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Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries (Review)

Uthman OA, Hartley L, Rees K, Taylor F, Ebrahim S, Clarke A

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[Intervention Review]

Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries

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ABSTRACT

Background

In many low- and middle-income countries (LMICs) morbidity and mortality associated with cardiovascular diseases (CVDs) have grown exponentially over recent years. It is estimated that about 80% of CVD deaths occur in LMICs. People in LMICs are more exposed to cardiovascular risk factors such as tobacco, and often do not have access to effective and equitable healthcare services (including early detection services). Evidence from high-income countries indicates that multiple risk factor intervention programmes do not result in reductions in CVD events. Given the increasing incidence of CVDs and lower CVD health awareness in LMICs it is possible that such programmes may have beneficial effects.

Objectives

To determine the effectiveness of multiple risk factor interventions (with or without pharmacological treatment) aimed at modifying major cardiovascular risk factors for the primary prevention of CVD in LMICs.

Search methods

We searched (from inception to 27 June 2014) the Cochrane Library (CENTRAL, HTA, DARE, EED), MEDLINE, EMBASE, Global Health and three other databases on 27 June 2014. We also searched two clinical trial registers and conducted reference checking to identify additional studies. We applied no language limits.

Selection criteria

We included randomised controlled trials (RCTs) of health promotion interventions to achieve behaviour change (i.e. smoking cessation, dietary advice, increasing activity levels) with or without pharmacological treatments, which aim to alter more than one cardiovascular risk factor (i.e. diet, reduce blood pressure, smoking, total blood cholesterol or increase physical activity) of at least six months duration of follow-up conducted in LMICs.

Data collection and analysis

Two authors independently assessed trial eligibility and risk of bias, and extracted data. We combined dichotomous data using risk ratios (RRs) and continuous data using mean differences (MDs), and presented all results with a 95% confidence interval (CI). The primary outcome was combined fatal and non-fatal cardiovascular disease events.

Main results

Thirteen trials met the inclusion criteria and are included in the review. All studies had at least one domain with unclear risk of bias. Some studies were at high risk of bias for random sequence generation (two trials), allocation concealment (two trials), blinding of outcome assessors (one trial) and incomplete outcome data (one trial). Duration and content of multiple risk factor interventions varied across the trials. Two trials recruited healthy participants and the other 11 trials recruited people with varying risks of CVD, such as participants with known hypertension and type 2 diabetes. Only one study reported CVD outcomes and multiple risk factor interventions did not reduce the incidence of cardiovascular events (RR 0.57, 95% CI 0.11 to 3.07, 232 participants, low-quality evidence); the result is imprecise (a wide confidence interval and small sample size) and makes it difficult to draw a reliable conclusion. None of the included trials reported all-cause mortality. The pooled effect indicated a reduction in systolic blood pressure (MD -6.72 mmHg, 95% CI -9.82 to -3.61, $I^2 = 91%$, 4868 participants, low-quality evidence), diastolic blood pressure (MD -4.40 mmHg, 95% CI -6.47 to -2.34, $I^2 = 92%$, 4701 participants, low-quality evidence), body mass index (MD -0.76 kg/m², 95% CI -1.29 to -0.22, $I^2 = 80%$, 2984 participants, low-quality evidence) and waist circumference (MD -3.31, 95% CI -4.77 to -1.86, $I^2 = 55%$, 393 participants, moderate-quality evidence) in favour of multiple risk factor interventions, but there was substantial heterogeneity. There was insufficient evidence to determine the effect of these interventions on consumption of fruit or vegetables, smoking cessation, glycated haemoglobin, fasting blood sugar, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and total cholesterol. None of the included trials reported on adverse events.

Authors' conclusions

Due to the limited evidence currently available, we can draw no conclusions as to the effectiveness of multiple risk factor interventions on combined CVD events and mortality. There is some evidence that multiple risk factor interventions may lower blood pressure levels, body mass index and waist circumference in populations in LMIC settings at high risk of hypertension and diabetes. There was considerable heterogeneity between the trials, the trials were small, and at some risk of bias. Larger studies with longer follow-up periods are required to confirm whether multiple risk factor interventions lead to reduced CVD events and mortality in LMIC settings.

PLAIN LANGUAGE SUMMARY

Concurrent health promotion interventions for preventing cardiovascular disease in low- and middle income countries (“resource-limited settings”)

Review question

This review examines the effectiveness of health promotion interventions that aim to reduce more than one major cardiovascular risk factor (multiple risk factor intervention) for the primary prevention of cardiovascular disease in low- and middle-income countries (LMICs). Such risk factors are overweight/obesity, high blood pressure, smoking, too much bad cholesterol or low physical activity levels.

Background

Evidence from high-income countries indicates that multiple risk factor intervention programmes do not result in reductions in cardiovascular disease (CVD) events. Given the increasing incidence of CVDs and lower CVD health awareness in LMICs it is possible that such programmes may have beneficial effects. One vital element in improving this situation is a comprehensive and relevant evidence base, which would equip LMICs to take informed action. The components of health promotion activities may include the following: (a) dietary advice to promote healthy eating habits; (b) reducing harmful alcohol intake; (c) advice on the cessation of cigarette smoking; (d) advice on increasing daily physical activity; and (e) reducing body weight.

Study characteristics

We performed a thorough search of the medical literature up to June 2014. We identified 13 trials that recruited 7310 participants. Two trials recruited healthy participants and the other 11 trials recruited people at varying risk of CVD, such as participants with known

hypertension (“high blood pressure”) and type 2 diabetes, and randomly assigned them to either a multiple risk factor intervention or to no intervention. The trials were conducted between 2001 and 2010, and published between 2004 and 2012. Three trials were conducted in Turkey. Two trials each were conducted in China and Mexico. One trial recruited participants from both China and Nigeria. The other trials were conducted in Brazil, India, Pakistan, Romania and Jordan. The content of the interventions varied across the trials; most of the trials included dietary advice and advice on physical activity. The trials follow-up the participants between six months to 30 months (average follow-up period was 13.3 months).

Key results

We found that evidence for effects on cardiovascular disease events was scarce, with only one trial reporting these. None of the included trials reported deaths from any cause. Multiple risk factors interventions may lower systolic blood pressure, diastolic blood pressure, body mass index and waist circumference. We found no difference for eating more fruit and vegetables, rates of smoking cessation, measure of blood glucose sugar was for the past two to three months, fasting blood sugar, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and total cholesterol. None of the included trials reported on harms.

Quality of the evidence

Overall, the studies included in this review were at some risk of bias and there was variation between the results of the studies when we analysed the data. Our findings should be treated with some caution.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries					
Patient or population: people with primary prevention of cardiovascular disease in Settings: Low- and middle-income countries Intervention: Multiple risk factor interventions					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Multiple risk factor interventions			
Cardiovascular event	32 per 1000	18 per 1000 (4 to 99)	RR 0.57 (0.11 to 3.07)	232 (1 study)	⊕⊕○○ low ¹
Systolic blood pressure, change from baseline (mmHg)	The mean change from baseline in systolic blood pressure was -8.69 mmHg	The mean systolic blood pressure, change from baseline (mmHg) in the intervention groups was 6.72 lower (9.82 to 3.61 lower)		4868 (11 studies)	⊕⊕○○ low ²
Diastolic blood pressure, change from baseline (mmHg)	The mean change from baseline in diastolic blood pressure was -4.96 mmHg	The mean diastolic blood pressure, change from baseline (mmHg) in the intervention groups was 4.4 lower (6.47 to 2.34 lower)		4701 (11 studies)	⊕⊕○○ low ²
Body mass index, change from baseline (kg/m²)	The mean change from baseline in body mass index was -0.94 kg/m ²	The mean body mass index, change from baseline (kg/m ²) in the intervention groups was 0.76 lower (1.29 to 0.22 lower)		2984 (7 studies)	⊕⊕○○ low ²

Waist circumference, change from baseline (cm)	The mean change from baseline in waist circumference was -3.68 cm	The mean waist circumference, change from baseline (cm). in the intervention groups was 3.31 lower (4.77 to 1.86 lower)	393 (4 studies)	⊕⊕⊕○ moderate ³
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹The effect estimate is limited by the small sample size of the study and wide confidence interval for the effect estimate

²Inconsistency rated very serious as there was moderate heterogeneity in treatment effect estimates ($I^2 > 75\%$).

³Inconsistency rated serious as there was considerable heterogeneity in treatment effect estimates ($I^2 > 50\%$).

BACKGROUND

Description of the condition

Non-communicable diseases (or chronic diseases), are not transmitted from person to person and are of slow progression (Hunter 2013; WHO 2015a). The four main types of non-communicable disease are cardiovascular disease, cancer, chronic respiratory disease and diabetes (Hunter 2013; WHO 2015a). In many low- and middle-income countries (LMICs) the morbidity and mortality associated with non-communicable diseases have grown exponentially over recent years (WHO 2005; WHO 2011). It is estimated that about 80% of non-communicable disease deaths occur in LMICs, which is a reflection of both the size of this population and epidemiological changes (WHO 2005; WHO 2011). In 2010, it was estimated that most non-communicable diseases-associated deaths occurred before 60 years of age, and that the preponderance of these deaths occurred in LMICs (Lim 2012). LMICs are now experiencing epidemiological transition, the change from a burden of infectious diseases to chronic diseases (Gaziano 2010), due to dramatic changes in diet and lifestyle. The epidemiological transition in LMICs is happening in a shorter time frame than that experienced historically by high-income countries (Miranda 2008). Urbanisation and consumption of unhealthy diets are the main causes of this epidemic in LMICs (BeLue 2009; Miranda 2008; WHO 2011). In addition, LMICs are not only dealing with the emerging burden of non-communicable diseases, but also the current burden of infectious diseases (Perel 2006; Reddy 2004; Yusuf 2001a; Yusuf 2001b).

Cardiovascular diseases account for most non-communicable disease deaths, or 17.3 million people annually, followed by cancers (7.6 million), respiratory diseases (4.2 million) and diabetes (1.3 million) (Lim 2012). It is estimated that these four groups of diseases account for around 80% of all non-communicable disease deaths and they share four risk factors: tobacco use, physical inactivity, the harmful use of alcohol, and unhealthy diets (Ezzati 2013; Lim 2012). 'Cardiovascular diseases' is a term for a group of diseases of blood vessels and the heart. The following are the major types of cardiovascular disease: cerebrovascular disease, congenital heart disease, and coronary heart disease (WHO 2015b). While people in LMICs are now exposed to increased intermediate cardiovascular risks, such as tobacco use, they have less access to preventive programmes and effective healthcare needs (WHO 2015b).

Description of the intervention

Multiple risk factor interventions (health promotion activities) are defined as interventions that address more than one cardiovascular disease risk factor at the same time, in addition to, or instead of,

pharmacological treatments, in order to modify major cardiovascular risk factors. The components of multiple risk factor interventions include, but are not limited to, the following: (a) dietary advice to modify the individual's eating habits in order to reduce the percentage of calories from saturated fats, decrease the dietary cholesterol intake, and increase the percentage of calories from polyunsaturated fats; (b) reducing harmful alcohol intake; (c) advice on the cessation of cigarette smoking; (d) advice on increasing daily physical activity; and (e) reducing body weight (Benfari 1981; Davey 2005; Kornitzer 1985). Since the incidence of cardiovascular disease is mainly explained by the presence of modifiable risk factors (blood lipid levels, blood pressure and cigarette smoking), reducing these risk factors through health promotion that focuses on lifestyles is a logical way to prevent cardiovascular disease. However, current evidence suggests that these interventions do not result in lower CVD events (Ebrahim 2011).

Therapeutic lifestyle modification, including increasing physical activity, changing eating habits and eliminating addictions, has been seen as a cornerstone of therapy for managing people with metabolic syndrome (Márquez-Celedonio 2009), a clinical entity characterised by a constellation of metabolically relevant abnormalities, and cardiovascular risk factors, including obesity, insulin resistance/glucose intolerance, dyslipidaemia and hypertension (Grundy 2005; Magkos 2009). Several intervention trials have reported the effects of lifestyle intervention programmes among high-risk groups (Ebrahim 2011; Mattila 2003; Muto 2001; Nilsson 2001). Lifestyle modifications have been shown to decrease the incidence of type 2 diabetes mellitus by 58% among people with impaired glucose intolerance (Knowler 2002; Tuomilehto 2001) and significantly lowered systolic blood pressure between -5.4 to -11.4 mmHg (Baena 2014). Therapeutic lifestyle interventions have been found to be at least as effective as pharmacotherapies (Gillies 2007), at little cost and with minimum risk (Appel 1997). In contrast to most pharmacotherapies, lifestyle modifications can also prevent or control other chronic conditions (Knowler 2002; Stamler 1989). However, it has been suggested that in order for therapeutic lifestyle modification to be effective, it is important to pay attention not only to one single cardiovascular risk factor but to several factors simultaneously (Tuomilehto 2011). It is therefore generally recommended that lifestyle modifications should be implemented as a group (JNC-VII 2003).

How the intervention might work

The majority of the models of health behaviour change that are currently used as a basis for multiple risk factor interventions for preventing cardiovascular disease are derived from traditional cognitive theory (Bandura 1977a). They include the health belief model (Maimen 1974), health promotion model (Pender 1988), theory of reasoned action (Ajzen 1980; Ajzen 1985; Ajzen 1991), theory of planned behaviour (Ajzen 1980; Ajzen 1985; Ajzen 1991), self-efficacy theory (Bandura 1977), and the 'stages of

change' model (Norcross 2011; Prochaska 1979; Prochaska 1983). The theory of planned behaviour proposes that a person's intention to perform a behaviour is the immediate determinant of that behaviour, as it reflects the level of motivation a person is willing to exert to perform the behaviour (Ajzen 1991). Another widely applied cognitive model is the 'stages of change' model (also referred to as the transtheoretical model) (Chouinard 2007; Mochari-Greenberger 2010; Salmela 2009). The transtheoretical model subdivides individuals into five categories (Norcross 2011; Prochaska 1979; Prochaska 1983); these represent different milestones or 'levels of motivational readiness' along a continuum of behaviour change (Heimlich 2008). These stages are: (i) precontemplation (the individual is unaware of the problem and there is no intention to change behaviour in the foreseeable future); (ii) contemplation (the individual is aware of the problem and there is a serious consideration of change in behaviour); (iii) preparation (the individual is willing to take action); (iv) actionable (the individual modifies their behaviour, experiences or environment or both in order to overcome the problem); and (v) maintenance (the individual works to prevent relapse and consolidate gains). The Isfahan Healthy Heart Program (IHHP) is a comprehensive, integrated, community-based programme for cardiovascular disease prevention and control, aiming to reduce cardiovascular disease risk factors and improve cardiovascular health behaviour among Iranians (Sarraf-Zadegan 2003). The IHHP advocated prevention and control of high blood pressure and diabetes, healthy eating patterns to lower cholesterol, non-smoking and regular physical activity. Sarraf-Zadegan 2003 reported that the prevalence of abdominal obesity, hypertension, hypercholesterolaemia and hypertriglyceridaemia decreased significantly in the intervention areas compared with reference areas in both sexes. Jeemon 2012, using a non-randomised comparison, examined the impact of a comprehensive cardiovascular risk reduction programme on risk factor clustering associated with elevated blood pressure, using a sentinel surveillance study in an Indian industrial population (SSIP), using a population-based approach (Jeemon 2012; Prabhakaran 2009; Reddy 2006). The components of the SSIP intervention included: "1) workplace-organised individual and group counselling sessions, health displays, cooking competitions and dance classes; 2) posters, banners, handouts, booklets and real-time videos with simple, captivating messages translated into seven Indian languages for health education; 3) initiation of changes by management and employees (e.g. increasing salads and decreasing salty and fried foods on canteen menus, and enforcing smoking bans); and 4) identifying high-risk individuals through screening who were referred to the on-site health facilities for risk management (individual and group counselling was also offered)" (Jeemon 2012). The results of the SSIP programme showed that a comprehensive cardiovascular disease risk reduction programme significantly reduced the cardiovascular risk burden, the proportion of participants with high blood pressure, and risk factors decreased from 10.6% to 4.7% in the intervention group

but increased from 13.3% to 17.8% in the no-intervention group (Jeemon 2012).

Why it is important to do this review

A comprehensive Cochrane review has examined the effectiveness of multiple risk factor interventions in all settings, predominantly high-income countries (Ebrahim 2011). It pooled data from 14 trials that randomised 139,256 participants and reported clinical event endpoints. Ebrahim 2011 found that "counselling and education interventions designed to change health behaviours do not reduce total or coronary heart disease mortality or clinical events in general populations, but they may be effective in reducing mortality in high-risk hypertensive and diabetic populations". The Ebrahim review, in which most studies were based in high-income countries, concluded that health promotion interventions have limited use in general populations. Caution is needed in generalising evidence from high-income countries to the current LMIC context because of the differences in settings and the nature of the communities, as well as the targeted populations.

OBJECTIVES

To determine the effectiveness of multiple risk factor interventions (with or without pharmacological treatment) aimed at modifying major cardiovascular risk factors for the primary prevention of cardiovascular disease in low- and middle-income countries (LMICs).

METHODS

Criteria for considering studies for this review

Types of studies

We include randomised controlled trials (RCTs) of at least six months duration of follow-up, conducted in LMICs. The trials' randomisation units could either be individuals or clusters (such as family, workplace site). We only include trials conducted in LMICs as defined in the World Bank Country Income Groups at the time of the trial's data collection (World Bank 2014).

Types of participants

Adult populations (≥ 18 years of age). We include workforce populations, population-based studies that include high-risk groups (such as hypertension, obesity, hyperlipidaemia, type 2 diabetes or a combination of these) or individuals without high risk of developing cardiovascular disease.

We exclude trials where there is evidence that more than 25% of the participants have diagnosed cardiovascular disease at baseline. As with previous systematic review on multiple risk factor interventions, our cut-off was 25% (Ebrahim 2011).

Types of interventions

Health promotion interventions to achieve behaviour change, such as smoking cessation, dietary advice, increasing activity levels, with or without pharmacological treatments, which aim to alter more than one cardiovascular risk factor including: diet, blood pressure, smoking, total blood cholesterol or physical activity.
Comparison: no intervention for the control group.

Types of outcome measures

Primary outcomes

1. Combined fatal and non-fatal cardiovascular disease events (including myocardial infarction, unstable angina, need for coronary bypass grafting or percutaneous coronary intervention, stroke, peripheral artery disease)
2. Adverse events

Secondary outcomes

1. All cause-mortality
2. Changes in cardiovascular disease risk factors (blood pressure, lipid levels, diabetes, and obesity)
3. Changes in health knowledge, attitudes and intention

Search methods for identification of studies

Electronic searches

We identified trials through systematic searches of the following bibliographic databases (from inception to 27 June 2014):

- Cochrane Central Register of Controlled Trials (CENTRAL, Issue 5 of 12, 2014) in the Cochrane Library;
- MEDLINE (Ovid, 1946 to June week 3 2014);
- EMBASE Classic + EMBASE (Ovid, 1947 to 2014 June 26);
- Science Citation Index Expanded (SCI-EXPANDED, 1970 to 25 June 2014) and Conference Proceedings Citation Index - Science (CPCI-S, 1990 to 25 June 2014) on Web of Science (Thomson Reuters);
- Database of Abstracts of Reviews of Effects (DARE, Issue 2 of 4, 2014) in the Cochrane Library;

- Health Technology Assessments (HTA, Issue 2 of 4, 2014) in the Cochrane Library;
- Economic Evaluation Database (EED, Issue 2 of 4, 2014) in the Cochrane Library;
- LILACS (Bireme);
- Global Health (OVID, 1910 to 2014 week 25);
- ELDIS (www.eldis.org).

We adapted the preliminary search strategy for MEDLINE (Ovid) for use in the other databases (Appendix 1). We applied the Cochrane sensitivity-maximising RCT filter to the MEDLINE (Ovid) strategy and adaptations of it to the other databases (except CENTRAL) (Lefebvre 2011).

We also searched the following clinical trial registries for trials that are near completion or completed but yet to be published:

1. Clinicaltrials (www.clinicaltrials.gov), search terms “(health promotion OR healthy lifestyle) AND cardiovascular disease” (searched on 4 July 2014)
2. WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/), search terms “(health promotion OR healthy lifestyle) AND cardiovascular disease” (searched on 4 July 2014)

We did not impose any restriction on language of publication.

Searching other resources

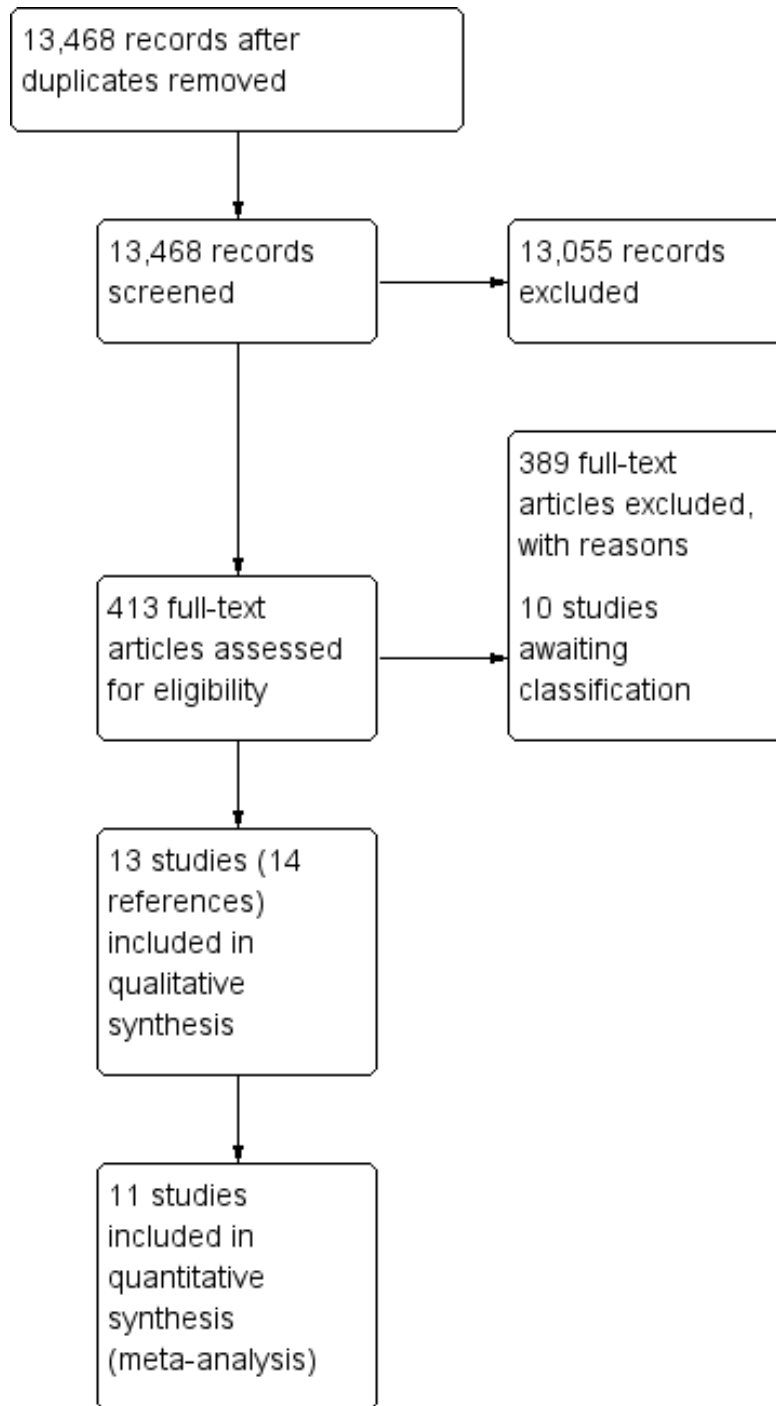
We checked the reference lists of all primary studies and review articles for additional references.

Data collection and analysis

Selection of studies

Two authors (OAU and LH) independently screened the titles and abstracts of all the potential studies we identified as a result of the search, and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. In case of any disagreements, we asked a third author (KR) to arbitrate. We retrieved the full-text study reports/publications and two authors (OAU and LH) independently screened these to identify studies for inclusion. We identified and recorded reasons for the exclusion of ineligible studies. We resolved any disagreements through discussion or, if required, we consulted a third author (KR). We identified and excluded duplicates and collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1) and 'Characteristics of excluded studies' table.

Figure 1. Study flow diagram.



Data extraction and management

We used a data collection form for study characteristics and outcome data, which had been piloted on at least one study in the review. One author (OAU) extracted study characteristics from the included studies. We extracted the following characteristics:

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals and date of study.
2. Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, baseline measures of physiological functioning (e.g. cardiovascular function, blood pressure, body mass index, blood glucose, HbA1C, smoking history), inclusion and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial and notable conflicts of interest of trial authors.

Two authors (OAU and LH) independently extracted outcome data from the included studies. We noted in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We resolved disagreements by consensus or by involving a third author (KR). One author (OAU) transferred data into the Review Manager 5 software (RevMan 2014). We double-checked that data had been entered correctly by comparing the data presented in the systematic review with the study reports. A second author (LH) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two authors (OAU and LH) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another author (KR). We assessed the risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of outcome assessment
4. Incomplete outcome data
5. Selective outcome reporting
6. Other bias

We graded each potential source of bias as high, low or unclear, and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' tables. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed.

For cluster-randomised trials, we assessed the following cluster-specific risks of bias as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

1. Recruitment bias - whether the individuals participating in the trial were blinded to the type of cluster they were in before agreeing to participate
2. Baseline imbalance - whether there were differences in baseline characteristics between the randomised groups
3. Loss of clusters - whether any complete clusters were lost to follow-up and the reasons
4. Incorrect analysis - whether the proper statistical analysis was carried out for a cluster-randomised design
5. Comparability with individually randomised trials - whether the cluster-randomisation method could have resulted in different intervention effects than an individually-randomised trial

When considering treatment effects, we took into account the risk of bias of the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to its published protocol (Uthman 2014) and reported any deviations from it in the 'Differences between protocol and review' section of the review.

Measures of treatment effect

We used Review Manager 5 to manage the data and to conduct the analyses. We reported dichotomous outcomes as risk ratios (RRs) with 95% confidence intervals (CIs). For continuous outcomes, we calculated mean differences (MDs) with 95% CIs when the studies use the same scale.

Unit of analysis issues

Cluster-randomised trials

We included cluster-randomised trials in the meta-analysis along with individually-randomised trials. Cluster-randomised trials are labelled with a (C). For cluster-randomised trials to be included in the meta-analyses, we adjusted for design effect using an 'approximation method' (Higgins 2011). The 'approximation method' entailed calculation of an 'effective sample size' for the comparison groups by dividing the original sample size by the 'design effect', which is $1 + (M - 1) ICC$, where M is the average cluster size and ICC is the intracluster correlation coefficient. For dichotomous data, we divided both the number of participants and the number who experienced the event by the same design effect, while for

continuous data, only the sample size was reduced (means and standard deviations (SDs) were left unchanged). We used the following reported (Mendis 2010 (C)) ICCs for calculating the 'design effects': systolic blood pressure: ICC 0.04; average cluster size (M): 59.92; design effect (DE) 3.36; and diastolic blood pressure: ICC 0.06; M: 59.92; DE: 4.54.

Studies with more than two treatment groups

For studies with more than two intervention groups (multi-arm studies), we included only the directly relevant arms. When we identified studies with various relevant arms, we combined the groups into a single pairwise comparison (Higgins 2011) and included the disaggregated data in the corresponding subgroup category.

Cross-over trials

We did not accept cross-over trials.

Dealing with missing data

We contacted investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as an abstract only).

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis (Higgins 2003). When we identified substantial heterogeneity (I^2 value greater than 50%), i.e. more than 50% of the variation is due to heterogeneity rather than chance (Schroll 2011), we reported it and explored possible causes by prespecified subgroup analysis.

Assessment of reporting biases

We used funnels plots and Egger tests (Egger 1997) to assess potential small-study biases and publication bias for those outcomes with more than 10 trials (i.e. systolic and diastolic blood pressure).

Data synthesis

We summarised and analysed all eligible studies in Review Manager 5. Two authors (OU and LH) extracted the data; the first author entered all data and the second author checked all entries. We resolved disagreements by discussion. We undertook meta-analyses only where this was meaningful, i.e. if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense. We combined the data using a random-effects model, due to anticipated heterogeneity that may result from the differences in methodology and study settings.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroups:

- High-risk groups (known diabetes, hypertension) compared with healthy/general population
- Low-income countries compared with low-middle-income countries

Sensitivity analysis

We planned to use sensitivity analysis to explore heterogeneity.

- Method of randomisation (clustered; clustered analyses as individual; individual).

'Summary of findings' table

We assessed the quality of evidence of the primary outcomes using the GRADE approach (Guyatt 2008) and present the results in the 'Summary of findings' table. The GRADE system considers 'quality' to be a judgement of the extent to which we can be confident that the estimates of effect are correct. The level of 'quality' is judged on a four-point scale:

1. High quality: Further research is very unlikely to change our confidence in the estimate of effect.
 2. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
 3. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
 4. Very low quality: We are very uncertain about the estimate.
- We initially graded evidence from RCTs as high, and downgraded it by either one, two, or three levels after full consideration of: any limitations in the design of the studies, the directness (or applicability) of the evidence, the consistency and precision of the results, and the possibility of publication bias.

RESULTS

Description of studies

Results of the search

The literature searches yielded 13,468 titles of potentially relevant articles after duplicates were removed. After scanning titles and abstracts, we identified 413 potentially relevant articles and assessed full-text copies against the inclusion criteria. Of these, 13 RCTs met the inclusion criteria. Details of the flow of studies through the review are given in Figure 1.

Included studies

Details of the methods, participants, intervention, comparison group and outcome measures for each of the included studies in the review are provided in the [Characteristics of included studies](#) table.

We included 13 trials (Avram 2011; Cakir 2006; Chao 2012; Garcia-Peña 2001; Hacıhasanoglu 2011; Hammad 2011; Jafar 2009 (C); Kisioglu 2004; Lu 2011; Márquez-Celedonio 2009; Mendis 2010 (C); Sartorelli 2005; Snehalatha 2008). Where this was reported, the trials were conducted between 2001 and 2010, and published between 2004 and 2012. Three trials were conducted in Turkey (Cakir 2006; Hacıhasanoglu 2011; Kisioglu 2004). Two trials each were conducted in China (Chao 2012; Lu 2011) and Mexico (Garcia-Peña 2001; Márquez-Celedonio 2009). One trial recruited participants from both China and Nigeria (Mendis 2010 (C)). The other trials were conducted in Brazil (Sartorelli 2005), India (Snehalatha 2008), Pakistan (Jafar 2009 (C)), Romania (Avram 2011) and Jordan (Hammad 2011).

Unit of randomisation

The randomisation unit for most trials was individual participants (Avram 2011; Cakir 2006; Chao 2012; Garcia-Peña 2001; Hacıhasanoglu 2011; Hammad 2011; Kisioglu 2004; Lu 2011; Márquez-Celedonio 2009; Sartorelli 2005; Snehalatha 2008). Two trials used cluster randomisation (primary care facilities (Mendis 2010 (C)) and households (Jafar 2009 (C))).

Trial participants:

Only two trials (Chao 2012; Kisioglu 2004) recruited participants from healthy or general population. Most trials (n = 11) recruited high-risk groups: known hypertensive people (Cakir 2006; Garcia-Peña 2001; Hacıhasanoglu 2011; Jafar 2009 (C); Mendis 2010 (C)); pre-hypertensive people (Márquez-Celedonio 2009); metabolic syndrome (Avram 2011; Hammad 2011); obese participants (Sartorelli 2005); and people with impaired glucose regulation (Lu 2011; Snehalatha 2008).

Intervention content:

The content of the interventions varied across the trials (see [Table 1](#)). Most of the trials included dietary advice and advice on physical activity. The follow-up period ranged from six months to 30 months (mean 13.3 months).

Excluded studies

We present details and reasons for exclusion for the studies that most nearly missed the inclusion criteria in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

We present details for each of the included trials in the 'Risk of bias' tables in the [Characteristics of included studies](#), and summaries in [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

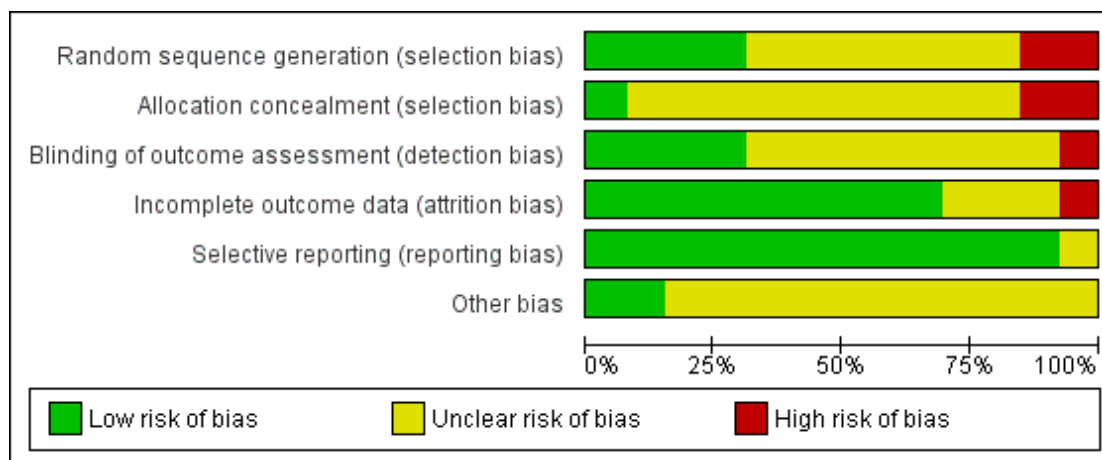


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Avram 2011	-	-	+	?	?	?
Cakir 2006	+	+	+	+	+	?
Chao 2012	+	?	?	+	+	?
Garcia-Peña 2001	?	?	?	+	+	?
Hacihasanoglu 2011	-	-	-	+	+	?
Hammad 2011	+	?	?	+	+	?
Jafar 2009 (C)	+	?	+	+	+	+
Kisioglu 2004	?	?	+	+	+	?
Lu 2011	?	?	?	+	+	?
Márquez-Celedonio 2009	?	?	?	+	+	?
Mendis 2010 (C)	?	?	?	?	+	+
Sartorelli 2005	?	?	?	-	+	?
Snehalatha 2008	?	?	?	?	+	?

Allocation

The generation of allocation sequence was adequate in four trials (Cakir 2006; Chao 2012; Hammad 2011; Jafar 2009 (C)), unclear in seven trials (Garcia-Peña 2001; Kisioglu 2004; Lu 2011; Márquez-Celedonio 2009; Mendis 2010 (C); Sartorelli 2005; Snehalatha 2008) and inadequate in two trials (Avram 2011; Hacıhasanoglu 2011). Avram 2011 and Hacıhasanoglu 2011 used the calendar date for generating allocation sequence. Allocation concealment was adequate in one trial (Cakir 2006), inadequate in two trials (Avram 2011; Hacıhasanoglu 2011) and unclear in the remaining 10 trials.

Blinding

Four trials (Avram 2011; Cakir 2006; Jafar 2009 (C); Kisioglu 2004) masked outcome assessors to treatment allocation and one trial (Hacıhasanoglu 2011) did not. It is not clear whether the remaining trials masked outcome assessors to treatment allocation.

Incomplete outcome data

The potential risk of bias likely to be introduced by incomplete data was high in only one trial (Sartorelli 2005), unclear in three trials (Avram 2011; Mendis 2010 (C); Snehalatha 2008), low in the remaining nine trials.

Selective reporting

The risk of selective reporting bias was unclear in Avram 2011, and low in the remaining 12 trials.

Other potential sources of bias

The risk of bias likely to be introduced by other potential sources of bias was low in two trials (Jafar 2009 (C); Mendis 2010 (C)) and unclear in the remaining 11 trials.

Overall, the studies included in this review were at some risk of bias. All studies had at least one domain with unclear risk of bias, and some studies were at high risk of bias for random sequence generation (two trials: Avram 2011; Hacıhasanoglu 2011), allocation concealment (two trials: Avram 2011; Hacıhasanoglu 2011), blinding of outcome assessors (Hacıhasanoglu 2011) and incomplete outcome data (Sartorelli 2005).

Cluster-specific risks of bias

We present details for each of the included trials in Figure 4. The risk of bias due to recruitment bias was low in one trial (Jafar 2009 (C)) and unclear in one trial (Mendis 2010 (C)). Baseline characteristics were generally similar in the two cluster trials. No complete clusters were lost to follow-up in the two trials. Jafar 2009 (C) accounted for the clustering effect in the main analysis while Mendis 2010 (C) did not. It is not clear whether the cluster-randomisation method could have resulted in different intervention effects than an individually-randomised trial in the two cluster trials.

Figure 4.

	Recruitment bias	Baseline imbalances	Loss of clusters	Incorrect analysis	Comparability with individually randomised trials
Jafar 2009 (C)	+	+	+	+	?
Mendis 2010 (C)	?	+	+	-	?

Effects of interventions

See: [Summary of findings for the main comparison Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries](#)

Primary outcomes:

Combined Cardiovascular events

One trial ([Snehalatha 2008](#)) reported cardiovascular events as an outcome. There was no significant difference between intervention and control groups in the rates of cardiovascular events (RR 0.57, 95% CI 0.11 to 3.07, 232 participants) ([Analysis 1.1](#)). This result is imprecise (wide confidence interval and small sample size) and makes it difficult to draw a reliable conclusion.

Adverse events

None of the included trials reported on adverse events.

Secondary outcomes:

All-cause mortality

None of the included trials reported all-cause mortality.

Changes in cardiovascular risk factors

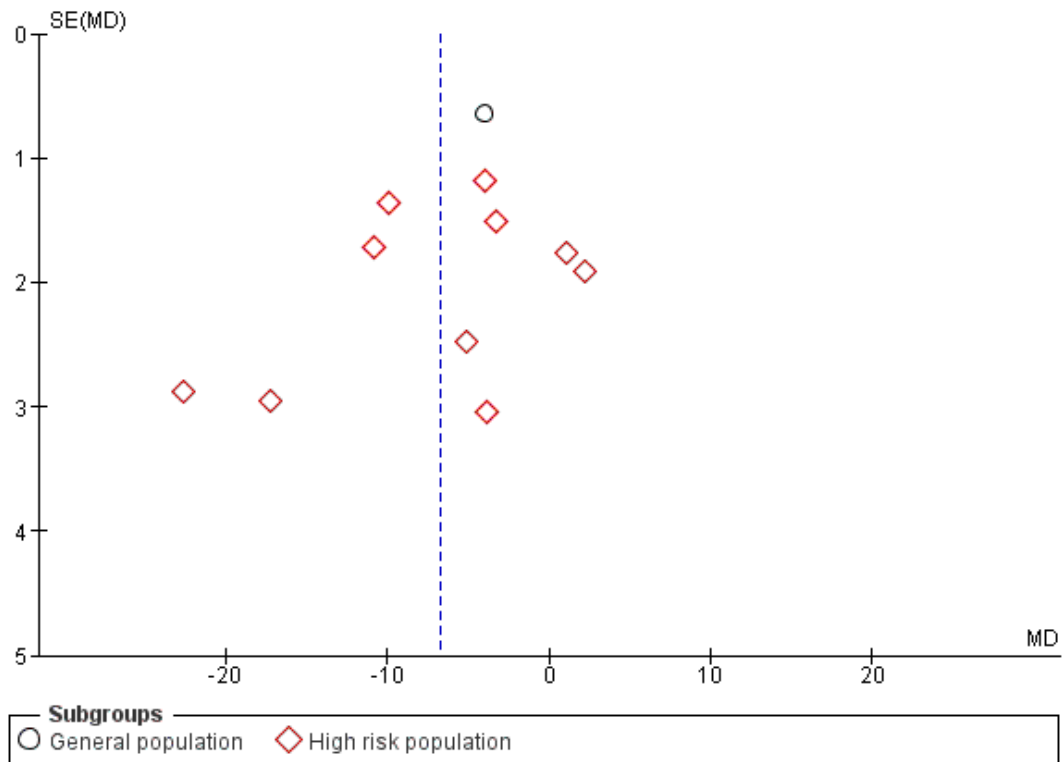
Blood pressure

Systolic blood pressure and diastolic blood pressure were reported in 11 trials (5106 participants randomised) ([Cakir 2006](#); [Chao](#)

2012; Garcia-Peña 2001; Hacıhasanoglu 2011; Hammad 2011; Jafar 2009 (C); Lu 2011; Márquez-Celedonio 2009; Mendis 2010 (C); Sartorelli 2005; Snehalatha 2008). The pooled effect showed a statistically significant reduction in systolic blood pressure (MD -6.72 mmHg, 95% CI -9.82 to -3.61, 4868 participants) (Analysis 1.2) in favour of multiple risk factors interventions, but with evidence of statistically significant substantial between-trial heterogeneity ($I^2 = 91\%$, $P = 0.0001$). There was no evidence of funnel plot asymmetry for systolic blood pressure (SBP) (Figure 5), suggesting no evidence of small-study bias ($P = 0.270$ for Egger's regression asymmetry test). In a prespecified subgroup analysis, the pooled intervention effect estimate tended to be more pronounced

among high-risk groups (MD -7.14, 95% CI -11.07 to -3.21, 10 trials, 2906 participants) than in the general population (MD -3.95, 95% CI -5.20 to -2.70, one trial, 1962 participants); however, this difference did not reach a statistically significant level ($P = 0.13$ for interaction). Sensitivity analysis showed that the beneficial effect of a multiple risk factor intervention on SBP was only significant among trials that randomised individual participants (MD -8.02 mmHg, 95% CI -11.79 to -4.24, 3549 participants) and not in trials that randomised clusters of participants (MD -1.65, 95% CI -6.52 to 3.22, 1319 participants) ($P = 0.04$ for interaction).

Figure 5. Funnel plot of comparison: 1 Multiple risk factor interventions, outcome: 1.2 Systolic blood pressure, change from baseline (mmHg).

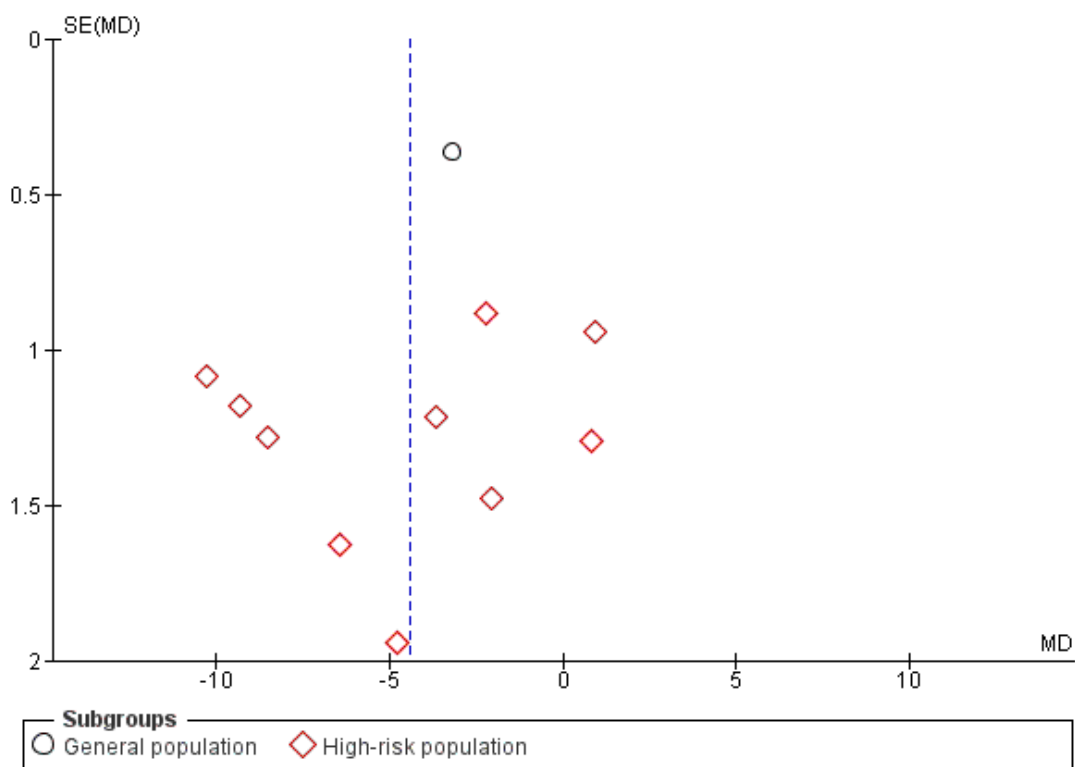


Similarly, the pooled effect showed a statistically significant reduction in diastolic blood pressure (DBP) (MD -4.40 mmHg, 95% CI -6.47 to -2.34, 4701 participants) (Analysis 1.4) in favour of multiple risk factors interventions, but with evidence of statistically significant substantial between-trial heterogeneity ($I^2 = 92\%$,

$P = 0.0001$). There was no evidence of funnel plot asymmetry for diastolic blood pressure (Figure 6), suggesting no evidence of small-study bias ($P = 0.446$ for Egger's regression asymmetry test). In a prespecified subgroup analysis, the pooled intervention effect

estimate tended to be more pronounced among high-risk groups (MD -4.55, 95% CI -7.26 to -1.85, 10 trials, 2739 participants) than in the general population (MD -3.18, 95% CI -3.90 to -2.46, one trial, 1962 participants); however, this difference did not reach a statistically significant level ($P = 0.34$ for interaction). [Kisioglu 2004](#) found no statistically significant difference between intervention and control groups in the rate of high blood pressure (RR 0.87, 95% CI 0.54 to 1.40, 400 participants). Sensitivity analysis showed that the beneficial effect of multiple risk factor interventions on DBP was only significant among trials that randomised individual participants (MD -5.29 mmHg, 95% CI -7.65 to -2.94, 3549 participants) and not in trials that randomised clusters of participants (MD -0.70, 95% CI -3.79 to 2.40, 1152 participants) ($P = 0.02$ for interaction).

Figure 6. Funnel plot of comparison: I Multiple risk factor interventions, outcome: I.4 Diastolic blood pressure, change from baseline (mmHg).



Anthropometric indices

Body mass index (BMI) was reported in seven trials ([Cakir 2006](#); [Chao 2012](#); [Hacihanoglu 2011](#); [Lu 2011](#); [Márquez-Celedonio](#)

[2009](#); [Mendis 2010 \(C\)](#); [Sartorelli 2005](#)). The pooled effect showed a statistically significant reduction in BMI (MD -0.76 kg/m², 95% CI -1.29 to -0.22, 2984 participants) ([Analysis 1.6](#)) in

favour of multiple risk factors interventions, but with evidence of statistically significant substantial between-trial heterogeneity ($I^2 = 80\%$, $P = 0.00003$). However, this effect was only significant among the high-risk groups (MD -0.94 kg/m^2 , 95% CI -1.54 to -0.33 , six trials, 1022 participants) and not among the general population (MD -0.14 kg/m^2 , 95% CI -0.47 to 0.19 , one trial, 1962 participants). Waist circumference was reported in four trials (Cakir 2006; Lu 2011; Márquez-Celedonio 2009; Snehalatha 2008). The pooled effect showed a statistically significant reduction in waist circumference (MD -3.31 , 95% CI -4.77 to -1.86 , $I^2 = 55\%$, four trials, 393 participants) (Analysis 1.7). Kisioglu 2004 found a significantly reduced rate of obesity in the intervention group compared with the control group (RR 0.71, 95% CI 0.52 to 0.97, 400 participants).

Fasting blood sugar

Six trials reported fasting blood sugar as an outcome (Chao 2012; Hammad 2011; Lu 2011; Márquez-Celedonio 2009; Sartorelli 2005; Snehalatha 2008). There was no statistically significant difference between intervention and control in mean change from baseline fasting blood glucose (MD -0.22 mmol/L , 95% CI -0.56 to 0.13 , 2726 participants) (Analysis 1.8).

Glycated haemoglobin (haemoglobin A1c)

One trial (Lu 2011) reported glycated haemoglobin as an outcome. There was no statistically significant difference between the intervention and control groups in mean change from baseline percentage HbA1c (MD -0.08% , 95% CI -0.38 to 0.22 , 181 participants).

Blood lipids

Six trials reported on blood lipids (Cakir 2006; Hammad 2011; Lu 2011; Márquez-Celedonio 2009; Sartorelli 2005; Snehalatha 2008). There were no statistically significant differences between intervention and control in mean change from baseline high density lipoprotein (HDL) cholesterol (MD 0.03 mmol/L , 95% CI -0.01 to 0.07 , 824 participants) (Analysis 1.9), low density lipoprotein (LDL) cholesterol (MD -0.13 mmol/L , 95% CI -0.53 to 0.27 , four trials, 544 participants) (Analysis 1.9) and total cholesterol (MD -0.22 mmol/L , 95% CI -0.48 to 0.04 , five trials, 625 participants) (Analysis 1.9). There was a small but statistically significant reduction in triglycerides with multiple risk factor interventions of -0.14 mmol/L (95% CI -0.23 to -0.04 , six trials, 2705 participants) (Analysis 1.10).

Changes in health knowledge, attitudes and intention.

Fruits and vegetables consumption

One trial (Mendis 2010 (C)) (2166 participants randomised) reported increased fruit and vegetable consumption as an outcome. At site B (Nigeria), participants in the intervention group showed a significantly greater increase in fruit consumption (RR 5.02, 95% CI 3.40 to 7.40, $P = 0.0001$, 247 participants) and a non-significant increase in vegetable consumption (RR 2.00, 95% CI 0.91 to 4.40, $P = 0.08$, 247 participants) compared to the control group. However, in site A (China), there was no significant difference between the intervention and control groups in the number of those that increased fruit consumption (RR 1.03, 95% CI 0.77 to 1.39, $P = 0.83$, 301 participants) and vegetable consumption (RR 0.88, 95% CI 0.53 to 1.46, $P = 0.62$, 301 participants) compared with the control group.

Smoking cessation

One trial (Mendis 2010 (C)) (2166 participants randomised) reported smoking cessation as an outcome. There was no significant difference between the intervention and control groups in the number of those that stopped smoking at both sites: Site A (China: RR 2.08, 95% CI 0.19 to 23.21, $P = 0.55$, 301 participants) and Site B (Nigeria: RR 0.62, 95% CI 0.21 to 1.83, $P = 0.38$, 247 participants).

DISCUSSION

Summary of main results

This review of multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries (LMICs) has brought together evidence from 13 randomised controlled trials primarily from the last 10 years, incorporating 7310 participants. We found that evidence for effects on CVD events was scarce, with only one trial reporting these. We found that multiple risk factor interventions have an effect on some risk factors, especially on systolic blood pressure, diastolic blood pressure, body mass index and waist circumference. However, the risk factor changes associated with interventions should be interpreted with caution. The meta-analyses of risk factor changes were highly heterogeneous, making pooled estimates of effect questionable. Furthermore, there are many problems in relating trial outcome to a risk measure which is itself dependent on the outcome in meta-analysis (Egger 1995).

Overall completeness and applicability of evidence

The majority of the trials included in our review recruited participants who were at varying levels of CVD risk. Only one trial provided usable data on the general population. In addition, only

one small trial of the effect of multiple risk factor interventions on cardiovascular events reported our primary outcome, combined fatal and non-fatal CVD events (including myocardial infarction, unstable angina, need for coronary bypass grafting or percutaneous coronary intervention, stroke, peripheral artery disease). The result for the CVD events is imprecise (a wide confidence interval and small sample size) as this outcome was reported by only a single small study, underpowered to detect differences. This small trial lacks statistical power and makes it difficult to draw a reliable conclusion.

Quality of the evidence

Overall, the studies included in this review were at some risk of bias, and the results should be treated with caution. We assessed the quality of the evidence in this review using the GRADE approach, and present the evidence in [Summary of findings for the main comparison](#). For cardiovascular events, systolic blood pressure, diastolic blood pressure and body mass index we judged the quality of evidence to be low, reflecting that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. We downgraded the evidence for cardiovascular events by two levels for very serious imprecision. The quality of evidence for the primary outcome of cardiovascular events was limited by the small sample size of the study and a wide confidence interval for the effect estimate. For systolic blood pressure, diastolic blood pressure and body mass index, we downgraded the evidence by two levels for very serious inconsistency because of considerable heterogeneity in treatment effect estimates ($I^2 > 75\%$). We graded the quality of evidence for waist circumference as moderate, suggesting that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. We downgraded the evidence for mean change waist circumference by one level for serious inconsistency because of moderate heterogeneity in treatment effect estimates ($I^2 > 50\%$). We found statistically significant heterogeneity in all the meta-analyses of changes in CVD risk factors, thus suggesting that the percentage of the variability in effect estimates that is due to heterogeneity rather than to sampling error (chance) is important. The heterogeneity may be due to differences in study follow-up, geographical location, baseline differences in blood pressure values and content of the multiple risk factor interventions.

Potential biases in the review process

We conducted a comprehensive search across major databases for multiple risk factor interventions. We also screened systematic review reference lists and we contacted trial authors when necessary. Two authors independently carried out all screening, inclusion and exclusion and data abstraction, and conducted data entry and

analysis. It is unlikely that the methods used in the review could have introduced bias.

Agreements and disagreements with other studies or reviews

[Ebrahim 2011](#) conducted a Cochrane review to assess the effects of multiple risk factor interventions for reducing total mortality, fatal and non-fatal coronary heart disease (CHD) events and cardiovascular risk from factoring, among adults assumed to be without clinical evidence of prior CHD. The review included 55 trials that enrolled 163,471 participants and found that “interventions using counselling and education aimed at behaviour change do not reduce total or CHD mortality or clinical events in general populations but may be effective in reducing mortality in high-risk hypertensive and diabetic populations” ([Ebrahim 2011](#)). Another recent systematic review ([Baena 2014](#)) examined the effects of lifestyle-related interventions on blood pressure in LMICs. The review included eight multiple-intervention trials (defined as more than one lifestyle-related intervention delivered at the same time) and found that the studies combining physical activity and diet or behavioural counselling interventions significantly reduced both the SBP (pooled MD -6.1 mmHg, 95% CI -8.9 to -3.3) and DBP (pooled MD -2.4 mmHg, 95% CI -3.7 to -1.1) ([Baena 2014](#)).

AUTHORS' CONCLUSIONS

Implications for practice

Due to the limited evidence available, currently we can draw no conclusions as to the effectiveness of multiple risk factor interventions on combined CVD events and mortality. Risk factor modification programmes may be effective in altering risk factors in people living in LMICs. However, the evidence comes from studies at some risk of bias and there was statistical variation between the results of the studies.

Implications for research

There is a paucity of randomised controlled trials looking at the effects of multiple risk factor interventions for the primary prevention of CVD events and mortality over the long term. There is therefore a need for well-designed randomised controlled trials to fill this research gap. Further research is also needed to identify which components of multiple risk factor interventions, which modes of delivery and which settings are key for an effective multiple risk factor programme.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Avram 2011

Methods	Randomised controlled trial Randomisation unit: individual	
Participants	<p>Setting: participants from EuroAspire III Romania 253 high-risk individuals (on anti-hypertensive drug therapy and/or lipid-lowering drug therapy and/or anti-diabetes therapies) under 80 years, without a history of coronary or other atherosclerotic disease, who met the revised NCEP-ATPIII criteria for MetSyn: waist circumference > 102 cm in men, > 88 cm in women; elevated triglycerides: ≥ 1.7 mmol/L (≥ 150 mg/dL); low HDL- cholesterol < 1.03 mmol/L (< 40 mg/dL) in men, < 1.29 mmol/L (< 50 mg/dL) in women; systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension; impaired fasting plasma glucose ≥ 5.6 mmol/L (≥ 100 mg/dL) or previously diagnosed type 2 diabetes</p> <p>N umber of participants : 253; Intervention (n=133), Control (120)</p>	
Interventions	<p>“Each subject in the intervention was offered a total of approximately 90 min of intervention contacts in 3 consecutive visits (every 6 months) to general practitioner (GP) offices, consisting in lifestyle habits in relation to diet, weight control and physical activity. Beside this, once a month the patients received a follow- up phone from their GP, emphasis was placed on weight loss, decreasing fat intake, portion control and healthier food group selection along with increasing in daily physical activity”</p>	
Outcomes	<p>Changes in health knowledge, attitudes and intention (physical activity, intention to loose weight)</p> <p>Maximum follow-up: 18 months</p>	
Notes	<p>Study period : Not reported Sources of funding : Executive Agency for Higher Education, Research, Development and Innovation Funding (UEFISCDI), Romania Declared conflicts of interest of the trialists : None declared</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	...randomisation by calendar date
Allocation concealment (selection bias)	High risk	Allocation not concealed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “The staff members who scheduled the study visits and those who performed the measurements were blind to randomization”

Avram 2011 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to judge
Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge
Other bias	Unclear risk	Insufficient information to judge

Cakir 2006

Methods	Randomised controlled trial Randomisation unit: individual
Participants	Setting: University hospital, Instabul, Turkey Persons were eligible if they were between 18 and 65 years of age, had been diagnosed with hypertension (i.e., mean SBP of ≥ 140 mmHg and/or mean DBP of ≥ 90 mmHg on 3 separate occasions during a 3-week period), and were able to complete the questionnaire unaided N umber of participants : 60; Intervention (n=30), Control (n=30)
Interventions	“The intervention group received a 30-minute lecture by a nurse on core knowledge and information on the behavioural skills necessary to manage hypertension. In the first month, two 60-minute classes were also held for groups of 6 to 8 participants. Participants were provided with information and detailed guidelines, especially on the daily number of servings from each of the six food groups (meats and protein, grains, vegetables, fruits, dairy, and fats and oils) and the requisite amount of fat intake, sodium intake, alcohol consumption, and physical activity The diet recommendations were mainly based on the DASH diet, which emphasizes fruits, vegetables, and low-fat dairy foods; includes whole grains, poultry, fish, and nuts; and recommends smaller amounts of red meat, sweets, and sugar-containing beverages The physical exercise goal of the lifestyle modification was 30 minutes of walking 3 days per week. Participants who had not previously been physically active started with 20 minutes of walking per session and increased the duration of exercise during several weeks until their goal was met. We followed a clinical practice guideline to help participants who smoked to decrease tobacco use and dependence Participants were encouraged to stop smoking and were given an appropriately planned time in which to quit smoking (within 2 weeks) The final educational class was held at the end of the 3rd month. The goal of the final class was to maintain active behavioural changes among the participants and attempt to reengage inactive participants.”
Outcomes	Changes in CVD risk factors (blood pressure, lipid levels, anthropometric indices) Maximum follow-up period: 6 months
Notes	Study period : Not reported Sources of funding : Not reported Declared conflicts of interest of the trialists : None declared
<i>Risk of bias</i>	

Cakir 2006 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer-generated random numbers
Allocation concealment (selection bias)	Low risk	... assigned centrally
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A trained nurse took BP measurements, and the trained nurse who measured and recorded these BP results was blinded to whether the participant belonged to the intervention or the control group."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were reasonably well balanced between groups
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were clearly stated and reported
Other bias	Unclear risk	Insufficient information to judge

Chao 2012

Methods	Randomised controlled trial Randomisation unit: individual	
Participants	Setting : Nanjing Community Health Service Center Healthy adults aged 60 and over N umber of participants : 1962; Intervention (n=957), Control (n=1005)	
Interventions	"The intervention group received a health management program on diet advice, psychological aspects of health, a tailor-made exercise program based on an earlier evaluation, education/skills training on health self-management, telephone consultation, lectures on health, and distribution of health promoting materials. The components of the intervention were 'administered' at least once per month by specifically-trained community health service center staff, managers and related researchers"	
Outcomes	Changes in CVD risk factors (blood pressure, lipid levels, diabetes, obesity) Maximum follow-up: 18 months	
Notes	Study period : November 2000 to September 2001 Sources of funding : Not reported Declared conflicts of interest of the trialists : None declared	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Chao 2012 (Continued)

Random sequence generation (selection bias)	Low risk	..random number table
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were reasonably well balanced between groups
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were clearly stated and reported
Other bias	Unclear risk	Insufficient information to judge

Garcia-Peña 2001

Methods	Randomised controlled trial Randomisation unit: individual
Participants	Setting : Family Medicine Centre run by the Institute in Mexico city Participants with hypertension aged > 60 years N umber of participants : 683; Intervention (n=345), Control (n=338)
Interventions	“Participants in the intervention group received regular visits from a nurse over 6 months. During visits (between once a month and fortnightly), the nurse measured blood pressure and the nurse and patient reviewed information from the baseline health check, and discussed possible lifestyle changes. The nurses tried to guide their patients to a healthier lifestyle and suggested different alternative ways to achieve the changes and negotiated specific targets.”
Outcomes	Changes in CVD risk factors (blood pressure) Maximum follow-up: 6 months
Notes	Study period : January 1998 to June 1999 Sources of funding : National Council of Science and Technology, Mexico (CONACYT) and Mexican Institute of Social Security (IMSS) Declared conflicts of interest of the trialists : None declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to judge

Garcia-Peña 2001 (Continued)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were reasonably well balanced between groups
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were clearly stated and reported
Other bias	Unclear risk	Insufficient information to judge

Hacihanoglu 2011

Methods	Randomised controlled trial Randomisation unit: individual
Participants	Setting : Residents of Erzincan, Turkey Hypertensive patients N umber of participants : 80; Intervention (n=40), Control (n=40)
Interventions	“The intervention group received six monthly nurse-led education on healthy lifestyle behaviours (nutrition, relevant diet, importance of reduced salt intake, how to deal with stress, weight control, exercise, risks of alcohol and smoking, etc.)”
Outcomes	Changes in CVD risk factors (blood pressure, body mass index) Maximum follow-up: 6 months
Notes	Study period : February 2006 to November 2006 Sources of funding : Not reported Declared conflicts of interest of the trialists : None declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	.. days of the week
Allocation concealment (selection bias)	High risk	allocation not concealed
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: “Allocation and outcomes data were not blind”

Hacihasanoglu 2011 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were reasonably well balanced between groups
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were clearly stated and reported
Other bias	Unclear risk	Insufficient information to judge

Hammad 2011

Methods	Randomised controlled trial Randomisation unit: individual
Participants	Setting : Six family medicine clinics at Jordan University Hospital People with metabolic syndrome as defined the NCEP/ATP III criteria N umber of participants : 199; Intervention (n=110), Control (n=89)
Interventions	“Pharmacists provided medication counselling for 30 minutes before seeing the physician, offered instructions on self-monitoring BP, and advised patients on healthy lifestyle choices (e.g., tobacco cessation and adhering to a healthy diet). Educational materials including brochures and pamphlets were provided to patients with information on the recommended dietary approaches to stop hypertension (DASH). The pharmacist emphasized lifestyle changes, particularly weight loss and physical activity, as a first-line therapy for at least 3 months.”
Outcomes	Changes in CVD risk factors (blood pressure, lipid levels, anthropometric indices) Maximum follow-up: 6 months
Notes	Study period : March 2009 to may 2009 Sources of funding : Deanship of Research, The University of Jordan, Amman, Jordan. Declared conflicts of interest of the trialists : None declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	... using a coin-toss method
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were reasonably well balanced between groups

Hammad 2011 (Continued)

Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were clearly stated and reported
Other bias	Unclear risk	Insufficient information to judge

Jafar 2009 (C)

Methods	Cluster randomised trial Randomisation unit: census-based clusters
Participants	Setting: Communities in Karachi, Pakistan Persons 40 years or older who resided in the 12 clusters and had known hypertension or consistently elevated blood pressure on 2 separate visits (mean of 2 of past 3 measurements of SBP \geq 140 mm Hg or DBP \geq 90 mm Hg) N umber of participants : 678; Intervention (n=348), Control (n=326)
Interventions	“The intervention group received community health worker-led advice on diet and the importance of engaging in moderate physical activity, maintaining normal body weight, and tobacco cessation. The nutritional recommendations were modelled on the dietary approaches to stop hypertension (DASH) diet. The first home health education session, lasting 90 minutes, was held at a time when all members of the household were present. Follow-up reinforcement visits of 30 minutes took place at three monthly intervals.”
Outcomes	Changes in CVD risk factor (blood pressure) Maximum follow-up : 24 months
Notes	Study period : Not reported Sources of funding : Wellcome Trust Declared conflicts of interest of the trialists : None declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer-generated
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Trained outcomes assessors masked to randomisation status evaluated all participants two years after randomisation. The outcomes assessors were not part of and had no relationship with the baseline data collection or the community health worker team.”

Jafar 2009 (C) (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were reasonably well balanced between groups
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were clearly stated and reported
Other bias	Low risk	The study appears to be free of other source of bias

Kisioglu 2004

Methods	Randomised controlled trial Randomisation unit: - individual
Participants	Setting: poor outskirts of the city of Isparta, Turkey Women of all ages Number of participants : 400; Intervention (n=200), Control (n=200)
Interventions	The health promotion on significance of balanced nutrition, diverse assortment of food and importance of physical exercise was delivered to women in groups of 5, the intervention was conducted only 1 to 3 intervention programmes per day. Daily and regular exercising, hiking, walking, or jogging were advised as having good health impact and reducing stress, obesity, hypertension, and osteoporosis in women
Outcomes	Changes in health knowledge, attitudes and intention Maximum follow-up: 6 months
Notes	Study period : August 2001 to September 2001 Sources of funding : Not reported Declared conflicts of interest of the trialists : None declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to judge
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The investigators and assessors were different independent persons, and the staff participating in the study were not the residents of Yenice and not related to the subjects"

Kisioglu 2004 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were reasonably well balanced between groups
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were clearly stated and reported
Other bias	Unclear risk	Insufficient information to judge

Lu 2011

Methods	Randomised controlled trial Randomisation unit: individual
Participants	Setting: 4 communities of the Shijingshan District, China Adults with impaired glucose regulation (IGR) using the 75 g OGTT Number of participants : 181; Intervention (n=95), Control (n=86)
Interventions	“Participants in the intervention group received lifestyle intervention, including lectures on diet and exercise given face-to-face once every 3 months and by telephone once per month”
Outcomes	Changes in CVD risk factors (blood pressure, lipid levels, diabetes, obesity) Maximum follow-up: 12 months
Notes	Study period : Not reported Sources of funding : Not reported Declared conflicts of interest of the trialists : None declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to judge
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were reasonably well balanced between groups
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were clearly stated and reported

Other bias	Unclear risk	Insufficient information to judge
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Mendis 2010 (C)

Methods	Cluster-randomised trial Randomisation unit: primary health care facilities
Participants	Settings : 10 pairs of primary care facilities in China Men and women 30 - 70 years of age with SBP between 140 and 179 mmHg were selected for the study if they were not on treatment for hypertension and did not have any exclusion factor N umber of participants : 2397; Intervention (n=1114), Control (n=1042)
Interventions	Participants in the intervention group were counselled on risk fact or control (tobacco cessation, diet, physical activity) at baseline, 4 months, 8 months and 12 months
Outcomes	Changes in CVD risk factors (blood pressure, obesity) and Changes in health knowledge Maximum follow-up : 12 months
Notes	Study period : 2005 to 2006 Sources of funding : Not reported Declared conflicts of interest of the trialists : None declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to judge
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to judge
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were clearly stated and reported
Other bias	Low risk	The study appears to be free of other source of bias

Márquez-Celedonio 2009

Methods	Randomised controlled trial Randomisation unit: individual
Participants	Setting: Primary health care clinics in Mexico Individuals with prehypertension, which is defined as a SBP between 120 mmHg and 139 mmHg and a DBP between 80 mmHg and 89 mmHg N umber of participants : 81; Intervention (n=38), Control (n=43)
Interventions	”Participants in the intervention group undertook a lifestyle modification program for a period of 6 months: assigned a low-sodium, DASH-type diet; undertook 3-5 sessions per week of aerobic physical exercise (walking, running, swimming) complemented by group sport sessions (soccer, basketball, volleyball, or “cachibol” [a form of volleyball often played by older persons]). Each session lasted 45 min, starting with stretching exercises followed by 30 min of specific exercise and a recovery phase.”
Outcomes	Changes in CVD risk factors (blood pressure, lipid levels, anthropometric indices, blood sugar) Maximum follow-up: 6 months
Notes	Study period : Not reported Sources of funding : No reported Declared conflicts of interest of the trialists : None declared

Risk of bias

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to judge
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were reasonably well balanced between groups
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were clearly stated and reported
Other bias	Unclear risk	Insufficient information to judge

Sartorelli 2005

Methods	Randomised clinical trial Randomisation unit: individual
Participants	Setting: primary health-care centre in Brazil High-risk groups such as overweight/obese adults or 1st-degree relatives of people with type 2 diabetes N umber of participants : 104; Intervention (n=51), Control (n=53)
Interventions	“Subjects in the intervention group were scheduled for three individualised dietary counselling sessions during the first 6 months of intensive lifestyle intervention and further health checks at 6 months and 1 year from baseline. The intervention group received a diet prescription provided by a nutritionist with a food exchange list and was encouraged to practise at least 30 min of walking per day. The dietary interventions included increased intakes of olive oil, fruits (at least 2 servings day ⁻¹), vegetables (at least 5 servings day ⁻¹) and skimmed dairy products (2 or 3 servings day ⁻¹), together with reduced intake of saturated fat (<10% of energy by reducing red meat - less than 2 servings day ⁻¹) and keeping the consumption of total fat around 30% of energy without emphasis on total energy restriction.”
Outcomes	Changes in CVD risk factors (blood pressure, lipid levels, diabetes, obesity) Maximum follow-up: 12 months
Notes	Study period : April 2000 to March 2001 Sources of funding : São Paulo Research Foundation (FAPESP) and The Brazilian National Council for Scientific and Technological Development (CNPq) Declared conflicts of interest of the trialists : None declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to judge
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout rates in control arm
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were clearly stated and reported
Other bias	Unclear risk	Insufficient information to judge

Snehalatha 2008

Methods	Randomised controlled trial Randomisation unit: individual
Participants	Setting: The Indian Diabetes Prevention Programme (IDPP) IGT on 2 occasions (2-hr post-glucose levels > 7.8 to < 11.1 mmol/L) N umber of participants : 232; Intervention (n=108), Control (n=124)
Interventions	Participants in the intervention group received lifestyle modification (LSM) involving dietary modification and regular physical activity
Outcomes	Changes in CVD risk factors (blood pressure, lipid levels, diabetes, obesity) Maximum follow-up: 30 months
Notes	Study period : Not reported Sources of funding : Not reported Declared conflicts of interest of the trialists : Director of USV Ltd (marketer of Oral Anti-Diabetic market and Cardiovascular diseases medications) contributed to the design of the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to judge
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to judge
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to judge
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were clearly stated and reported
Other bias	Unclear risk	Insufficient information to judge

CVD: cardiovascular disease
 DBP: diastolic blood pressure
 HDL: high density lipoprotein
 IGR: impaired glucose regulation
 LDL: low density lipoprotein
 NCEP-ATP: National cholesterol education program - adult treatment panel
 OGTT: oral glucose tolerance test
 SBP: systolic blood pressure

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cezaretto 2012	Control group received some intervention
Jeemon 2012	Non-random allocation
Jiang 2002	Quasi-experimental study
Jiang 2010	Quasi-experimental study
Jordan 2008	Non-random allocation
Joshi 2012 (C)	People with CVD at baseline and no relevant outcomes reported
Kelishadi 2010	Non-random allocation
Kelishadi 2011	Non-random allocation
Kelishadi 2012	Non-random allocation
Kozlov 1997	Secondary prevention of CVD
Lafay 2006	No relevant outcome reported
Molazem 2013	Secondary prevention
Moreira 2005	Quasi-experimental study
Naser 2008	Secondary prevention
Pahkala 2013	Participants with congenital heart disease
Prabhakaran 2009	Non-random allocation
Rabiei 2010	Non-random allocation
Sarrafadegan 2013	Quasi-experimental study
Satpute 2009	Both groups received an intervention
Seligman 2011	Both groups received an intervention
Shahamfar 2010	Secondary prevention
Shehu 2013	Non-random allocation

(Continued)

Singh 2002	Secondary prevention
Siqueira-Catania 2013	Both groups received an intervention
Steinbach 1982	Non-random allocation
Steinbach 1982a	Non-random allocation
Steinbach 1984	Non-random allocation
Sun 2013	Non-random allocation
Suwanphan 2009	Non-random allocation
Torres 2011	Non-random allocation
Tsao 2007	Non-random allocation
Tu 1999	Both groups received an intervention
Wang 2002	People with CVD at baseline
Yao 2009	People with CVD at baseline
Zhang 2012	Secondary prevention

Characteristics of studies awaiting assessment *[ordered by study ID]*

Belenkov 2004a

Methods	Full-text article not yet retrieved
Participants	
Interventions	
Outcomes	
Notes	

Belenkov 2004b

Methods	Full-text article not yet retrieved
Participants	
Interventions	
Outcomes	
Notes	

Chen 2011

Methods	Full-text article not yet retrieved
Participants	
Interventions	
Outcomes	
Notes	

Granel 1999

Methods	Full-text article not yet retrieved
Participants	
Interventions	
Outcomes	
Notes	

Marín 2009

Methods	Article written in Spanish with no English abstract - awaiting translation
Participants	
Interventions	
Outcomes	
Notes	

Neves 2010

Methods	Article written in Portuguese with no English abstract - awaiting translation
Participants	
Interventions	
Outcomes	
Notes	

Oganov 2009

Methods	Article written in Russian with no English abstract - awaiting translation
Participants	
Interventions	
Outcomes	
Notes	

Oganov 2010

Methods	Article written in Russian with no English abstract - awaiting translation
Participants	
Interventions	
Outcomes	
Notes	

Sans 1993

Methods	Article written in Spanish with no English abstract - awaiting translation
Participants	
Interventions	
Outcomes	
Notes	

Stamler 1983

Methods	Article written in Russian with no English abstract - awaiting translation
Participants	
Interventions	
Outcomes	
Notes	

DATA AND ANALYSES

Comparison 1. Multiple risk factor interventions

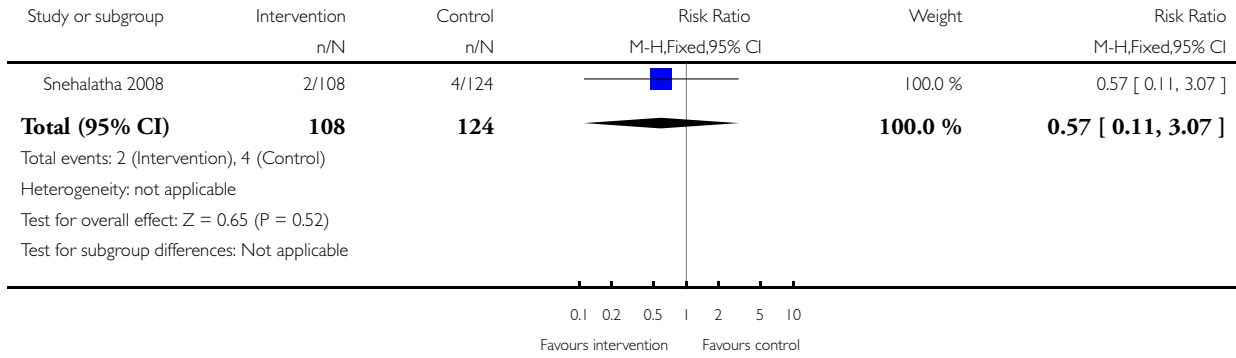
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiovascular event	1	232	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.11, 3.07]
2 Systolic blood pressure, change from baseline (mmHg)	11	4868	Mean Difference (IV, Random, 95% CI)	-6.72 [-9.82, -3.61]
2.1 General population	1	1962	Mean Difference (IV, Random, 95% CI)	-3.95 [-5.20, -2.70]
2.2 High risk population	10	2906	Mean Difference (IV, Random, 95% CI)	-7.14 [-11.07, -3.21]
3 Systolic blood pressure, by method of randomisation	11	4868	Mean Difference (IV, Random, 95% CI)	-6.72 [-9.82, -3.61]
3.1 Individual	9	3549	Mean Difference (IV, Random, 95% CI)	-8.02 [-11.79, -4.24]
3.2 Clustered	2	1319	Mean Difference (IV, Random, 95% CI)	-1.65 [-6.52, 3.22]
4 Diastolic blood pressure, change from baseline (mmHg)	11	4701	Mean Difference (IV, Random, 95% CI)	-4.40 [-6.47, -2.34]
4.1 General population	1	1962	Mean Difference (IV, Random, 95% CI)	-3.18 [-3.90, -2.46]
4.2 High-risk population	10	2739	Mean Difference (IV, Random, 95% CI)	-4.55 [-7.26, -1.85]
5 Diastolic blood pressure, by method of randomisation	11	4701	Mean Difference (IV, Random, 95% CI)	-4.40 [-6.47, -2.34]
5.1 Individual	9	3549	Mean Difference (IV, Random, 95% CI)	-5.29 [-7.65, -2.94]
5.2 Clustered	2	1152	Mean Difference (IV, Random, 95% CI)	-0.70 [-3.79, 2.40]
6 Body mass index, change from baseline (kg/m ²)	7	2984	Mean Difference (IV, Random, 95% CI)	-0.76 [-1.29, -0.22]
6.1 General population	1	1962	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.47, 0.19]
6.2 High-risk population	6	1022	Mean Difference (IV, Random, 95% CI)	-0.94 [-1.54, -0.33]
7 Waist circumference, change from baseline (cm).	4	393	Mean Difference (IV, Random, 95% CI)	-3.31 [-4.77, -1.86]
7.1 High-risk population	4	393	Mean Difference (IV, Random, 95% CI)	-3.31 [-4.77, -1.86]
8 Fasting blood glucose, change from baseline (mmol/L)	6	2726	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.56, 0.13]
8.1 General population	1	1962	Mean Difference (IV, Random, 95% CI)	-0.79 [-0.99, -0.59]
8.2 High-risk population	5	764	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.27, 0.12]
9 Cholesterol, change from baseline (mmol/L)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 HDL-cholesterol	6	824	Mean Difference (IV, Random, 95% CI)	0.03 [-0.01, 0.07]
9.2 LDL-cholesterol	4	544	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.53, 0.27]
9.3 Total cholesterol	5	625	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.48, 0.04]
10 Triglyceries, change from baseline (mmol/L)	6	2705	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.23, -0.04]
10.1 General population	1	1962	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.34, -0.08]
10.2 High-risk population	5	743	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.22, 0.01]

Analysis 1.1. Comparison 1 Multiple risk factor interventions, Outcome 1 Cardiovascular event.

Review: Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries

Comparison: 1 Multiple risk factor interventions

Outcome: 1 Cardiovascular event

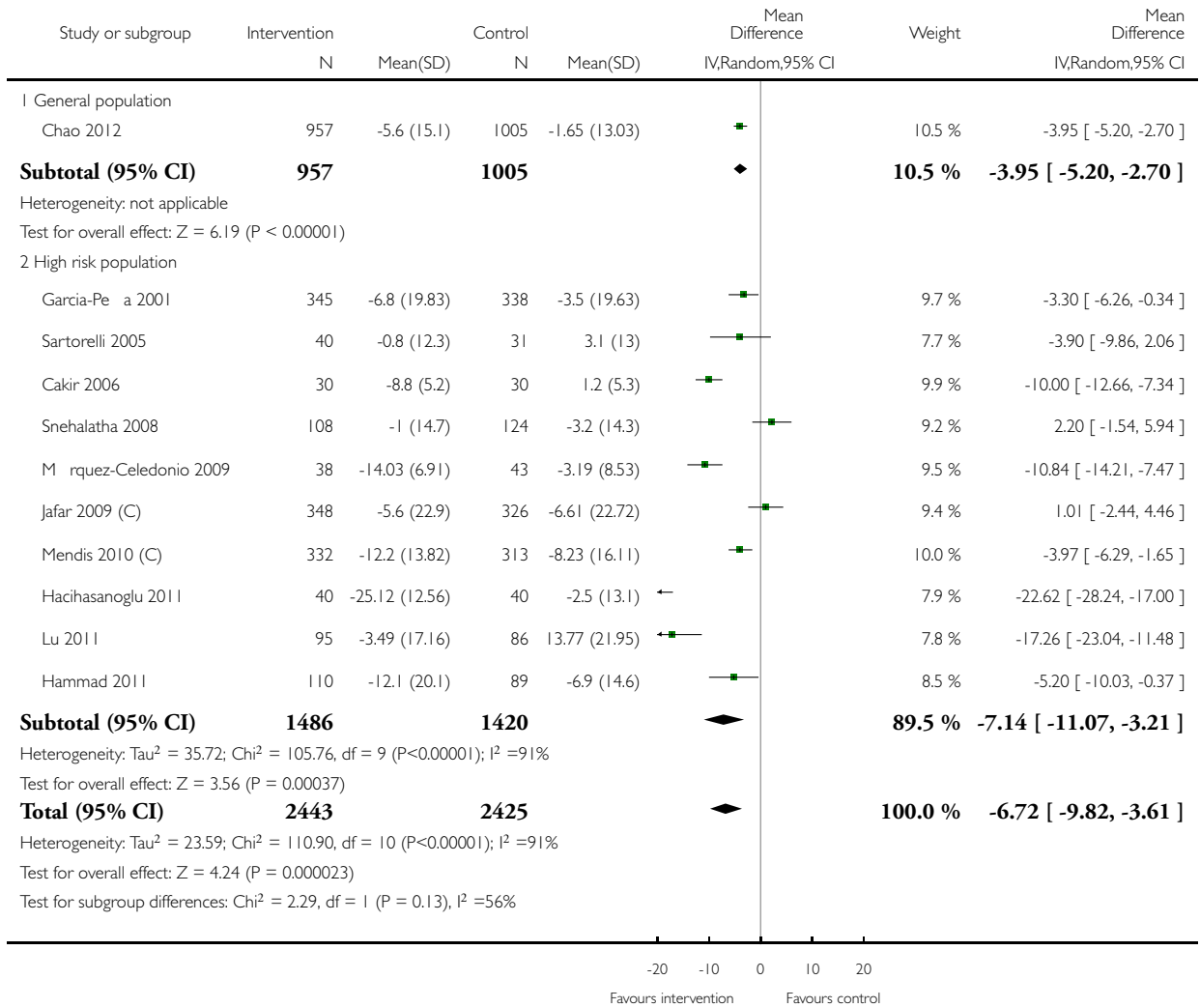


Analysis 1.2. Comparison 1 Multiple risk factor interventions, Outcome 2 Systolic blood pressure, change from baseline (mmHg).

Review: Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries

Comparison: 1 Multiple risk factor interventions

Outcome: 2 Systolic blood pressure, change from baseline (mmHg)

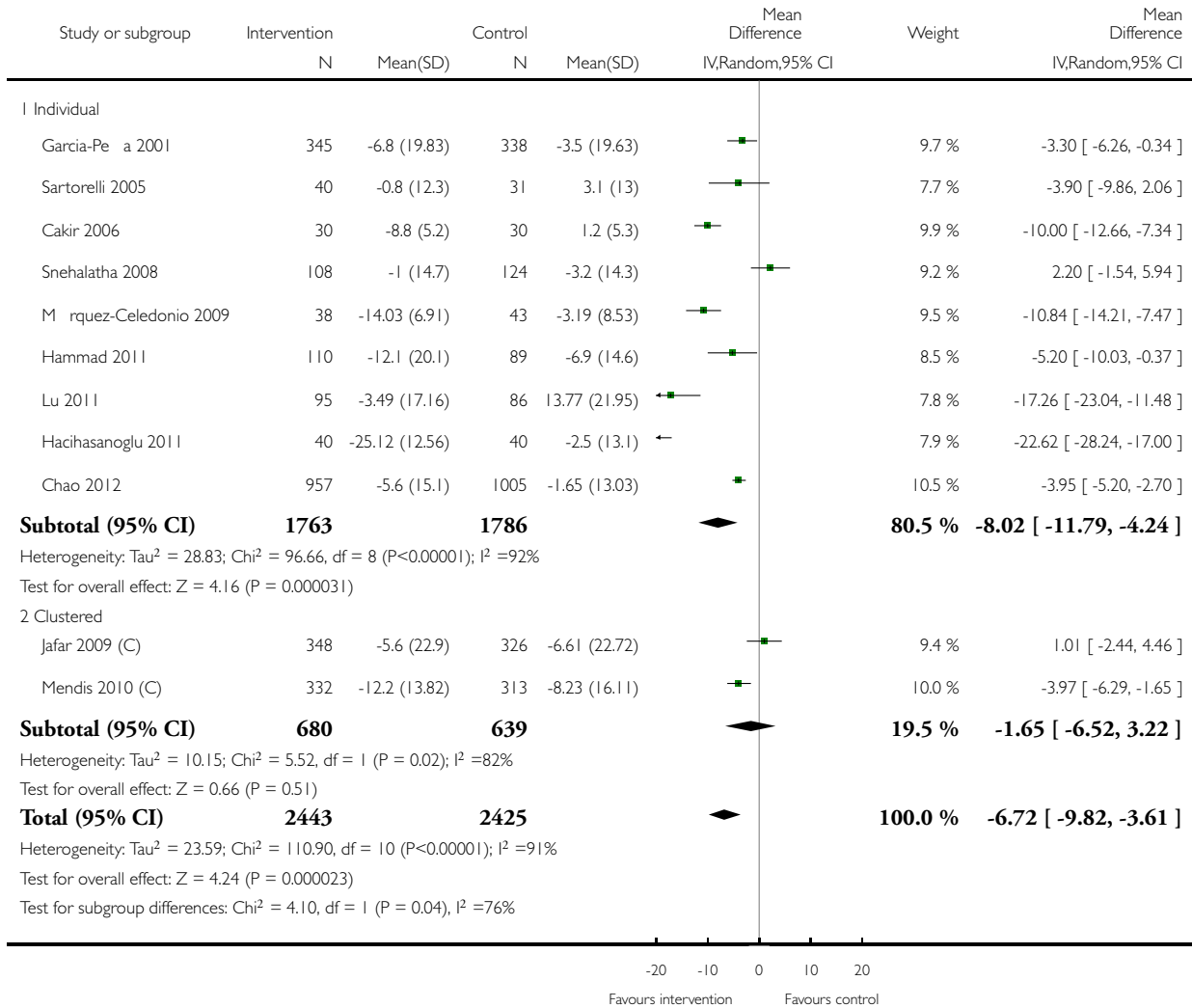


Analysis 1.3. Comparison 1 Multiple risk factor interventions, Outcome 3 Systolic blood pressure, by method of randomisation.

Review: Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries

Comparison: 1 Multiple risk factor interventions

Outcome: 3 Systolic blood pressure, by method of randomisation

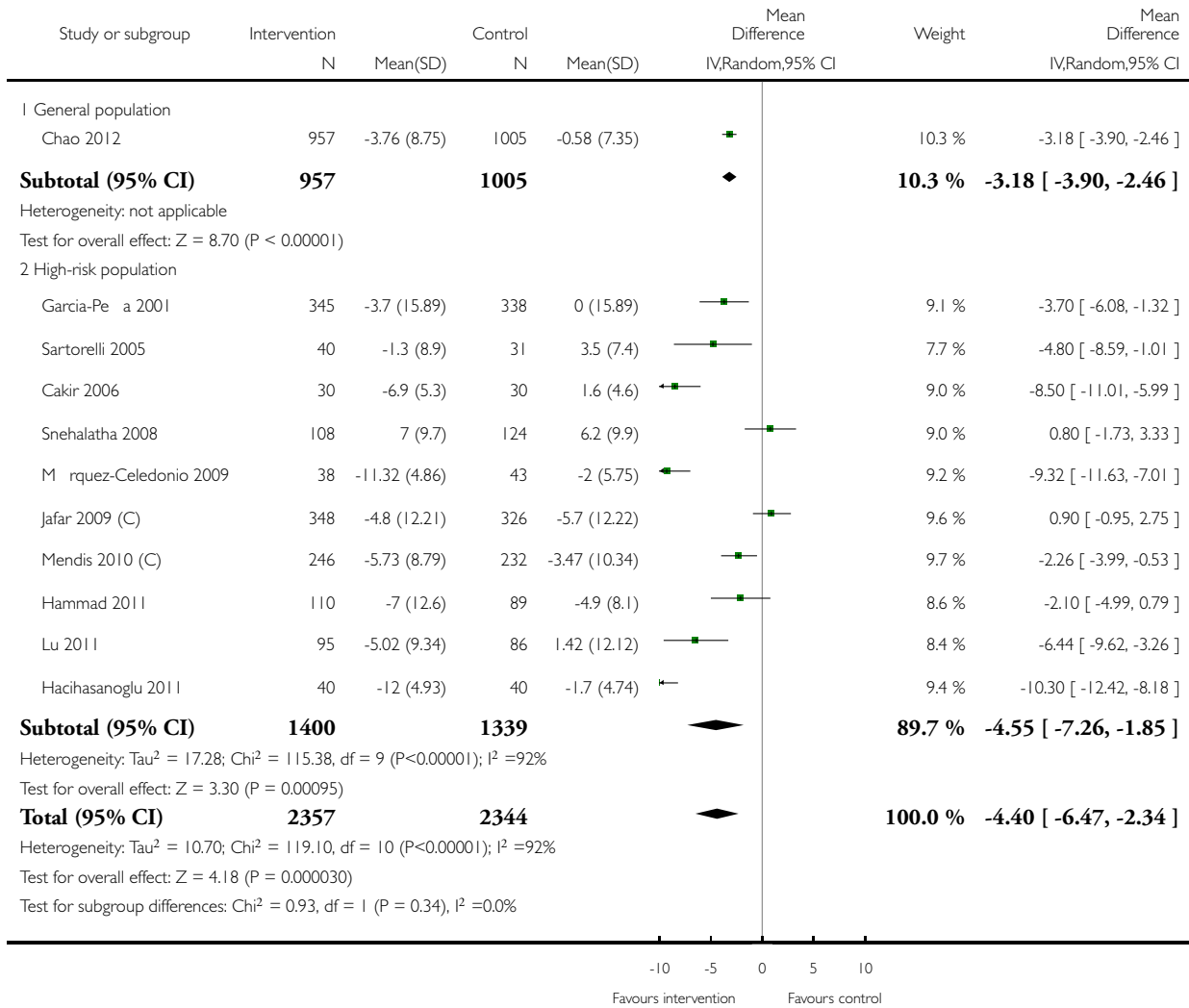


Analysis 1.4. Comparison 1 Multiple risk factor interventions, Outcome 4 Diastolic blood pressure, change from baseline (mmHg).

Review: Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries

Comparison: 1 Multiple risk factor interventions

Outcome: 4 Diastolic blood pressure, change from baseline (mmHg)

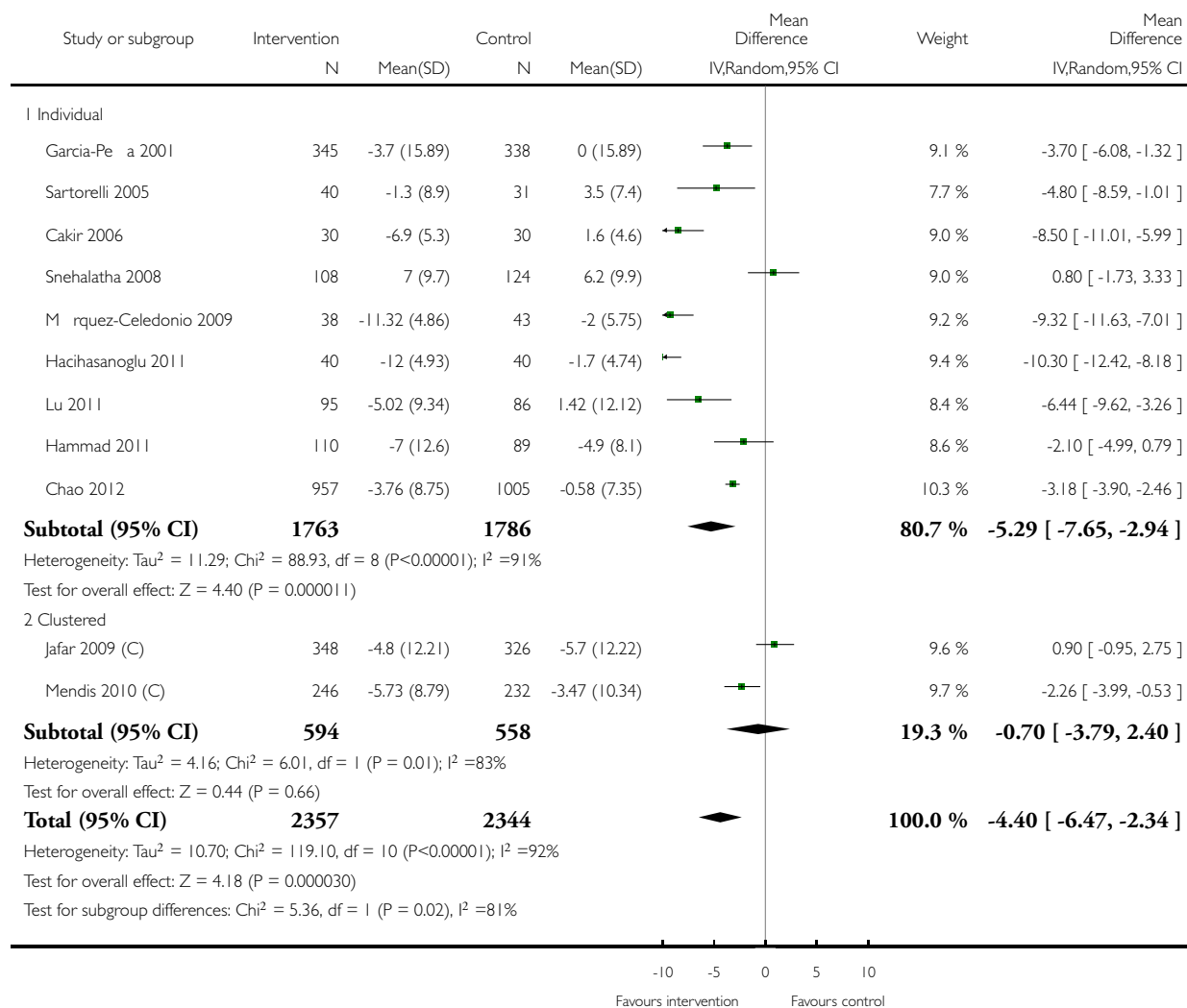


Analysis 1.5. Comparison 1 Multiple risk factor interventions, Outcome 5 Diastolic blood pressure, by method of randomisation.

Review: Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries

Comparison: 1 Multiple risk factor interventions

Outcome: 5 Diastolic blood pressure, by method of randomisation

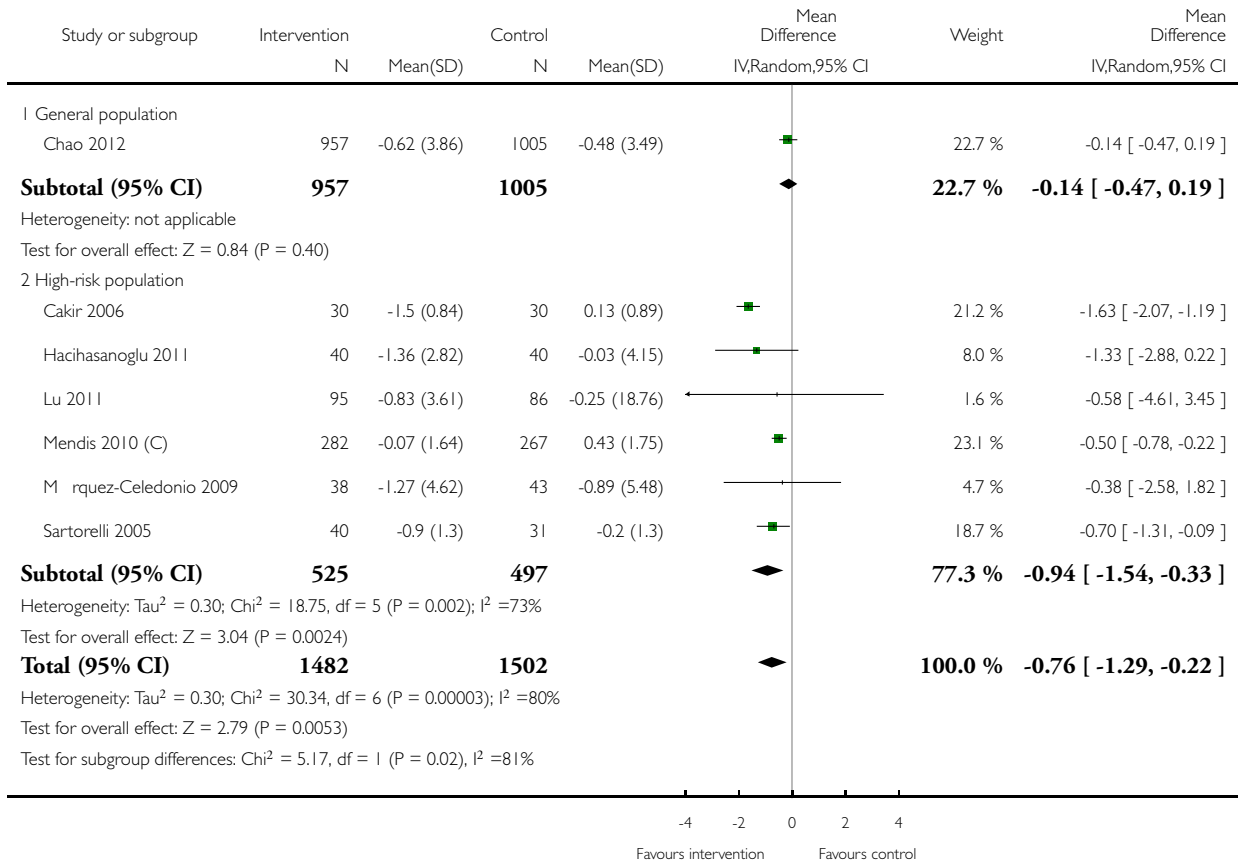


Analysis 1.6. Comparison 1 Multiple risk factor interventions, Outcome 6 Body mass index, change from baseline (kg/m²).

Review: Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries

Comparison: 1 Multiple risk factor interventions

Outcome: 6 Body mass index, change from baseline (kg/m²)

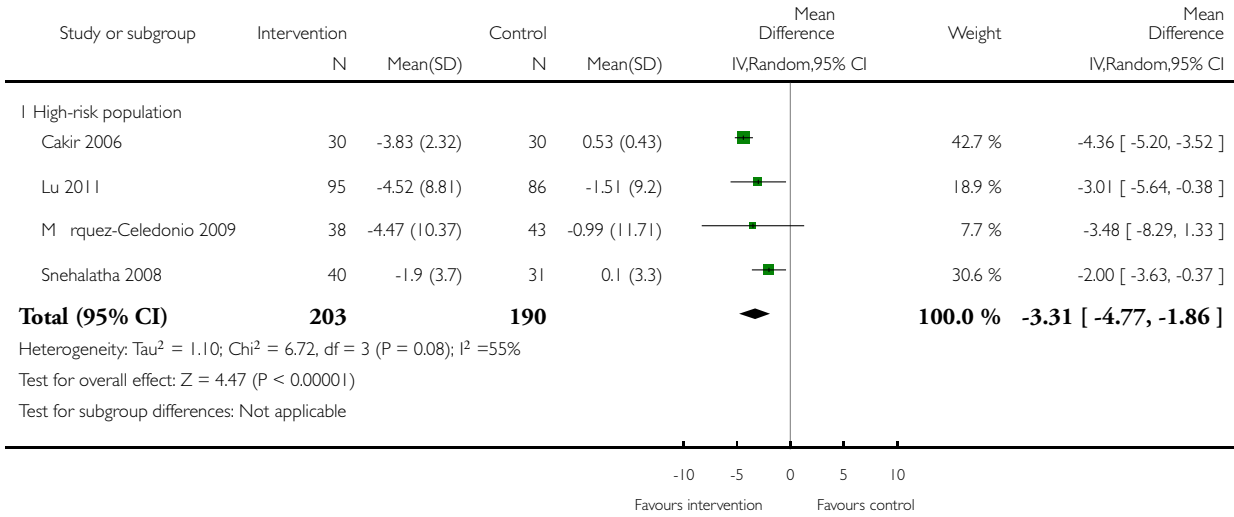


Analysis 1.7. Comparison 1 Multiple risk factor interventions, Outcome 7 Waist circumference, change from baseline (cm)..

Review: Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries

Comparison: 1 Multiple risk factor interventions

Outcome: 7 Waist circumference, change from baseline (cm).

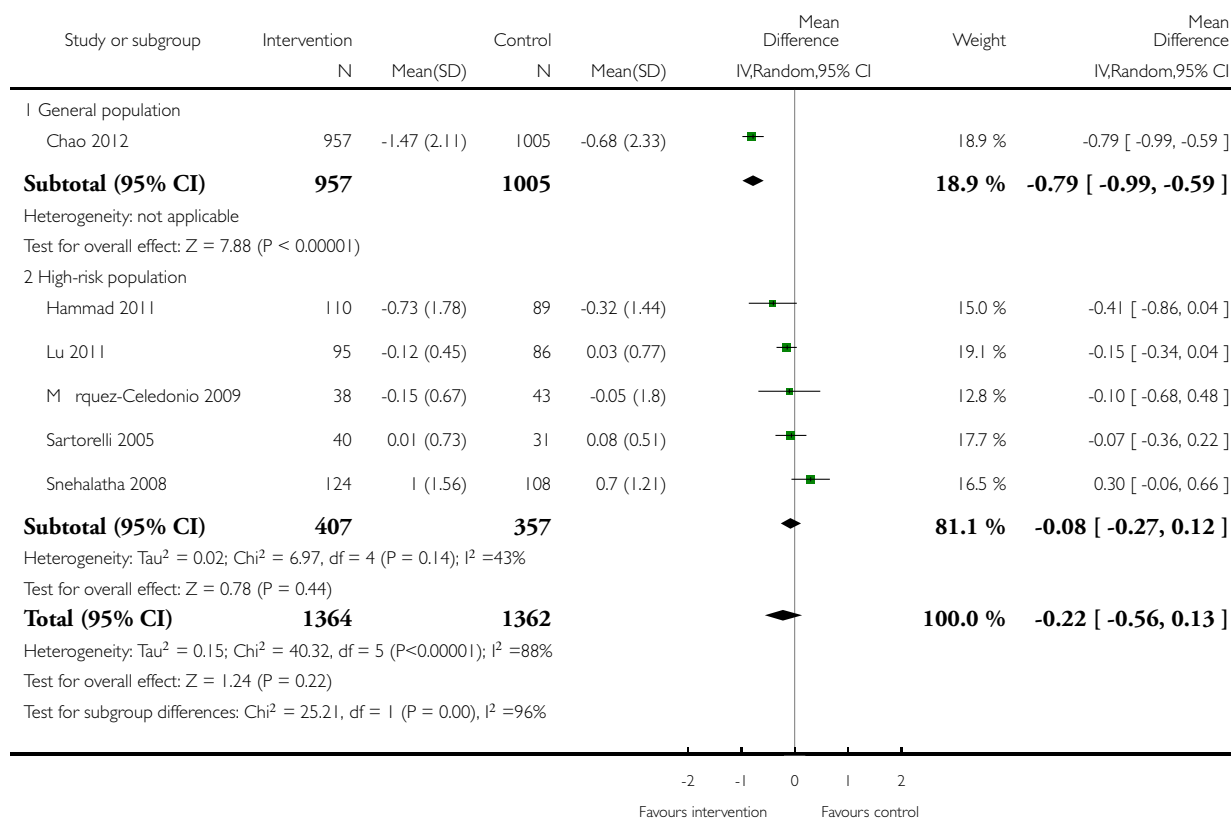


Analysis 1.8. Comparison 1 Multiple risk factor interventions, Outcome 8 Fasting blood glucose, change from baseline (mmol/L).

Review: Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries

Comparison: 1 Multiple risk factor interventions

Outcome: 8 Fasting blood glucose, change from baseline (mmol/L)

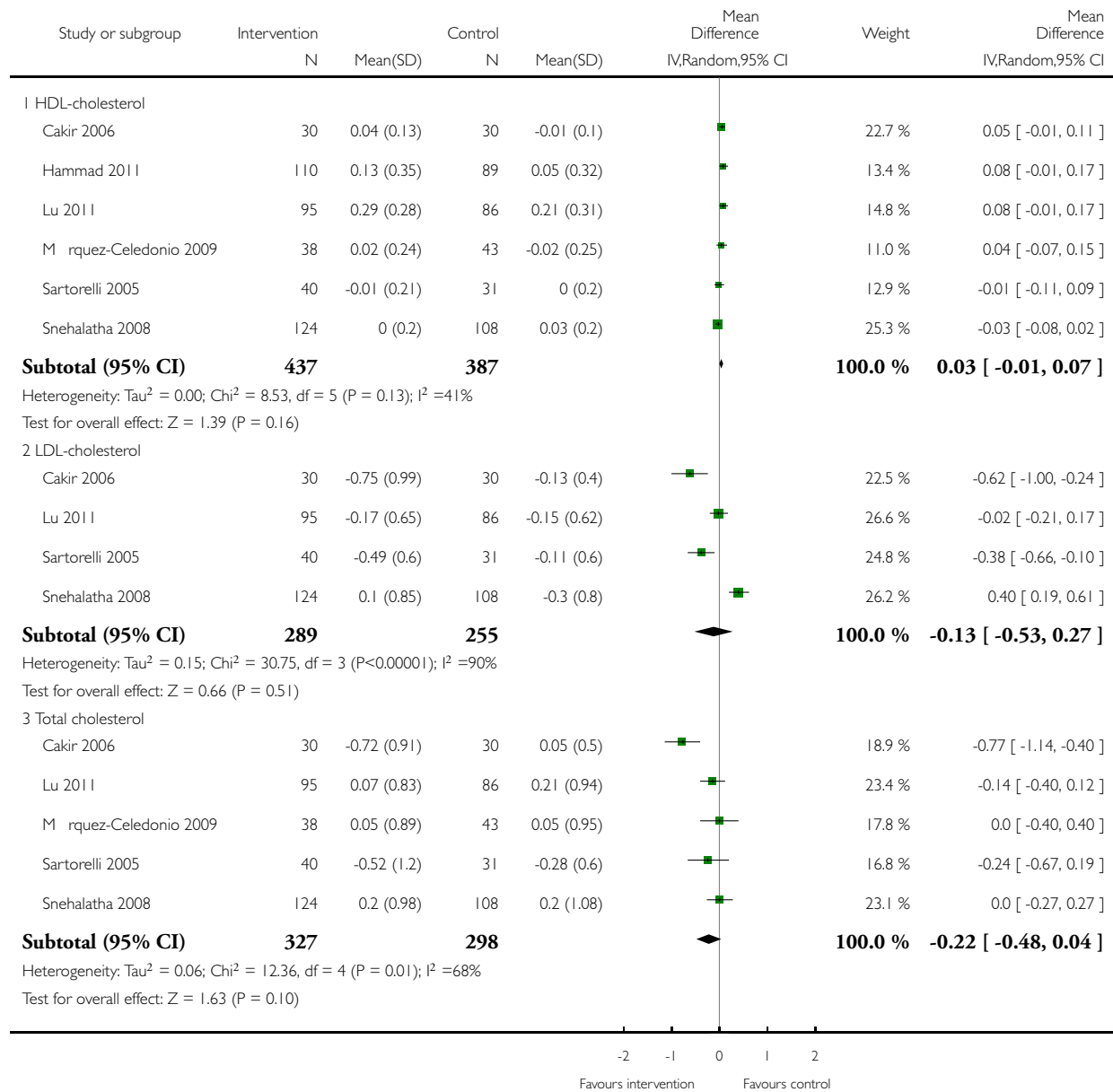


Analysis 1.9. Comparison 1 Multiple risk factor interventions, Outcome 9 Cholesterol, change from baseline (mmol/L).

Review: Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries

Comparison: 1 Multiple risk factor interventions

Outcome: 9 Cholesterol, change from baseline (mmol/L)

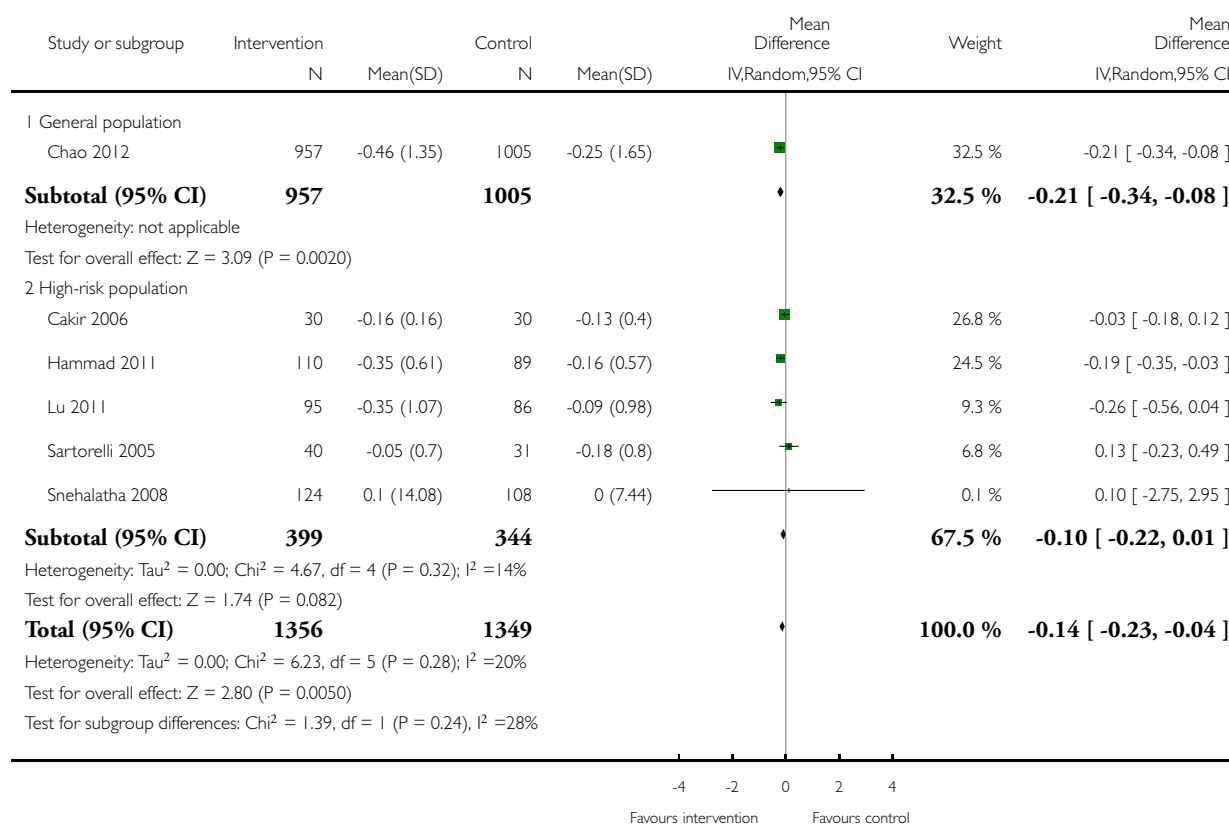


Analysis 1.10. Comparison 1 Multiple risk factor interventions, Outcome 10 Triglyceries, change from baseline (mmol/L).

Review: Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries

Comparison: 1 Multiple risk factor interventions

Outcome: 10 Triglyceries, change from baseline (mmol/L)



ADDITIONAL TABLES

Table 1. Intervention contents

	Dietary advice	Weight control / loss	Exercise / Advice on Physical activity	Smoking cessation	Psychological aspect of health	Pharmacotherapy
Avram 2011	X	X	X			
Chao 2012	X		X		X	

Table 1. Intervention contents (Continued)

Jafar 2009 (C)	X		X	X		
Kisioglu 2004	X	X	X			
Lu 2011	X		X			
Mendis 2010 (C)	X		X	X		X
Sartorelli 2005	X		X			
Snehalatha 2008	X		X			
Garcia-Peña 2001	X	X	X			
Cakir 2006	X	X	X	X		
Márquez-Celedonio 2009	X		X	X		
Hammad 2011	X			X		
Hacihanoglu 2011	X	X	X			

APPENDICES

Appendix I. Search strategies

CENTRAL

#1MeSH descriptor: [Cardiovascular Diseases] explode all trees

#2cardio*

#3cardia*

#4heart*

#5coronary*

#6angina*

#7ventric*

#8myocard*

#9pericard*

#10isch?em*

#11emboli*

#12arrhythmi*

#13thrombo*
 #14atrial next fibrillat*
 #15tachycardi*
 #16endocardi*
 #17(sick next sinus)
 #18MeSH descriptor: [Stroke] explode all trees
 #19(stroke or stokes)
 #20cerebrovasc*
 #21cerebral next vascular
 #22apoplexy
 #23(brain near/2 accident*)
 #24((brain* or cerebral or lacunar) near/2 infarct*)
 #25MeSH descriptor: [Hypertension] explode all trees
 #26hypertensi*
 #27(peripheral next arter* next disease*)
 #28((high or increased or elevated) near/2 blood pressure)
 #29MeSH descriptor: [Hyperlipidemias] explode all trees
 #30hyperlipid*
 #31hyperlip?emia*
 #32hypercholesterol*
 #33hypercholester?emia*
 #34hyperlipoprotein?emia*
 #35hypertiglycerid?emia*
 #36MeSH descriptor: [Arteriosclerosis] explode all trees
 #37MeSH descriptor: [Cholesterol] explode all trees
 #38cholesterol
 #39“multiple risk factor*”
 #40MeSH descriptor: [Blood Pressure] this term only
 #41“blood pressure”
 #42#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or
 #39 or #40 or #41
 #43MeSH descriptor: [Health Promotion] explode all trees
 #44MeSH descriptor: [Health Education] explode all trees
 #45MeSH descriptor: [Health Behavior] explode all trees
 #46MeSH descriptor: [Counseling] explode all trees
 #47MeSH descriptor: [Primary Prevention] this term only
 #48(multifactor* near/5 (interven* or prevent*))
 #49((lifestyle or life-style or behavior?r*) near/3 (interven* or educat* or advice* or alter* or change* or inform*))
 #50(primary near/3 prevent*)
 #51(risk factor* near/3 (reduc* or manage* or managing or interven* or program*))
 #52(educat* near/3 (program* or patient*))
 #53((health* or wellness or weight or diet* or smok*) near/2 (promot* or program* or campaign* or advic* or educat*))
 #54(nonpharmacologic* or non-pharmacologic*)
 #55((lifestyle or life style or life-style or behavior?r* or risk factor*) near/3 modif*)
 #56#43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55
 #57#42 and #56
 #58MeSH descriptor: [Developing Countries] this term only
 #59((developing or “less* developed” or “under developed” or underdeveloped or “middle income” or “low* income” or underserved
 or “under served” or deprived or poor*) near (count* or nation? or population? or world))
 #60((developing or “less* developed” or “under developed” or underdeveloped or “middle income” or “low* income”) near (economy
 or economies))
 #61(low* near (gdp or gnp or “gross domestic” or “gross national”))

#62(low near/3 middle near/3 countr*)
#63(lmic or lmic3 or third world or lami countr*)
#64“transitional countr*”
#65MeSH descriptor: [Asia, Southeastern] explode all trees
#66cambodia* or Kampuchea or myanmar or burma or burmese or indonesia* or laos or lao near/1 democratic republic or lao near/2 people or marshall island* or Malaysia* or Philippines or filipino* or Thailand or thai* or Vietnam* or tuvalu or ellice islands
#67MeSH descriptor: [Far East] explode all trees
#68“north korea*” or democratic people* republic near/2 korea or mongolia* or china or chinese
#69MeSH descriptor: [Melanesia] explode all trees
#70fiji* or Papua New Guinea or Vanuatu or Solomon Islands or Timor-Leste or Melanesia*
#71MeSH descriptor: [Micronesia] explode all trees
#72Micronesia* or Kiribati or Palau or Belau or Pelew
#73MeSH descriptor: [Samoa] explode all trees
#74MeSH descriptor: [Tonga] this term only
#75samoa* or tonga* or tuvalu or ellice islands
#76MeSH descriptor: [Asia, Central] explode all trees
#77kyrgyzstan or kyrgyz or kirghizia or kirghiz or tajikistan or tadjhik or tadjhikistan or tajikistan or Kazakhstan or kazakh or turk* or Uzbekistan
#78MeSH descriptor: [Europe, Eastern] explode all trees
#79Albania* or Jugoslavija* or Yugoslavia* or serbo-croat* or macedonia* or sloven* or kosovo or Moldova* or Ukrain* or Bulgaria* or belarus or byelarus or belorussia or bosnia* or Montenegro or Romania* or russia* or ussr or soviet or ccp or serbia* or Latvia* or Lithuania*
#80MeSH descriptor: [Transcaucasia] explode all trees
#81Armenia* or georgia* or Azerbaijan*
#82MeSH descriptor: [West Indies] explode all trees
#83Haiti or Cuba* or Dominica* or Antigua or Barbuda or Jamaica* or Grenad* or St Lucia* or Saint Lucia* or Grenadines
#84MeSH descriptor: [Central America] explode all trees
#85Belize or Costa Rica* or El Salvador or Guatemala* or Hondura* or Nicaragua or Panama*
#86MeSH descriptor: [South America] explode all trees
#87Bolivia* or Argentin* or Brazil* or Chile* or Colombia* or Ecuador* or Guyana* or Paraguay or Peru* or Surinam* or Uruguay or Venezuela*
#88MeSH descriptor: [Mexico] explode all trees
#89Mexic*
#90MeSH descriptor: [Africa, Eastern] explode all trees
#91Djibouti or Burundi* or Ethiopia* or Kenya* or Rwanda* or Ruanda* or Somali* or Sudan* or Tanzania* or Uganda* or Eritrea*
#92MeSH descriptor: [Africa, Northern] explode all trees
#93Egypt* or Algeria* or Libya* or Morocc* or Tunisia*
#94MeSH descriptor: [Asia, Western] explode all trees
#95Bangladesh* or Bhutan* or Nepal* or india* or Pakistan* or Sri Lanka* or Syria* or gaza* or turk* or Afghan* or Iran* or Iraq* or jordan* or Leban* or yemen*
#96MeSH descriptor: [Indian Ocean Islands] explode all trees
#97Maldiv* or Madagasca* or Malagasy Republic or Seychelles or comoros or comores or Mauriti* or Agalega Islands
#98MeSH descriptor: [Africa, Western] explode all trees
#99Benin or Dahomey or Burkina Faso or Burkina Fasso or Upper Volta or Gambia* or Ghan* or Gold Coast or Guinea-Bissau or Portuguese Guinea or Cote d’Ivoire or Ivory Coast or Liberia* or Mali* or Mauritania* or Niger or Nigeria* or Senegal* or Sierra Leone* or Togo* or Guinea* or Cape Verde*
#100MeSH descriptor: [Africa, Central] explode all trees
#101Central African Republic or Ubangi-Shari or african* or Chad or Cameroon* or congo* or Gabon* or zaire
#102MeSH descriptor: [Africa, Southern] explode all trees
#103Malawi* or Nyasaland or Mozambi* or Portuguese East Africa or Zimbabwe* or Rhodesia* or Lesotho or Basutoland or Swazi* or Zambia* or Northern Rhodesia* or Angola* or Botswana* or Bechuanaland or Kalahari or Namibia* or South Africa*
#104MeSH descriptor: [Atlantic Islands] explode all trees
#105sao tome near/2 principe

#106#58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105
#107#57 and #106

MEDLINE

1. exp Cardiovascular Diseases/
2. cardio*.tw.
3. cardia*.tw.
4. heart*.tw.
5. coronary*.tw.
6. angina*.tw.
7. ventric*.tw.
8. myocard*.tw.
9. pericard*.tw.
10. isch?em*.tw.
11. emboli*.tw.
12. arrhythmi*.tw.
13. thrombo*.tw.
14. atrial fibrillat*.tw.
15. tachycardi*.tw.
16. endocardi*.tw.
17. (sick adj sinus).tw.
18. exp Stroke/
19. (stroke or stokes).tw.
20. cerebrovasc*.tw.
21. cerebral vascular.tw.
22. apoplexy.tw.
23. (brain adj2 accident*).tw.
24. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
25. exp Hypertension/
26. hypertensi*.tw.
27. peripheral arter* disease*.tw.
28. ((high or increased or elevated) adj2 blood pressure).tw.
29. exp Hyperlipidemias/
30. hyperlipid*.tw.
31. hyperlip?emia*.tw.
32. hypercholesterol*.tw.
33. hypercholester?emia*.tw.
34. hyperlipoprotein?emia*.tw.
35. hypertriglycerid?emia*.tw.
36. exp Arteriosclerosis/
37. exp Cholesterol/
38. cholesterol.tw.
39. Blood Pressure/
40. blood pressure.tw.
41. multiple risk factor*.tw.
42. or/1-41
43. exp Health Promotion/
44. exp Health Education/
45. exp Health Behavior/
46. exp Counseling/

47. Primary Prevention/
48. (multifactor* adj5 (interven* or prevent*)).tw.
49. ((lifestyle or life-style or behavior*) adj3 (interven* or educat* or advice* or alter* or change* or inform*)).tw.
50. (primary adj3 prevent*).tw.
51. (risk factor* adj3 (reduc* or manage* or managing or interven* or program*)).tw.
52. (educat* adj3 (program* or patient*)).tw.
53. ((health* or wellness or weight or diet* or smok*) adj2 (promot* or program* or campaign* or advic* or educat*)).tw.
54. (nonpharmacologic* or non-pharmacologic*).tw.
55. ((lifestyle or life style or life-style or behavior* or risk factor*) adj3 modif*).tw.
56. or/43-55
57. 42 and 56
58. randomized controlled trial.pt.
59. controlled clinical trial.pt.
60. randomized.ab.
61. placebo.ab.
62. drug therapy.fs.
63. randomly.ab.
64. trial.ab.
65. groups.ab.
66. 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65
67. exp animals/ not humans.sh.
68. 66 not 67
69. 57 and 68
70. Developing Countries.sh,kf.
71. ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (count? or nation? or population? or world)).ti,ab.
72. ((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)).ti,ab.
73. (low* adj (gdp or gnp or gross domestic or gross national)).ti,ab.
74. (low adj3 middle adj3 count*).ti,ab.
75. (lmic or lmics or third world or lami count*).ti,ab.
76. transitional count*.ti,ab.
77. Cambodia/
78. (cambodia* or Kampuchea).cp,in,jw,mp.
79. "Democratic People's Republic of Korea"/
80. (north korea* or (democratic people* republic adj2 korea)).cp,in,jw,mp.
81. Myanmar/
82. (myanmar or burma or burmese).cp,in,jw,mp.
83. Fiji/
84. fiji*.cp,in,jw,mp.
85. Indonesia/
86. indonesia*.cp,in,jw,mp.
87. Micronesia/
88. (Micronesia* or Kiribati).cp,in,jw,mp.
89. Laos/
90. (laos or (lao adj1 democratic republic) or (lao adj2 people) or marshall island*).cp,in,jw,mp.
91. Mongolia/
92. mongolia*.cp,in,jw,mp.
93. Papua New Guinea/
94. Papua New Guinea.cp,in,jw,mp.
95. Philippines/
96. (Philippines or filipino*).cp,in,jw,mp.
97. samoa/ or "independent state of samoa"/

98. samoa*.cp,in,jw,mp.
99. Melanesia/
100. (Solomon Islands or Timor-Leste or Melanesia*).cp,in,jw,mp.
101. Tonga/
102. tonga*.cp,in,jw,mp.
103. Vanuatu/
104. Vanuatu.cp,in,jw,mp.
105. Vietnam/
106. Vietnam*.cp,in,jw,mp.
107. exp China/
108. (china or chinese).cp,in,jw,mp.
109. Malaysia/
110. Malaysia*.cp,in,jw,mp.
111. Palau/
112. (Palau or Belau or Pelew).cp,in,jw,mp.
113. Thailand/
114. (Thailand or thai*).cp,in,jw,mp.
115. (tuvalu or ellice islands).cp,in,jw,mp.
116. Kyrgyzstan/
117. (kyrgyzstan or kyrgyz or kirghizia or kirghiz).cp,in,jw,mp.
118. Tajikistan/
119. (tajikistan or tadjhik or tadjhikistan or tajikistan).cp,in,jw,mp.
120. Albania/
121. Albania*.cp,in,jw,mp.
122. Armenia/
123. Armenia*.cp,in,jw,mp.
124. "Georgia (Republic)"/
125. georgia*.cp,in,jw,mp.
126. Yugoslavia/
127. (Jugoslavija* or Yugoslavia* or serbo-croat* or macedonia* or sloven* or kosovo).cp,in,jw,mp.
128. Moldova/
129. Moldova*.cp,in,jw,mp.
130. Ukraine/
131. Ukrain*.cp,in,jw,mp.
132. Uzbekistan/
133. Uzbekistan.cp,in,jw,mp.
134. Azerbaijan/
135. Azerbaijan*.cp,in,jw,mp.
136. "Republic of Belarus"/
137. (belarus or byelarus or belorussia).cp,in,jw,mp.
138. Bosnia-Herzegovina/
139. bosnia*.cp,in,jw,mp.
140. Bulgaria/
141. Bulgaria*.cp,in,jw,mp.
142. Kazakhstan/
143. (Kazakhstan or kazakh).cp,in,jw,mp.
144. Latvia/
145. Latvia*.cp,in,jw,mp.
146. Lithuania/
147. Lithuania*.cp,in,jw,mp.
148. "Macedonia (Republic)"/
149. Macedonia*.cp,in,jw,mp.
150. Montenegro/

151. Montenegro.cp,in,jw,mp.
152. Romania/
153. Romania*.cp,in,jw,mp.
154. exp Russia/
155. USSR/
156. (russia* or ussr or soviet or cccp).cp,in,jw,mp.
157. Serbia/
158. serbia*.cp,in,jw,mp.
159. Turkey/
160. turk*.cp,in,jw,mp. not animal/
161. Turkmenistan/
162. Haiti/
163. Haiti.cp,in,jw,mp.
164. Belize/
165. Belize.cp,in,jw,mp.
166. Bolivia/
167. Bolivia*.cp,in,jw,mp.
168. El Salvador/
169. El Salvador.cp,in,jw,mp.
170. Guatemala/
171. Guatemala*.cp,in,jw,mp.
172. Guyana/
173. Guyana*.cp,in,jw,mp.
174. Honduras/
175. Hondura*.cp,in,jw,mp.
176. Nicaragua/
177. Nicaragua.cp,in,jw,mp.
178. Paraguay/
179. Paraguay.cp,in,jw,mp.
180. "Antigua and Barbuda"/
181. (Antigua or Barbuda).cp,in,jw,mp.
182. Argentina/
183. Argentin*.cp,in,jw,mp.
184. Brazil/
185. Brazil*.cp,in,jw,mp.
186. Chile/
187. Chile*.cp,in,jw,mp.
188. Colombia/
189. Colombia*.cp,in,jw,mp.
190. Costa Rica/
191. Costa Rica*.cp,in,jw,mp.
192. Cuba/
193. Cuba*.cp,in,jw,mp.
194. Dominica/
195. Dominican Republic/
196. Dominica*.cp,in,jw,mp.
197. Ecuador/
198. Ecuador*.cp,in,jw,mp.
199. Grenada/
200. Grenad*.cp,in,jw,mp.
201. Jamaica/
202. Jamaica*.cp,in,jw,mp.
203. Mexico/

204. Mexic*.cp,in,jw,mp.
205. exp Panama/
206. Panama*.cp,in,jw,mp.
207. Peru/
208. Peru*.cp,in,jw,mp.
209. Saint Lucia/
210. (St Lucia* or Saint Lucia*).cp,in,jw,mp.
211. "Saint Vincent and the Grenadines"/
212. Grenadines.cp,in,jw,mp.
213. Suriname/
214. Surinam*.cp,in,jw,mp.
215. Uruguay/
216. Uruguay.cp,in,jw,mp.
217. Venezuela/
218. Venezuela*.cp,in,jw,mp.
219. Djibouti/
220. Djibouti.cp,in,jw,mp.
221. Egypt/
222. Egypt*.cp,in,jw,mp.
223. Iraq/
224. Iraq*.cp,in,jw,mp.
225. Morocco/
226. Morocc*.cp,in,jw,mp.
227. Syria/
228. (Syria* or gaza*).cp,in,jw,mp.
229. Yemen/
230. yemen*.cp,in,jw,mp.
231. Algeria/
232. Algeria*.cp,in,jw,mp.
233. Iran/
234. Iran*.cp,in,jw,mp.
235. Jordan/
236. jordan*.cp,in,jw,mp.
237. Lebanon/
238. Leban*.cp,in,jw,mp.
239. Libya/
240. Libya*.cp,in,jw,mp.
241. Tunisia/
242. Tunisia*.cp,in,jw,mp.
243. Afghanistan/
244. Afghan*.cp,in,jw,mp.
245. Bangladesh/
246. Bangladesh*.cp,in,jw,mp.
247. Nepal/
248. Nepal*.cp,in,jw,mp.
249. Bhutan/
250. Bhutan*.cp,in,jw,mp.
251. exp India/
252. india*.cp,in,jw,mp.
253. Pakistan/
254. Pakistan*.cp,in,jw,mp.
255. Sri Lanka/
256. Sri Lanka*.cp,in,jw,mp.

257. Indian Ocean Islands/
258. Maldiv*.cp,in,jw,mp.
259. Benin/
260. (Benin or Dahomey).cp,in,jw,mp.
261. Burkina Faso/
262. (Burkina Faso or Burkina Fasso or Upper Volta).cp,in,jw,mp.
263. Burundi/
264. Burundi*.cp,in,jw,mp.
265. Central African Republic/
266. (Central African Republic or Ubangi-Shari or african*).cp,in,jw,mp.
267. Chad/
268. Chad.cp,in,jw,mp.
269. Comoros/
270. (comoros or comores).cp,in,jw,mp.
271. "Democratic Republic of the Congo"/
272. (congo* or zaire).cp,in,jw,mp.
273. Eritrea/
274. Eritrea*.cp,in,jw,mp.
275. Ethiopia/
276. Ethiopia*.cp,in,jw,mp.
277. Gambia/
278. Gambia*.cp,in,jw,mp.
279. Guinea/
280. (Guinea* not (New Guinea or Guinea Pig* or Guinea Fowl)).cp,in,jw,mp.
281. Guinea-Bissau/
282. (Guinea-Bissau or Portuguese Guinea).cp,in,jw,mp.
283. Kenya/
284. Kenya*.cp,in,jw,mp.
285. Liberia/
286. Liberia*.cp,in,jw,mp.
287. Madagascar/
288. (Madagasca* or Malagasy Republic).cp,in,jw,mp.
289. Malawi/
290. (Malawi* or Nyasaland).cp,in,jw,mp.
291. Mali/
292. Mali*.cp,in,jw,mp.
293. Mauritania/
294. Mauritania*.cp,in,jw,mp.
295. Mozambique/
296. (Mozambi* or Portuguese East Africa).cp,in,jw,mp.
297. Niger/
298. (Niger not (Aspergillus or Peptococcus or Schizothorax or Cruciferae or Gobius or Lasius or Agelastes or Melanosuchus or radish or Parastromateus or Orius or Apergillus or Parastromateus or Stomoxys)).cp,in,jw,mp.
299. Rwanda/
300. (Rwanda* or Ruanda*).cp,in,jw,mp.
301. Sierra Leone/
302. Sierra Leone*.cp,in,jw,mp.
303. Somalia/
304. Somali*.cp,in,jw,mp.
305. Tanzania/
306. Tanzania*.cp,in,jw,mp.
307. Togo/
308. Togo*.cp,in,jw,mp.

309. Uganda/
310. Uganda*.cp,in,jw,mp.
311. Zimbabwe/
312. (Zimbabwe* or Rhodesia*).cp,in,jw,mp.
313. Cameroon/
314. Cameroon*.cp,in,jw,mp.
315. Cape Verde/
316. Cape Verde*.cp,in,jw,mp.
317. Congo/
318. (congo* not ((democratic republic adj3 congo) or congo red or crimean-congo)).cp,in,jw,mp.
319. Cote d'Ivoire/
320. (Cote d'Ivoire or Ivory Coast).cp,in,jw,mp.
321. Ghana/
322. (Ghan* or Gold Coast).cp,in,jw,mp.
323. Lesotho/
324. (Lesotho or Basutoland).cp,in,jw,mp.
325. Nigeria/
326. Nigeria*.cp,in,jw,mp.
327. Atlantic Islands/
328. (sao tome adj2 principe).cp,in,jw,mp.
329. Senegal/
330. Senegal*.cp,in,jw,mp.
331. Sudan/
332. Sudan*.cp,in,jw,mp.
333. Swaziland/
334. Swazi*.cp,in,jw,mp.
335. Zambia/
336. (Zambia* or Northern Rhodesia*).cp,in,jw,mp.
337. Angola/
338. Angola*.cp,in,jw,mp.
339. Botswana/
340. (Botswana* or Bechuanaland or Kalahari).cp,in,jw,mp.
341. Gabon/
342. Gabon*.cp,in,jw,mp.
343. Mauritius/
344. (Mauriti* or Agalega Islands).cp,in,jw,mp.
345. Namibia/
346. Namibia*.cp,in,jw,mp.
347. Seychelles/
348. Seychelles.cp,in,jw,mp.
349. South Africa/
350. South Africa*.cp,in,jw,mp.
351. or/70-350
352. 69 and 351

EMBASE

1. exp cardiovascular disease/
2. cardio*.tw.
3. cardia*.tw.
4. heart*.tw.
5. coronary*.tw.
6. angina*.tw.

7. ventric*.tw.
8. myocard*.tw.
9. pericard*.tw.
10. isch?em*.tw.
11. emboli*.tw.
12. arrhythmi*.tw.
13. thrombo*.tw.
14. atrial fibrillat*.tw.
15. tachycardi*.tw.
16. endocardi*.tw.
17. (sick adj sinus).tw.
18. exp cerebrovascular disease/
19. (stroke or stokes).tw.
20. cerebrovasc*.tw.
21. cerebral vascular.tw.
22. apoplexy.tw.
23. (brain adj2 accident*).tw.
24. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
25. exp hypertension/
26. hypertensi*.tw.
27. peripheral arter* disease*.tw.
28. ((high or increased or elevated) adj2 blood pressure).tw.
29. exp hyperlipidemia/
30. hyperlipid*.tw.
31. hyperlip?emia*.tw.
32. hypercholesterol*.tw.
33. hypercholester?emia*.tw.
34. hyperlipoprotein?emia*.tw.
35. hypertriglycerid?emia*.tw.
36. exp Arteriosclerosis/
37. exp Cholesterol/
38. cholesterol.tw.
39. Blood Pressure/
40. blood pressure.tw.
41. multiple risk factor*.tw.
42. or/1-41
43. exp health education/
44. exp health behavior/
45. exp counseling/
46. primary prevention/
47. (multifactor* adj5 (interven* or prevent*)).tw.
48. ((lifestyle or life-style or behavio?r*) adj3 (interven* or educat* or advice* or alter* or change* or inform*)).tw.
49. (primary adj3 prevent*).tw.
50. (risk factor* adj3 (reduc* or manage* or managing or interven* or program*)).tw.
51. (educat* adj3 (program* or patient*)).tw.
52. ((health* or wellness or weight or diet* or smok*) adj2 (promot* or program* or campaign* or advic* or educat*)).tw.
53. (nonpharmacologic* or non-pharmacologic*).tw.
54. ((lifestyle or life style or life-style or behavio?r* or risk factor*) adj3 modif*).tw.
55. or/43-54
56. 42 and 55
57. random\$.tw.
58. factorial\$.tw.
59. crossover\$.tw.

60. cross over\$.tw.
61. cross-over\$.tw.
62. placebo\$.tw.
63. (doubl\$ adj blind\$).tw.
64. (singl\$ adj blind\$).tw.
65. assign\$.tw.
66. allocat\$.tw.
67. volunteer\$.tw.
68. crossover procedure/
69. double blind procedure/
70. randomized controlled trial/
71. single blind procedure/
72. 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71
73. (animal/ or nonhuman/) not human/
74. 72 not 73
75. 56 and 74
76. developing country.sh,hw.
77. ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).ti,ab.
78. ((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)).ti,ab.
79. (low* adj (gdp or gnp or gross domestic or gross national)).ti,ab.
80. (low adj3 middle adj3 countr*).ti,ab.
81. (lmic or lmics or third world or lami countr*).ti,ab.
82. transitional countr*.ti,ab.
83. Cambodia/
84. (cambodia* or Kampuchea).cp,in,jw,mp.
85. "Democratic People's Republic of Korea"/
86. (north korea* or (democratic people* republic adj2 korea)).cp,in,jw,mp.
87. Myanmar/
88. (myanmar or burma or burmese).cp,in,jw,mp.
89. Fiji/
90. fiji*.cp,in,jw,mp.
91. Indonesia/
92. indonesia*.cp,in,jw,mp.
93. Micronesia/
94. (Micronesia* or Kiribati).cp,in,jw,mp.
95. Laos/
96. (laos or (lao adj1 democratic republic) or (lao adj2 people) or marshall island*).cp,in,jw,mp.
97. Mongolia/
98. mongolia*.cp,in,jw,mp.
99. Papua New Guinea/
100. Papua New Guinea.cp,in,jw,mp.
101. Philippines/
102. (Philippines or filipino*).cp,in,jw,mp.
103. samoa/ or "independent state of samoa"/
104. samoa*.cp,in,jw,mp.
105. Melanesia/
106. (Solomon Islands or Timor-Leste or Melanesia*).cp,in,jw,mp.
107. Tonga/
108. tonga*.cp,in,jw,mp.
109. Vanuatu/
110. Vanuatu.cp,in,jw,mp.

111. Vietnam/
112. Vietnam*.cp,in,jw,mp.
113. exp China/
114. (china or chinese).cp,in,jw,mp.
115. Malaysia/
116. Malaysia*.cp,in,jw,mp.
117. Palau/
118. (Palau or Belau or Pelew).cp,in,jw,mp.
119. Thailand/
120. (Thailand or thai*).cp,in,jw,mp.
121. (tuvalu or ellice islands).cp,in,jw,mp.
122. Kyrgyzstan/
123. (kyrgyzstan or kyrgyz or kirghizia or kirghiz).cp,in,jw,mp.
124. Tajikistan/
125. (tajikistan or tadjhik or tadjhikistan or tajikistan).cp,in,jw,mp.
126. Albania/
127. Albania*.cp,in,jw,mp.
128. Armenia/
129. Armenia*.cp,in,jw,mp.
130. "Georgia (Republic)"/
131. georgia*.cp,in,jw,mp.
132. Yugoslavia/
133. (Jugoslavija* or Yugoslavia* or serbo-croat* or macedonia* or sloven* or kosovo).cp,in,jw,mp.
134. Moldova/
135. Moldova*.cp,in,jw,mp.
136. Ukraine/
137. Ukrain*.cp,in,jw,mp.
138. Uzbekistan/
139. Uzbekistan.cp,in,jw,mp.
140. Azerbaijan/
141. Azerbaijan*.cp,in,jw,mp.
142. "Republic of Belarus"/
143. (belarus or byelarus or belorussia).cp,in,jw,mp.
144. Bosnia-Herzegovina/
145. bosnia*.cp,in,jw,mp.
146. Bulgaria/
147. Bulgaria*.cp,in,jw,mp.
148. Kazakhstan/
149. (Kazakhstan or kazakh).cp,in,jw,mp.
150. Latvia/
151. Latvia*.cp,in,jw,mp.
152. Lithuania/
153. Lithuania*.cp,in,jw,mp.
154. "Macedonia (Republic)"/
155. Macedonia*.cp,in,jw,mp.
156. Montenegro/
157. Montenegro.cp,in,jw,mp.
158. Romania/
159. Romania*.cp,in,jw,mp.
160. exp Russia/
161. USSR/
162. (russia* or ussr or soviet or cccp).cp,in,jw,mp.
163. Serbia/

164. serbia*.cp,in,jw,mp.
165. Turkey/
166. turk*.cp,in,jw,mp. not animal/
167. Turkmenistan/
168. Haiti/
169. Haiti.cp,in,jw,mp.
170. Belize/
171. Belize.cp,in,jw,mp.
172. Bolivia/
173. Bolivia*.cp,in,jw,mp.
174. El Salvador/
175. El Salvador.cp,in,jw,mp.
176. Guatemala/
177. Guatemala*.cp,in,jw,mp.
178. Guyana/
179. Guyana*.cp,in,jw,mp.
180. Honduras/
181. Hondura*.cp,in,jw,mp.
182. Nicaragua/
183. Nicaragua.cp,in,jw,mp.
184. Paraguay/
185. Paraguay.cp,in,jw,mp.
186. "Antigua and Barbuda"/
187. (Antigua or Barbuda).cp,in,jw,mp.
188. Argentina/
189. Argentin*.cp,in,jw,mp.
190. Brazil/
191. Brazil*.cp,in,jw,mp.
192. Chile/
193. Chile*.cp,in,jw,mp.
194. Colombia/
195. Colombia*.cp,in,jw,mp.
196. Costa Rica/
197. Costa Rica*.cp,in,jw,mp.
198. Cuba/
199. Cuba*.cp,in,jw,mp.
200. Dominica/
201. Dominican Republic/
202. Dominica*.cp,in,jw,mp.
203. Ecuador/
204. Ecuador*.cp,in,jw,mp.
205. Grenada/
206. Grenad*.cp,in,jw,mp.
207. Jamaica/
208. Jamaica*.cp,in,jw,mp.
209. Mexico/
210. Mexic*.cp,in,jw,mp.
211. exp Panama/
212. Panama*.cp,in,jw,mp.
213. Peru/
214. Peru*.cp,in,jw,mp.
215. Saint Lucia/
216. (St Lucia* or Saint Lucia*).cp,in,jw,mp.

217. "Saint Vincent and the Grenadines"/
218. Grenadines.cp,in,jw,mp.
219. Suriname/
220. Surinam*.cp,in,jw,mp.
221. Uruguay/
222. Uruguay.cp,in,jw,mp.
223. Venezuela/
224. Venezuela*.cp,in,jw,mp.
225. Djibouti/
226. Djibouti.cp,in,jw,mp.
227. Egypt/
228. Egypt*.cp,in,jw,mp.
229. Iraq/
230. Iraq*.cp,in,jw,mp.
231. Morocco/
232. Morocco*.cp,in,jw,mp.
233. Syria/
234. (Syria* or gaza*).cp,in,jw,mp.
235. Yemen/
236. yemen*.cp,in,jw,mp.
237. Algeria/
238. Algeria*.cp,in,jw,mp.
239. Iran/
240. Iran*.cp,in,jw,mp.
241. Jordan/
242. jordan*.cp,in,jw,mp.
243. Lebanon/
244. Leban*.cp,in,jw,mp.
245. Libya/
246. Libya*.cp,in,jw,mp.
247. Tunisia/
248. Tunisia*.cp,in,jw,mp.
249. Afghanistan/
250. Afghan*.cp,in,jw,mp.
251. Bangladesh/
252. Bangladesh*.cp,in,jw,mp.
253. Nepal/
254. Nepal*.cp,in,jw,mp.
255. Bhutan/
256. Bhutan*.cp,in,jw,mp.
257. exp India/
258. india*.cp,in,jw,mp.
259. Pakistan/
260. Pakistan*.cp,in,jw,mp.
261. Sri Lanka/
262. Sri Lanka*.cp,in,jw,mp.
263. Indian Ocean Islands/
264. Maldiv*.cp,in,jw,mp.
265. Benin/
266. (Benin or Dahomey).cp,in,jw,mp.
267. Burkina Faso/
268. (Burkina Faso or Burkina Fasso or Upper Volta).cp,in,jw,mp.
269. Burundi/

270. Burundi*.cp,in,jw,mp.
271. Central African Republic/
272. (Central African Republic or Ubangi-Shari or african*).cp,in,jw,mp.
273. Chad/
274. Chad.cp,in,jw,mp.
275. Comoros/
276. (comoros or comores).cp,in,jw,mp.
277. "Democratic Republic of the Congo"/
278. (congo* or zaire).cp,in,jw,mp.
279. Eritrea/
280. Eritrea*.cp,in,jw,mp.
281. Ethiopia/
282. Ethiopia*.cp,in,jw,mp.
283. Gambia/
284. Gambia*.cp,in,jw,mp.
285. Guinea/
286. (Guinea* not (New Guinea or Guinea Pig* or Guinea Fowl)).cp,in,jw,mp.
287. Guinea-Bissau/
288. (Guinea-Bissau or Portuguese Guinea).cp,in,jw,mp.
289. Kenya/
290. Kenya*.cp,in,jw,mp.
291. Liberia/
292. Liberia*.cp,in,jw,mp.
293. Madagascar/
294. (Madagasca* or Malagasy Republic).cp,in,jw,mp.
295. Malawi/
296. (Malawi* or Nyasaland).cp,in,jw,mp.
297. Mali/
298. Mali*.cp,in,jw,mp.
299. Mauritania/
300. Mauritania*.cp,in,jw,mp.
301. Mozambique/
302. (Mozambi* or Portuguese East Africa).cp,in,jw,mp.
303. Niger/
304. (Niger not (Aspergillus or Peptococcus or Schizothorax or Cruciferae or Gobius or Lasius or Agelastes or Melanosuchus or radish or Parastromateus or Orius or Apepgillus or Parastromateus or Stomoxys)).cp,in,jw,mp.
305. Rwanda/
306. (Rwanda* or Ruanda*).cp,in,jw,mp.
307. Sierra Leone/
308. Sierra Leone*.cp,in,jw,mp.
309. Somalia/
310. Somali*.cp,in,jw,mp.
311. Tanzania/
312. Tanzania*.cp,in,jw,mp.
313. Togo/
314. Togo*.cp,in,jw,mp.
315. Uganda/
316. Uganda*.cp,in,jw,mp.
317. Zimbabwe/
318. (Zimbabwe* or Rhodesia*).cp,in,jw,mp.
319. Cameroon/
320. Cameroon*.cp,in,jw,mp.
321. Cape Verde/

322. Cape Verde*.cp,in,jw,mp.
 323. Congo/
 324. (congo* not ((democratic republic adj3 congo) or congo red or crimean-congo)).cp,in,jw,mp.
 325. Cote d'Ivoire/
 326. (Cote d'Ivoire or Ivory Coast).cp,in,jw,mp.
 327. Ghana/
 328. (Ghan* or Gold Coast).cp,in,jw,mp.
 329. Lesotho/
 330. (Lesotho or Basutoland).cp,in,jw,mp.
 331. Nigeria/
 332. Nigeria*.cp,in,jw,mp.
 333. Atlantic Islands/
 334. (sao tome adj2 principe).cp,in,jw,mp.
 335. Senegal/
 336. Senegal*.cp,in,jw,mp.
 337. Sudan/
 338. Sudan*.cp,in,jw,mp.
 339. Swaziland/
 340. Swazi*.cp,in,jw,mp.
 341. Zambia/
 342. (Zambia* or Northern Rhodesia*).cp,in,jw,mp.
 343. Angola/
 344. Angola*.cp,in,jw,mp.
 345. Botswana/
 346. (Botswana* or Bechuanaland or Kalahari).cp,in,jw,mp.
 347. Gabon/
 348. Gabon*.cp,in,jw,mp.
 349. Mauritius/
 350. (Mauriti* or Agalega Islands).cp,in,jw,mp.
 351. Namibia/
 352. Namibia*.cp,in,jw,mp.
 353. Seychelles/
 354. Seychelles.cp,in,jw,mp.
 355. South Africa/
 356. South Africa*.cp,in,jw,mp.
 357. or/76-356
 358. 75 and 357
 359. limit 358 to embase

Web of Science

34 #33 AND #19

33 #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20

32 TS=(Central African Republic or Ubangi-Shari or african* or Chad or Cameroon* or congo* or Gabon* or zaire OR Malawi* or Nyasaland or Mozambi* or Portuguese East Africa or Zimbabwe* or Rhodesia* or Lesotho or Basutoland or Swazi* or Zambia* or Northern Rhodesia* or Angola* or Botswana* or Bechuanaland or Kalahari or Namibia* or South Africa* OR sao tome)

31 TS=(Benin or Dahomey or Burkina Faso or Burkina Fasso or Upper Volta or Gambia* or Ghan* or Gold Coast or Guinea-Bissau or Portuguese Guinea or Cote d'Ivoire or Ivory Coast or Liberia* or Mali* or Mauritania* or Niger or Nigeria* or Senegal* or Sierra Leone* or Togo* or Guinea* or Cape Verde*)

30 TS=(Mexic* OR Djibouti or Burundi* or Ethiopia* or Kenya* or Rwanda* or Ruanda* or Somali* or Sudan* or Tanzania* or Uganda* or Eritrea* OR Egypt* or Algeria* or Libya* or Morocc* or Tunisia* OR Bangladesh* or Bhutan* or Nepal* or india* or Pakistan* or Sri Lanka* or Syria* or gaza* or turk* or Afghan* or Iran* or Iraq* or jordan* or Leban* or yemen* OR Maldiv* or Madagascar* or Malagasy Republic or Seychelles or comoros or comores or Mauriti* or Agalega Islands)

29 TS=(Armenia* or georgia* or Azerbaijan* OR Haiti or Cuba* or Dominica* or Antigua or Barbuda or Jamaica* or Grenad* or St Lucia* or Saint Lucia* or Grenadines OR Belize or Costa Rica* or El Salvador or Guatemala* or Hondura* or Nicaragua or Panama* OR Bolivia* or Argentin* or Brazil* or Chile* or Colombia* or Ecuador* or Guyana* or Paraguay or Peru* or Surinam* or Uruguay or Venezuela*)

28 TS=(kyrgyzstan or kyrgyz or kirghizia or kirghiz or tajikistan or tadjhik or tadjhikistan or tajikistan or Kazakhstan or kazakh or turk* or Uzbekistan OR Albania* or Jugoslavija* or Yugoslavia* or serbo-croat* or macedonia* or sloven* or kosovo or Moldova* or Ukrain* or Bulgaria* or belarus or byelarus or belorussia or bosnia* or Montenegro or Romania* or russia* or ussr or soviet or ccp or serbia* or Latvia* or Lithuania*)

27 TS=(korea* or mongolia* or china or chinese OR fiji* or Papua New Guinea or Vanuatu or Solomon Islands or Timor-Leste or Melanesia* OR Micronesia* or Kiribati or Palau or Belau or Pelew OR samoa* or tonga* or tuvalu or ellice islands)

26 TS=(cambodia* or Kampuchea or myanmar or burma or burmese or indonesia* or laos or lao democratic republic or lao people or marshall island* or Malaysia* or Philippines or filipino* or Thailand or thai* or Vietnam* or tuvalu or ellice islands)

25 TS=(transitional countr*)

24 TS=(lmic or lmics or third world or lami countr*)

23 TS=(low near/3 middle near/3 countr*)

22 TS=(low* NEAR (gdp or grnp or “gross domestic” or “gross national”))

21 TS=((developing or “less* developed” or “under developed” or underdeveloped or “middle income” or “low* income”) NEAR (economy or economies))

20 TS=((developing or “less* developed” or “under developed” or underdeveloped or “middle income” or “low* income” or underserved or “under served” or deprived or poor*) NEAR (countr* or nation? or population? or world))

19 #18 AND #17

18 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)

17 #16 AND #8

16 #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9

15 TS=((lifestyle or life style or life-style or behavio?r* or risk factor*) SAME modif*)

14 TS=(nonpharmacologic* or non-pharmacologic*)

13 TS=((health* or wellness or weight or diet* or smok*) NEAR/2 (promot* or program* or campaign* or advic* or educat*))

12 TS=(educat* NEAR/3 (program* or patient*))

11 TS=(risk NEAR/2 factor* NEAR/3 (reduc* or manage* or managing or interven* or program*))

10 TS=((lifestyle or life-style or behavio?r*) NEAR/3 (interven* or educat* or advice* or alter* or change* or inform*))

9 TS=((multifactor* NEAR/5 (interven* or prevent*)) OR (primary NEAR/3 prevent*))

8 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

7 TS=(hyperlipid* OR hyperlip?emia* OR hypercholesterol* OR hypercholester?emia* OR hyperlipoprotein?emia* OR hypertriglycerid?emia*)

6 TS=(“high blood pressure”)

5 TS=(hypertensi* OR “peripheral arter* disease”)

4 TS=(stroke OR stokes OR cerebrovasc* OR cerebral OR apoplexy OR (brain SAME accident*) OR (brain SAME infarct*))

3 TS=(“atrial fibrillat*” OR tachycardi* OR endocardi*)

2 TS=(pericard* OR isch?em* OR emboli* OR arrhythmi* OR thrombo*)

1 TS=(cardio* OR cardia* OR heart* OR coronary* OR angina* OR ventric* OR myocard*)

LILACS

cardio\$ or cardia\$ or heart\$ or coronary or angina\$ or myocard\$ or ischem\$ or ischaem\$ or hypertens\$ or hyperlipid\$ or cholesterol or “risk factor\$” [Words] and “primary prevent\$” or “health intervent\$” or “health educat\$” or “lifestyle modif\$” [Words] and trial or random\$ or control\$ [Words]

Global Health

1. exp cardiovascular diseases/
2. cardio*.tw.
3. cardia*.tw.
4. heart*.tw.

5. coronary*.tw.
6. angina*.tw.
7. ventric*.tw.
8. myocard*.tw.
9. pericard*.tw.
10. isch?em*.tw.
11. emboli*.tw.
12. arrhythmi*.tw.
13. thrombo*.tw.
14. atrial fibrillat*.tw.
15. tachycardi*.tw.
16. endocardi*.tw.
17. (sick adj sinus).tw.
18. stroke/
19. (stroke or stokes).tw.
20. cerebrovasc*.tw.
21. cerebral vascular.tw.
22. apoplexy.tw.
23. (brain adj2 accident*).tw.
24. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
25. exp hypertension/
26. hypertensi*.tw.
27. peripheral arter* disease*.tw.
28. ((high or increased or elevated) adj2 blood pressure).tw.
29. exp hyperlipaemia/
30. hyperlipid*.tw.
31. hyperlip?emia*.tw.
32. hypercholesterol*.tw.
33. hypercholester?emia*.tw.
34. hyperlipoprotein?emia*.tw.
35. hypertriglycerid?emia*.tw.
36. exp atherosclerosis/
37. cholesterol/
38. cholesterol.tw.
39. blood pressure/
40. blood pressure.tw.
41. multiple risk factor*.tw.
42. or/1-41
43. health promotion/
44. health education/
45. health behaviour/
46. exp counselling/
47. exp prevention/
48. (multifactor* adj5 (interven* or prevent*)).tw.
49. ((lifestyle or life-style or behavio?r*) adj3 (interven* or educat* or advice* or alter* or change* or inform*)).tw.
50. (primary adj3 prevent*).tw.
51. (risk factor* adj3 (reduc* or manage* or managing or interven* or program*)).tw.
52. (educat* adj3 (program* or patient*)).tw.
53. ((health* or wellness or weight or diet* or smok*) adj2 (promot* or program* or campaign* or advic* or educat*)).tw.
54. (nonpharmacologic* or non-pharmacologic*).tw.
55. ((lifestyle or life style or life-style or behavio?r* or risk factor*) adj3 modif*).tw.
56. or/43-55
57. 42 and 56

58. random*.tw.
59. trial*.tw.
60. placebo*.tw.
61. groups.tw.
62. control*.tw.
63. or/58-62
64. exp animals/ not man/
65. 63 not 64
66. 57 and 65
67. exp developing countries/
68. ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).ti,ab.
69. ((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)).ti,ab.
70. (low* adj (gdp or gnp or gross domestic or gross national)).ti,ab.
71. (low adj3 middle adj3 countr*).ti,ab.
72. (lmic or lmics or third world or lami countr*).ti,ab.
73. transitional countr*.ti,ab.
74. (cambodia* or Kampuchea or north korea* or (democratic people* republic adj2 korea) or myanmar or burma or burmese or fiji* or indonesia* or micronesia* or kiribati or laos or (lao adj1 democratic republic) or (lao adj2 people) or marshall island*).cp,in,jx,tw.
75. (mongolia* or Papua New Guinea or Philippines or filipino* or samoa* or Solomon Islands or Timor-Leste or Melanesia* or tonga* or vanuatu or vietnam* or china or chinese or malaysia* or palau or belau or pelew or Thailand or thai* or tuvalu or ellice islands).cp,in,jx,tw.
76. (kyrgyzstan or kyrgyz or kirghizia or kirghiz or tajikistan or tadjhik or tadjhikistan or tajikistan or albania* or armenia* or georgia* or Jugoslavija* or Yugoslavia* or serbo-croat* or macedonia* or sloven* or kosovo or moldova* or ukrain* or Uzbekistan or Azerbaijan* or belarus or byelarus or belorussia or bosnia*).cp,in,jx,tw.
77. (Bulgaria* or Kazakhstan or kazakh or latvia* or lithuania* or macedonia* or montenegro or romania* or russia* or ussr or soviet or ccp or serbia* or turk*).cp,in,jx,tw.
78. (haiti or belize or bolivia* or el salvador or guatemala* or guyana* or hondura* or nicaragua or paraguay or antigua or barbuda).cp,in,jx,tw.
79. (Argentin* or brazil* or chile* or colombia* or costa rica* or cuba* or dominica* or ecuador* or grenad* or jamaica* or mexic* or panama* or peru* or st lucia* or saint lucia* or grenadines or surinam* or uruguay or venezuela* or djibouti or egypt* or iraq* or morocc*).cp,in,jx,tw.
80. (Syria* or gaza* or yemen* or algeria* or iran* or jordan* or leban* or libya* or tunisia* or afghan* or bangladesh* or nepal* or bhutan* or india* or pakistan* or sri lanka* or maldiv* or benin or dahomey or brukina faso or burkina fasso or upper volta or burundi* or Central African Republic or Ubangi-Shari or african* or chad or comoros or comores or congo* or zaire or eritrea*).cp,in,jx,tw.
81. ((Ethiopia* or gambia* or Guinea* or Guinea-Bissau or Portuguese Guinea or kenya* or liberia* or Madagasca* or Malagasy Republic or malawi* or nyalaland or mali* or mauritania* or mozambi* or portuguese east africa) not (New Guinea or Guinea Pig* or Guinea Fowl)).cp,in,jx,tw.
82. (Niger not (Aspergillus or Peptococcus or Schizothorax or Cruciferae or Gobius or Lasius or Agelastes or Melanosuchus or radish or Parastromateus or Orius or Apepgillus or Parastromateus or Stomoxys)).cp,in,jx,tw.
83. ((Rwanda* or Ruanda* or sierra leone* or somali* or tanzania* or togo* or uganda* or zimbabwe* or rhodesia* or cameroon* or cape verde* or congo*) not ((democratic republic adj3 congo) or congo red or crimean-congo)).cp,in,jx,tw.
84. (((Cote d'Ivoire or Ivory Coast or ghan* or gold coast or Lesotho or Basutoland or nigeria* or sao tome) adj2 principe) or senegal* or sudan* or swazi* or zambia* or northern rhodesia* or angola* or botswana* or Bechuanaland or Kalahari or gabon* or Mauriti* or Agalega Islands or namibia* or seychelles or south africa*).cp,in,jx,tw.
85. or/67-84
86. 66 and 85

ELDIS

(cardio* or heart*) and (risk* or interven* or educat* or program* or prevent*) and (random* or trial*)

CONTRIBUTIONS OF AUTHORS

OAU and LH screened titles and abstracts and assessed studies for formal inclusion and exclusion. OAU and LH abstracted data and assessed methodological rigour. OAU analysed the data, which were checked by LH. OAU wrote the first draft of the review and all review authors contributed to later drafts.

DECLARATIONS OF INTEREST

OAU: None known.

LH: None known.

KR: None known.

FT: None known.

SE: Research is supported by a grant from UK Department for International Development.

AC: None known.

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Internal sources

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- Center for Evidence-based Health Care, Stellenbosch University, South Africa.

External sources

- NIHR Cochrane Programme Grant, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Assessment of risk of bias in included studies

Deleted: “Blinding of participants and personnel.”

Dealing with missing data

Deleted: “Where this is not possible and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.”

Data synthesis

Deleted: “We will express time-to-event outcomes or generic inverse variance outcomes, such as survival time and time to development of cardiovascular disease, as the log hazard ratio and 95% CI.

When studies cannot be combined for meta-analysis due to diversity of interventions, we will conduct narrative syntheses and display the results of individual studies graphically to enable a more succinct summary of the evidence. We will also narratively describe skewed data reported as medians and interquartile ranges.”

Subgroup analysis and investigation of heterogeneity

Deleted: “Evidence of prescribed drug treatment (prescribed medication during trial and no prescribed medication or drug treatment not stated).

Co-morbidity (diabetes, hypertension, obesity, no co-morbidity).

Age.

Sex.

Age of trial (publication year: before 2000 versus after 2000).

We will use meta-regression methods to examine the effects of baseline mean values for age, sex and blood pressure, if sufficiently reported.”

The planned subgroup analysis for low-income vs low-and middle-income countries could not be performed because all the studies were from middle-income countries.

INDEX TERMS

Medical Subject Headings (MeSH)

*Developing Countries; Cardiovascular Diseases [*prevention & control]; Diabetes Mellitus, Type 2 [therapy]; Diet; Exercise; Health Promotion [*methods]; Hypertension [therapy]; Primary Prevention [*methods]; Randomized Controlled Trials as Topic; Risk Factors

MeSH check words

Humans