparison group (usual treatment or placebo) related to pharmacologic treatment, diet and physical activity in people with primary hypertension.

Search methods for identification of studies

Electronic search

Systematic electronic search strategy will be designed aiming to locate and retrieve those studies meeting the inclusion criteria established in the PICOt question in the following databases: PubMed/MEDLINE, BVS, CINAHL, Embase, Cochrane and Scopus.

Next is an advanced, independent search for interventions for each event

(medication, diet and physical activity) by means of combination of controlled and free language terms. Search strategies will adapt to database characteristics. The following restrictions will apply: studies conducted in humans, published along 2009-2019. Finally, search process record will be kept for each information source. **(See Table 2. Search Strategy**).

Table 2. Search strategy PICOt

	Participants/patients (P)	Intervention (I)	Outcomes (O)	Type studio (t) **
Pharmacological treatment	((((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension [Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]	"Treatment Adherence and Compliance"[Mesh] OR Adherence[tiab] OR compliance[tiab] OR Nonadherence[tiab] OR Noncompliance [tiab] OR Non-Adherence[tiab] OR Non-Compliance[tiab] OR medication intake adherence[tiab] OR drug therap*[tiab] OR medication therapy management[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]

Diet	((((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]	"Diet" [MeSH] OR diet [tiab] OR dietar*[tiab] OR food*[tiab] OR nutrition*[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]
Exercise	((((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab]	"Exercise" [MeSH] OR Exercise*[tiab] OR Physical Activit*[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

	("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]		OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]

Filters: Publication date from 2009/01/01 to 2019/11/

Searching other resources

The search will include the clinical trials registers identified in the following databases: ClinicalTrials.org, BVS (doctoral theses), International Clinical Trials Registry Platform (ICTRP, OMS), Open Access Theses and Dissertations (OATD).

Data collection and analysis

Selection of studies

Search will be conducted independently by two researchers assigned per database (DP, JS, PS, JH, ST, CE, LL, LR) following the strategy set. Documents retrieved in this first phase will go to folders classified by topic and database on EndNote. Then, a reviewer (CE) will eliminate duplicates and export each single study to Rayyan QCRI to evaluate eligibility criteria. This stage will determine eligibility of the studies by means of blinded review procedure, based on titles and summaries, to be conducted by seven reviewers (DP, JS, JH, ST, CE, LL, LR) on Rayyan QCRI platform. Once the process is completely finished by every reviewer, the blind will be lifted to again review those studies lacking consensus. If disagreement stands, an external evaluator's (LV, PS, IT, FG) intervention will solve discrepancies.

In case disagreement persists, the whole study text will be loaded to an independent ledger on Rayyan OCRI, to be reviewed once more, blinded. Elimination of every document must be justified in this phase.

When consensus is reached about inclusion of studies, upon review of titles and summaries, the whole text will be reviewed, selecting those to include in the qualitative synthesis. To ease eligibility process, a table with exclusion criteria will be produced, and its results will be documented following the PRISMA flow diagram. **(See Figure 1).**

Data extraction and management

Two independent evaluators will retrieve the information using formats designed by Cochrane for extraction of results from the studies included (categorical or continuous data). Then, validation in duplicate will be made to prevent mistakes. This process will be made on Epidata.

Assessment of risk of bias in included studies

Two independent reviewers will carry out evaluation of the methodological quality of the articles.

The domains and criteria established by the Cochrane [47] group will be followed, and they correspond to the following:

Selection bias: random assignment and selection of participants.

Performance bias: corresponds to blinding of investigators and participants.

Detection bias: corresponds to blinding of the intervention assessment.

Attrition bias: it refers to losses in participants and information.

Reporting bias: it refers to selection of the report.

Other bias: for example, the intent to treat, for conflict of interest.

Risk degree will be evaluated for each domain as: “low risk”, “high risk” or “unclear”.

To evaluate evidence degree of the studies, the GRADE [48] system will be used, availing of four categories: “high quality”, “moderate quality”, “low quality” and “very low quality”.

In case of discrepancies regarding these procedures, a third reviewer will intervene. The authors of studies with a high risk of bias or incomplete information will be contacted to clarify pertinent aspects and in case of no reply or if the information available does not allow it, they will be included in the systematic review description, but not in the meta-analysis.

Measures of treatment effect

Instead of adherence measuring availing of just one method, other direct and indirect methods will be included (Table 1).

Also, taking into account that interventions can be varied and have a direct influence on results obtained, they will be classified according to the designed method and the number of strategies utilized. In the case of continuous data, the change estimator in the measures will be recorded with its respective dispersion measure.

For categorical data, absolute and relative frequency measures, or effect measures reported as RR, HR, OR, NNT, RAR, will be reported with 95% confidence interval.

Unit analysis issues

As previously mentioned, high variability exists in the methods to evaluate adherence to therapeutic regime (Table 1), and it can prevent both information grouping for quantitative analysis and adequate control by heterogeneity sources.

Dealing with missing data

In case of identifying missing data, the study authors will be contacted to obtain it for analysis; in case of no reply, sensitivity analysis will be conducted eliminating this kind of publications.

Assessment of heterogeneity

Heterogeneity will be evaluated by means of the Chi^2 (p <0.05), Q Cochrane (over 25%) and I^2 (over 50%) [49] tests, and in case it is considerable, random-effects model will be estimated. Heterogeneity sources (type and duration of intervention, population, region or country, sociodemographic variables, effect measures, etc.), will be explored in a subgroup analysis and/or meta regressions.

Assessment of reporting bias

Publication bias will be determined with funnel plot as the graphic method, and bias numeric evaluation will be run through Egger and Begg [50] asymmetry tests.

Data synthesis

Data synthesis and statistical analyses will be performed by means of Cochrane Review Manager, and meta-analysis thru RevMan 5.3 [51] and Stata 15 [52], if the criteria to do so are met.

Subgroup analysis and sources of heterogeneity

If possible, analysis of subgroups or meta-regressions will be carried out according to type of: measuring, intervention, participants at study start-up (e.g. controlled and non-controlled patients), and study; also sex, age groups and other sociodemographic features of interest that may explain differences in the results.

Sensitivity analysis

Sensitivity analysis will be conducted to examine bias risk effect through evaluation of study feature changes in the funnel plot graph; next, analyses will be conducted excluding those studies with the most and least weight on the effect measure, observing the change in the punctual estimator, and those statistically significant will be reported.

Patient and Public Involvement

Not patient involved.

DISCUSSION

Review results will be useful in directing the usual clinical practice of health providers because it enables follow-up of hypertension out-patients.

Identification of interventions with the most effectiveness to improve therapeutic adherence, understood as a multi-factor phenomenon involving life-styles changes, will lead to reduction of the disease and economic burden of hypertension. The existence of multiple methods to measure adherence enables detection of high heterogeneity.

However, adequate analysis of its main sources will be relevant to adapt interventions in function of context and available resources (human, technical, and financial).

Ethics and dissemination

This is a systematic review study, where the source of information will be documents published in scientific databases, without human participation, so there will be no need for approval of an ethics committee. The results will be disseminated in scientific journals, as well as in other media, such as: conferences, seminars, congresses or symposia. In addition, copyright will be respected, giving the corresponding credit

through the bibliographic reference system.

Figure 1. Flow Diagram, process of the systematic review

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Authors' contributions

DP contributed with the study conception. DP, JS, LR, wrote the manuscript. Every author reviewed and contributed observations to the text.

Search strategy will be conducted DP, JS, PS, CE, LV and it will be reviewed and adjusted by every author. It will be applied by DP, JS, PS, CE, JH, ST, LR, and LL.

Retrieval of data from the studies included, bias evaluation, and synthesis will be developed by DP, JS, JH, ST, LL, and LR. Analyses will be the work of DP, JS, JH, ST, LL, LR, FG, and LV.

Authors PS, LV, IT, and FG, will both make sure no errors will be introduced along the different stages or review, and arbitrate disagreement.

Writing of manuscripts product of the systematic review will be agreed on and distributed among the different authors by topic (pharmacologic adherence, diet and

physical activity).

Approval by the authors of the final version of this manuscript was unanimous.

Conflicts of interest

None

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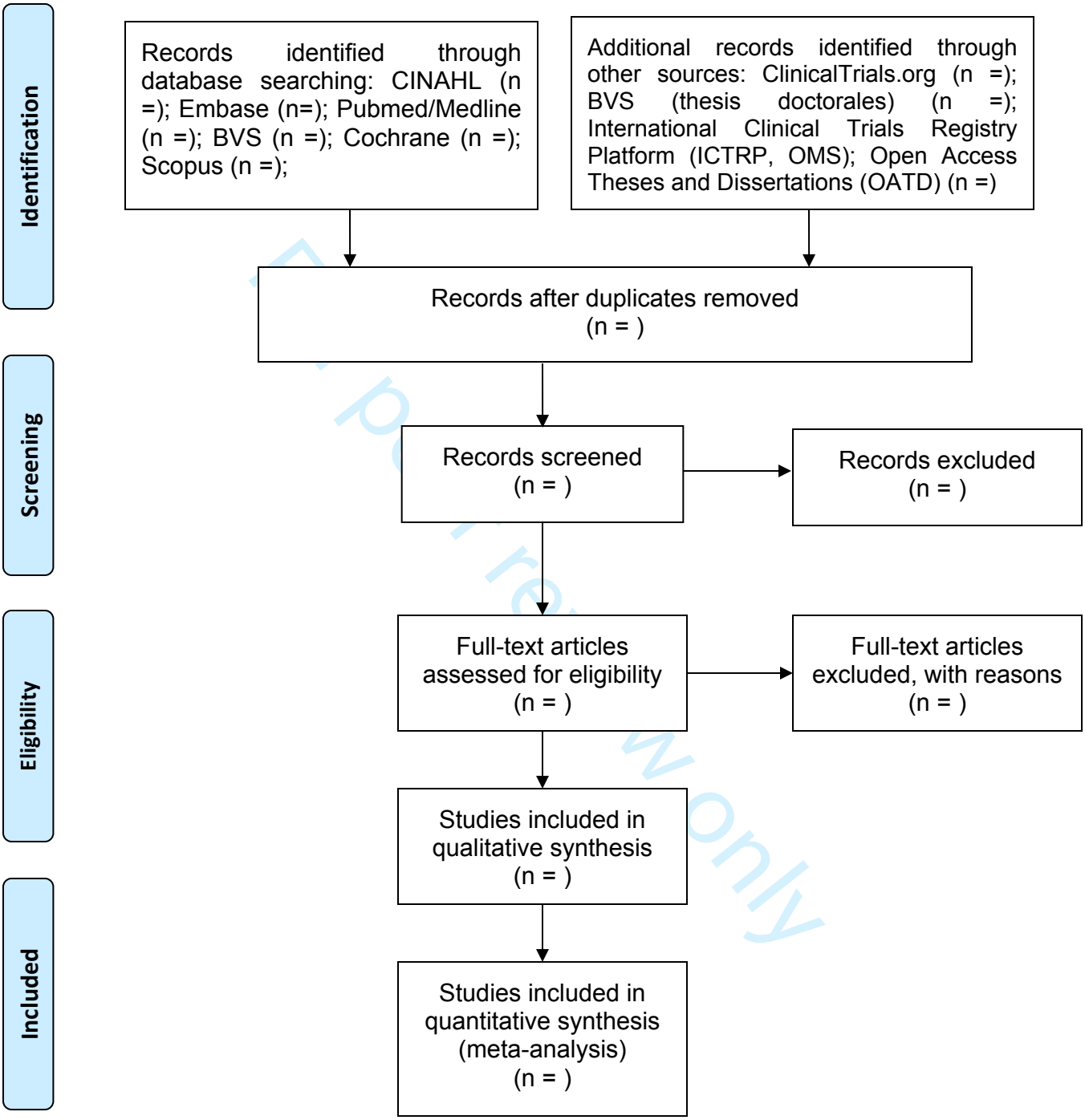
Table 2. Search strategy PICOt

	Participants/patients (P)	Intervention (I)	Outcomes (O)	Type studie (t) **
Pharmacological treatment	((((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension [Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]	"Treatment Adherence and Compliance"[Mesh] OR Adherence[tiab] OR compliance[tiab] OR Nonadherence[tiab] OR Noncompliance[tiab] OR Non-Adherence[tiab] OR Non-Compliance[tiab] OR medication intake adherence[tiab] OR drug therap*[tiab] OR medication therapy management[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-experimental [tiab]
Diet	((((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]	"Diet" [MeSH] OR diet [tiab] OR dietar*[tiab] OR food*[tiab] OR nutrition*[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-experimental [tiab]

Exercise	((((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]	"Exercise" [MeSH] OR Exercise*[tiab] OR Physical Activit*[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]

Filters: Publication date from 2009/01/01 to 2019/11/

Figure 1. Flow Diagram, process of the systematic review



PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X		3-4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		X	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		62-63
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		5-38
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		322-335
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		NA	
Sources	5a	Indicate sources of financial or other support for the review	X		317-321
Sponsor	5b	Provide name for the review funder and/or sponsor		NA	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X		320-321
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		73-136
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		137-189
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X		137-189
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X		190-207
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X		201-203
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		208-227
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X		208-227
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X		228-232
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X		253-261
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		168-185
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X		233-252
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		279-282
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	X		271-275
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		283-293
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		280-282
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		233-252
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		244-247

BMJ Open

INDIVIDUAL INTERVENTIONS TO IMPROVE ADHERENCE TO PHARMACEUTICAL TREATMENT, DIET AND PHYSICAL ACTIVITY AMONG ADULTS WITH PRIMARY HYPERTENSION. A SYSTEMATIC REVIEW PROTOCOL.

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INDIVIDUAL INTERVENTIONS TO IMPROVE ADHERENCE TO PHARMACEUTICAL TREATMENT, DIET AND PHYSICAL ACTIVITY AMONG ADULTS WITH PRIMARY HYPERTENSION. A SYSTEMATIC REVIEW PROTOCOL.

Authors

1. Dora Inés Parra, Nursing School professor at Universidad Industrial de Santander, Bucaramanga, Colombia. Clinical and Community Nursing Doctoral student, Universidad de Valencia, Spain. e-mail: doiparra@uis.edu.co

2. María Isabel Trapero Gimeno, Nursing and Podology School professor at Universidad de Valencia, Spain. e-mail: isabel.trapero@uv.es.

3. Javier Mauricio Sánchez Rodríguez, Fundación Universitaria Sanitas professor. Bogotá, Colombia. e-mail: jmsanchezro@unisanitas.edu.co.

4. Lizeth Catherine Rodríguez Corredor, epidemiologist, Instituto Neumológico del Oriente, Bucaramanga, Colombia; Public Health Department professor at Universidad Industrial de Santander, Bucaramanga, Colombia**.** e-mail: lizk263@hotmail.com.

5. Juliana Alexandra Hernández Vargas, epidemiologist at Colombian High Cost Diseases Fund, Bogotá, Colombia. e-mail: jhernandez@cuentadealtocosto.org.

6. Luis Alberto López Romero, epidemiologist, Fundación Cardiovascular de Colombia. e-mail: alberlop25@hotmail.com.

7. Fernando García López, epidemiologist, Centro Nacional de Epidemiología. Instituto de Salud Carlos III, Madrid, Spain. e-mail: fjgarcial@isciii.es.

8. Cristina Escudero-Gómez, documentalist, Hospital Universitario Puerta de Hierro

Majadahonda, Madrid, Spain. e-mail: cescuderog@salud.madrid.org.

9. Silvia Juliana Trujillo Cáceres, epidemiologist at Colombian High-Cost Diseases Fund Account, Bogotá, Colombia. e-mail: strujillo@cuentadealtocosto.org

10. Pilar Serrano Gallardo, Nursing Department professor, School of Medicine at Universidad Autónoma de Madrid, España. e-mail: pilar.serrano@uam.es.

11. Lina María Vera Cala, Medical Doctor, PhD in epidemiologist, Public Health Department professor at Universidad Industrial de Santander, Bucaramanga, Colombia. e-mail: limavera@uis.edu.co.

Correspondence author

Dora Inés Parra, associated professor, School of Nursing, Universidad Industrial de Santander; Bucaramanga, Colombia. Clinical and Community Nursing doctorate student, Universidad de Valencia, Spain.

Address: Calle 32 #32-70, Bucaramanga, Colombia, Postal code: 680002. Phone: +57 6345745 e-mail: doiparra@uis.edu.co.

Lina María Vera Cala, Public Health Department professor at the School of Health, Universidad Industrial de Santander, Bucaramanga, Colombia. e-mail: limavera@uis.edu.co.

ABSTRACT

Introduction. Hypertension is a chronic disease with 31% worldwide prevalence in adults. It has been associated with non-adherence to therapeutic regime with a negative impact on the prognosis of the disease and healthcare associated costs. The previous makes it necessary to identify effective interventions to improve adherence among this population. The objective of this protocol is to describe the methods for

a systematic review that will evaluate the effect of individual interventions to improve adherence to the prescribed pharmacologic treatment, diet and physical activity in adults with primary hypertension.

Methods and analysis: A systematic search of studies will be conducted in PubMed/MEDLINE, BVS, CINAHL, Embase, Cochrane and Scopus databases. Randomized and non-randomized clinical studies conducted in human beings, published from 01/01/2009 to 12/13/2019, will be included, with no language restriction. Adherence to pharmacologic treatment, diet and physical activity, measured by direct and indirect methods, will be the primary outcome. Two independent reviewers will select relevant studies and will extract the data following the Cochrane's Handbook for Systematic Reviews of Approach and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P). Methodologic quality will be evaluated by the ROBIS-2 Scale. Risk of bias will also be evaluated, and if the criteria are met, a meta-analysis will be finally performed.

Ethics and dissemination. Information to be analyzed is of a grouped nature, and given that it sources from published studies, no ethics committee approval is required. Results will be published in scientific journals, and through conferences, seminars, conferences, and symposiums. Copyrights will be respected by corresponding accrediting through the system of bibliographic references.

Key words: hypertension, interventions, adherence, diet, exercise, adults.

Register in PROSPERO: CRD42020147655

Strengths and limitations of this study

_The procedures of the study will be conducted in an independent and blinded manner by at least two reviewers.

_Bibliographic search will have no language restriction.

_Ample modality of individual interventions will be included, and adherence will be evaluated globally (pharmacological treatment, diet and physical activity).

_Variability in adherence measures can be associated with high heterogeneity, which may lead to conduct analysis by sub-groups and meta-regressions.

_The study will be conducted by an interdisciplinary group.

INTRODUCTION

Description of the condition

According to the guidelines of the European Societies of Cardiology and Hypertension (ESC/ESH) 2018, for diagnosis and treatment of hypertension, it is defined with values equal to or over 140 mmHg for systolic blood pressure (SBP), or 90 mmHg for diastolic blood pressure (DBP) [1]. It is the most common chronic non-communicable disease, and it has been described as one of the main risk factors associated with cardiovascular morbidity and mortality worldwide [2]. Its occurrence around the world stands at 31.0% (CI 95%: 30.0-32.2), and in low-to-middle-income countries, at 31.5% (CI 95%: 30.2-32.9), or 1.04 billion adults [3]. As to incidence, a follow-up study in young adults, (median age 33), for over two decades estimated an incidence rate of 58.6 cases per 100,000 people (CI 95%: 52.8-64.9) [4]. According to the World Health Organization (WHO), hypertension increases the risk of ischemic cardiopathy by three or four times and between two and three times for general cardiovascular risk [5] .

Additionally, prospective studies have shown hypertension to be one of the risk factors with the highest levels (31.0%) of contribution to incidence of cardiovascular events, followed by hypercholesterolemia (27.0%) and smoking (18.0%) [6]. Also,

inadequate control of hypertension has been documented to be associated with 58.0% ischemic stroke, 50.0% hemorrhagic stroke, 55.0% ischemic cardiopathies, and 58.0% of other forms of cardiovascular disease [7]. Regarding disability-adjusted life years lost, hypertension is the main reason worldwide, rising from 95.9 million to 143.01 million between 1990 and 2015 [8].

Although efficacious drugs exist [9,10] that actuate against the disease and prevent its complications, only half the individuals treated achieve proper control of hypertension [11], and many will abandon treatment without consulting with the doctor [9], a fact attributable largely to non-adherence and self-management [12]

Non-adherence to therapeutic regime is a worldwide phenomenon with grave repercussions that, according to the WHO is the consequence of multiple factors and is present in almost all patients with chronic diseases who show high rates of non-compliance [5,13–15].

As to hypertension patients, prevalence of adherence to pharmacologic treatment is variable, ranging between 24.1% and 92.7% [16], while for life-style-related aspects, non-compliance figures for physical exercise and diet stand at 68.8% and 30.9%, respectively [17].

Direct and indirect methods exist to assess adherence (See Table 1), and using one or the other can result in advantages and disadvantages related to objectivity and cost, [18]. Scientific literature shows that hypertension control takes both, pharmacologic and non-pharmacologic interventions, which makes it fundamental to measure adherence to all and every intervention, so as to identify the most effective strategy to achieve optimal adherence level to not only medication intake by patients, but also physical activity parameters that will lead to positive results in

hypertension control, for diminished consequences on health and health system's costs [19,20].

Regarding the previous, several studies have shown the clinical benefits of adherence to pharmacologic treatment, diet and exercise [17,21,22] diminished risk of clinical events such as death and myocardial infarction hospitalization, heart failure, or stroke [23]. In the same way, the higher the compliance with DASH (Dietary Approaches to Stop Hypertension) [24,25], the lower the levels of mortality arising from all causes including cardiovascular disease. Likewise, adherence to diet consistent with dietary guidelines has been associated with lower metabolic syndrome risk prevalence, and some of its factors, such as hypertension [26,27]. As to physical activity and exercise, lack of physical activity has been reported as a factor in non-hypertension control, entailing higher cardiovascular risk [28–30].

In terms of economic impact, studies conducted by Weaver et at, [31] estimated the cost attributable to hypertension in Alberta (Canada) by 2010 at CAD$1.4 billion, and for the whole of Canada, at CAD$13.9 billion for the same period. The same study foresees this figure to go up to CAD$20.5 billion along 2020, due to demographic changes, raised prevalence, and higher per-patient costs, adding that hypertension represents around 10.2% of Canada's sanitary budget. The same authors, in a systematic review, hold the cost associated to hypertension and specific cardiovascular disease episode, which showed uniform intra-studies figures, to reach between US$500 and $1,500 in low-to-mid-income countries, while costs for cerebrovascular accident and coronary disease exceeded $5,000 per episode [32].

The high prevalence of hypertension, non-adherence to therapeutic regime, the clinical implications and the costs related to disability associated with hypertension make it necessary to identify interventions that can efficaciously solve this problem

and can be adapted to the diverse scenarios of Primary Health Care (PHC) centers.

Description of the intervention

Adherence to therapeutic regime is defined as "the degree to which a person's behavior regarding medication intake, proper diet regime and modification of life habits fits the recommendations of their health care provider" [5], and they include both, the pharmaceutical and non-pharmaceutical component.

The WHO acknowledges the need to implement effective strategies to achieve changes in health results, because despite advances in treatment of chronic diseases, and research into the problem of adherence, it remains the single most important reason for unreached blood pressure control [33–35].

In this sense, the health team in charge of PHC plays a key role in facing this problem [36,37] through individual teaching that may be offered thru educational, behavioral, and affective interventions, or a combination of the previous, (multifaceted) [38,39]. Although diverse studies [38–48] have shown their efficacy to improve adherence and hypertension control, a focus is required not only on the pharmacologic component, but also on life habits related to cardiovascular risk, like physical activity and diet [44, 46, 48, 49].

How the intervention can work

There are different theoretical models to explain the phenomenon of adherence to therapeutic regime in chronic disease patients, based mainly on individual health behavior models [50] like the theories of cognition and self-efficacy, models of belief in health, behavioral changes, motivation, and self-regulation [51–53]. Self-management has been recently highlighted; it offers the chronic disease patient a series of support measures to improve confidence, with positive effect on adherence

to therapeutic regime[12,53–55]. Although some authors have found intervention based on individual health models to be more effective in different degrees[56], the intention of this review is finding individual interventions that will improve adherence to therapeutic regime in patients with hypertension, independently of the theoretical model proposed by the authors, implicitly or explicitly.

Scientific evidence suggests that interventions developed by the health team to increase adherence to therapeutic regime in patients with hypertension have focused mainly on the pharmacologic component, with an emphasis on not only pedagogic component with an individual focus, but also involving other dimensions like conduct and affective factors, or in some cases, combinations of the above mentioned aspects, and they are denominated multifaceted [10,57,58], which calls for research not only in pharmacological, but also non-pharmacological aspects of adherence.

OBJECTIVES

This article describes the protocol for a systematic review that will evaluate the effects of individual interventions to improve adherence to recommendations of the PHC team regarding medication treatment, diet and physical activity among adults with primary hypertension.

METHODS AND ANALYSIS

Eligibility criteria of the studies in this review

They were defined according to the criteria included in the PICOt question.

Participants (P)

Adult people aged 18 or older, with primary hypertension diagnosis defined with SBP ≥140 mmHg or DBP ≥90 mmHg, or according to the definition used by the authors of

the studies; who are receiving health care from a PHC team that normally includes medical doctors, nurses, nutritionists, etc., and whose aim is providing interventions of promotion of health, prevention of cardio-cerebrovascular events; patients who are covered by some modality of antihypertensive treatment.

Pregnant women, inpatients or those with secondary hypertension will be excluded.

Primary hypertension is defined as that whose primary origin cause is unknown, and taken to be linked to genetics, diet, sedentary lifestyle and obesity [59,60].

On the other hand, secondary hypertension is that resulting from diseases affecting other organs and systems [60,61]. In this review, identification will be made according to the criteria defined by the authors of the studies.

Types of interventions (I)

Interventions meeting these criteria will be included in this review:

1. Classification: Educational, behavioral, affective or multifaceted interventions oriented toward the individual will be included.

2. Application scenario: institutional and extramural

3. Methodology: in-person strategies like individual home visits, attention at PHC and similar centers. Non-in-person, like text messages, phone calls, videos and health applications, among others.

4. Personnel applying the intervention: interventions led by any health team member (nurses, medical doctors, pharmacologists, nutritionists, and physiotherapists, etc.) will be included.

5. Objective: improve adherence to medication treatment, diet, and, or physical activity.

The following will be specifically considered for each intervention type:

-Physical activity and exercise: all those interventions directed by health professionals, intent on promotion physical activity understood as every human body motion driven by skeletal muscles generating energy expenditure superior to basal expenditure, including moderate intensity [62] aerobic dynamics (walking, running, cycling or swimming) for at least 30 minutes 5 to 7 weekly days (150 min/wk), or vigorous intensity cardio-respiratory exercises no less than 20 minutes for 3 days (75 min/wk), or a combination of moderate and intense activity to achieve energy expenditure of between 500 – 1000 metabolic equivalents (METs) [62[63]]. Physical activity includes exercising, a structured, planned activity repeated in time so as to improve or preserve some physical aptitude elements, [64].

-Diet: interventions aiming to control caloric necessity, obesity indexes, lipid profile, or specific recommendations of clinical practice guidelines, like restricted intake of salt, sugar, and fats among others, in arterial hypertension patients[1,62].

-Pharmacologic: interventions related to promotion or improvement of adherence to medication prescribed for hypertension control by individuals or participants.

Comparison (C)

No comparator will be included, as the objective is to evaluate the effect of the different interventions, rather than of one in particular in any specific manner.

Types of outcome measures (O)

***Primary outcomes**

The main outcome will be the difference of proportions or means in adherence to pharmacologic treatment, diet and physical activity [18,19,65,66] pre and post

intervention. Measurements can be obtained through direct and indirect methods **(Table 1).**

Table 1. Direct and indirect methods reported in literature to evaluate adherence to therapeutic regime.

Pharmacologic treatment	**Diet**	**Prescribed physical activity**
Tablet Counting	Degree of adherence to DASH* diet	Accelerometry changes International Physical Activity Questionnaire (IPAQ)
Questionnaires (Morisky-Green, MARS, SMAQ)*	Anthropometric changes (IMC, ICC)*	
-Medication-contained electronic microchip[19] -Electronic monitors of medication -Rates of prescription refills [19] -Measure of clinical response or physiologic markers[19] -Patient's diaries[19]	Lipid profile changes	
Concentration of pharmaceutical or its metabolite in bodily fluids		Strain test

(blood, urine)		
Directly observed therapy		Six-minute walk test

MARS (Medication Adherence Report Scale), SMAQ (Simplified Medication Adherence Questionnaire), DASH (Dietary Approaches to Stop Hypertension), BMI (Body Mass Index), WHI (Waist-Hip Index.).

***Secondary outcomes**

- Percentage of participants with controlled hypertension.
- Rate or proportion of morbidity-mortality by major cardiovascular events (ischemic disease and stroke).
- Incremental rate of cost-effectiveness or cost-efficacy, cost-usefulness of interventions.
- Self-reported outcomes such as quality of life and burden of disease.

Types of studies (t)

This review will include randomized and non-randomized clinical trials that have had a comparison group (usual treatment or placebo) related to pharmacologic treatment, diet and physical activity in adults with primary hypertension.

Search methods for identification of studies

Electronic search

A systematic electronic search strategy will be designed to identify those studies meeting the inclusion criteria established in the PICOt question in the following databases: PubMed/MEDLINE, BVS, CINAHL, Embase, Cochrane and Scopus. The date established for the search was from 01/01/2009 to 12/13/2009, and the date to start out

and finish this review, according to the record by PROSPERO is from 11/30/2019 to 06/30/2021.

Next is an advanced, independent search for interventions for each event (medication, diet and physical activity) by a combination of controlled and free language terms. Search strategies will adapt to database characteristics. The following restrictions will apply: studies conducted in humans, published along 2009-2019. Finally, search process record will be kept for each information source. **(Table 2**).

Table 2. Search strategy PICOt

	Participants/patients (P)	**Intervention (I)**	**Outcomes (O)**	**Type of studio (t) ****
Pharmacological treatment	((((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension [Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR	"Treatment Adherence and Compliance"[Mesh] OR Adherence[tiab] OR compliance[tiab] OR Nonadherence[tiab] OR Noncompliance[tiab] OR Non-Adherence[tiab] OR Non-Compliance[tiab] OR medication intake	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind

		behaviour therapy [tiab]	adherence [tiab] OR drug therap*[tiab] OR medication therapy management[tiab]	method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]
Diet	((((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]	"Diet"[MeSH] OR diet [tiab] OR dietar*[tiab] OR food*[tiab] OR nutrition*[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized*

				[tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]
Exercise	((((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]	"Exercise"[MeSH] OR Exercise*[tiab] OR Physical Activit*[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized*

				[tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]

Filters: Publication date from 01/01/2009 to 12/13/2019.

Eligibility criteria

The following inclusion criteria will be applied: studies conducted in humans, published from 01/01/2009 to 12/13/2019 in the English, Spanish and Portuguese languages. The reason to have chosen these languages is that in a preliminary search strategy, in which language was not restricted, a low percentage was found in other languages (less than 1%)

Searching other resources

In order to reduce publication bias, the review will include the clinical trials records identified in the following bases: ClinicalTrials.org, BVS (doctoral theses), International Clinical Trials Registry Platform (ICTRP, OMS), Open Access Theses and Dissertations (OATD).

Data collection and analysis

Selection of studies

Search will be conducted independently by two researchers assigned per database (DP, JS, PS, JH, ST, CE, LL, LR) following the strategy set, previously defined in Table 2.

Documents retrieved in this first phase will go to folders classified by topic and database on EndNote. Then, a reviewer (CE) will eliminate duplicates and export each unique study to Rayyan QCRI to evaluate eligibility criteria.

In the screening phase, selection of studies will be determined thru a blinded and

independent reviewing procedure based on titles and abstracts, to be carried out by seven reviewers (DP, JS, JH, ST, CE, LL, LR) two reviewers per topic, and one in charge of blinding on the Rayyan QCRI platform. Each reviewer will classify the articles as included, excluded or dubious. Once each pair of reviewers completes this process, the blinding will be lifted and those studies lacking consensus will be reevaluated, reactivating the blind. Articles classified as dubious will be subjected to a new independent review, by title and abstract. In case disagreement continues on conflicted articles, an external evaluator (LV, PS, IT, FG) will resolve the discrepancy by determining inclusion or exclusion of documents. Studies in discrepancy will be exported to the Rayyan QCRI (CE) platform, to be reassessed blinded.

Upon achievement of consensus on studies to include in the screening phase, they will go thru eligibility phase, where each reviewer team will evaluate the full text independently, selecting those articles to be included in the qualitative synthesis. In case of discrepancy, the same procedure by third reviewer described in the screening phase, will be conducted. In order to facilitate the eligibility process, a table will be produced with the inclusion and exclusion criteria, and the results will be documented following the PRISMA flow chart **(Figure 1).**

Data extraction and management

Data extraction will be carried out independently by two reviewers, availing of the formats established by Cochrane for categorical or continuous data, and any difference will be settled or solved by a third investigator, as the case may be. For data processing, a pilot test will be run among reviewers to guarantee the quality of data extraction, and if necessary, pertaining adjustments will be made to the formats before definitive extraction of information.

Then, validation will be carried out in duplicate to avoid typos in the information extracted. This process will be conducted on Epidata.

Whenever the full text of the article cannot be accessed, or supplementary information on results is required, authors will be contacted for information.

Assessment of risk of bias in included studies

Two independent reviewers will carry out evaluation of the methodological quality of the articles for each topic, and in case of discrepancy, a third reviewer will settle differences.

Dominions and criteria established by the Cochrane [67] team will be followed using the ROBIS-2 scale, for both experimental and quasi-experimental, corresponding as follows:

- Selection bias: random assignment and selection of participants.
- Execution bias: corresponds to blinding of investigators and participants.
- Detection bias: corresponds to blinding of the intervention evaluators.
- Attrition bias: it refers to losses in participants and information.
- Reporting bias: it refers to selection of the report.
- Other bias: for example, the intent to try, out of conflict of interest.

Risk degree will be evaluated for each domain as “low risk”, “high risk” or “unclear”.

To evaluate evidence degree of the studies, the GRADE [68] system will be used, availing of four categories: “high quality”, “moderate quality”, “low quality” and “very low quality”.

In case of discrepancies regarding these procedures, a third reviewer will intervene. The

authors of studies with a high risk of bias or incomplete information will be contacted to clarify pertinent aspects and in case of no reply or if the information available does not allow it, they will be included in the systematic review description, but not in the meta-analysis.

Measures of treatment effect

Instead of adherence measuring availing of just one method, other direct and indirect methods will be included (Table 1).

Also, taking into account that interventions can be varied and have a direct influence on results obtained, they will be classified according to the designed method and the number of strategies utilized. In the case of continuous data, the change estimator in the measures will be recorded with its respective dispersion measure.

For categorical data, absolute and relative frequency measures, or effect measures reported as RR, HR, OR, NNT, RAR, will be reported with their 95% confidence interval.

Unit analysis issues

As previously, mentioned, high variability exists in the methods to evaluate adherence to therapeutic regime (Table 1), and this can prevent both information grouping for quantitative analysis and adequate control by heterogeneity sources.

Dealing with missing data

In case of identifying missing data, the authors will be contacted to obtain it for analysis; in case of no reply, sensitivity analysis will be conducted eliminating this kind of publications.

Assessment of heterogeneity

Heterogeneity will be evaluated using the Chi^2 (p <0.05), Q Cochrane (over 25%) and I^2 (over 50%) [69] tests, and in case it is considerable, random-effects models will be estimated. Heterogeneity sources (type and duration of intervention, population, region or country, sociodemographic variables, effect measures, etc.), will be explored in a subgroup analysis and/or meta regressions.

Assessment of reporting bias

Publication bias will be determined with funnel plot as the graphic method, and bias numeric evaluation will be run through Egger and Begg [70] asymmetry tests.

Data synthesis

Data synthesis and statistical analyses will be performed by means of Cochrane Review Manager, and meta-analysis thru RevMan 5.3 [71] and Stata 15 [72], if the criteria to do so are met.

Otherwise, results will be grouped according to review topics (diet, physical activity and pharmacological component), intervention type, methods used to measure adherence, study design, and the effect size of the measures reported will be presented. In general terms, in order to communicate the qualitative findings, the following aspects will be extracted from each study, as recommended by Cochrane[73]: authors, publication year, language, location, study design, intervention, comparer, results, etc.

Subgroup analysis and sources of heterogeneity

If possible, analysis of subgroups or meta-regressions will be carried out according to type of: measuring, intervention, participants at the baseline (e.g. controlled and non-controlled patients), and study; also sex, age groups and other sociodemographic characteristics of interest that may explain differences in the results.

Sensitivity analysis

Sensitivity analysis will be conducted to examine bias risk effect through evaluation of study feature changes in the funnel plot graph; next, analyses will be conducted excluding those studies with the most and least weight on the effect measure, observing the change in the punctual estimator, and those statistically significant will be reported.

Patient and public involvement

Not patient involved.

DISCUSSION

Review results will be useful in directing the usual clinical practice of PHC providers because it enables follow-up of hypertension ambulatory patients. Identification of interventions with the most effectiveness to improve therapeutic adherence, understood as a multi-factor phenomenon involving life-styles changes, will lead to reduction of the disease and economic burden of arterial hypertension.

Limitations of the review

As we has been previously mentioned in this text, it is highly likely that no general summary measure like meta-analysis will be obtained, explained by the high heterogeneity of the interventions, as a consequence of the lack of a control group, the presence of three topics or areas (medication, diet, exercise), as well as the different methods to assess adherence, among others. However, adequate analysis of their main sources will be relevant to adapt interventions in function of context and available resources (human, technical, and financial).

Ethics and dissemination

This is a systematic review study, where the source of information will be documents published in scientific databases, without human participation, so there will be no need for approval of an ethics committee. The results will be disseminated in scientific journals, as well as in other media, such as conferences, seminars, congresses or symposia. In addition, copyright will be respected, giving the corresponding credit through the bibliographic reference system.

Figure 1. Systematic review flowchart.

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Authors' contributions

DP contributed with the study conception. DP, JS, LR, wrote the manuscript. Every author reviewed and contributed observations to the text.

Search strategy will be conducted DP, JS, PS, CE, LV and it will be reviewed and adjusted by every author. DP, JS, PS, CE, JH, ST, LR, and LL will apply it.

Retrieval of data from the studies included, bias evaluation, and synthesis will be developed by DP, JS, JH, ST, LL, and LR. Analyses will be the work of DP, JS, JH,

ST, LL, LR, FG, and LV.

Authors PS, LV, IT, and FG, will both make sure no errors will be introduced along the different stages or review, and arbitrate disagreement.

Writing of manuscripts product of the systematic review will be agreed on and distributed among the different authors by topic (pharmacologic adherence, diet and physical activity).

Approval by the authors of the final version of this manuscript was unanimous.

Conflicts of interest

None

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Figure 1. Flow Diagram, process of the systematic review

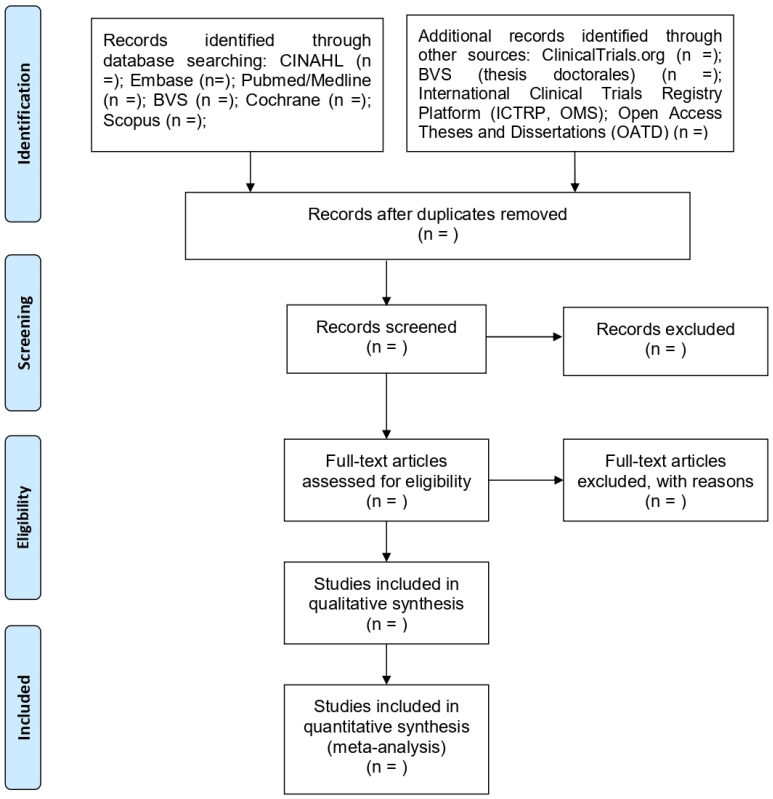

Figure 1: Flow Diagram, process of the systematic review

107x139mm (300 x 300 DPI)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X		3-4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		NA	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		67
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		5 to 40
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		421 to 434
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		NA	
Sources	5a	Indicate sources of financial or other support for the review	X		416 to 420
Sponsor	5b	Provide name for the review funder and/or sponsor		NA	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		NA	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		77 to 179
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		180 to 250
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X		251 to 255; 271 to 276
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X		255 to 270; 277 to 281
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X		269 to 270
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		282 to 306
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X		282 to 306
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X		307 to 317
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X		340 to 349
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		233 to 250
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X		318 to 339
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		367 to 376
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	X		358 to 363
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		377 to 387
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		367 to 370
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		364 to 366
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		332 to 334

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INDIVIDUAL INTERVENTIONS TO IMPROVE ADHERENCE TO PHARMACEUTICAL TREATMENT, DIET AND PHYSICAL ACTIVITY AMONG ADULTS WITH PRIMARY HYPERTENSION. A SYSTEMATIC REVIEW PROTOCOL.

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INDIVIDUAL INTERVENTIONS TO IMPROVE ADHERENCE TO PHARMACEUTICAL TREATMENT, DIET AND PHYSICAL ACTIVITY AMONG ADULTS WITH PRIMARY HYPERTENSION. A SYSTEMATIC REVIEW PROTOCOL.

Authors

1. Dora Inés Parra, Nursing School professor at Universidad Industrial de Santander, Bucaramanga, Colombia. Clinical and Community Nursing Doctoral student, Universidad de Valencia, Spain. e-mail: doiparra@uis.edu.co

2. Isabel Trapero Gimeno, Nursing and Podology School professor at Universidad de Valencia, Spain. e-mail: isabel.trapero@uv.es.

3. Javier Mauricio Sánchez Rodríguez, Fundación Universitaria Sanitas professor. Bogotá, Colombia. e-mail: jmsanchezro@unisanitas.edu.co.

4. Lizeth Catherine Rodríguez Corredor, epidemiologist, Instituto Neumológico del Oriente, Bucaramanga, Colombia; Public Health Department professor at Universidad Industrial de Santander, Bucaramanga, Colombia**.** e-mail: lizk263@hotmail.com.

5. Juliana Alexandra Hernández Vargas, epidemiologist at Colombian High Cost Diseases Fund, Bogotá, Colombia. e-mail: jhernandez@cuentadealtocosto.org.

6. Luis Alberto López Romero, epidemiologist, Fundación Cardiovascular de Colombia. e-mail: alberlop25@hotmail.com.

7. Fernando García López, epidemiologist, Centro Nacional de Epidemiología. Instituto de Salud Carlos III, Madrid, Spain. e-mail: fjgarcial@isciii.es.

8. Cristina Escudero-Gómez, documentalist, Hospital Universitario Puerta de Hierro

Majadahonda, Madrid, Spain. e-mail: cescuderog@salud.madrid.org.

9. Silvia Juliana Trujillo Cáceres, epidemiologist at Colombian High-Cost Diseases Fund Account, Bogotá, Colombia. e-mail: strujillo@cuentadealtocosto.org

10. Pilar Serrano Gallardo, Nursing Department professor, School of Medicine at Universidad Autónoma de Madrid, España. e-mail: pilar.serrano@uam.es.

11. Lina María Vera Cala, Medical Doctor, PhD in epidemiologist, Public Health Department professor at Universidad Industrial de Santander, Bucaramanga, Colombia. e-mail: limavera@uis.edu.co.

Correspondence author

Dora Inés Parra, associated professor, School of Nursing, Universidad Industrial de Santander; Bucaramanga, Colombia. Clinical and Community Nursing doctorate student, Universidad de Valencia, Spain.

Address: Calle 32 #32-70, Bucaramanga, Colombia, Postal code: 680002. Phone: +57 6345745 e-mail: doiparra@uis.edu.co.

Lina María Vera Cala, Public Health Department professor at the School of Health, Universidad Industrial de Santander, Bucaramanga, Colombia. e-mail: limavera@uis.edu.co.

ABSTRACT

Introduction. Hypertension is a chronic disease with 31% worldwide prevalence in adults. It has been associated with non-adherence to therapeutic regime with a negative impact on the prognosis of the disease and healthcare associated costs. So, it is necessary to identify effective interventions to improve adherence among the afflicted population. The objective of this protocol is to describe the methods for a

systematic review that will evaluate the effect of individual interventions so as to improve adherence to the prescribed pharmacologic treatment, as well as to prescribed diet and physical activity in adults with primary hypertension.

Methods and analysis: A systematic search of studies will be conducted in PubMed/MEDLINE, BVS, CINAHL, Embase, Cochrane and Scopus databases. Randomized and non-randomized clinical studies conducted in human beings, published from 01/01/2009 to 12/13/2019, are to be included, in any language. Adherence to pharmacologic treatment, diet and physical activity, measured by direct and indirect methods, will be the primary outcome. Two independent reviewers will select relevant studies and will extract the data following the Cochrane's Handbook for Systematic Reviews of Approach and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P). Methodologic quality will be evaluated using the RoB 2 and ROBINS-I Tools. Risk of bias will also be evaluated, and if the criteria are met, a meta-analysis will be finally performed.

Ethics and dissemination. Information to be analyzed is of a grouped nature, and given that it sources are published studies, no Ethics Committee approval is required. Results will be published in scientific journals, and in conferences, seminars, and symposiums. Copyrights will be—addressed by giving due credit through bibliographic references.

Key words: hypertension, interventions, adherence, diet, exercise, adults.

Register in PROSPERO: CRD42020147655

Strengths and limitations of the study

_The procedures of the study will be conducted in an independent and blinded

manner by at least two reviewers.

_Bibliographic search will have no language restriction.

_Ample modality of individual interventions will be included, and adherence will be evaluated globally (pharmacological treatment, diet and physical activity).

_Variability in adherence measures can be associated with high heterogeneity, which may lead to conduct analysis by sub-groups and meta-regressions.

_The study will be conducted by an interdisciplinary group.

INTRODUCTION

Description of the condition

Hypertension or High blood pressure is one of the most frequent non-communicable diseases (NCD), and it has been described as one of the main risk factors associated with cardiovascular morbid-mortality worldwide.(1–3) According to the guidelines of the European Societies of Cardiology and Hypertension (ESC/ESH) 2018, hypertension is defined as values equal to or higher than 140 mmHg for systolic blood pressure (SBP), or 90 mmHg for diastolic blood pressure (DBP) measured in consultation.(1)

In 2010, worldwide prevalence of hypertension were 31.0% (CI 95%: 30.0-32.2) or 1.39 (CI 95%: 1.34-1.44) billion adults aged ≥20, and for low-to-middle-income countries it was 31.5% (CI 95%: 30.2-32.9), or 1.04 billion adults.(4) According to estimates, hypertension will keep increasing reaching 1.56 billion (CI 95%: 1.54-1.58 billon) people in 2025. (5) As to incidence, rates have been reported of 58.6 cases per 100,000 people, (CI 95%: 52.8-64.9) in young adults (median age 33 years).(6)

According to the World Health Organization (WHO), hypertension increases the risk

of coronary heart disease by three to four times, and the risk of cardiovascular disease by two to three times.(7) In this regard, a study of the Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg between 1990 and 2015, reported that most of the SBP-related deaths were caused by ischemic cardiopathy (54.5%), hemorrhagic stroke (58.3%), and ischemic stroke (50,0%).(3) Likewise, prospective studies indicate that hypertension is one of the risk factors with the highest contribution (31.0%) to the incidence of cardiovascular events, followed by hypercholesterolemia (27.0%) and smoking (18.0%).(8)

Related to the loss of disability adjusted life years associated with SBP ≥ 140 mmHg, figures oscillated between 95.9 million (CI 95%: 87.0-104.9 million) and 143.01 million (CI 95%: 130.2-157.0 million) for the 1990-2015 period.(3)

Although there are effective medications(1,9–11) to treat hypertension and prevent complications, a substantial proportion of cardiovascular events are attributed to poor adherence and a lack of control of high blood pressure (12) In this regard, inadequate control of hypertension increases risk cardiovascular mortality by 1.74 times (IC 95%: 1.36-2.22) as compared to treated controlled hypertension.(13)

Non-adherence to therapeutical regime is the consequence of multiple factors that have been described by the WHO and are present in almost all patients with chronic diseases, who show high non-compliance rates.(14,15) In terms of hypertensive patients, non-compliance with pharmacologic treatment oscillates between 45.2% (CI 95%: 34.4–56.1) and 63.35% (CI: 38.78–87.91) (14,15), while for factors related to changes in life style, figures for non-compliance with physical activity and diet stand at 68.8% and 30.9%, respectively.(16)

Scientific literature shows that reaching an optimal SBP or DBP level demands both

pharmaceutical and non-pharmaceutical interventions, in order for patients to get to take medications at optimal level and adhere to diet and physical activity changes. Thus, they will obtain positive results in hypertension control, with a subsequent reduction in the disease burden and health care costs.(17,18)

Several studies have shown the clinical benefits of adherence to pharmacologic treatment, diet and physical activity changes (18–20) in the reduction of risk of health events such as death and hospitalization after myocardial infarction, cardiac insufficiency or stroke.(20–22) In this sense, it has been inferred that the stricter the compliance with Dietary Approaches to Stop Hypertension (DASH) (20,22), the lower the mortality related to all causes, including cardiovascular disease. Also, adherence to diet guidelines has been associated with lower prevalence of metabolic syndrome and some of its factors, like hypertension.(23,24) Lack of physical activity has been determined as a factor associated to non-control of hypertension, which leads to higher cardiovascular risk.(25)

In terms of economic impact, studies conducted by Weaver et at,(26) estimated the cost attributable to hypertension in Alberta (Canada) by 2010 at CAD$1.4 billion, and for the whole of Canada, at CAD$13.9 billion for the same period, adding that hypertension represents around 10.2% of Canada's health budget. The same study foresees this figure to go up to CAD$20.5 billion along 2020, due to demographic changes, population ageing, and higher costs per patient. The same authors, through a systematic review, estimate costs associated with hypertension and the specific episode of cardiovascular disease, to oscillate between US$500 and $1,500 in low-to-mid-income countries, while costs of stroke and coronary disease went over $5,000 per episode.(27)

High prevalence of hypertension, non-adherence to therapeutic regime, clinical implications and costs associated to hypertension-related disability make it necessary to find interventions that will efficaciously improve this problem while adapting to the different Primary Health Care (PHC) scenarios.

Description of the intervention

Adherence to therapeutic regime is defined as "the degree to which a person's behavior regarding medication intake, proper diet regime and modification of life habits fits the recommendations of their health care provider"(7), and they include both, the pharmaceutical and non-pharmaceutical component.

The WHO acknowledges the need to implement effective strategies to achieve changes in health results, because despite advances in treatment of chronic diseases, lack of adherence to the therapeutic regimen remains the most important reason for failure to control blood pressure.(7,14,28,29)

In this sense, the health team in charge of PHC plays a key role in facing this problem (30,31) through individual teaching that may be offered through educational, behavioral, and affective interventions, or a combination of the previous (Multifaceted).(32,33) Although diverse studies(32–41) have shown their efficacy to improve adherence and hypertension control, a focus is required not only on the pharmacologic component, but also on life habits related to cardiovascular risk, like physical activity and diet.(34,42)

There are different theoretical models to explain the phenomenon of adherence to therapeutic regime in chronic disease patients, based mainly on individual health behavior models (43) such as the theories of cognition and self-efficacy, models of belief in health, behavioral changes, motivation, and self-regulation.(44–48) Self-

management has been recently highlighted; it offers the chronic disease patient a series of support measures to improve confidence, with positive effect on adherence to therapeutic regime.(49,50) Some authors have found a higher effect of interventions based on individual health models,(51) in different degrees; however, the intention of this review is to find individual interventions that will improve adherence to therapeutic regime in patients with hypertension, independently of the theoretical model proposed by the authors, implicitly or explicitly.

Scientific evidence has prioritized interventions focused mainly on adherence to the pharmacologic component of hypertension treatment, using either a pedagogic, behavioral or affective focus, or a combination of one or more of these focuses (Multifaceted). Therefore, it is necessary to look into not only the pharmacologic, but also the non-pharmacologic aspects of adherence to the therapeutic regimen.(42,52,53)

OBJECTIVES

This article describes the protocol for a systematic review that will evaluate the effects of individual interventions to improve adherence to recommendations of the PHC team regarding medication treatment, diet and physical activity among adults with primary hypertension.

METHODS AND ANALYSIS

Eligibility criteria of the studies in this review

They were defined according to the criteria included in the PICOt question.

Participants (P)

Adult people aged 18 or older, with diagnosis of primary hypertension defined as SBP

≥140 mmHg or DBP ≥90 mmHg, or according to the definition used by the authors of the studies; who are receiving health care from a PHC team that normally includes medical doctors, nurses, nutritionists, etc., and whose aim is providing interventions of promotion of health, prevention of cardio-cerebrovascular events; and patients who are covered by some modality of antihypertensive treatment.

Pregnant women, in-patients or those with secondary hypertension will be excluded.

Primary hypertension is defined as that whose primary origin cause is unknown, and taken to be linked to genetics, diet, sedentary lifestyle and obesity.(1,54)

On the other hand, secondary hypertension is due to an identifiable cause that resulting from diseases affecting other organs and systems.(1) In this review, identification will be made according to the criteria defined by the authors of the studies.

Types of interventions (I)

Interventions meeting the following criteria will be included in this review:

1. Classification: Educational, behavioral, affective or multifaceted interventions oriented toward the individual will be included.

2. Application scenario: institutional and extramural

3. Methodology: in-person strategies like individual home visits, attention at PHC and similar centers. Non-in-person, like text messages, phone calls, videos and health applications, among others.

4. Personnel applying the intervention: interventions led by any health team member (nurses, medical doctors, pharmacologists, nutritionists, and physiotherapists, etc.) will be included.

5. Objective: improve adherence to medication treatment, diet, and, or physical

activity.

The following will be specifically considered for each intervention type:

-Physical activity and exercise: all those interventions directed by health professionals, intent on promoting physical activity understood as every motion driven by skeletal muscles generating energy expenditure superior to basal expenditure, including moderate intensity(55) aerobic dynamics (walking, running, cycling or swimming) for at least 30 minutes 5 to 7 weekly days (150 min/wk), or vigorous intensity cardio-respiratory exercises no less than 20 minutes for 3 days (75 min/wk), or a combination of moderate and intense activity to achieve energy expenditure of between 500 – 1000 metabolic equivalents (METs).(55,56) Physical activity includes exercising, a structured, planned activity repeated in time so as to improve or preserve some physical aptitude elements.(57)

-Diet: interventions aiming to control caloric necessity, obesity indexes, lipid profile, or specific recommendations of clinical practice guidelines, like restricted intake of salt, sugar, and fats among others, in arterial hypertension patients.(1,55)

-Pharmacologic: interventions related to promotion or improvement of adherence to medication prescribed for hypertension control by individuals or participants.

Comparison (C)

No comparator will be included, given that the objective of the systematic review is to evaluate the effect of different interventions, rather than of one specific in particular.

Types of outcome measures (O)

***Primary outcomes**

The main outcome will be the difference of proportions or means in adherence to pharmacologic treatment, diet and physical activity(17,58–60) pre and post intervention. Measurements can be obtained through direct and indirect methods **(Table 1).**

Table 1. Direct and indirect methods reported in literature to evaluate adherence to therapeutic regime.

Pharmacologic treatment	**Diet**	**Prescribed physical activity**
Tablet Counting	Degree of adherence to DASH* diet	Accelerometry changes International Physical Activity Questionnaire (IPAQ)
Questionnaires (Morisky-Green, MARS, SMAQ)*	Anthropometric changes (IMC, ICC)*	
-Medication-contained electronic microchip(17) -Electronic monitors of medication -Rates of prescription refills(17) -Measure of clinical response or physiologic markers(17) -Patient's diaries(17)	Lipid profile changes	
Concentration of		Strain test

pharmaceutical or its metabolite in bodily fluids (blood, urine)		
Directly observed therapy		Six-minute walk test

MARS (Medication Adherence Report Scale), SMAQ (Simplified Medication Adherence Questionnaire), DASH (Dietary Approaches to Stop Hypertension), BMI (Body Mass Index), WHI (Waist-Hip Index.).

***Secondary outcomes**

- Percentage of participants with controlled hypertension.
- Rate or proportion of morbidity-mortality by major cardiovascular events (ischemic disease and stroke).
- Incremental rate of cost-effectiveness or cost-efficacy, cost-usefulness of interventions.
- Self-reported outcomes such as quality of life and burden of disease.

Types of studies (t)

This review will include randomized and non-randomized clinical trials that have had a comparison group (usual treatment or placebo) related to pharmacologic treatment, diet and physical activity in adults with primary hypertension.

Search methods for identification of studies

Electronic search

A systematic electronic search strategy will be designed to identify those studies meeting the inclusion criteria established in the PICOt question in the following databases:

PubMed/MEDLINE, BVS, CINAHL, Embase, Cochrane and Scopus. The dates established for studies to be included were between 01/01/2009 and 12/13/2019, and according to the PROSPERO record the starting date for the study is 11/30/2019 and the finishing date is 06/30/2021.

Next activity is an advanced, independent search for interventions for each event (medication, diet and physical activity) by a combination of controlled and free language terms. Search strategies will adapt to the characteristics of each database. The following restrictions will apply: studies conducted in humans, and published between 2009 and 2019. Finally, a search process record will be kept for each information source. **(Table 2)**.

Table 2. Search strategy PICOt

	Participants/patients (P)	**Intervention (I)**	**Outcomes (O)**	**Type of studio (t) ****
Pharmacological treatment	((((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension [Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education "[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation" [Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[M	"Treatment Adherence and Compliance"[Mesh] OR Adherence [tiab] OR compliance[tiab] OR Nonadherence[tiab] OR Noncompliance[tiab] OR Non-Adherence [tiab] OR Non-Complian	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR

		esh] OR "Mentoring "[Mesh] OR behaviour therapy [tiab]	ce[tiab] OR medicatio n intake adherence [tiab] OR drug therap*[tia b] OR medicatio n therapy manageme nt[tiab]	double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]
Diet	((((("Essential hypertension"[MeS H Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title /Abstract]) OR "hypertension"[Me SH Terms]) OR Hypertension[Title /Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education "[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mes h]) OR "Program Evaluation" [Mesh] OR interventio n*[tiab] OR educat*[tia b] OR prevent*[ti ab] OR "Behavior therapy"[M esh] OR "Mentoring "[Mesh] OR behaviour therapy [tiab]	"Diet" [MeSH] OR diet [tiab] OR dietar*[tia b] OR food*[tiab] OR nutrition*[tiab]	Clinical Query de Pubmed: ((clinical[Title/A bstract] AND trial[Title/Abstra ct]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/A bstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non

				Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]
Exercise	((((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]	"Exercise"[MeSH] OR Exercise*[tiab] OR Physical Activit*[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]

271 Filters: Publication date from 01/01/2009 to 12/13/2019.

Eligibility criteria

The following inclusion criteria will be applied: studies conducted in humans, published from 01/01/2009 to 12/13/2019 in the English, Spanish and Portuguese languages. The reason to have chosen these languages is that in a preliminary search strategy, in which language was not restricted, a low percentage was found in other languages (less than 1%).

Searching other resources

In order to reduce publication bias, the review will include the clinical trials records identified in the following databases: ClinicalTrials.org, International Clinical Trials Registry Platform (ICTRP, OMS), Open Access Theses and Dissertations (OATD).

Data collection and analysis

Selection of studies

Search will be conducted independently by two researchers assigned per database (DP, JS, PS, JH, ST, CE, LL, and LR) following the strategy set, previously defined in Table 2.

Documents retrieved in this first phase will go to folders classified by topic and database on EndNote. Then, a reviewer (CE) will eliminate duplicates and export each unique study to Rayyan QCRI to evaluate eligibility criteria.

In the screening phase, selection of studies will be determined through a blinded and independent reviewing procedure based on titles and abstracts, to be carried out by seven reviewers (DP, JS, JH, ST, CE, LL, LR) two reviewers per topic, and one in charge of blinding on the Rayyan QCRI platform. Each reviewer will classify the articles as included, excluded or maybe. Once each pair of reviewers completes this

process, the blinding will be lifted and those studies lacking consensus will be reevaluated, reactivating the blind. Articles classified as conflict and maybe will be subjected to a new independent review, by title and abstract. In case disagreement continues on conflicted articles, an external evaluator (LV, PS, IT, FG) will resolve the discrepancy by determining inclusion or exclusion of documents. Studies in discrepancy will be exported to the Rayyan QCRI (CE) platform, to be reassessed blinded.

Upon achievement of consensus on studies to include in the screening phase, they will go through eligibility phase, where each reviewer team will evaluate the full text independently, selecting those articles to be included in the qualitative synthesis. In case of discrepancy, the same procedure by a third reviewer described in the screening phase, will be conducted. In order to facilitate the eligibility process, a table will be produced with the inclusion and exclusion criteria, and the results will be documented following the PRISMA flow chart **(Figure 1).**

Data extraction and management

Data extraction will be carried out independently by two reviewers, availing of the formats established by Cochrane for categorical or continuous data, and any difference will be settled or solved by a third investigator, as the case may be. For data processing, a pilot test will be run among reviewers to guarantee the quality of data extraction, and if necessary, corresponding adjustments will be made to the formats before definitive extraction of information.

Then, validation will be carried out in duplicate to avoid typos in the information extracted. This process will be conducted on Epidata.

Whenever the full text of the article cannot be accessed, or supplementary

information on results is required, authors will be contacted for information.

Assessment of risk of bias in included studies

Two independent reviewers will carry out evaluation of the methodological quality of the articles for each topic, and in case of discrepancy, a third reviewer will settle differences.

Dominions and criteria established by the Cochrane (61) team will be followed to evaluate bias risk in the studies.

To evaluate the methodological quality of the experimental studies, RoB 2 tool will be used(62), which encompasses the following 5 domains: randomization process, deviations arising from the foreseen interventions, data missing from the outcomes, measure of the outcomes, and selection of the results reported, which will be evaluated through the signaling questions and also through an algorithm in which global risk is evaluated as: low, high, and some concerns.

ROBINS-I tool(63) will be used for quasi-experimental studies, and it encompasses 7 domains to evaluate risks distributed in three parts: pre-intervention, intervention, and post-intervention. In this scale, the studies risk will be reported as low risk, moderate risk, serious risk, critical risk, and no information.

To evaluate the evidence degree of the studies, the GRADE(64) system will be used, availing of four categories: “high quality”, “moderate quality”, “low quality” and “very low quality”.

In case of discrepancies regarding these procedures, a third reviewer will intervene. The authors of studies with a high risk of bias or incomplete information will be contacted to clarify pertinent aspects and in case of no reply or if the information available does not allow it, they will be included in the systematic review description, but not in the

meta-analysis.

Measures of treatment effect

Instead of adherence measuring availing of just one method, other direct and indirect methods will be included (Table 1).

Also, taking into account that interventions can be varied and have a direct influence on results obtained, they will be classified according to the designed method and the number of strategies utilized. In the case of continuous data, the change estimator in the measures will be recorded with its respective dispersion measure.

For categorical data, absolute and relative frequency measures, or effect measures reported as RR, HR, OR, NNT, ARR, will be reported with their 95% confidence interval.

Unit analysis issues

As previously mentioned, high variability exists in the methods to evaluate adherence to therapeutic regime (Table 1) and this can prevent both information grouping for quantitative analysis and adequate control by heterogeneity sources.

Dealing with missing data

In case of finding missing data, the authors will be contacted to obtain it for analysis; in case of no reply, sensitivity analysis will be conducted eliminating this kind of publications.

Assessment of heterogeneity

Heterogeneity will be evaluated using the Chi^2 (p <0.05), Q Cochrane (over 25%) and I^2 (over 50%) (65) tests, and if it is considerable, random-effects models will be

estimated. Heterogeneity sources (type and duration of intervention, population, region or country, sociodemographic variables, effect measures, etc.), will be explored in a subgroup analysis and/or meta-regressions.

Assessment of reporting bias

Publication bias will be determined with funnel plot as the graphic method, and bias numeric evaluation will be run through Egger and Begg(66) asymmetry tests.

Data synthesis

Data synthesis and statistical analyses will be performed by means of Cochrane Review Manager, and meta-analysis through RevMan 5.3(67) and Stata 15(68), if the criteria to do so are met.

Otherwise, results will be grouped according to review topics (diet, physical activity and pharmacological component), intervention type, methods used to measure adherence, study design, and the effect size of the measures reported will be presented. In general terms, in order to communicate the qualitative findings, the following aspects will be extracted from each study, as recommended by Cochrane(69): authors, publication year, language, location, study design, intervention, comparator, results, etc.

Subgroup analysis and sources of heterogeneity

If possible, analysis of subgroups or meta-regressions will be carried out according to type of: measuring, intervention, participants at the baseline (e.g. controlled and non-controlled patients), and study; also sex, age groups and other sociodemographic characteristics of interest that may explain differences in the results.

Sensitivity analysis

Sensitivity analysis will be conducted to examine bias risk effect through evaluation

of study feature changes in the funnel plot graph; next, analyses will be conducted excluding those studies with the most and least weight on the effect measure, observing the change in the punctual estimator, and those statistically significant will be reported.

Patient and public involvement

Not patient involved.

DISCUSSION

Review results will be useful in directing the usual clinical practice of PHC providers because it enables follow-up of hypertension ambulatory patients. Identification of interventions with the most effectiveness to improve therapeutic adherence, understood as a multi-factor phenomenon involving life-styles changes, will lead to reduction of the disease and economic burden of arterial hypertension.

Limitations of the review

As has been previously mentioned in this text, it is highly likely that no general summary measure like meta-analysis will be obtained, explained by the high heterogeneity of the interventions, as a consequence of the lack of a control group, the presence of three topics or areas (medication, diet, exercise), as well as the different methods to assess adherence, among others. However, adequate analysis of their main sources will be relevant to adapt interventions in function of context and available resources (human, technical, and financial).

Ethics and dissemination

This is a systematic review study, where the source of information will be documents published in scientific databases, without human participation, so there will be no need

for approval of an Ethics Committee. The results will be disseminated in scientific journals, as well as in other media, such as conferences, seminars, congresses or symposia. In addition, copyright will be respected, giving the corresponding credit through the bibliographic reference system.

Figure 1. Systematic review flowchart.

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Authors' contributions

DP contributed with the study conception. DP, JS, LR, wrote the manuscript. Every author reviewed and contributed observations to the text.

Search strategy will be conducted DP, JS, PS, CE, LV and it will be reviewed and adjusted by every author. DP, JS, PS, CE, JH, ST, LR, and LL will apply it.

Retrieval of data from the studies included, bias evaluation, and synthesis will be conducted by DP, JS, JH, ST, LL, and LR. Analyses will be the work of DP, JS, JH, ST, LL, LR, FG, and LV.

Authors PS, LV, IT, and FG, will both make sure no errors will be introduced along

the different stages or review, and arbitrate disagreement.

Writing of manuscripts product of the systematic review will be agreed on and distributed among the different authors by topic (pharmacologic adherence, diet and physical activity).

Approval by the authors of the final version of this manuscript is to be unanimous.

Conflicts of interest

None declared

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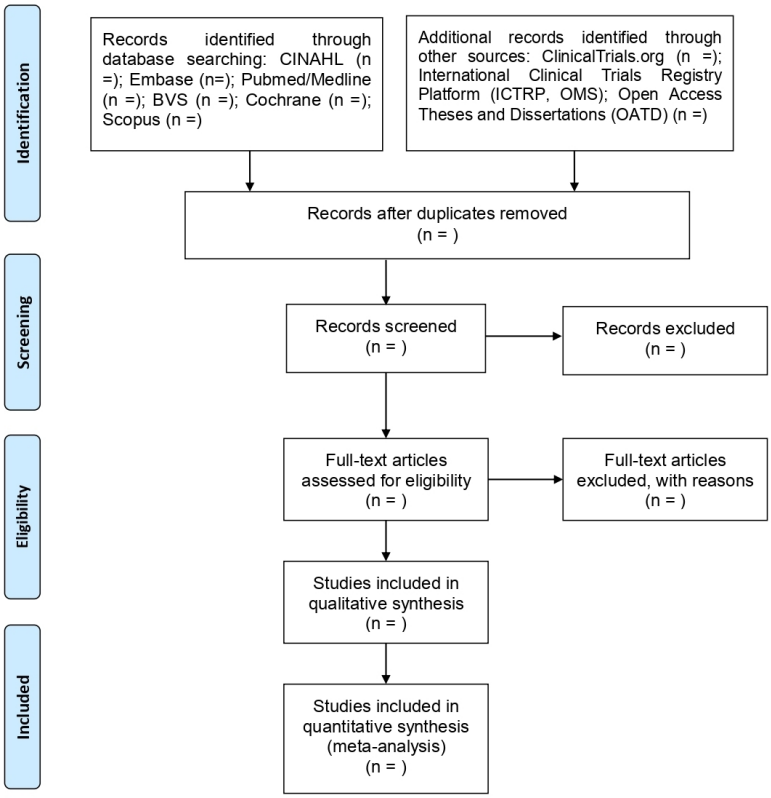
Figure 1. Systematic review flowchart



107x139mm (300 x 300 DPI)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X		3-4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		NA	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		68
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		5 to 40
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		426 to 438
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments		NA	
Sources	5a	Indicate sources of financial or other support for the review	X		421 to 425
Sponsor	5b	Provide name for the review funder and/or sponsor		NA	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		NA	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		78 to 179
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		180 to 184
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X		185 to 255
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X		256 to 269; 278 to 282
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X		270 to 277
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		283 to 309
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X		285 to 309
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X		310 to 320
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X		240 to 244
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		345 to 358
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X		321 to 344
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		382 to 386
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	X		363 to 368

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		387 to 392
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		348 to 354
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		369 to 371
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		337 to 344