# Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries: a Cochrane review

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# Abstract

## Background: Given the increasing incidence of cardiovascular diseases (CVDs) and lower CVD health awareness in low- and middle-income countries (LMICs) it is possible that multiple risk factor intervention programmes may have beneficial effects.

## Objectives: To determine the effectiveness of multiple risk factor interventions aimed at modifying major cardiovascular risk factors for the primary prevention of CVD in LMICs.

## Methods: We searched major electronic databases for randomised controlled trials of health promotion interventions to achieve behaviour change (i.e. smoking cessation, dietary advice, increasing activity levels). 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).

## Results: Thirteen trials met the inclusion criteria. 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. The pooled effect indicated a reduction in systolic blood pressure (MD -6.72 mmHg, 95% CI -9.82 to -3.61, I² = 91%, 4868 participants), diastolic blood pressure (MD -4.40 mmHg, 95% CI -6.47 to -2.34, I² = 92%, 4701 participants), body mass index (MD -0.76 kg/m², 95% CI -1.29 to -0.22, I² = 80%, 2984 participants) and waist circumference (MD -3.31, 95% CI -4.77 to -1.86, I² = 55%, 393 participants) in favour of multiple risk factor interventions.

## Conclusions: 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.

# Introduction

Many low- and middle-income countries (LMICs) are now experiencing epidemiological transition, the change from a burden of infectious diseases to chronic diseases[1], 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[2]. Urbanisation and consumption of unhealthy diets are the main causes of this epidemic in LMICs [2-4]. In addition, LMICs are not only dealing with the emerging burden of non-communicable diseases, but also the current burden of infectious diseases[5-8]. 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[9]. Lifestyle modifications have been shown to decrease the incidence of type 2 diabetes mellitus by 58% among people with impaired glucose intolerance[10, 11] and significantly lowered systolic blood pressure between -5.4 to -11.4 mmHg [12]. Therapeutic lifestyle interventions have been found to be at least as effective as pharmacotherapies [13], at little cost and with minimum risk [14]. In contrast to most pharmacotherapies, lifestyle modifications can also prevent or control other chronic conditions[10, 15]. 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[16]. It is therefore generally recommended that lifestyle modifications should be implemented as a group[17].

A comprehensive Cochrane review has examined the effectiveness of multiple risk factor interventions in all settings, predominantly high-income countries [18] and 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". This Cochrane review[18], 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. The objective of this review was 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 LMICs[19].

# Methods

## Protocol and registration

## This systematic review rational and methods were specified in advance and documented in a protocol which was published in the PROSPERO register (CRD42015019312)[20].

## Eligibility criteria

We include randomised controlled trials (RCTs) of at least six months duration of follow-up, that examined the effects of health promotion interventions to achieve behaviour change, such as smoking cessation, dietary advice, increasing activity levels in adult populations (≥ 18 years of age); conducted LMICs; and reported at least of one the following 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; (3) all cause-mortality, (4) changes in cardiovascular disease risk factors (blood pressure, lipid levels, diabetes, and obesity), and (5) changes in health knowledge, attitudes and intention.

**Information sources and search strategy**

We identified trials through systematic searches of the following bibliographic databases (from inception to 27 June 2014): Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE Classic + EMBASE, Science Citation Index Expanded (SCI-EXPANDED), Conference Proceedings Citation Index – Science (CPCI-S) on Web of Science, Database of Abstracts of Reviews of Effects, LILACS (Bireme), Global Health and ELDIS ([www.eldis.org](http://www.eldis.org)). We adapted the preliminary search strategy for MEDLINE (Ovid) for use in the other databases ([**Appendix 1**](#APP-01)). We checked the reference lists of all primary studies and review articles for additional references.

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### Study selection

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.

### Data abstraction

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. Two authors (OAU and LH) independently extracted outcome data from the included studies. We resolved disagreements by consensus or by involving a third author (KR). One author (OAU) transferred data into the Review Manager 5 software. 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. We resolved any disagreements by discussion or by involving another author (KR). We assessed the risk of bias according to the following domains: random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias. We graded each potential source of bias as high, low or unclear.

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### 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. 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’[21]. 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[22] 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.

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### 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. We used the I² statistic to measure heterogeneity among the trials in each analysis[23]. When we identified substantial heterogeneity (I² value greater than 50%), i.e. more than 50% of the variation is due to heterogeneity rather than chance[24], we reported it and explored possible causes by pre-specified subgroup analysis. We used funnels plots and Egger tests [25] to assess potential small-study biases and publication bias for those outcomes with more than 10 trials (i.e. systolic and diastolic blood pressure).

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# Results

### Study selection and characteristics

The literature searches yielded 13,468 titles of potentially relevant articles after duplicates were removed (**Figure 1**). 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**.** We included 13 trials [9, 22, 26-36]. **eTable 1** present details and reasons for exclusion for the studies that most nearly missed the inclusion criteria. The characteristics of the included studies is summarised in **Table 1**. Where this was reported, the trials were conducted between 2001 and 2010, and published between 2004 and 2012. Three trials were conducted in Turkey [27, 29, 33]. Two trials each were conducted in China [35, 36] and Mexico [9, 26]. One trial recruited participants from both China and Nigeria[22]. The other trials were conducted in Brazil[28], India [30], Pakistan[31], Romania[32] and Jordan[34]. The randomisation unit for most trials was individual participants [9, 26-30, 32-36]. Two trials used cluster randomisation (primary care facilities [22] and households [31]. Only two trials [27, 36] recruited participants from healthy or general population. Most trials (n = 11) recruited high-risk groups: known hypertensive people [22, 26, 29, 31, 33]; pre-hypertensive people[9]; metabolic syndrome[32, 34]; obese participants [28]; and people with impaired glucose regulation [30, 35]. The content of the interventions varied across the trials. 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).

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## Risk of bias in included studies

The risk of bias of included studies is shown in **Figure 2**. he generation of allocation sequence was adequate in four trials [29, 31, 34, 36], unclear in seven trials [9, 22, 26-28, 30, 35] and inadequate in two trials [32, 33]. [Avram et al. 2011](#STD-Avram-2011) [32] and [Hacihasanoglu et al. 2011](#STD-Hacihasanoglu-2011) [33] used the calendar date for generating allocation sequence. Allocation concealment was adequate in one trial[29], inadequate in two trials [32, 33] and unclear in the remaining 10 trials. Four trials[27, 29, 31, 32] masked outcome assessors to treatment allocation and one trial [33] did not. It is not clear whether the remaining trials masked outcome assessors to treatment allocation. The potential risk of bias likely to be introduced by incomplete data was high in only one trial[28], unclear in three trials[22, 30, 32], low in the remaining nine trials. The risk of selective reporting bias was unclear in [Avram et al. 2011](#STD-Avram-2011)[32], and low in the remaining 12 trials. The risk of bias likely to be introduced by other potential sources of bias was low in two trials [22, 31] and unclear in the remaining 11 trials.

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## Effects of interventions

#### Combined Cardiovascular events

One trial[30] 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). This result is imprecise (wide confidence interval and small sample size) and makes it difficult to draw a reliable conclusion.

##### Blood pressure

Systolic blood pressure and diastolic blood pressure were reported in 11 trials (5106 participants randomised) [9, 22, 26, 28-31, 33-36]. 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) (**Figure 3**) in favour of multiple risk factors interventions, but with evidence of statistically significant substantial between-trial heterogeneity (I² = 91%, P = 0.0001). There was no evidence of funnel plot asymmetry for systolic blood pressure (SBP) (**Figure 4**), suggesting no evidence of small-study bias (P = 0.270 for Egger's regression asymmetry test). In a pre-specified 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).

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) ([**Figure**](#CMP-001.04) **3**) in favour of multiple risk factors interventions, but with evidence of statistically significant substantial between-trial heterogeneity (I² = 92%, P = 0.0001). There was no evidence of funnel plot asymmetry for diastolic blood pressure ([**Figure**](#FIG-06) **4**), 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 and colleagues[27] 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).

##### Anthropometric indices

Body mass index (BMI) was reported in seven trials [9, 22, 28, 29, 33, 35, 36]. The pooled effect showed a statistically significant reduction in BMI (MD -0.76 kg/m², 95% CI -1.29 to -0.22, 2984 participants) ([**Figure**](#CMP-001.06) **5**) in favour of multiple risk factors interventions, but with evidence of statistically significant substantial between-trial heterogeneity (I² = 80%, P = 0.00003). However, this effect was only significant among the high-risk groups (MD -0.94 kg/m², 95% CI -1.54 to -0.33, six trials, 1022 participants) and not among the general population (MD -0.14 kg/m², 95% CI -0.47 to 0.19, one trial, 1962 participants). Waist circumference was reported in four trials [9, 29, 30, 35]. The pooled effect showed a statistically significant reduction in waist circumference (MD -3.31, 95% CI -4.77 to -1.86, I² = 55%, four trials, 393 participants) **(**[**Figure**](#CMP-001.07) **5**). Kisioglu and colleagues[27] 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 [9, 28, 30, 34-36]. 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) **(**[**Figure**](#CMP-001.08) **6**).

##### Glycated haemoglobin (haemoglobin A1c)

One trial [35] 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[9, 28-30, 34, 35]. 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), low density lipoprotein (LDL) cholesterol (MD -0.13 mmol/L, 95% CI -0.53 to 0.27, four trials, 544 participants) and total cholesterol (MD -0.22 mmol/L, 95% CI -0.48 to 0.04, five trials, 625 participants) (**Figure 6**). 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) ([**Figure**](#CMP-001.10) **6**).

##### Fruits and vegetables consumption

One trial [22] (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[22] (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).

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# 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. The observed risk factor changes associated with multiple risk factor interventions though were modest, but are probably spurious as attribution of effect are inherently difficult to demonstrate in these interventions. These apparent reductions in risk factors may well be due to several factors, including failure to carry out intention to treat analysis owing to losses to follow up, regression to the mean, non-blinded assessment of outcomes etc[18]. Furthermore, there are many problems in relating trial outcome to a risk measure which is itself dependent on the outcome in meta-analysis [37], it is not possible to separate the benefits of the use of antihypertensive drugs in this set of trials since trials that included participants at high of developing cardiovascular diseases are more likely to include participants with high rates of use of antihypertensive drugs[18].

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## Study limitations and strengths

Overall, the studies included in this review were at some risk of bias, and the results should be treated with caution. 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. 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.

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## Comparison with similar studies

Ebrahim and colleagues [18] 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" [18]. Another recent systematic review [12] 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)[12]. Joshi and colleagues conducted a cluster randomized trial in rural Andhra Pradesh to develop, implement and evaluate two CVD prevention strategies (clinical and health promotion interventions)[38]. The health promotion intervention included posters, street theatre, rallies and community presentations designed to increase the knowledge of the adult population about stopping tobacco use, heart-healthy eating and physical activity[38]. The trial found no detectable effect of the health promotion interventions on the primary outcome of knowledge about six lifestyle factors affecting CVD risk and on both systolic and diastolic blood pressures[38]. The trial was excluded from this review because they reported no usable outcomes for the meta-analyses.

# Conclusions

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. 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.

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# 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.

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**Table 1: Characteristics of included studies**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Country | Sample Size | Mean age | % male | Population | Lifestyle contents | Mode of delivery | Follow-up duration | % loss to follow-up |
| Garcia-Pena 2001[26] | Mexico | 718 | 70.6 | 36.1 | Hypertensive | Diet, exercise, weight loss | Nurse-led | 6 | 2.6 |
| Kisioglu 2004[27] | Turkey | 400 | 45.0 | 0.0 | Middle-aged women | Diet, exercise, weight loss | Trained expert | 6 | 7.0 |
| Sartorelli 2005[28] | Brazil | 104 | 45.5 | 20.2 | Overweight/obesity, first degree of patients with Type 2 diabetes mellitus | Diet, exercise, weight loss | Nutritionist-led | 12 | 31.7 |
| Cakir 2006[28, 29] | Turkey | 70 | 53.9 | 38.3 | Hypertensive | Diet, exercise, weight loss | Nurse-led | 6 | 14.3 |
| Snehalatha 2008[30] | India | 232 | 45.6 | 81.1 | Impaired glucose tolerance | Diet, exercise | Trained researcher-led plus telephonic contacts | 30 | 11.1 |
| Marquez-Celedonio 2009[9] | Mexico | 81 | 43.3 | Not reported | Pre- Hypertensive | Diet, exercise, smoking cessation | Trained researcher-led | 6 | 11.1 |
| Jafar 2009 (C)[31] | Pakistan | 1341 | 53.0 | 39.7 | Hypertensive | Diet, exercise, smoking cessation | Community worker-led | 24 | 7.7 |
| Mendis 2010 (C)[22] | China & Nigeria | 2397 | 54.5 | 44.7 | Hypertensive | Diet, exercise, smoking cessation | Primary healthcare worker-led | 12 | 9.9 |
| Avram 2011[32] | Romania | 253 | 56.5 | 79.8 | Hypertensive | Diet, exercise, weight loss | General practitioners | 18 | NR |
| Hacihasanoglu 2011[33] | Turkey | 80 | 56.3 | 47.5 | Hypertensive | Diet, exercise, smoking cessation, weight loss, alcohol reduction | Nurse-led | 6 | 0 |
| Hammad 2011[34] | Jordan | 199 | 56.7 | 38.0 | Metabolic syndrome | Diet, exercise smoking cessation | Pharmacist-led | 6 | 1.5 |
| Lu 2011[34] | China | 181 | 63.6 | 52.5 | Impaired glucose tolerance | Diet, exercise | Trained researcher-led plus telephonic contacts | 12 | 13.8 |
| Chao 2012[36] | China | 1962 | 69.6 | 47.6 | Healthy adults | Diet, exercise | Specifically-trained community health service center staff, managers and related researchers | 18 | 16.9 |

### FIGURES

**Figure 1: PRISMA flow for study selection**

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**Figure 2: Risk of bias assessment of included studies**

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**Figure 3: Forest plot of effect of multiple risk factor interventions on blood pressure**

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**Figure 4: Funnel plot of studies included in meta-analysis of blood pressure**

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**Figure 5: Forest plot of effect of multiple risk factor interventions on anthropometric indices**

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**Figure 6: Forest plot of effect of multiple risk factor interventions on blood cholesterol levels, triglycerides and fasting blood glucose**

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**SUPPLEMENTARY DIGITAL CONTENT**

**ONLINE ONLY TABLE**

eTable 1: Table of excluded studies

**APPENDICIES**

Appendix 1: Medline search strategy

Appendix 2: PRISMA checklist