



Research Article

Interventions for primary prevention of cardiovascular disease: umbrella review of systematic reviews

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Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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Abstract

Background: Cardiovascular diseases are the leading cause of death globally. The aim of this overview of systematic reviews was to compare the effectiveness of different pharmacological and non-pharmacological interventions for the primary prevention of cardiovascular disease.

Methods: A structured search of the Cochrane Database of Systematic Reviews, MEDLINE, EMBASE and the Database of Abstracts of Reviews of Effects archive was conducted to find systematic reviews that reported the effect of various pharmacological and non-pharmacological interventions for the primary prevention of cardiovascular disease from inception to March 2021. References of included studies were also checked. The included systematic reviews' methodological quality was assessed using the Assessment of Multiple Systematic Reviews 2 instrument (range, 0–16). The outcomes of each included review's meta-analysis were extracted and described narratively.

Results: This study analysed 95 systematic reviews, including 41 on non-pharmacological interventions and 54 on pharmacological interventions for cardiovascular health. The majority of the reviews focused on lipid-lowering interventions ($n = 25$) and antiplatelet medications ($n = 21$), followed by nutritional supplements, dietary interventions, physical activity, health promotion and other interventions. Only 1 of the 10 reviews addressing cardiovascular mortality showed a potential benefit, while the others found no effect. Antiplatelets were found to have a beneficial effect on all-cause mortality in 2 out of 12 meta-analyses and on major cardiovascular disease events in 8 out of 17 reviews. Lipid-lowering interventions showed beneficial effects on cardiovascular disease mortality, all-cause mortality and major cardiovascular disease events in varying numbers of the reviews. Glucose-lowering medications demonstrated significant benefits for major cardiovascular events, coronary heart disease events and mortality. However, the combination of dietary interventions, physical activities, nutritional supplements and polypills showed little or no significant benefit for major cardiovascular outcomes or mortality.

Future work and limitations: More research is needed to determine whether the effect of treatment varies depending on population characteristics. The findings of this review should be interpreted with caution because the majority of studies of non-pharmacological interventions compare primary prevention with usual care, which may include recommended pharmacological treatment in higher-risk patients (e.g. statins and/or antihypertensive medications, etc.). In addition, randomised controlled trial evidence may be better suited to the study of pharmacological interventions than dietary and lifestyle interventions.

Conclusions: This umbrella review captured the variability in different interventions on randomised controlled trial evidence on interventions for primary prevention of cardiovascular disease and identified areas that may benefit from

further research. Specifically, this review focused on randomised controlled trial evidence on interventions for primary prevention of cardiovascular disease. Researchers may use these findings as a resource to direct new intervention studies and network meta-analyses to compare the efficacy of various interventions based on these findings.

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Introduction

In high-income countries, such as the UK, cardiovascular disease (CVD) is one of the primary causes of morbidity and mortality.¹ Heart and circulation disorders account for a quarter of all deaths in the UK, or over 160,000 each year – an average of 460 deaths per day, or 1 every 3 minutes.¹ In the UK, around 7.6 million people (4 million men and 3.6 million women) suffer from heart or circulatory disease. The most common type of heart illness is coronary heart disease (CHD).¹ It is the leading cause of heart attack and the leading cause of death for both men and women worldwide in 2019.¹ Heart attacks cause 100,000 hospital admissions in the UK each year, or one every 5 minutes. In the UK today, around 1.4 million people have survived a heart attack and heart failure affects around 900,000 people. Strokes kill about 35,000 people in the UK every year and are the leading cause of severe disability.¹

Many of the risk factors for developing CVD are modifiable, and data suggest that a substantial percentage of the current CVD burden is either entirely or partially preventable.^{2–4} Primary prevention of CVD at the community level is ideal, as the aim is to delay or avoiding the start of CVD. Several systematic reviews and meta-analyses have examined strategies for the primary prevention of CVD, but there has been no consensus regarding the strategy with the best overall results.^{5,6} Some have concluded that these interventions may be successful in reducing the burden of CVD, whereas others have questioned their efficacy for CVD primary prevention.^{5,6} Determining the effectiveness of various strategies for the primary prevention of CVD necessitates a systematic evaluation and synthesis of the available evidence.^{7–9} This study seeks to provide such a synthesis giving an overview of existing systematic reviews. This is a relatively new strategy for summing up evidence which can help researchers synthesise evidence across interventions. This is particularly valuable when conflicting evidence has been reported in previous systematic reviews. We aim to produce a comprehensive overview of the current best evidence by identifying, analysing and synthesising the numerous published systematic reviews assessing the comparative effectiveness of different interventions for primary prevention of CVD.

This publication is part of a series of publications on ‘Determining optimal strategies for primary prevention of CVD: systematic review, network meta-analysis and cost-effectiveness review (National Institute for Health and Care Research (NIHR)/Health Technology Assessment (HTA): 17/148/05)’. Other publications in this series include:

1. Effectiveness of policies and structural interventions in reducing CVD and mortality: a systematic review of simulation-based studies.
2. Increasing comprehensiveness and reducing workload in the preparation of a systematic review of complex interventions using automated machine learning.
3. Determining optimal primary prevention interventions for major CVD events and all-cause mortality – findings from systematic review and hierarchical network meta-analysis of randomised controlled trials (RCTs).
4. How conclusive is the evidence for interventions in primary prevention of CVD: 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 CVD: systematic review of cost-effectiveness analyses in the UK.

The findings from all the workstreams, including those from the systematic review of modelling studies, will be summarised in a synopsis paper to be published alongside this series.

Methods

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the following number: CRD42019123940. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).¹⁰

Review eligibility criteria

The review question guiding this overview is presented in PICOTSS format (patient, intervention, comparators, outcomes, timing, setting and study design):

Patients: The review includes adult populations (18 years and older) from population-based studies, which may target moderate/high CVD risk groups such as those with hypertension, obesity, hyperlipidaemia, type 2 diabetes or a combination of these factors. The focus of the review is on primary prevention of CVD, so we excluded trials involving individuals who have had a previous myocardial infarction (MI), stroke, revascularisation procedure coronary artery bypass grafting or percutaneous transluminal coronary angioplasty and those with angina or angiographically defined CHD. Studies with mixed populations, including both individuals with and without CVD, were included if data relevant to 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, blood pressure (BP)-lowering medications, antiplatelet agents], diet (nutritional supplements, dietary interventions), physical activity or public health (health promotion programmes, structural and policy interventions).

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

Outcome measures: The primary outcome was all-cause mortality. Secondary outcomes were CVD-related mortality, major cardiovascular events (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) and incremental costs per quality-adjusted life-years gained reported alongside a randomised trial.

Timing: Studies of any duration.

Setting: Any setting.

Study design: Systematic reviews of RCTs. Units of randomisation could be either individuals or clusters (such as family, workplace).

Search strategy

A sensitive literature search for existing systematic reviews was developed iteratively. The process involved

testing each iteration's effectiveness in retrieving a high proportion of records for a broad cross-section of more than 70 known, relevant systematic reviews of RCTs that had been found in previous work via a variety of sources. After only a few iterations, we found that by adding a few specific medical subject heading (MeSH) and title terms we were able to find all of the known reviews. Searches were based on the concepts of prevention, CVD outcomes and systematic reviews. From inception until March 2021, we searched the Cochrane Database of Systematic Reviews (via Wiley), MEDLINE (via Ovid), EMBASE (via Ovid) and Database of Abstracts of Reviews of Effects (DARE) (via Centre for Reviews and Dissemination) databases. All searches were carried out by one of us (RC), an experienced information specialist. [Appendix 1](#) of the supplement contains detailed search strategies. References of included studies were also checked for relevant reviews. Records were exported to EndAAfnote X9 and systematically de-duplicated.

Study selection and data extraction

All study selection, data extraction, evidence synthesis and quality assessment processes were completed by two authors separately (CN and SA). Any disagreement was handled by consensus or referral to a third investigator (OAU). We independently abstracted key participant and intervention information and reported data on pre-specified outcomes using standardised data extraction templates for studies that met the inclusion criteria. For outcomes that were meta-analysed, we also retrieved pooled effect estimates. Risk ratios (RRs) or odds ratios with 95% confidence intervals (CI) were used to report dichotomous data.

Risk of bias

We independently assessed the methodological quality of each systematic review using the Assessment of Multiple SysTemAtic Reviews (AMSTAR) 2 tool.¹¹

Results

Study characteristics and evidence mapping

Our search identified 10,883 records, of which 111 records were evaluated as full-text articles after title and abstract screening ([Figure 1](#)). In total, we selected 95 systematic reviews for inclusion (see [Appendix 2](#)). The systematic reviews were published between 1997 and 2020. On average, the systematic reviews included 18 RCTs (range: 2–287). The largest systematic review included 287 RCTs. The number of participants included in the systematic reviews ranged from as few as 47 to as many as 963,829 (mean: 73,937). When reported, final searches for each reported review were performed

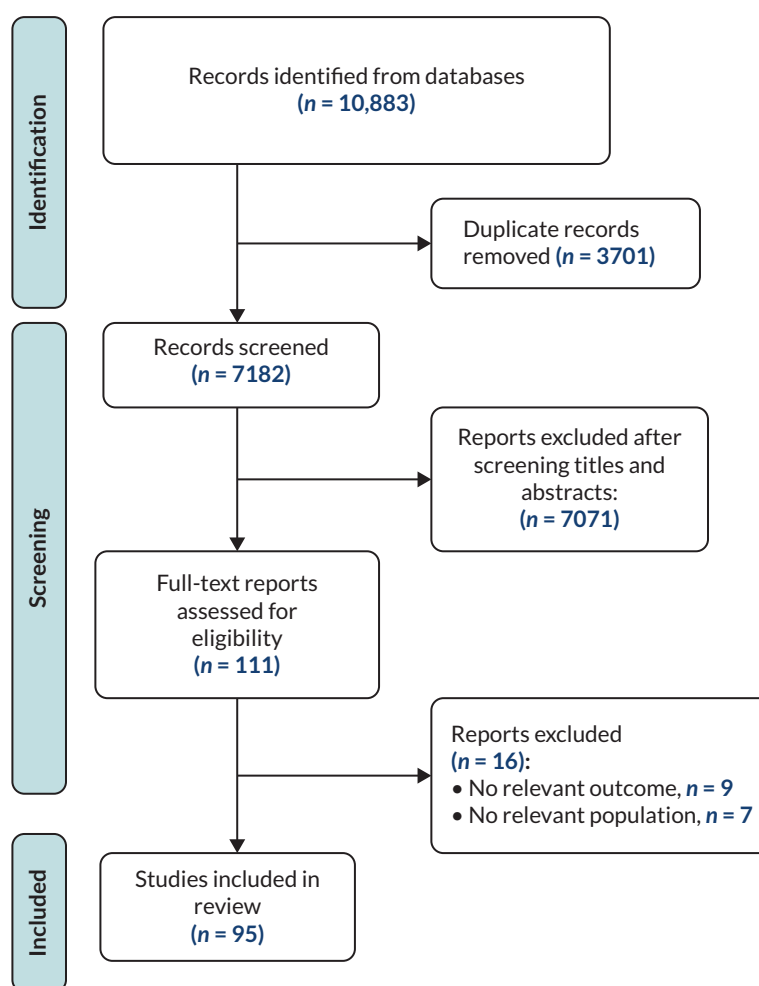


FIGURE 1 PRISMA study flow and selection.

between August 2014 and September 2019. [Table 1](#) shows results from the most recent and most comprehensive systematic reviews for each intervention for major cardiovascular events, CHD events, CVD mortality and all-cause mortality.

Risk of bias of included reviews

Assessment of Multiple SysTEmAtic Reviews 2 rating is summarised in [Appendix 3](#). A majority of the reviews (81 out of 95) addressed research questions and inclusion criteria using the population, intervention, comparison and outcomes (PICO) components. Just under half (42 out of 95) mentioned that the review methods were predetermined and justified any significant deviations from the protocol. Most authors (85 out of 95) clarified the chosen study designs for inclusion in their reviews.

Just over half of the authors employed a comprehensive literature search strategy (55 out of 95), conducted study selection in duplicate (67 out of 95) and performed data extraction in duplicate (68 out of 95). Only about half (51 out of 95) provided a list of excluded studies and justified

their exclusions, while most (75 out of 95) described the included studies in adequate detail.

A limited number of authors (47 out of 95) utilised a satisfactory technique to assess the risk of bias (RoB) in the individual studies included in the review, and even fewer (37 out of 95) reported on the funding sources for the included studies. Only 45 authors applied appropriate methods for statistically combining results, while 42 assessed the potential impact of RoB in individual studies on the meta-analysis or other evidence synthesis results and another 42 accounted for RoB in primary studies when interpreting or discussing the review findings.

The majority of authors (84 out of 95) offered a satisfactory explanation and discussion of any observed heterogeneity in their review results. About 58 authors conducted an adequate investigation of publication bias (small study bias) and discussed its probable impact on the review results. Lastly, 75 authors reported any potential sources of conflict of interest, including any funding received for conducting their reviews.

TABLE 1 Summary of key findings for the effect of interventions for primary prevention of CVD from included systematic reviews and meta-analyses

Intervention	Major cardiovascular events	CHD events	CVD mortality	All-cause mortality
Non-pharmacological				
Dietary				
Dietary intervention	0.96 (0.92–1.01)	0.91 (0.85–0.97)	0.92 (0.86–0.99)	0.97 (0.93–1.01)
Folic acid	0.98 (0.95–1.02)	1.03 (0.98–1.08)		1.00 (0.98–1.02)
Reduced fat	0.84 (0.72–1.07)		0.91 (0.77–1.07)	0.98 (0.86–1.12)
Reduced salt	0.76 (0.57–1.01)		0.67 (0.45–1.01)	0.96 (0.83–1.10)
Health promotion				
Digital health	1.21 (0.58–2.54)			
Multifactorial			0.99 (0.92–1.07)	1.00 (0.96–1.05)
Multicomponent intervention				
Diet and physical activity advice	0.57 (0.11–3.07)			
Nutritional supplements				
Beta-carotene	1.01 (0.93–1.09)			1.04 (0.99–1.09)
Calcium	1.14 (0.92–1.41)			1.04 (0.96–1.12)
Folic acid				0.52 (0.24–1.10)
Homocysteine-Folic	0.90 (0.81–1.00)			
Multivitamin	0.95 (0.85–1.06)	0.91 (0.84–0.98)	0.92 (0.87–0.98)	0.98 (0.94–1.02)
Niacin	0.66 (0.49–0.89)	0.75 (0.59–0.96)		
Omega 3	0.95 (0.82–1.12)		0.85 (0.68–1.06)	0.87 (0.73–1.03)
Selenium	1.03 (0.95–1.11)		0.97 (0.79–1.20)	0.97 (0.88–1.08)
Vitamin A				1.09 (0.77–1.54)
Vitamin B3	0.95 (0.74–1.22)	0.93 (0.87–1.00)	1.02 (0.93–1.12)	1.05 (0.97–1.12)
Vitamin C	0.99 (0.89–1.10)			1.06 (0.97–1.16)
Vitamin D	0.95 (0.95–0.98)	0.93 (0.89–0.96)	0.94 (0.89–0.99)	0.94 (0.88–1.01)
Vitamin D + Calcium	1.01 (0.95–1.07)			0.92 (0.83–1.01)
Vitamin E	0.97 (0.92–1.03)			1.01 (0.98–1.04)
Pharmacological				
Antiplatelet				
Antiplatelet	0.97 (0.96–0.99)			
Aspirin	0.90 (0.85–0.94)	0.86 (0.79–0.92)	0.99 (0.87–1.11)	0.96 (0.90–1.03)
BP lowering				
Angiotensin-converting enzyme (ACE) inhibitors	1.03 (1.00–1.06)	0.95 (0.90–1.01)		1.01 (0.97–1.05)
Alpha-blockers	1.20 (0.85–1.69)	0.84 (0.63–1.14)		1.04 (0.88–1.23)
Angiotensin receptor blockers	0.98 (0.93–1.02)	1.06 (0.98–1.15)		0.99 (0.94–1.04)

continued

TABLE 1 Summary of key findings for the effect of interventions for primary prevention of CVD from included systematic reviews and meta-analyses (*continued*)

Intervention	Major cardiovascular events	CHD events	CVD mortality	All-cause mortality
Antihypertensive	0.64 (0.53–0.76)		0.69 (0.51–0.94)	
Beta-blockers	1.17 (1.11–1.24)	1.03 (0.96–1.10)		1.06 (1.01–1.12)
Ca channel blockers	0.97 (0.94–0.99)	0.98 (0.94–1.03)		0.97 (0.94–1.00)
Diuretics	0.97 (0.94–1.00)	1.02 (0.97–1.09)		1.02 (0.97–1.06)
Glucose lowering				
Glucose-lowering drugs	0.92 (0.89–0.95)		0.92 (0.87–0.97)	0.94 (0.90–0.98)
Sodium-glucose linked transporter (SGLT) -2 inhibitors	0.83 (0.71–0.96)	0.86 (0.79–0.94)	0.74 (0.67–0.81)	0.85 (0.79–0.92)
Lipid lowering				
Fibrates	0.88 (0.73–1.05)	0.84 (0.74–0.96)	0.86 (0.56–1.32)	0.97 (0.074–1.26)
Homocysteine lowering	0.90 (0.82–0.99)	1.02 (0.95–1.10)		1.01 (0.96–1.06)
Statins	0.74 (0.61–0.89)	0.80 (0.71–0.90)	0.85 (0.74–0.98)	0.96 (0.88–1.04)
Polypills				
Polypills	1.38 (0.91–2.10)			1.26 (0.67–2.38)

Antiplatelets

Antiplatelets were examined in 21 systematic reviews published between 2000 and 2020. When reported, the last searches ranged from September 1997 to December 2018. Drugs examined in the reviews included antiplatelets (1 review included) and aspirin (20 reviews included). The AMSTAR ratings ranged from a score of 1 to 12 out of a possible 16. Only of 10 meta-analyses reported a beneficial effect of antiplatelets on CVD mortality. Two of 12 meta-analyses reported a beneficial effect of antiplatelets on all-cause mortality. Eight of 17 systematic reviews reported a beneficial effect of antiplatelets on major CVD events (RR ranging from 0.85 to 0.97, 95% CI ranging from 0.78 to 0.99). Five of eight systematic reviews reported a beneficial effect of antiplatelets on CHD events (RR ranging from 0.70 to 0.86, 95% CI ranging from 0.60 to 0.95).

Blood pressure lowering

Blood pressure-lowering medications were examined in three systematic reviews. When reported, the last searches ranged from January 1998 to November 2015; and these reviews were published between 2001 and 2015. The drugs examined in the reviews included angiotensin-converting enzyme (ACE) inhibitors (one review included), antihypertensives (one review included) and diuretics (one review included). The AMSTAR ratings ranged from a score of 2 to 14 out of 16. None of the reviews showed a benefit

of BP lowering in primary prevention of cardiovascular events or mortality, apart from calcium channel blockers which demonstrated a reduction in major cardiovascular events (RR = 0.97, 95% CI 0.94 to 0.99).

Dietary interventions

Dietary interventions were examined in 14 systematic reviews. When reported, the last searches ranged from July 1993 to August 2019; and these reviews were published between 1997 and 2020. Interventions included different types of dietary interventions such as reduced salt (two reviews included), dietary intervention (two reviews included), nuts (one review), folic acid (one review included), green tea (one review included), Mediterranean diet (one review included), low-glycaemic-index diets (one review included), reduced fat (one review included), whole grain cereals (one review included), fibre (one review included) and garlic (one review included). The AMSTAR ratings ranged from a score of 5 to 15 of 16. The dietary interventions showed little or no significant beneficial effect of major cardiovascular events, CHD events and mortality.

Glucose-lowering medications

Glucose-lowering medications were examined in the three systematic reviews. When reported, the last searches ranged from May 2019 and January 2020; and

these reviews were published between 2019 and 2020. The drugs examined in the reviews included sodium-glucose linked transporter (SGLT)-2 inhibitors (two reviews included) and glucose-lowering drugs (one review included). The AMSTAR ratings ranged from a score of 11 to 13 of 16. All glucose-lowering medications showed a significant beneficial effect on major cardiovascular events (RR = 0.92, 95% CI 0.89 to 0.95), CHD events (RR = 0.92, 95% CI 0.87 to 0.97) and mortality (RR = 0.94, 95% CI 0.90 to 0.98).

Health promotion

Health promotion interventions were examined in four systematic reviews. When reported, the last searches ranged from June 2006 to January 2014; and these reviews were published between 2010 and 2015. There were various health promotion interventions such as multifactorial interventions (two reviews included), tele-health (one review included) and digital health (one review included). The AMSTAR ratings ranged from a score of 8 to 11 of 16. The health promotion interventions showed little or no significant beneficial effect of major cardiovascular events, CHD events and mortality.

Lipid lowering

Lipid-lowering medications were examined in 25 systematic reviews. When reported, the last searches ranged from June 1996 to August 2020; and these reviews were published between 1999 and 2020. The drugs examined in the reviews included statins (20 reviews included), fibrates (4 reviews included) and homocysteine lowering (1 review included). The AMSTAR ratings ranged from a score of 1 to 16 of 16. Three of nine systematic reviews reported a beneficial effect of lipid lowering on CVD mortality (RR ranging from 0.71 to 0.89, 95% CI ranging from 0.56 to 0.98). Five of 18 systematic reviews reported a beneficial effect of lipid lowering on all-cause mortality (RR ranging from 0.66 to 0.93, 95% CI ranging from 0.49 to 0.99). Fifteen of 18 systematic reviews reported a beneficial effect of lipid lowering on major CVD events (RR ranging from 0.59 to 0.90, 95% CI ranging from 0.48 to 0.99). Eight of 10 systematic reviews reported a beneficial effect of lipid lowering on CHD events (RR ranging from 0.55 to 0.84, 95% CI ranging from 0.42 to 0.96).

Multicomponent intervention

Multicomponent interventions were examined in one systematic review. The last searches were conducted in June 2014 and published in 2015. Interventions included different types of nutrition supplements such as diet and physical activity advice (one review included). The AMSTAR rating was a score of 15 of 16. The combination of dietary

intervention and physical activities showed little or no significant beneficial effect of major cardiovascular events.

Nutritional supplements

Nutrition supplements were examined in 19 systematic reviews. When reported, the last searches ranged from February 2002 to September 2019; and these reviews were published between 2004 and 2020. Interventions included different types of nutrition supplements such as multivitamin (nine reviews included), vitamin D (three reviews included), vitamin B3 (one review included), omega 3 (one review included), omega 6 (one review included), homocysteine-folic (one review included), tomato and lycopene supplement (one review included), selenium (one review included), coenzyme q10 (one review included) and niacin (one review included). The AMSTAR ratings ranged from a score of 3 to 16 of 16.

Most of the nutritional supplements showed little or no significant beneficial effect of major cardiovascular events, CHD events and mortality.

Physical activity

Physical activity was examined in five systematic reviews. When reported, the last searches ranged from December 2013 to October 2016; and these reviews were published between 2014 and 2017. Interventions included different types of physical activity interventions such as workplace physical activity (workplace intervention that aims to boost health literacy and encourage the adoption of healthy lifestyles, with a focus on physical activity as the primary outcome) (one review included), yoga (one review included), meditation (one review included), tai chi (one review included) and physical activity (any form of health education intervention that aims to boost health literacy and encourage the adoption of healthy lifestyles, with a focus on physical activity as the primary outcome at any location) (one review included). The AMSTAR ratings ranged from a score of 14 to 16 of 16. None of the included systematic reviews reported effects of physical activities on major cardiovascular events, CHD events, CVD associated mortality or all-cause mortality.

Polypills

Polypills were examined in the two systematic reviews. When reported, the last searches ranged from December 2010 to July 2013; and these reviews were published between 2012 and 2014. There were two reviews (two reviews included). The AMSTAR ratings ranged from a score of 4 to 15 of 16. Polypills showed little or no significant beneficial effect of major cardiovascular events, CHD events and all-cause mortality.

Discussion

Main findings

This umbrella review provides information about diverse interventions for primary prevention of CVD. Our work constitutes the first comprehensive and systematic summary of diverse non-pharmacological and pharmacological interventions based on the umbrella review methodology. We included 95 systematic reviews, 41 were on various non-pharmacological interventions and 54 concerned various pharmacological interventions. Most of the reviews examined lipid-lowering interventions ($n = 25$) followed by antiplatelet medications ($n = 21$). Other reviews included nutritional supplements ($n = 19$), dietary interventions ($n = 13$) physical activity ($n = 5$), health promotion interventions ($n = 4$), BP-lowering medications ($n = 3$), blood glucose-lowering medications ($n = 3$), polypills ($n = 2$) and multicomponent intervention ($n = 1$). Out of 95 reviews analysed, most addressed research questions and inclusion criteria using PICO components and clarified their chosen study designs. Approximately half employed comprehensive literature search strategies, conducted study selection and performed data extraction in duplicate. Only a limited number of authors assessed the RoB in individual studies, applied appropriate methods for combining results and accounted for bias when interpreting findings. The majority provided explanations for heterogeneity, investigated publication bias and reported potential conflicts of interest.

We found potential promising effects, indicated by statistically significant pooled treatment effects in more than one systematic review reported for SGLT-2 inhibitors, vitamin D, dietary interventions, reduced salt, fibrates and multifactorial interventions. In addition, several systematic reviews provided evidence of the potential lack of effectiveness across more than one systematic review, such as BP-lowering medications and multivitamins.

The most comprehensive and high-quality systematic reviews of aspirin reported a 10% reduction in major cardiovascular events and a 14% reduction in CHD events; SGLT-2 inhibitors reported a 17% reduction in major cardiovascular events, a 14% reduction in CHD, a 26% in CVD associated mortality and a 15% reduction in all-cause mortality; statins reported a 26% reduction in major cardiovascular events, a 20% reduction in CHD events and a 15% in CVD associated mortality; and niacin reported an 34% reduction in major cardiovascular events and a 25% reduction in CHD events.

Results of our overview of systematic reviews can be also compared with those of previous overviews of systematic

reviews of both pharmacological⁵ and non-pharmacological⁶ interventions for preventing CVD. Karmali and colleagues⁵ conducted an overview of systematic reviews to compare the efficacy and safety of aspirin, BP-lowering therapy, statins and tobacco cessation drugs for fatal and nonfatal atherosclerotic cardiovascular disease (ASCVD) outcomes in primary ASCVD prevention. There were 35 systematic reviews of RCTs found in a total of 1967 reports, including 15 reviews of aspirin, 4 reviews of BP-lowering medication, 12 reviews of statins and 4 reviews of cigarette cessation drugs. According to the review, high-quality data support the use of aspirin, BP-lowering treatment and statins for primary ASCVD prevention, as well as tobacco cessation medicines for smoking cessation.

Martin Ruiz and colleague⁶ conducted an umbrella review to determine the effectiveness of non-pharmacological interventions for prevention of CVD events and mortality in healthy adults or those at high risk of CVD. There were 24 reviews in total, with 13 of them reporting results of interest. Vitamin D supplements, increased omega 3 fatty acid consumption, Qigong and counselling or education to modify more than one cardiovascular risk factor were all found to reduce risk in a statistically meaningful way. The authors concluded that these four non-pharmacological interventions have been shown to provide a statistically significant reduction in risk of CVD events or overall mortality.

Strengths and limitations

Our study has numerous strengths. It presents a thorough, complete evaluation of the data from all published meta-analyses regarding pharmacological and non-pharmacological therapies for CVD primary prevention. First, we concentrated this evidence synthesis on systematic reviews and meta-analyses of RCTs, as RCTs provide the highest-quality evidence for determining the benefits of healthcare interventions. Second, we employed a comprehensive, transparent search approach to locate papers and a predefined procedure to guide our evidence synthesis, documenting any protocol deviations. Third, we did all-title screening, data extraction and quality evaluations in duplicate to reduce the possibility of bias during compilation of this summary. Fourth, we employed a validated instrument (the AMSTAR 2 tool) to evaluate the methodological quality of the included systematic reviews, and we used this evaluation to inform our conclusions regarding the effects of pharmacologic therapies. This methodical procedure, which includes the evaluation of study quality using standardised instruments, could serve as a model for the expedited creation of reliable guidelines.

Our umbrella review also has some limitations. We did not retrieve data from primary RCTs; thus we had to rely on the information provided by the authors of the systematic reviews we retrieved. Selection criteria, search methodologies and definitions of main prevention frequently differed across reviews, and authors of included reviews frequently employed different criteria to define primary prevention, resulting in varying numbers of trials for systematic reviews of the same intervention. In addition, primary studies that were not included in any published meta-analyses may have been omitted, and new studies that were published after the publication of each meta-analysis may have altered the results. Finally, we selected the most recent meta-analysis for each intervention that included the greatest number of primary studies. Therefore, it is possible that the chosen meta-analysis may not be that of the highest quality.

Implications for future research and policy

Because the RCTs included in each systematic review may have been undertaken in very diverse populations, the observed results may not be generalisable. More research is needed to determine whether the effect of treatment varies depending on population characteristics. The findings of this review should be interpreted with caution because the majority of studies investigating non-pharmacological interventions for primary prevention compare them to usual care, which may include recommended pharmacological treatment in higher-risk patients (e.g. statins and/or antihypertensive medications, etc.). This means that the combined effect of non-pharmacological interventions and standard pharmacological practise is being measured in these trials, rather than the effect of these interventions as an alternative to pharmacology. More research is also recommended to evaluate different intervention combinations. Identifying the most effective intervention, on the other hand, continues to be a challenge for researchers and policy-makers. There is a need for an up-to-date comprehensive evidence synthesis of all interventions to inform the NHS and UK Health Security Agency's rational choice of a minimum set of strategies for primary prevention of CVD in order to avoid targeting relatively fewer effective interventions.

While numerous pairwise systematic reviews and meta-analyses have investigated the effectiveness of various interventions for primary prevention of CVD, no systematic review has yet comprehensively synthesised all available evidence to understand the comparative effectiveness of different drug, lifestyle and structural interventions in order to support evidence-based

recommendations. Another issue is that most trials use a 'no intervention' control group as the comparator, which limits the usefulness of pairwise analyses in informing practical decisions about the most effective interventions. Network meta-analysis methods are designed to address this question and provide more valuable insights for policy-makers, health service commissioners and care providers when choosing between multiple intervention alternatives. Therefore, we recommend conducting an innovative network meta-analysis to better inform decision-making in primary prevention of CVD.

Patient and public involvement

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

Conclusion

In conclusion, this study examined various interventions for the primary prevention of CVD. Antiplatelet medications showed beneficial effects in some reviews on CVD mortality, all-cause mortality and major cardiovascular events. BP-lowering medications had no significant effect on cardiovascular events or mortality, except for calcium channel blockers, which reduced major cardiovascular events. Dietary interventions had little to no significant impact on major cardiovascular events, CHD events and mortality.

Glucose-lowering medications showed a significant beneficial effect on major cardiovascular events, CHD events and mortality. Health promotion interventions had little to no significant impact on major cardiovascular events, CHD events and mortality. Lipid-lowering medications demonstrated beneficial effects on CVD mortality, all-cause mortality, major cardiovascular events and CHD events in various reviews.

Multicomponent interventions, which combined dietary intervention and physical activities, showed little to no significant impact on major cardiovascular events. Most nutritional supplements had little or no significant effect on major cardiovascular events, CHD events and mortality. Physical activity interventions did not report significant effects on major cardiovascular events, CHD events, CVD-associated mortality or all-cause mortality. Polypills had little or no significant impact on major cardiovascular events, CHD events and all-cause mortality.

Additional information

Contributions of authors

Olalekan A Uthman (<https://orcid.org/0000-0002-8567-3081>) (Professor, Evidence Synthesis) contributed to the protocol, study selection, data extraction, validity assessments and synthesis of the included studies. He developed the classifiers and undertook the analyses. He also contributed to the interpretation of the results and the writing of the report and had overall responsibility for the project.

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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 have 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

This project did not involve the handling of personal information.

Study registration details

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List of abbreviations

ASCVD	atherosclerotic cardiovascular disease
CHD	coronary heart disease
CVD	cardiovascular disease
MeSH	medical subject heading
MI	myocardial infarction
RoB	risk of bias

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Appendix 1 Search strategy

MEDLINE (Ovid)

Search date: 14 March 2019 (note: see below for update searches).

Actual databases searched: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) < 1946 to March 13, 2019>.

Search Strategy:

```

1  exp Primary Prevention/ (143046)
2  primary prevention.ti,ab,kf. (17517)
3  1 or 2 (156409)
4  exp Cardiovascular Diseases/ or exp Stroke/
   (2253958)

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5  (cardiovascular* or coronary* or heart* or myocardial
   infarction* or cardiac* or stroke* or cerebrovascular
   accident*).ti,ab,kf. (602893)
6  4 or 5 (2507942)
7  3 and 6 (13417)
8  *Cardiovascular Diseases/pc or exp *Coronary Dis-
   ease/pc or exp *Myocardial Infarction/pc or exp
   *Heart Failure/pc or exp *Heart Arrest/pc or exp
   *Stroke/pc (47349)
9  ((prevent* or (reduc* adj risk*)) and (cardiovascular* or
   coronary* or heart* or myocardial infarction* or cardi-
   ac* or stroke* or cerebrovascular accident*).ti. (20124)
10 7 or 8 or 9 (65565)
11 (metaanalys* or 'meta analys*' or 'meta-analys*').mp.
   (171776)
12 (systematic* adj2 review*).mp. (161842)
13 11 or 12 (261344)
14 10 and 13 (3434)

```

- 15 limit 10 to (meta analysis or 'systematic review') (2006)
- 16 14 or 15 (3434)
- 17 limit 16 to (comment or editorial or letter) (229)
- 18 16 not 17 (3205)

Update 23 October 2019

Actual databases searched: Ovid MEDLINE All.

Search strategy:

Re-ran search above plus...

- 19 limit 18 to ed = 20190314-20191023 (203)
- 20 limit 18 to ep = 20190314-20191023 (66)
- 21 (201903* or 201904* or 201905* or 201906* or 201907* or 201908* or 201909* or 201910*).dt,ez. (826293)
- 22 18 and 21 (93)
- 23 19 or 20 or 22 (276)

Update 3 March 2021

Actual databases searched: Ovid MEDLINE All

Search strategy:

- 19 limit 18 to ed = 20191023-20210303 (459)
- 20 limit 18 to ep = 20191023-20210303 (233)
- 21 (201910* or 201911* or 201912* or 2020* or 2021*).dt,ez. (2085624)
- 22 18 and 21 (339)
- 23 19 or 20 or 22 (578)

EMBASE (Ovid)

Search date: 14 March 2019 (note: see below for update searches)

Actual databases searched: EMBASE Classic+EMBASE < 1947 to 2019 March 13>

Search Strategy:

-
- 1 primary prevention/ (37798)
 - 2 primary prevention.ti,ab,kw. (26632)
 - 3 1 or 2 (50311)
 - 4 exp cardiovascular disease/ or exp cerebrovascular accident/ (4109044)

- 5 (cardiovascular* or coronary* or heart* or myocardial infarction* or cardiac* or stroke* or cerebrovascular accident*).ti,ab,kw. (2609271)
- 6 4 or 5 (4920793)
- 7 3 and 6 (24747)
- 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 (36993)
- 9 ((prevent* or (reduc* adj risk*)) and (cardiovascular* or coronary* or heart* or myocardial infarction* or cardiac* or stroke* or cerebrovascular accident*)).ti. (31542)
- 10 7 or 8 or 9 (75904)
- 11 (metaanalys* or 'meta analys*' or 'meta-analys*').mp. (252681)
- 12 (systematic* adj2 review*).mp. (271759)
- 13 11 or 12 (403426)
- 14 10 and 13 (5597)
- 15 limit 10 to (meta analysis or 'systematic review') (3674)
- 16 14 or 15 (5597)
- 17 limit 16 to (conference abstract or conference paper or 'conference review' or editorial or letter) (1043)
- 18 16 not 17 (4554)

Update 23 October 2019

Actual databases searched: EMBASE Classic+EMBASE 1947 to 2019 Week 42

Search strategy:

Re-ran search above plus...

- 19 limit 18 to dd = 20190314-20191023 (30)
- 20 limit 18 to em = 201903-201910 (67)
- 21 limit 18 to dc = 20190314-20191023 (220)
- 22 19 or 20 or 21 (287)

Update 3 March 2021

Actual databases searched: EMBASE Classic+EMBASE 1947 to 2021 Week 08

Search strategy:

Re-ran search above plus...

- 19 limit 18 to dd = 20191023-20210303 (62)
- 20 limit 18 to em = 201910-202103 (497)
- 21 limit 18 to dc = 20191023-20210303 (450)

22 19 or 20 or 21 (593)

Cochrane Database of Systematic Reviews (Wiley)

Date Run: 14 March 2019 (note: see below for update search)

ID Search Hits

- #1 MeSH descriptor: [Primary Prevention] explode all trees3804
- #2 'primary prevention':ti,ab,kw3139
- #3 #1 or #26141
- #4 MeSH descriptor: [Cardiovascular Diseases] explode all trees95561
- #5 MeSH descriptor: [Stroke] explode all trees8034
- #6 (cardiovascular* or coronary* or heart* or (myocardial next infarction*) or cardiac* or stroke* or (cerebrovascular next accident*)):ti,ab,kw1318
- #7 #4 or #5 or #696699
- #8 #3 and #7934
- #9 [mh ^'cardiovascular diseases'[mj]/PC]51
- #10 [mh 'coronary disease'[mj]/PC]1482
- #11 [mh 'myocardial infarction'[mj]/PC]653
- #12 [mh 'heart failure'[mj]/PC]260
- #13 [mh 'heart arrest'[mj]/PC]197
- #14 [mh 'stroke'[mj]/PC]810
- #15 #9 or #10 or #11 or #12 or #13 or #143278
- #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*)):ti5631
- #17 #8 or #15 or #168568

Cochrane Reviews: 149

Update 23 October 2019

Re-ran search above plus...

Limits: with Cochrane Library publication date from Mar 2019 to Oct 2019, in Cochrane Reviews9

Update 3 March 2021

Re-ran search above. Noticed an error in line 6 (a full stop rather than a colon before the field codes). As this

may have affected the final number of Cochrane Reviews retrieved in the original search and the previous update, we retrieved all Cochrane Reviews found (226) and de-duplicated in EndNote against those already found in previous searches of both the Cochrane Database of Systematic Reviews, MEDLINE and EMBASE.

Cochrane Reviews: 226

DARE (CRD)

Date searched: 14 March 2019

- 1 MeSH DESCRIPTOR Primary Prevention EXPLODE ALL TREES914
- 2 (primary prevention)1551
- 3 #1 OR #22001
- 4 MeSH DESCRIPTOR Cardiovascular Diseases EXPLODE ALL TREES10675
- 5 MeSH DESCRIPTOR Stroke EXPLODE ALL TREES1354
- 6 (cardiovascular* or coronary* or heart* or myocardial infarction* or cardiac* or stroke* or cerebrovascular accident*)11754
- 7 #4 OR #5 OR #615077
- 8 #3 AND #7602
- 9 MeSH DESCRIPTOR Cardiovascular Diseases WITH QUALIFIER PC475
- 10 MeSH DESCRIPTOR Myocardial Infarction EXPLODE ALL TREES WITH QUALIFIER PC202
- 11 MeSH DESCRIPTOR Heart Failure EXPLODE ALL TREES WITH QUALIFIER PC38
- 12 MeSH DESCRIPTOR Heart Arrest EXPLODE ALL TREES WITH QUALIFIER PC90
- 13 MeSH DESCRIPTOR Stroke EXPLODE ALL TREES WITH QUALIFIER PC347
- 14 MeSH DESCRIPTOR coronary disease EXPLODE ALL TREES WITH QUALIFIER PC286
- 15 #9 OR #10 OR #11 OR #12 OR #13 OR #141255
- 16 (((prevent* or (reduc* adj2 risk*)) and (cardiovascular* or coronary* or heart* or myocardial infarction* or cardiac* or stroke* or cerebrovascular accident*)):ti733
- 17 #8 OR #15 OR #161910
- 18 (#17) IN DARE1006

Not updated since 2015.

Appendix 2 Characteristics of included studies

Study	Intervention	Number of RCTs	Number of participants	Last searches	AMSTAR 2 rating score
Non-pharmacological					
Dietary					
Abdelhamid (2020) ¹²	Dietary intervention	82	162,796	August 2019	14
Adler (2014) ¹³	Reduced salt	8	7284	May 2013	14
Brunner (1997) ¹⁴	Dietary intervention	17	7141	July 1993	5
Clar (2017) ¹⁵	Low glycaemic index diets	21	2538	July 2016	16
Hartley (2013) ¹⁶	Green tea	11	821	October 2012	15
Hartley (2016) ¹⁷	Fibre	23	1513	January 2015	16
Hooper (2001) ¹⁸	Reduced fat	27	30,902	May 1999	8
Kelly (2017) ¹⁹	Whole grain cereals	9	1414	July 2017	16
Martin (2015) ²⁰	Nuts	7	435	July 2015	16
Rees (2013) ²¹	Mediterranean diet	11	52,044	September 2012	14
Stabler (2012) ²²	Garlic	1	47	November 2011	16
Taylor (2013) ²³	Reduced salt	6	6489	October 2008	13
Yang (2012) ²⁴	Folic acid	26	58,804	May 2012	9
Health promotion					
Angermayr (2010) ²⁵	Multifactorial	25	7703	July 2007	16
Ebrahim (2011) ²⁶	Multifactorial	55	163,471	June 2006	11
Merriel (2014) ²⁷	Telehealth	8	5106	June 2013	16
Widmer (2015) ²⁸	Digital health	2	1055	January 2014	8
Uthman (2015) ²⁹	Diet and physical activity advice	11	7310	June 2014	15
Nutritional supplements					
Al-Khudairy (2015) ³⁰	Omega 6	4	660	September 2014	16
Al-Khudairy (2017) ³¹	Multivitamin	8	11,445	May 2016	15
Bjelakovic (2011) ³²	Multivitamin	50	94,148	January 2011	16
Cheng (2017) ³³	Tomato and lycopene supplement	15	1197		16
Flowers (2014) ³⁴	Coenzyme Q10	6	102	December 2013	16
Fortmann (2013) ³⁵	Multivitamin	26	27,955	January 2013	16
Hartley (2015) ³⁶	Multivitamin	1	60	September 2014	16
Hooper (2004) ³⁷	Omega 3	48	36,913	February 2002	15
Lavigine (2013) ³⁸	Niacin	11	9959	December 2011	5
Mahmoud (2019) ³⁹	Multivitamin	21	83,291	December 2018	10
Marco (2020) ⁴⁰	Multivitamin	14	125,763	February 2019	13
Maria Cabiddu (2020) ⁴¹	Vitamin D	11	100,609	September 2019	7

Study	Intervention	Number of RCTs	Number of participants	Last searches	AMSTAR 2 rating score
Myung (2013) ⁴²	Multivitamin	50	294,478	November 2012	8
Pham (2005) ⁴³	Multivitamin	8	104,221	July 2005	3
Qin (2012) ⁴⁴	Homocysteine-Folic	9	8234	July 2012	11
Rees (2013) ⁴⁵	Selenium	12	19,715	October 2012	15
Schandelmaier (2017) ⁴⁶	Vitamin B3	23	39,195	August 2016	14
Wang (2010) ⁴⁷	Vitamin D	17	2988	July 2009	9
Yang (2019) ⁴⁸	Vitamin D	13	127,477		9
Physical activity					
Castro (2016) ⁴⁹	Physical activity	15	6727	October 2016	14
Hartley (2014) ⁵⁰	Tai chi	13	1520	December 2013	16
Hartley (2014) ⁵¹	Meditation	4	430	January 2014	16
Hartley (2014)	Yoga	11	800	December 2013	16
Reed (2017) ⁵²	Workplace physical activity	20	4074	October 2014	16
Pharmacological					
Antiplatelet					
ATC (2002) ⁵³	Antiplatelet	287	212,000	September 1997	4
Bartolucci (2011) ⁵⁴	Aspirin	9	90,000		1
Berger (2006) ⁵⁵	Aspirin	6	95	March 2005	7
Calvin (2009) ⁵⁶	Aspirin	9	89,392	November 2008	12
Campbell (2007) ⁵⁷	Aspirin	8	10,067	February 2007	3
Daniel Caldeira (2020) ⁵⁸	Aspirin	10	34,058	November 2018	11
De Berardis (2009) ⁵⁹	Aspirin	6	10,117	November 2008	6
Desai (2015) ⁶⁰	Aspirin	8	121,850	December 2014	3
Eidelman (2003) ⁶¹	Aspirin	5	55,580	January 2003	2
Georg (2019) ⁶²	Aspirin	13	164,225	November 2018	7
Gerardo (2020) ⁶³	Aspirin	13	164,225	December 2018	10
Hart (2000) ⁶⁴	Aspirin	5	52,251		1
Hayden (2002) ⁶⁵	Aspirin	5	53,035	January 2001	3
Matthew (2020) ⁶⁶	Aspirin	12	963,829	January 2018	12
Raju (2011) ⁶⁷	Aspirin	9	100,076	May 2010	12
Sanmuganathan (2001) ⁶⁸	Aspirin	4	48,540	January 2001	2
Stavakis (2011) ⁶⁹	Aspirin	7	7384	November 2009	8
Sutcliffe (2013) ⁷⁰	Aspirin	27	102,594	September 2012	9
Xie (2014) ⁷¹	Aspirin	14	107,686	December 2012	11
Younis (2010) ⁷²	Aspirin	6	7374		5
Zhang (2009) ⁷³	Aspirin	7	11,618	June 2009	5

Study	Intervention	Number of RCTs	Number of participants	Last searches	AMSTAR 2 rating score
BP lowering					
Ettehad (2015) ⁷⁴	ACE inhibitors	124	613,815	November 2015	14
Fretheim (2012) ⁷⁵	Diuretics	25	10,881	February 2011	9
Wei (2001) ⁷⁶	Antihypertensive	4	10,400	January 1998	2
Glucose lowering					
Cai-Yan (2019) ⁷⁷	SGLT-2 inhibitors	41	61,076	May 2019	11
Dario (2020) ⁷⁸	SGLT-2 inhibitors	5	34,323	January 2020	11
Olivia (2020) ⁷⁹	Glucose-lowering drugs	30	225,305	November 2019	13
Lipid lowering					
Allemann (2006) ⁸⁰	Fibrates	8	12,249	November 05	9
Avash (2020) ⁸¹	Statins	7	122,164	November 2019	10
Baris (2020) ⁸²	Statins	6	244,090	August 2020	12
Berger (2011) ⁸³	Statins	9	102,621	January 2005	7
Bukkapatnam (2009) ⁸⁴	Statins	6	21,963	January 2009	6
Chang (2013) ⁸⁵	Statins	22	137,441		7
Chen (2012) ⁸⁶	Statins	7	12,711	January 2011	6
Loomba (2010) ⁸⁷	Fibrates	10	125,763		5
Major (2015) ⁸⁸	Statins	6	8834	September 2013	10
Marti-Carvajal (2017) ⁸⁹	Homocysteine-lowering	15	71,422	June 2017	16
Mills (2008) ⁹⁰	Statins	19	63,899	May 2008	8
Mills (2011) ⁹¹	Statins	10	41,778	December 2010	8
Mora (2010) ⁹²	Statins	5	13,154	July 2009	3
Pignone (2000) ⁹³	Statins	4	21,087	June 1999	5
Saha (2007) ⁹⁴	Fibrates	10	36,489	July 2006	5
Saha (2010) ⁹⁵	Fibrates	6	11,590	December 2007	7
Taylor (2013) ⁹⁶	Statins	18	56,934	January 2012	14
Taylor (2013) ⁹⁷	Statins	18	56,934	May 2013	1
Teng (2015) ⁹⁸	Statins	8	25,952	August 2014	14
Thavendiranathan (2006) ⁹⁹	Statins	7	42,848	June 2005	6
Tonelli (2011) ¹⁰⁰	Statins	29	80,711	January 2011	11
Warshafsky (1999) ¹⁰¹	Statins	4	7808	June 1996	7
de Vries (2014) ¹⁰²	Statins	9	9156	September 2013	8
de Vries (2012) ¹⁰³	Statins	4	10,187	November 2011	9
Polypills					
Sepanlou (2012) ¹⁰⁴	Polypills	11	64,639	December 2010	4
de Cates (2014) ¹⁰⁵	Polypills	9	7047	July 2013	15

Appendix 3 Assessment of multiple systematic reviews 2 rating of including studies

Author	Did the research questions and inclusion criteria use PICO?	Explicit statement that the review methods?	Explain their selection of the study designs?	Use a comprehensive literature search strategy?	Perform study selection in duplicate?	Perform data extraction in duplicate?	Provide a list of excluded studies – reason?	Describe the included studies in adequate detail?	Assess the RoB (RoB)?	Sources of funding	Meta-analysis – use appropriate methods?	Meta-analysis – potential impact of RoB?	Account for RoB in individual studies?	Provide explanation for heterogeneity?	Publication bias likely impact?	Potential sources of conflict of interest?
Adler (2014) ¹³	Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Al-Khudairy (2015) ³⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Al-Khudairy (2017) ³¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes
Allemann (2006) ⁸⁰	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No		No	No	Yes	No	Yes
Angermayr (2010) ²⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Abdelhamid (2020) ¹²	Yes	Partial Yes	Yes	Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ATC (2002) ⁵³	Yes	No	Yes	No	No	No	No	Partial Yes	No	No		No	No	Yes	No	Yes
Avash Das (2020) ⁸¹	Yes	Yes	No	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Baris Gencer (2020) ⁸²	Yes	No	Yes	Yes	Yes	Yes	Partial Yes	Partial Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Bartolucci AA (2011) ⁵⁴	No	No	No	No	No	No	No	Partial Yes	No	No		No	No	Yes	No	No
Berger JS (2006) ⁵⁵	Yes	No	Yes	No	No	No	No	Yes	No	Yes		No	No	Yes	Yes	Yes
Berger JS (2011) ⁸³	Yes	No	Yes	No	No	No	Yes	Yes	No	No		No	No	Yes	Yes	Yes
Bjelakovic (2011) ³²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Brunner (1997) ¹⁴	Yes									Yes	Yes	Yes				Yes
Bukkapatnam RN (2009) ⁸⁴	Yes	No	Yes	Partial Yes	No	No	No	Yes	No	Yes		No	No	Yes	Yes	No
Cai-Yan (2019) ⁷⁷	Yes	Partial Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
Calvin (2009) ⁵⁶	Yes	Partial Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes		Yes	Yes	No	Yes	Yes
Campbell (2007) ⁵⁷	Yes	No	Yes	Partial Yes	No	No	No	Yes	No	No	No meta-analysis	No meta-analysis	No	No	No meta-analysis	No

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Castro (2016) ⁴⁹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Chang (2013) ⁸⁵	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	No	No		No	No	Yes	Yes	
Chen (2012) ⁸⁶	Yes	No	Yes	Partial Yes	No	No	No	Partial Yes	No	No	Yes	No	No	Yes	Yes	Yes
Cheng (2017) ³³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clar (2017) ¹⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Daniel (2020) ⁵⁸	Yes	No	Yes	Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	Yes	No	No	Yes	No;Yes	Yes
Dario (2020) ⁷⁸	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes		Yes	No	Yes	Yes
De Berardis (2009) ⁵⁹	Yes	No	Yes	Partial Yes	Yes	No	No	Partial Yes	No	Yes		No	No	Yes	No	Yes
de Cates (2014) ¹⁰⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
de Vries (2012) ¹⁰³	Yes	No	Yes	Partial Yes	Yes	Yes	Yes	Yes	No	No		No	No	Yes	Yes	Yes
de Vries (2014) ¹⁰²	Yes	No	Yes	No	Yes	Yes	Yes	Partial Yes	No	No		No	No	Yes	Yes	Yes
Desai (2015) ⁶⁰	Yes	Yes	Yes	Partial Yes	No	No	No	Partial Yes	No	No	No meta-analysis	No meta-analysis	No	No	No meta-analysis	
Ebrahim (2011) ²⁶	Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	Yes	Partial Yes	No		No	Yes	Yes	Yes	Yes
Eidelman (2003) ⁶¹	No	No	Yes	No	No	No	No	Partial Yes	No	No		No	No	Yes	No	No
Ettehad (2015) ⁷⁴	Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Flowers (2014) ³⁴	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fortmann (2013) ³⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fretheim (2012) ⁷⁵	Yes	Partial Yes	Yes	Partial Yes	Yes	Yes	Yes	Yes	No	No		Yes	No	No	Yes	Yes
George (2019) ⁶²	Yes	Yes	Yes	Yes	No	No	Partial Yes	Yes	No	No	No	No	No	Yes	No	Yes

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Gerardo (2020) ⁶³	Yes	No	Yes	Yes	Yes	Yes	Partial Yes	Yes	No	No	Yes		No	Yes	Yes	Yes
Hart (2000) ⁶⁴	No	No	Yes	No	No	No	No	No	No	No		No	No	No	No	No
Hartley (2013) ¹⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Hartley (2014) ⁵⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hartley (2015) ³⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hartley (2016) ¹⁷	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hartley (2014) ⁵¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hartley L (2014) ¹⁰⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hayden (2002) ⁶⁵	No	No	No	No	No	No	Yes	Partial Yes	No	No		No	No	Yes	No	Yes
Hooper (2001) ¹⁸	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No		No	No	No	No	Yes
Hooper (2004) ³⁷	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Kelly (2017) ¹⁹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lavigne PM (2013) ³⁸	Yes	No	Yes	No	No	No	Yes	Partial Yes	No	No		No	No	Yes	Yes	No
Loomba RS (2010) ⁸⁷	Yes	No	Yes	No	No	No	No	Yes	No	No		No	No	Yes	Yes	No
Mahmoud Barbarawi (2019) ³⁹	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No		No	Yes	Yes	Yes
Major RW (2015) ⁸⁸	Yes	Yes				Yes	Yes	Yes		Yes	Yes			Yes	Yes	Yes
Marco Lombardi (2020) ⁴⁰	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Maria Francesca Cabiddu (2020) ⁴¹	Yes	No	No	Yes	Yes	Yes	Partial Yes	Partial Yes	Partial Yes	No	Yes	No	No	Yes	No	Yes
Marti-Carvajal (2017) ⁸⁹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

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Martin N (2015) ²⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Matthew Nudy (2020) ⁶⁶	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
Merriel S (2014) ²⁷	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mills E (2008) ⁷⁰	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No		No	No	Yes	No	No
Mills EJ (2011) ⁹¹	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No		No	No	No	No	Yes
Mora S (2010) ⁹²	No	No	No	No	No	No	No	Yes	No	No		No	No	Yes	No	Yes
Myung SK (2013) ⁴²	Yes	No	Yes	Partial Yes	Yes	No	Partial Yes	Yes	Partial Yes	Yes		No	No	Yes	Yes	Yes
Olivia R Ghosh-Swaby (2020) ⁷⁹	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes		Yes	Yes	Yes	Yes
Pham DQ (2005) ⁴³	No	No	Yes	No	No	No	No	Yes	No	No	No meta-analysis	No meta-analysis	No	Yes	No meta-analysis	No
Pignone (2000) ⁹³	No	No	Yes	No	Yes	Yes	No	Partial Yes	No	No		No	No	Yes	No	Yes
Qin X (2012) ⁴⁴	Yes	Yes	Yes			Yes	Yes	Yes		Yes	Yes			Yes	Yes	Yes
Raju N (2011) ⁶⁷	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No		Yes	Yes	Yes	Yes	Yes
Reed (2017) ⁵²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rees K (2013) ⁴⁵	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Rees K <i>et al.</i> (2013) ²¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Saha SA (2007) ⁹⁴	No	No	No	Partial Yes	Yes	Yes	No	Yes	No	No		No	No	Yes	Yes	No
Saha SA (2010) ⁹⁵	Yes	No	Yes	No	No	Yes	No	Yes	No	No		No	No	Yes	Yes	Yes
Sanmuganathan (2001) ⁶⁸	No	No	Yes	No	No	No	No	Partial Yes	No	No		No	No	Yes	No	No
Schandelmaier (2017) ⁴⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	No	Yes
Sepanlou SG (2012) ¹⁰⁴	No	No	No	No	Yes	Yes	No	Partial Yes	No	No		No	No	Yes	Yes	No

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Stabler SN (2012) ²²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stavrakis S (2011) ⁶⁹	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No		No	No	Yes	No	No
Sutcliffe P (2013) ⁷⁰	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No		No	No	Yes	No	Yes
Taylor F (2013) ⁹⁶	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Taylor RS (2013) ²³	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	No	Yes
Taylor F (2013) ⁹⁷	No	No	No	No	No	No	No	No	No	No	No meta-analysis	No meta-analysis	No	No	No meta-analysis	Yes
Teng M (2015) ⁹⁸	Yes	Yes	Yes	Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes
Thavendiranathan P (2006) ⁹⁹	Yes	No	Yes	Partial Yes	No	Yes	No	Yes	No	No		No	No	Yes	No	Yes
Tonelli (2011) ¹⁰⁰	Yes	Yes	Yes	Yes	Yes	Yes	Partial Yes	Yes	Partial Yes	No		Yes	No	Yes	Yes	Yes
Uthman OA (2015) ²⁹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Wang L (2010) ⁴⁷	Yes	No	Yes	Partial Yes	Yes	Yes	No	Yes	Yes	No		No	No	Yes	Yes	Yes
Warshafsky (1999) ¹⁰¹	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	No		No	No	Yes	No	No
Wei (2001) ⁷⁶	No	No	Yes	No	No	No	No	Partial Yes	No	No		No	No	Yes	No	No
Widmer R (2015) ²⁸	No	No	Yes	Partial Yes	Yes	No	No	Partial Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Xie M (2014) ⁷¹	Yes	Partial Yes	Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	No		No	Yes	Yes	Yes	Yes
Yang HT (2012) ²⁴	Yes	No	Yes	Partial Yes	Yes	Yes	Yes	Yes	No	No		No	No	Yes	Yes	Yes
Yang Hu (2019) ⁴⁸	Yes	No	Yes	Yes	No	No	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Younis N (2010) ⁷²	Yes	No	Yes	Partial Yes	No	No	No	Yes	No	No		No	No	Yes	No	Yes
Zhang C (2009) ⁷³	Yes	Partial Yes	Yes	No	No	No	No	Yes	No	No		No	No	Yes	No	Yes