


BMJ Open Exercise versus fixed-dose combination therapy for cardiovascular risk factors control and atherosclerotic disease prevention: a network meta-analysis protocol

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ABSTRACT

Introduction Despite the consistent evidence of the benefits of physical activity on preventing atherosclerotic cardiovascular diseases (ASCVD) and some cardiovascular risk factors, such as hypertension and dyslipidaemia, the prescription of drugs remains the most widely used approach to prevent ASCVD in clinical settings. The purpose of this study protocol is to provide a meta-synthesis methodology for comparing the effect of fixed-dose combination therapy and physical exercise on controlling cardiovascular risk factors and preventing ASCVD.

Methods and analysis This protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols and the recommendations of the Cochrane Collaboration Handbook. We plan to conduct a computerised search in Medline, Web of Science, Embase, Cochrane Database of Systematic Reviews and SPORTDiscus from inception to May 2020 for studies testing the effectiveness of physical exercise or fixed-dose combination drug therapy in preventing ASCVD, all-cause and cardiovascular mortality and controlling some cardiovascular risk factors (hypertension and dyslipidaemia). Since performing network meta-analyses (NMA) is a statistical approach that allows direct and indirect comparisons of interventions, where sufficient studies are included, we plan to perform the following NMA comparing the effect of fixed-dose combination therapy and physical exercise interventions on (1) improving lipid profile, (2) reducing blood pressure, (3) preventing cardiovascular events and all-cause and cardiovascular mortality and (4) improving compliance with the therapeutic strategy and reducing adverse events.

Ethics and dissemination Ethical approval will not be needed because data included in the NMA will be extracted from published trials that meet accepted ethical standards. The results will be published in academic peer-reviewed journals, and the evidence gathered by this project could be included in the preventive cardiovascular disease guidelines.

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Strengths and limitations of this study

- The evidence obtained could help patients and practitioners make appropriate evidence-based decisions in the management of some cardiovascular risk factors.
- This will be the most comprehensive review of published studies of fixed-dose combination therapy and exercise treatments to improve cardiovascular risk factors and prevent cardiovascular disease events.
- The main anticipated limitations are inherent to meta-analyses, such as limited or incoherent information from studies, high heterogeneity and risk-of-bias assessments; in addition, the quality of the included studies could influence the consistency of the conclusion.
- An exhaustive literature search will be carried out to identify studies aimed at analysing the relationship between fixed-dose combination therapy and/or exercise treatments and cardiovascular risk factors and diseases.
- To reduce and control the limitations, this work will follow Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and PRISMA-network meta-analysis guidelines and the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.

INTRODUCTION

Atherosclerotic cardiovascular diseases (ASCVD) is a term that encompasses a group of disorders of the heart and blood vessels that are the principal cause of death worldwide, as evidenced by the fact that in 2015, ASCVD was responsible for more than 17 million deaths in the world.¹ Furthermore, in most countries, these mortality figures are increasing, probably due to worldwide increases in population size and ageing.² Among ASCVD,

ischaemic heart disease and stroke are the main drivers of those deaths.^{1 2} The main modifiable factors among the atherosclerosis process include elevated blood pressure levels, dyslipidaemia, tobacco use, physical inactivity and unhealthy diet.^{3 4}

One of the most promising strategies to control atherosclerotic risk factors and prevent ASCVD in clinical practice is the polypill, which consists of a fixed-dose combination of three drugs: an antihypertensive, a statin and aspirin.^{5 6} Several studies have assessed the effect of this polypill in preventing ASCVD events and treating some cardiovascular risk factors, namely, hypertension and dyslipidaemia,^{7 8} and other studies have analysed the effectiveness of physical exercise interventions for the same goal.^{9 10} Nevertheless, there is a lack of studies directly comparing the effectiveness of the polypill versus physical exercise interventions in preventing ASCVD events and controlling cardiovascular risk factors.

The network meta-analysis (NMA) approach allows us to estimate pooled effect sizes not only from direct comparisons but also from indirect comparisons of interventions that have not been compared in a head-to-head manner; thus, this novel approach is suitable when there is not sufficient evidence of competing interventions for the same outcome, in our case, the prevention of ASCVD events.

OBJECTIVE

The main objectives of this study protocol are to provide standardised and clear procedures for a set of NMAs (or meta-analysis if NMAs will be not possible) aimed at synthesising all the available evidence about the independent effects of physical exercise and fixed-dose combination therapy interventions, as well as the pooled effect differences between these two interventions, on (1) preventing ASCVD events (coronary heart disease, stroke and peripheral artery disease), all-cause mortality and cardiovascular mortality; (2) improving lipid levels; (3) decreasing blood pressure and (4) reducing their adverse events and improving adherence rates.

METHODS AND DESIGN

The present NMA protocol was planned, conducted and reported according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) and The Cochrane Handbook for Systematic Reviews of Interventions.¹¹⁻¹⁴

Eligibility criteria

Type of studies

Randomised controlled trials (RCTs) aimed to assess the effectiveness of physical exercise interventions or fixed-dose combination drug therapy in controlling and improving some cardiovascular risk factors (hypercholesterolaemia and/or high blood pressure). In addition, prospective and cohort studies will be included in

the study aimed to compare the effectiveness of physical exercise with fixed-dose combination therapy in preventing ASCVD events (coronary heart disease, stroke and peripheral artery disease) and all-cause and cardiovascular mortality due to the nature of these outcomes.

Types of participants

We will include primary and/or secondary atherosclerosis prevention RCTs (in addition to prospective cohort studies on mortality and ACVD event outcomes) written in English or Spanish, including high-risk adults treated with fixed-dose combination therapy and/or physical exercise interventions.

Studies in children or adolescents and/or those involving treatments other than exercise or fixed-dose combination therapy in the intervention group will be excluded.

Type of interventions

We will consider for inclusion RCTs that report any type of supervised and structured exercise interventions (aerobic, resistance, anaerobic, high-interval training, balance, stretching, Tai Chi, Pilates or yoga) or a combination (eg, aerobic+balance), with a frequency higher than one session/week and with a programme duration of at least 4 weeks. We will exclude studies that combine physical exercise with other interventions (eg, nutritional intervention) when data cannot be separately extracted.

Predictably, in the cohort studies included to assess the effectiveness of physical exercise and fixed-dose combination therapy in preventing ACVD and mortality, it is possible that physical exercise will not be supervised and structured interventions, and only data about self-reported physical activity amounts and the type of exercise realised will be reported.

Regarding pharmacological treatment, we will consider all RCTs aimed at assessing the effectiveness of fixed-dose combination drug therapy used to treat or prevent the following pathologies: ASCVD events (ischaemic heart disease, stroke and peripheral artery disease), hypercholesterolaemia or high blood pressure. The polypill represents a therapeutic strategy that usually combines single-pill blood pressure-lowering drugs and high-potency statins with or without aspirin.¹⁵

Type of outcome measures

We plan to conduct four NMAs in which the primary outcomes will be the following:

- ▶ Outcomes about the blood lipid profile (low-density lipoprotein cholesterol (LDL-c), triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-c)) for the first NMA.
- ▶ Outcomes about blood pressure (systolic blood pressure and diastolic blood pressure) for the second NMA.
- ▶ Ischaemic heart disease, stroke and peripheral artery disease events, all-cause mortality, cardiovascular mortality and total cardiovascular events for the third

NMA. Apart from individual outcomes (eg, incidence of coronary heart disease), we will also consider composite cardiovascular outcomes (eg, 10-year Framingham cardiovascular disease risk reduction).

- ▶ Finally, in the fourth NMA, the primary outcomes will be adverse events and adherence.

Search strategy

The electronic search will be conducted by DPP-C and IC-R, and differences will be solved by discussion with a third reviewer (VM-V). We will conduct the searches using the following electronic databases: Medline (via PubMed), Web of Science, Embase, Cochrane Database of Systematic Reviews and SPORTDiscus from inception to May 2020.

For each NMA, the search will be based on the PICO strategy (Patients/Population, Intervention, Comparison and Outcomes) and will include terms related to physical exercise intervention and fixed-dose combination therapy, cardiovascular risk factors (hypercholesterolaemia and high blood pressure), ASCVD events (ischaemic heart disease, stroke and peripheral artery disease), mortality, adverse events and adherence, depending on each NMA (online supplementary file 1).

The search strategy will be adapted for each NMA and database. Moreover, we will explore the reference lists from the retrieved articles to search for further relevant studies that potentially meet the inclusion criteria. There will be no restrictions by publication year or country of the study.

Study selection process and data extraction

Two reviewers will independently screen titles and abstracts after removing duplicate retrieved records. Reviewers will examine the full text articles applying the inclusion/exclusion criteria. Inconsistencies in study selection will be solved by consensus. A third reviewer (VM-V) will be consulted when disagreements persist. A flow chart will display the study selection process and the reasons for exclusions (figure 1). When several studies provide data from the same sample, we will include the one containing the most detailed information or providing the largest sample size. If relevant data are missing, we will send mail to corresponding authors requesting them.

Equally, for each NMA, two reviewers will extract the following study characteristics, which are summarised in tables 1–4: (1) the first author; (2) year of publication; (3) country; (4) length of follow-up; (5) characteristics of participants (age, sample size, sex); (6) outcomes: levels of HDL-c, LDL-c, total cholesterol, triglycerides, blood pressure, ASCVD events (ischaemic heart disease, stroke and peripheral artery disease), mortality (total and cardiovascular mortality), adverse events and data regarding adherence and (7) characteristics of treatment and control groups: type of treatment (drug name, composition, dose) and/or type of exercise, intensity, duration and frequency.

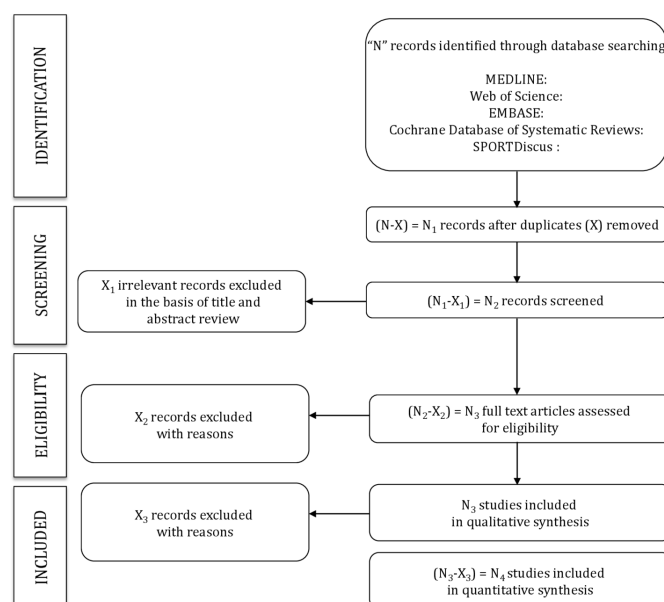


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of identification, screening, eligibility and inclusion of studies.

Assessment of risk of bias

Two authors will independently assess the included full-text RCTs for methodological quality using the risk-of-bias assessment tool from the Cochrane Collaboration.¹⁶ This tool includes the following domains: (1) bias arising from the randomisation process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome and (5) bias in selection of the reported results. Each domain will be assessed as ‘low’, ‘high’ or ‘some concerns’ risk of bias, so that overall bias will be considered ‘low risk of bias’ when the paper is classified as ‘low risk’ in all domains, as ‘some concerns’ when there is at least one domain with rating of ‘some concern’ and as ‘high risk of bias’ if there is at least one domain with a ‘high risk’, or when there are several domains with ‘some concerns’ rating.

The validated Newcastle-Ottawa Scale for cohort studies will be used to assess the quality of the studies assessing the effectiveness of physical activity on the incidence of ACVD events and mortality.¹⁷ This scale assigns four points for quality of selection, two points for comparability and three points for quality of outcome and adequacy of follow-up, with a maximal score of nine points.

The agreement rate between reviewers will be reported by calculating kappa statistics. A third researcher (VM-V) will assess inconsistencies

Grading the quality evidence

The Grading of Recommendations, Assessment, Development and Evaluation tool will be used to evaluate the quality of evidence.¹⁸ For each outcome variable, an evidence value will be assigned (high, moderate, low or very low) depending on the study’s design, risk of bias, inconsistency, indirect evidence, imprecision and publication bias.

Table 1 Characteristics of studies included in the network meta-analysis

Study characteristics		Population characteristics		Outcomes		Intervention/control groups							
Authors/year	Country	Follow-up	Age (years (mean±SD))/ sample size (n (% male))	HDL-c	LDL-c	Triglycerides	Total cholesterol	IG: Dose	Drug	Type of exercise	Frequency	Duration	Intensity
								CG: Dose	Drug	Type of exercise	Frequency	Duration	Intensity

CG, control group; HDL-c, high-density lipoprotein cholesterol; IG, intervention group; LDL-c, low-density lipoprotein cholesterol.

Table 2 Characteristics of studies included in the network meta-analysis

Study characteristics		Population characteristics		Outcomes		Intervention/control groups					
Authors/year	Country	Follow-up	Age (years (mean±SD))/ sample size (n (% male))	SBP	DBP	IG: Dose	Drug	Type of exercise	Frequency	Duration	Intensity
						CG: Dose	Drug	Type of exercise	Frequency	Duration	Intensity

CG, control group; DBP, diastolic blood pressure; IG, intervention group; SBP, systolic blood pressure.

Table 3 Characteristics of studies included in the network meta-analysis

Study characteristics		Population characteristics		Outcomes		Intervention/control groups								
Authors/year	Country	Follow-up	Age (years (mean±SD))/sample size (n (% male))	Ischaemic heart disease	Stroke	Peripheral artery disease	Mortality Total: CVD:	IG: CG:	Dose	Drug	Type of exercise	Frequency	Duration	Intensity

CG, control group; CVD, cardiovascular diseases; IG, intervention group.

Table 4 Characteristics of studies included in the network meta-analysis

Study characteristics		Population characteristics		Outcomes		Intervention/control groups							
Authors/year	Country	Follow-up	Age (years (mean±SD))/sample size (n (% male))	Adverse events	Adherence		IG: CG:	Dose	Drug	Type of exercise	Frequency	Duration	Intensity

CG, control group; IG, intervention group.

Data synthesis

We will conduct the NMAs according to the PRISMA-NMA statement,¹⁹ distinguishing the following phases:

First, by using a network graph for each outcome, we will present direct comparisons between the intervention group (physical exercise or fixed-dose combination therapy) and the control group.²⁰ For that, we will perform random effects pairwise meta-analyses in terms of the post intervention scores or the changes from baseline values of the different treatment options for each outcome. For this, the standardised mean difference (SMD) and the risk ratio (RR) (for continuous and dichotomous variables, respectively) from preintervention to post intervention and between groups (intervention vs control) in each study will be calculated and pooled using the random-effect DerSimonian-Laird method.²¹ Second, in cases where it is possible to carry out an NMA, it will be used to conduct simultaneous comparisons of several interventions creating a connected network using the totality of the available evidence (direct and indirect comparisons).^{20 22} For each outcome, we will report the mean treatment effect with its 95% credible CI of all interventions relative to the control and other interventions and the estimated common network-specific heterogeneity parameter.²³ The statistical heterogeneity will be examined using the I^2 statistic, and according to its values, the heterogeneity will be considered not important (0%–40%), moderate (30%–60%), substantial (50%–90%) and considerable (75%–100%). Furthermore, the τ^2 statistic will be calculated using the following values for its interpretation: 0.04 as a low, 0.14 as a moderate and 0.40 as a substantial degree of clinical relevance of heterogeneity.^{24 25} These results will be displayed by creating both forest plots and a league table. In addition, we will calculate the relative ranking of the different treatments for each outcome using the distribution of the ranking probabilities and the surface under the cumulative ranking (SUCRA). SUCRA represents an inversely scaled average rank of the intervention, with a numerical value between 0 and 1. The best treatment would obtain a value close to 1, and the worst intervention would obtain a value close to 0.²⁰

Consistency will be assessed using the Wald test, and we will use sidesplitting as an additional assessment of inconsistency. For the transitivity assessment, we will check that all participants in the studies included in the NMA had similar baseline important clinical and methodological characteristics that might modify the treatment effect.^{26 27}

The small study effect and publication bias will be analysed, and a network funnel plot will be used to visually scrutinise the criterion of symmetry. All analyses will be conducted with Stata V.15.0 (Stata).

DISCUSSION

The benefits of regular physical activity to prevent and treat ASCVD have been extensively described in the scientific literature. This is because physical activity prevents and helps treat many atherosclerotic risk-related factors,

such as insulin resistance, glucose intolerance, elevated blood pressure, elevated triglyceride levels, high LDL-c concentrations, low levels of HDL-c and obesity.²⁸

Pharmacological interventions are commonly used to improve cardiovascular risk factor levels and prevent ASCVD, although an active lifestyle and a healthy diet are considered the first line in primary prevention, as several guidelines suggest.^{4 29 30} In fact, a recent NMA found a modest but consistent reduction in systolic blood pressure through structured exercise interventions (aerobic, resistance and combined) of any frequency, duration or intensity; this study reported, in patients with hypertension, effects for exercise interventions similar to those of antihypertensive medication, although we should consider that the characteristics of patients included in the studies differed substantially.³¹ In addition, other studies have shown improvements in other cardiometabolic risk factors, such as triglycerides, HDL-c, fasting glucose, HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) and/or HbA1c (Hemoglobin A1c), associated with exercise practice.^{32 33}

Thus, physical activity seems to be an attractive alternative to pharmacological intervention as a first-line treatment in managing cardiovascular risk factors such as hypertension and dyslipidaemia due to its comparatively less frequent and severe side effects; nevertheless, because of the low level of long-term adherence to exercise, more research addressing this issue is needed.³⁴

Among the pharmacological strategies, the fixed-dose combination has emerged as a promising strategy, although its effectiveness in the prevention of all-cause mortality or ASCVD events is uncertain.⁷ In fact, some authors recommend not using the polypill in isolation but as a part of a comprehensive ASCVD prevention strategy that includes, among other components, physical activity.⁴

Given the importance of controlling cardiovascular risk factors and the multiple health benefits of physical activity, a more detailed and comprehensive review on the effects of exercise on cardiovascular health risk factors seems necessary. This protocol provides clear and structured procedures for maximising the extraction of relevant information and provides summarised information. The results of these studies could influence evidence-based decisions for patients and practitioners and may potentially be included in guidelines for the management of some cardiovascular risk factors, such as blood lipids and overall cardiovascular risk.

Strengths and limitations

The main anticipated limitations are inherent to meta-analyses, such as limited or incoherent information from studies, high heterogeneity and risk-of-bias assessments; thus, conclusions should be interpreted cautiously and with consideration of these limiting factors. To reduce and control these limitations, this work will follow PRISMA³⁵ and PRISMA-NMA¹⁹ guidelines and

the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.¹⁴

ETHICS AND DISSEMINATION

Ethical approval will not be needed because data included in the NMA will be extracted from published trials that meet accepted ethical standards, and there will be no concerns about privacy. With the aim of disseminating the evidence obtained, the results will be published in a peer-reviewed international journal to improve clinical practices with scientific evidence. The evidence obtained could be included in guidelines to prevent cardiovascular diseases.

Patients and practitioner's involvement

The prevention of ASCVDs is a major concern for both clinicians and patients. The results of these studies will potentially be useful for providing the best available evidence regarding the comparative effect of a polypill and exercise on preventing ASCVD events and all-cause mortality, but because our design is a secondary analysis of published studies, we felt that clinician and patient involvement was not required at this time. However, to reach the highest impact, as noted above, we will widely disseminate our findings in scientific symposiums and journals, as well as via social networks and the media.

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