NIHR | National Institute for Health and Care Research

Health Technology Assessment

Check for updates

Research article

Identifying optimal primary prevention interventions for major cardiovascular disease events and all-cause mortality: a systematic review and hierarchical network meta-analysis of RCTs

Olalekan A Uthman,[1*] Rachel Court,[1] Jodie Enderby,[1] Chidozie Nduka,[1] Lena Al-Khudairy,[1] Seun Anjorin,[1] Hema Mistry,[2,3] G J Melendez-Torres,[4] Sian Taylor-Phillips[1] and Aileen Clarke[1]

[1]Division of Health Sciences, Warwick Medical School, The University of Warwick, Coventry, UK
[2]Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK
[3]University Hospitals Coventry and Warwickshire, Coventry, UK
[4]Peninsula Technology Assessment Group (PenTAG), College of Medicine and Health, University of Exeter, Exeter, UK

[*]**Corresponding author** olalekan.uthman@warwick.ac.uk

Published July 2025
DOI: 10.3310/RLDH7432

Abstract

Background: Cardiovascular disease accounts for substantial mortality and healthcare costs worldwide. Numerous interventions exist for primary prevention but lack head-to-head comparisons on long-term impacts.

Objective: To determine the comparative effectiveness of interventions for primary cardiovascular disease prevention through network meta-analysis of randomised trials.

Data sources: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, conference abstracts and trial registries from inception to March 2021.

Review methods: Randomised controlled trials of pharmacologic therapies, nutritional supplements, lifestyle changes, behavioural approaches and health policies with at least 6 months' follow-up were included. Pairwise and network meta-analyses were conducted for all-cause mortality, cardiovascular disease events, coronary heart disease and cardiovascular disease mortality.

Results: Data from 139 randomised trials, including 1,053,772 participants, proved suitable for quantitative synthesis. Blood pressure-lowering medications (risk ratio 0.82, 95% confidence interval 0.71 to 0.94), tight blood pressure control (risk ratio 0.66, 95% confidence interval 0.46 to 0.96), statins (risk ratio 0.81, 95% confidence interval 0.71 to 0.91) and multifactorial lifestyle interventions (risk ratio 0.75, 95% confidence interval 0.61 to 0.92) reduced composite cardiovascular events and mortality.

Limitations: Residual confounding may exist. Few direct head-to-head comparisons limited differentiation between some specific modalities.

Conclusions: We found evidence that blood pressure treatments, intense blood pressure targets, statins when appropriate and multifactorial lifestyle changes are the most effective strategies for primary prevention of cardiovascular disease, with unclear effects from other interventions. These findings can inform clinical guidelines and health policies prioritising interventions.

Funding: This research article presents independent research funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme as award number 17/148/05.

A plain language summary of this research article is available on the NIHR Journals Library Website https://doi.org/10.3310/RLDH7432.

This research article should be referenced as follows:
Uthman OA, Court R, Enderby J, Nduka C, Al-Khudairy L, Anjorin S, *et al.* Identifying optimal primary prevention interventions for major cardiovascular disease events and all-cause mortality: a systematic review and hierarchical network meta-analysis of RCTs. *Health Technol Assess* 2025;**29**(37):75–140. https://doi.org/10.3310/RLDH7432

Introduction

Cardiovascular diseases (CVDs), including coronary artery disease, stroke and heart failure, are the leading cause of mortality worldwide, resulting in over 17 million deaths per year.[1] CVD risk is influenced by non-modifiable factors such as genetics and age, as well as modifiable lifestyle behaviours and health factors.[2] Up to 80% of premature CVD [i.e. occurrence of cardiovascular events (CVEs) at an age younger, often defined as below 65 years for men and below 55 years for women] is potentially preventable through risk factor control, including blood pressure (BP)/cholesterol reduction, smoking cessation and lifestyle changes.[3,4] Consequently, primary prevention represents a major opportunity to substantially reduce CVD burden through evidence-based strategies.[5]

While numerous pairwise meta-analyses have evaluated pharmacological agents, nutritional supplements, behavioural interventions and health policies for CVD prevention, no overarching synthesis compares their relative impact.[6–8] This hinders consensus on the most clinically and cost-effective approaches to prioritise at both individual and population levels. Network meta-analysis enables integrated analysis leveraging direct and indirect evidence to delineate optimal regimens.[9]

Therefore, this systematic review and network meta-analysis aim to address this knowledge gap by determining the comparative effectiveness of interventions for primary prevention of CVD based on randomised trial data. Quantitative synthesis enhances precision around treatment rankings and components most strongly associated with improved outcomes. Subgroup and metaregression analyses elucidate efficacy modifiers. Findings can help inform guidelines and health system priorities regarding CVD prevention.

This publication on determining optimal primary prevention interventions for major CVD events and all-cause mortality (ACM) – findings from systematic review and hierarchical network meta-analysis of randomised controlled trials (RCTs) – is part of a series of publications on 'Determining optimal strategies for primary prevention of cardiovascular disease: systematic review, network meta-analysis and cost-effectiveness review (NIHR/HTA: 17/148/05)'.

Other publications in these series include:

1. Interventions for primary prevention of cardiovascular disease: umbrella review of systematic reviews.
2. Increasing comprehensiveness and reducing workload in a systematic review of complex interventions using automated machine learning.
3. The potential impact of policies and structural interventions in reducing cardiovascular disease and mortality: a systematic review of simulation-based studies.
4. How conclusive is the evidence for interventions primary prevention of cardiovascular disease: a trial sequential analysis?
5. Mind the gap! A multilevel analysis of factors associated with variation in published CVD primary prevention interventions effect estimates within and between countries.
6. Determining optimal strategies for primary prevention of cardiovascular disease: systematic review of cost-effectiveness analyses in the United Kingdom.

The findings from all the workstreams will be summarised in a synopsis paper to be published alongside these series.

Methods

This systematic review was registered and published in the International Prospective Register of Systematic Reviews (PROSPERO) under the following number: CRD42019123940 and published protocol.[10] We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist,[11] and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of healthcare interventions.[12]

Eligibility criteria

We evaluated each identified study against the following selection criteria:

Study population: adult populations (≥ 18 years of age) included in population-based studies, which may or may not have been targeted at moderate/high CVD risk groups (such as hypertension, obesity, hyperlipidaemia, type 2 diabetes or a combination of these). As the review focused on the primary prevention of CVD, we excluded trials that included those who had experienced a previous myocardial infarction (MI), stroke, revascularisation procedure (coronary artery bypass graft or percutaneous transluminal coronary angioplasty), and those with angina or angiographically defined coronary heart disease (CHD). Studies with mixed populations, that is, both population with and without CVD, were included if data for the relevant primary prevention could be extracted.

Intervention: any form of intervention aimed at the primary prevention of CVD, including but not limited to drugs (lipid-lowering medications, BP-lowering medications, antiplatelet agents), diet (nutritional supplements, dietary interventions), physical activity or public health (health promotion programmes, structural and policy interventions) (see *Appendix 1*).

Comparators: other forms of intervention (such as a minimal intervention, active intervention, concomitant intervention), placebo, usual care or no intervention control group, or wait list control.

Outcome measures: the primary outcome was ACM. Secondary outcomes included but not limited to CVD-related mortality (defined as fatal MI, sudden cardiac death, fatal stroke and fatal heart failure), major CVEs (defined as fatal and non-fatal MI, sudden cardiac death, revascularisation, fatal and non-fatal stroke, and fatal and non-fatal heart failure), CHD (fatal and non-fatal MI and sudden cardiac death, excluding silent MI), incremental costs per quality-adjusted life-years gained reported alongside a randomised trial.

Study design: RCTs of at least 6 months' duration of follow-up. Units of randomisation could have been either individuals or clusters (such as family, workplace).

Information sources and search strategy

Due to the likelihood of a high volume of relevant trials to be included, we followed standard guidelines for integrating existing systematic reviews into new reviews.[13,14] Where existing systematic reviews with acceptable search and study selection methods (especially Cochrane reviews) were available for any of the intervention categories, these were used as a starting point to identify relevant studies. Initial searches for relevant systematic reviews were not restricted by date. Searches were not restricted by language. A comprehensive literature search for existing systematic reviews was developed iteratively and undertaken in March 2019 (with updates in October 2019 and March 2021) in major medical and health-related electronic bibliographic databases, including MEDLINE (Ovid), EMBASE (Ovid), Cochrane Database of Systematic Reviews (Wiley) and Database of Abstracts of Reviews of Effects [Centre for Reviews and Dissemination (CRD)]. Systematic reviews that potentially included primary studies meeting our inclusion criteria were selected. Records for the included (and, if available, excluded) studies in all selected systematic reviews were identified and imported into EndNote [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA] using Citation Finder (formerly known as HubMed),[15,16] systematically de-duplicated and screened.

The most recent systematic review for any intervention or intervention category was assessed using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR-2)[17] items 4, 5 and 7 to help determine whether or not the search and study identification methods were acceptable for the purpose of identifying studies for this network meta-analysis. If not, the next most recent review where available was assessed using the same criteria. An analysis of the search dates of the chosen reviews informed the date limit used for the search for more recent trials (i.e. those that were not yet included in a published review). The aim of this was to ensure all time periods were covered.

The search for recent trials was developed iteratively and was informed by records of a broad cross-section of known studies. Searching based on the concepts of prevention and CVD outcomes, or on intervention terms and CVD outcomes, was considered and tested. Scoping searches had retrieved very high numbers of trials in Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley) using either approach. Our initial trial search was run in June 2019 in CENTRAL (via Wiley). In order to capture studies with more obscure records and those that may have been excluded by previous systematic reviews, we also ran a more sensitive search in June 2019 with no date limit and used machine learning to identify a proportion of these records for screening (see *Selection process*). We updated this search in June 2020 and March 2021. A full record of searches is provided in *Appendix 2*. Finally, the reference lists of included studies were examined for additional relevant studies.

Selection process

In the initial phase of our research, we focused on identifying existing, relevant systematic reviews and conducting a less sensitive search specific to the year 2019, employing a date limit to manage the volume and relevance of the findings. For this phase, the selection process involved two independent reviewers systematically screening the search results. Each reviewer independently assessed the titles and abstracts against pre-defined inclusion and exclusion criteria. Discrepancies between reviewers were resolved through discussion, and if consensus could not be reached, a third, senior reviewer was consulted to make the final decision. This standard protocol ensured a rigorous and unbiased selection of studies for inclusion in our review.

Following this initial phase, to further reduce the workload of screening search results from the highly sensitive search with no date limit, we developed a bespoke classifier/algorithm.[18] This tool was designed to identify potentially relevant studies by leveraging machine learning techniques. We trained the algorithm using a data set

composed of studies that were previously included and excluded, as identified through our other searches. This training process enabled the machine to make predictions on whether to include or exclude other titles and abstracts that it had not previously encountered. To validate the algorithm's accuracy, we manually screened the titles and abstracts of a small proportion, specifically 10%, of these results. This dual approach, combining traditional review methods with advanced machine learning, allowed for an efficient and effective screening process.

Data collection process

Data were independently extracted using a pre-specified piloted proforma by two reviewers, with discrepancies resolved by a third reviewer. We used a data collection form for study characteristics and outcome data. One author extracted study characteristics from the included studies, and a second author checked study characteristics for accuracy. Any inconsistencies were resolved through discussion.

We extracted the following characteristics:

Study citation: years of study, registration number to trial registries, year of publication, location, setting, number of centres, sample size, diagnostic criteria, funding/sponsor.

Methods: including study design (type of RCT), number of arms, risk of bias (see below).

Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, baseline measures of physiological functioning [e.g. cardiovascular function, BP, body mass index, blood glucose, glycated haemoglobin (HbA1C), smoking history], inclusion and exclusion criteria.

Interventions: intervention, comparison, concomitant medications and excluded medications.

Outcomes: primary and secondary outcomes specified and collected; and time points reported, including information on whether an intention-to-treat approach had been used and how it was defined.

Data items and measurement of treatment effect

Clinical effectiveness

We reported dichotomous outcomes as risk ratios (RRs). If possible, we used the intention-to-treat population for all analyses. We included cluster-randomised trials in the meta-analysis along with individually randomised trials (unit of analysis issues). Cluster-randomised trials were labelled with a (C). For cluster-randomised trials to be included in the network meta-analyses, we adjusted for design effect using an 'approximation method'[19] if the trial did not use a cluster-adjusting analytical strategy. 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 of those who experienced the event by the same design effect, while for continuous data, only the sample size was reduced (means and standard deviations were left unchanged).

Risk of bias in individual studies

We used the Cochrane Collaboration's tool for assessing risk of bias 2 for quality assessment of the included trials at trial level.[20] The trials were graded (unclear, high or low risk of bias) based on bias arising from the randomisation process, deviations from intended intervention, missing outcome data, measurement of the outcome and selection of the reported result.

Statistical analysis

We conducted network meta-analyses[9,21] to compare the effectiveness of the different types of interventions for primary prevention of CVD. Given the substantial number of interventions and the limited evidence base available to construct the network of evidence (in terms of both the number of trials and the number of direct comparisons between active interventions), we used a two-level hierarchical network meta-analysis to borrow strength within the classes of intervention, strengthening inferences and potentially reducing the uncertainty around individual intervention effects. This consequently increased our ability to rank these and to inform decision-making frameworks.[22] The two-level hierarchical network meta-analysis (level 1: intervention type; and level 2: intervention class) incorporated exchangeability between interventions of the same class to predict an effect estimate for each of the interventions individually.[22]

We calculated the probability of a given intervention having the largest beneficial effects as the proportion of simulations in which that intervention was ranked as the 'best' according to the relative prevention effect estimate. In addition, we calculated alternative rankings (second- and third-best, etc.) because in some policy and practice areas, the best intervention might be unavailable, too costly or contraindicated. Probability values (*p*-values) were summarised and reported as surface under the

cumulative ranking (SUCRA) and graphically ranked using rankograms. SUCRA = 1 if an intervention always ranks first, and SUCRA = 0 if it always ranks last.

For each intervention, we calculated a *p*-score, which represents the probability that the intervention is the most effective based on a Bayesian interpretation of the estimated treatment effects and their uncertainty.[23] The *p*-score ranges from 0 to 1, with higher values indicating a greater likelihood of being the most effective intervention. In our primary analysis, we estimated the pairwise relative effects of individual interventions (e.g. specific BP-lowering drugs or lifestyle programmes) on each outcome. To provide a more succinct comparison of broad approaches to CVD prevention, we also conducted class effect analyses, in which interventions were grouped into categories based on their primary mechanism of action (e.g. BP lowering, lipid lowering, health promotion).[12] The class effect analysis provides an estimate of the average effect of all interventions within a given category, which may be more relevant for informing high-level guidelines and policies.

Investigation of heterogeneity and inconsistency

We anticipated several sources of heterogeneity relating to the content of the intervention and study design. We tested effect modification of intervention effectiveness using subgroup analyses and metaregression analyses. For example, where there were sufficient data, we stratified our analyses (subgroup) by population risk groups (healthy vs. high-risk), trial period (older vs. recent), sex (male vs. female) and age (young adult vs. elderly population); by intervention components; and by characteristics of outcome measures. Metaregression analyses were used to explore components of interventions, participant characteristics and outcome measure characteristics that can predict prevention effect estimates within and across different types of interventions. The network metaregression was performed by allowing for a common treatment-covariate interaction for each intervention in the network meta-analysis.[24]

Results

Study selection and characteristics

Our literature search initially yielded 133,260 citations. To streamline the screening process, we developed a specialised classifier/algorithm to identify potentially relevant studies. We labelled 16,611 articles, of which 676 (4.0%) were deemed 'relevant' and 15,935 (96%) 'irrelevant'. The most effective model achieved a recall of 96.4%, precision of 99.1%. Subsequently, this classifier was used to screen all remaining, unreviewed citations from our search. It identified 1323 citations as potentially relevant. After examining the titles and abstracts of these citations, 200 articles were chosen for full-text review. Ultimately, 193 (139 unique articles) met our inclusion criteria and were included in the review (see *Appendix 3*).

The studies were published between 1969 and 2019 (see *Appendix 4*). The majority utilised a parallel RCT design and were published in academic journals. Studies were predominantly conducted in North America and Europe, though a substantial number took place in Asia. The sample size of included RCTs ranged from 90 to 49,781 participants, with a median of 1828. Mean baseline age spanned the continuum of adulthood, with most trials focusing on middle-aged and older populations. Gender distribution was roughly balanced overall (median 48% female).

Baseline cardiovascular risk profiles, where reported, demonstrated inclusion of both lower-risk general populations and those at heightened risk. The median hypertension prevalence was 50%, type 2 diabetes prevalence 23.5% and smoking prevalence 15%. A variety of interventions were employed, including pharmacological approaches (e.g. BP lowering, lipid lowering, antiplatelet medications), non-pharmacological strategies (e.g. dietary changes, nutritional supplements, physical activity, health education) and mixed intervention modalities. The duration of interventions ranged from 1 month to 30 years (median 4 years).

Risk-of-bias assessment

The included studies demonstrated generally low risk of bias (see *Appendix 5*), with the majority receiving favourable ratings across all assessed domains. Randomisation processes were well reported, with 73% of the studies having clear methods and only 9 studies showing evidence of improper randomisation. Intended interventions were properly delivered and adhered to in about 65% of the studies, though 38 studies did reveal some concerns about protocol deviations or lack of blinding that could bias results. Regarding completeness of outcome data, 83% of the studies had low attrition or appropriate imputation methods for missing data. Just 12% of the studies had clearly inadequate handling of incomplete data that may threaten validity. Outcome measurement methods were felt to be valid and reliable in 87% of the studies, with only 7% of the studies showing deficiencies in this domain. Lastly, selective reporting was avoided in most studies based on protocol alignment and publication of expected outcomes.

This research article should be referenced as follows:
Uthman OA, Court R, Enderby J, Nduka C, Al-Khudairy L, Anjorin S, *et al.* Identifying optimal primary prevention interventions for major cardiovascular disease events and all-cause mortality: a systematic review and hierarchical network meta-analysis of RCTs. *Health Technol Assess* 2025;**29**(37):75–140. https://doi.org/10.3310/RLDH7432

Prevention effect estimates for all-cause mortality

The network evaluating ACM consists of 102 studies involving 47 different interventions tested among 793,183 patients (*Figure 1*). There are a large number of possible pairwise comparisons (n = 1081) between interventions, but only 69 comparisons are directly informed by studies in the data set. The included studies predominantly feature two intervention arms (n = 95), though seven studies evaluated three or more groups. In total, there were 63,920 ACM events observed across all studies.

There was substantial heterogeneity detected across trials (I^2 = 88.4%) (*Figure 2*). In comparison to control, use of antihypertensive medication regimens (RR 0.76, 95% CI 0.64 to 0.90; p = 0.002) and multiple risk factor interventions (MRFIs) (RR 0.80, 95% CI 0.69 to 0.94; p = 0.006) were associated with statistically significant reductions in ACM. The probability of these interventions having the most beneficial impact on survival was 80.4% for antihypertensive regimens and 72.2% for MRFI. Intensive BP lowering to tighter targets also demonstrated an association with lower ACM risk versus control (RR 0.66, 95% CI 0.46 to 0.96; p = 0.03). The probability of tight BP control being the most effective intervention was 87.0%. In contrast, no statistically significant differences were noted for other interventions compared to control, including use of aspirin, statins, vitamins, nutritional supplements, dietary changes, diabetes medications and lifestyle measures. Point estimates for these ranged from 0.88 to 1.27 in relation to control. There were no significant differences for pairwise comparisons between the types of interventions.

In the class effect analysis from a network meta-analysis of interventions for ACM in primary prevention of CVD, the most notable finding was for BP-lowering interventions (*Table 1*). These interventions were associated with a significant reduction in the risk of ACM, with an 18% decrease (RR 0.82, 95% CI 0.71 to 0.94; p = 0.003). This suggests that among the various classes of interventions analysed, BP-lowering strategies were the most effective in reducing the risk of ACM. Other interventions such as aspirin, blood glucose lowering, dietary changes, health promotion, lipid lowering, multicomponent interventions and nutritional supplements did not show a statistically significant impact on ACM. Their respective RRs and confidence intervals (CIs) indicate that these interventions did not significantly differ from the control in terms of their effect on ACM in the context of primary prevention of CVD. The health promotion interventions approached statistical significance (RR 0.87, 95% CI 0.75 to 1.01; p = 0.060), suggesting a potential trend towards

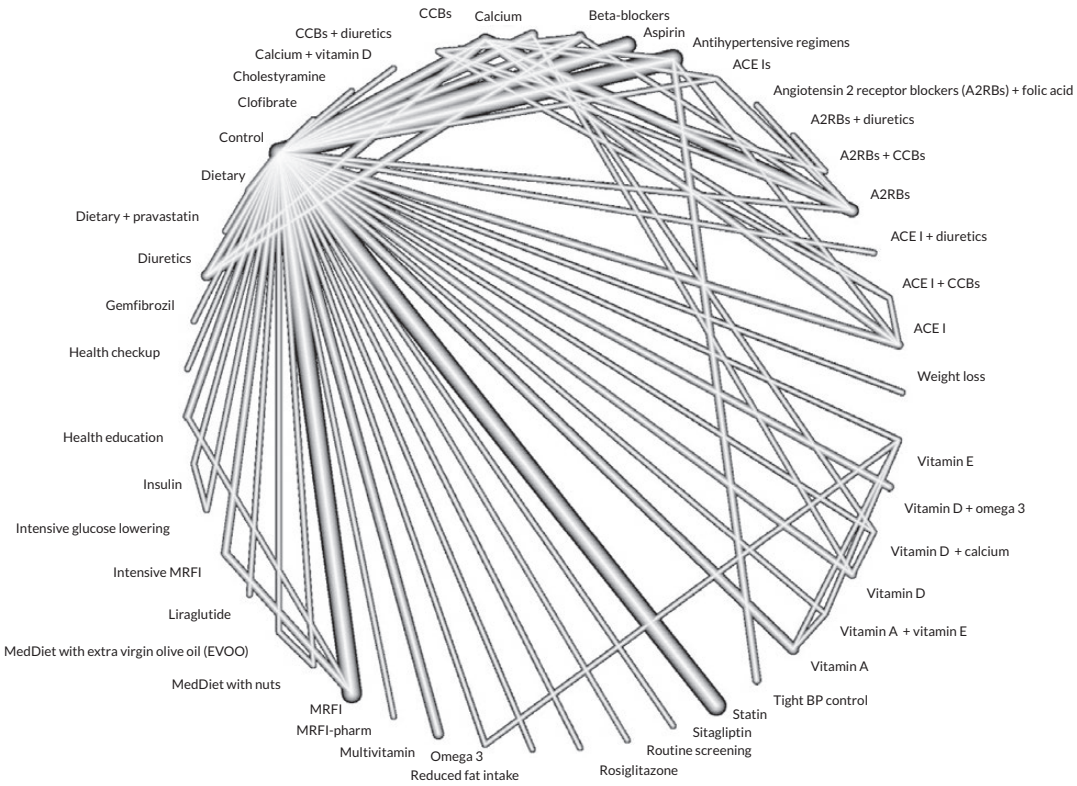

FIGURE 1 Network of eligible comparisons for the network meta-analysis for ACM.

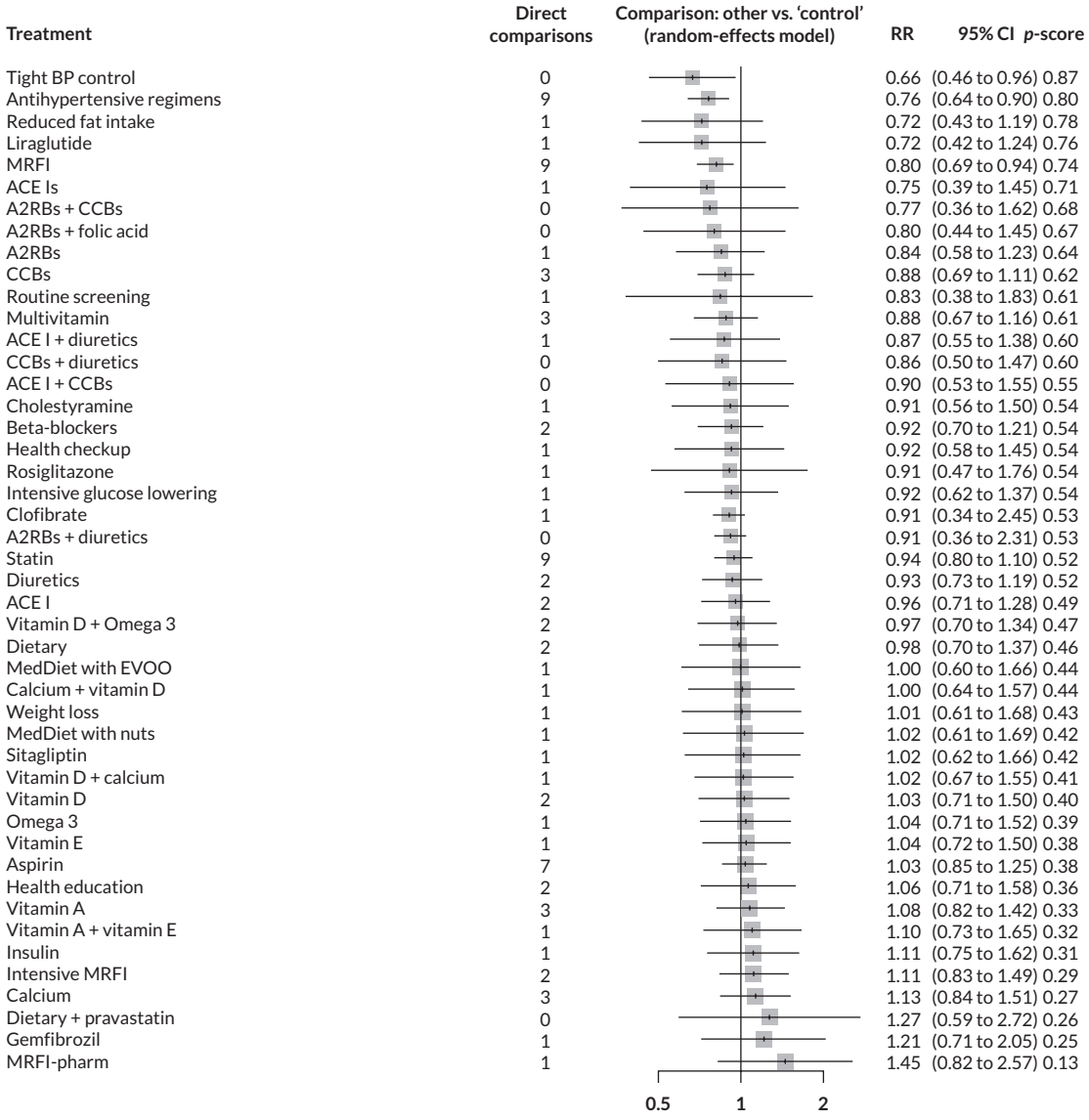

FIGURE 2 Forest plots for network meta-analysis for ACM vs. control as reference group.

effectiveness, but this did not reach the conventional threshold for statistical significance.

In the metaregression analysis of interventions for primary prevention of CVD focusing on ACM, two key findings emerged (*Table 2*). Firstly, a longer follow-up period was significantly associated with an increased risk of ACM, with an 8% higher risk for each 1-month increase in the follow-up duration (RR 1.08, 95% CI 1.01 to 1.16; $p = 0.029$). Secondly, a trend suggested that more recent studies might show interventions to be slightly more effective in reducing ACM, although this did not reach statistical significance (RR 0.87, 95% CI 0.76 to 1.00; $p = 0.052$). Other factors such as indirectness of evidence, loss to follow-up and percentage of females did not show significant associations with mortality risk in this context.

Prevention effect estimates for major cardiovascular events

The network evaluating major CVEs consists of 121 studies testing 51 interventions among 956,999 patients (*Figure 3*). With 51 interventions, there are 1275 possible pairwise comparisons, of which only 70 (5.5%) are directly informed by available trials. However, the network is connected, enabling indirect estimates for the remaining comparisons. Included studies predominantly have two intervention arms ($n = 114$), with seven studies evaluating three or more groups. Across all trials, there were 63,800 major CVEs recorded. In comparison to control (*Figure 4*), bezafibrate (RR 0.36, 95% CI 0.14 to 0.93; p), use of antihypertensive medication regimens (RR 0.80, 95% CI 0.71 to 0.91; $p = 0.0009$), statins (RR 0.81, 95% CI 0.71 to 0.91; $p = 0.0008$), tight BP control (RR 0.70, 95% CI 0.53 to 0.92; $p = 0.011$) and intensive MRFIs

This research article should be referenced as follows:
Uthman OA, Court R, Enderby J, Nduka C, Al-Khudairy L, Anjorin S, *et al.* Identifying optimal primary prevention interventions for major cardiovascular disease events and all-cause mortality: a systematic review and hierarchical network meta-analysis of RCTs. *Health Technol Assess* 2025;**29**(37):75–140. https://doi.org/10.3310/RLDH7432

NIHR Journals Library www.journalslibrary.nihr.ac.uk

DOI: 10.3310/RLDH7432

TABLE 1 Results of network meta-analyses for the class effect of different interventions for ACM

	RR (95% CI)	*p*-value
BP lowering	**0.82 (0.71 to 0.94)**	**0.003**
Health promotion	0.87 (0.75 to 1.01)	0.060
Dietary	0.89 (0.68 to 1.15)	0.357
Lipid lowering	0.95 (0.80 to 1.12)	0.527
Blood glucose lowering	0.95 (0.73 to 1.23)	0.690
Aspirin	1.02 (0.82 to 1.27)	0.870
Nutritional supplement	1.02 (0.88 to 1.18)	0.825
Multicomponent	1.02 (0.70 to 1.48)	0.920

Note
Results are ordered by decreasing effectiveness. Statistically significant outcomes are highlighted in bold and underlined.

TABLE 2 Results of metaregression analyses for the study-level factors associated with the treatment effect estimates for ACM

	RR (95% CI)	*p*-value
Indirectness of evidence	0.86 (0.12 to 5.98)	0.880
Publication year	0.87 (0.76 to 1.00)	0.052
Longest follow-up	1.08 (1.01 to 1.16)	0.029
Loss to follow-up	1.00 (0.99 to 1.01)	0.965
Per cent female	1.03 (0.93 to 1.15)	0.538

(RR 0.75, 95% CI 0.61 to 0.92; $p = 0.005$) were associated with statistically significant reductions in risk of major CVEs. The probabilities of these interventions having the greatest impact were 72.8% for antihypertensive regimens, 72.2% for statins, 82.4% for tight BP targets and 78.5% for intensive MRFI. Use of calcium channel blockers (CCB) (RR 0.80, 95% CI 0.67 to 0.94; $p = 0.008$) and diuretics (RR 0.81, 95% CI 0.67 to 0.99; $p = 0.04$) were also linked with significantly lower major CVE rates compared to control. There were no significant differences for pairwise comparisons between the types of interventions.

In the class effect analysis from a network meta-analysis focusing on major CVEs, two types of interventions showed statistically significant effects (*Table 3*). BP-lowering interventions were associated with a 16% reduction in the risk of major CVEs (RR 0.84, 95% CI 0.76 to 0.93; $p < 0.001$), indicating their effectiveness in this context. Similarly, lipid-lowering interventions demonstrated a significant impact, with an 18% reduction in risk (RR 0.82, 95% CI 0.73 to 0.92; $p < 0.001$). Other interventions, including aspirin, blood glucose lowering, dietary changes, health promotion, multicomponent interventions, nutritional supplements, other categories and physical activity, did not show a statistically significant effect on major CVEs. While aspirin, dietary interventions and health promotion approached statistical significance, they did not reach the conventional threshold for a significant impact on the risk of major CVEs. This suggests that within the context of this analysis, BP- and lipid-lowering

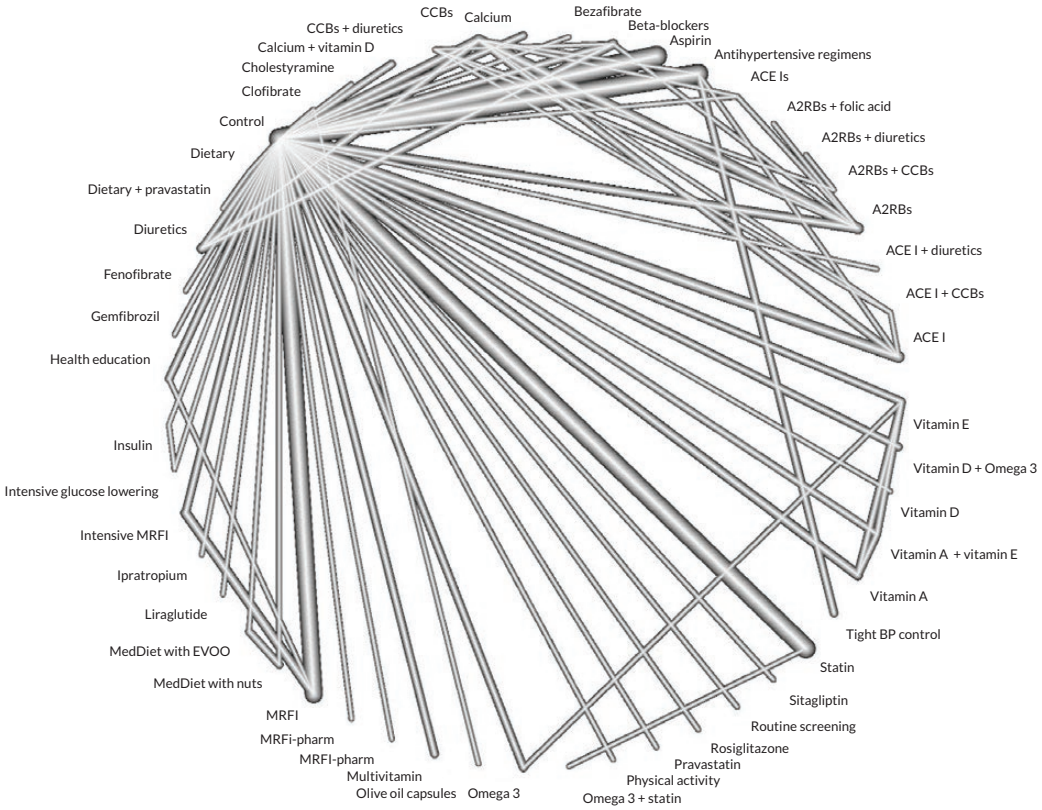

FIGURE 3 Network of eligible comparisons for the network meta-analysis for major CVEs.

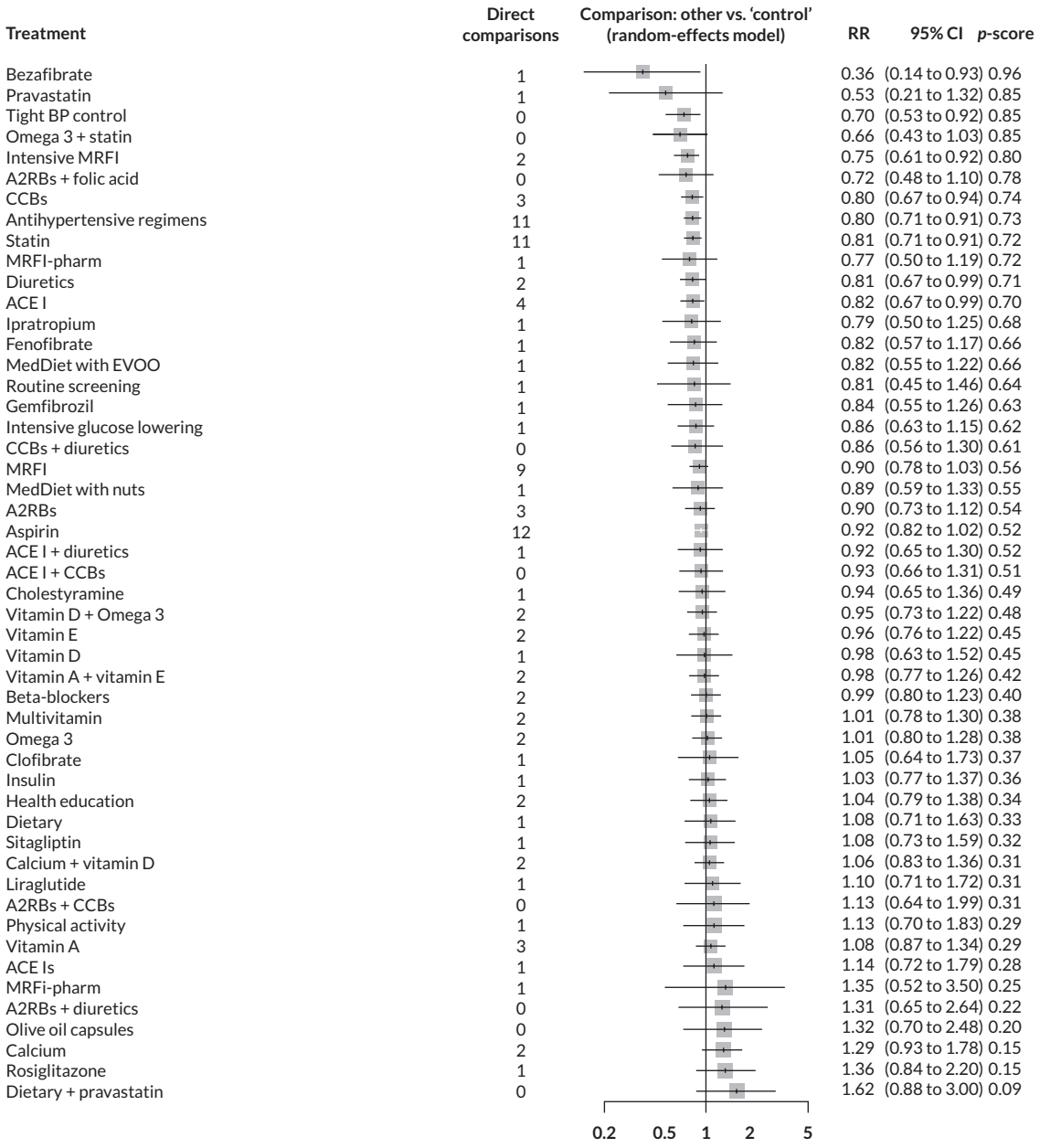

FIGURE 4 Forest plots for network meta-analysis for major CVEs vs. control as reference group.

interventions were the most effective in reducing the risk of major CVEs.

For major CVEs in the context of interventions for primary prevention of CVD, the metaregression analysis highlighted two significant findings (*Table 4*). First, the publication year of studies was notably associated with the risk of major CVEs. Specifically, more recent studies were associated with a 17% reduction in risk (RR 0.83, 95% CI 0.74 to 0.94; $p = 0.002$), per 1-year increase in publication year, indicating that newer interventions might be more effective. Second, the duration of the longest follow-up was also significant, with a slight increase in risk associated with each 1-month increase in follow-up duration (RR 1.02, 95% CI 1.01 to 1.04; $p = 0.001$). Other factors, including risk of bias, indirectness of evidence, loss to follow-up and percentage of females, did not show a statistically significant impact on the risk of major CVEs.

Prevention effect estimates for coronary heart disease

The network evaluating CHD consists of 92 studies testing 45 interventions among 789,507 patients (*Figure 5*). With 45 interventions, there are 822 possible pairwise comparisons, of which only 57 (6.9%) have direct evidence available. Included studies predominantly have two intervention arms ($n = 86$), with six studies evaluating three or more groups. Collectively across all trials, there

TABLE 3 Results of network meta-analyses for the class effect of different interventions for major CVEs

	RR (95% CI)	*p*-value
Dietary	0.79 (0.60 to 1.04)	0.095
Others	0.77 (0.46 to 1.28)	0.309
Lipid lowering	**0.82 (0.73 to 0.92)**	**≤ 0.001**
BP lowering	**0.84 (0.76 to 0.93)**	**≤ 0.001**
Multicomponent	0.84 (0.63 to 1.11)	0.211
Health promotion	0.88 (0.76 to 1.00)	0.058
Aspirin	0.90 (0.79 to 1.03)	0.121
Nutritional supplement	1.00 (0.90 to 1.12)	0.989
Blood glucose lowering	1.07 (0.86 to 1.32)	0.534
Physical activity	1.15 (0.66 to 2.01)	0.624

Note
Results are ordered by decreasing effectiveness. Statistically significant outcomes are highlighted in bold and underlined.

TABLE 4 Results of metaregression analyses for the study-level factors associated with the treatment effect estimates for major CVEs

	RR (95% CI)	*p*-value
Risk of bias	0.28 (0.03 to 2.21)	0.225
Indirectness of evidence	0.36 (0.06 to 2.13)	0.261
Publication year	**0.83 (0.74 to 0.94)**	**0.002**
Longest follow-up	**1.02 (1.01 to 1.04)**	**0.001**
Loss to follow-up	1.00 (0.99 to 1.01)	0.529
Per cent female	1.02 (0.96 to 1.09)	0.498

Note
Statistically significant outcomes are highlighted in bold and underlined.

were 29,430 CHD events recorded. In comparison to control, use of antihypertensive medication regimens was associated with a significantly lower risk of CVD mortality (RR 0.72, 95% CI 0.56 to 0.91; $p = 0.006$) (*Figure 6*). The probability of antihypertensive regimens having the greatest mortality reduction impact was 68.9%. Intensive MRFIs also demonstrated a significant association with lower CVD mortality versus control (RR 0.67, 95% CI 0.51 to 0.88; $p = 0.003$). While none of the other evaluated interventions showed statistically significant differences in CVD mortality compared with control, point estimates suggested potentially lowered risks with health education programmes and routine screening. There were no significant differences for pairwise comparisons between the types of interventions.

In the class effect analysis from a network meta-analysis focusing on CVD mortality, two types of interventions demonstrated statistically significant effects (*Table 5*). BP-lowering interventions were associated with a 21% reduction in the risk of CVD mortality (estimate = 0.79, CI 0.66 to 0.94; $p = 0.007$), indicating their effectiveness in reducing the risk of death from CVDs. Health promotion interventions also showed a significant impact, with a 32% reduction in risk (estimate = 0.68, CI 0.53 to 0.87; $p = 0.002$). Other intervention types, including aspirin, blood glucose lowering, dietary changes, lipid lowering, multicomponent interventions and nutritional supplements, did not show a statistically significant impact on CVD mortality. While some of these interventions, such as nutritional supplements, approached statistical significance, they did not meet the conventional threshold for a significant impact on CVD mortality. This suggests that in the context of this analysis, BP-lowering and health promotion interventions were the most effective in reducing the risk of mortality due to CVDs.

This research article should be referenced as follows:
Uthman OA, Court R, Enderby J, Nduka C, Al-Khudairy L, Anjorin S, *et al.* Identifying optimal primary prevention interventions for major cardiovascular disease events and all-cause mortality: a systematic review and hierarchical network meta-analysis of RCTs. *Health Technol Assess* 2025;**29**(37):75–140. https://doi.org/10.3310/RLDH7432

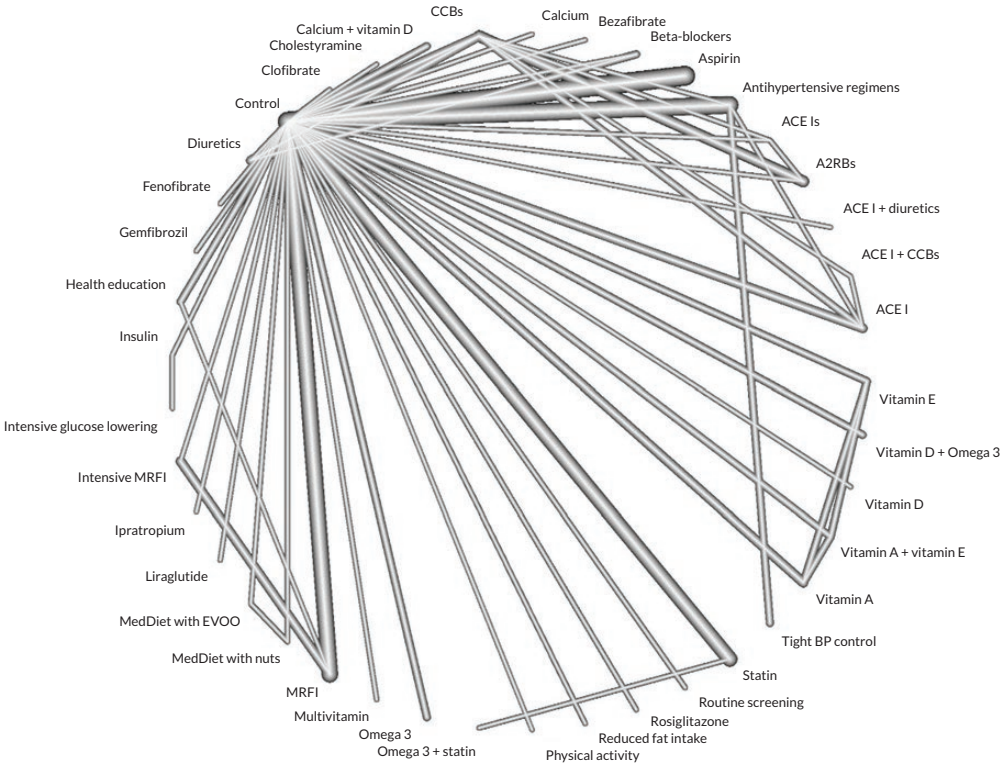

FIGURE 5 Network of eligible comparisons for the network meta-analysis for CHD.

In the analysis of interventions for the primary prevention of CHD, the metaregression analysis yielded two statistically significant findings (*Table 6*). Firstly, the duration of the longest follow-up was associated with a slight increase in the risk of CHD, with a 2% increase in risk for each 1-month increase in follow-up duration (RR 1.02, 95% CI 1.00 to 1.03; $p = 0.009$). Secondly, the percentage of female participants in the study was linked with a higher risk of CHD, showing a 10% increase in risk (RR 1.10, 95% CI 1.01 to 1.21; $p = 0.034$). Other factors such as risk of bias, indirectness of evidence, publication year and loss to follow-up did not demonstrate a significant impact on the risk of CHD in this context.

Prevention effect estimates for cardiovascular disease mortality

The network evaluating CVD mortality consists of 95 studies testing 49 interventions among 828,809 patients (*Figure 7*). With 49 interventions, there are 1038 possible pairwise comparisons, of which only 67 (6.5%) are directly informed by available trials. However, the network created is connected, allowing indirect estimates for the remaining comparisons. Included studies predominantly have two intervention arms ($n = 88$), with seven studies evaluating three or more groups. In total, across all trials, there were 24,630 CVD death events recorded. In the network meta-analysis concerning CVD mortality, the random-effects model has identified a select few interventions that demonstrate statistically significant benefits over the control (*Figure 8*). 'Antihypertensive regimens', with a RR of 0.72 and a *p*-value of 0.0064, indicate a substantial reduction in CVD mortality risk by approximately 28.46%. 'MRFI' also shows a significant effect, with a RR of 0.67 and a *p*-value of 0.0034, suggesting a potential reduction in CVD mortality risk by approximately 32.95%. There were no significant differences for pairwise comparisons between the types of interventions.

In the analysis for primary prevention of CVD mortality, 'BP lowering' and 'Health promotion' interventions emerge as statistically significant (*Table 7*). 'BP lowering' shows a risk reduction with an estimate of 0.79 and a *p*-value of 0.007, indicating a 21% decrease in CVD mortality risk. 'Health promotion' presents a significant effect with an estimate of 0.68 and a *p*-value of 0.002, suggesting a 32% reduction in risk. These results underscore the efficacy of these interventions in decreasing the risk of CVD mortality. Other interventions did not demonstrate statistically significant impacts on CVD mortality in this analysis.

In the context of CVD mortality for interventions aimed at the primary prevention of CVD, the metaregression analysis highlighted one key finding (*Table 8*). The publication year of the studies showed a significant association with the risk of CVD mortality. Specifically, suggesting a 15% rise in the risk of CVD mortality per

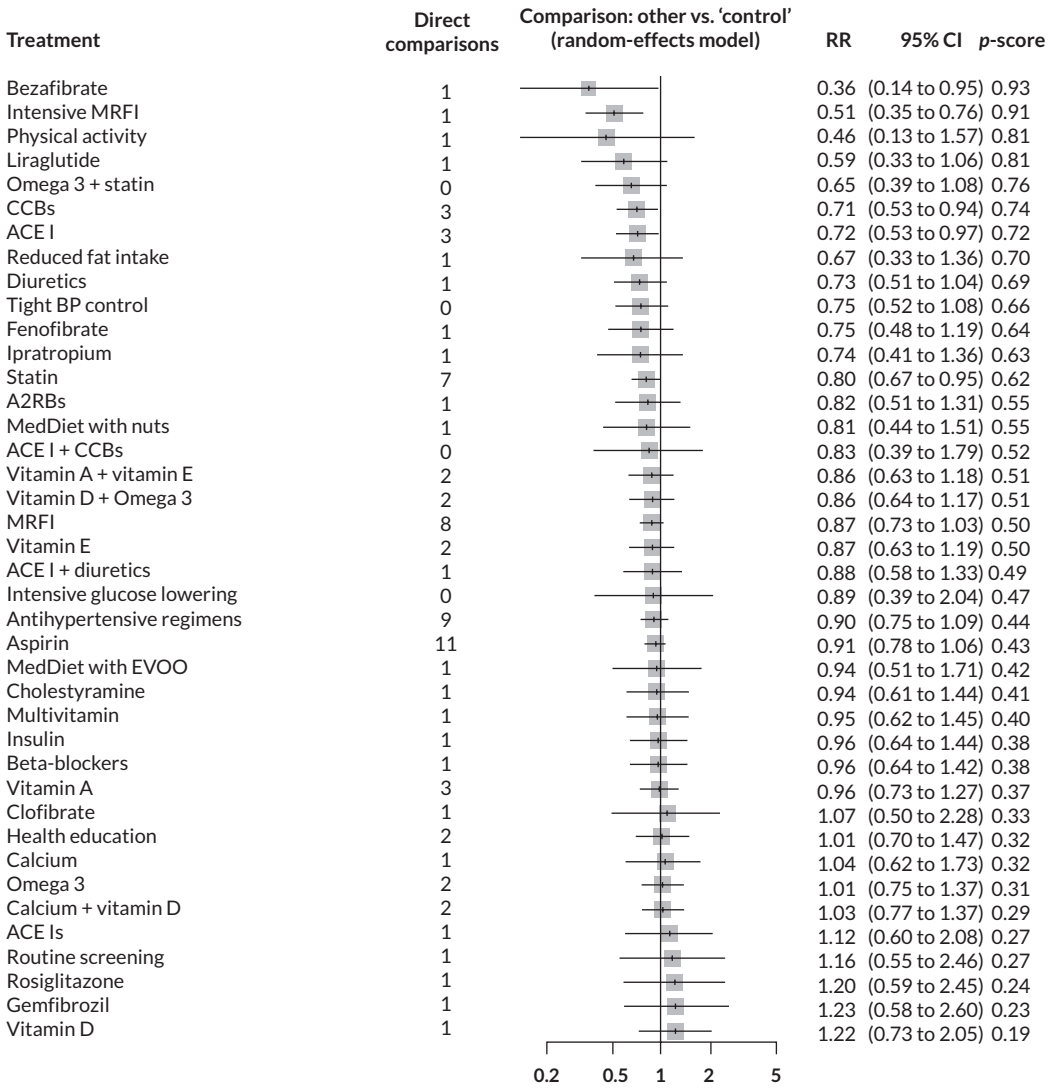

FIGURE 6 Forest plots for network meta-analysis for CHD vs. control as reference group.

TABLE 5 Results of network meta-analyses for the class effect of different interventions for CHD

	Estimate (CI)	*p*-value
Physical activity	0.48 (0.13 to 1.77)	0.268
Dietary	0.76 (0.48 to 1.20)	0.239
Others	0.71 (0.36 to 1.37)	0.305
BP lowering	**0.82 (0.70 to 0.96)**	**0.013**
Lipid lowering	**0.83 (0.71 to 0.98)**	**0.026**
Blood glucose lowering	0.87 (0.61 to 1.23)	0.424
Aspirin	0.89 (0.74 to 1.06)	0.180
Health promotion	0.90 (0.75 to 1.08)	0.241
Nutritional supplement	0.94 (0.81 to 1.08)	0.395
Multicomponent	1.07 (0.49 to 2.32)	0.871

Note
Results are ordered by decreasing effectiveness. Statistically significant outcomes are highlighted in bold and underlined.

This research article should be referenced as follows:
Uthman OA, Court R, Enderby J, Nduka C, Al-Khudairy L, Anjorin S, *et al.* Identifying optimal primary prevention interventions for major cardiovascular disease events and all-cause mortality: a systematic review and hierarchical network meta-analysis of RCTs. *Health Technol Assess* 2025;**29**(37):75–140. https://doi.org/10.3310/RLDH7432

TABLE 6 Results of metaregression analyses for the study-level factors associated with the treatment effect estimates for CHD

	RR (95% CI)	*p*-value
Risk of bias	0.44 (0.04 to 4.58)	0.494
Indirectness of evidence	0.95 (0.18 to 5.05)	0.952
Publication year	1.00 (0.89 to 1.13)	0.964
Longest follow-up	1.02 (1.00 to 1.03)	0.009
Loss to follow-up	1.01 (1.00 to 1.02)	0.211
Per cent female	1.10 (1.01 to 1.21)	0.034

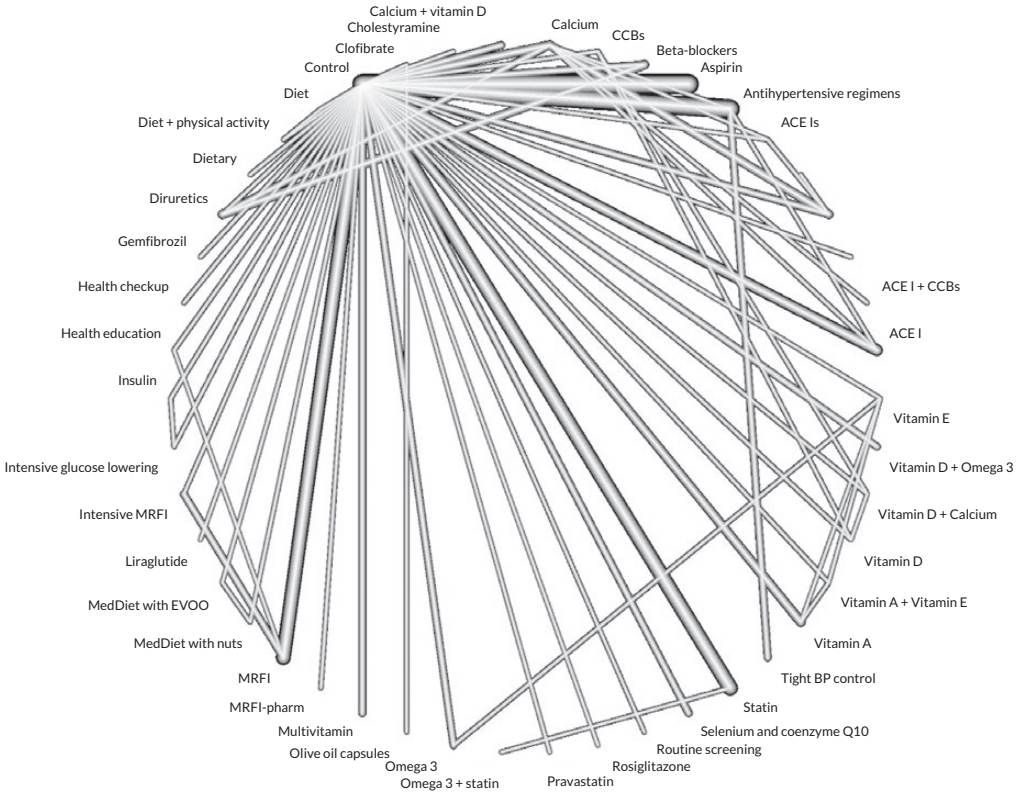

FIGURE 7 Network of eligible comparisons for the network meta-analysis for CVD mortality.

1-year increase in publication year. (RR 1.15, 95% CI 1.06 to 1.24; $p = 0.001$). This suggests that newer interventions might be correlated with a higher risk of CVD mortality. Other factors, including risk of bias, indirectness of evidence, the duration of the longest follow-up and loss to follow-up, did not demonstrate a significant impact on the risk of CVD mortality in this analysis.

Discussion

Main findings

This systematic review and network meta-analysis synthesised evidence from over 100 unique randomised trials to delineate optimal strategies for primary prevention of CVDs. We found high-certainty evidence that BP-lowering medications, intensive BP control, statins and multifactorial lifestyle interventions help prevent CVEs and mortality. Specifically, antihypertensive agents and aggressive BP targets reduced risk of all-cause and cardiovascular deaths, while also lowering rates of major atherosclerotic complications. Statins and composite lifestyle changes offered consistent benefits in reducing major CVE rates as well. Other modalities, including aspirin, glucose-lowering treatments, dietary modifications and vitamin supplementation, generally showed unclear impacts.

Our analysis provides a comprehensive ranking of preventive strategies, clarifying the highest yield

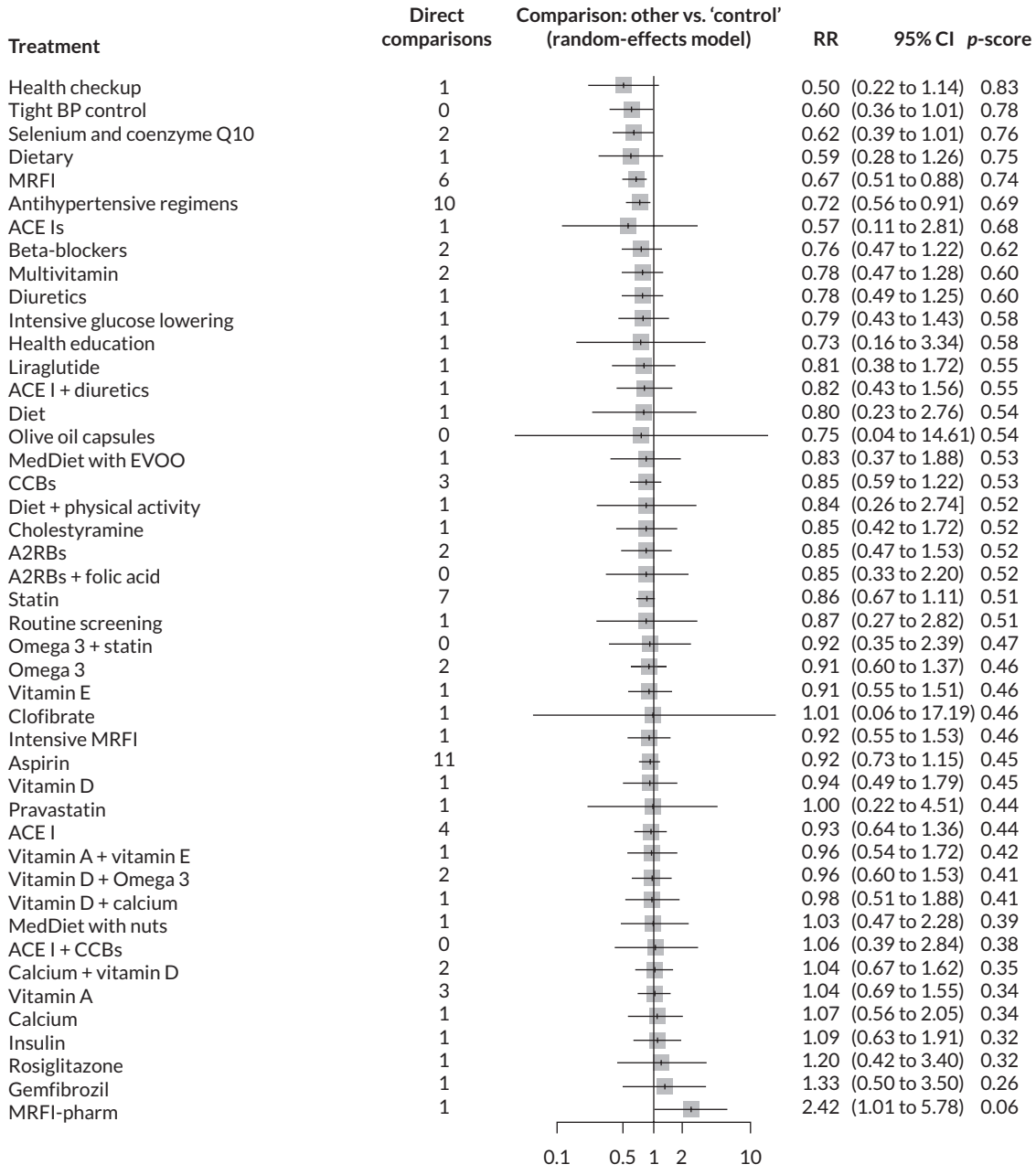

FIGURE 8 Forest plots for network meta-analysis for CVD mortality vs. control as reference group.

approaches. For ACM, tight BP control demonstrated the greatest likelihood of superiority, followed by BP regimens and MRFIs. Regarding major CVEs, BP- and lipid-lowering medications had the highest probability of maximal efficacy. ForCHD, intensive multifactorial lifestyle approaches appeared optimal. Lastly, for cardiovascular mortality, diverse antihypertensive agents and health education initiatives had the most favourable profiles.

In assessing comparative effectiveness between specific agents, we found little differentiation in impacts. However, there was a trend towards declining efficacy over calendar time for interventions targeting major events or mortality. Interestingly, increased proportions of female participants and longer maximum follow-up durations augmented observed prevention benefits across some outcomes. Ultimately, these findings provide a granular framework to inform clinical practice guidelines and population-level policies targeting CVDs amid the complexity of available options. Future research can clarify outstanding uncertainties around aspirin, nutritional supplements and emerging modalities.

The comparative effectiveness of different interventions for CVD prevention is likely influenced by the prevalence and severity of risk factors in the populations studied.

This research article should be referenced as follows:
Uthman OA, Court R, Enderby J, Nduka C, Al-Khudairy L, Anjorin S, *et al.* Identifying optimal primary prevention interventions for major cardiovascular disease events and all-cause mortality: a systematic review and hierarchical network meta-analysis of RCTs. *Health Technol Assess* 2025;**29**(37):75–140. https://doi.org/10.3310/RLDH7432

TABLE 7 Results of network meta-analyses for the class effect of different interventions for CVD mortality

	RR (95% CI)	*p*-value
Health promotion	**0.68 (0.53 to 0.87)**	**0.002**
BP lowering	**0.79 (0.66 to 0.94)**	**0.007**
Dietary	0.78 (0.48 to 1.26)	0.307
Nutritional supplement	0.87 (0.73 to 1.04)	0.120
Aspirin	0.89 (0.71 to 1.12)	0.326
Lipid lowering	0.88 (0.71 to 1.10)	0.269
Blood glucose lowering	0.95 (0.65 to 1.38)	0.776
Multicomponent	1.16 (0.69 to 1.96)	0.580

Note
Results are ordered by decreasing effectiveness. Statistically significant outcomes are highlighted in bold and underlined.

TABLE 8 Results of metaregression analyses for the study-level factors associated with the treatment effect estimates for CVD mortality

	RR (95% CI)	*p*-value
Risk of bias	0.42 (0.09 to 2.00)	0.276
Indirectness of evidence	0.88 (0.21 to 3.70)	0.859
Publication year	1.15 (1.06 to 1.24)	0.001
Longest follow-up	1.01 (0.99 to 1.04)	0.174
Loss to follow-up	1.01 (1.00 to 1.02)	0.162

Strategies targeting highly prevalent or poorly controlled risk factors, such as hypertension, diabetes or dyslipidaemia, may yield larger risk reductions compared to interventions directed at less-common exposures. This could partly explain the trend towards declining effect sizes over calendar time observed in our metaregression analyses. As population risk factor profiles have improved due to more widespread primary prevention efforts, the incremental benefits of additional interventions may be attenuated.[25,26] This highlights the importance of tailoring prevention strategies to the specific risk factor distributions and treatment gaps in a given population. Future studies should evaluate whether the relative ranking of interventions varies across populations with different risk factor burdens, and whether this can inform more personalised approaches to CVD prevention.

Comparison with other studies

Although broader in scope and scale, our findings align with several previous network meta-analyses and systematic reviews examining primary prevention strategies for CVD. Recent meta-analyses found significant reductions in MI, stroke, revascularisation and cardiovascular death with the use of statins, BP-lowering agents and combination therapy.[27–29] Concordant impacts were seen regardless of estimated baseline CVD risk. An earlier meta-analysis by Brunström and Carlberg reported lower risks of mortality and CHD events with intensive BP treatment among patients with diabetes.[30]

Our results similarly demonstrate lower all-cause and cause-specific CVD mortality along with protective composite effects from statins and antihypertensive medications for event prevention. A systematic review also described potent benefits from comprehensive diet and physical activity interventions in lowering cardiometabolic risk.[31] We extend this prior work through expansive evidence synthesis placing multiple modalities, including lifestyle approaches, on a common metric to enable head-to-head comparisons and probability-based rankings.

However, our findings differ from previous analyses regarding aspirin for primary prevention of CVD.[32,33] This likely reflects emerging data questioning the risk–benefit balance driving recent guideline revisions.[34] Prior umbrella reviews described beneficial effects from the use of omega-3 supplements[35] and folic acid[36] in contrast to null

associations seen here, potentially reflecting variance in assessed outcomes and underlying data sets over time.

Overall, this systematic review and network meta-analysis largely confirms conclusions from preceding syntheses but uniquely integrates all available randomised trial data into a single comparative framework to delineate optimal practices for combating CVD burden.

Study strengths and limitations

This systematic review and network meta-analysis carries several strengths bolstering the validity of its findings. An exhaustive literature search was undertaken, meeting key criteria for comprehensiveness by accessing multiple bibliographic databases, trial registries, conference abstracts and other sources. Reference list mining and machine learning supplementation further enhanced the retrieval yield. Inclusion criteria emphasised RCT data to prioritise methodologic rigor and internal validity. Quantitative network meta-analysis synthesis provides enhanced statistical power for comparative effectiveness assessments,[9,37] while inclusion of multiple outcomes captures both short- and long-term impacts. Formal risk-of-bias appraisals using validated instruments affirmed most included trials as having adequate safeguards against distorted outcomes.

The strengths of our study are multifaceted, primarily hinging on the comprehensive nature of our network meta-analysis, which allowed for the direct and indirect comparison of a wide array of interventions aimed at the primary prevention of CVD. The inclusiveness of the study design enabled the analysis of a large number of observations, providing robust statistical power. Additionally, the utilisation of a random-effects model accounts for variability between studies, offering a more generalised conclusion applicable to a broader patient population. Our study also benefits from the inclusion of a diverse range of interventions, from pharmacological to lifestyle modifications, reflecting the multifactorial approach needed in CVD prevention. The assessment of SUCRA values provides a hierarchy of treatment effectiveness, adding a layer of interpretative value for clinicians and policy-makers.[38]

However, our analysis is not without limitations. The high heterogeneity detected in the meta-analysis indicates variability in study design, populations and intervention types, which could affect the validity of the comparisons made. While the random-effects model mitigates this to some extent, the underlying causes of heterogeneity need to be explored further. Another limitation stems from the reliance on published data, which may be subject to publication bias. Studies with non-significant findings are less likely to be published, and this could skew the overall effect estimates. Additionally, the network meta-analysis approach, while robust, does depend on the assumption that underlying studies are sufficiently similar in terms of study populations and designs to be considered combinable.

Our systematic review did not examine differences in intervention effects by geographic region (Europe, North America, Asia) due to the limited and inconsistent reporting of setting in the included studies, as well as the small numbers of studies and participants from each region. Previous research has suggested that the relative effectiveness of CVD prevention strategies may vary across populations due to differences in risk factor distributions, healthcare systems and cultural factors.[39,40] For example, salt reduction interventions may have larger benefits in populations with higher baseline sodium intake, while tobacco control policies may be more impactful in regions with higher smoking rates. Future studies should investigate potential effect modification by geographic setting, as this could inform the tailoring of prevention guidelines to local contexts. Standardised reporting of the countries and populations studied would facilitate such analyses.

Another limitation of our systematic review is that the latest search date was over 3 years ago (March 2021). Given the dynamic nature of the CVD prevention evidence base, it is possible that more recent studies could modify our comparative effectiveness findings. Timely updating of systematic reviews is essential to ensure that guideline recommendations and policy decisions are based on the most current and comprehensive evidence.[41,42] Future updates of this review should incorporate newer studies and assess whether the relative rankings of interventions remain stable over time. In the rapidly evolving field of CVD prevention, living systematic reviews that are continuously updated as new evidence emerges may be particularly valuable for informing clinical practice and public health policies.[43] Nonetheless, we believe our results provide a solid foundation for understanding the relative benefits of key CVD prevention strategies over the past few decades.

Lastly, while we have identified statistically significant interventions, the clinical significance and the practical application of these findings require careful consideration. The translation of RRs into actual clinical practice must be done in the context of individual patient values, preferences and risk profiles.

Implications for practice

Our findings carry several implications to optimise cardiovascular prevention in clinical practice. First, the use of BP-lowering medications, intensive BP targets, statins when indicated and composite lifestyle interventions should be strongly encouraged given the benefits they confer in relation to mortality and event risk reduction.[44–46] Second, specific recommendations around utilising antihypertensives and achieving tighter BP control versus standard targets can help guide physician practices and patient counselling.[30,47,48] Third, while single behaviour change has modest effects, stressing multicomponent diet and activity improvements in tandem can maximise adherence and efficacy at the individual level.[49]

It is important to note that our systematic review primarily reflects the evidence on CVD prevention strategies that were available up to our search date of March 2021. Since then, there have been significant advancements in the development and evaluation of novel therapies, particularly glucagon-like peptide 1 (GLP-1) receptor agonists and cholesterol-lowering agents such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and inclisiran. For example, recent trials have demonstrated substantial reductions in CVEs with the use of GLP-1 receptor agonists such as semaglutide and liraglutide in patients with type 2 diabetes or established CVD.[50,51] Similarly, PCSK9 inhibitors and inclisiran have shown impressive lipid-lowering effects and improvements in cardiovascular outcomes in high-risk populations.[52,53] As these agents become more widely adopted in clinical practice, the comparative effectiveness landscape for CVD prevention may evolve. Future updates of this review will need to incorporate evidence on these emerging therapies to provide a more comprehensive and up-to-date assessment of the optimal prevention strategies.

Lastly, our work provides an evidentiary foundation for guidelines to make strong, graded recommendations comparing available modalities such as differing low-density lipoprotein targets for statins therapy versus the addition of non-statin agents.[54] These findings enable several best-practice takeaways to promote the adoption of lifestyle interventions alongside appropriate pharmacological regimens to mitigate atherosclerotic CVD burden at both individual patient and population-wide levels.[46]

Implications for research

Our findings suggest several implications to guide future research based on remaining uncertainties or need to expand the evidence base. Dedicated head-to-head trials comparing combinations of impactful interventions could determine optimal treatment sequences or stacking approaches. For example, factorial designs randomising participants to statins, antihypertensives and multimodal lifestyle interventions in parallel can delineate single versus multi-intervention efficacy. Second, the effect of emerging or higher dosing regimens for drugs warrants examination, given the declining temporal effectiveness trends we observed. Molecules like PCSK9 inhibitors, newer antihypertensives or high-intensity statins require comparative assessment. Third, the unclear impact of interventions like aspirin calls for revisiting with contemporary trial data and standardised outcomes. Effects may hinge on baseline CVD risk, highlighting the need for stratified analyses. Finally, head-to-head evaluation of single behavioural change techniques versus composite lifestyle programmes can optimise health promotion efficiency by determining essential components. Revisiting nutritional supplements can also help clarify their adjunctive role if any.

Patient and public involvement

Drawing on INVOLVE guidance and support for best practice, we worked closely with three dedicated patient and public involvement advisors, and we welcomed guidance and support from our advisors at the preparatory phase of the project.

Conclusion

Our systematic review and network meta-analysis provides a comprehensive and up-to-date synthesis of the comparative effectiveness of different strategies for the primary prevention of CVD. While we found strong evidence supporting the use of BP-lowering medications, intensive BP control, statins and multifactorial lifestyle interventions, the optimal combination and sequencing of these approaches remain uncertain. Moreover, the rapidly evolving landscape of CVD prevention therapies, including the emergence of GLP-1 receptor agonists, PCSK9 inhibitors and other novel agents, may soon reshape the relative effectiveness and cost-effectiveness of different prevention strategies. As the evidence base continues to grow and evolve, it will be crucial for researchers, clinicians and policy-makers to engage in an ongoing dialogue to translate the latest findings into actionable recommendations for patient care and population health. This will require not only rigorous and timely synthesis of the available evidence but also critical appraisal of the limitations and uncertainties in the data, as well as consideration of the broader social, economic and ethical implications of different prevention approaches. Ultimately, the goal should be to develop personalised, evidence-based prevention strategies that are tailored to

the unique needs and preferences of individual patients and communities, while also promoting health equity and maximising the impact of limited healthcare resources.

Additional information

CRediT contribution statement

Olalekan A Uthman (https://orcid.org/0000-0002-8567-3081): Conceptualisation (lead), Data curation (lead), Formal analysis (lead), Investigation (equal), Methodology (equal), Project administration (lead), Supervision (lead), Validation (equal), Visualisation (lead), Writing – original draft (equal), Writing – review and editing (equal).

Rachel Court (https://orcid.org/0000-0002-4567-2586): Conceptualisation (supporting), Data curation (equal), Investigation (supporting), Methodology (supporting), Project administration (supporting), Resources (lead), Writing – original draft (supporting), Writing – review and editing (supporting).

Jodie Enderby (https://orcid.org/0000-0002-1446-7512): Conceptualisation (supporting), Data curation (equal), Investigation (equal), Methodology (supporting), Validation (equal), Writing – original draft (supporting), Writing – review and editing (supporting).

Chidozie Nduka (https://orcid.org/0000-0001-7031-5444): Conceptualisation (supporting), Data curation (equal), Investigation (equal), Methodology (supporting), Validation (equal), Writing – original draft (supporting), Writing – review and editing (supporting)

Lena Al-Khudairy (https://orcid.org/0000-0003-0638-583X): Conceptualisation (supporting), Data curation (equal), Investigation (equal), Methodology (supporting), Validation (equal), Writing – original draft (supporting), Writing – review and editing (supporting).

Seun Anjorin (https://orcid.org/0000-0003-0187-6410): Conceptualisation (supporting), Data curation (equal), Investigation (equal), Methodology (supporting), Validation (equal), Writing – original draft (supporting), Writing – review and editing (supporting).

Hema Mistry (https://orcid.org/0000-0002-5023-1160): Conceptualisation (supporting), Data curation (equal), Investigation (equal), Methodology (supporting), Validation (equal), Writing – original draft (supporting), Writing – review and editing (supporting).

G J Melendez-Torres (https://orcid.org/0000-0002-9823-4790): Conceptualisation (supporting), Data curation (equal), Investigation (equal), Methodology (supporting), Validation (equal), Writing – original draft (supporting), Writing – review and editing (supporting).

Sian Taylor-Phillips (https://orcid.org/0000-0002-1841-4346): Conceptualisation (supporting), Data curation (equal), Investigation (equal), Methodology (supporting), Validation (equal), Writing – original draft (supporting), Writing – review and editing (supporting).

Aileen Clarke (https://orcid.org/0000-0001-8299-3146): Conceptualisation (equal), Funding acquisition (lead), Investigation (supporting), Methodology (lead), Project administration (supporting), Supervision (supporting), Validation (supporting), Writing – original draft (supporting), Writing – review and editing (equal).

Data-sharing statement

No new data have been created in the preparation of this article and therefore there is nothing available for access and further sharing. All queries should be submitted to the corresponding author.

Ethics statement

This work is a systematic review of accessing, processing and analysing data that has already been published and is available to the public. As a result, no patient data were processed, and patient consent and/or registration via human research ethics committees were, therefore, not relevant.

Information governance statement

University of Warwick is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, University of Warwick is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here (https://warwick.ac.uk/services/legalandcomplianceservices/dataprotection/).

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/RLDH7432.

Primary conflicts of interest: Sian Taylor-Philips was supported by a Career Development Fellowship [reference number NIHR-CDF-2016-09-018]. Aileen Clarke and Lena Al-Khudiary were supported by the National Institute for Health and Care Research (NIHR) Applied Research Collaboration (ARC) West Midlands [grant number NIHR200165].

Department of Health and Social Care disclaimer

This publication presents independent research commissioned by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, NIHR Coordinating Centre, the Health Technology Assessment programme or the Department of Health and Social Care.

This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Study registration

This study is registered as PROSPERO CRD42019123940.

Funding

This article presents independent research funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme as award number 17/148/05.

This article reports on one component of the research award Determining optimal strategies for primary prevention of cardiovascular disease: systematic review, network meta-analysis and cost-effectiveness review. For more information about this research please view the award page (https://fundingawards.nihr.ac.uk/award/17/148/05).

About this article

The contractual start date for this research was in February 2019. This article began editorial review in March 2024 and was accepted for publication in November 2024. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The Health Technology Assessment editors and publisher have tried to ensure the accuracy of the authors' article and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

List of abbreviations

ACM	all-cause mortality
BP	blood pressure
CCB	calcium channel blocker
CHD	coronary heart disease
CVD	cardiovascular disease
CVE	cardiovascular event
GLP-1	glucagon-like peptide 1
MI	myocardial infarction
MRFI	multiple risk factor intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
RCT	randomised controlled trial
RR	risk ratio
SUCRA	surface under the cumulative ranking

References

1. Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors: 2020 and beyond. *J Am Coll Cardiol* 2019;**74**:2529–32. https://doi.org/10.1016/j.jacc.2019.10.009
2. Joseph P, Leong D, McKee M, Anand SS, Schwalm JD, Teo K, *et al*. Reducing the global burden of cardiovascular disease, part 1: the epidemiology and risk factors. *Circ Res* 2017;**121**:677–94. https://doi.org/10.1161/CIRCRESAHA.117.308903
3. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, *et al*. ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–81. https://doi.org/10.1093/eurheartj/ehw106
4. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, *et al*. Executive summary: heart disease and stroke statistics – 2016 update: a report from the American Heart Association. *Circulation* 2016;**133**:447–54. https://doi.org/10.1161/CIR.0000000000000366

5. Gellert C, Schöttker B, Brenner H. Smoking and all-cause mortality in older people: systematic review and meta-analysis. *Arch Intern Med* 2012;**172**:837–44. https://doi.org/10.1001/archinternmed.2012.1397

6. Turnbull F, Neal B, Ninomiya T, Algert C, Arima H, Barzi F, *et al*. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *Br Med J* 2008;**336**:1121–3. https://doi.org/10.1136/bmj.39548.738368.BE

7. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, *et al*. PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med* 2018;**378**:e34. https://doi.org/10.1056/NEJMoa1800389

8. Taylor F, Ward K, Moore TH, Burke M, Davey Smith G, Casas JP, *et al*. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2011;**1**:CD004816. https://doi.org/10.1002/14651858.CD004816.pub4

9. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *Br Med J* 2005;**331**:897–900. https://doi.org/10.1136/bmj.331.7521.897

10. Uthman OA, Al-Khudairy L, Nduka CU, Court R, Mistry H, Melendez-Torres GJ, *et al*. Determining optimal strategies for primary prevention of cardiovascular disease: systematic review, cost-effectiveness review and network meta-analysis protocol. *Syst Rev* 2020;**9**:105. https://doi.org/10.1186/s13643-020-01366-x

11. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al*.; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *Br Med J* 2015;**350**:g7647. https://doi.org/10.1136/bmj.g7647

12. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;**162**:777–84. https://doi.org/10.7326/M14-2385

13. Robinson KA, Chou R, Berkman ND, Newberry SJ, Fu R, Hartling L, *et al*. Twelve recommendations for integrating existing systematic reviews into new reviews: EPC guidance. *J Clin Epidemiol* 2016;**70**:38–44. https://doi.org/10.1016/j.jclinepi.2015.05.035

14. Robinson KA, Whitlock EP, Oneil ME, Anderson JK, Hartling L, Dryden DM, *et al*. Integration of existing systematic reviews into new reviews: identification of guidance needs. *Syst Rev* 2014;**3**:60. https://doi.org/10.1186/2046-4053-3-60

15. Claude Moore Health Science Library. *How do I import references into Zotero, EndNote, or other citation management program from the Web, PDF, or a Word document?* 2023. URL: https://guides.hsl.virginia.edu/faq-import-pdf-citations (accessed 8 December 2023).

16. *Citation Finder*. 2023. URL: https://citation-finder.vercel.app/ (accessed 8 December 2023).

17. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Br Med J* 2017;**358**:j4008. https://doi.org/10.1136/bmj.j4008

18. Uthman OA, Court R, Enderby J, Al-Khudairy L, Nduka C, Mistry H, *et al*. Increasing comprehensiveness and reducing workload in a systematic review of complex interventions using automated machine learning. *Health Technol Assess* 2022. https://doi.org/10.3310/UDIR6682

19. Higgins JPT, Deeks JJ, Altman DG. Special Topics in Statistics. In *Cochrane Handbook for Systematic Reviews of Interventions*. Wiley; 2008. pp. 481–529. https://doi.org/10.1002/9780470712184.ch16

20. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, *et al*.; Cochrane Bias Methods Group. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *Br Med J* 2011;**343**:d5928. https://doi.org/10.1136/bmj.d5928

21. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;**23**:3105–24. https://doi.org/10.1002/sim.1875

22. Owen RK, Tincello DG, Keith RA. Network meta-analysis: development of a three-level hierarchical modeling approach incorporating dose-related constraints. *Value Health* 2015;**18**:116–26. https://doi.org/10.1016/j.jval.2014.10.006

23. Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol* 2015;**15**:58. https://doi.org/10.1186/s12874-015-0060-8

24. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity – subgroups, meta-regression, bias, and bias-adjustment. *Med Decis Making* 2013;**33**:618–40. https://doi.org/10.1177/0272989X13485157

25. Ezzati M, Obermeyer Z, Tzoulaki I, Mayosi BM, Elliott P, Leon DA. Contributions of risk factors and medical care to cardiovascular mortality trends. *Nat Rev*

Cardiol 2015;**12**:508–30. https://doi.org/10.1038/nrcardio.2015.82

26. Yusuf S, Joseph P, Rangarajan S, Islam S, Mente A, Hystad P, *et al*. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet* 2020;**395**:795–808. https://doi.org/10.1016/S0140-6736(19)32008-2
27. Mills EJ, Wu P, Chong G, Ghement I, Singh S, Akl EA, *et al*. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. *QJM* 2011;**104**:109–24. https://doi.org/10.1093/qjmed/hcq165
28. Wang N, Woodward M, Huffman MD, Rodgers A. Compounding benefits of cholesterol-lowering therapy for the reduction of major cardiovascular events: systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2022;**15**:e008552. https://doi.org/10.1161/circoutcomes.121.008552
29. Wei J, Galaviz KI, Kowalski AJ, Magee MJ, Haw JS, Narayan KMV, Ali MK. Comparison of cardiovascular events among users of different classes of antihypertension medications: a systematic review and network meta-analysis. *JAMA Netw Open* 2020;**3**:e1921618. https://doi.org/10.1001/jamanetworkopen.2019.21618
30. Brunstrom M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *Br Med J* 2016;**352**:i717. https://doi.org/10.1136/bmj.i717
31. Ebrahim S, Taylor F, Ward K, Beswick A, Burke M, Davey Smith G. Multiple risk factor interventions for primary prevention of coronary heart disease. *Cochrane Database Syst Rev* 2011;**1**:CD001561. https://doi.org/10.1002/14651858.CD001561.pub3
32. Mahmoud AN, Gad MM, Elgendy AY, Elgendy IY, Bavry AA. Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials. *Eur Heart J* 2019;**40**:607–17. https://doi.org/10.1093/eurheartj/ehy813
33. Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. *JAMA* 2019;**321**:277–87. https://doi.org/10.1001/jama.2018.20578
34. Sutcliffe P, Connock M, Gurung T, Freeman K, Johnson S, Ngianga-Bakwin K, *et al*. Aspirin in primary prevention of cardiovascular disease and cancer: a systematic review of the balance of evidence from reviews of randomized trials. *PLOS ONE* 2013;**8**:e81970. https://doi.org/10.1371/journal.pone.0081970
35. Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, *et al*. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2020;**3**:CD003177. https://doi.org/10.1002/14651858.CD003177.pub5
36. Clarke R, Halsey J, Lewington S, Lonn E, Armitage J, Manson JE, *et al*.; B-Vitamin Treatment Trialists' Collaboration. Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: meta-analysis of 8 randomized trials involving 37 485 individuals. *Arch Intern Med* 2010;**170**:1622–31. https://doi.org/10.1001/archinternmed.2010.348
37. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. *Br Med J* 2013;**346**:f2914. https://doi.org/10.1136/bmj.f2914
38. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;**64**:163–71. https://doi.org/10.1016/j.jclinepi.2010.03.016
39. Basu S, Yudkin JS, Sussman JB, Millett C, Hayward RA. Alternative strategies to achieve cardiovascular mortality goals in China and India: a microsimulation of target- versus risk-based blood pressure treatment. *Circulation* 2016;**133**:840–8. https://doi.org/10.1161/CIRCULATIONAHA.115.019985
40. Singh GM, Danaei G, Farzadfar F, Stevens GA, Woodward M, Wormser D, *et al*.; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group; Asia-Pacific Cohort Studies Collaboration (APCSC). The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. *PLOS ONE* 2013;**8**:e65174. https://doi.org/10.1371/journal.pone.0065174
41. Garner P, Hopewell S, Chandler J, MacLehose H, Schunemann HJ, Akl EA, *et al*.; Panel for Updating Guidance for systematic reviews (PUGs). When and how to update systematic reviews: consensus and checklist. *Br Med J* 2016;**354**:i3507. https://doi.org/10.1136/bmj.i3507
42. Martinez Garcia L, Pardo-Hernandez H, Superchi C, Nino de Guzman E, Ballesteros M, Ibargoyen Roteta N, *et al*. Methodological systematic review identifies major limitations in prioritization processes for updating. *J Clin Epidemiol* 2017;**86**:11–24. https://doi.org/10.1016/j.jclinepi.2017.05.008
43. Elliott JH, Synnot A, Turner T, Simmonds M, Akl EA, McDonald S, *et al*.; Living Systematic Review Network. Living systematic review: 1. Introduction-the why,

what, when, and how. *J Clin Epidemiol* 2017;**91**:23–30. https://doi.org/10.1016/j.jclinepi.2017.08.010

44. Allen NB, Siddique J, Wilkins JT, Shay C, Lewis CE, Goff DC, *et al*. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. *JAMA* 2014;**311**:490–7. https://doi.org/10.1001/jama.2013.285122
45. Cohen JB, Lotito MJ, Trivedi UK, Denker MG, Cohen DL, Townsend RR. Cardiovascular events and mortality in white coat hypertension: a systematic review and meta-analysis. *Ann Intern Med* 2019;**170**:853–62. https://doi.org/10.7326/M19-0223
46. Webster R, Castellano JM, Onuma OK. Putting polypills into practice: challenges and lessons learned. *Lancet* 2017;**389**:1066–74. https://doi.org/10.1016/S0140-6736(17)30558-5
47. Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, *et al*. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. *JAMA Cardiol* 2017;**2**:775–81. https://doi.org/10.1001/jamacardio.2017.1421
48. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, *et al*. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;**387**:957–67. https://doi.org/10.1016/S0140-6736(15)01225-8
49. Micha R, Penalvo JL, Cudhea F, Imamura F, Rehm CD, Mozaffarian D. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. *JAMA* 2017; **317**:912–24. https://doi.org/10.1001/jama.2017.0947.
50. Dagenais GR, Ryden L, Leiter LA, Lakshmanan M, Dyal L, Probstfield JL, *et al*. Total cardiovascular or fatal events in people with type 2 diabetes and cardiovascular risk factors treated with dulaglutide in the REWIND trail: a post hoc analysis. *Cardiovasc Diabetol* 2020;**19**:199. https://doi.org/10.1186/s12933-020-01179-1
51. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, *et al*.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;**375**:1834–44. https://doi.org/10.1056/NEJMoa1607141
52. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, *et al*.; ORION-10 and ORION-11 Investigators. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med* 2020;**382**:1507–19. https://doi.org/10.1056/NEJMoa1912387
53. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, *et al*.; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;**376**:1713–22. https://doi.org/10.1056/NEJMoa1615664
54. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, *et al*. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA* 2016;**316**:1289–97. https://doi.org/10.1001/jama.2016.13985

Appendix 1 Health technologies (interventions)

Pharmacologic interventions			
Lipid-lowering medications	BP-lowering medications	Nutritional supplements	Others
Atorvastatin Fluvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Fenofibrate Bezafibrate Ezetimibe	Angiotensin-converting enzyme inhibitors (ACE Is) Angiotensin receptor blockers Calcium channel blockers Thiazide diuretics Adrenergic receptor antagonists (alpha and beta blockers) Vasodilators Renin inhibitors	Vitamin D, E, K and multivitamins; niacin Omega-3 and fatty acids Antioxidants Calcium Coenzyme Q10 Selenium Folic acid Garlic	Fixed dose combinations 'Polypill' Antiplatelet agent (aspirin)
Lifestyle-modification interventions			
Dietary interventions	Health promotion	Exercise/physical activity in general	

Mediterranean diet (MedDiet)	Smoking cessation	Endurance (or aerobic) exercise
Fibres	Weight reduction	Strengthening exercise
Nut consumption	Reduction in alcohol intake	Balance
Chocolate	MRFI	Tai-chi
Fruits and vegetables	Digital health promotion	Flexibility
Green and black tea		Yoga
Reduced salt intake		Aquatic
Reduced fat intake		Qigong
		Transcendental meditation
		Combined exercise
Structural and policy-based interventions (population-wide interventions)		
Taxation and subsidies		
Mass media campaigns		
Food and menu labelling		
Local food environment		
Worksite wellness programmes		
Marketing restrictions		
Quality standards		
Healthy local environment		
Addressing air pollution		

Appendix 2 Searches for randomised controlled trials

CENTRAL (Wiley)

Date run: 12 June 2019
Search name: CVD primary prevention RCTs 2013–2019
Date run: 12 June 2019 23 : 47 : 13
Comment: 12 June 2019
Eighty-three per cent sensitive in picking up known RCTs from a group of 36 RCTs.

ID	Search	Hits
#1	MeSH descriptor: [Primary Prevention] explode all trees	3852
#2	"primary prevention":ti,ab,kw	3970
#3	#1 or #2	7009
#4	MeSH descriptor: [Cardiovascular Diseases] explode all trees	96852
#5	MeSH descriptor: [Stroke] explode all trees	8236
#6	(CVD or cardiovascular* or coronary* or heart* or myocardial* or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or "blood pressure" or cholesterol or lipid*):ti,ab,kw	337471
#7	#4 or #5 or #6	352773
#8	#3 and #7	2498
#9	[mh ^"cardiovascular diseases"/PC]	3054
#10	[mh "coronary disease"/PC]	2001
#11	[mh "myocardial ischemia"/PC]	3891
#12	[mh "heart failure"/PC]	364
#13	[mh "heart arrest"/PC]	354
#14	[mh "stroke"/PC]	1222
#15	[mh "carotid stenosis"/PC]	19
#16	[mh "arteriosclerosis"/PC]	790
#17	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	8697
#18	((prevent* or reduc* or lower* or decreas* or change* or effect or effects or progression or level* or incidence) near/10 (CVD or cardiovascular* or coronary* or heart* or myocardial or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or "blood pressure" or cholesterol or lipid*)):ti in Trials	47340
#19	#8 or #17 or #18 with Publication Year from 2013 to 2019, in Trials	18393

Broader searches for RCTs for text mining using classifier/algorithm.
CENTRAL (Wiley)
Date run: 18 June 2019 (note: see below for update search)
Search name: CVD primary prevention RCTs broader search
Date run: 18 June 2019 12 : 16 : 05
Comment: 18 June 2019
94% sensitive in picking up known RCTs from a group of 36 RCTs.

ID	Search	Hits
#1	MeSH descriptor: [Primary Prevention] explode all trees	3852
#2	"primary prevention":ti,ab,kw	3970
#3	#1 or #2	7009
#4	MeSH descriptor: [Cardiovascular Diseases] explode all trees	96852
#5	MeSH descriptor: [Stroke] explode all trees	8236

#6 (CVD or cardiovascular* or coronary* or heart* or myocardial* or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or "blood pressure" or cholesterol or lipid*):ti,ab,kw 337473
#7 #4 or #5 or #6 352775
#8 #3 and #7 2498
#9 [mh ^"cardiovascular diseases"/PC] 3054
#10 [mh "coronary disease"/PC] 2001
#11 [mh "myocardial ischemia"/PC] 3891
#12 [mh "heart failure"/PC] 364
#13 [mh "heart arrest"/PC] 354
#14 [mh "stroke"/PC] 1222
#15 [mh "carotid stenosis"/PC] 19
#16 [mh "arteriosclerosis"/PC] 790
#17 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 8697
#18 ((prevent* or reduc* or lower* or decreas* or change* or effect or effects or progression or level* or incidence) near/10 (CVD or cardiovascular* or coronary* or heart* or myocardial or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or "blood pressure" or cholesterol or lipid*)):ti 47620
#19 ((prevent* or reduc* or lower* or decreas* or change* or effect or effects) near/6 (CVD or cardiovascular* or coronary* or heart* or myocardial or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or "blood pressure" or cholesterol or lipid*)):ti,ab,kw 144639
#20 #8 or #17 or #18 or #19 153770
#21 (((prevent* or reduc* or lower* or decreas* or change* or effect or effects) near/2 (mortality or death)) and (CVD or cardiovascular* or coronary* or heart* or myocardial or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or "blood pressure" or cholesterol or lipid*)):ti,ab,kw 8573
#22 #8 or #17 or #18 or #19 or #21 156277

155,077 Trials
After removing duplicates with the more precise CENTRAL search above dated 12 June 2019
136,684 Trials
After removing easily identifiable duplicates (i.e. matching on at least all these fields: author, year, title, journal, pages) using EndNote:
133,261

Update 30 June 2020

Re-ran above search with the following limit:
with Cochrane Library publication date from June 2019 to June 2020, in Trials 13790

Update 5 March 2021

Re-ran above search with the following limit:
with Cochrane Library publication date from June 2020 to March 2021, in Trials 7137

MEDLINE (Ovid)

Date run: 1 July 2020
Actual database: Ovid MEDLINE(R) ALL < 1946 to 30 June 2020 >
Search strategy:

1 exp Primary Prevention/ (151270)
2 primary prevention.ti,ab,kf. (19284)
3 1 or 2 (165832)
4 exp Cardiovascular Diseases/ (2376132)
5 exp Stroke/ (133892)
6 (CVD or cardiovascular* or coronary* or heart* or myocardial* or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or blood pressure or cholesterol or lipid*).ti,ab,kf. (3244970)
7 4 or 5 or 6 (4212409)
8 3 and 7 (18225)
9 cardiovascular diseases/pc (33590)
10 exp coronary disease/pc (20312)
11 exp myocardial ischemia/pc (38267)
12 exp heart failure/pc (4036)
13 exp heart arrest/pc (7270)
14 exp stroke/pc (17025)
15 exp carotid stenosis/pc (292)
16 exp arteriosclerosis/pc (12424)
17 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (103644)
18 ((prevent* or reduc* or lower* or decreas* or change* or effect or effects or progression or level* or incidence) adj10 (CVD or cardiovascular* or coronary* or heart* or myocardial or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or blood pressure or cholesterol or lipid*)).ti. (236471)
19 ((prevent* or reduc* or lower* or decreas* or change* or effect or effects) adj6 (CVD or cardiovascular* or coronary* or heart* or myocardial or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or blood pressure or cholesterol or lipid*)).ti,ab,kf. (686390)
20 8 or 17 or 18 or 19 (803660)
21 (((prevent* or reduc* or lower* or decreas* or change* or effect or effects) adj2 (mortality or death)) and (CVD or cardiovascular* or coronary* or heart* or myocardial or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis

or vascular or hypertension or blood pressure or cholesterol or lipid*)).ti,ab,kf. (30238)
22 8 or 17 or 18 or 19 or 21 (818238)
23 randomized controlled trial.pt. (508643)
24 controlled clinical trial.pt. (93738)
25 randomized.ab. (484617)
26 placebo.ab. (209038)
27 clinical trials as topic.sh. (191820)
28 randomly.ab. (336266)
29 trial.ti. (221004)
30 23 or 24 or 25 or 26 or 27 or 28 or 29 (1297998)
31 exp animals/ not humans.sh. (4712329)
32 30 not 31 (1194663)
33 randomized controlled trial.pt. (508643)
34 (random* or "controlled trial*" or "clinical trial*" or rct).tw. (1401692)
35 33 or 34 (1516177)
36 22 and 32 (107926)
37 22 and 35 (123029)
38 36 or 37 (141385)
39 limit 38 to ed=20200601-20200701 (553)
40 limit 38 to ep=20200601-20200701 (407)
41 limit 38 to dt=20200601-20200701 (597)
42 limit 38 to ez=20200601-20200701 (323)
43 39 or 40 or 41 or 42 (1145)

Update 5 March 2021
Re-ran above search to line 38 with the following limits:
39 limit 38 to ed=20210205-20210305 (443)
40 limit 38 to ep=20210205-20210305 (410)
41 limit 38 to dt=20210205-20210305 (633)
42 limit 38 to ez=20210205-20210305 (654)
43 39 or 40 or 41 or 42 (1076)

EMBASE (Ovid)
Date run: 1 July 2020
Actual database: Database: EMBASE Classic + EMBASE < 1947 to 2020 Week 26 >
Search strategy:

1 primary prevention/ (40760)
2 primary prevention.ti,ab,kw. (29436)
3 1 or 2 (54373)
4 exp cardiovascular disease/ or exp cerebrovascular accident/ (4433393)
5 (CVD or cardiovascular* or coronary* or heart* or myocardial* or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or blood pressure or cholesterol or lipid*).ti,ab,kw. (4618261)
6 4 or 5 (6380746)
7 3 and 6 (27948)
8 *cardiovascular disease/pc or exp *coronary artery disease/pc or exp *heart infarction/pc or *heart failure/pc or exp *heart arrest/pc or exp *cerebrovascular accident/pc (38541)
9 ((prevent* or reduc* or lower* or decreas* or change* or effect or effects or progression or level* or incidence) adj10 (CVD or cardiovascular* or coronary* or heart* or myocardial or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or blood pressure or cholesterol or lipid*)).ti. (328083)
10 ((prevent* or reduc* or lower* or decreas* or change* or effect or effects) adj6 (CVD or cardiovascular* or coronary* or heart* or myocardial or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or blood pressure or cholesterol or lipid*)).ti,ab,kw. (991791)
11 (((prevent* or reduc* or lower* or decreas* or change* or effect or effects) adj2 (mortality or death)) and (CVD or cardiovascular* or coronary* or heart* or myocardial or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or blood pressure or cholesterol or lipid*)).ti,ab,kw. (48234)
12 7 or 8 or 9 or 10 or 11 (1127654)
13 Randomized controlled trial/ (610620)
14 Controlled clinical study/ (464568)
15 Random$.ti,ab. (1556851)
16 randomization/ (87319)
17 intermethod comparison/ (260984)
18 placebo.ti,ab. (312159)
19 (compare or compared or comparison).ti. (541898)
20 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2130059)
21 (open adj label).ti,ab. (79644)
22 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (238343)
23 double blind procedure/ (176066)
24 parallel group$1.ti,ab. (25643)
25 (crossover or cross over).ti,ab. (106698)
26 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. (333286)
27 (assigned or allocated).ti,ab. (392258)
28 (controlled adj7 (study or design or trial)).ti,ab. (353682)
29 (volunteer or volunteers).ti,ab. (253335)
30 human experiment/ (501114)
31 trial.ti. (309867)
32 or/14-31 (5089916)
33 32 not 13 (4498705)

34 (random$ adj sampl$ adj7 (“cross section$” or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (8192)
35 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) (237974)
36 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. (17287)
37 (Systematic review not (trial or study)).ti. (144929)
38 (nonrandom$ not random$).ti,ab. (16284)
39 “Random field$”.ti,ab. (2315)
40 (random cluster adj3 sampl$).ti,ab. (1278)
41 (review.ab. and review.pt.) not trial.ti. (804056)
42 “we searched”.ab. and (review.ti. or review.pt.) (32092)
43 “update review”.ab. (104)
44 (databases adj4 searched).ab. (35925)
45 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1065352)
46 Animal experiment/ not (human experiment/ or human/) (2251713)
47 or/34-46 (3481297)
48 33 not 47 (3963172)
49 12 and 48 (205633)
50 limit 49 to dd=20200501-20200701 (1055)
51 limit 49 to em=202005-202007 (732)
52 limit 49 to dc=20200501-20200701 (2099)
53 50 or 51 or 52 (2831)

Update 5 March 2021

Re-ran above search to line 49 with the following limits:
50 limit 49 to dd=20210105-20210305 (1490)
51 limit 49 to em=202101-202103 (1181)
52 limit 49 to dc=20210105-20210305 (2676)
53 50 or 51 or 52 (3212)

Searches for structural and policy randomised controlled trials and other controlled trials

CENTRAL (Wiley)

Search name: Structural and policy interventions with CVD primary prevention broader search
Last saved: 18 March 2021 17 : 19 : 27
Comment: 18 March 2021

ID Search
#1 MeSH descriptor: [Primary Prevention] explode all trees
#2 “primary prevention”:ti,ab,kw
#3 #1 or #2
#4 MeSH descriptor: [Cardiovascular Diseases] explode all trees
#5 MeSH descriptor: [Stroke] explode all trees
#6 (CVD or cardiovascular* or coronary* or heart* or myocardial* or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or “blood pressure” or cholesterol or lipid*):ti,ab,kw
#7 #4 or #5 or #6
#8 #3 and #7
#9 [mh ^“cardiovascular diseases”/PC]
#10 [mh “coronary disease”/PC]
#11 [mh “myocardial ischemia”/PC]
#12 [mh “heart failure”/PC]
#13 [mh “heart arrest”/PC]
#14 [mh “stroke”/PC]
#15 [mh “carotid stenosis”/PC]
#16 [mh “arteriosclerosis”/PC]
#17 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 ((prevent* or reduc* or lower* or decreas* or change* or effect or effects or progression or level* or incidence) near/10 (CVD or cardiovascular* or coronary* or heart* or myocardial or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or “blood pressure” or cholesterol or lipid*)):ti
#19 ((prevent* or reduc* or lower* or decreas* or change* or effect or effects) near/6 (CVD or cardiovascular* or coronary* or heart* or myocardial or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or “blood pressure” or cholesterol or lipid*)):ti,ab,kw
#20 #8 or #17 or #18 or #19
#21 (((prevent* or reduc* or lower* or decreas* or change* or effect or effects) near/2 (mortality or death)) and (CVD or cardiovascular* or coronary* or heart* or myocardial or cardiac* or stroke* or cerebrovascular or atherosclerosis or arteriosclerosis or vascular or hypertension or “blood pressure” or cholesterol or lipid*)):ti,ab,kw
#22 #8 or #17 or #18 or #19 or #21
#23 (food NEXT secur*):ti,ab,kw
#24 (food NEXT insecur*):ti,ab,kw
#25 “food poverty”:ti,ab,kw
#26 (food NEXT sufficien*):ti,ab,kw
#27 (food NEXT insufficien*):ti,ab,kw
#28 (food NEXT desert*):ti,ab,kw
#29 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR restaurant* OR (fast NEXT food*) OR (take NEXT away*)) NEAR/3 environment*):ti,ab,kw

#30 ((food OR garden* OR cook*) NEAR/3 skill*):ti,ab,kw
#31 (food NEAR/5 (prepar* OR budget* OR shop* OR purchas* OR buy* OR acquisition OR acquir*) NEAR/5 skill*):ti,ab,kw
#32 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR supermarket* OR (grocery NEXT store*) OR (food NEXT store*) OR (food NEXT shop*) OR (corner NEXT store*) OR cafeteria* OR canteen* OR (food NEXT outlet*) OR restaurant* OR (fast NEXT food*) OR (take NEXT away*)) NEAR/3 access*):ti,ab,kw
#33 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR supermarket* OR (grocery NEXT store*) OR (food NEXT store*) OR (food NEXT shop*) OR (corner NEXT store*) OR cafeteria* OR canteen* OR (food NEXT outlet*) OR restaurant* OR (fast NEXT food*) OR (take NEXT away*)) NEAR/3 access*):ti,ab,kw
#34 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR supermarket* OR (grocery NEXT store*) OR (food NEXT store*) OR (food NEXT shop*) OR (corner NEXT store*) OR cafeteria* OR canteen* OR (food NEXT outlet*) OR restaurant* OR (fast NEXT food*) OR (take NEXT away*)) NEAR/3 availab*):ti,ab,kw
#35 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR supermarket* OR (grocery NEXT store*) OR (food NEXT store*) OR (food NEXT shop*) OR (corner NEXT store*) OR cafeteria* OR canteen* OR (food NEXT outlet*) OR restaurant* OR (fast NEXT food*) OR (take NEXT away*)) NEAR/3 cost*):ti,ab,kw
#36 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR supermarket* OR (grocery NEXT store*) OR (food NEXT store*) OR (food NEXT shop*) OR (corner NEXT store*) OR cafeteria* OR canteen* OR (food NEXT outlet*) OR bodega* OR tienda*) NEAR/3 pric*):ti,ab,kw
#37 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR diet OR dietary) NEAR/3 variet*):ti,ab,kw
#38 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer*) NEAR/4 (supply OR supplies)):ti,ab,kw
#39 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer*) NEAR/3 (purchas* OR expenditure* OR spend* OR spent)):ti,ab,kw
#40 ((food* OR fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR supermarket* OR cafeteria OR (corner NEXT store*) OR canteen* OR meal*) NEAR/5 sale*):ti,ab,kw
#41 (food* NEAR/3 (environment* OR access* OR cost* OR availab* OR pric* OR variet* OR supply* OR supplies OR purchas* OR expenditure* OR spend OR spent OR spending) NEAR/5 (fresh OR health* OR unhealthy* OR junk* OR nutriti* OR adequate OR quality OR sufficient OR insufficient OR secure OR insecure* OR safe)):ti,ab
#42 (food* NEXT (environment* OR access* OR cost* OR availab* OR pric* OR expenditure* OR spending*)):ti,ab
#43 ((food NEXT system*) AND (fresh OR health* OR unhealthy* OR junk* OR nutriti* OR adequate OR quality OR sufficient OR insufficient OR secure OR insecure* OR safe)):ti,ab,kw
#44 ((policy OR policies) NEAR/3 (food* OR fruit* OR vegetable* OR fat* OR salt* OR sugar* OR nutritio* OR grocer* OR meal*)):ti,ab,kw
#45 ((council* OR coalition* OR co-op* OR co-operative*) NEAR/3 (food* OR fruit* OR vegetable* OR nutritio* OR fat* OR salt* OR sugar* OR grocer*)):ti,ab,kw
#46 (((deliver* OR transport* OR distribut*) NEAR/3 (grocer* OR meal* OR fruit* OR vegetable* OR fat* OR salt* OR sugar*)) AND (outreach OR service* OR scheme OR program* OR policy OR policies OR project* OR nutritio* OR home OR homes OR communit* OR neighbour* OR neighbor* OR rural* OR urban* OR provide* OR choice OR control)):ti,ab,kw
#47 (((deliver* OR transport* OR distribut*) NEAR/2 food*) AND (outreach OR service* OR scheme OR program* OR policy OR policies OR project* OR nutritio* OR home OR homes OR communit* OR neighbour* OR neighbor* OR rural* OR urban* OR provide* OR choice OR control)):ti,ab,kw
#48 (("public transport" OR (transport* NEXT service*) OR (transport* NEXT scheme) OR mobile OR ((transport* OR travel) AND (infrastructure OR local OR access OR communit*))) AND ((food NEXT store*) OR (food NEXT shop*) OR (food NEXT retail*) OR supermarket OR grocer*)):ti,ab,kw
#49 ((payment* OR benefit* OR money OR purchas* OR buy* OR welfare OR financ* OR cash OR income) NEAR/5 (food* OR grocer* OR fruit* OR vegetable* OR nutritio* OR meal*) NEAR/5 (supplement* OR assist* OR extra OR aid OR support OR help)):ti,ab,kw
#50 ((tax OR taxes OR taxation OR subsid* OR voucher* OR coupon*) NEAR/3 (food* OR grocer* OR fruit* OR vegetable* OR nutritio* OR meal*)):ti,ab,kw
#51 (garden* NEAR/3 (communit* OR food* OR nutritio* OR kitchen* OR home* OR school*)):ti,ab,kw

#52 (market* NEAR/3 (garden* OR food* OR nutritio* OR produce OR fruit* OR vegetable* OR farm* OR grower*)):ti,ab,kw
#53 ((food* OR meal*) NEAR/3 service*):ti,ab,kw
#54 (("community nutrition" OR "public health nutrition") NEAR/3 (project* OR program*)):ti,ab,kw
#55 (((agricultural NEXT polic*) OR (land NEXT (use* OR usage*)) OR (land NEXT zone*) OR "land zoning" OR "urban planning" OR "town planning") AND (food* OR grocer* OR fruit* OR vegetable* OR nutritio* OR meal*)):ti,ab,kw
#56 ("urban agriculture" OR (edible NEXT landscape*) OR "civic agriculture"):ti,ab,kw
#57 ("community supported agriculture" OR "community shared agriculture"):ti,ab,kw
#58 ((commun* OR collective OR farm*) NEAR/3 kitchen*):ti,ab,kw
#59 "food for work":ti,ab,kw
#60 ((food NEXT stamp*) OR WIC OR "supplemental nutrition program" OR "supplemental nutrition assistance program"):ti,ab,kw
#61 (grow* NEXT your NEXT own):ti,ab,kw
#62 ((veg* NEXT box*) OR (food NEXT box*) OR (food NEXT basket*) OR (fruit NEXT basket*) OR (veg* NEXT basket*)):ti,ab,kw
#63 ([mh ^diet] OR [mh ^food] OR [mh ^cookery]) AND ([mh ^"health promotion"] OR [mh ^"health policy"] OR [mh ^"public health"]) AND ([mh ^poverty] OR [mh ^"social class"] OR [mh ^"socioeconomic factors"] OR [mh ^"social welfare"])
#64 [mh ^"Food supply"]
#65 [mh ^"Food Industry"]
#66 ([mh ^Vegetables] OR [mh ^"food industry"] OR [mh ^fruit]) AND [mh marketing]
#67 [mh "Food Services"] AND ((supply* OR supplie* OR secur* OR insecur* OR access* OR availab* OR fruit* OR vegetable* OR nutritio* OR "health promotion" OR poverty OR "social welfare" OR hunger OR "social responsibility" OR "food habits"):ti,ab,kw)
#68 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67
#69 #22 AND #68 in Trials
#70 [mh ^taxes] OR [mh ^"tax exemption"]
#71 [mh ^"Government Programs"]
#72 [mh ^"financing, organized"] OR [mh ^"financing, government"]
#73 [mh ^"Cost Sharing"]
#74 (tax OR taxation OR taxes OR price OR prices OR pricing OR cost OR costs OR subsidy OR subsidi* OR "demand elasticity"):ti,ab,kw
#75 (financial NEAR/3 (incentive* OR disincentive*)):ti,ab,kw
#76 (fiscal NEXT measure*):ti,ab,kw
#77 #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76
#78 (food OR fruit* OR vegetable* OR "soft drink*" OR soda OR beverage* OR petrol* OR diesel OR gasoline OR tobacco OR cigarette* OR smoking):ti,ab,kw
#79 #77 AND #78
#80 #22 AND #79 in Trials
#81 [mh "communications media"]
#82 [mh ^"consumer health information"]
#83 [mh Internet]
#84 [mh marketing]
#85 (radio OR television OR tv OR campaign* OR advert* OR boards OR newspaper* OR magazin* OR brochure* OR leaflet* OR pamphlet* OR cinema* OR (mass NEXT (communication OR media)) OR internet OR "social media" OR blog* OR facebook OR twitter OR instagram OR podcast* OR broadcast* OR audiovisual OR film* OR movie* OR ((cell OR cellular OR mobile) NEXT (telephone* OR phone*))):ti,ab,kw
#86 ((cd OR cds OR dvd OR dvds OR video OR videos) NEAR/3 distribut*):ti,ab,kw
#87 #81 OR #82 OR #83 OR #84 OR #85 OR #86
#88 [mh "drinking behavior"]
#89 [mh "tobacco use"]
#90 [mh "Food Habits"]
#91 [mh ^"Motor Activity"]
#92 [mh exercise]
#93 [mh "physical fitness"]
#94 [mh sports]
#95 ((alcohol* NEAR/2 (drink* OR consumption)) OR (drinking NEAR/5 (behavio?r OR habit*)) OR nutrition* OR diet* OR food* OR feed* OR eating OR meal OR meals OR ((physical OR motor) NEAR/5 (activ* OR exercis*)) OR "physical conditioning" OR running OR jogging OR swimming OR walking OR skiing OR cycling OR climbing OR smok* OR tobacco* OR cigarette*):ti,ab,kw
#96 #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95
#97 #87 AND #96
#98 #22 AND #97 in Trials
#99 [mh "Food Packaging"]
#100 (label* OR (content* NEXT sign*) OR symbol* OR ticket* OR sticker* OR diet* OR health* OR calori*

OR nutritio* OR ("guideline daily" NEXT amount*) OR ("recommended daily" NEXT amount*) OR ("nutrient reference" NEXT value*) OR ("nutrient daily" NEXT value*)):ti,ab,kw
#101 #99 AND #100
#102 (food NEXT pack*):ti,ab,kw
#103 [mh "Product Labeling"]
#104 (food* OR fat* OR sugar* OR salt OR diet* OR health* OR calori* OR nutritio* OR ("guideline daily" NEXT amount*) OR ("recommended daily" NEXT amount*) OR ("nutrient reference" NEXT value*) OR ("nutrient daily" NEXT value*) OR snack* OR eat*):ti,ab,kw
#105 #103 AND #104
#106 (((soft OR sugar* OR sweet* OR carbonated OR energy OR sport? OR diet OR flavo?red OR fruit* OR milk* OR dairy OR yoghurt OR caffein* OR cold OR hot OR nonalcohol* OR non-alcohol*) NEAR/3 (drink* OR beverage*)) OR soda? OR (flavo?red NEXT water*) OR (fruit NEXT water?) OR cordial? OR squash? OR juice? OR smoothie? OR milkshake? OR tea OR teas OR coffee?):ti,ab,kw
#107 #103 AND #106
#108 [mh "Food Labeling"]
#109 ((nutritio* OR nutrient*) NEAR/3 (label* OR (content* NEXT sign*) OR symbol* OR ticket* OR sticker*)):ti,ab,kw
#110 ((nutrition* NEXT information) OR (nutrient* NEXT information)):ti,ab,kw
#111 ((food* NEXT label*) OR (food* NEXT content* NEXT label*) OR (food* NEXT content* NEXT sign*) OR (food* NEXT content NEXT symbol*) OR (food* NEXT content* NEXT tag*) OR (food* NEXT content* NEXT ticket*) OR (food* NEXT content* NEXT sticker*)):ti,ab,kw
#112 (traffic NEXT light*):ti,ab,kw
#113 (("guideline daily" NEXT amount*) OR ("nutrient reference" NEXT value*) OR ("nutrient daily" NEXT value*)):ti,ab,kw
#114 (("recommended dietary" NEXT allowance*) NEAR/3 (label* OR (content* NEXT sign*) OR symbol* OR information OR ticket* OR sticker*)):ti,ab,kw
#115 "healthy choice":ti,ab,kw
#116 ((calorific OR calorie* OR caloric) AND (label* OR (content* NEXT sign*) OR symbol* OR ticket* OR sticker*)):ti,ab,kw
#117 ((calorific OR calorie* OR caloric) NEXT information):ti,ab,kw
#118 (fat NEAR/3 (label* OR (content* NEXT sign*) OR symbol* OR tag* OR ticket* OR sticker*)):ti,ab,kw
#119 (salt NEAR/3 (label* OR (content* NEXT sign*) OR symbol* OR tag* OR ticket* OR sticker*)):ti,ab,kw
#120 (sugar NEAR/3 (label* OR (content* NEXT sign*) OR symbol* OR tag* OR ticket* OR sticker*)):ti,ab,kw
#121 (menu NEAR/3 (label* OR (content* NEXT sign*) OR symbol* OR tag* OR ticket* OR sticker*)):ti,ab,kw
#122 (menu AND ((nutritional NEXT content*) OR "nutritional information" OR (traffic NEXT light*) OR "guideline daily amount" OR GDA OR "healthy choice" OR calorie OR fat OR sugar OR salt)):ti,ab,kw
#123 (label* NEAR/2 (legislation* OR regulation* OR policies OR policy)):ti,ab,kw
#124 ((drink* NEXT label*) OR (drink* NEXT content* NEXT label*) OR (drink* NEXT content* NEXT sign*) OR (drink* NEXT content NEXT symbol*) OR (drink* NEXT content* NEXT tag*) OR (drink* NEXT content* NEXT ticket*) OR (drink* NEXT content* NEXT sticker*)):ti,ab,kw
#125 ((((soft OR sugar? OR sweet* OR carbonated OR energy OR sport? OR diet OR flavo?red OR fruit* OR milk* OR dairy OR yoghurt OR caffein* OR cold OR hot OR nonalcohol* OR non-alcohol*) NEAR/3 (drink? OR beverage?)) OR soda? OR (flavo?red NEXT water?) OR (fruit NEXT water?) OR cordial? OR squash? OR juice? OR smoothie? OR milkshake? OR tea OR teas OR coffee?) AND (label* OR (content* NEXT sign*) OR symbol* OR ticket* OR sticker*)):ti,ab,kw
#126 #101 OR #102 OR #105 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125
#127 #22 AND #126 in Trials
#128 [mh ^"Health Promotion"]
#129 ("well being" OR wellbeing OR wellness OR health* OR diet* OR nutrition OR food* OR exercis* OR (physical NEXT activ*) OR stress* OR smoking OR cigarette* OR tobacco):ti,ab,kw
#130 (intervention OR programme OR program*):ti,ab,kw
#131 #129 AND #130
#132 #128 OR #131
#133 (worksite* OR workplace* OR worker* OR occupation* OR job OR jobs OR employee* OR employment OR corporate):ti,ab,kw
#134 [mh ^Workplace]
#135 #133 OR #134
#136 #132 AND #135
#137 #22 AND #136 in Trials

#138 ((limit* OR restrict* OR regulat* OR standard*) AND (marketing OR adverti* OR promot*)):ti,ab,kw
#139 [mh ^"Advertising as Topic"]
#140 [mh marketing]
#141 #139 OR #140
#142 (limit* OR restrict* OR regulat* OR standard*):ti,ab,kw
#143 #141 AND #142
#144 #138 OR #143
#145 (food* OR fat* OR sugar* OR salt OR diet* OR nutritio* OR snack* OR eat*):ti,ab,kw
#146 (((soft OR sugar? OR sweet* OR carbonated OR energy OR sport? OR diet OR flavo?red OR fruit* OR milk* OR dairy OR yoghurt OR caffein* OR cold OR hot OR nonalcohol* OR non-alcohol*) NEAR/3 (drink? OR beverage?)) OR soda? OR (flavo?red NEXT water?) OR (fruit NEXT water?) OR cordial? OR squash? OR juice? OR smoothie? OR milkshake? OR tea OR teas OR coffee?):ti,ab,kw
#147 (tobacco OR cigarette* OR smoking):ti,ab,kw
#148 #145 OR #146 OR #147
#149 #144 AND #148
#150 #22 AND #149 in Trials
#151 "air pollution":ti,ab,kw
#152 [mh "Air Pollution"]
#153 "particulate matter":ti,ab,kw
#154 [mh "Particulate Matter"]
#155 "carbon monoxide":ti,ab,kw
#156 [mh "Carbon Monoxide"]
#157 [mh "Air Pollutants"]
#158 [mh "Sulfur Dioxide"]
#159 "sulphur dioxide":ti,ab,kw
#160 "nitrogen dioxide":ti,ab,kw
#161 [mh "Nitrogen Dioxide"]
#162 ozone:ti,ab,kw
#163 [mh Ozone]
#164 #151 OR #152 OR #153 OR #154 OR #155 OR #156 OR #157 OR #158 OR #159 OR #160 OR #161 OR #162 OR #163
#165 #22 AND #164 in Trials
#166 ((availability OR accessibility) AND (supermarket* OR ((recreation OR exercise OR (physical NEXT activit*)) NEAR/3 (space* OR facilit* OR ground*)) OR (park OR parks OR playground*))):ti,ab,kw
#167 ((improve* OR increas* OR expand*) AND (((land-use OR pavement* OR sidewalk* OR street) NEAR/1 design) OR "traffic safety" OR (neighbo?rhood NEXT a?sthetics) OR walkability OR "pedestrian infrastructure" OR ((local OR neighbo?rhood OR built) NEAR/3 environment*))):ti,ab,kw
#168 (((limit* OR restrict* OR reduc*) NEAR/3 (density OR number)) AND ((shop* OR outlet*) NEAR/3 (tobacco OR cigarette* OR smoking))):ti,ab,kw
#169 #166 OR #167 OR #168
#170 #22 AND #169 in Trials
#171 (population-level OR "population level"):ti,ab,kw
#172 (structural OR policy OR policies OR population*) NEXT (approach* or intervention* OR strateg*):ti,ab,kw
#173 #171 OR #172
#174 #22 AND #173 in Trials
#175 #69 OR #80 OR #98 OR #127 OR #137 OR #150 OR #165 OR #170 OR #174

Total: 4593
Total after duplicates' removal: 4385

Searches for structural and policy systematic reviews – double check of original main search results

Totals

Database name	Search date (update dates)	Number of results
MEDLINE ALL (Ovid)	22 March 2021	217
EMBASE (Ovid)	24 March 2021	199
Cochrane Database of Systematic Reviews (Wiley)	24 March 2021	14

Total from database searches: 430
Total after duplicates removed: 339

MEDLINE (Ovid)

Search date: 22 March 2021
Actual databases searched: Ovid MEDLINE(R) ALL < 1946 to 19 March 2021 >

1 food secur$.ti,ab,kf. 8233
2 food insecur$.ti,ab,kf. 4917
3 food poverty.ti,ab,kf. 79
4 food sufficien$.ti,ab,kf. 73
5 food insufficien$.ti,ab,kf. 163
6 food desert$.ti,ab,kf. 265
7 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$1 or grocer$ or restaurant$1 or fast food$1 or take away$1) adj3 environment$).ti,ab,kf. 5010
8 ((food or garden$ or cook$) adj3 skill$).ti,ab,kf. 520
9 (food adj5 (prepar$ or budget$ or shop$ or purchas$ or buy$ or acquisition or acquir$) adj5 skill$).ti,ab,kf. 101
10 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$1 or grocer$ or supermarket$1 or grocery store$1 or food store$1 or food shop$1 or corner

store$1 or cafeteria$1 or canteen$1 or food outlet$1 or restaurant$1 or fast food$1 or take away$1) adj3 access$3).ti,ab,kf. 952

11 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$1 or grocer$ or supermarket$1 or grocery store$1 or food store$1 or food shop$1 or corner store$1 or cafeteria$1 or canteen$1 or food outlet$1 or restaurant$1 or fast food$1 or take away$1) adj3 access$).ti,ab,kf. 1309

12 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$1 or grocer$ or supermarket$1 or grocery store$1 or food store$1 or food shop$1 or corner store$1 or cafeteria$1 or canteen$1 or food outlet$1 or restaurant$1 or fast food$1 or take away$1) adj3 availab$).ti,ab,kf. 3102

13 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$1 or grocer$ or supermarket$1 or grocery store$1 or food store$1 or food shop$1 or corner store$1 or cafeteria$1 or canteen$1 or food outlet$1 or restaurant$1 or fast food$1 or take away$1) adj3 cost$3).ti,ab,kf. 529

14 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$1 or grocer$ or supermarket$1 or grocery store$1 or food store$1 or food shop$1 or corner store$1 or cafeteria$1 or canteen$1 or food outlet$1 or bodega$1 or tienda$1) adj3 pric$).ti,ab,kf. 426

15 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$ or grocer$ or diet or dietary) adj3 variet$).ti,ab,kf. 2903

16 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$ or grocer$) adj4 (supply or supplies)).ti,ab,kf. 886

17 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$ or grocer$) adj3 (purchas$ or expenditure$1 or spend$ or spent)).ti,ab,kf. 1480

18 ((food$1 or fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$ or grocer$ or supermarket$1 or cafeteria or corner store$1 or canteen$1 or meal$1) adj5 sale$1).ti,ab,kf. 913

19 (food$1 adj3 (environment$ or access$ or cost$ or availab$ or pric$ or variet$ or supply$ or supplies or purchas$ or expenditure$1 or spend or spent or spending) adj5 (fresh or health$ or unhealthy$ or junk$ or nutriti$ or adequate or quality or sufficient or insufficient or secure or insecure$ or safe)).ti,ab. 5654

20 (food$1 adj (environment$ or access$ or cost$ or availab$ or pric$ or expenditure$1 or spending$1)).ti,ab. 9139

21 (food system$1 and (fresh or health$ or unhealthy$ or junk$ or nutriti$ or adequate or quality or sufficient or insufficient or secure or insecure$ or safe)).ti,ab,kf. 1598

22 ((policy or policies) adj3 (food$1 or fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$ or nutritio$ or grocer$ or meal$1)).ti,ab,kf. 3883

23 ((council$1 or coalition$1 or co-op$1 or co-operative$1) adj3 (food$1 or fruit$ or vegetable$1 or nutritio$ or fat$1 or salt$1 or sugar$ or grocer$)).ti,ab,kf. 378

24 (((deliver$ or transport$ or distribut$) adj3 (grocer$ or meal$1 or fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$)) and (outreach or service$ or scheme or program$ or policy or policies or project$ or nutritio$ or home$1 or communit$ or neighbour$ or neighbor$ or rural$ or urban$ or provide$ or choice or control)).ti,ab,kf. 6644

25 (((deliver$ or transport$ or distribut$) adj2 food$1) and (outreach or service$ or scheme or program$ or policy or policies or project$ or nutritio$ or home$1 or communit$ or neighbour$ or neighbor$ or rural$ or urban$ or provide$ or choice or control)).ti,ab,kf. 1976

26 ((public transport or transport* service* or transport* scheme or mobile or ((transport* or travel) and (infrastructure or local or access or communit*))) and (food store* or food shop* or food retail* or supermarket or grocer*)).ti,ab,kf. 265

27 ((payment$1 or benefit$1 or money or purchas$ or buy$ or welfare or financ$ or cash or income) adj5 (food$1 or grocer$ or fruit$1 or vegetable$1 or nutritio$ or meal$1) adj5 (supplement$ or assist$ or extra or aid or support or help)).ti,ab,kf. 1247

28 ((tax or taxes or taxation or subsid$ or voucher$1 or coupon$1) adj3 (food$1 or grocer$ or fruit$1 or vegetable$1 or nutritio$ or meal$1)).ti,ab,kf. 765

29 (garden$ adj3 (communit$ or food$1 or nutritio$ or kitchen$1 or home$1 or school$1)).ti,ab,kf. 1139

30 (market$1 adj3 (garden$ or food$1 or nutritio$ or produce or fruit$1 or vegetable$1 or farm$ or grower$)).ti,ab,kf. 2681

31 ((food$1 or meal$1) adj3 service$1).ti,ab,kf. 3607

32 ((community nutrition or public health nutrition) adj3 (project$1 or program$)).ti,ab,kf. 119

33 ((agricultural polic$ or land us$3 or land zone$1 or land zoning or urban planning or town planning) and (food$1 or grocer$ or fruit$1 or vegetable$1 or nutritio$ or meal$1)).ti,ab,kf. 1762

34 (urban agriculture or edible landscape$1 or civic agriculture).ti,ab,kf. 284

35 (community supported agriculture or community shared agriculture).ti,ab,kf. 41

36 ((commun$ or collective or farm$) adj3 kitchen$).ti,ab,kf. 106

37 food for work.ti,ab,kf. 10

38 (food stamp$ or WIC or supplemental nutrition program or supplemental nutrition assistance program).ti,ab,kf. 2395
39 grow$ your own.ti,ab,kf. 49
40 (veg* box* or food box* or food basket* or fruit basket* or veg* basket*).ti,ab,kf. 237
41 (diet/ or food/ or cookery/) and (health promotion/ or health policy/ or public health/) and (poverty/ or social class/ or socioeconomic factors/ or social welfare/) 689
42 Food supply/st, es, td, og, sn, ec, cl 4533
43 Food Industry/st, es, td, og, sn, ec 1461
44 (Vegetables/ or food industry/ or fruit/) and exp marketing/ 719
45 exp Food Services/ and ((supply$ or supplie$ or secur$ or insecur$ or access$ or availab$ or fruit$ or vegetable$ or nutritio$).ti,ab. or (health promotion or fruit or vegetables or poverty areas or poverty or social welfare or hunger or social responsibility or food habits or food supply).sh.) 5524
46 or/1-45 67625
47 taxes/ or tax exemption/ 7756
48 Government Programs/ 5560
49 financing, organized/ or financing, government/ 27429
50 "Cost Sharing"/ 2583
51 (tax or taxation or taxes or price or prices or pricing or cost or costs or subsidy or subsidi* or demand elasticity).ti,ab,kf. 631991
52 (financial adj3 (incentive* or disincentive*)).ti,ab,kf. 5179
53 fiscal measure*.ti,ab,kf. 68
54 or/47-53 668182
55 (food or fruit* or vegetable* or soft drink* or soda or beverage* or petrol* or diesel or gasoline or tobacco or cigarette* or smoking).ti,ab,kf. 918262
56 54 and 55 37312
57 exp communications media/ 340351
58 consumer health information/ 3985
59 exp Internet/ 83702
60 exp marketing/ 35545
61 (radio or television or "tv" or campaign* or advert* or boards or newspaper* or maga?in* or brochure* or leaflet* or pamphlet* or cinema* or (mass adj (communication or media)) or internet or social media or blog* or facebook or twitter or instagram or podcast* or broadcast* or audiovisual or film* or movie* or ((cell or cellular or mobile) adj (telephone* or phone*))).ti,ab,kf. 455192
62 (("cd" or "cds" or dvd or dvds or video or videos) adj3 distribut*).ti,ab,kf. 1286
63 or/57-62 812502
64 exp drinking behavior/ 77546
65 exp "tobacco use"/ 5848
66 exp Food Habits/ 175223
67 Motor Activity/ 97705
68 exp exercise/ 205459
69 exp physical fitness/ 31709
70 exp sports/ 189327
71 ((alcohol* adj2 (drink* or consumption)) or (drinking adj5 (behavio?r or habit*)) or nutrition* or diet* or food* or feed* or eating or meal or meals or ((physical or motor) adj5 (activ* or exercis*)) or physical conditioning or running or jogging or swimming or walking or skiing or cycling or climbing or smok* or tobacco* or cigarette*).ti,ab,kf. 2245316
72 or/64-71 2553112
73 63 and 72 79867
74 exp Food Packaging/ 8875
75 (label$ or content$ sign$ or symbol$ or ticket$ or sticker$ or diet$ or health$ or calori$ or nutritio$ or guideline daily amount$ or recommended daily amount$ or nutrient reference value$ or nutrient daily value$).ti,ab,kf. 4180314
76 74 and 75 4029
77 food pack$.ti,ab,kf. 3084
78 exp Product Labeling/ 2684
79 (food$ or fat$ or sugar$ or salt or diet$ or health$ or calori$ or nutritio$ or guideline daily amount$ or recommended daily amount$ or nutrient reference value$ or nutrient daily value$ or snack$ or eat$).ti,ab,kf. 4831168
80 78 and 79 1075
81 (((soft or sugar$ or sweet$ or carbonated or energy or sport? or diet or flavo?red or fruit$ or milk$ or dairy or yoghurt or caffein$ or cold or hot or nonalcohol$ or non-alcohol$) adj3 (drink$ or beverage$)) or soda? or flavo?red water$ or fruit water? or cordial? or squash? or juice? or smoothie? or milkshake? or tea or teas or coffee?).ti,ab,kf. 101551
82 78 and 81 32
83 exp Food Labeling/ 3962
84 ((nutritio$ or nutrient$) adj3 (label$ or content$ sign$ or symbol$ or ticket$ or sticker$)).ti,ab,kf. 1426
85 (nutrition$ information or nutrient$ information).ti,ab,kf. 1710
86 (food$ label$ or food$ content$ label$ or food$ content$ sign$ or food$ content symbol$ or food$ content$ tag$ or food$ content$ ticket$ or food$ content$ sticker$).ti,ab,kf. 1565
87 traffic light$.ti,ab,kf.965
88 (guideline daily amount$ or nutrient reference value$ or nutrient daily value$).ti,ab,kf. 143

89 (recommended dietary allowance$ adj3 (label$ or content$ sign$ or symbol$ or information or ticket$ or sticker$)).ti,ab,kf. 1
90 healthy choice.ti,ab,kf. 100
91 ((calorific or calorie$ or caloric) and (label$ or content$ sign$ or symbol$ or ticket$ or sticker$)).ti,ab,kf. 1254
92 ((calorific or calorie$ or caloric) adj information).ti,ab,kf. 125
93 (fat adj3 (label$ or content$ sign$ or symbol$ or tag$ or ticket$ or sticker$)).ti,ab,kf. 477
94 (salt adj3 (label$ or content$ sign$ or symbol$ or tag$ or ticket$ or sticker$)).ti,ab,kf. 196
95 (sugar adj3 (label$ or content$ sign$ or symbol$ or tag$ or ticket$ or sticker$)).ti,ab,kf. 404
96 (menu adj3 (label$ or content$ sign$ or symbol$ or tag$ or ticket$ or sticker$)).ti,ab,kf. 247
97 (menu and (nutritional content$ or nutritional information or traffic light$ or guideline daily amount or GDA or healthy choice or calorie or fat or sugar or salt)).ti,ab,kf. 572
98 (label$ adj2 (legislation$ or regulation$ or policies or policy)).ti,ab,kf. 602
99 (drink* label* or drink* content* label* or drink* content* sign* or drink* content symbol* or drink* content* tag* or drink* content* ticket* or drink* content* sticker*).ti,ab,kf. 42
100 ((((soft or sugar? or sweet* or carbonated or energy or sport? or diet or flavo?red or fruit* or milk* or dairy or yoghurt or caffein* or cold or hot or nonalcohol* or non‐alcohol*) adj3 (drink? or beverage?)) or soda? or flavo?red water? or fruit water? or cordial? or squash? or juice? or smoothie? or milkshake? or tea or teas or coffee?) and (label* or content* sign* or symbol* or ticket* or sticker*)).ti,ab,kf. 2189
101 76 or 77 or 80 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 10016195
102 Health Promotion/ 75697
103 (well being or wellbeing or wellness or health* or diet* or nutrition or food* or exercis* or physical activ* or stress* or smoking or cigarette* or tobacco).ti,ab,kf. 4993512
104 (intervention or programme or program*).ti,ab,kf. 1477235
105 103 and 104 593629
106 102 or 105643447
107 (worksite* or workplace* or worker* or occupation* or job or jobs or employee* or employment or organisation* or organization* or corporate).mp. 1524562
108 Workplace/24192
109 107 or 1081524562
110 106 and 109 160761
111 ((limit* or restrict* or regulat* or standard*) and (marketing or adverti* or promot*)).ti,ab,kf. 443857
112 Advertising as Topic/ 14894
113 exp marketing/ 35545
114 112 or 11335545
115 (limit* or restrict* or regulat* or standard*).ti,ab,kf. 5045057
116 114 and 115 4922
117 111 or 116445373
118 (food$ or fat$ or sugar$ or salt or diet$ or nutritio$ or snack$ or eat$).ti,ab,kf. 2184808
119 (((soft or sugar? or sweet* or carbonated or energy or sport? or diet or flavo?red or fruit* or milk* or dairy or yoghurt or caffein* or cold or hot or nonalcohol* or non-alcohol*) adj3 (drink? or beverage?)) or soda? or flavo?red water? or fruit water? or cordial? or squash? or juice? or smoothie? or milkshake? or tea or teas or coffee?).ti,ab,kf. 99418
120 (tobacco or cigarette* or smoking).ti,ab,kf. 313988
121 118 or 119 or 1202515640
122 117 and 121 56670
123 air pollution.ti,ab,kf. 30289
124 exp Air Pollution/ 60150
125 particulate matter.ti,ab,kf.21463
126 exp Particulate Matter/ 65974
127 carbon monoxide.ti,ab,kf. 28613
128 exp Carbon Monoxide/ 18162
129 exp Air Pollutants/ 94949
130 exp Sulfur Dioxide/ 5471
131 sulphur dioxide.ti,ab,kf. 1153
132 nitrogen dioxide.ti,ab,kf. 5804
133 exp Nitrogen Dioxide/ 5037
134 ozone.ti,ab,kf. 22150
135 exp Ozone/ 15337
136 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135219403
137 ((availability or accessibility) and (supermarket* or ((recreation or exercise or physical activit*) adj3 (space* or facilit* or ground*)) or (park or parks or playground*))).ti,ab,kf. 1371
138 ((improve* or increas* or expand*) and (((land-use or pavement* or sidewalk* or street) adj1 design) or traffic safety or neighbo?rhood a?sthetics or walkability or pedestrian infrastructure or ((local or neighbo?rhood or built) adj3 environment*))).ti,ab,kf. 8068
139 (((limit* or restrict* or reduc*) adj3 (density or number)) and ((shop* or outlet*) adj3 (tobacco or cigarette* or smoking))).ti,ab,kf. 30
140 137 or 138 or 139 9368

141 ("population-level" or "population level").ti,ab,kf. 20018
142 ((structural or policy or policies or population*) adj (approach* or intervention* or strateg*)).ti,ab,kf. 8726
143 141 or 14228589
144 46 or 56 or 73 or 101 or 110 or 122 or 136 or 140 or 143630624
145 exp Primary Prevention/ 156514
146 primary prevention.ti,ab,kf. 20174
147 145 or 146171680
148 exp Cardiovascular Diseases/ or exp Stroke/ 2462482
149 (cardiovascular* or coronary* or heart* or myocardial infarction* or cardiac* or stroke* or cerebrovascular accident*).ti,ab,kf. 2003207
150 148 or 1493350164
151 147 and 150 16888
152 *Cardiovascular Diseases/pc or exp *Coronary Disease/pc or exp *Myocardial Infarction/pc or exp *Heart Failure/pc or exp *Heart Arrest/pc or exp *Stroke/pc 51812
153 ((prevent* or (reduc* adj risk*)) and (cardiovascular* or heart* or myocardial infarction* or cardiac* or stroke*)).ti. 22393
154 151 or 152 or 153 74014
155 (metaanalys* or "meta analys*" or "meta-analys*").mp. 227453
156 (systematic* adj2 review*).mp. 233311
157 155 or 156 350112
158 154 and 157 4229
159 limit 154 to (meta analysis or "systematic review") 2553
160 158 or 159 4229
161 limit 160 to (comment or editorial or letter) 264
162 160 not 161 3965
163 144 and 162 217

EMBASE (Ovid)
Search date: 24 March 2021
Actual database searched: EMBASE Classic + EMBASE 1947 to 23 March 2021
EMBASE Classic + EMBASE < 1947 to 23 March 2021 >

1 food secur$.ti,ab,kw. 9292
2 food insecur$.ti,ab,kw. 6362
3 food poverty.ti,ab,kw. 97
4 food sufficien$.ti,ab,kw. 92
5 food insufficien$.ti,ab,kw. 183
6 food desert$.ti,ab,kw. 353
7 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$1 or grocer$ or restaurant$1 or fast food$1 or take away$1) adj3 environment$).ti,ab,kw. 6003
8 ((food or garden$ or cook$) adj3 skill$).ti,ab,kw. 756
9 (food adj5 (prepar$ or budget$ or shop$ or purchas$ or buy$ or acquisition or acquir$) adj5 skill$).ti,ab,kw. 149
10 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$1 or grocer$ or supermarket$1 or grocery store$1 or food store$1 or food shop$1 or corner store$1 or cafeteria$1 or canteen$1 or food outlet$1 or restaurant$1 or fast food$1 or take away$1) adj3 access$3).ti,ab,kw. 1246
11 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$1 or grocer$ or supermarket$1 or grocery store$1 or food store$1 or food shop$1 or corner store$1 or cafeteria$1 or canteen$1 or food outlet$1 or restaurant$1 or fast food$1 or take away$1) adj3 access$).ti,ab,kw. 1638
12 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$1 or grocer$ or supermarket$1 or grocery store$1 or food store$1 or food shop$1 or corner store$1 or cafeteria$1 or canteen$1 or food outlet$1 or restaurant$1 or fast food$1 or take away$1) adj3 availab$).ti,ab,kw. 3864
13 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$1 or grocer$ or supermarket$1 or grocery store$1 or food store$1 or food shop$1 or corner store$1 or cafeteria$1 or canteen$1 or food outlet$1 or restaurant$1 or fast food$1 or take away$1) adj3 cost$3).ti,ab,kw. 629
14 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$1 or grocer$ or supermarket$1 or grocery store$1 or food store$1 or food shop$1 or corner store$1 or cafeteria$1 or canteen$1 or food outlet$1 or bodega$1 or tienda$1) adj3 pric$).ti,ab,kw. 554
15 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$ or grocer$ or diet or dietary) adj3 variet$).ti,ab,kw. 3519
16 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$ or grocer$) adj4 (supply or supplies)).ti,ab,kw. 1144
17 ((fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$ or grocer$) adj3 (purchas$ or expenditure$1 or spend$ or spent)).ti,ab,kw. 1843
18 ((food$1 or fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$ or grocer$ or supermarket$1 or cafeteria or corner store$1 or canteen$1 or meal$1) adj5 sale$1).ti,ab,kw. 1133
19 (food$1 adj3 (environment$ or access$ or cost$ or availab$ or pric$ or variet$ or supply$ or supplies or purchas$ or expenditure$1 or spend or spent or spending) adj5 (fresh or health$ or unhealthy$ or junk$ or nutriti$ or adequate or quality or

sufficient or insufficient or secure or insecure$ or safe)).ti,ab,kw. 7373
20 (food$1 adj (environment$ or access$ or cost$ or availab$ or pric$ or expenditure$1 or spending$1)).ti,ab. 10509
21 (food system$1 and (fresh or health$ or unhealthy$ or junk$ or nutriti$ or adequate or quality or sufficient or insufficient or secure or insecure$ or safe)).ti,ab,kw. 1813
22 ((policy or policies) adj3 (food$1 or fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$ or nutritio$ or grocer$ or meal$1)).ti,ab,kw. 4920
23 ((council$1 or coalition$1 or co-op$1 or co-operative$1) adj3 (food$1 or fruit$ or vegetable$1 or nutritio$ or fat$1 or salt$1 or sugar$ or grocer$)).ti,ab,kw. 533
24 (((deliver$ or transport$ or distribut$) adj3 (grocer$ or meal$1 or fruit$1 or vegetable$1 or fat$1 or salt$1 or sugar$)) and (outreach or service$ or scheme or program$ or policy or policies or project$ or nutritio$ or home$1 or communit$ or neighbour$ or neighbor$ or rural$ or urban$ or provide$ or choice or control)).ti,ab,kw. 8775
25 (((deliver$ or transport$ or distribut$) adj2 food$1) and (outreach or service$ or scheme or program$ or policy or policies or project$ or nutritio$ or home$1 or communit$ or neighbour$ or neighbor$ or rural$ or urban$ or provide$ or choice or control)).ti,ab,kw. 2439
26 ((public transport or transport* service* or transport* scheme or mobile or ((transport* or travel) and (infrastructure or local or access or communit*))) and (food store* or food shop* or food retail* or supermarket or grocer*)).ti,ab,kw. 339
27 ((payment$1 or benefit$1 or money or purchas$ or buy$ or welfare or financ$ or cash or income) adj5 (food$1 or grocer$ or fruit$1 or vegetable$1 or nutritio$ or meal$1) adj5 (supplement$ or assist$ or extra or aid or support or help)).ti,ab,kw. 1677
28 ((tax or taxes or taxation or subsid$ or voucher$1 or coupon$1) adj3 (food$1 or grocer$ or fruit$1 or vegetable$1 or nutritio$ or meal$1)).ti,ab,kw. 919
29 (garden$ adj3 (communit$ or food$1 or nutritio$ or kitchen$1 or home$1 or school$1)).ti,ab,kw. 1443
30 (market$1 adj3 (garden$ or food$1 or nutritio$ or produce or fruit$1 or vegetable$1 or farm$ or grower$)).ti,ab,kw. 3212
31 ((food$1 or meal$1) adj3 service$1).ti,ab,kw. 3817
32 ((community nutrition or public health nutrition) adj3 (project$1 or program$)).ti,ab,kw. 153
33 ((agricultural polic$ or land us$3 or land zone$1 or land zoning or urban planning or town planning) and (food$1 or grocer$ or fruit$1 or vegetable$1 or nutritio$ or meal$1)).ti,ab,kw. 1930
34 (urban agriculture or edible landscape$1 or civic agriculture).ti,ab,kw. 320
35 (community supported agriculture or community shared agriculture).ti,ab,kw. 59
36 ((commun$ or collective or farm$) adj3 kitchen$).ti,ab,kw. 162
37 food for work.ti,ab,kw. 9
38 (food stamp$ or WIC or supplemental nutrition program or supplemental nutrition assistance program).ti,ab,kw. 2899
39 grow$ your own.ti,ab,kw. 55
40 (veg* box* or food box* or food basket* or fruit basket* or veg* basket*).ti,ab,kw. 286
41 (diet/ or healthy diet/ or food/ or cooking/) and (exp health promotion/ or exp health care policy/ or public health/) and (poverty/ or social class/ or exp socioeconomics/ or social welfare/ or community care/)1803
42 food security/ or food insecurity/ 8391
43 food availability/ 4558
44 (exp vegetable/ or food industry/ or exp fruit/) and (marketing/ or exp social marketing/)1451
45 (exp catering service/ or food industry/) and ((supply$ or supplie$ or secur$ or insecur$ or access$ or availab$ or fruit$ or vegetable$ or nutritio$).ti,ab. or (health promotion or fruit or vegetable or poverty or social welfare or hunger or social responsibility or feeding behavior).sh.)20131
46 or/1-4590793
47 tax/16238
48 exp finance/ and exp government/ 1494
49 exp economics/ and exp government/ 17512
50 reimbursement/ 59250
51 (tax or taxation or taxes or price or prices or pricing or cost or costs or subsidy or subsidi* or demand elasticity).ti,ab,kw. 867644
52 (financial adj3 (incentive* or disincentive*)).ti,ab,kw. 6465
53 fiscal measure*.ti,ab,kw. 92
54 or/47-53931691
55 (food or fruit* or vegetable* or soft drink* or soda or beverage* or petrol* or diesel or gasoline or tobacco or cigarette* or smoking).ti,ab,kw. 1216568
56 54 and 55 48299
57 exp mass communication/ 607456
58 consumer health information/ 4018
59 exp multimedia/ 4328
60 marketing/ or exp social marketing/ 32409
61 (radio or television or "tv" or campaign* or advert* or boards or newspaper* or maga?in* or brochure* or leaflet* or pamphlet* or cinema* or (mass adj

(communication or media)) or internet or social media or blog* or facebook or twitter or instagram or podcast* or broadcast* or audiovisual or film* or movie* or ((cell or cellular or mobile) adj (telephone* or phone*))).ti,ab,kw. 565092
62 (("cd" or "cds" or dvd or dvds or video or videos) adj3 distribut*).ti,ab,kw. 1658
63 or/57-62 1075865
64 alcohol consumption/ 135634
65 exp "tobacco use"/ or smoking cessation/ 456481
66 exp feeding behavior/ 190944
67 exp physical activity/ 467335
68 exp exercise/ 388475
69 fitness/ 41648
70 exp sport/ 184330
71 ((alcohol* adj2 (drink* or consumption)) or (drinking adj5 (behavio?r or habit*)) or nutrition* or diet* or food* or feed* or eating or meal or meals or ((physical or motor) adj5 (activ* or exercis*)) or physical conditioning or running or jogging or swimming or walking or skiing or cycling or climbing or smok* or tobacco* or cigarette*).ti,ab,kw. 3014988
72 or/64-713693704
73 63 and 72 136608
74 food packaging/ and (label$ or content$ sign$ or symbol$ or ticket$ or sticker$ or diet$ or health$ or calori$ or nutritio$ or guideline daily amount$ or recommended daily amount$ or nutrient reference value$ or nutrient daily value$).ti,ab,kw. 4795
75 food pack$.ti,ab,kw. 3193
76 ((Nutritio$ or Nutrient$) adj5 (label$ or content$ sign$ or symbol$ or ticket$ or sticker$)).ti,ab,kw. 2380
77 (nutrition$ information or nutrient$ information).ti,ab,kw. 2379
78 (Food$ label$ or food$ content$ label$ or food$ content$ sign$ or food$ content symbol$ or food$ content$ tag$ or food$ content$ ticket$ or food$ content$ sticker$).ti,ab,kw. 2253
79 traffic light$.ti,ab,kw. 1514
80 (guideline daily amount$ or nutrient reference value$ or nutrient daily value$).ti,ab,kw. 173
81 (recommended dietary allowance$ adj5 (label$ or content$ sign$ or symbol$ or information or ticket$ or sticker$)).ti,ab,kw. 6
82 ((calorific or calorie$ or caloric) and (label$ or content$ sign$ or symbol$ or ticket$ or sticker$)).ti,ab,kw. 1900
83 ((calorific or calorie$ or caloric) adj information).ti,ab,kw. 173
84 (fat adj5 (label$ or content$ sign$ or symbol$ or tag$ or ticket$ or sticker$)).ti,ab,kw. 1207
85 (salt adj5 (label$ or content$ sign$ or symbol$ or tag$ or ticket$ or sticker$)).ti,ab,kw. 505
86 (sugar adj5 (label$ or content$ sign$ or symbol$ or tag$ or ticket$ or sticker$)).ti,ab,kw. 731
87 (menu adj5 (label$ or content$ sign$ or symbol$ or tag$ or ticket$ or sticker$)).ti,ab,kw. 331
88 (menu and (nutritional content$ or nutritional information or traffic light$ or guideline daily amount or GDA or healthy choice or calorie or fat or sugar or salt)).ti,ab,kw. 832
89 (label$ adj2 (legislation$ or regulation$ or policies or policy)).ti,ab,kw. 793
90 healthy choice.ti,ab,kw. 144
91 (drink* label* or drink* content* label* or drink* content* sign* or drink* content symbol* or drink* content* tag* or drink* content* ticket* or drink* content* sticker*).ti,ab,kw. 55
92 ((((soft or sugar? or sweet* or carbonated or energy or sport? or diet or flavo?red or fruit* or milk* or dairy or yoghurt or caffein* or cold or hot or nonalcohol* or non-alcohol*) adj3 (drink? or beverage?)) or soda? or flavo?red water? or fruit water? or cordial? or squash? or juice? or smoothie? or milkshake? or tea or teas or coffee?) and (label* or content* sign* or symbol* or ticket* or sticker*)).ti,ab,kw. 2974
93 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 9219860
94 exp health promotion/ 103726
95 (well being or wellbeing or wellness or health* or diet* or nutrition or food* or exercis* or physical activ* or stress* or smoking or cigarette* or tobacco).ti,ab,kw. 6725566
96 (intervention or programme or program*).ti,ab,kw. 2095843
97 95 and 96 838109
98 94 or 97 911460
99 (worksite* or workplace* or worker* or occupation* or job or jobs or employee* or employment or corporate).ti,ab,kw. 616522
100 work/ or workplace/ or occupation/ or employee/ or employment/ 212811
101 99 or 100 693390
102 98 and 101 83630
103 ((limit* or restrict* or regulat* or standard*) and (marketing or adverti* or promot*)).ti,ab,kw. 576681
104 exp advertising/ 5348
105 exp marketing/ 25673
106 104 or 10530328
107 (limit* or restrict* or regulat* or standard*).ti,ab,kw. 6764100
108 106 and 107 8320

109 103 or 108 578513
110 (food$ or fat$ or sugar$ or salt or diet$ or nutritio$ or snack$ or eat$).ti,ab,kw. 2933519
111 (((soft or sugar? or sweet* or carbonated or energy or sport? or diet or flavo?red or fruit* or milk* or dairy or yoghurt or caffein* or cold or hot or nonalcohol* or non-alcohol*) adj3 (drink? or beverage?)) or soda? or flavo?red water? or fruit water? or cordial? or squash? or juice? or smoothie? or milkshake? or tea or teas or coffee?).ti,ab,kw. 128725
112 (tobacco or cigarette* or smoking).ti,ab,kw. 447883
113 110 or 111 or 112 3392265
114 109 and 113 76257
115 air pollution.ti,ab,kw. 42869
116 exp air pollution/ 173278
117 particulate matter.ti,ab,kw. 30155
118 particulate matter/ 45025
119 carbon monoxide.ti,ab,kw. 37415
120 carbon monoxide/ 42348
121 exp air pollutant/ 83469
122 sulfur dioxide/ 16555
123 sulphur dioxide.ti,ab,kw. 2608
124 nitrogen dioxide.ti,ab,kw. 7883
125 nitrogen dioxide/ 14668
126 ozone.ti,ab,kw. 31715
127 ozone/ 30604
128 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 281539
129 ((availability or accessibility) and (supermarket* or ((recreation or exercise or physical activit*) adj3 (space* or facilit* or ground*)) or (park or parks or playground*))).ti,ab,kw. 1705
130 ((improve* or increas* or expand*) and (((land-use or pavement* or sidewalk* or street) adj1 design) or traffic safety or neighbo?rhood a?sthetics or walkability or pedestrian infrastructure or ((local or neighbo?rhood or built) adj3 environment*))).ti,ab,kw. 9502
131 (((limit* or restrict* or reduc*) adj3 (density or number)) and ((shop* or outlet*) adj3 (tobacco or cigarette* or smoking))).ti,ab,kw. 37
132 129 or 130 or 131 11115
133 ("population-level" or "population level").ti,ab,kw. 24730
134 ((structural or policy or policies or population*) adj (approach* or intervention* or strateg*)).ti,ab,kw. 10746
135 133 or 134 35286
136 46 or 56 or 73 or 93 or 102 or 114 or 128 or 132 or 135731547
137 primary prevention/ 42522
138 primary prevention.ti,ab,kw. 31070
139 137 or 138 56732
140 exp cardiovascular disease/ or exp cerebrovascular accident/ 4641897
141 (cardiovascular* or coronary* or heart* or myocardial infarction* or cardiac* or stroke* or cerebrovascular accident*).ti,ab,kw. 2975541
142 140 or 141 5547762
143 139 and 142 28578
144 *cardiovascular disease/pc or exp *coronary artery disease/pc or exp *heart infarction/pc or *heart failure/pc or exp *heart arrest/pc or exp *cerebrovascular accident/pc 39364
145 ((prevent* or (reduc* adj risk*)) and (cardiovascular* or coronary* or heart* or myocardial infarction* or cardiac* or stroke* or cerebrovascular accident*)).ti. 35525
146 143 or 144 or 145 84112
147 (metaanalys* or "meta analys*" or "meta-analys*").mp. 333616
148 (systematic* adj2 review*).mp. 389427
149 147 or 148 544925
150 146 and 149 6438
151 limit 146 to (meta analysis or "systematic review") 4294
152 150 or 151 6438
153 limit 152 to (conference abstract or conference paper or "conference review" or editorial or letter) 1252
154 152 not 153 5186
155 136 and 154 199

Cochrane Database of Systematic Reviews (Wiley)
Date Run: 24 March 2021

ID Search
#1 MeSH descriptor: [Primary Prevention] explode all trees
#2 "primary prevention":ti,ab,kw
#3 #1 or #2
#4 MeSH descriptor: [Cardiovascular Diseases] explode all trees
#5 MeSH descriptor: [Stroke] explode all trees
#6 (cardiovascular* or coronary* or heart* or (myocardial next infarction*) or cardiac* or stroke* or (cerebrovascular next accident*)):ti,ab,kw
#7 #4 or #5 or #6
#8 #3 and #7
#9 [mh ^"cardiovascular diseases"[mj]/PC]
#10 [mh "coronary disease"[mj]/PC]
#11 [mh "myocardial infarction"[mj]/PC]
#12 [mh "heart failure"[mj]/PC]
#13 [mh "heart arrest"[mj]/PC]
#14 [mh "stroke"[mj]/PC]
#15 #9 or #10 or #11 or #12 or #13 or #14

#16 ((prevent* or (reduc* near/2 risk)) and (cardiovascular* or coronary* or heart* or (myocardial next infarction*) or cardiac* or stroke* or (cerebrovascular next accident*))):ti
#17 #8 or #15 or #16
#18 (food NEXT secur*):ti,ab,kw
#19 (food NEXT insecur*):ti,ab,kw
#20 "food poverty":ti,ab,kw
#21 (food NEXT sufficien*):ti,ab,kw
#22 (food NEXT insufficien*):ti,ab,kw
#23 (food NEXT desert*):ti,ab,kw
#24 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR restaurant* OR (fast NEXT food*) OR (take NEXT away*)) NEAR/3 environment*):ti,ab,kw
#25 ((food OR garden* OR cook*) NEAR/3 skill*):ti,ab,kw
#26 (food NEAR/5 (prepar* OR budget* OR shop* OR purchas* OR buy* OR acquisition OR acquir*) NEAR/5 skill*):ti,ab,kw
#27 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR supermarket* OR (grocery NEXT store*) OR (food NEXT store*) OR (food NEXT shop*) OR (corner NEXT store*) OR cafeteria* OR canteen* OR (food NEXT outlet*) OR restaurant* OR (fast NEXT food*) OR (take NEXT away*)) NEAR/3 access*):ti,ab,kw
#28 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR supermarket* OR (grocery NEXT store*) OR (food NEXT store*) OR (food NEXT shop*) OR (corner NEXT store*) OR cafeteria* OR canteen* OR (food NEXT outlet*) OR restaurant* OR (fast NEXT food*) OR (take NEXT away*)) NEAR/3 access*):ti,ab,kw
#29 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR supermarket* OR (grocery NEXT store*) OR (food NEXT store*) OR (food NEXT shop*) OR (corner NEXT store*) OR cafeteria* OR canteen* OR (food NEXT outlet*) OR restaurant* OR (fast NEXT food*) OR (take NEXT away*)) NEAR/3 availab*):ti,ab,kw
#30 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR supermarket* OR (grocery NEXT store*) OR (food NEXT store*) OR (food NEXT shop*) OR (corner NEXT store*) OR cafeteria* OR canteen* OR (food NEXT outlet*) OR restaurant* OR (fast NEXT food*) OR (take NEXT away*)) NEAR/3 cost*):ti,ab,kw
#31 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR supermarket* OR (grocery NEXT store*) OR (food NEXT store*) OR (food NEXT shop*) OR (corner NEXT store*) OR cafeteria* OR canteen* OR (food NEXT outlet*) OR bodega* OR tienda*) NEAR/3 pric*):ti,ab,kw
#32 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR diet OR dietary) NEAR/3 variet*):ti,ab,kw
#33 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer*) NEAR/4 (supply OR supplies)):ti,ab,kw
#34 ((fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer*) NEAR/3 (purchas* OR expenditure* OR spend* OR spent)):ti,ab,kw
#35 ((food* OR fruit* OR vegetable* OR fat* OR salt* OR sugar* OR grocer* OR supermarket* OR cafeteria OR (corner NEXT store*) OR canteen* OR meal*) NEAR/5 sale*):ti,ab,kw
#36 (food* NEAR/3 (environment* OR access* OR cost* OR availab* OR pric* OR variet* OR supply* OR supplies OR purchas* OR expenditure* OR spend OR spent OR spending) NEAR/5 (fresh OR health* OR unhealthy* OR junk* OR nutriti* OR adequate OR quality OR sufficient OR insufficient OR secure OR insecure* OR safe)):ti,ab
#37 (food* NEXT (environment* OR access* OR cost* OR availab* OR pric* OR expenditure* OR spending*)):ti,ab
#38 ((food NEXT system*) AND (fresh OR health* OR unhealthy* OR junk* OR nutriti* OR adequate OR quality OR sufficient OR insufficient OR secure OR insecure* OR safe)):ti,ab,kw
#39 ((policy OR policies) NEAR/3 (food* OR fruit* OR vegetable* OR fat* OR salt* OR sugar* OR nutritio* OR grocer* OR meal*)):ti,ab,kw
#40 ((council* OR coalition* OR co-op* OR co-operative*) NEAR/3 (food* OR fruit* OR vegetable* OR nutritio* OR fat* OR salt* OR sugar* OR grocer*)):ti,ab,kw
#41 (((deliver* OR transport* OR distribut*) NEAR/3 (grocer* OR meal* OR fruit* OR vegetable* OR fat* OR salt* OR sugar*)) AND (outreach OR service* OR scheme OR program* OR policy OR policies OR project* OR nutritio* OR home OR homes OR communit* OR neighbour* OR neighbor* OR rural* OR urban* OR provide* OR choice OR control)):ti,ab,kw
#42 (((deliver* OR transport* OR distribut*) NEAR/2 food*) AND (outreach OR service* OR scheme OR program* OR policy OR policies OR project* OR nutritio* OR home OR homes OR communit* OR neighbour* OR neighbor* OR rural* OR urban* OR provide* OR choice OR control)):ti,ab,kw
#43 (("public transport" OR (transport* NEXT service*) OR (transport* NEXT scheme) OR mobile OR ((transport* OR travel) AND (infrastructure OR local OR access OR communit*))) AND ((food NEXT

store*) OR (food NEXT shop*) OR (food NEXT retail*) OR supermarket OR grocer*)):ti,ab,kw

#44 ((payment* OR benefit* OR money OR purchas* OR buy* OR welfare OR financ* OR cash OR income) NEAR/5 (food* OR grocer* OR fruit* OR vegetable* OR nutritio* OR meal*) NEAR/5 (supplement* OR assist* OR extra OR aid OR support OR help)):ti,ab,kw

#45 ((tax OR taxes OR taxation OR subsid* OR voucher* OR coupon*) NEAR/3 (food* OR grocer* OR fruit* OR vegetable* OR nutritio* OR meal*)):ti,ab,kw

#46 (garden* NEAR/3 (communit* OR food* OR nutritio* OR kitchen* OR home* OR school*)):ti,ab,kw

#47 (market* NEAR/3 (garden* OR food* OR nutritio* OR produce OR fruit* OR vegetable* OR farm* OR grower*)):ti,ab,kw

#48 ((food* OR meal*) NEAR/3 service*):ti,ab,kw

#49 (("community nutrition" OR "public health nutrition") NEAR/3 (project* OR program*)):ti,ab,kw

#50 (((agricultural NEXT polic*) OR (land NEXT (use* OR usage*)) OR (land NEXT zone*) OR "land zoning" OR "urban planning" OR "town planning") AND (food* OR grocer* OR fruit* OR vegetable* OR nutritio* OR meal*)):ti,ab,kw

#51 ("urban agriculture" OR (edible NEXT landscape*) OR "civic agriculture"):ti,ab,kw

#52 ("community supported agriculture" OR "community shared agriculture"):ti,ab,kw

#53 ((commun* OR collective OR farm*) NEAR/3 kitchen*):ti,ab,kw

#54 "food for work":ti,ab,kw

#55 ((food NEXT stamp*) OR WIC OR "supplemental nutrition program" OR "supplemental nutrition assistance program"):ti,ab,kw

#56 (grow* NEXT your NEXT own):ti,ab,kw

#57 ((veg* NEXT box*) OR (food NEXT box*) OR (food NEXT basket*) OR (fruit NEXT basket*) OR (veg* NEXT basket*)):ti,ab,kw

#58 ([mh ^diet] OR [mh ^food] OR [mh ^cookery]) AND ([mh ^"health promotion"] OR [mh ^"health policy"] OR [mh ^"public health"]) AND ([mh ^poverty] OR [mh ^"social class"] OR [mh ^"socioeconomic factors"] OR [mh ^"social welfare"])

#59 [mh ^"Food supply"]

#60 [mh ^"Food Industry"]

#61 ([mh ^Vegetables] OR [mh ^"food industry"] OR [mh ^fruit]) AND [mh marketing]

#62 [mh "Food Services"] AND ((supply* OR supplie* OR secur* OR insecur* OR access* OR availab* OR fruit* OR vegetable* OR nutritio* OR "health promotion" OR poverty OR "social welfare" OR hunger OR "social responsibility" OR "food habits"):ti,ab,kw)

#63 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62

#64 [mh ^taxes] OR [mh ^"tax exemption"]

#65 [mh ^"Government Programs"]

#66 [mh ^"financing, organized"] OR [mh ^"financing, government"]

#67 [mh ^"Cost Sharing"]

#68 (tax OR taxation OR taxes OR price OR prices OR pricing OR cost OR costs OR subsidy OR subsidi* OR "demand elasticity"):ti,ab,kw

#69 (financial NEAR/3 (incentive* OR disincentive*)):ti,ab,kw

#70 (fiscal NEXT measure*):ti,ab,kw

#71 #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70

#72 (food OR fruit* OR vegetable* OR "soft drink*" OR soda OR beverage* OR petrol* OR diesel OR gasoline OR tobacco OR cigarette* OR smoking):ti,ab,kw

#73 #71 AND #72

#74 [mh "communications media"]

#75 [mh ^"consumer health information"]

#76 [mh Internet]

#77 [mh marketing]

#78 (radio OR television OR tv OR campaign* OR advert* OR boards OR newspaper* OR magazin* OR brochure* OR leaflet* OR pamphlet* OR cinema* OR (mass NEXT (communication OR media)) OR internet OR "social media" OR blog* OR facebook OR twitter OR instagram OR podcast* OR broadcast* OR audiovisual OR film* OR movie* OR ((cell OR cellular OR mobile) NEXT (telephone* OR phone*))):ti,ab,kw

#79 ((cd OR cds OR dvd OR dvds OR video OR videos) NEAR/3 distribut*):ti,ab,kw

#80 #74 OR #75 OR #76 OR #77 OR #78 OR #79

#81 [mh "drinking behavior"]

#82 [mh "tobacco use"]

#83 [mh "Food Habits"]

#84 [mh ^"Motor Activity"]

#85 [mh exercise]

#86 [mh "physical fitness"]

#87 [mh sports]

#88 ((alcohol* NEAR/2 (drink* OR consumption)) OR (drinking NEAR/5 (behavio?r OR habit*)) OR

nutrition* OR diet* OR food* OR feed* OR eating OR meal OR meals OR ((physical OR motor) NEAR/5 (activ* OR exercis*)) OR "physical conditioning" OR running OR jogging OR swimming OR walking OR skiing OR cycling OR climbing OR smok* OR tobacco* OR cigarette*):ti,ab,kw

#89 #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88

#90 #80 AND #89

#91 [mh "Food Packaging"]

#92 (label* OR (content* NEXT sign*) OR symbol* OR ticket* OR sticker* OR diet* OR health* OR calori* OR nutritio* OR ("guideline daily" NEXT amount*) OR ("recommended daily" NEXT amount*) OR ("nutrient reference" NEXT value*) OR ("nutrient daily" NEXT value*)):ti,ab,kw

#93 #91 AND #92

#94 (food NEXT pack*):ti,ab,kw

#95 [mh "Product Labeling"]

#96 (food* OR fat* OR sugar* OR salt OR diet* OR health* OR calori* OR nutritio* OR ("guideline daily" NEXT amount*) OR ("recommended daily" NEXT amount*) OR ("nutrient reference" NEXT value*) OR ("nutrient daily" NEXT value*) OR snack* OR eat*):ti,ab,kw

#97 #95 AND #96

#98 (((soft OR sugar* OR sweet* OR carbonated OR energy OR sport? OR diet OR flavo?red OR fruit* OR milk* OR dairy OR yoghurt OR caffein* OR cold OR hot OR nonalcohol* OR non-alcohol*) NEAR/3 (drink* OR beverage*)) OR soda? OR (flavo?red NEXT water*) OR (fruit NEXT water?) OR cordial? OR squash? OR juice? OR smoothie? OR milkshake? OR tea OR teas OR coffee?):ti,ab,kw

#99 #95 AND #98

#100 [mh "Food Labeling"]

#101 ((nutritio* OR nutrient*) NEAR/3 (label* OR (content* NEXT sign*) OR symbol* OR ticket* OR sticker*)):ti,ab,kw

#102 ((nutrition* NEXT information) OR (nutrient* NEXT information)):ti,ab,kw

#103 ((food* NEXT label*) OR (food* NEXT content* NEXT label*) OR (food* NEXT content* NEXT sign*) OR (food* NEXT content NEXT symbol*) OR (food* NEXT content* NEXT tag*) OR (food* NEXT content* NEXT ticket*) OR (food* NEXT content* NEXT sticker*)):ti,ab,kw

#104 (traffic NEXT light*):ti,ab,kw

#105 (("guideline daily" NEXT amount*) OR ("nutrient reference" NEXT value*) OR ("nutrient daily" NEXT value*)):ti,ab,kw

#106 (("recommended dietary" NEXT allowance*) NEAR/3 (label* OR (content* NEXT sign*) OR symbol* OR information OR ticket* OR sticker*)):ti,ab,kw

#107 "healthy choice":ti,ab,kw

#108 ((calorific OR calorie* OR caloric) AND (label* OR (content* NEXT sign*) OR symbol* OR ticket* OR sticker*)):ti,ab,kw

#109 ((calorific OR calorie* OR caloric) NEXT information):ti,ab,kw

#110 (fat NEAR/3 (label* OR (content* NEXT sign*) OR symbol* OR tag* OR ticket* OR sticker*)):ti,ab,kw

#111 (salt NEAR/3 (label* OR (content* NEXT sign*) OR symbol* OR tag* OR ticket* OR sticker*)):ti,ab,kw

#112 (sugar NEAR/3 (label* OR (content* NEXT sign*) OR symbol* OR tag* OR ticket* OR sticker*)):ti,ab,kw

#113 (menu NEAR/3 (label* OR (content* NEXT sign*) OR symbol* OR tag* OR ticket* OR sticker*)):ti,ab,kw

#114 (menu AND ((nutritional NEXT content*) OR "nutritional information" OR (traffic NEXT light*) OR "guideline daily amount" OR GDA OR "healthy choice" OR calorie OR fat OR sugar OR salt)):ti,ab,kw

#115 (label* NEAR/2 (legislation* OR regulation* OR policies OR policy)):ti,ab,kw

#116 ((drink* NEXT label*) OR (drink* NEXT content* NEXT label*) OR (drink* NEXT content* NEXT sign*) OR (drink* NEXT content NEXT symbol*) OR (drink* NEXT content* NEXT tag*) OR (drink* NEXT content* NEXT ticket*) OR (drink* NEXT content* NEXT sticker*)):ti,ab,kw

#117 ((((soft OR sugar? OR sweet* OR carbonated OR energy OR sport? OR diet OR flavo?red OR fruit* OR milk* OR dairy OR yoghurt OR caffein* OR cold OR hot OR nonalcohol* OR non-alcohol*) NEAR/3 (drink? OR beverage?)) OR soda? OR (flavo?red NEXT water?) OR (fruit NEXT water?) OR cordial? OR squash? OR juice? OR smoothie? OR milkshake? OR tea OR teas OR coffee?) AND (label* OR (content* NEXT sign*) OR symbol* OR ticket* OR sticker*)):ti,ab,kw

#118 #93 OR #94 OR #97 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117

#119 [mh ^"Health Promotion"]

#120 ("well being" OR wellbeing OR wellness OR health* OR diet* OR nutrition OR food* OR exercis* OR (physical NEXT activ*) OR stress* OR smoking OR cigarette* OR tobacco):ti,ab,kw

#121 (intervention OR programme OR program*):ti,ab,kw

#122 #120 AND #121
#123 #119 OR #122
#124 (worksite* OR workplace* OR worker* OR occupation* OR job OR jobs OR employee* OR employment OR corporate):ti,ab,kw
#125 [mh ^Workplace]
#126 #124 OR #125
#127 #123 AND #126
#128 ((limit* OR restrict* OR regulat* OR standard*) AND (marketing OR adverti* OR promot*)):ti,ab,kw
#129 [mh ^"Advertising as Topic"]
#130 [mh marketing]
#131 #129 OR #130
#132 (limit* OR restrict* OR regulat* OR standard*):ti,ab,kw
#133 #131 AND #132
#134 #128 OR #133
#135 (food* OR fat* OR sugar* OR salt OR diet* OR nutritio* OR snack* OR eat*):ti,ab,kw
#136 (((soft OR sugar? OR sweet* OR carbonated OR energy OR sport? OR diet OR flavo?red OR fruit* OR milk* OR dairy OR yoghurt OR caffein* OR cold OR hot OR nonalcohol* OR non-alcohol*) NEAR/3 (drink? OR beverage?)) OR soda? OR (flavo?red NEXT water?) OR (fruit NEXT water?) OR cordial? OR squash? OR juice? OR smoothie? OR milkshake? OR tea OR teas OR coffee?):ti,ab,kw
#137 (tobacco OR cigarette* OR smoking):ti,ab,kw
#138 #135 OR #136 OR #137
#139 #134 AND #138
#140 "air pollution":ti,ab,kw
#141 [mh "Air Pollution"]
#142 "particulate matter":ti,ab,kw
#143 [mh "Particulate Matter"]
#144 "carbon monoxide":ti,ab,kw
#145 [mh "Carbon Monoxide"]
#146 [mh "Air Pollutants"]
#147 [mh "Sulfur Dioxide"]
#148 "sulphur dioxide":ti,ab,kw
#149 "nitrogen dioxide":ti,ab,kw
#150 [mh "Nitrogen Dioxide"]
#151 ozone:ti,ab,kw
#152 [mh Ozone]
#153 #140 OR #141 OR #142 OR #143 OR #144 OR #145 OR #146 OR #147 OR #148 OR #149 OR #150 OR #151 OR #152
#154 ((availability OR accessibility) AND (supermarket* OR ((recreation OR exercise OR (physical NEXT activit*)) NEAR/3 (space* OR facilit* OR ground*)) OR (park OR parks OR playground*))):ti,ab,kw
#155 ((improve* OR increas* OR expand*) AND (((land-use OR pavement* OR sidewalk* OR street) NEAR/1 design) OR "traffic safety" OR (neighbo?r-hood NEXT a?sthetics) OR walkability OR "pedestrian infrastructure" OR ((local OR neighbo?rhood OR built) NEAR/3 environment*))):ti,ab,kw
#156 (((limit* OR restrict* OR reduc*) NEAR/3 (density OR number)) AND ((shop* OR outlet*) NEAR/3 (tobacco OR cigarette* OR smoking))):ti,ab,kw
#157 #154 OR #155 OR #156
#158 ("population-level" OR "population level"):ti,ab,kw
#159 ((structural or policy or policies or population*) NEAR/1 (approach* or intervention* or strateg*)):ti,ab,kw
#160 #158 OR #159
#161 #63 OR #73 OR #90 OR #118 OR #127 OR #139 OR #153 OR #157 OR #160
#162 #17 AND #161

Appendix 3 Included studies references

1. Dayton S, Pearce ML. Prevention of coronary heart disease and other complications of atherosclerosis by modified diet. *Am J Med* 1969;**46**:751–62.
2. Holme I, Kjeldsen SE. Long-term survival in the randomized trial of drug treatment in mild to moderate hypertension of the Oslo study 1972–3. *Eur J Intern Med* 2015;**26**:123–6. https://doi.org/10.1016/j.ejim.2015.01.013
3. Holme I, Retterstol K, Norum KR, Hjermann I. Lifelong benefits on myocardial infarction mortality: 40-year follow-up of the randomized Oslo diet and antismoking study. *J Intern Med* 2016;**280**:221–7. https://doi.org/10.1111/joim.12485
4. Virtamo J, Rapola JM, Ripatti S, Heinonen OP, Taylor PR, Albanes D, Huttunen JK. Effect of vitamin E and beta carotene on the incidence of primary nonfatal myocardial infarction and fatal coronary heart disease. *Arch Intern Med* 1998;**158**:668–75. https://doi.org/10.1001/archinte.158.6.668
5. Kitas GD, Nightingale P, Armitage J, Sattar N, Belch JJF, Symmons DPM. A multicenter, randomized, placebo-controlled trial of atorvastatin for the primary prevention of cardiovascular events in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2019;**71**:1437–49. https://doi.org/10.1002/art.40892
6. Alehagen U, Lindahl TL, Aaseth J, Svensson E, Johansson P. Levels of sP-selectin and hs-CRP decrease with dietary intervention with selenium and coenzyme Q10 combined: a secondary analysis of a randomized clinical trial. *PLOS ONE* 2015;**10**:e0137680. https://doi.org/10.1371/journal.pone.0137680
7. Alehagen U, Aaseth J, Alexander J, Johansson P. Still reduced cardiovascular mortality 12 years after supplementation with selenium and coenzyme Q10 for four

years: A validation of previous 10-year follow-up results of a prospective randomized double-blind placebo-controlled trial in elderly. *PLOS ONE* 2018;**13**:e0193120. https://doi.org/10.1371/journal.pone.0193120
8. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;**358**:580–91. https://doi.org/10.1056/NEJMoa0706245
9. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, *et al.* Rosuvastatin to prevent vascular events in men and women with elevated c-reactive protein. *N Engl J Med* 2008;**359**:2195–207. https://doi.org/doi:10.1056/NEJMoa0807646
10. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005;**142**:233–9. https://doi.org/10.7326/0003-4819-142-4-200502150-00005
11. Beishuizen ED, van de Ree MA, Jukema JW, Tamsma JT, van der Vijver JC, Meinders AE, *et al.* 2-year statin therapy does not alter the progression of intima-media thickness in patients with type 2 diabetes without manifest cardiovascular disease. *Diabetes Care* 2004;**27**:2887–92. https://doi.org/10.2337/diacare.27.12.2887
12. Berglund G, Sannerstedt R, Andersson O, Wedel H, Wilhelmsen L, Hansson L, *et al.* Coronary heart-disease after treatment of hypertension. *Lancet* 1978;**1**:1–5. https://doi.org/10.1016/s0140-6736(78)90356-2
13. Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, *et al.* Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *Br Med J* 2008;**336**:262–6. https://doi.org/10.1136/bmj.39440.525752.BE
14. Buring JE. Aspirin prevents stroke but not MI in women; vitamin E has no effect on CV disease or cancer. *Cleve Clin J Med* 2006;**73**:863–70.
15. Chang HY, Hu YW, Yue CS, Wen YW, Yeh WT, Hsu LS, *et al.* Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. *Am J Clin Nutr* 2006;**83**:1289–96. https://doi.org/10.1093/ajcn/83.6.1289
16. Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. *Br Med J (Clin Res Ed)* 1986;**293**:1145–51. https://doi.org/10.1136/bmj.293.6555.1145
17. Corella D, Carrasco P, Sorli JV, Estruch R, Rico-Sanz J, Martinez-Gonzalez MA, *et al.* Mediterranean diet reduces the adverse effect of the TCF7L2-rs7903146 polymorphism on cardiovascular risk factors and stroke incidence: a randomized controlled trial in a high-cardiovascular-risk population. *Diabetes Care* 2013;**36**:3803–11. https://doi.org/10.2337/dc13-0955
18. Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, *et al.*; Cardiovascular Outcome Investigators. Cardiovascular efficacy and safety of bococizumab in high-risk patients. *N Engl J Med* 2017;**376**:1527–39. https://doi.org/doi:10.1056/NEJMoa1701488
19. Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, *et al.*; Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. *JAMA* 2010;**303**:841–8. https://doi.org/10.1001/jama.2010.221
20. Frantz ID Jr, Dawson EA, Ashman PL, Gatewood LC, Bartsch GE, Kuba K, Brewer ER. Test of effect of lipid lowering by diet on cardiovascular risk. The Minnesota Coronary Survey. *Arteriosclerosis* 1989;**9**:129–35. https://doi.org/10.1161/01.atv.9.1.129
21. Gaede P, Vedel P, Larsen N, Jensen G, Parving HH, Pedersen O. The Steno-2 study: intensified multifactorial intervention reduces the risk of cardiovascular disease in patients with Type 2 diabetes and microalbuminuria. 38th Annual Meeting of the European Association for the Study of Diabetes (EASD); 2002 September 1-5; Budapest, Hungary; 2002.
22. Gong J, Chen X, Li S. Efficacy of a community-based physical activity program KM2H2 for stroke and heart attack prevention among senior hypertensive patients: a cluster randomized controlled phase-II trial. *PLOS ONE* 2015;**10**:e0139442. https://doi.org/10.1371/journal.pone.0139442
23. Hackett G, Cole N, Mulay A, Strange RC, Ramachandran S. Long-term testosterone therapy in type 2 diabetes is associated with reduced mortality without improvement in conventional cardiovascular risk factors. *BJU Int* 2019;**123**:519–29. https://doi.org/10.1111/bju.14536
24. Hao G, Li W, Wang W, Yang J, Wang Y, Wang Z, *et al.* Pp.Lb03.21. *J Hypertens* 2015;**33**:e522. https://doi.org/10.1097/01.hjh.0000469039.45061.d9
25. Hinderliter AL, Smith P, Sherwood A, Blumenthal J. Lifestyle interventions to reduce blood pressure also lower predicted lifetime risk of atherosclerotic cardiovascular disease events. *J Am Soc Hypertension* 2015;**9**:e98
26. Hsia J, Langer RD, Manson JE, Kuller L, Johnson KC, Hendrix SL, *et al.* Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med* 2006;**166**:357–65. https://doi.org/10.1001/archinte.166.3.357
27. Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, *et al.* Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* 1993;**85**:1483–92. https://doi.org/10.1093/jnci/85.18.1483

28. Jarrett RJ, Keen H, Fuller JH, McCartney M. Treatment of borderline diabetes: controlled trial using carbohydrate restriction and phenformin. *Br Med J* 1977;**2**:861–5. https://doi.org/10.1136/bmj.2.6091.861
29. Leonetti G, Cuspidi C, Sampieri L, Ambrosioni E, Malini PL, Pessina A, *et al.* Evaluation of the efficacy and safety of enalapril plus hydrochlorothiazide plus methyldopa vs standard triple therapy in the treatment of moderate to severe hypertension: results from a multicentre study. *J Hum Hypertens* 1990;**4**:5–11.
30. Li G, Zhang P, Wang J, An Y, Gong Q, Gregg E, *et al.* Abstracts of the 72nd scientific sessions of the American Diabetes Association. June 8–12, 2012. Philadelphia, Pennsylvania, USA. *Diabetes* 2012;**61 Suppl 1**:A1–722. https://doi.org/10.2337/db12-1-377
31. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, *et al.* Marine n-3 Fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med* 2019;**380**:23–32. https://doi.org/10.1056/NEJMoa1811403
32. Lonn EM, Jung H, Yusuf S. Blood-Pressure and cholesterol lowering in the HOPE-3 trial. *N Engl J Med* 2016;**375**:1193–4. https://doi.org/10.1056/NEJMc1608916
33. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, *et al.* Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med* 2019;**380**:33–44. https://doi.org/10.1056/NEJMoa1809944
34. Mark SD, Wang W, Fraumeni JF Jr, Li JY, Taylor PR, Wang GQ, *et al.* Lowered risks of hypertension and cerebrovascular disease after vitamin/mineral supplementation: the Linxian Nutrition Intervention Trial. *Am J Epidemiol* 1996;**143**:658–64. https://doi.org/10.1093/oxfordjournals.aje.a008798
35. Miettinen TA, Huttunen JK, Naukkarinen V, Strandberg T, Mattila S, Kumlin T, Sarna S. Multifactorial primary prevention of cardiovascular diseases in middle-aged men. Risk factor changes, incidence, and mortality. *JAMA* 1985;**254**:2097–102.
36. Natvig H, Borchgrevink CF, Dedichen J, Owren PA, Schiotz EH, Westlund K. A controlled trial of the effect of linolenic acid on incidence of coronary heart disease. The Norwegian vegetable oil experiment of 1965-66. *Scand J Clin Lab Invest Suppl* 1968;**105**:1–20.
37. Naukkarinen VA, Strandberg TE, Vanhanen HT, Salomaa VV, Sarna SJ, Miettinen TA. Mortality rates after multifactorial primary prevention of cardiovascular diseases. *Ann Med* 1989;**21**:441–6. https://doi.org/10.3109/07853898909149236
38. Oellgaard J, Gaede P, Rossing P, Rorth R, Kober L, Parving HH, *et al.* Reduced risk of heart failure with intensified multifactorial intervention in individuals with type 2 diabetes and microalbuminuria: 21 years of follow-up in the randomised Steno-2 study. *Diabetologia* 2018;**61**:1724–33. https://doi.org/10.1007/s00125-018-4642-y
39. Patel C, Marmot MG, Terry DJ, Carruthers M, Hunt B, Patel M. Trial of relaxation in reducing coronary risk: four year follow up. *Br Med J (Clin Res Ed)* 1985;**290**:1103–6. https://doi.org/10.1136/bmj.290.6475.1103
40. Rachmani R, Levi Z, Slavachevski I, Avin M, Ravid M. Teaching patients to monitor their risk factors retards the progression of vascular complications in high-risk patients with Type 2 diabetes mellitus – a randomized prospective study. *Diabetic Med* 2002;**19**:385–92.
41. Radford LT, Bolland MJ, Mason B, Horne A, Gamble GD, Grey A, Reid IR. The Auckland calcium study: 5-year post-trial follow-up. *Osteoporos Int* 2014;**25**:297–304. https://doi.org/10.1007/s00198-013-2526-z
42. Scragg R, Stewart AW, Waayer D, Lawes CMM, Toop L, Sluyter J, *et al.* Effect of Monthly high-dose vitamin d supplementation on cardiovascular disease in the vitamin D assessment study: a randomized clinical trial. *JAMA Cardiol* 2017;**2**:608–16. https://doi.org/10.1001/jamacardio.2017.0175
43. Strandberg TE, Salomaa VV, Naukkarinen VA, Vanhanen HT, Sarna SJ, Miettinen TA. Long-term mortality after 5-year multifactorial primary prevention of cardiovascular diseases in middle-aged men. *JAMA* 1991;**266**:1225–9.
44. Effects of treatment on morbidity in hypertension. 3. Influence of age, diastolic pressure, and prior cardiovascular disease; further analysis of side effects. *Circulation* 1972;**45**:991–1004.
45. Woods KL, Fletcher S. Long-term outcome after intravenous magnesium sulphate in suspected acute myocardial infarction: the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 1994;**343**:816–9. https://doi.org/10.1016/s0140-6736(94)92024-9
46. Yamashita K, Kondo T, Muramatsu T, Matsushita K, Nagahiro T, Maeda K, *et al.* Effects of valsartan versus amlodipine in diabetic hypertensive patients with or without previous cardiovascular disease. *Am J Cardiol* 2013;**112**:1750–6. https://doi.org/10.1016/j.amjcard.2013.07.043
47. Schrier RW, Estacio RO. Additional follow-up from the ABCD trial in patients with type 2 diabetes and hypertension. *N Engl J Med* 2000;**343**:1969. https://doi.org/10.1056/nejm200012283432614
48. Bakris GL, Oparil S, Purkayastha D, Yadao AM, Alessi T, Sowers JR. Randomized study of antihypertensive efficacy and safety of combination aliskiren/valsartan vs valsartan monotherapy in hypertensive participants

with type 2 diabetes mellitus. *J Clin Hypertens (Greenwich)* 2013;**15**:92–100. https://doi.org/10.1111/jch.12032
49. Patel A, Group AC, MacMahon S, Chalmers J, Neal B, Woodward M, *et al.* Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;**370**:829–40. https://doi.org/10.1016/S0140-6736(07)61303-8
50. Downs JR, Clearfield M, Tyroler HA, Whitney EJ, Kruyer W, Langendorfer A, *et al.* Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS): additional perspectives on tolerability of long-term treatment with lovastatin. *Am J Cardiol* 2001;**87**:1074–9. https://doi.org/10.1016/s0002-9149(01)01464-3
51. Han BH, Sutin D, Williamson JD, Davis BR, Piller LB, Pervin H, *et al.* Effect of statin treatment vs usual care on primary cardiovascular prevention among older adults: The ALLHAT-LLT randomized clinical trial. *JAMA Intern Med* 2017;**177**:955–65. https://doi.org/10.1001/jamainternmed.2017.1442
52. Gaziano JM, Brotons C, Coppolecchia R, Cricelli C, Darius H, Gorelick PB, *et al.* Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2018;**392**:1036–46. https://doi.org/10.1016/S0140-6736(18)31924-X
53. McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, *et al.* Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med* 2018;**379**:1509–18. https://doi.org/10.1056/NEJMoa1805819
54. Group ASC, Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, *et al.* Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med* 2018;**379**:1540–50. https://doi.org/10.1056/NEJMoa1804989
55. Kataja-Tuomola MK, Kontto JP, Mannisto S, Albanes D, Virtamo JR. Effect of alpha-tocopherol and beta-carotene supplementation on macrovascular complications and total mortality from diabetes: results of the ATBC Study. *Ann Med* 2010;**42**:178–86. https://doi.org/10.3109/07853890903508887
56. Doyle AE. The Australian therapeutic trial in mild hypertension. *Nephron* 1987;**47**:115–9. https://doi.org/10.1159/000184567
57. De Backer G. Multicentre study of the efficacy and tolerance of acebutolol versus atenolol in the long term treatment of mild arterial hypertension. *Drugs* 1988;**36**:51–6. https://doi.org/10.2165/00003495-198800362-00009
58. Ruggenenti P, Fassi A, Ilieva A, Iliev IP, Chiurchiu C, Rubis N, *et al.* Effects of verapamil added-on trandolapril therapy in hypertensive type 2 diabetes patients with microalbuminuria: the BENEDICT-B randomized trial. *J Hypertens* 2011;**29**:207–16. https://doi.org/10.1097/hjh.0b013e32834069bd
59. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, *et al.* Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). *Am J Kidney Dis* 2009;**54**:810–9. https://doi.org/10.1053/j.ajkd.2009.03.022
60. Goodman GE, Thornquist MD, Balmes J, Cullen MR, Meyskens FL Jr, Omenn GS, *et al.* The Beta-Carotene and Retinol Efficacy Trial: incidence of lung cancer and cardiovascular disease mortality during 6-year follow-up after stopping beta-carotene and retinol supplements. *J Natl Cancer Inst* 2004;**96**:1743–50. https://doi.org/10.1093/jnci/djh320
61. Nakao K, Hirata M, Oba K, Yasuno S, Ueshima K, Fujimoto A, *et al.* Role of diabetes and obesity in outcomes of the candesartan antihypertensive survival evaluation in Japan (CASE-J) trial. *Hypertens Res* 2010;**33**:600–6. https://doi.org/10.1038/hr.2010.38
62. Casiglia E, Spolaore P, Mazza A, Ginocchio G, Colangeli G, Onesto C, *et al.* Effect of two different therapeutic approaches on total and cardiovascular mortality in a Cardiovascular Study in the Elderly (CASTEL). *Jpn Heart J* 1994;**35**:589–600. https://doi.org/10.1536/ihj.35.589
63. Kaczorowski J, Chambers LW, Dolovich L, Paterson JM, Karwalajtys T, Gierman T, *et al.* Improving cardiovascular health at population level: 39 community cluster randomised trial of Cardiovascular Health Awareness Program (CHAP). *Br Med J* 2011;**342**:d442. https://doi.org/10.1136/bmj.d442
64. Wang SM, Taylor PR, Fan JH, Pfeiffer RM, Gail MH, Liang H, *et al.* Effects of Nutrition intervention on total and cancer mortality: 25-year post-trial follow-up of the 5.25-year linxian nutrition intervention trial. *J Natl Cancer Inst* 2018;**110**:1229–38. https://doi.org/10.1093/jnci/djy043
65. Ogihara T, Saruta T, Rakugi H, Saito I, Shimamoto K, Matsuoka H, *et al.* Combinations of olmesartan and a calcium channel blocker or a diuretic in elderly hypertensive patients: a randomized, controlled trial. *J Hypertens* 2014;**32**:2054–63; discussion 2063. https://doi.org/10.1097/HJH.0000000000000281
66. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Report from the committee of principal investigators. *Br Heart J* 1978;**40**:1069–118. https://doi.org/10.1136/hrt.40.10.1069

67. Huo Y, Li J, Qin X, Huang Y, Wang X, Gottesman RF, *et al*. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA* 2015;**313**:1325–35. https://doi.org/10.1001/jama.2015.2274
68. Li G, Zhang P, Wang J, An Y, Gong Q, Gregg EW, *et al*. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. *Lancet Diabetes Endocrinol* 2014;**2**:474–80. https://doi.org/10.1016/S2213-8587(14)70057-9
69. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: The DCCT/EDIC study 30-year follow-up. *Diabetes Care* 2016;**39**:686–93. https://doi.org/10.2337/dc15-1990
70. Kochen MM. Primary prevention of ischemic stroke: the rebirth of folic acid. *Zeitschrift fur allgemeinmedizin* 2015;**91**:244–6.
71. Marre M, Lievre M, Chatellier G, Mann JF, Passa P, Menard J. Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). *Br Med J* 2004;**328**:495. https://doi.org/10.1136/bmj.37970.629537.0D
72. Hanefeld M, Fischer S, Schmechel H, Rothe G, Schulze J, Dude H, *et al*. Diabetes Intervention study. multi-intervention trial in newly diagnosed NIDDM. *Diabetes Care* 1991;**14**:308–17. https://doi.org/10.2337/diacare.14.4.308
73. Investigators DT, Dagenais GR, Gerstein HC, Holman R, Budaj A, Escalante A, *et al*. Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. *Diabetes Care* 2008;**31**:1007–14. https://doi.org/10.2337/dc07-1868
74. Suzuki H, Kanno Y; Efficacy of Candesartan on Outcome in Saitama Trial. Effects of candesartan on cardiovascular outcomes in Japanese hypertensive patients. *Hypertens Res* 2005;**28**:307–14. https://doi.org/10.1291/hypres.28.307
75. Staessen J, Amery A, Birkenhäger W, Bulpitt C, Clement D, de Leeuw P, *et al*. Is a high serum cholesterol level associated with longer survival in elderly hypertensives? *J Hypertens* 1990;**8**:755–61. https://doi.org/10.1097/00004872-199008000-00010
76. Tatti P, Pahor M, Byington RP, Di Mauro P, Guarisco R, Strollo G, Strollo F. Outcome results of the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998;**21**:597–603. https://doi.org/10.2337/diacare.21.4.597
77. Muhlestein JB, Lappe DL, Lima JA, Rosen BD, May HT, Knight S, *et al*. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. *JAMA* 2014;**312**:2234–43. https://doi.org/10.1001/jama.2014.15825
78. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. *J Hypertens* 2005;**23**:2157–72. https://doi.org/10.1097/01.hjh.0000194120.42722.ac
79. Tonkin A, Hunt D, Voysey M, Kesaniemi A, Hamer A, Waites J, *et al*. Effects of fenofibrate on cardiovascular events in patients with diabetes, with and without prior cardiovascular disease: The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Am Heart J* 2012;**163**:508–14. https://doi.org/10.1016/j.ahj.2011.12.004
80. The IPPPSH Collaborative Group. Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: the International Prospective Primary Prevention Study in Hypertension (IPPPSH). *J Hypertens* 1985;**3**:379–92. https://doi.org/10.1097/00004872-198508000-00011
81. Maitland-van der Zee AH, Boerwinkle E, Arnett DK, Davis BR, Leiendecker-Foster C, Miller MB, *et al*. Absence of an interaction between the angiotensin-converting enzyme insertion-deletion polymorphism and pravastatin on cardiovascular disease in high-risk hypertensive patients: the Genetics of Hypertension-Associated Treatment (GenHAT) study. *Am Heart J* 2007;**153**:54–8. https://doi.org/10.1016/j.ahj.2006.10.019
82. Wilhelmsen L, Berglund G, Elmfeldt D, Tibblin G, Wedel H, Pennert K, *et al*. The multifactor primary prevention trial in Goteborg, Sweden. *Eur Heart J* 1986;**7**:279–88. https://doi.org/10.1093/oxfordjournals.eurheartj.a062065
83. Wilhelmsen L, Berglund G, Elmfeldt D, Fitzsimons T, Holzgreve H, Hosie J, *et al*. Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. *J Hypertens* 1987;**5**:561–72. https://doi.org/10.1097/00004872-198710000-00009
84. Huttunen JK, Heinonen OP, Manninen V, Koskinen P, Hakulinen T, Teppo L, *et al*. The Helsinki Heart Study: an 8.5-year safety and mortality follow-up. *J Intern Med* 1994;**235**:31–9. https://doi.org/10.1111/j.1365-2796.1994.tb01029.x
85. Asayama K, Ohkubo T, Metoki H, Obara T, Inoue R, Kikuya M, *et al*. Cardiovascular outcomes in the first trial

of antihypertensive therapy guided by self-measured home blood pressure. *Hypertens Res* 2012;**35**:1102–10. https://doi.org/10.1038/hr.2012.125
86. Bulbulia R, Bowman L, Wallendszus K, Collins R, Meade T, Sleight P, *et al.* Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial. *Lancet* 2011;**378**:2013–20. https://doi.org/10.1016/S0140-6736%2811%2961125-2
87. Mancia G, Brown M, Castaigne A, de Leeuw P, Palmer CR, Rosenthal T, *et al*. Outcomes with nifedipine GITS or Co-amilozide in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). *Hypertension* 2003;**41**:431–6. https://doi.org/10.1161/01.HYP.0000057420.27692.AD
88. Jorgensen T, Jacobsen RK, Toft U, Aadahl M, Glumer C, Pisinger C. Effect of screening and lifestyle counselling on incidence of ischaemic heart disease in general population: Inter99 randomised trial. *Br Med J* 2014;**348**:g3617. https://doi.org/10.1136/bmj.g3617
89. Ueki K, Sasako T, Okazaki Y, Kato M, Okahata S, Katsuyama H, *et al*. Effect of an intensified multifactorial intervention on cardiovascular outcomes and mortality in type 2 diabetes (J-DOIT3): an open-label, randomised controlled trial. *Lancet Diabetes Endocrinol* 2017;**5**:951–64. https://doi.org/10.1016/S2213-8587(17)30327-3
90. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, *et al*. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis Lancet. 2007 Jul 21;370(9583): 220. *Lancet* 2007;**369**:1090–8.
91. Saito Y, Okada S, Ogawa H, Soejima H, Sakuma M, Nakayama M, *et al*. Low-dose aspirin for primary prevention of cardiovascular events in patients with type 2 diabetes mellitus: 10-year follow-up of a randomized controlled trial. *Circulation* 2017;**135**:659–70. https://doi.org/10.1161/CIRCULATIONAHA.116.025760
92. Uchiyama S, Ishizuka N, Shimada K, Teramoto T, Yamazaki T, Oikawa S, *et al*. Aspirin for stroke prevention in elderly patients with vascular risk factors: Japanese primary prevention project. *Stroke* 2016;**47**:1605–11. https://doi.org/10.1161/STROKEAHA.115.012461
93. Sugawara M, Goto Y, Yamazaki T, Teramoto T, Oikawa S, Shimada K, *et al*. Low-dose aspirin for primary prevention of cardiovascular events in elderly Japanese patients with atherosclerotic risk factors: subanalysis of a randomized clinical trial (JPPP-70). *Am J Cardiovasc Drugs* 2019;**19**:299–311. https://doi.org/10.1007/s40256-018-0313-0
94. Everett BM, Glynn RJ, MacFadyen JG, Ridker PM. Rosuvastatin in the prevention of stroke among men and women with elevated levels of C-reactive protein: justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). *Circulation* 2010;**121**:143–50. https://doi.org/10.1161/CIRCULATIONAHA.109.874834
95. Kyushu Lipid Intervention Study Group. Pravastatin use and risk of coronary events and cerebral infarction in Japanese men with moderate hypercholesterolemia: the Kyushu Lipid Intervention Study. *J Atheroscler Thromb* 2000;**7**:110–21. https://doi.org/10.5551/jat1994.7.110
96. Gong Q, Zhang P, Ma J, Wang J, An Y, Cheng YJ, *et al.* Lifestyle interventions lower cardiovascular disease in Chinese adults with IgT – thirty-year follow-up of Da Qing diabetes prevention study. *Diabetes* 2018;**67**:A35.
97. Gilbert M, Bain S, Franek E, Jodar-Gimeno E, Nauck M, Pratley R, *et al.* Effect of liraglutide on cardiovascular outcomes in elderly patients in the leader trial. *J Am Coll Cardiol* 2018;**71**:A1718. https://doi.org/10.1016/s0735-1097(18)32259-9
98. Newman AB, Dodson JA, Church TS, Buford TW, Fielding RA, Kritchevsky S, *et al.*; LIFE Study Group. Cardiovascular Events in a Physical Activity Intervention Compared With a Successful Aging Intervention: The LIFE Study Randomized Trial. *JAMA Cardiol* 2016;**1**:568–74. https://doi.org/10.1001/jamacardio.2016.1324
99. Sasaki J, Yamamoto K, Ageta M. Effects of fenofibrate on high-density lipoprotein particle size in patients with hyperlipidemia: a randomized, double-blind, placebo-controlled, multicenter, crossover study. *Clin Ther* 2002;**24**:1614–26. https://doi.org/10.1016/s0149-2918(02)80064-9
100. The Lipid Research Clinics Coronary Primary Prevention Trial. Results of 6 years of post-trial follow-up. The Lipid Research Clinics Investigators. *Arch Intern Med* 1992;**152**:1399–410.
101. Olsson G, Tuomilehto J, Berglund G, Elmfeldt D, Warnold I, Barber H, *et al.* Primary prevention of sudden cardiovascular death in hypertensive patients. Mortality results from the MAPHY Study. *Am J Hypertens* 1991;**4**:151–8. https://doi.org/10.1093/ajh/4.2.151
102. Kushiro T, Nakamura H. Primary prevention of cardiovascular events with pravastatin in patients with hypertension in the MEGA study: a multicenter randomized controlled trial. *J Hypertens* 2006;**24**:32.
103. Party, MRC Working. Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. *Br Med J* 1992;**304**:405–12. https://doi.org/10.1136/bmj.304.6824.405
104. Multiple Risk Factor Intervention Trial Research Group. Mortality after 16 years for participants randomized to the Multiple Risk Factor Intervention Trial. *Circulation* 1996;**94**:946–51. https://doi.org/10.1161/01.cir.94.5.946

105. Treatment of mild hypertension in the elderly. A study initiated and administered by the National Heart Foundation of Australia. *Med J Aust* 1981;**2**:398–402.
106. ORIGIN Trial Investigators. Cardiovascular and Other Outcomes Postintervention With Insulin Glargine and Omega-3 Fatty Acids (ORIGINALE). *Diabetes Care* 2016;**39**:709–16. https://doi.org/10.2337/dc15-1676
107. Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, Schvartz M, *et al.* Multivitamins in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA* 2012;**308**:1751–60. https://doi.org/10.1001/jama.2012.14805
108. Sacco M, Pellegrini F, Roncaglioni MC, Avanzini F, Tognoni G, Nicolucci A; PPP Collaborative Group. Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. *Diabetes Care* 2003;**26**:3264–72. https://doi.org/10.2337/diacare.26.12.3264
109 Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, *et al.* Primary Prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med* 2018;**378**:e34. https://doi.org/10.1056/NEJMoa1800389
110. Maruthur NM, Wang NY, Appel LJ. Lifestyle interventions reduce coronary heart disease risk: results from the PREMIER Trial. *Circulation* 2009;**119**:2026–31. https://doi.org/10.1161/CIRCULATIONAHA.108.809491
111. Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA, *et al.* Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation* 2004;**110**:2809–16. https://doi.org/10.1161/01.CIR.0000146378.65439.7A
112. Matsuzaki M, Ogihara T, Umemoto S, Rakugi H, Matsuoka H, Shimada K, *et al.* Prevention of cardiovascular events with calcium channel blocker-based combination therapies in patients with hypertension: a randomized controlled trial. *J Hypertens* 2011;**29**:1649–59. https://doi.org/10.1097/HJH.0b013e328348345d
113. Lloyd SM, Stott DJ, de Craen AJ, Kearney PM, Sattar N, Perry I, *et al.* Long-term effects of statin treatment in elderly people: extended follow-up of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). *PLOS ONE* 2013;**8**:e72642. https://doi.org/10.1371/journal.pone.0072642
114. Fagerberg B, Wikstrand J, Berglund G, Samuelsson O, Agewall S. Mortality rates in treated hypertensive men with additional risk factors are high but can be reduced: a randomized intervention study. *Am J Hypertens* 1998;**11**:14–22. https://doi.org/10.1016/s0895-7061(97)00363-4
115. Eight-year follow-up results from the Rome Project of Coronary Heart Disease Prevention. Research group of the Rome project of coronary heart disease prevention. *Prev Med* 1986;**15**:176–91. https://doi.org/10.1016/0091-7435(86)90087-3
116. Howard BV, Roman MJ, Devereux RB, Fleg JL, Galloway JM, Henderson JA, *et al.* Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. *JAMA* 2008;**299**:1678–89. https://doi.org/10.1001/jama.299.14.1678
117. Trenkwalder P, Regourd E, Kluth-Pepper B, Sauerbrey-Wullkopf N. Amlodipine besylate versus candesartan cilexetil in hypertensive patients – office and self-measured blood pressure: a randomised, double-blind, comparative, multicentre trial. *Clin Drug Investig* 2005;**25**:567–77. https://doi.org/10.2165/00044011-200525090-00002
118. Kostis JB, Cabrera J, Cheng JQ, Cosgrove NM, Deng Y, Pressel SL, Davis BR. Association between chlorthalidone treatment of systolic hypertension and long-term survival. *JAMA* 2011;**306**:2588–93. https://doi.org/10.1001/jama.2011.1821
119. Shea MK, Nicklas BJ, Marsh AP, Houston DK, Miller GD, Isom S, *et al.* The effect of pioglitazone and resistance training on body composition in older men and women undergoing hypocaloric weight loss. *Obesity (Silver Spring)* 2011;**19**:1636–46. https://doi.org/10.1038/oby.2010.327
120. Elkeles RS, Diamond JR, Poulter C, Dhanjil S, Nicolaides AN, Mahmood S, *et al.* Cardiovascular outcomes in type 2 diabetes. A double-blind placebo-controlled study of bezafibrate: the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study. *Diabetes Care* 1998;**21**:641–8. https://doi.org/10.2337/diacare.21.4.641
121. Malacco E, Vari N, Capuano V, Spagnuolo V, Borgnino C, Palatini P; Val-Syst study. A randomized, double-blind, active-controlled, parallel-group comparison of valsartan and amlodipine in the treatment of isolated systolic hypertension in elderly patients: the Val-Syst study. *Clin Ther* 2003;**25**:2765–80. https://doi.org/10.1016/s0149-2918(03)80332-6
122. Gong L, Zhang W, Zhu Y, Zhu J, Kong D, Page V, *et al.* Shanghai trial of nifedipine in the elderly (STONE). *J Hypertens* 1996;**14**:1237–45. https://doi.org/10.1097/00004872-199610000-00013
123. Dahlof B, Hansson L, Lindholm LH, Schersten B, Ekbom T, Wester PO. Swedish Trial in old patients with hypertension (STOP-Hypertension) analyses performed up to 1992. *Clin Exp Hypertens* 1993;**15**:925–39. https://doi.org/10.3109/10641969309037082
124. Lindholm LH, Hansson L, Ekbom T, Dahlof B, Lanke J, Linjer E, *et al.* Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old

Patients with Hypertension-2. STOP Hypertension-2 Study Group. *J Hypertens* 2000;**18**:1671–5. https://doi.org/10.1097/00004872-200018110-00020
125. Hercberg S, Kesse-Guyot E, Druesne-Pecollo N, Touvier M, Favier A, Latino-Martel P, *et al.* Incidence of cancers, ischemic cardiovascular diseases and mortality during 5-year follow-up after stopping antioxidant vitamins and minerals supplements: a postintervention follow-up in the SU.VI.MAX Study. *Int J Cancer* 2010;**127**:1875–81. https://doi.org/10.1002/ijc.25201
126. Lisheng L. Effects of hypertension control on stroke incidence and fatality: report from Syst.-China and post-stroke antihypertensive treatment. *J Hum Hypertens* 1996;**10**:S9–11.
127. Cauley JA, Chlebowski RT, Wactawski-Wende J, Robbins JA, Rodabough RJ, Chen Z, *et al.* Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative. *J Womens Health (Larchmt)* 2013;**22**:915–29. https://doi.org/10.1089/jwh.2013.4270
128. Thijs L, Richart T, De Leeuw PW, Kuznetsova T, Grodzicki T, Kawecka-Jaszcz K. Posters. *The Journal of Clinical Hypertension* 2010;**12**:A115. https://doi.org/10.1111/j.1751-7176.2010.00282.x
129. Bethel MA, Engel SS, Green JB, Huang Z, Josse RG, Kaufman KD, *et al.* Assessing the safety of sitagliptin in older participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). *Diabetes Care* 2017;**40**:494–501. https://doi.org/10.2337/dc16-1135
130. Cook NR, Appel LJ, Whelton PK. Weight change and mortality: Long-term results from the trials of hypertension prevention. *J Clin Hypertens (Greenwich)* 2018;**20**:1666–73. https://doi.org/10.1111/jch.13418
131. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med* 2008;**359**:1565–76. https://doi.org/10.1056/NEJMoa0806359
132. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;**359**:1577–89. https://doi.org/10.1056/NEJMoa0806470
133. Takano H, Hasegawa H, Narumi H, Shindo S, Mizuma H, Kuwabara Y, *et al.* Effects of valsartan and amlodipine on home blood pressure and cardiovascular events in Japanese hypertensive patients: a subanalysis of the VART. *J Hum Hypertens* 2012;**26**:656–63. https://doi.org/10.1038/jhh.2011.91
134. Hayward RA, Reaven PD, Wiitala WL, Bahn GD, Reda DJ, Ge L, *et al.*; VADT Investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;**372**:2197–206. https://doi.org/10.1056/NEJMoa1414266
135. Rosei EA, Dal Palu C, Leonetti G, Magnani B, Pessina A, Zanchetti A. Clinical results of the Verapamil in Hypertension and Atherosclerosis Study. VHAS Investigators. *J Hypertens* 1997;**15**:1337–44. https://doi.org/10.1097/00004872-199715110-00019
136. Rose G, Colwell L. Randomised controlled trial of anti-smoking advice: final (20 year) results. *J Epidemiol Community Health* 1992;**46**:75–7. https://doi.org/10.1136/jech.46.1.75
137. Margolis KL, O'Connor PJ, Morgan TM, Buse JB, Cohen RM, Cushman WC, *et al.* Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. *Diabetes Care* 2014;**37**:1721–8. https://doi.org/10.2337/dc13-2334
138. World Health Organisation European Collaborative Group. European collaborative trial of multifactorial prevention of coronary heart disease: final report on the 6-year results. *Lancet* 1986;**1**:869–72.
139. Kurth T, Diener HC, Buring JE. Migraine and cardiovascular disease in women and the role of aspirin: subgroup analyses in the Women's Health Study. *Cephalalgia* 2011;**31**:1106–15. https://doi.org/10.1177/0333102411412628
140. Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. Beta-carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. *J Natl Cancer Inst* 1999;**91**:2102–6. https://doi.org/10.1093/jnci/91.24.2102
141. Ford I, Murray H, McCowan C, Packard CJ. Long-term safety and efficacy of lowering low-density lipoprotein cholesterol with statin therapy: 20-year follow-up of West of Scotland Coronary Prevention Study. *Circulation* 2016;**133**:1073–80. https://doi.org/10.1161/CIRCULATIONAHA.115.019014
142. Bhatt DL, Eikelboom JW, Connolly SJ, Steg PG, Anand SS, Verma S, *et al.* Role of combination antiplatelet and anticoagulation therapy in diabetes mellitus and cardiovascular disease: insights from the COMPASS trial. *Circulation* 2020;**141**:1841–54. https://doi.org/10.1161/CIRCULATIONAHA.120.046448
143. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, *et al.* Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet* 2019;**394**:131–8. https://doi.org/10.1016/S0140-6736(19)31150-X
144. Manson JAE, Cook NR, Lee IM, Christen W, Mora S, Gibson H, *et al.* Late-breaking science abstracts from the American Heart Association's Scientific Sessions 2018 and late-breaking abstracts in resuscitation science from the Resuscitation Science Symposium 2018. *Circulation* 2018;**138**:e751–e82. https://doi.org/10.1161/CIR.0000000000000636

DOI: 10.3310/RLDH7432

Appendix 4 Characteristics of included studies

Study ID	Trial name	Country	Study period	Study design	Publication type	Study site	Study settings	Interventions	Intervention group	Intervention duration	Longest follow-up period	Sample size	Mean age	Per cent female	Mean BMI	Hypertension	Type 2 diabetes	Smoking
Dayton (1969)		USA	1959	Parallel RCT	Journal	Not reported	Hospital	Dietary/control	Non-pharmacological		96	846						
Holme (2015)	OSLO Study	Norway	1972–2012	Parallel RCT	Journal	Not reported	Community	BP lowering/control	Pharmacological	60	480	785					12.5	50.5
Holme (2016)	OSLO Diet and Antismoking	Norway	1972–2012	Parallel RCT	Journal	Not reported	Community	Health promotion/control	Non-pharmacological	60	480	296					10	24
Virtamo (1998)	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Finland		Parallel RCT	Journal	Multicentre	Others	Nutritional supplement/nutritional supplement/vitamin A/control	Non-pharmacological	96		27,271	57		26		4	100
Kitas (2019)	TRACE RA	UK	2007–12	Parallel RCT	Journal	Multicentre	Others	Lipid lowering/control	Pharmacological	16	42	3002	61	73.5	26.6			16
Alehagen (2015)		Sweden	2003–10	Parallel RCT	Journal	Not reported	Community	Nutritional supplement/control	Non-pharmacological	48	120	443	88	54.5			17.5	6.5
Alehagen (2018)		Sweden	2003–11	Parallel RCT	Journal	Not reported	Community	Nutritional supplement/control	Non-pharmacological	48	144	443	75.5	59			17.5	3.5
Gæde (2008)	Steno-2 Study	Sweden	1993–2006	Parallel RCT	Journal	Single centre	Others	Health promotion/health promotion	Mixed interventions	96	160	130	66		31		100	24
Alexander (2008)	JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin)	USA	?–2008	Parallel RCT	Conference abstract	Multicentre	Not reported	Lipid lowering/control	Pharmacological		21	17,802						
Anthonisen (2005)	Lung Health Study	Canada or USA?	1984–2005	Parallel RCT	Journal	Multicentre	Clinic	Others/control	Non-pharmacological	3	174	5887	48	45	25			100
Beishuizen (2004)		Netherlands	2001–4	Parallel RCT	Journal	Multicentre	Hospital	Lipid lowering/control	Pharmacological	24	24	250	58	52.5	31	50.5		24

Study ID	Trial name	Country	Study period	Study design	Publication type	Study site	Study settings	Interventions	Intervention group	Intervention duration	Longest follow-up period	Sample size	Mean age	Per cent female	Mean BMI	Hypertension	Type 2 diabetes	Smoking
Berglund (1978)		Sweden	1970–3	Parallel RCT	Journal	Single centre	Clinic	BP lowering/control	Pharmacological		52	1026	51.5					15
Bolland (2008)		New Zealand		Parallel RCT	Journal	Single centre	Others	Nutritional supplement/control	Non-pharmacological		60	1471	74	100	26.5		3	3
Buring (2006)		USA	1992–2004	Parallel RCT	Journal	Not reported	Workplace	Aspirin/control	Pharmacological		120	39,876		100				
Chang (2006)		Taiwan	1995–9	Parallel RCT	Journal	Single centre	Others	Dietary/control	Non-pharmacological	31	44	1981	75		23	40		
Coope (1986)		UK	1978–		Journal	Multicentre	Others	BP lowering/control	Pharmacological		53	904	68	37.5				5.5
Corella (2013)	PREvención con DIetaMEDiterranea	Spain	2003–10	Parallel RCT	Journal	Multicentre	Community	Dietary/dietary/control	Non-pharmacological		69	7016	67	57.7	30	83	48.7	14.3
EUCTR (2013)			2013–7	Parallel RCT		Multicentre	Not reported	Others/control	Pharmacological	36	1							
Fowkes (2010)		UK	1998–2008	Parallel RCT	Journal	Not reported	Community	Aspirin/control	Pharmacological		97	3350	62	61.5			3	32.5
Frantz (1989)				Parallel RCT	Journal	Multicentre	Hospital	Dietary/control	Pharmacological	36	15	9057		51.5				
Gæde (2016)	The Steno-2 Study	Denmark	1993–2014	Parallel RCT	Journal	Single centre	Others	Health promotion/health promotion	Mixed interventions	93	254	160	72	31.5	30.5	96.5	100	
Gæde (2003)	Steno-2 Study	Denmark	1993–2001	Parallel RCT	Journal	Single centre	Others	Health promotion/health promotion	Mixed interventions	96	96	160				41		
Gong (2015)		China	2011	Cluster RCT	Journal	Multicentre	Community	Physical activity/control	Non-pharmacological		6	450	64	58				19
Hackett (2019)	BLAST			Parallel RCT	Journal	Multicentre	Others	Others/others/others	Pharmacological		46	857	62.7		31.7			8
Hao (2015)		China		Cluster RCT	Conference abstract	Not reported	Not reported	Health promotion/control	Non-pharmacological			12,245						
Hinderliter (2015)	ENCORE	USA		Parallel RCT	Conference abstract	Not reported	Not reported	Multicomponent/dietary/control	Non-pharmacological	4		131						
Hsia (2006)			1995–2000	Parallel RCT	Journal	Multicentre	Clinic	Nutritional supplement/control	Non-pharmacological	84	101	36,282	62	100	29	33.5	6	

This research article should be referenced as follows: Uthman OA, Court R, Enderby J, Nduka C, Al-Khudairy L, Anjorin S, *et al.* Identifying optimal primary prevention interventions for major cardiovascular disease events and all-cause mortality: a systematic review and hierarchical network meta-analysis of RCTs. *Health Technol Assess* 2025;**29**(37):75–140. https://doi.org/10.3310/RLDH7432

DOI: 10.3310/RLDH7432

Study ID	Trial name	Country	Study period	Study design	Publication type	Study site	Study settings	Interventions	Intervention group	Intervention duration	Longest follow-up period	Sample size	Mean age	Per cent female	Mean BMI	Hypertension	Type 2 diabetes	Smoking
Blot (1993)		China	1986–91	Parallel RCT	Journal	Multicentre	Others		Non-pharmacological									
Jarrett (1977)		UK	1968–	Parallel RCT	Journal	Not reported	Workplace	Blood glucose lowering/control	Mixed interventions	60								
Leonetti (1990)					Journal	Multicentre	Clinic	BP lowering/control	Pharmacological	6	0	2184	59	48				
Li (2012)			1986–92		Conference abstract	Multicentre	Clinic	Multicomponent/control	Non-pharmacological	72	276							
Manson (a) (2019)		USA	2011–7	Parallel RCT	Journal	Not reported	Not reported	Nutritional supplement/control	Non-pharmacological	73	73	25,871	67	51	28	50	13.5	7
Lonn (2016)	Heart Outcomes Prevention Evaluation (HOPE) – 3 trials		2007–15	Parallel RCT	Journal	Multicentre		BP lowering/control	Pharmacological	42	103	12,705	66	46.5	27	38	5.5	27.5
Lu (2018){Lu, 2018 #216}		China		Parallel RCT	Conference abstract	Not reported	Clinic	BP lowering/BP lowering	Pharmacological		41	13,542						
Manson (b) (2019)		USA	2011–7	Parallel RCT	Journal	Not reported	Not reported	Nutritional supplement/control	Non-pharmacological	73	73	25,871	67	51	28	50	13.5	7
Mark (1996)		China	1985–91	Parallel RCT	Journal	Not reported	Not reported	Nutritional supplement/control	Non-pharmacological	72	0			56				
Miettinen (1985)				Parallel RCT	Journal	Not reported	Workplace	Health promotion/health promotion/control	Mixed interventions		60	1815	47.7			22.7		16.7
Natvig (1968)		Norway	1965–66	Parallel RCT	Journal	Not reported	Workplace hospital	Nutritional supplement/nutritional supplement	Non-pharmacological			10,000						
Naukkarinen (1989)		Finland	1974–?	Parallel RCT	Journal	Not reported	Not reported	BP lowering/control	Mixed interventions	60	132	1815	47.7			22.7		16.7
Oellgaard (2018)				Parallel RCT	Journal	Not reported	Not reported	Health promotion/health promotion	Mixed interventions	94	254						100	
Patel (1985)				Parallel RCT	Journal	Single centre	Workplace	Physical activity/control	Non-pharmacological	2	50	192		39				75.5
Rachmani (2001)			1995–	Parallel RCT	Journal	Single centre	Clinic hospital	Health promotion/control	Non-pharmacological		48	141	57	51	28.5			

Study ID	Trial name	Country	Study period	Study design	Publication type	Study site	Study settings	Interventions	Intervention group	Intervention duration	Longest follow-up period	Sample size	Mean age	Per cent female	Mean BMI	Hypertension	Type 2 diabetes	Smoking
Radford (2013)	The Auckland Calcium Study	USA	1998–2005	Parallel RCT	Journal	Not reported	Not reported	Nutritional supplement/control	Non-pharmacological	60	60	1408	67	100	26.5	29	2.5	3
Scragg (2017)		New Zealand	2011–5	Parallel RCT	Journal	Multicentre	Clinic	Nutritional supplement/control	Non-pharmacological	50	50	5108		42		36.5		6
Strandberg (1991)		Finland	1974–89	Parallel RCT	Journal	Not reported	Community workplace	Multicomponent/ control	Mixed interventions	60	180	1222	48					0.5
VETCOOP (1970)			1964–9	Parallel RCT	Journal	Not reported	Hospital	BP lowering/control	Pharmacological		60	380	48.5					
Wood (1994)				Parallel RCT	Journal	Multicentre	Community others	Health promotion/ control	Non-pharmacological	12	12	12,472	50					
Yamashita (2013)		Japan	2004–9	Parallel RCT	Journal	Multicentre	Others	BP lowering/BP lowering	Pharmacological		42	818	63.5	29.5	25.3			19.5
Schrier (2007)	ABCD	USA			Journal	Not reported	Not reported	BP lowering/control	Pharmacological	60	60	480	58	42	32		100	62
Bakris (2013)	ACCOMPLISH	USA, Sweden, Norway and Finland		Parallel RCT	Journal	Multicentre	Others	BP lowering/BP lowering	Pharmacological		36	6191		38.5				
Patel (2007)	ADVANCE	Asia, Australasia, Europe, and North America	–2007	Parallel RCT	Journal	Multicentre	Hospital/clinic	BP lowering/control	Pharmacological	2	60	11,140	66	43	28	68.5	100	15
Downs (2001)	AFCAPS/TexCAPS	USA		Parallel RCT	Journal	Multicentre	Workplace	Lipid lowering/control	Pharmacological	3	60	6608	58	15	27			12.5
Han (2017)	ALLHAT-LLT		1994–2002	Parallel RCT	Journal	Multicentre	Clinic	Lipid lowering/control	Pharmacological		94	2867	71	49.5	29		51	22
Gaziano (2018)	ARRIVE Study	Germany, Italy, Ireland, Poland, Spain, the UK, and the USA		Parallel RCT	Journal	Multicentre	Others	Aspirin/control	Pharmacological		60	12,546	64	30	28			28.5
ASCENDa (2018)	The ASCEND Study	UK		Parallel RCT	Journal	Multicentre	Community/ clinic/others	Aspirin/control	Pharmacological		89	15,480	63	47.5	31	62	100	8
ASCENDb (2018)	The ASCEND Study			Parallel RCT	Journal	Multicentre	Community clinic/others	Nutritional supplement/control	Non-pharmacological		89	15,480	63	37	31	62	94	8
McNeil (a) (2018)	Australia	ASPREE	2010–7	Parallel RCT	Journal	Not reported	Community	Aspirin/control	Pharmacological	1	57	19,114		56		74.5	11	

This research article should be referenced as follows: Uthman OA, Court R, Enderby J, Nduka C, Al-Khudairy L, Anjorin S, *et al.* Identifying optimal primary prevention interventions for major cardiovascular disease events and all-cause mortality: a systematic review and hierarchical network meta-analysis of RCTs. *Health Technol Assess* 2025;**29**(37):75–140. https://doi.org/10.3310/RLDH7432

DOI: 10.3310/RLDH7432

Study ID	Trial name	Country	Study period	Study design	Publication type	Study site	Study settings	Interventions	Intervention group	Intervention duration	Longest follow-up period	Sample size	Mean age	Per cent female	Mean BMI	Hypertension	Type 2 diabetes	Smoking
Kataja-Tuomola (2010)	ATBC Study	Finland	1985–93	Parallel RCT	Journal	Not reported	Community	Nutritional supplement/nutritional supplement/nutritional supplement/control	Non-pharmacological		96	1700	58		28.5			
Doyle (1987)	The Australian Therapeutic Trial in Mild Hypertension	Australia	1972–	Parallel RCT	Journal	Multicentre	Others	BP lowering/control	Pharmacological		0	3427	50	36.5				25
De Backer (1988)	The Belgian Heart Disease Prevention Project	Belgium		Cluster RCT	Journal	Multicentre	Others	Health promotion/control	Non-pharmacological	72	120	36,730						
Ruggenenti (2011)	BENEDICT-B	Italy	1998–2006	Parallel RCT	Journal	Multicentre	Not reported	BP lowering/BP lowering	Pharmacological	24	71	281	62	26	30	100	100	20
Colhoun (2009)	CARDS		1997–2003	Parallel RCT	Journal	Multicentre	Clinic	Lipid lowering/control	Pharmacological		48	2838	61.5	32			100	
Goodman (a) (2004)	Beta-Carotene and Retinol Ef?cacy Trial (CARET)	USA	1983–2001	Parallel RCT	Journal	Multicentre	Community clinic/others	Nutritional supplement/control	Non-pharmacological		72	14,254	57.5	44				66.5
Goodman (b) (2004)	Beta-Carotene and Retinol Ef?cacy Trial (CARET)	USA	1983–2001	Parallel RCT	Journal	Multicentre	Workplace	Nutritional supplement/control	Non-pharmacological		72	4060	57					38.5
Nakao (a) (2010)	CASE-J	Japan		Parallel RCT	Journal	Multicentre	Not reported	BP lowering/BP lowering	Pharmacological		48	2018	64	44	25	100	100	32
Nakao (b) (2010)	CASE-J	Japan		Parallel RCT	Journal	Multicentre	Not reported	BP lowering/BP lowering	Pharmacological		48	2685	64	45	24	100		32
Casiglia (1994)	CASTEL (CArdiovascular STudy in the ELderly)	Italy	1983–90?	Parallel RCT	Journal	Not reported	Community	BP lowering/control	Pharmacological		84	655	73.5		27		10	
Kaczorowski (2011)	CHAP	Canada	2005–08	Cluster RCT	Journal	Multicentre	Community	Health promotion/control	Non-pharmacological	3	12	145,441	75	57				
Wang (2018)	CHIEF	China			Conference abstract			BP lowering	Pharmacological		41	13,542						
Ogihara (2014)	COLM (Combination of OLMesartan)	Japan	2007–11	Parallel RCT	Journal	Multicentre	Clinic	BP lowering/BP lowering	Pharmacological	36	40	5141	74	48	24			

Study ID	Trial name	Country	Study period	Study design	Publication type	Study site	Study settings	Interventions	Intervention group	Intervention duration	Longest follow-up period	Sample size	Mean age	Per cent female	Mean BMI	Hypertension	Type 2 diabetes	Smoking
Coop (1978)	Coop	Edinburgh, Budapest, and Prague	1965–?	Parallel RCT	Journal	Multicentre	Not reported	Lipid lowering/nutritional supplement	Pharmacological		60	10,627	46					56
Huo (2015)	CSPPT	China	2008–13	Parallel RCT	Journal	Multicentre	Community	Multicomponent/BP lowering	Mixed interventions	60	60	20,702	60	69	25			
Li (2014)	CSQDPS	China	1986–2009	Cluster RCT	Journal	Multicentre	Clinic	Multicomponent/control	Non-pharmacological	72	276	568	46	45	4			44
DCCT-EDIC (2015)	Diabetes Control and Complications Trial (DCCT)	Canada	1983–2012	Parallel RCT	Journal	Multicentre	Clinic	Blood glucose lowering/blood glucose lowering	Mixed interventions	84	324	1441	27	47	23		100	18.5
Diabetes (2016)	DCCT-EDIC		1983?–2013	Parallel RCT	Journal	Multicentre	Clinic	Blood glucose lowering/blood glucose lowering	Mixed interventions		360	1441					100	
Kochen (2015)	DEGAM Benefits	China	2008–13	Parallel RCT	Journal	Multicentre	Community	Multicomponent/BP lowering	Mixed interventions			20,702				100		
Marre (2004)	DIABHYCAR	European and north African countries	1995–2001	Parallel RCT	Journal	Multicentre	Community clinic	BP lowering/control	Pharmacological		72	4912	65	30	29	55.5	100	15.5
Hanefield (1991)	DIS			Parallel RCT	Journal	Multicentre	Clinic	Lipid lowering/control	Mixed interventions		60	1139	45.7	44.7	29	30.7	100	33.3
DREAM (2008)	DREAM	International	2001–6	Parallel RCT	Journal	Multicentre	Others	BP lowering/control	Pharmacological	2	36	5269						
Suzuki (2005)	E-Cost		1999–2002	Parallel RCT	Journal	Multicentre	Clinic	BP lowering/control	Pharmacological	2	42	2048	50	51.5				
Staessen (1990)	European Working Party on High Blood Pressure in the Elderly (EWPHE) Study			Parallel RCT	Journal	Multicentre	Clinic	BP lowering/control	Pharmacological		97	4695						
Tatti (1998)	FACET	Italy	1992–5	Parallel RCT	Journal	Multicentre	Clinic	BP lowering/BP lowering	Pharmacological		35	380	63	40	30.5	100		6
Muhlestein (2014)	FACTOR-64		2007–14	Parallel RCT	Journal	Multicentre	Clinic	Health promotion/control	Pharmacological		85	899	61.5	47.5	33	66	100	

This research article should be referenced as follows: Uthman OA, Court R, Enderby J, Nduka C, Al-Khudairy L, Anjorin S, *et al.* Identifying optimal primary prevention interventions for major cardiovascular disease events and all-cause mortality: a systematic review and hierarchical network meta-analysis of RCTs. *Health Technol Assess* 2025;**29**(37):75–140. https://doi.org/10.3310/RLDH7432

DOI: 10.3310/RLDH7432

Study ID	Trial name	Country	Study period	Study design	Publication type	Study site	Study settings	Interventions	Intervention group	Intervention duration	Longest follow-up period	Sample size	Mean age	Per cent female	Mean BMI	Hypertension	Type 2 diabetes	Smoking
Liu (2005)	FEVER	China		Parallel RCT	Journal	Multicentre		BP lowering/control	Pharmacological	2	60	9711	61	39.5	26			30
Tonkin (2012)	FIELD	France	1998–2000	Parallel RCT	Journal	Multicentre	Not reported	Lipid lowering/control	Pharmacological		60						100	
IPPPSH (1985)	IPPPSH		1977–?	Parallel RCT	Journal	Not reported	Not reported	BP lowering/control	Pharmacological		60	6357						
Maitland-van (2007)	GenHat		1994–2002	Parallel RCT	Journal	Multicentre	Clinic	Lipid lowering/control	Pharmacological		72	9467	66	50	30			
Wilhelmsen (1986)	Goteborg	Sweden	1970–983	Parallel RCT	Journal	Not reported	Community	BP lowering/control	Non-pharmacological		142	30,022						
Wilhelmson (1987)	HAPPHY	Belgium, Canada, Czechoslovakia, Denmark, Finland, France, Germany, Greece, Iceland, Italy, the Netherlands, Norway, Sweden, UK and USA	1975–85	Parallel RCT	Journal	Multicentre	Others	BP lowering/BP lowering	Pharmacological		45	6569	52		27	100		34.5
Huttunen (1994)	HHS	Finland		Parallel RCT	Journal	Multicentre	Clinic	Lipid lowering/control	Pharmacological	54	102	4081						
Asayama (2012)	HOMED-BP	Japan	2001–10	Parallel RCT	Journal	Multicentre	Clinic	BP lowering/BP lowering/BP lowering/control	Non-pharmacological	18	64	3518	60	50	24			
Bulbulia (2011)	HPS		1994–2001	Parallel RCT	Journal	Not reported	Not reported	Lipid lowering/control	Pharmacological	60	132	17,519						
Mancia (2003)	INSIGHT	Europe and Israel	1994–?	Parallel RCT	Journal	Multicentre	Not reported	BP lowering/BP lowering	Pharmacological			1302		52				13.5
Jørgensen (2014)	Inter99	Denmark	1999–2001	Parallel RCT	Journal	Multicentre	Community	Health promotion/control	Non-pharmacological		120	59,616		50				
Ueki (2017)	J-DOIT3	Japan	2006–09	Parallel RCT	Journal	Multicentre	Clinic	Multicomponent/control	Mixed interventions		120	2540	59	38	25	100	100	23.5
Yokoyama (2007)	JELIS	Japan		Parallel RCT	Journal		Clinic	Nutritional supplement/lipid lowering	Mixed interventions		60	18,645	61	67.5	24			19

Study ID	Trial name	Country	Study period	Study design	Publication type	Study site	Study settings	Interventions	Intervention group	Intervention duration	Longest follow-up period	Sample size	Mean age	Per cent female	Mean BMI	Hypertension	Type 2 diabetes	Smoking
Saito (2017)	JPAD	Japan		Parallel RCT	Journal	Multicentre	Clinic	Aspirin/control	Pharmacological		120	2539	64.5	44.5	24	58		21
Uchiyama (2016)	JPP	Japan		Parallel RCT	Journal	Multicentre	Clinic	Aspirin/control	Pharmacological		78	14,464	70.5	58	24	85	34	13
Sugawara (2019)	JPP-70	Japan		Parallel RCT	Journal	Multicentre	Clinic	Aspirin/control	Pharmacological		62	7971	75	69	24			10
Everett (2010)	JUPITER	26 countries		Parallel RCT	Journal	Multicentre	Not reported	Lipid lowering/control	Pharmacological		60	17,802	66	38	28			16
KLIS (2000)	KLIS	Japan	1990–?	Parallel RCT	Journal	Multicentre	Clinic Hospital	Lipid lowering/control	Pharmacological		60	3853	58		24	42.5	23	
Gong (2018)	KM2H-squared	China		Cluster RCT	Journal	Multicentre	Community	Health promotion/ control	Non-pharmacological		30	900	64	58				18
Gilbert (2018)	LEADER			Parallel RCT	Conference abstract	Not reported	Not reported	Blood glucose lowering/control	Pharmacological		60	836					100	
Newman (2016)	LIFE	USA	2010–?	Parallel RCT	Journal	Multicentre	Clinic/others	Physical activity/ control	Non-pharmacological		31	1635	79	67		70.5	25.5	3
Sasaki (2002)	LISK	Japan	1989–97		Journal	Multicentre	Clinic	Lipid lowering/control	Pharmacological	60	38	1085	55	62.5				18.5
LRC-CPPT (1992)	LRC-CPPT		1973–89	Parallel RCT	Journal	Multicentre	Clinic	Lipid lowering/control	Pharmacological	48	161	3806						
Olsson (1991)	MAPHY		1978–87	Parallel RCT	Journal	Multicentre	Clinic	BP lowering/BP lowering	Pharmacological		132	3234	53			100		33.5
Kushiro (2008)	MEGA	Japan	1994–2004	Parallel RCT	Journal	Not reported	Not reported	Dietary/ multicomponent	Pharmacological		60	3277	58.5	68.5	24		20.5	15.5
MRC trial (1992)	MRC trial			Parallel RCT	Journal	Multicentre	Others	BP lowering/BP lowering/control	Pharmacological		72	25,355	70		26.7			
MRFIT (1996)	MRFIT	USA		Parallel RCT	Journal	Multicentre	Clinic	Health promotion/ control	Non-pharmacological	84	192	12,866						
NHFA (1981)	NHFA	Australia		Parallel RCT	Journal	Multicentre	Community	BP lowering/control	Pharmacological		48	582	63.5	45.5				17.5
ORIGINALE (a) (2016)	OIRGINALE			Parallel RCT	Journal	Not reported	Not reported	Blood glucose lowering/control	Mixed interventions		84	9489	63	33.8		76.3		11.3

This research article should be referenced as follows: Uthman OA, Court R, Enderby J, Nduka C, Al-Khudairy L, Anjorin S, *et al.* Identifying optimal primary prevention interventions for major cardiovascular disease events and all-cause mortality: a systematic review and hierarchical network meta-analysis of RCTs. *Health Technol Assess* 2025;**29**(37):75–140. https://doi.org/10.3310/RLDH7432

Study ID	Trial name	Country	Study period	Study design	Publication type	Study site	Study settings	Interventions	Intervention group	Intervention duration	Longest follow-up period	Sample size	Mean age	Per cent female	Mean BMI	Hypertension	Type 2 diabetes	Smoking
ORIGINALE (b) (2016)	OIRGINALE			Parallel RCT	Journal	Not reported	Not reported	Nutritional supplement/control	Mixed interventions		84	9489	63	33.8		76.3		11.3
Sesso (2012)	PHS		1988–2007	Parallel RCT	Journal	Multicentre	Clinic	Nutritional supplement/control	Non-pharmacological	36	160	14,641	64		26	42.5	5.5	
Sacco (a) (2003)	PPP		1994–?	Parallel RCT	Journal	Multicentre	Clinic	Aspirin/control	Mixed interventions	48	60	1031	64	52	29	63.5		16.5
Sacco (b) (2003)	PPP		1994–?	Parallel RCT	Journal	Multicentre	Clinic	Aspirin/control	Mixed interventions	48	60	1031	64	52	29	63.5		16.5
Estruch (2018)	PREDIMED	Spain	2003–	Parallel RCT	Journal	Multicentre	Clinic	Dietary/dietary/control	Non-pharmacological		72	7447	67	57.7	30	82.7	48.3	14
Maruthur (2009)	PREMIER	USA	2000–?	Parallel RCT	Journal	Multicentre	Clinic	Health promotion/ health promotion/ health promotion	Non-pharmacological		120	1620	50	61.8	33	100		5
Asselbergs (a) (2004)	PREVEND IT	Netherlands	1997–?	Parallel RCT	Journal	Single centre	Clinic	BP lowering/control	Pharmacological		50	1728	51	45.5	26			40
Asselbergs (b) (2004)	PREVEND IT	Netherlands	1997–?	Parallel RCT	Journal	Single centre	Clinic	BP lowering/control	Pharmacological		50	1728	51	45.5	26			40
Matsuzaki (2011)	PROBE	Japan	2003–?	Parallel RCT	Journal	Multicentre	Clinic	BP lowering/BP lowering/BP lowering	Pharmacological	36	48	3293	63	49	24.7			
Lloyd (2013)	PROSPER	UK, Ireland and Netherlands	1993–	Parallel RCT	Journal	Multicentre	Not reported	Lipid lowering/control	Pharmacological	38	135	5804						
Fagerberg (1998)	RIS		1987–95	Parallel RCT	Journal	Single centre	Clinic	Health promotion/ control	Non-pharmacological		93	508						
ROME (1986)	ROME	Great Britain, Belgium, Italy, Poland, and Spain		Parallel RCT	Journal	Multicentre	Workplace	Health promotion/ control	Non-pharmacological		96	6027	1		26.5			60.5
Howard (2008)	SAND	USA	2003–7	Parallel RCT	Journal	Multicentre	Clinic	Multicomponent/ control	Pharmacological	36	36	499	56	65.5	34		100	51
Trenkwalder (2005)	SCOPE	15 countries		Parallel RCT	Journal	Multicentre	Clinic	BP lowering/control	Pharmacological		60	4923	64.5			100	12	9
Kostis (2011)	SHEP	USA?	1984–2006	Parallel RCT	Journal	Multicentre	Clinic	BP lowering/control	Pharmacological	54	264	4736	71.7	57.3	27		10	13

Study ID	Trial name	Country	Study period	Study design	Publication type	Study site	Study settings	Interventions	Intervention group	Intervention duration	Longest follow-up period	Sample size	Mean age	Per cent female	Mean BMI	Hypertension	Type 2 diabetes	Smoking
Shea (2011)	TONE	USA	1992–2006	Parallel RCT	Journal	Multicentre	Not reported	Health promotion/control	Non-pharmacological	18	144	585		52	31			5
Elkeles (1998)	SENDCAP	UK		Parallel RCT	Journal	Multicentre	Clinic	Lipid lowering/control	Pharmacological		66	164	51	29	29		100	17.5
Malacco (2003)	SHELL	Italy	1993–2000	Parallel RCT	Journal	Multicentre	Others	BP lowering/BP lowering	Pharmacological		60	1882	72	61			13.5	10.5
Gong (1996)	STONE	China?	1987–90	Parallel RCT	Journal	Multicentre	Not reported	BP lowering/control	Pharmacological	1	36	1632	66		24			
Dahlof (1993)	STOP-Hypertension	Sweden	1985–92	Parallel RCT	Journal	Multicentre	Clinic	BP lowering/control	Pharmacological		25	1627	76	63	26.5	100	8	8
Lindholm (2000)	STOP Hypertension-2	Sweden		Parallel RCT	Journal	Multicentre	Not reported	BP lowering/BP lowering/BP lowering	Pharmacological			1438	76	60.3	28			6.8
Hercberg (2010)	SU.VI.MAX	France	1994–2002	Parallel RCT	Journal	Not reported	Community	Nutritional supplement/control	Non-pharmacological	90	60	11,054	56	60	25			13
Lisheng (1996)	Syst-China	China	1989–?	Parallel RCT	Journal	Multicentre	Not reported	BP lowering/control	Pharmacological		36	2394						
Cauley (2013)	WHI		1997–2010	Parallel RCT	Journal	Not reported	Not reported	Nutritional supplement/control	Non-pharmacological	60	133	29,862						7
Thijs (2009)	Syst-Eur	Only says Europe	1990–97	Parallel RCT	Journal	Multicentre	Not reported	BP lowering/BP lowering	Pharmacological	12	72	2401						
Bethel (2017)	TECOS	38 countries?	2008–?	Parallel RCT	Journal	Multicentre	Not reported	Blood glucose lowering/control	Pharmacological		36	2004	78	37.5	29		100	
Cook (2018)	TOHP		1987–2004	Parallel RCT	Journal	Multicentre	Not reported	Health promotion/control	Non-pharmacological	48	312	2946						
Holman (a) (2008)	UKPDS	UK	1987–	Parallel RCT	Journal	Multicentre	Clinic	BP lowering/BP lowering	Pharmacological	48	120	1148	64	54	30		100	
Holman (b) (2008)	UKPDS	UK	1987–	Parallel RCT	Journal	Multicentre	Clinic	BP lowering/BP lowering	Pharmacological	48	120	1148	64	54	30		100	
Takano (2012)	VART	Japan	2002–9	Parallel RCT	Journal	Multicentre	Clinic	BP lowering/BP lowering	Pharmacological		37	621	60.5	44.5	12.5			20
Hayward (2015)	Veteran Affairs		?–2008	Parallel RCT	Journal	Multicentre	Community Workplace	Blood glucose lowering/control	Pharmacological		120	1655	60	3	31	72.5	100	

This research article should be referenced as follows: Uthman OA, Court R, Enderby J, Nduka C, Al-Khudairy L, Anjorin S, *et al.* Identifying optimal primary prevention interventions for major cardiovascular disease events and all-cause mortality: a systematic review and hierarchical network meta-analysis of RCTs. *Health Technol Assess* 2025;**29**(37):75–140. https://doi.org/10.3310/RLDH7432

NIHR Journals Library www.journalslibrary.nihr.ac.uk

DOI: 10.3310/RLDH7432

Study ID	Trial name	Country	Study period	Study design	Publication type	Study site	Study settings	Interventions	Intervention group	Intervention duration	Longest follow-up period	Sample size	Mean age	Per cent female	Mean BMI	Hypertension	Type 2 diabetes	Smoking
Veterans (1972)	Veteran Coop			Parallel RCT	Journal	Not reported	Not reported	BP lowering/control	Pharmacological		66	380	48.5					
Rosei (1997)	VHAS			Parallel RCT	Journal	Multicentre	Clinic	BP lowering/BP lowering	Pharmacological	48	48	1414	54	51	27			18
Rose (1992)	Whitehall	UK	1968–1990	Parallel RCT	Journal	Not reported	Community	Health promotion/control	Non-pharmacological	12	240	1445	53					100
Margolis (2014)	ACCORD			Parallel RCT	Journal	Multicentre			Pharmacological		152							
World Health Organisation European Collaborative Group (1986)	WHOEUCollab	Belgium, Italy, Poland and UK		Parallel RCT	Journal	Multicentre	Workplace	Health promotion/control	Non-pharmacological		72	49,781						
Kurth (2011)	WHS		1992	Parallel RCT	Journal	Not reported	Community	Aspirin/control	Pharmacological	26	120	39,757	55	100	26	26	3	13
Lee (1999)	WHS			Parallel RCT	Journal	Not reported	Community	Nutritional supplement/control	Non-pharmacological	26	24	39,873						
Ford (2016)	WOSCOPS	UK		Parallel RCT	Journal	Multicentre	Community	Lipid lowering/control	Pharmacological	59	240	6595	55		26	15.5	1	44
Bhatt (2020)	COMPASS trial			Parallel RCT	Journal	Multicentre	Not reported	Aspirin/aspirin	Pharmacological		36	18,308					48	
Gerstein (2019)	The REWIND Trial	24 ccountries	2011–18	Parallel RCT	Journal	Multicentre	Not reported	Blood glucose lowering/control	Pharmacological		96	9901	66	46.5	32			14
Manson (2018)		USA	2011–17	Parallel RCT	Journal	Not reported	Not reported	Nutritional supplement/control	Non-pharmacological		12	25,871	67	51	28			7
ORIGIN (2012) [Gerstein, 2012 #217]	ORIGIN	Canada	2003–11	Parallel RCT	Journal	Multicentre	Not reported	Blood glucose lowering/control	Pharmacological		84	12,537	63.5	35	30	79		12

BMI, body mass index; MRC, Medical Research Council.

Appendix 5 Risk of bias of included studies

Study identification	Randomisation process	Deviation from intended intervention	Missing data	Measure of outcome	Selective reported result
Dayton (1969)	Unclear	Unclear	Unclear	Unclear	Unclear
Holme (2015)	Low risk of bias	Some concerns	Some concerns	Some concerns	Low risk of bias
Holme (2016)	Low risk of bias	Some concerns	High risk of bias	Low risk of bias	Low risk of bias
Virtamo (1998)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Kitas (2019)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias
Alehagen (2015)	Unclear	Unclear	Unclear	Unclear	Low risk of bias
Alehagen (2018)	Unclear	Unclear	Unclear	Unclear	Low risk of bias
Gæde (2008)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Alexander (2008)	Unclear	Unclear	Unclear	Unclear	Unclear
Anthonisen (2005)	Unclear	Unclear	Unclear	Unclear	Low risk of bias
Beishuizen (2004)	Low risk of bias	Unclear	Unclear	Unclear	Unclear
Berglund (1978)	Unclear	Unclear	Unclear	Unclear	Low risk of bias
Bolland (2008)	Unclear	Unclear	Unclear	Unclear	Low risk of bias
Buring (2006)	Unclear	Unclear	Unclear	Unclear	Low risk of bias
Chang (2006)	Unclear	Low risk of bias	Low risk of bias	Unclear	Low risk of bias
Coope (1986)	High risk of bias	Unclear	Unclear	Unclear	Unclear
Corella (2013)	Unclear	Unclear	Unclear	Unclear	Low risk of bias
EUCTR (2013)	Unclear	Unclear	Unclear	Unclear	Unclear
Fowkes (2010)	Unclear	Unclear	Unclear	Unclear	Low risk of bias
Frantz (1989)	Unclear	Unclear	Unclear	Unclear	Low risk of bias
Gæde (2016)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Gæde (2003)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Gong (2015)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Hackett (2019)	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Hao (2015)	Unclear	Unclear	Unclear	Unclear	Unclear
Hinderliter (2015)	Unclear	Unclear	Unclear	Unclear	Unclear
Hsia (2006)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Blot (1993)					
Jarrett (1977)	Low risk of bias	Low risk of bias	Some concerns	Some concerns	Low risk of bias
Leonetti (1990)	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Li (2012)	Unclear	Unclear	Unclear	Unclear	Unclear
Manson (a) (2019)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Lonn (2016)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Lu (2018){Lu, 2018 #216}	Unclear	Unclear	Unclear	Unclear	Unclear
Manson (b) (2019)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

Study identification	Randomisation process	Deviation from intended intervention	Missing data	Measure of outcome	Selective reported result
Mark (1996)			Low risk of bias		Low risk of bias
Miettinen (1985)	Some concerns	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Natvig (1968)	Unclear	Unclear	Some concerns	Some concerns	Some concerns
Naukkarinen (1989)	Unclear	Unclear	Low risk of bias	Low risk of bias	Low risk of bias
Oellgaard (2018)	Unclear	Unclear	Unclear	Unclear	Unclear
Patel (1985)	Unclear	Unclear	Low risk of bias	Low risk of bias	Low risk of bias
Rachmani (2001)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Radford (2013)	Unclear	Unclear	Low risk of bias	Low risk of bias	Low risk of bias
Scragg (2017)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Strandberg (1991)	Some concerns	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
VETCOOP (1970)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Wood (1994)	Low risk of bias	Some concerns	Some concerns	Some concerns	Some concerns
Yamashita (2013)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Schrier (2007)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Bakris (2013)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Patel (2007)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Downs (2001)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Han (2017)	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Gaziano (2018)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
ASCENDa (2018)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
ASCENDb (2018)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
McNeil (a) (2018)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Some concerns
Kataja-Tuomola (2010)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Doyle (1987)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
De Backer (1988)			Low risk of bias	Low risk of bias	Low risk of bias
Ruggenenti (2011)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Colhoun (2009)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Goodman (a) (2004)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Goodman (b) (2004)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Nakao (a) (2010)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Nakao (b) (2010)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Casiglia (1994)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Some concerns
Kaczorowski (2011)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Wang (2018)	Unclear	Unclear	Unclear	Unclear	Unclear
Ogihara (2014)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Coop (1978)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Huo (2015)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

Study identification	Randomisation process	Deviation from intended intervention	Missing data	Measure of outcome	Selective reported result
Li (2014)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
DCCT-EDIC (2015)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Diabetes (2016)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Kochen (2015)	Low risk of bias	Low risk of bias	Low risk of bias		Low risk of bias
Marre (2004)	Low risk of bias	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias
Hanefield (1991)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
DREAM (2008)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Suzuki (2005)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Staessen (1990)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Tatti (1998)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Muhlestein (2014)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Liu (2005)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Tonkin (2012)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
IPPPSH (1985)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Maitland-van (2007)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Wilhelmsen (1986)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Wilhelmson (1987)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Huttunen (1994)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Asayama (2012)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Bulbulia (2011)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Mancia (2003)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Jørgensen (2014)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Ueki (2017)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Yokoyama (2007)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Saito (2017)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Uchiyama (2016)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Sugawara (2019)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Everett (2010)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
KLIS (2000)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Gong (2018)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Gilbert (2018)	Unclear	Unclear	Unclear	Unclear	Unclear
Newman (2016)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Sasaki (2002)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
LRC-CPPT (1992)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Olsson (1991)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Kushiro (2008)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
MRC trial (1992)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

Study identification	Randomisation process	Deviation from intended intervention	Missing data	Measure of outcome	Selective reported result
MRFIT (1996)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
NHFA (1981)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
ORIGINALE (a) (2016)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
ORIGINALE (b) (2016)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Sesso (2012)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Sacco (a) (2003)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Sacco (b) (2003)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Estruch (2018)[7]	Low risk of bias	Unclear	Low risk of bias	Low risk of bias	Low risk of bias
Maruthur (2009)	Low risk of bias	Low risk of bias	Low risk of bias	Some concerns	Low risk of bias
Asselbergs (a) (2004)	Low risk of bias	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias
Asselbergs (b) (2004)	Low risk of bias	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias
Matsuzaki (2011)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Lloyd (2013)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Fagerberg (1998)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
ROME (1986)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Howard (2008)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Trenkwalder (2005)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Kostis (2011)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Shea (2011)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Elkeles (1998)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Malacco (2003)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Gong (1996)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Dahlof (1993)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Lindholm (2000)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Hercberg (2010)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Lisheng (1996)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Cauley (2013)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Thijs (2009)	Low risk of bias	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias
Bethel (2017)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Cook (2018)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Holman (a) (2008)	Low risk of bias	Some concerns	High risk of bias	Low risk of bias	Low risk of bias
Holman (b) (2008)	Low risk of bias	Some concerns	High risk of bias	Low risk of bias	Low risk of bias
Takano (2012)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Hayward (2015)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias
Veterans (1972)	Unclear	Unclear	Unclear	Unclear	Unclear
Rosei (1997)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Rose (1992)	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias

Study identification	Randomisation process	Deviation from intended intervention	Missing data	Measure of outcome	Selective reported result
Margolis (2014)	Low risk of bias	Some concerns			
WHOEUCollab (1986)	Low risk of bias	Some concerns	Some concerns	Low risk of bias	Low risk of bias
Kurth (2011)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Lee (1999)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Ford (2016)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Bhatt (2020)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Gerstein (2019)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Manson (2018)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
ORIGIN (2012)(Gerstein, 2012 #217)	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

MRFIT, Multiple Risk Factor Intervention Trial.