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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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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 pharmacological 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. Randomised and non-randomised clinical studies conducted in human beings, published from 1 January 2009 to 13 December 2019, are to be included, in any language. Adherence to pharmacological 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. Methodological quality will be evaluated using the risk-of-bias (RoB) 2 and Risk of Bias in Non-randomised Studies - of Interventions (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 analysed is of a grouped nature, and given that its 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.

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 subgroups and meta-regressions.
- The study will be conducted by an interdisciplinary group.

PROSPERO registration number CRD42020147655

INTRODUCTION

Description of the condition

Hypertension or high blood pressure is one of the most frequent non-communicable diseases, 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 2018, hypertension is defined as values ≥140 mm Hg for systolic blood pressure (SBP), or ≥ 90 mm Hg for diastolic blood pressure (DBP) measured in consultation.[1]

In 2010, worldwide prevalence of hypertension were 31.0% (95% CI 30.0 to 32.2) or

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

According to 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 110–115 mm Hg between 1990 and 2015, reported that most of the SBP-related deaths were caused by ischaemic cardiopathy (54.5%), haemorrhagic stroke (58.3%) and ischaemic 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 hypercholesterolaemia (27.0%) and smoking (18.0%).[8]

Related to the loss of disability-adjusted life years associated with SBP ≥140 mm Hg, figures oscillated between 95.9 million (95% CI 87.0 to 104.9 million) and 143.01 million (95% CI 130.2 to 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 of cardiovascular mortality by 1.74 times (95% CI 1.36 to 2.22) as compared with treated controlled hypertension.[13]

Non-adherence to therapeutical regime is the consequence of multiple factors that have been described by 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 pharmacological treatment oscillates between 45.2% (95% CI 34.4 to 56.1) and 63.35% (95% CI 38.78 to 87.91),[14 15] while for factors related to changes in lifestyle, 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 healthcare costs.[17 18]

Several studies have shown the clinical benefits of adherence to pharmacological treatment, diet and physical activity changes[18–20] in the reduction of risk of health events such as death and hospitalisation 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,[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 with non-control of hypertension, which leads to higher cardiovascular risk.[25]

In terms of economic impact, studies conducted by Weaver *et al*[26] estimated the cost attributable to hypertension in Alberta (Canada) by 2010 at CAD$1.4 billion, and for the whole of Canada, at $C13.9 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 $C20.5 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 US$1500 in low-income to middle-income countries, while costs of stroke and coronary disease went over US$5000 per episode.[27]

High prevalence of hypertension, non-adherence to therapeutic regime, clinical implications and costs associated with 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 behaviour regarding medication intake, proper diet regime and modification of life habits fits the recommendations of their healthcare provider',[7] and they include both, the pharmaceutical and non-pharmaceutical component.

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 regime 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, behavioural 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 on the pharmacological component, and 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 patients with chronic disease, based mainly on individual health behaviour models[43] such as the theories of cognition and self-efficacy, models of belief in health, behavioural 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 prioritised interventions focused mainly on adherence to the pharmacological component of hypertension treatment, using either a pedagogic, behavioural or affective focus, or a combination of one or more of these focuses (multifaceted). Therefore, it is necessary to look into the pharmacological and the non-pharmacological aspects of adherence to the therapeutic regime.[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 years or older, with diagnosis of primary hypertension defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg, or according to the definition used by the authors of the studies; who are receiving healthcare from a PHC team that normally includes medical doctors, nurses, nutritionists and so on, 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 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, behavioural, 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 centres. 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) 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 min 5 to 7 weekly days (150 min/week), or vigorous intensity cardiorespiratory exercises no <20 min for 3 days (75 min/week), or a combination of moderate and intense activity to achieve energy expenditure of between 500 and 1000 metabolic equivalents.[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]
- Pharmacological: 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 pharmacological treatment, diet and physical activity[17 58–60] preintervention and postintervention. Measurements can be obtained through direct and indirect methods (table 1).

Secondary outcomes

- Percentage of participants with controlled hypertension.
- Rate or proportion of morbidity-mortality by major cardiovascular events (ischaemic disease and stroke).
- Incremental rate of cost-effectiveness or cost-efficacy, cost-usefulness of interventions.

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

Pharmacological treatment	Diet	Prescribed physical activity
Tablet counting	Degree of adherence to DASH diet	Accelerometry changes International Physical Activity Questionnaire
Questionnaires (Morisky-Green, MARS, SMAQ)	Anthropometric changes (BMI, WHI)	
► Medication-contained electronic microchip[17] ► Electronic monitors of medication ► Rates of prescription refills[17] ► Measure of clinical response or physiological markers[17] ► Patient's diaries[17]	Lipid profile changes	
Concentration of pharmaceutical or its metabolite in bodily fluids (blood, urine)		Strain test
Directly observed therapy		Six-minute walk test

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

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

Types of studies (T)

This review will include randomised and non-randomised clinical trials that have had a comparison group (usual treatment or placebo) related to pharmacological 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 1 January 2009 and 13 December 2019, and according to the PROSPERO record (CRD42020147655), the starting date for the study is 30 November 2019 and the finishing date is 30 June 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).

Eligibility criteria

The following inclusion criteria will be applied: studies conducted in humans, published from 1 January 2009 to 13 December 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 (<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 (WHO), Open Access Theses and Dissertations.

Data collection and analysis

Selection of studies

Search will be conducted independently by two researchers assigned per database (DIP, JMSR, PS-G, JAHV, SJT-C, CE-G, LALR and LCRC) 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-G) 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 (DIP, JMSR, JAHV, SJT-C, CE-G, LALR, LCRC)—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 re-evaluated, 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 (LMV-C, PS-G, ITG, FJGL) will resolve the discrepancy by determining inclusion or exclusion of documents. Studies in discrepancy will be exported to the Rayyan QCRI (CE-G) platform, to be reassessed blinded.

On achievement of consensus on studies to include in the screening phase, they will go through eligibility

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 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 1 January 2009 to 13 December 2019.

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 flowchart for systematic reviews and meta-analyzes (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 3.1.

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 five domains: randomisation 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 signalling 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 seven domains to evaluate

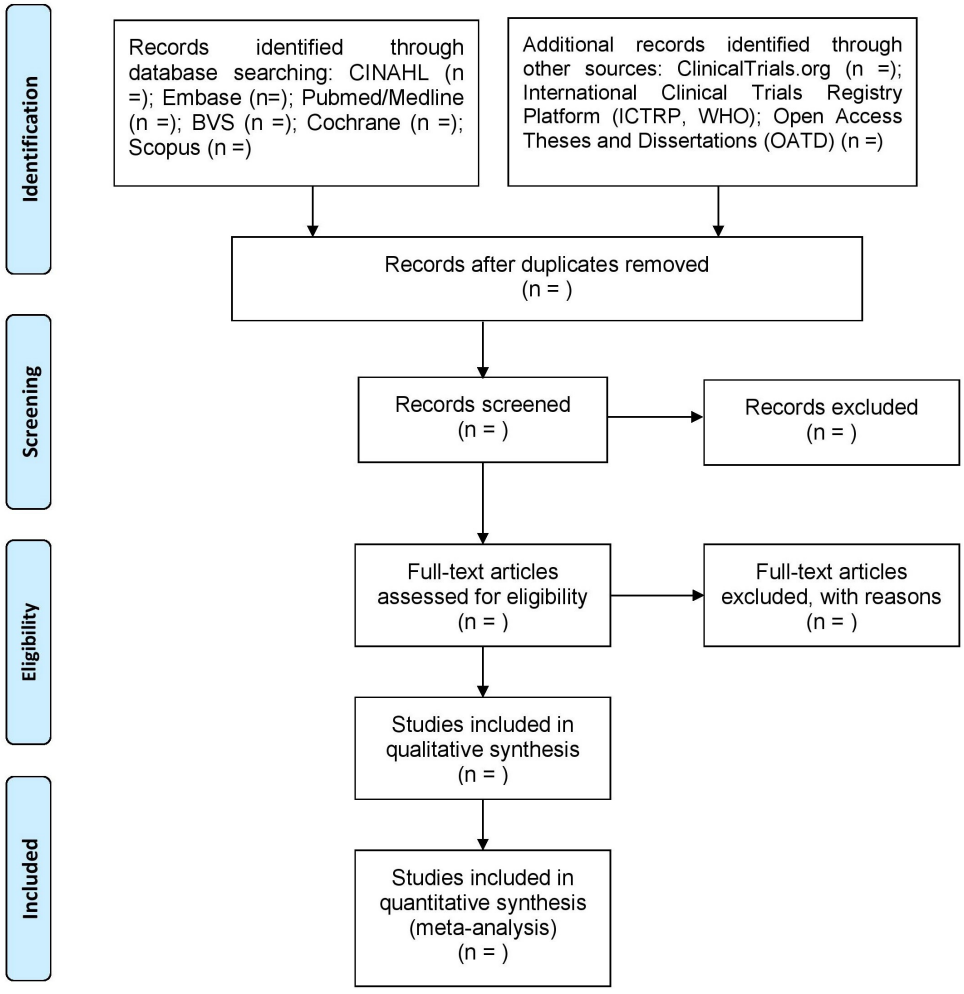

Figure 1 Systematic review flow chart.

risks distributed in three parts: preintervention, intervention and postintervention. 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 Grading of Recommendations, Assessment, Development and Evaluations (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 bias risk 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 used. 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 relative risk, Hazard ratio (HR), Odds ratio (OR), number needed to treat, absolute risk reduction will be reported with their 95% CI.

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 χ^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 and so on), 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 V.5.3[67] and Stata V.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 and results.

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 (eg, 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 multifactor phenomenon involving lifestyle 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.

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Contributors DIP contributed with the study conception. DIP, JMSR, LCRC wrote the manuscript. Every author reviewed and contributed observations to the text. Search strategy will be conducted by DIP, JMSR, PS-G, CE-G, LMV-C and it will be reviewed and adjusted by every author. It will be applied by DIP, JMSR, PS-G, CE-G, JAHV, SJT-C, LCRC and LALR. Retrieval of data from the studies included bias evaluation, and synthesis will be developed by DIP, JMSR, JAHV, SJT-C, LALR and LR. Analyses will be the work of DIP, JMSR, JAHV, SJT-C, LALR, LCRC, FJGL and LMV-C. PS-G, LMV-C, ITG and FJGL 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 (pharmacological adherence, diet and physical activity). Approval by the authors of the final version of this manuscript was unanimous.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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