Multiple Risk Factor Interventions for Primary Prevention of CVD in LMIC

A Cochrane Review

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ABSTRACT

This study sought to determine the effectiveness of multiple risk factor interventions aimed at modifying major cardiovascular risk factors for the primary prevention of cardiovascular disease in low- and middle-income countries (LMIC). We searched electronic databases for randomized controlled trials of health promotion interventions to achieve behavior change. The pooled effect indicated a reduction in systolic blood pressure (−6.72 mm Hg; 95% confidence interval [CI]: −9.82 to −3.61; I^2 = 91%), diastolic blood pressure (−4.40 mm Hg; 95% CI: −6.47 to −2.34; I^2 = 92%), body mass index (−0.76 kg/m^2; 95% CI: −1.29 to −0.22; I^2 = 80%), and waist circumference (−3.31 cm; 95% CI: −4.77 to −1.86; I^2 = 55%) in favor of multiple risk factor interventions. There is some evidence that multiple risk factor interventions may lower blood pressure levels and anthropometrics in populations in LMIC settings at high risk of hypertension and diabetes.

Many low- and middle-income countries (LMIC) 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 LMIC is happening in a shorter time frame than that experienced historically by high-income countries [2]. Urbanization and consumption of unhealthy diets are the main causes of this epidemic in LMIC [2–4]. In addition, LMIC are dealing not only with the emerging burden of noncommunicable diseases, but also with 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 and −11.4 mm Hg [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 just to a 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 behaviors 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 generalizing 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 (CVD) in LMIC [19].

METHODS

Protocol and registration

This systematic review's rationale and methods were specified in advance and documented in a protocol that was published in the PROSPERO (International Prospective Register of Systematic Reviews) (http://www.crd.york.ac.uk/PROSPERO/CRD42015019312) [20].

Eligibility criteria

We include randomized controlled trials of at least 6 months' duration of follow-up that examined the effects of health promotion interventions to achieve behavior change, such as smoking cessation, dietary advice,

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This paper presents independent research and the views expressed are those of the author(s) and not necessarily those of the National Health Service, the NIHR, or the Department of Health. The authors report no relationships that could be construed as a conflict of interest.

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increasing activity levels in adult populations (≥18 years of age); conducted in LMIC; and reported at least of 1 the following outcomes: 1) combined fatal and nonfatal CVD 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 CVD 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 January 1, 1950 to June 27, 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. We adapted the preliminary search strategy for MEDLINE (Ovid) for use in the other databases (Online Appendix 1). We checked the reference lists of all primary studies and review articles for additional references.

Study selection

Two authors (O.A.U. and L.H.) 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 (K.R.) to arbitrate.

Data abstraction

We used a data collection form for study characteristics and outcome data, which had been piloted on at least 1 study in the review. One author (O.A.U.) extracted study characteristics from the included studies. Two authors (O.A.U. and L.H.) independently extracted outcome data from the included studies. We resolved disagreements by consensus or by involving a third author (K.R.). One author (O.A.U.) transferred data into the Review Manager 5 software (Cochrane Informatics and Knowledge Management Department, Copenhagen, Denmark). 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 (L.H.) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two authors (O.A.U. and L.H.) independently assessed risk of bias for each study. We resolved any disagreements by discussion or by involving another author (K.R.). 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.

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 (RR) with 95% confidence intervals (CI). For continuous outcomes, we calculated mean differences (MD) with 95% CI when the studies use the same scale. We included cluster-randomized trials in the meta-analysis along with individually randomized trials. Cluster-randomized trials are labelled with a (C). For cluster-randomized 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, whereas for continuous data, only the sample size was reduced (means ± SD were left unchanged). We used the following reported ICCs for calculating the "design effects" (DE) [22]: systolic blood pressure: ICC: 0.04, M: 59.92, DE: 3.36; and diastolic blood pressure: ICC: 0.06, M: 59.92, DE: 4.54.

Data synthesis

We summarized and analyzed all eligible studies in Review Manager 5. Two authors (O.A.U. and L.H.) 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, that is, 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 I^2 statistic to measure heterogeneity among the trials in each analysis [23]. When we identified substantial heterogeneity (I^2 value >50%), that is, 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 funnel 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).

RESULTS

Study selection and characteristics

The literature searches yielded 13,468 potentially relevant articles after duplicates were removed (Figure 1, Online

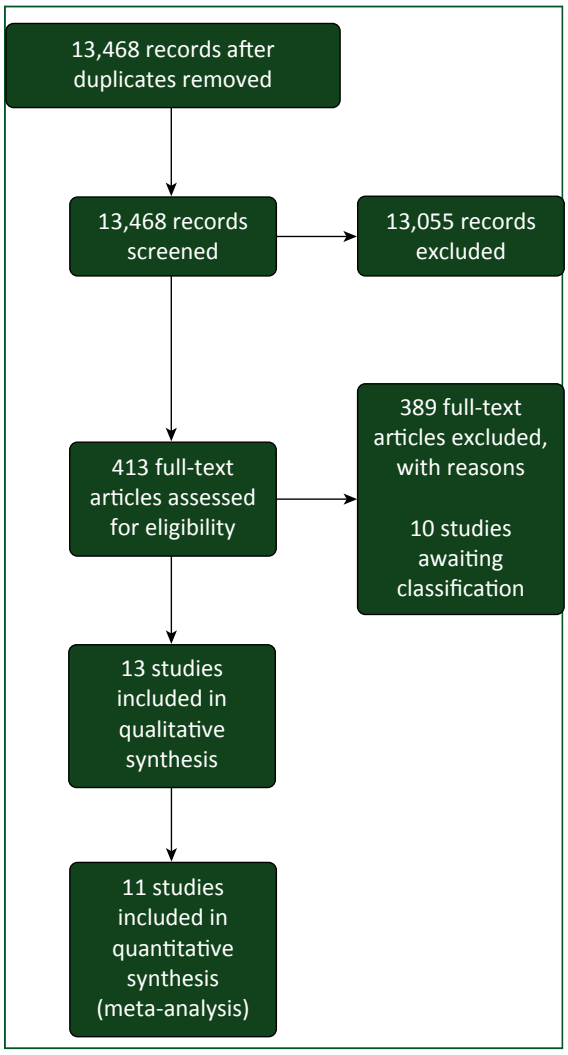

FIGURE 1. PRISMA flow for study selection. (See Online Appendix 2 for checklist.)

Appendix 2). After scanning titles and abstracts, we identified 413 potentially relevant articles and assessed full-text copies against the inclusion criteria. Of these, 13 randomized controlled trials met the inclusion criteria [9,22,26–36]. Online Table 1 presents details and reasons for exclusion for the studies that most nearly missed the inclusion criteria. The characteristics of the included studies are summarized in Table 1. Where this was reported, the trials were conducted between 2001 and 2010 and were 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 randomization unit for most trials was individual participants [9,26–30,32–36]. Two trials used cluster randomization (primary care facilities [22] and households [31]). Only 2 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 6 months to 30 months (mean 13.3 months).

Risk of bias in included studies

The risk of bias of included studies is shown in Figure 2. The generation of allocation sequence was adequate in 4 trials [29,31,34,36], unclear in 7 trials [9,22,26–28,30,35], and inadequate in 2 trials [32,33]. Avram et al. [32] and Hacihasanoglu et al. [33] used the calendar date for generating allocation sequence. Allocation concealment was adequate in 1 trial [29], inadequate in 2 trials [32,33], and unclear in the remaining 10 trials. Four trials [27,29,31,32] masked outcome assessors to treatment allocation and 1 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 1 trial [28], unclear in 3 trials [22,30,32], and low in the remaining 9 trials. The risk of selective reporting bias was unclear in Avram et al. 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 2 trials [22,31] and unclear in the remaining 11 trials.

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 (5,106 participants randomized) [9,22,26,28–31,33–36]. The pooled effect showed a statistically significant reduction in systolic blood pressure (MD: −6.72 mm Hg; 95% CI: −9.82 to −3.61; 4,868 participants) (Figure 3) in favor 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 (Figure 4), suggesting no evidence of small-study bias (p = 0.270 for the Egger regression asymmetry test). In a pre-specified subgroup analysis, the pooled intervention effect estimate tended to be more pronounced

TABLE 1. Characteristics of included studies and Cakir and Pinar [29]

Study	Year	Country	Sample Size	Mean Age	% Male	Population	Lifestyle Contents	Mode of Delivery	Follow-Up Duration (mos)	% Loss to Follow-Up
Garcia-Pena et al. [26]	2001	Mexico	718	70.6	36.1	Hypertensive	Diet, exercise, weight loss	Nurse-led	6	2.6
Kisioglu et al. [27]	2004	Turkey	400	45.0	0.0	Middle-aged women	Diet, exercise, weight loss	Trained expert	6	7.0
Sartorelli et al. [28]	2005	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 and Pinar [29]	2006	Turkey	70	53.9	38.3	Hypertensive	Diet, exercise, weight loss	Nurse-led	6	14.3
Snehalatha et al. [30]	2008	India	232	45.6	81.1	Impaired glucose tolerance	Diet, exercise	Trained researcher-led plus telephonic contacts	30	11.1
Márquez-Celedonio et al. [9]	2009	Mexico	81	43.3	Not reported	Pre-hypertensive	Diet, exercise, smoking cessation	Trained researcher-led	6	11.1
Jafar et al. (C) [31]	2009	Pakistan	1,341	53.0	39.7	Hypertensive	Diet, exercise, smoking cessation	Community worker-led	24	7.7
Mendis et al. (C) [22]	2010	China & Nigeria	2,397	54.5	44.7	Hypertensive	Diet, exercise, smoking cessation	Primary healthcare worker-led	12	9.9
Avram et al. [32]	2011	Romania	253	56.5	79.8	Hypertensive	Diet, exercise, weight loss	General practitioners	18	NR
Hacihasanoglu and Gozum [33]	2011	Turkey	80	56.3	47.5	Hypertensive	Diet, exercise, smoking cessation, weight loss, alcohol reduction	Nurse-led	6	0.0
Hammad et al. [34]	2011	Jordan	199	56.7	38.0	Metabolic syndrome	Diet, exercise smoking cessation	Pharmacist-led	6	1.5
Lu et al. [35]	2011	China	181	63.6	52.5	Impaired glucose tolerance	Diet, exercise	Trained researcher-led plus telephonic contacts	12	13.8
Chao et al. [36]	2012	China	1,962	69.6	47.6	Healthy adults	Diet, exercise	Specifically trained community health service center staff, managers, and related researchers	18	16.9

NR = not reported.

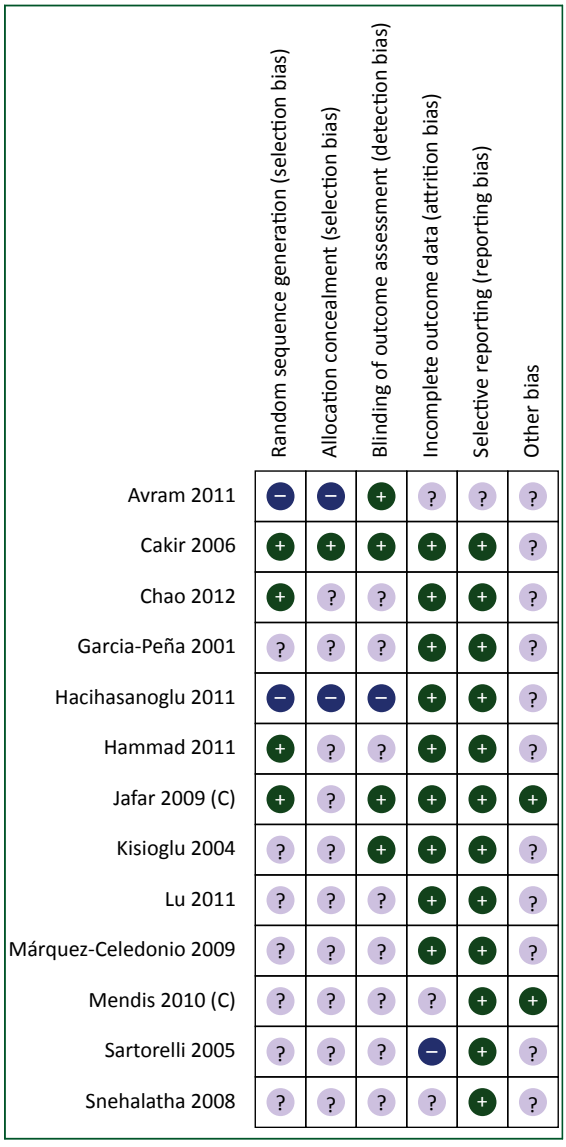

FIGURE 2. Risk of bias assessment of included studies.

among high-risk groups (MD: −7.14; 95% CI: −11.07 to −3.21; 10 trials, 2,906 participants) than in the general population (MD: −3.95; 95% CI: −5.20 to −2.70; one trial, 1,962 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 (MD: −4.40 mm Hg; 95% CI: −6.47 to −2.34; 4,701 participants) (Figure 3) in favor 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 4), suggesting no evidence of small-study bias (p = 0.446 for the Egger regression asymmetry test). In a pre-specified 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, 2,739 participants) than in the general population (MD: −3.18; 95% CI: −3.90 to −2.46; 1 trial, 1,962 participants); however, this difference did not reach a statistically significant level (p = 0.34 for interaction). Kisioglu et al. [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 was reported in 7 trials [9,22,28,29,33,35,36]. The pooled effect showed a statistically significant reduction in body mass index (MD: −0.76 kg/m^2; 95% CI: −1.29 to −0.22; 2,984 participants) (Figure 5) in favor 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; 6 trials, 1,022 participants) and not among the general population (MD: −0.14 kg/m^2; 95% CI: −0.47 to 0.19; 1 trial, 1,962 participants). Waist circumference was reported in 4 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; I^2 = 55%; 4 trials, 393 participants) (Figure 5). Kisioglu et al. [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; 2,726 participants) (Figure 6).

Glycosylated hemoglobin (hemoglobin A_{1c})

One trial [35] reported glycosylated hemoglobin as an outcome. There was no statistically significant difference between the intervention and control groups in mean change from baseline percentage hemoglobin A_{1c} (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 cholesterol (MD: 0.03 mmol/l; 95% CI: −0.01 to 0.07; 824 participants), to low-density lipoprotein cholesterol (MD: −0.13 mmol/l; 95% CI: −0.53 to 0.27; 4 trials, 544 participants), and to total cholesterol

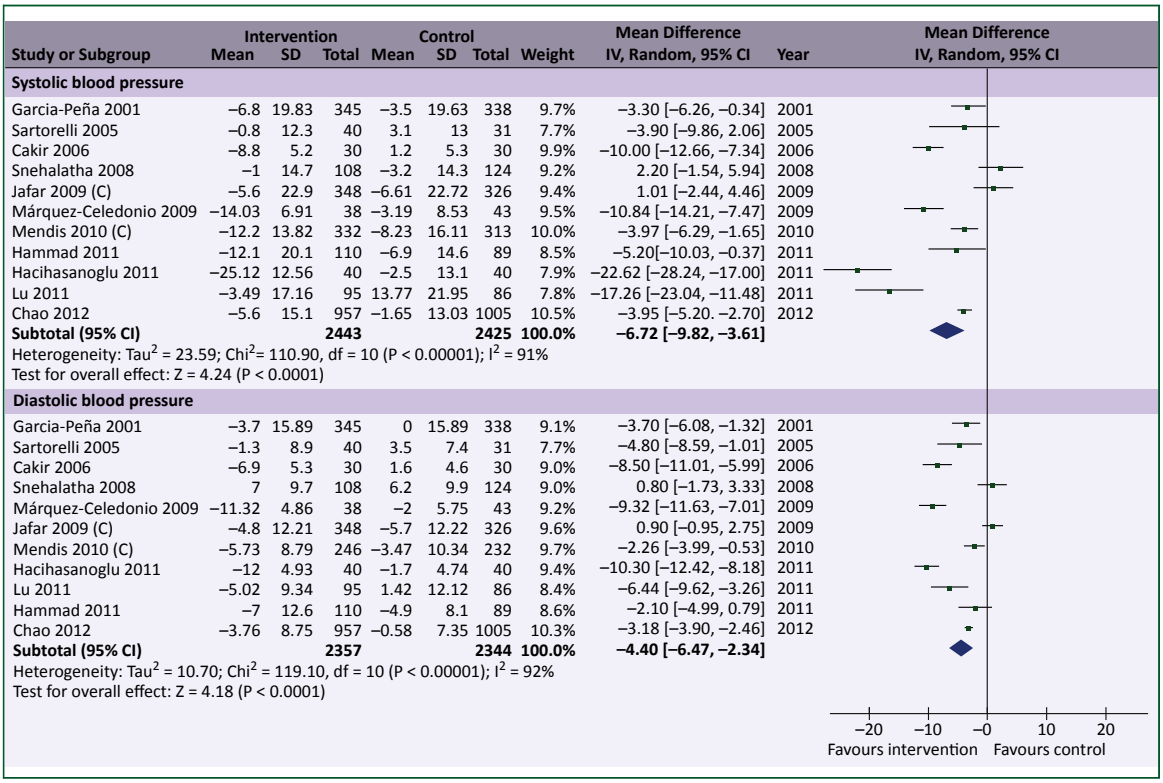

FIGURE 3. Forest plot of effect of multiple risk factor interventions on blood pressure. C, cluster-randomized trial; CI, confidence interval; IV, inverse variance.

(MD: −0.22 mmol/l; 95% CI: −0.48 to 0.04; 5 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; 6 trials, 2,705 participants) (Figure 6).

Fruits and vegetables consumption

One trial [22] (2,166 participants randomized) reported increased fruit and vegetable consumption as an outcome.

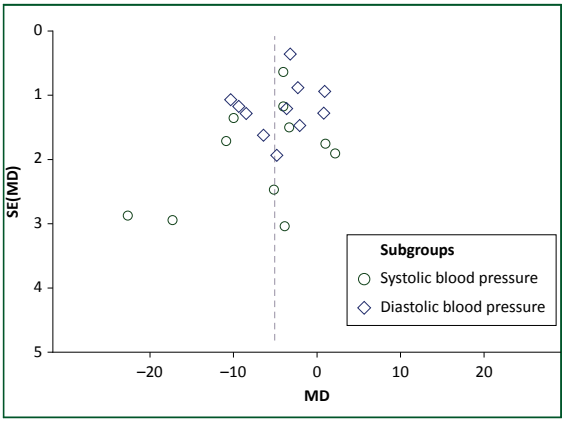

FIGURE 4. Funnel plot of studies included in meta-analysis of blood pressure. MD, mean difference.

At site B (Nigeria), participants in the intervention group, compared with the control 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 nonsignificant increase in vegetable consumption (RR: 2.00; 95% CI: 0.91 to 4.40; p = 0.08; 247 participants). 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).

Smoking cessation

One trial [22] (2,166 participants randomized) 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 CVD in LMICs has brought together

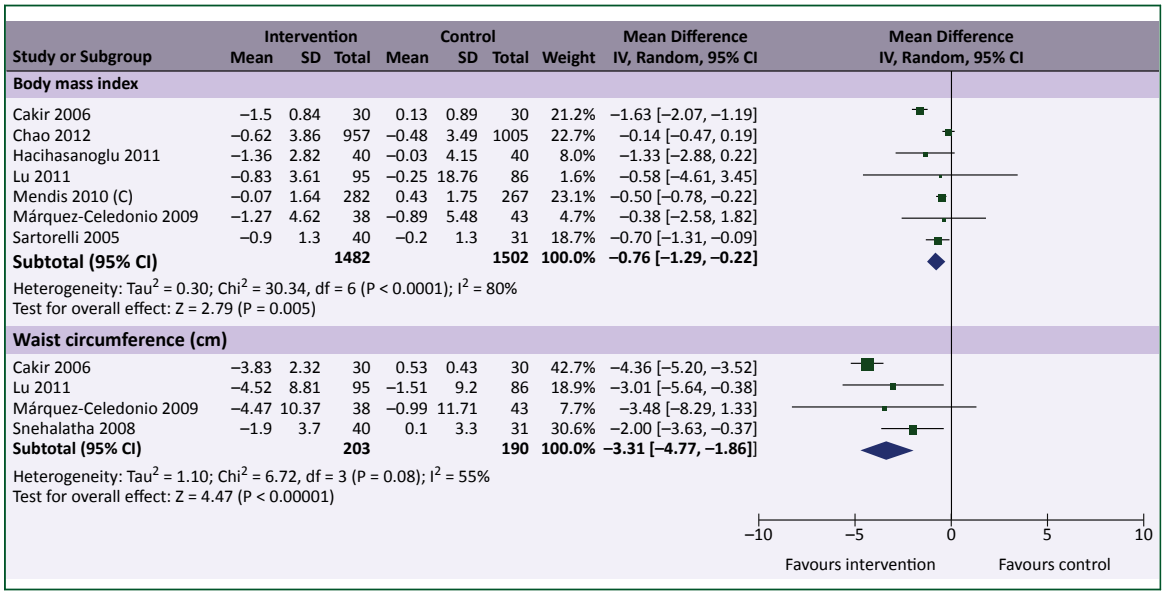

FIGURE 5. Forest plot of effect of multiple risk factor interventions on anthropometric indices. Abbreviations as in Figure 3.

evidence from 13 randomized controlled trials primarily from the last 10 years, incorporating 7,310 participants. We found that evidence for effects on CVD events was scarce, with only 1 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 were modest, but are probably spurious as attributions 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, nonblinded assessment of outcomes, etc. [18]. Furthermore, there are many problems in relating trial outcome to a risk measure that 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 because trials that included participants at high risk of developing CVD are more likely to include participants with high rates of use of antihypertensive drugs [18].

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, data abstraction, and data entry and analysis. It is unlikely that the methods used in the review could have introduced bias.

Comparison with similar studies

Ebrahim et al. [18] conducted a Cochrane review to assess the effects of multiple risk factor interventions for reducing total mortality, fatal and nonfatal coronary heart disease events, and cardiovascular risk from factoring, among adults assumed to be without clinical evidence of previous coronary heart disease. The review included 55 trials that enrolled 163,471 participants and found that "interventions using counselling and education aimed at behavior change do not reduce total or [coronary heart disease] 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 LMIC. The review included 8 multiple-intervention trials (defined as more than 1 lifestyle-related intervention delivered at the same time)

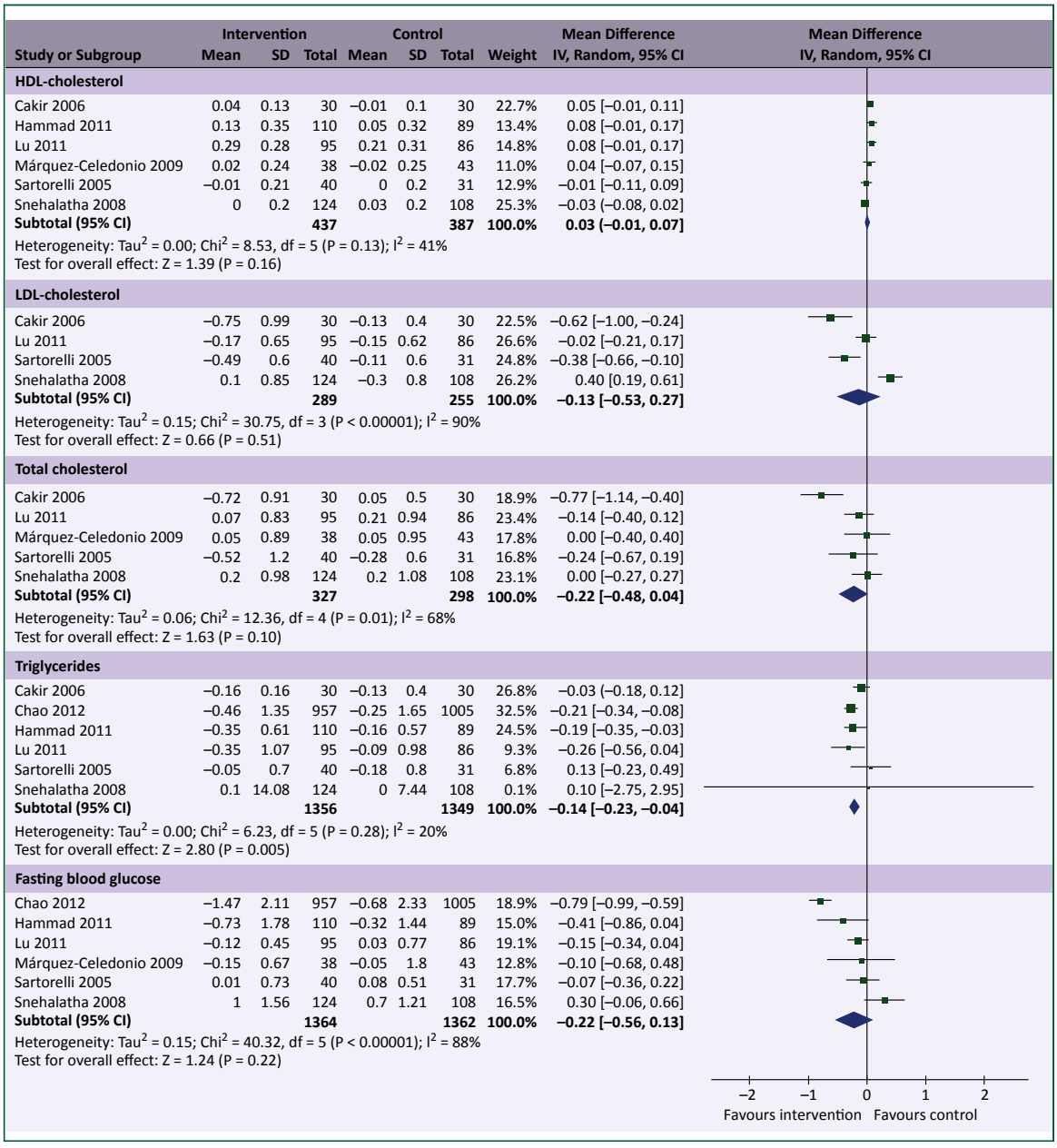

FIGURE 6. Forest plot of effect of multiple risk factor interventions on blood cholesterol levels, triglycerides, and fasting blood glucose. HDL, high-density lipoprotein; LDL, low-density lipoprotein; other abbreviations as in Figure 3.

and found that the studies combining physical activity and diet or behavioral counselling interventions significantly reduced both systolic blood pressure (pooled MD: −6.1 mm Hg; 95% CI: −8.9 to −3.3) and diastolic blood pressure (pooled MD: −2.4 mm Hg; 95% CI: −3.7 to −1.1) [12]. Joshi et al. [38] conducted a cluster randomized trial in rural Andhra Pradesh to develop, implement, and evaluate 2 CVD prevention strategies (clinical and health promotion interventions). The health promotion intervention included posters, street theater, 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 6 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 programs may be effective in altering risk factors in people living in LMIC. 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 randomized controlled trials looking at the effects of multiple risk factor interventions for the primary prevention of CVD events and mortality over the long term. Therefore, there is a need for well-designed randomized 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 program.

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APPENDIX

ONLINE APPENDIX 1. Medline search strategy

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 behavio?r*) adj3 (interven* or educat* or advice* or alter* or change* or inform*)).tw.

(continued)

ONLINE APPENDIX 1. Continued

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. 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 (countr* 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 countr*).ti,ab.
75. (lmic or lmics or third world or lami countr*).ti,ab.
76. transitional countr*.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/

(continued)

ONLINE APPENDIX 1. Continued

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 tadzhik or tadzhikistan 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/

(continued)

ONLINE APPENDIX 1. Continued

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/

(continued)

ONLINE APPENDIX 1. Continued

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/

(continued)

ONLINE APPENDIX 1. Continued

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/

(continued)

ONLINE APPENDIX 1. Continued

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/

(continued)

ONLINE APPENDIX 1. Continued

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

ONLINE APPENDIX 2. PRISMA checklist

Section/Topic	No.	Checklist Item	Reported on Page
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3—4
Methods			
Protocol and registration	5	Indicate whether a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least 1 database, including any limits used, so that it could be repeated.	5
Study selection	9	State the process for selecting studies (e.g., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7—8

(continued)

ONLINE APPENDIX 2. Continued

Section/Topic	No.	Checklist Item	Reported on Page
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9—12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]).	9—12
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy-makers).	12—13
Limitations	25	Discuss limitations at study and outcome levels (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	12—13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research.	14
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data) and role of funders for the systematic review.	14

ONLINE TABLE 1. Excluded studies

Study, Year	Reason for Exclusion
Cezaretto et al. [1], 2012	Control group received some intervention
Jeemon et al. [2], 2012	Nonrandom allocation
Jiang et al. [3], 2002	Quasi-experimental study
Jiang et al. [4], 2010	Quasi-experimental study
Jordan et al. [5], 2008	Nonrandom allocation
Joshi et al. [6], 2012	People with CVD at baseline and no relevant outcomes reported
Kelishadi and Hashemipour [7], 2010	Nonrandom allocation
Kelishadi et al. [8], 2011	Nonrandom allocation
Kelishadi et al. [9], 2012	Nonrandom allocation
Kozlov et al. [10], 1997	Secondary prevention of CVD
Lafay et al. [11], 2006	No relevant outcome reported
Molazem et al. [12], 2013	Secondary prevention
Moreira et al. [13], 2005	Quasi-experimental study
Naser et al. [14], 2008	Secondary prevention
Pahkala et al. [15], 2013	Participants with congenital heart disease
Prabhakaran et al. [16], 2009	Nonrandom allocation
Rabiei et al. [17], 2010	Nonrandom allocation
Sarrafzadegan et al. [18], 2013	Quasi-experimental study
Satpute et al. [19], 2009	Both groups received an intervention
Seligman et al. [20], 2011	Both groups received an intervention
Shahamfar et al. [21], 2010	Secondary prevention
Shehu et al. [22], 2013	Nonrandom allocation
Singh et al. [23], 2002	Secondary prevention
Siqueira-Catania et al. [24], 2013	Both groups received an intervention
Steinbach et al. [25], 1982	Nonrandom allocation
Steinbach et al. [26], 1982	Nonrandom allocation
Steinbach et al. [27], 1984	Nonrandom allocation
Sun et al. [28], 2013	Nonrandom allocation
Suwanphan et al. [29], 2009	Nonrandom allocation
Torres et al. [30], 2011	Nonrandom allocation
Tsao et al. [31], 2007	Nonrandom allocation
Tu [32], 1999	Both groups received an intervention
Wang and Park [33], 2002	People with CVD at baseline
Yao [34], 2009	Nonrandom allocation
Zhang [35], 2012	Secondary prevention

CVD, cardiovascular disease.

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