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A systematic review and meta-analysis testing the effect of lifestyle modification and medication optimization programs on cholesterol and blood pressure in patients with cardiovascular disease

Semagn Mekonnen Abate[1,2*], Shivshankar Thanigaimani[2,3], Mallika Sinha[3], David Sun[4] and Jonathan Golledge[2,3,4]

Abstract

Background Cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity globally, and a number of treatment and preventive strategies have been tried for years. Lifestyle modification programs have been widely implemented as a primary prevention strategy to reduce the burden of CVDs. However, their effectiveness in patients with established CVD in monitoring modifiable risk factors is controversial and requires further investigation.

Methods A comprehensive search was conducted in PubMed, Cochrane, Science Direct, and LILACS without date and language restrictions. All randomized controlled trials (RCT) comparing the effectiveness of lifestyle modification and/ or optimization of drug therapies among patients with established cardiovascular disease were included. The primary outcomes were changes in systolic blood pressure and low-density lipoprotein cholesterol. Secondary outcomes included changes in total cholesterol, diastolic blood pressure, and medication adherence. Meta-analysis results were reported as standardized mean difference (SMD) or risk ratio (RR) and 95% confidence intervals (CI). Sub-analyses examined programs that included both lifestyle modification and drug optimization or type of intervention alone if a minimum of three trials were identified. The quality of evidence was evaluated using GRADE and trial sequential analyses.

Results Sixteen trials including 4450 participants were included in testing programs focused on both lifestyle modification and drug optimisation (seven RCTs) and lifestyle modification alone (nine RCTs). Overall the programs significantly reduced systolic blood pressure (SMD = −0.30, 95% CI −0.43 to −0.17, $P < 0.001$), diastolic blood pressure (SMD = −0.18, 95% CI −0.28 to −0.08 $P < 0.001$), total cholesterol (SMD = −0.28, 95% CI −0.49 to −0.07, $P = 0.009$); however, the quality of evidence was rated as low.

Conclusion Lifestyle modification and medication optimization interventions had a significant effect on monitoring blood pressure and serum cholesterol; however, the provision of the firm conclusion is less optimal with current evidence as the quality of evidence was low.

*Correspondence:
Semagn Mekonnen Abate
semmek17@gmail.com
Full list of author information is available at the end of the article

Systematic review registration The systematic review and meta-analysis protocol was registered in PROSPERO CRD42024523078.

Keywords Lifestyle modifications, Modifiable risk factors, Drug optimization, Cardiovascular interventions, Blood pressure

Background

Description of the condition

Cardiovascular disease is a leading cause of mortality and morbidity worldwide [1–3]. The number of individuals affected by cardiovascular disease nearly doubled from 271 million in 1990 to 523 million in 2019, with the number of related deaths increasing from 12.1 to 18.6 million during the same period [2]. Global trends for disability-adjusted life years (DALYs) and years of life lost also showed significant increases over this time period [2].

Randomized controlled trials (RCTs) demonstrate that medication that reduces blood pressure and low-density lipoprotein-cholesterol (LDL-c) limits the risk of major adverse cardiovascular events (MACE) [4–6]. Programs that integrate lifestyle modification and optimization of drug therapy to control these risk factors have been developed but their effectiveness is controversial [7–10]. Past studies have shown inconsistent effectiveness of lifestyle modification and optimization of drug therapy programs, which typically include interventions aimed to improve diet, increase physical activity, reduce stress, facilitate smoking cessation, and adhere to prescribed medication to treat hypertension, dyslipidemia, and diabetes [11–15].

A meta-analysis of 25 RCTs investigating lifestyle modification with digital technology showed improvements in healthy behavioral risk factors such as physical activity, healthy diet, and medication adherence; however, it did not reveal a significant effect on smoking cessation, blood pressure, and alcohol intake [16].

A meta-analysis including 27 RCTs testing the effects of a mobile health intervention on secondary prevention of cardiovascular disease did not demonstrate a reduction in LDL-c and smoking cessation, but there was a significant improvement in medication adherence, physical activity, and monitoring of blood pressure [17].

Lifestyle modification intervention programs have had a positive impact on patients' physical activity, medication adherence, psychological state, and healthy diet; however, their effectiveness is still controversial in optimizing patients' blood pressure, serum cholesterol, and cessation of smoking [18, 19].

Description of the intervention

Lifestyle modification intervention programs that include dietary improvements, increased physical activity, smoking cessation, stress management, and alcohol moderation can significantly reduce the burden of CVD [12, 14, 16, 17]. These programs could be delivered through patient education [20], risk factor monitoring [21], coaching [22], behavioral and motivational consultation [23], and pharmacological management [24, 25] using remote digital technology platforms [26–28], and/or face-to-face communications [29, 30].

With the help of telehealth, it is possible to incorporate theoretical constructs of health behavior changes and evidence-based behavioral change techniques in managing cardiovascular risk factors [31–33]. Patients are also able to communicate with health professionals with the help of digital technology such as emails, chats, web addresses, and discussion forums which are feasible in terms of cost-effectiveness, reliance, and time management [34–36]. However, addressing challenges related to digital accessibility, data security, user engagement, and clinical validation is essential to fully realize their benefits [34, 37].

How the intervention might work

Lifestyle and risk factor modification programs have been widely implemented as a primary prevention strategy to reduce the burden of CVDs [7–10]. However, their effectiveness in patients with established CVD in optimizing modifiable risk factors is controversial [12, 14, 38, 39].

A meta-analysis investigating the effectiveness of telehealth intervention on secondary prevention of coronary heart disease found that Telehealth interventions had moderately significant effects in reducing weight, total cholesterol, and triglyceride, improving medication adherence. However, it showed a small significant effect in reducing blood pressure and smoking [39].

Another systematic review examining the impacts of technology-based patient education intervention on modifiable CVS risk factors through telephone follow-up, text messaging, webpage, and smartphone application could help patients to control modifiable risk factors demonstrated minimal effect in reducing blood sugar and cessation of use of tobacco [15].

Another systematic review was conducted on the effectiveness of nurse-led patient-centered care behavioral risk modification in secondary prevention of coronary heart disease. However, the study did not show a significant improvement in patients' blood sugar, high-density lipoprotein, blood pressure, and mortality, and further studies with long follow-ups are required [13].

Similarly, a systematic review by Fernandez et al. examining the effectiveness of brief structural interventions on risk factor modification for patients with coronary heart disease failed to identify strong evidence for recommendation [14].

A meta-analysis to test the effect of digital technology interventions for risk factor modification in patients with cardiovascular disease demonstrated that the intervention improves protective behavioral factors including physical activity, healthy diet, and medication adherence. However, it didn't seem to optimize the patients' blood pressure [11].

Why it is important to do this review

The available body evidence on the effectiveness of lifestyle modification for monitoring modifiable risk factors in patients with cardiovascular diseases is controversial [13–16]. Furthermore, previous systematic reviews were conducted on heterogeneous outcomes of interest with different types of interventions [12, 14, 16, 17, 40]. This meta-analysis focused on the effect of lifestyle modification and medical therapy on change in patients' blood pressure and serum cholesterol, while other meta-analyses primarily target major adverse cardiovascular events (MACE) [12], optimization of behavioral risk factors [14, 40], improvement of exercise capacity and quality of life [17], all-cause mortality [41], and healthy behavioral factors such as physical activity, healthy diet, and medication adherence [11]. Furthermore, our meta-analysis included recent RCTs investigating the effectiveness of lifestyle modification and medical optimization on blood pressure and cholesterol, and GRADEpro and trial sequential analysis were employed to evaluate the quality of evidence.

Methods

Protocol registration

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic and Meta-Analysis and registered in PROSPERO (CRD42024523078) on March 23, 2024 [42].

Design and search strategy

The search method was designed to explore all available published and unpublished RCTs assessing the effectiveness of programs that integrate lifestyle modification and optimization of drug therapy among people with established CVD without language and date restrictions. A comprehensive first search in PubMed/MEDLINE, Cochrane Library, Science Direct, and Latin American and Caribbean Health Sciences Literature (LILACS) was conducted, and EndNote reference manager was used to remove the duplicates. The full-search strategy was described in Supplemental texts 1 and 2.

Criteria for inclusion

The inclusion criteria for the systematic review were (1) adults who were ≥18 years old with established CVD, (2) a randomized controlled study of lifestyle modification and medication optimization, (3) all subjects were diagnosed with coronary heart disease, peripheral artery disease and/or cerebrovascular disease, and (3) studies reporting systolic blood pressure and LDL-C as a primary outcome [43–58]. The interventions were delivered through patient education, monitoring of risk factors, coaching, behavioral and motivational consultation, and pharmacological management with the help of remote digital technology platforms and/or face-to-face communications. The interventions were being employed in the form of mobile applications or individual/group-based sessions targeted to manage blood lipid and blood pressure and reduce the risk of MACE. The control group received usual medical management without any specialized intervention programs.

Criteria for exclusion

Studies were excluded if (1) studies did not report systolic blood pressure and LDL, (2) the study reported insufficient details to extract the study outcomes, (3) the study had other interventions, and (4) the full text of the study was not available in the databases [18, 19, 59–94].

Outcomes of interest

The primary outcome was defined as changes in systolic blood pressure and serum LDL-C. The studies reported lifestyle modification intervention alone, medication optimization alone, or a combination of lifestyle and medication optimizations, but any trial reporting one of the interventions was considered for overall analysis. Secondary outcomes were defined as changes in diastolic blood pressure, serum TC, and medication adherence. Other outcomes including cessation of smoking and MACE defined as myocardial infarction, coronary revascularization, and cerebrovascular events were also assessed.

Data extraction

The data from each study was retrieved using a data extraction template in Microsoft Excel 2013 format.

Two authors (SA and DS) independently extracted the data, and any disagreements were discussed with another author (ST). Data extracted included sample size, descriptions of the intervention and control groups, changes in concentrations of LDL-C, high-density lipoprotein, TC and blood pressure, medication adherence, cessation of smoking, and MACE incidences such as myocardial infarction, stroke, and rate of coronary revascularization. Finally, the data were imported into Review Manager for analysis.

Critical appraisal

The methodological quality of the included studies was evaluated based on the Cochrane Handbook risk of bias 2 (ROB2) tool [95] by two independent authors (SA and DS), and the disagreement was resolved with another author (ST). The random sequence generation, allocation concealment, blinding of participants and treatment providers, blinding of result assessment, incomplete outcome data, selective outcome reporting, and other bias risks were assessed (Supplementary Table S6).

Data analysis

The standardized mean difference was used to estimate the change in lipid profile and the blood pressure with the inverse variance method, while dichotomous outcomes were estimated with the Mantel–Haenszel method with either odds ratio or relative risk effect estimates. A random effect model with the restricted maximum likelihood (REML) method was used as there was substantial heterogeneity between the included studies as depicted by the forest plot, chi-square test, I^2 value, and Galbraith plot. Subgroup analyses were conducted to investigate the effect of lifestyle modification alone, medication optimization alone, and combined interventions, modes of intervention delivery (patient education, monitoring of risk factors, coaching, and consultation), and types of CVD. A minimum of 3 RCTs were required for subgroup analyses leave one out (LOO) sensitivity analyses were conducted for the primary outcome to investigate the influence of individual trials on the summary effect. Furthermore, subgroup analyses were conducted by the duration of follow-up as <1 year, 1 to 3 years, and >3 years follow-up period to see how the length of intervention impacts the primary outcomes. Trial sequential analysis was conducted to control for the risks of type I and II errors on the outcomes, and it was used to calculate the number of participants needed to detect or reject primary hypotheses and the cumulative *Z*-curve's breach of relevant trial sequential monitoring boundaries. The overall quality of evidence was determined using the GRADE system (Grading of Recommendations, Assessment, Development, and Evaluation) [96, 97]. The system incorporates study quality (risk of bias), inconsistency (comparison of effect estimates across studies), indirectness (applicability of the population, intervention, comparator and outcomes to the clinical decision), imprecision (certainty of confidence interval), and probability of publication bias. The overall quality of evidence was categorized as high, moderate, low, and very low by combining the aforementioned five parameters.

Results

Selection of studies

A total of 374 articles were identified from the initial search of which 54 full-text publications were reviewed. Sixteen publications incorporating 4450 participants ultimately met inclusion criteria, while 38 articles were excluded for reasons (Supplementary Table 1, Fig. 1).

Description of the included studies

Sixteen RCTs met the inclusion criteria (Table 1, Supplementary Table S1, and Fig. 1). The included trials were conducted between 1998 and 2023, with a sample size ranging from 48 to 5034 participants, and the eligibility criteria for all included trials were shown in Supplementary Table S2. The detailed description of primary and secondary outcomes was outlined in Supplementary Table S3, while the other outcomes including cessation of smoking and MACE were detailed in Supplementary Table S4. The effects of the intervention on primary and secondary outcomes in the included RCTs were described in Supplementary Table S5. The mean age of the participants ranged from 40.8 to 76.5 years, and the duration of follow-up varied from 8 weeks to 5 years. Eight trials were evaluated as low-risk of bias [43–45, 48, 49, 52, 53, 58], two as high-risk of bias [54, 55], and six as having some concerns [46, 47, 50, 51, 56, 57] (Supplementary Table S6).

Description of the interventions

Eight of the included trials tested a multifaceted combination of in-person and/or remote education, exercise, and diet consultations with nurses, physiotherapists, and exercise health professionals [43, 47, 48, 50, 51, 55–57], while another eight trials used digital technology interventions in the form of web-based applications, websites, text messaging, SMART phone applications, and regular phone calls [44, 46, 48, 52–54, 98, 99] (Supplementary Table S7). Nine trials focused on lifestyle intervention alone [44, 47, 48, 55–58, 98, 99], while seven trials focused on both lifestyle modifications and medication optimization [43, 46, 50–54] (Table 1). The majority of trials described the control group as having usual care but how this was delivered was poorly reported (Supplementary Table S3).

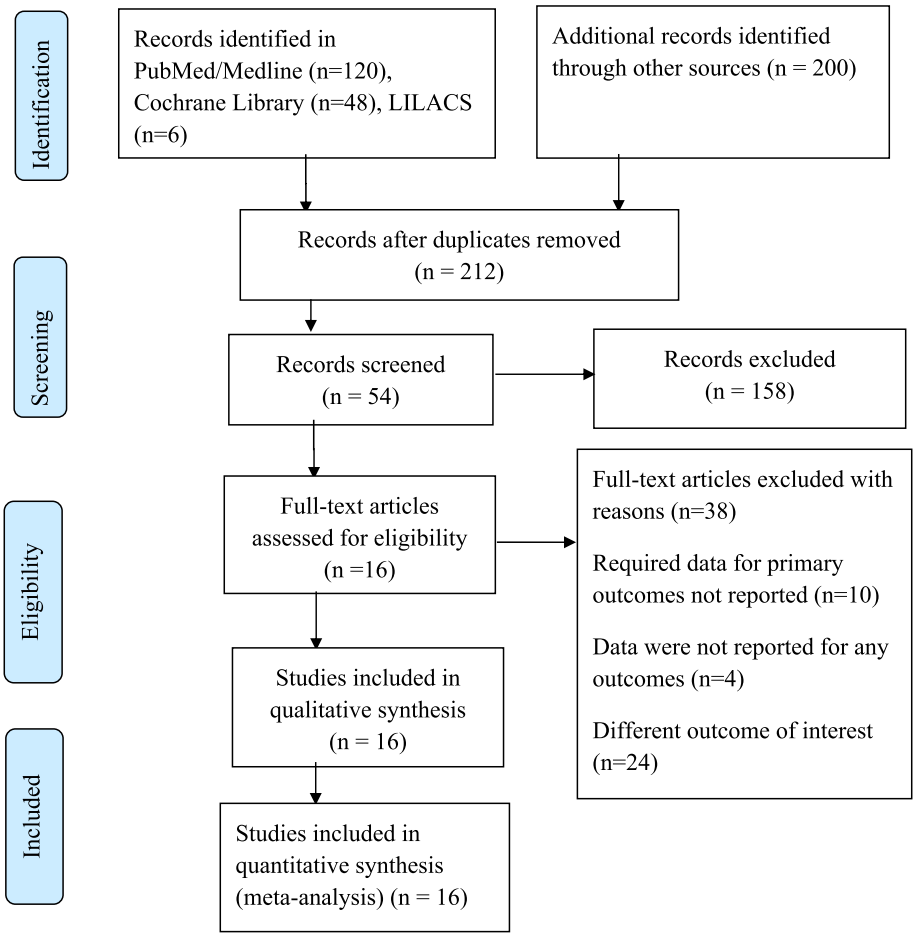

Fig. 1 Prisma flow chart showing the study identification, screening process, and included studies

Effectiveness of the interventions

Systolic blood pressure (SBP)

All trials reporting primary outcome A meta-analysis of 15 RCTs including 4386 participants revealed the overall effect of interventions reduced systolic blood pressure compared to usual care with a moderate degree of heterogeneity (SMD = − 0.30, 95% CI −0.42 to −0.17, $P<$ 0.001, Fig. 2), and the funnel plot was symmetrical (Supplementary results, Fig. 1.1.1). The LOO sensitivity analysis did not show a significant difference in effect estimate and heterogeneity (Supplementary results, Table 2.1.1.). Furthermore, the exclusion of studies with a high risk of bias did not change the effect estimate and heterogeneity significantly (Supplementary results, Fig. 3.1.1). The subgroup analysis by mode of intervention delivery with individual and group education (SMD = − 0.31, 95% CI −0.44 to −0.19, $P<$ 0.001), monitoring of risk factors (SMD = − 0.32, 95% CI −0.43 to −0.21, $P<$ 0.001), coaching for risk factors (SMD = − 0.26, 95% CI −0.45 to −0.04, $P<$ 0.001), and consultation (SMD = − 0.30, 95% CI −0.43 to −0.17, $P<$ 0.001) revealed a significant reduction in systolic blood pressure (SBP) compared to usual care (Supplementary results, Fig. 4.1.1 to 4.1.4). The subgroup analysis by the duration of follow-up showed that the longer the follow-up of the intervention, the lower the systolic blood pressure (SBP) might be. Systolic blood pressure (SBP) was lowered the most at >3 years follow-up period (SMD = − 0.49, 95% CI −0.82 to −0.16, $P<$ 0.001) compared to standard care (Supplemental results Fig. 5.1).

Lifestyle modification alone Eight RCTs with 3169 participants targeting integrated lifestyle intervention alone showed a significant reduction in systolic blood pressure compared to usual care (SMD = − 0.22, 95% CI −0.38 to −0.06, $P=$ 0.008, Fig. 2), and the funnel plot was found to be symmetrical (Supplementary results, Fig. 1.1.2.). The LOO sensitivity analysis did not show a significant difference in the summary effect and heterogeneity (Supplementary results, Table 2.1.2).

Table 1 Characteristics of the included randomized controlled trials ($n = 26$)

Overall sample							Focus of the included trials			Intervention		Control	
Authors	**Year**	**Country**	***N***	**Population description**	**Mean age**	**Follow-up**	**Integrated lifestyle intervention alone**	**Medication optimization alone**	**Both**	***N***	**Intervention type**	***N***	**Control description**
Abed et al. [43]	2013	Australia	150	Arrhythmia	59.2	15 months			X	42	Written exercise for weight loss	39	Written and verbal nutrition and exercise advice
Bae et al. [44]	2021	Korea	727	CHD	60.4	6 months	X			377	Website and Text messaging	350	Standard care
Chow et al. [98]	2015	Australia	710	CHD	57.6	6 months	X			319	Text messaging and motivation	333	Usual care
Dorje et al. [46]	2019	Australia	312	CHD	60.5	5 years			X	156	WeChat-based education	156	Standard care, as provided by their community doctors and cardiologists
Engelen et al	2020	Netherlands	208	CVD	63.5	12 months	X			103	Web-based self-management	105	Usual care
Fernandez et al. [48]	2009	Australia	51	CVD	57	8 weeks	X			29	multifaceted Health-related lifestyle self-management	22	Standard care
Gallagher et al. [49]	2023	Australia	390	CHD	61.2	1 year	X			194	game-based app	196	Usual care and visits with the cardiac team at 6 weeks
Goessensa et al. [50]	2006	Netherlands	236	CVD	60.1	12 months			X	24	Nurse-led intervention	37	Usual care provided by the GP and the treating vascular specialist
Lehmanna et al. [51]	2011	Germany	96	CHD	59.3	6 months			X	47	Mediterranean diet, stress reduction with mind–body	49	Written advice only
Li et al. [101]	2022	China	300	CHD	61.38	12 months			X	143	self-management mobile app	147	Traditional electronic health records
Liu et al. [53]	2022	China	98	CHD	69.2	1 year			X	49	Home-based	49	Usual daily activities and attended non-exercise community activities
Michelson et al. [54]	2022	Sweden	149	MI	61.1	6 months			X	101	Text messaging and email	49	Five outpatient follow-up visits
Ornish et al. [55]	1998	USA	48	CHD	59.6	5 years	X			20	Intensive lifestyle change programs	18	Attending an advice for their personal lifestyle changes
Park et al. [56]	2017	Korea	64	MI	56.1	6 months	X			32	nurse-led theory-based education program	32	Routine inpatient cardiac rehabilitation program by a nurse

Table 1 (continued)

Overall sample							Focus of the included trials			Intervention		Control	
Authors	**Year**	**Country**	***N***	**Population description**	**Mean age**	**Follow-up**	**Integrated lifestyle intervention alone**	**Medication optimization alone**	**Both**	***N***	**Intervention type**	***N***	**Control description**
Saffi et al. [57]	2014	Brazil	74	CHD	58	12 months	X			38	Nurse-led guidance with face-to-face and telephone	36	Standard medical care
Zheng et al. [58]	2019	China	822	CHD	56.4	24 weeks	X			411	Automated computerized system text messaging	411	Usual care and 2 thank you text messages per month

The detail of mode of intervention and usual care in the included RCTs were described in Supplementary table 3. *CHD* Coronary heart diseases, *CVD* CVD, *MI* myocardial infarction, *GP* general practitioner, *HW* health workers, *NR* not reported

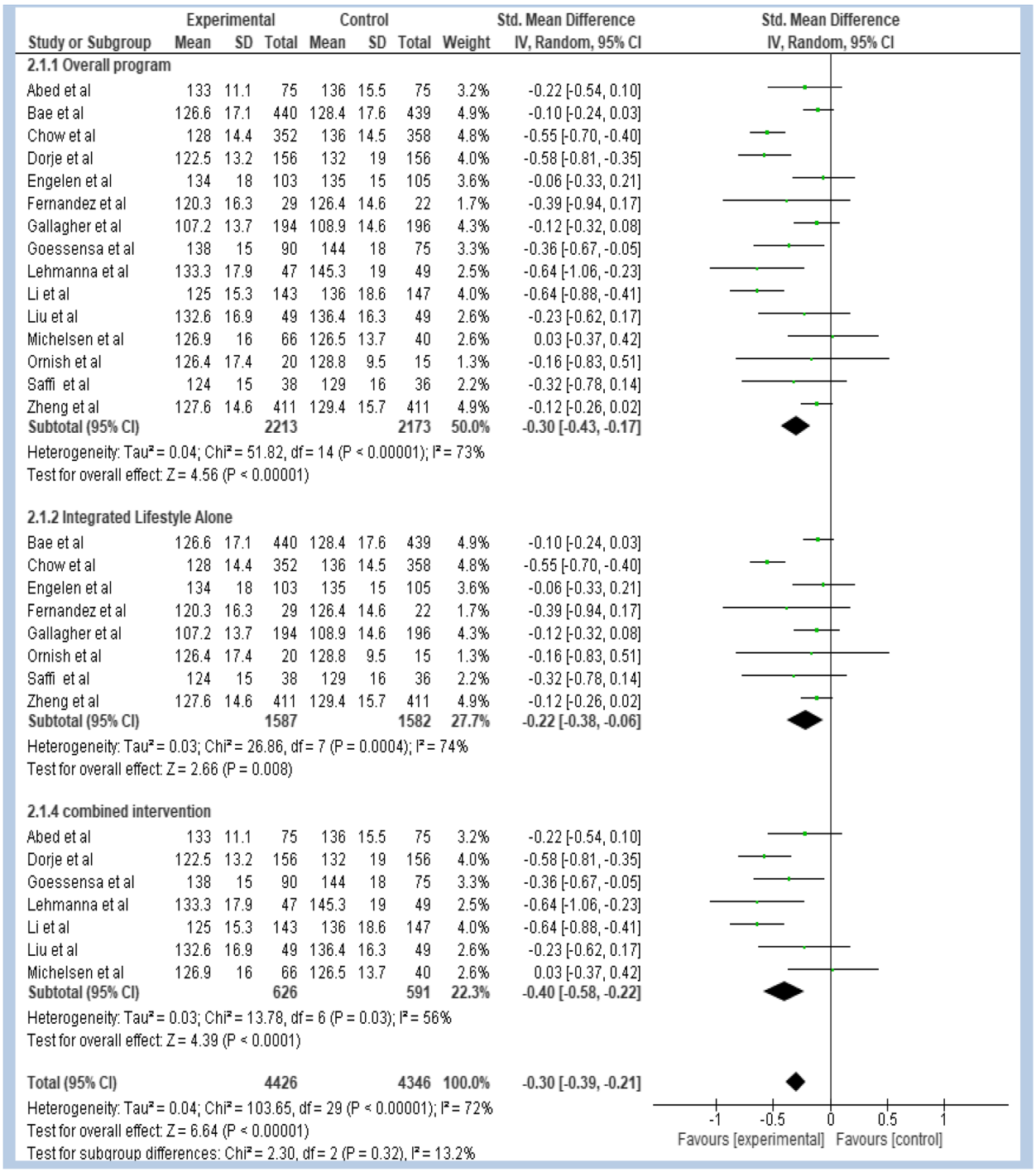

Fig. 2 Forest plot for meta-analysis of systolic blood pressure for overall programs, integrated lifestyle alone, and combined intervention alone: individual trials and meta-analysis total, the total number of participants in intervention and control. Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR inverse variance

Combined interventions alone A subgroup analysis of 7 RCTs with 1217 participants targeting combined intervention of integrated lifestyle and medication optimization alone revealed a significant reduction in patients' systolic blood pressure (SMD = − 0.40, 95% CI −0.58 to −0.22, P< 0.001, Fig. 2), and the funnel plot was found to be symmetrical (Supplementary results, Fig. 1.1.3). Furthermore, the LOO sensitivity analysis did not

demonstrate a significant effect on the summary effect and heterogeneity (Supplementary results, Table 2.1.3).

DBP

All trials reporting DBP A meta-analysis of 12 RCTs with 2374 participants showed that the overall programs reduced mean DBP significantly in the intervention group compared to usual care with a low degree of heterogeneity (SMD = − 0.18, 95% CI −0.28, −0.08, P= 0.0003, Fig. 3), and the funnel plot was symmetrical (Supplementary results, Fig. 1.2.1). The LOO sensitivity analysis demonstrated a significant difference in summary effect and heterogeneity (Supplementary results, Table 2.2.1.). Similarly, the exclusion of studies with a high risk of bias did not affect the effect estimate and heterogeneity (Supplementary results, Fig. 3.2). The subgroup analysis by mode of intervention delivery showed that patient education showed a significant reduction in DBP (SMD = − 19, 95% CI −0.28 to −0.11, P< 0.0001), where group education significantly reduced DBP (SMD = − 0.28 95% CI −0.39 to −0.17, P< 0.00001) compared to individual education (SMD = − 0.12, 95% CI −0.23 to −0.01, P= 0.03). Similarly, monitoring of risk factors reduced DBP in the intervention group (SMD = − 0.18, 95% CI −0.28 to −0.4, P= 0.001). Furthermore, coaching for risk factors with behavioral changes revealed a significant difference (SMD = − 0.19, 95% CI −0.30 to −0.08, P= 0.0005); however, coaching for lifestyle modification (SMD = − 0.12, 95% CI −0.26 to 0.02, P= 0.09) and medication adherence (SMD = − 0.18 95% CI −0.40 to 0.04, P= 0.10) did not show significant benefit (Supplementary results, 4.2.1 and 4.2.2).

Lifestyle modification alone A subgroup analysis by lifestyle interventions alone failed to demonstrate a significant reduction in patients' DBP compared to usual care (SMD = − 0.16, 95% CI −0.32 to 0.00, P= 0.05, Fig. 3), and the funnel plot was asymmetrical (Supplementary results, Fig. 1.2.2.). The LOO sensitivity analysis demonstrated that the removal of studies at a time did not affect the summary effect; however, the removal of studies by Engelen et al. and Michelsen et al. showed a significant difference in summary effect with minimal change in heterogeneity (Supplementary results, Table 2.2.2.).

Combined intervention alone A subgroup analysis of RCTs targeting both lifestyle modification and medication optimization interventions revealed a significant difference compared to usual care (SMD = − 0.19, 95% CI −0.32 to −0.05, 6 RCTs, 1189 participants, P= 0.007, Fig. 3). However, the funnel plot was asymmetrical suggesting potential publication bias (Supplementary results, Fig. 1.2.3.). Furthermore, the LOO sensitivity analysis did not show a significant change in the summary effect (Supplementary results, Table 2.2.3.).

LDL-C

All trials reporting LDL-C A meta-analysis of 15 RCTs including 4330 participants showed that overall programs demonstrated a significant effect on LDL-C, but with a substantial heterogeneity (SMD = − 0.19, 95% CI −0.36 to −0.02, P= 0.03, Fig. 4), and the funnel plot was found to be asymmetrical (Supplementary results, Fig. 1.3.1). The LOO sensitivity analysis also did not show significant differences between groups; however, the removal of four studies [50–53] revealed a significant difference in the summary effect (Supplementary results, Table 2.3.1.). However, the exclusion of studies with a high risk of bias failed to show a significant difference (Supplementary results, Fig. 3.3.). The subgroup analysis by mode of intervention delivery with education (17 RCTs with 3801 participants), monitoring of risk factors (16 RCTs with 5245 participants), and consultation reduced LDL-C (13 RCTs with 3622 participants) (Supplementary results, Fig. 4.3.1. 4.3.2., and 4.3.4.); however, coaching for risk factor modification failed to show a significant difference on LDL-C (Supplementary results, Fig. 4.3.3.).

Lifestyle modification alone A subgroup analysis of 8 RCTs testing lifestyle-alone interventions failed to demonstrate a significant reduction in LDL-C (SMD = − 0.18, 95% CI −42 to −0.005, P= 0.13, Fig. 4), and the funnel plot was asymmetrical (Supplementary results, Fig. 1.3.2.). LOO analysis suggested that the effect estimates were influenced by one study [55] (Supplementary results, Table 2.3.2.).

Combined intervention alone A subgroup analysis of 7 RCTs with 1148 participants investigating the effect of both lifestyle and medication optimization alone failed to show a significant reduction in LDL-C (SMD = − 0.22, 95% CI −0.50 to −0.06, P= 0.12, Fig. 4) with symmetrical funnel plot (Supplementary results, Fig. 1.3.3). A LOO sensitivity analysis showed that one study influences the effect estimates [46] (Supplementary results, Table 2.3.3). The subgroup analysis by the duration of follow-up showed that LDL-C was lower at < 1-year follow-up (SMD = − 0.16, 95% CI −0.29 to −0.03, P< 0.001); however, there was no significant difference at 1 to 3 years (SMD = − 0.16, 95% CI −0.38 to 0.06, P= 0.15) and > 3 years (SMD = − 2.94, 95% CI −9.42 to 3.53, P= 0.37) (Supplemental results, Fig. 5.2.).

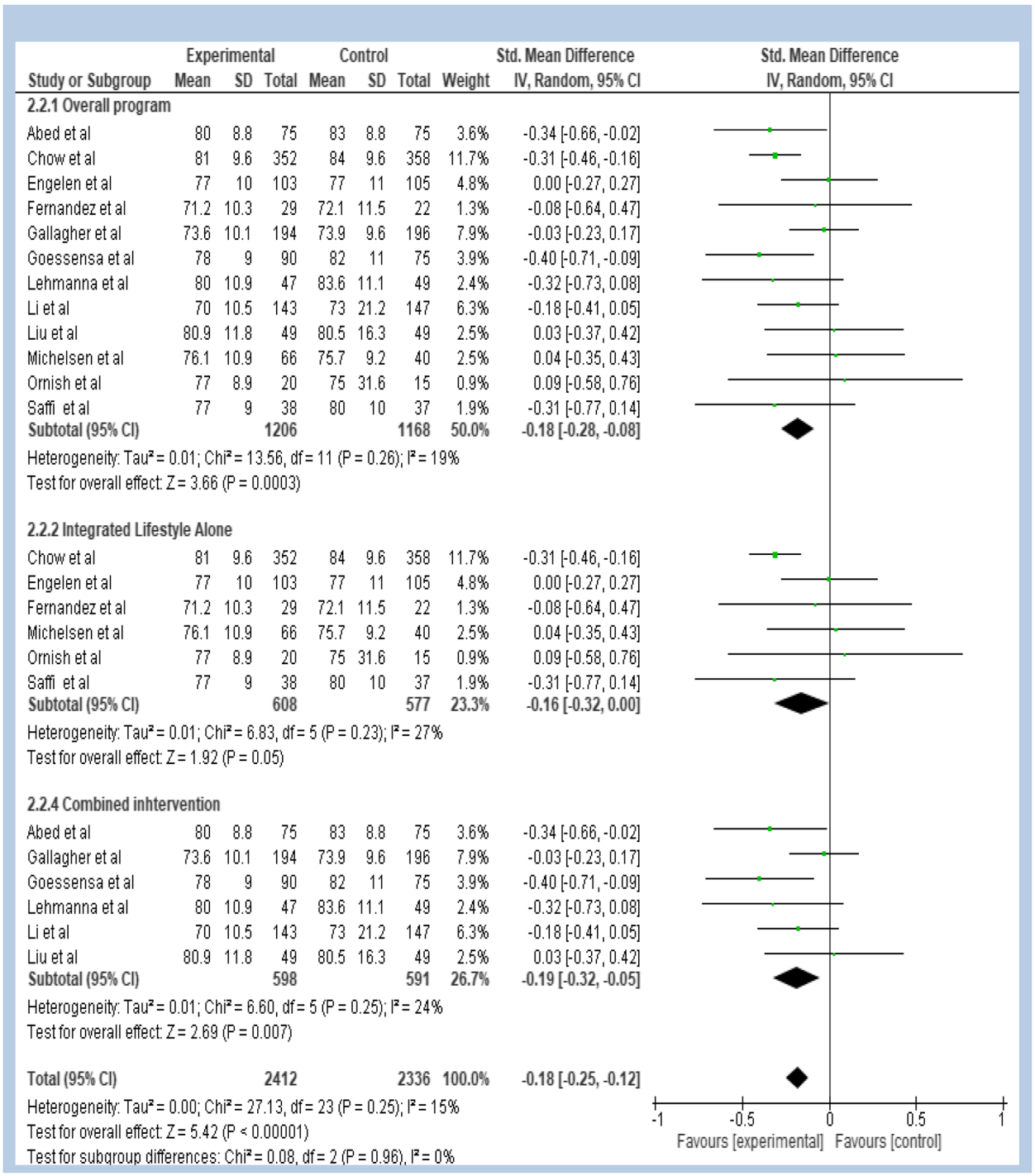

Fig. 3 Forest plot for lipid profile within 6 months of intervention. **A** Total cholesterol. **B** Low-density lipoprotein: individual trials and meta-analysis total, the total number of participants in intervention and control. Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. *IR* inverse variance

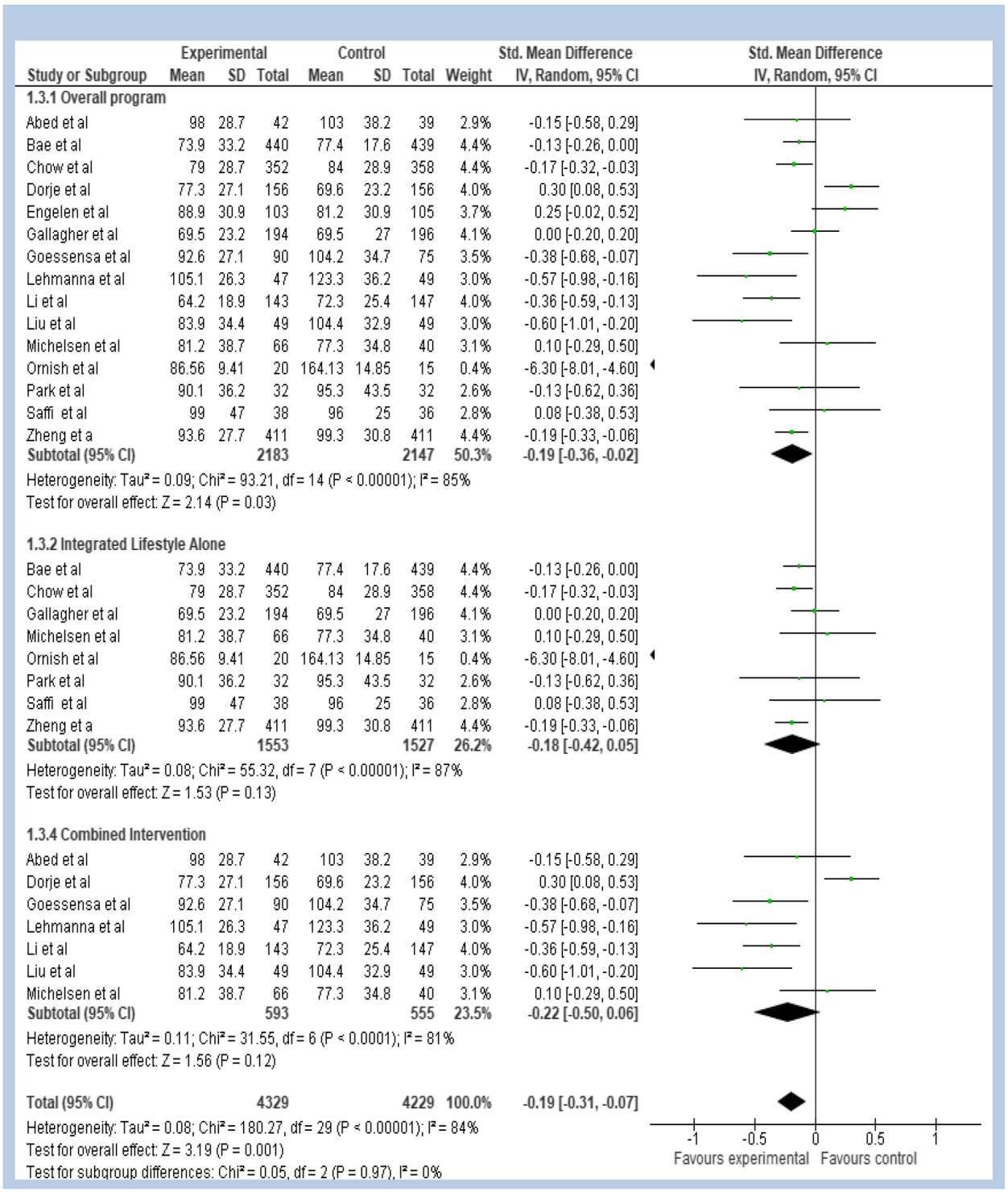

Fig. 4 Forest plot for meta-analysis for the overall program, integrated lifestyle alone interventions, and combined interventions for LDL-C: individual trials and meta-analysis total, the total number of participants in intervention and control. Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR inverse variance

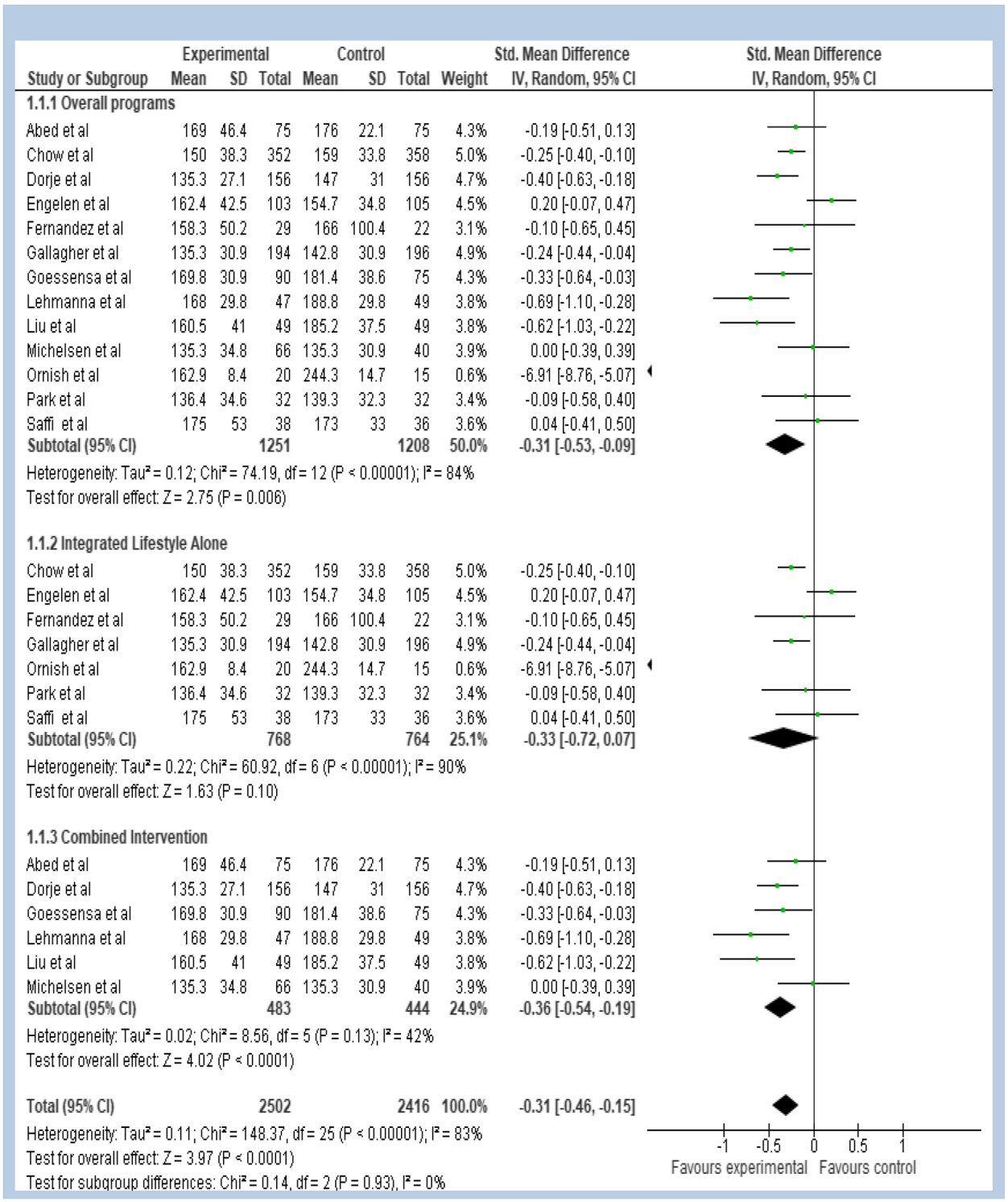

Fig. 5 Forest plot for meta-analysis of the overall program, lifestyle modification interventions alone, and combined intervention alone for total cholesterol: individual trials and meta-analysis total, the total number of participants in intervention and control. Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR inverse variance

TC

All trials reporting TC The meta-analysis of 13 RCTs with 2459 participants showed that the overall intervention significantly reduced serum total cholesterol compared to the usual care (SMD = − 0.31 (95% CI −0.53 to −0.09, P= 0.006, Fig. 5), and the funnel plot was asymmetrical (Supplementary results, Fig. 1.4.1.). A LOO sensitivity analysis showed that the removal of one study at a time did not change the effect estimate and degree of heterogeneity (Supplementary results, Table 2.4.1.). Exclusion of studies with a high risk of bias did not change the effect estimate (Supplementary results, Fig. 3.4), and subgroup analysis by mode of intervention delivery revealed that education (SMD = − 0.31, 95% CI −051 to −0.11), monitoring of risk factors (SMD = − 0.20, 95% CI −0.43 to −0.03, P= 0.03), coaching for risk factors (SMD = − 0.22, 95% CI −0.35 to −0.09, P= 0.008), and consultation (SMD = − 0.24, 95% CI −0.42 to −0.07, P= 0.007), a significant impact on the reduction of total cholesterol (Supplementary Fig. 4.4.1. to 4.4.4.)

Lifestyle modification alone A subgroup analysis of 7 RCTs with 1532 participants investigating the effectiveness of lifestyle modification intervention alone on TC failed to reveal a significant difference (SMD = − 0.33, 95% CI −0.72 to 0.07, P= 0.10, Fig. 5). Similarly, there was substantial heterogeneity with asymmetrical funnel plot (Supplementary results, Fig. 1.4.2.). The LOO sensitivity analysis did not show a significant effect on the summary effect (Supplementary results, Table 2.4.2.).

Combined intervention alone A subgroup analysis of intervention testing lifestyle and medication optimization alone demonstrated a significant reduction in TC (SMD = − 0.36, 95% CI −0.54 to −0.19, I^2= 42%, P< 0.0001, Fig. 5), and the funnel plot was symmetrical (Supplementary results, Fig. 1.4.3.). The LOO sensitivity analysis did not show a significant difference (Supplementary result, Table 2.4.3).

Other outcomes

All trials reporting medication adherence

This meta-analysis revealed that there was a 49% risk of non-adherence to medication in the control group, RR =1.51 (95% CI 1.15 to 1.99, 2 studies, 702 participants, P< 0.001, Fig. 6A). The meta-analysis showed a significant benefit on cessation of smoking (RR =0.81, 95% CI 0.73 to 0.90, 6 RCTs, 2245 participants, P= 0.03, Fig. 6B). The LOO sensitivity analysis did not influence the effect estimates.

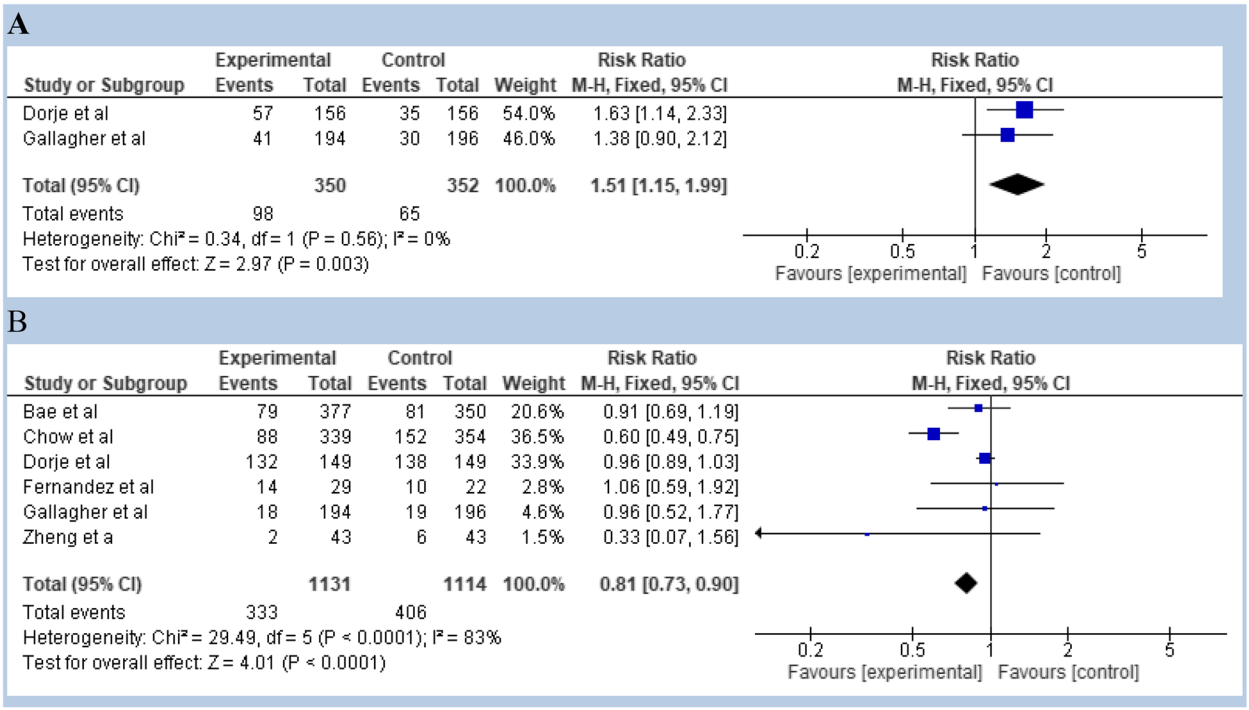

Fig. 6 Forest plot for behavioral changes. **A** Medication adherence. **B** Cessation of smoking; individual trials and meta-analysis total: the total number of participants in intervention and control. Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR inverse variance. All the events in this analysis were self-reported outcomes

All trials reporting MACE

MACE and other adverse events were reported in two studies [51, 55], which include myocardial infarction, incidence of percutaneous coronary intervention (PCI), coronary bypass graft (CABG), and hospital readmission. The meta-analysis demonstrated a 47% reduction in the incidence of PCI in the treatment group compared to the control (RR = 0. 0.53, 95% CI 0.30 to 0.95, 2 studies, 144 participants, P= 0.03, SupplementalFig. 6A). However, the meta-analysis failed to demonstrate a significant difference in the pooled incidence of MI (RR = 0.36, 95% CI 0.09 to 1.48, 2 studies, 144 participants, P= 0.16, Supplemental Fig. 6B) and CABG (RR = 0.82, 95% CI 0.08 to 8.55, 2 studies, 144 participants, P= 0.87, Supplemental Fig. 6C).

Trial sequential analysis

We performed TSA for both primary and secondary outcomes which had a significant effect on conventional meta-analysis, and the details were presented in Supplementary results, Fig. 7.1 to 7.4. Besides, the TSA of each primary and secondary outcome were discussed somewhere in this review along with the GRADEpro summary of the table (Tables 2 and 3). The trial sequential analysis for the outcome "systolic blood pressure" showed that the cumulative Z-curve crossed both alpha-spending boundaries, and reached the required information size threshold, revealing a strong power for current evidence to reject or accept the intervention effect on systolic blood pressure. The estimated required information size of 3642 patients was calculated using α= 0.05 (two-sided) and β= 0.20 (power 80%), an anticipated estimated MD of 26%, and a heterogeneity correction of 79.6% (Fig. 7).

Discussion

This meta-analysis revealed that overall, lifestyle modification intervention alone and a combination of lifestyle modification intervention and medication optimization interventions alone reduced blood pressure, LDL-C, and TC in patients with established CVD.

The meta-analysis revealed that interventions targeting lifestyle modification and medication optimization resulted in a significant reduction in patient's blood pressure when compared to usual care, which is consistent with some previous meta-analyses [17, 39], although others have failed to find this [11, 40]. The disparities in findings on the effectiveness of lifestyle modification interventions in patients with coronary heart disease are multifaceted, emphasizing the need for thorough research, individualized approaches, and ongoing evaluation to optimize outcomes in this patient population. Our meta-analysis focused on the effect of lifestyle modification and medical therapy on change in patients' blood pressure and serum cholesterol, while other meta-analyses primarily target exercise-based cardiac rehabilitation (CR) on MACE [12], lifestyle modification on optimization of behavioral risk factors [14, 40], mHealth intervention on improvement of exercise capacity and quality of life [17], lifestyle modification programs on all-cause mortality [41], and digital interventions on healthy behavior factors such as physical activity, healthy diet, and medication adherence [11]. Furthermore, our meta-analysis included recent RCTs investigating the effectiveness of lifestyle modification and medical optimization on blood pressure and cholesterol, and GRADEpro and trial sequential analysis were employed to evaluate the quality of evidence.

The meta-analysis also demonstrated a significant reduction in patients' LDL-C and TC, which is consistent with some [11, 39] but not other prior reports [14, 17, 40]. Lifestyle modification interventions can involve various components such as diet modification, medication adherence, physical exercise, smoking cessation, and stress management and the effectiveness of various interventions may vary depending on the specific strategies used in each study, leading to different outcomes in the meta-analysis. For instance, our meta-analysis investigating the effect of lifestyle modification on blood pressure and serum lipids, a meta-analysis by Gandhi et al. targeted medication adherence [17], and a meta-analysis by Cruz-Cobo et al. tested exercise capacity [40]. Furthermore, some of the systematic reviews were narrative reviews in which case the quality of evidence might be trivial [13–15].

Though the quality of evidence was low to moderate, and trial sequential analysis showed that the cumulative Z-curve did not cross TSA monitoring boundaries for harm or benefit revealing insufficient evidence to accept or reject the intervention effect, this meta-analysis demonstrated that interventions targeting either lifestyle modification alone or combination of lifestyle modification and medication optimization reduced patients' serum cholesterol.

The meta-analysis demonstrated that the intervention improved medication adherence in the intervention group which is in line with a systematic review by Aubeeluck et al. including 8 RCTs of which 5 RCTs targeting medication adherence revealed improvement of patients' medication adherence [100]. A systematic review by Fernandez et al. showed that the odds of continuing smoking at 6-month follow-up reduced by 30% in the intervention group [14]. This meta-analysis assessed the strength of the evidence using grading and TSA; nonetheless, the quality of evidence was low due to imprecision and inconsistency. The disparities in the findings of the meta-analyses could be attributed to different levels

Table 2 GRADEpro summary of findings table for continuous outcomes

Outcomes	Number of participants	Overall certainty of the evidence	Anticipated absolute effect RD with intervention	Comments
Systolic blood pressure	4386 (15RCTs)	⊕⊕◯◯: Low quality of evidence due to inconsistency and imprecision	SMD 0.3 SD lower (0.43 lower to 0.17 lower)	Trial sequential analysis showed that the cumulative *Z*-curve crossed both the conventional and TSA monitoring boundaries for benefit, but it did not reach the required information size threshold, revealing inconclusive evidence. Furthermore, the quality of evidence was low because of inconsistency and imprecision
Diastolic blood pressure	2374 (12RCTs)	⊕⊕◯◯: Low quality of evidence due to inconsistency and imprecision	SMD 0.18 SD lower (0.28 lower to 0.08 lower)	Trial sequential analysis showed that the cumulative *Z*-curve did not cross TSA monitoring boundaries for harm or benefit revealing insufficient evidence to accept or reject the intervention effect, and the quality of evidence was low due to downgrading for imprecision and inconsistency
Total Cholesterol	4516 (18 RCTs)	⊕⊕◯◯: Low quality of evidence due to inconsistency and imprecision	SMD 0.31 SD lower (0.53 lower to 0.09 lower)	Trial sequential analysis showed that the cumulative *Z*-curve crossed both the conventional and TSA monitoring boundaries for benefit, but it didn't reach the required information size threshold, revealing inconclusive evidence. Furthermore, the quality of evidence was low because of inconsistency and imprecision
Low-density lipoprotein	5867 (17 RCTs)	⊕⊕◯◯: Low quality of evidence due to inconsistency and imprecision	SMD 0.19 SD lower (0.36 lower to 0.02 lower)	Trial sequential analysis showed that the cumulative *Z*-curve did not cross TSA monitoring boundaries for harm or benefit revealing insufficient evidence to accept or reject the intervention effect, and the quality of evidence was low due to downgrading for imprecision and inconsistency

SMD standardized mean difference, *TSA* trial sequential analysis, *SD* standard deviation, *RCTs* randomized controlled trials

Table 3 GRADEpro summary of finding a table for dichotomous outcomes

Outcomes	Number of participants	Overall certainty of the evidence	Studies event rates (%)		Relative effect (95% CI)	Relative effect (TSA 95% CI)	Comments
			Control	intervention			
Medication adherence	702 (2RCTs)	⊕⊕◯◯:Low of quality of evidence due to imprecision and inconsistency	98/350 (28.0%)	65/352 (18.5%)	RR 1.52 (1.16 to 2.00)	RR 1.51 (1.15 to 1.98)	Trial sequential analysis showed that the cumulative *Z*-curve cross both alpha-spending boundaries, and it reached the required information size threshold, revealing a high power for current evidence. However, the quality of evidence was low due to downgrading for imprecision and inconsistency
Cessation of smoking	2245 (6RCTs)	⊕⊕◯◯:Low of quality of quality of evidence due to imprecision and inconsistency	333/1131 (29.4%)	406/1114 (36.4%)	RR 0.81 (0.73 to 0.90)	RR 0.84 (0.72 to 0.97)	Trial sequential analysis showed that the cumulative *Z*-curve cross both alpha-spending boundaries, but does not reach the required information size threshold, revealing a low power for current evidence and the quality of evidence was low due to downgrading for imprecision and inconsistency
MI	144 (2 RCTs)	⊕⊕◯◯Low of quality of evidence due to imprecision and inconsistency	2/75 (2.7%)	5/69 (7.2%)	RR 0.36 (0.09 to 1.48)	RR 0.35(0.08 to 1.49)	Trial sequential analysis showed that the cumulative *Z*-curve does not cross both alpha-spending boundaries and does not reach the required information size threshold, revealing a low power for current evidence. However, the quality of evidence was moderate due to downgrading for imprecision and inconsistency

Table 3 (continued)

Outcomes	Number of participants	Overall certainty of the evidence	Studies event rates (%)		Relative effect (95% CI)	Relative effect (TSA 95% CI)	Comments
			Control	intervention			
PCI	144 (2 RCTs)	⨁⨁◯◯ Low of quality of evidence due to imprecision and inconsistency	12/75 (16.0%)	18/69 (26.1%)	RR 0.53 (0.30 to 0.95)	RR 0.53 (0.30 to 095)	Trial sequential analysis showed that the cumulative *Z*-curve does not cross both alpha-spending boundaries and does not reach the required information size threshold, revealing a low power for current evidence. However, the quality of evidence was low due to downgrading for imprecision and inconsistency

The effect estimate with 95% CI were consistent with meta-analysis and TSA values

CI Confidence interval, *MI* Myocardial infarction, *RR* Risk Ratio, *PCI* percutaneous coronary intervention

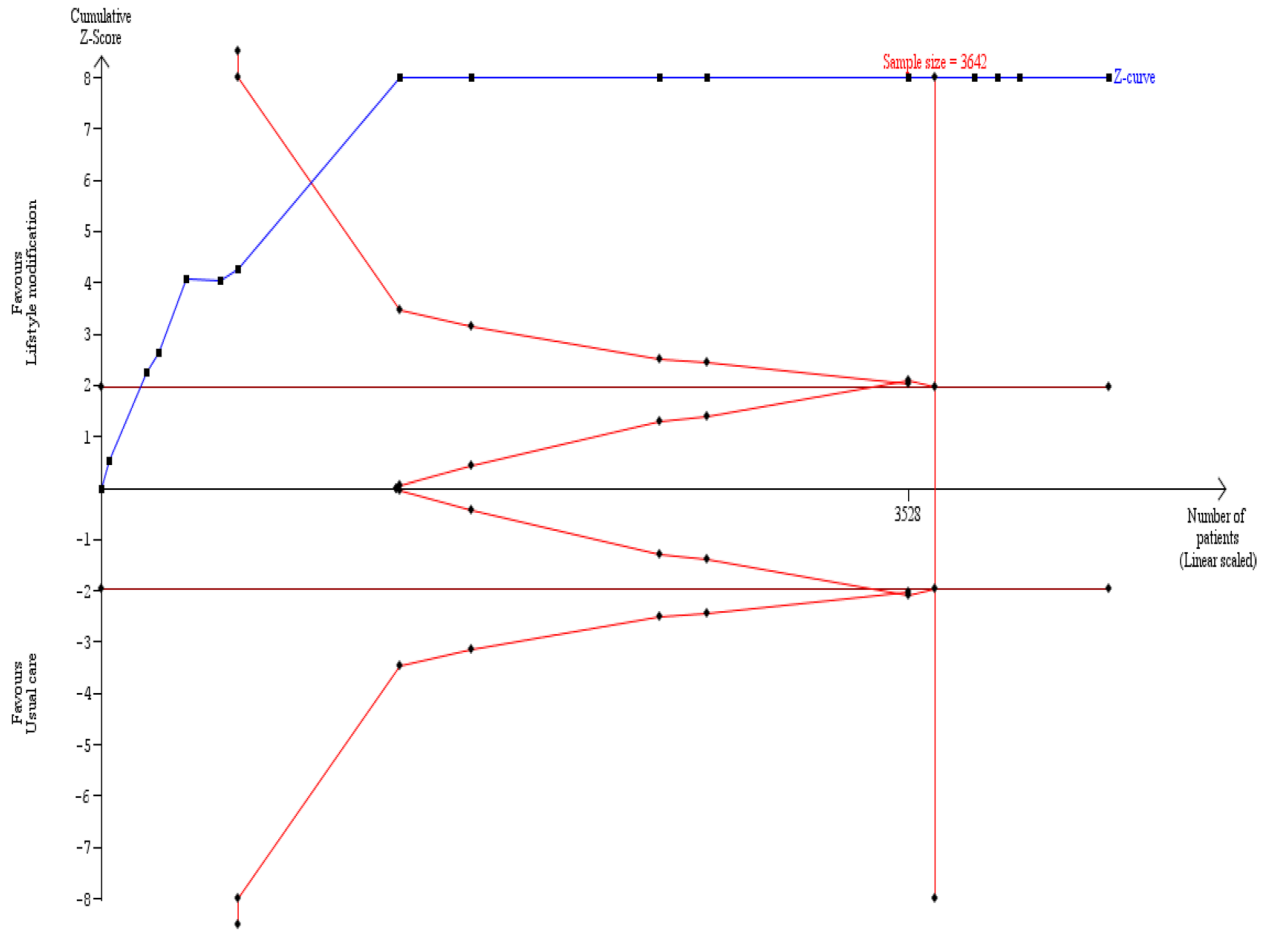

Fig. 7 Trial sequential analysis for the outcome "systolic blood pressure." The cumulative *Z*-curve crossed both alpha-spending boundaries and reached the required information size threshold, revealing a strong power for current evidence

of motivation to quit smoking, smoking histories, and differences in the delivery of smoking cessation interventions, such as counselling sessions, medication adherence, and follow-up procedures.

Strength and limitation

This meta-analysis has several strengths. First, the protocol was registered in the international prospective register of systematic reviews. Second, new randomized controlled trials with relatively large samples were included. Third, the review included RCTs reporting specific outcomes to reduce heterogeneity. Fourth, TSA was employed to assess the impact of random error and repetitive testing to improve the robustness of our meta-analysis. Finally, we evaluated the quality of evidence for the outcomes using GRADE to help healthcare professionals make better clinical decisions. This meta-analysis has also some limitations. There is a high risk of heterogeneity in our meta-analysis because the included trials were conducted with a variety of patients with different CVDs, different types of interventions, and other sociodemographic characteristics. However, the subgroup analysis by risk of bias, mode of intervention, and duration of follow-up failed to identify the sources of heterogeneity, and the interpretation of the findings was deemed to be cautious. Besides, the included studies were low-powered with low to moderate quality of evidence.

Implication for policy-makers

This systematic review demonstrated that either lifestyle modification intervention alone or a combination of medication and lifestyle interventions among patients with established CVD showed a significant reduction in cholesterol and optimization of blood pressure. This calls for collaboration with researchers, healthcare professionals, and public health experts to develop evidence-based strategies that can effectively reduce CVD risk factors and improve outcomes for those already diagnosed with the disease. This could involve implementing

more targeted and personalized interventions, increasing access to preventive care services, and promoting healthy behaviors at the population level.

Implication for further research

This meta-analysis included a number of randomized controlled trials investigating integrated lifestyle alone, medication optimization alone, and a combination of lifestyle and medication optimization, on different lifestyle modification interventions. Though the meta-analysis demonstrated a significant reduction in blood cholesterol and blood pressure, the quality of evidence was low to moderate, and there was substantial heterogeneity in some of the outcomes as the RCTs were conducted among different types of intervention, CVD, and sociodemographic characteristics. These entail further multicentre randomized controlled trials with homogenous populations, CVDs, and specific intervention types.

Conclusion

A lifestyle modification intervention alone and/or a combination of lifestyle interventions and medication optimization had a significant effect on total cholesterol, low-density lipoprotein, and blood pressure; however, the provision of the firm conclusion is less optimal with current evidence as the included studies were unpowered with low quality of evidence. Besides, there was considerable heterogeneity between studies in the meta-analysis, which entails further multi-center randomized controlled trials with large sample sizes, homogenous participants, and specific interventions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-025-02857-5.

Supplementary Material 1.

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Authors' contributions
SA and JG conceived the idea design of the project. SA, JG, ST, MS, and DS were involved in searching strategy, data extraction, quality assessment, analysis, and manuscript preparation. All authors read and approved the manuscript.

Data availability
Data and material can be available where appropriate.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that there are no competing interests.

Author details
[1]Department of Anesthesia, College of Health Sciences and Medicine, Wollo University, Dese, Ethiopia. [2]Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, James Cook University, Townsville, QLD, Australia. [3]The Australian Institute of Tropical Health and Medicine, Townsville, QLD, Australia. [4]The Department of Vascular and Endovascular Surgery, Townsville University Hospital, Townsville, QLD, Australia.

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