1. Full title of project:

Determining optimal strategies for primary prevention of cardiovascular disease: systematic review, cost-effectiveness review and network meta-analysis

2. Background and Rationale

Cardiovascular disease (CVD) includes all the diseases of the heart and circulation including coronary heart disease (CHD) and stroke. CVD accounts for the highest proportion of non-communicable disease deaths, resulting in 160,000 deaths in the UK annually2. A substantial proportion of these deaths are in people under 75 years of age3 (premature CVD death). An estimated 7 million people (3.5 million men and 3.5 million women) are currently living with CVD in the UK. In the UK, the CVD's cost to the UK economy due to disability and premature death is estimated to be more than £15 billion annually and in addition, the healthcare costs associated with CVD are up to £11 billion annually. Cardiovascular risk is determined by a variety of 'upstream' factors (such as food production and availability, access to a safe environment that encourages physical activity and access to education); as well as 'downstream' behavioural issues (such as unhealthy diet, smoking and physical inactivity). In more than 90% of cases, the risk of a first heart attack is related to nine potentially modifiable risk factors 1: smoking/tobacco use, poor diet, high blood cholesterol, high blood pressure, insufficient physical activity, overweight/obesity, diabetes, psychosocial stress and excess alcohol consumption. A significant proportion of CVD morbidity and mortality can be prevented through population strategies for primary prevention.

Identifying the most effective intervention however remains 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 rational choice of a minimum set of strategies for primary prevention of cardiovascular disease needed by NHS and Public Health England to avoid targeting relatively less effective interventions. The work will build on the evidence that underpins the current NICE guidance on prevention of cardiovascular disease; draw on new trials and identify effective strategies for improving cardiovascular health. We will interpret our findings within the context of current NICE guidelines on prevention of cardiovascular disease. The proposed project is important given that numerous evaluations of interventions have been conducted. Results from the proposed network meta-analyses will draw these together making this body of evidence more accessible, available and useful to policy makers, health service commissioners and care providers when making choices between multiple alternatives. The results from the cost-effectiveness review will demonstrate which interventions are potentially the most cost-effective for primary prevention of CVD.

There is a major potential population health impact of improving our understanding of CVD prevention. Optimising drug treatment for primary prevention and addressing diet, physical inactivity, smoking, excessive alcohol consumption and implementing population-wide structural and policy interventions could reduce substantial numbers of people living with preventable ill health and dying prematurely. If CVD were reduced even by 10%, 16,000 deaths would be prevented in the UK annually. The numbers living with CVD in the UK (estimated at 7 million people) and the cost of CVD to the UK economy particularly the NHS could be substantially reduced.

3. Aims and objectives

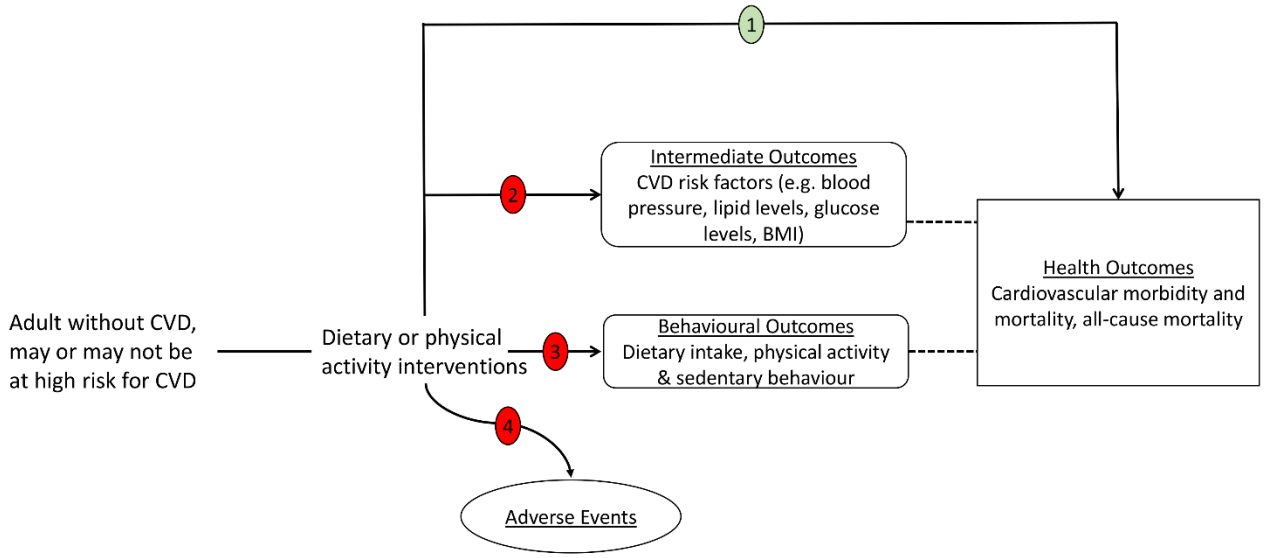
The overarching aim is to synthesise evidence for the comparative effectiveness of different interventions for the primary prevention of CVD, comprehensively using network meta-analysis.

Specific objectives:

1. To use comprehensive searches and to describe the scale and range of interventions that have been conducted and categorise the interventions and their components
2. To determine which interventions, have the greatest probability of effectiveness for primary prevention of CVD (see Figure 1).
3. To identify which components of interventions are associated with the greatest effectiveness for primary prevention of CVD.

4. To examine reliability and conclusiveness of the available evidence on interventions for primary prevention of CVD and identify the areas with post potential benefit for future research.
5. To identify trial characteristics associated with prevention effect estimates.
6. To identify, appraise and summarise published models of cost-effectiveness of interventions for the primary prevention of CVD
7. To determine the applicability and generalisability of interventions and work with PPI advisers and BHF to disseminate and present results to patients, policy makers and the public.

Figure 1: Analytic Framework



Note: Pathway 1 will be systematically reviewed (in green), while pathways 2, 3 and 4 will not be reviewed (in red).

4. Research Plan / Methods

We propose to undertake a series of six inter-related work-streams:

Work stream #1: Evidence harvest and mapping

The first stage aims to provide a comprehensive search, selection and mapping of the literature (described in Search strategy sub-section).

Health Technologies being assessed

Any form of intervention aimed at primary prevention of CVD, including but not limited to lipid lowering medications, blood pressure lowering medications, antiplatelet agents, nutritional supplements, dietary interventions, health promotion programmes, physical activity, or structural and policy interventions (**Table 1**).

Table 1: Health Technologies

Pharmacologic interventions			
Lipid lowering medications	Blood pressure lowering medications	Nutritional supplements	Others
Atorvastatin Fluvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Fenofibrate Bezafibrate Ezetimibe	ACE inhibitors Angiotensin receptor blockers (ARBs) Calcium Channel blockers Thiazide diuretics Adrenergic receptor antagonists (alpha and beta blockers)	Vitamin D, E, K & multivitamins, Niacin Omega 3 & fatty acids, Anti-oxidants, Calcium Co-enzyme Q10 Selenium Folic acid Garlic	Fixed Dose combinations 'polypill' Antiplatelet agent (Aspirin)

	Vasodilators Renin inhibitors		
Lifestyle-modification interventions			
Dietary interventions	Health promotion	Exercise / physical activity in general	
Mediterranean diet Fibres Nut consumption Chocolate Fruits & vegetables Green and black tea Reduced salt intake Reduced fat intake	Smoking cessation Weight reduction Reduction in alcohol intake Multiple risk factors intervention Digital health promotion	Endurance (or aerobic) exercise Strengthening exercise Balance Tai-chi Flexibility Yoga Aquatic Qiqong Transcendental meditation Combined exercise	
Structural and policy-based interventions (Population-wide interventions)			
Taxation and subsidies Mass media campaigns Food & menu labelling Local food environment Worksite wellness programs Marketing restrictions Quality standards Healthy local environment Addressing air pollution			

Comparators: Other forms of intervention, usual care or no intervention control group

Eligibility criteria

Clinical Effectiveness

We will evaluate each identified study against the following predetermined selection criteria:

Study population: Adult populations (≥18 years of age) included in population-based studies, which may or may not be targeted at high risk groups (such as hypertension, obesity, hyperlipidaemia, type 2 diabetes or a combination of these). We will exclude trials where there is evidence that more than 25% of the participants have diagnosed CVD at baseline.

Intervention:

Any form of interventions or combination of interventions aimed at primary prevention of cardiovascular disease, listed above (see Health technologies being assessed).

Comparators: Other forms of intervention, usual care or no intervention control group.

Outcome measure:

1. Major cardiovascular disease events (defined as fatal and non-fatal myocardial infarction, sudden cardiac death, revascularisation, fatal and non-fatal stroke, and fatal and non-fatal heart failure)

2. Coronary heart disease (fatal and non-fatal myocardial infarction and sudden cardiac death, excluding silent myocardial infarction),
3. All-cause mortality

Study design: Randomised controlled trials (RCTs) of at least six months' duration of follow-up. Units of randomisation could be either individuals or clusters (such as family, workplace). For structural and policy interventions, if we identified no relevant RCT, we will include well conducted non-randomised studies, including modelling and simulation studies.

Cost-effectiveness

We will include full economic evaluation studies (i.e., cost-effectiveness analyses, cost–utility analyses, cost–benefit analyses) based on either randomised controlled trial(s) and/or economic models.

Information sources & Search strategy

Clinical effectiveness

Due to the likely high volume of potentially relevant trials to be included and to make the project manageable, we will follow standard guidelines for integrating existing systematic reviews into new reviews(1, 2). Where existing systematic reviews (especially Cochrane reviews) exist for any of the intervention categories, these will be used as a starting point to identify relevant studies and searches will be modified accordingly using the reviews' search dates. Initial searches for relevant systematic reviews will not be restricted by date. Searches will not be restricted by language.

We have already carried out a scoping exercise to provide a marker for the likely number of trials available to contribute data to the NMA. Many of the trials are already included in the published 20 Cochrane reviews1-20. Further searches will identify more recent trials which may contribute data to the analysis.

a) Literature search: We will utilise a variety of sources and search techniques to identify relevant literature. A comprehensive and efficient literature search will be undertaken in the major medical and health-related electronic bibliographic databases including Medline, Embase, Web of Science, Cochrane Heart Group specialist register, and the Cochrane Library (all sections).

b) In addition, various health services research and guideline producing bodies (e.g. the National Institute for Health and Care Excellence, the Scottish Intercollegiate Guidelines Network and the National Guidelines Clearinghouse) will be consulted via the internet and key organisations (e.g. in areas identified to be of priority) will be contacted.

c) Ongoing and recently completed research in the field will be identified through searching ClinicalTrials.gov, WHO Clinical Trials Registry Search Portal and the UK Clinical Research Network Study Portfolio, Current Controlled Trials and PROSPERO.

d) Finally, the reference lists of included studies will be examined for additional relevant references and, where appropriate, the citation facility in Web of Science will be used to search for articles which have cited specific key papers and authors.

Cost-effectiveness

We will undertake comprehensive, efficient searches in a range of relevant sources. Search terms will include economic, cost, and health-related quality of life related terms combined with CVD terms. Other concepts may be added as necessary. We will develop searches iteratively, referring to known articles, existing strategies and assessed search filters(3). Databases will include: MEDLINE (Ovid); MEDLINE In-Process Citations and Daily Update (Ovid); Embase (Ovid); Cochrane Library (Wiley),

including NHS EED, and HTA databases; Science Citation Index (Web of Knowledge), Research Papers in Economics (RePEC), and the Cost-effectiveness Analysis (CEA) Registry. Searches will be limited to studies in the English Language, to humans. We will also check the reference lists of included studies and any relevant reviews and undertake grey literature searches using the online resources of HTA organisations. Inclusion and exclusion criteria will be used to identify relevant papers, agreed independently by two reviewers. Disagreements will be resolved by a third reviewer. All relevant full-text articles will be obtained.

Selection process and data collection process

In order to reduce the workload of screening the searches result from the highly sensitive search with no date limit, we will develop a bespoke classifier/algorithm to identify potentially relevant studies. We will aim to achieve a high-performing algorithm comparable to human screening[13]. The computer will be fed with training data using the included and excluded studies found via our other searches. From this algorithm, the machine can make predictions (include or exclude) on other titles and abstracts that it has never seen. We will screen the titles/abstracts of a small proportion 10% of these results.

Clinical effectiveness

Based on titles, abstracts and subject indexing, initial judgements on study inclusion will be made by two independent reviewers. A third reviewer will resolve disagreements. Data will be independently extracted using a pre-specified proforma by two reviewers, with discrepancies resolved by a third. Core details will be extracted for all relevant studies including population, setting, interventions, and outcomes.

Measures of effectiveness

We will report dichotomous outcomes as risk ratios (RRs). For continuous outcomes, we will calculate mean differences (MDs) when the studies use the same scale. For continuous outcomes that are not measured on the same scale, we will standardize the measurements on a uniform scale (i.e. by dividing the absolute mean difference by the standard deviation [SD]). Where the rating scales used in the studies have a reasonably large number of categories (more than 10), the data will be treated as continuous variables arising from a normal distribution. When the rating scales used are fewer than 10 and more than 2, we will concatenate the data into two categories that best represent the contrasting states of interest and treat the outcome measure as binary. Time-to-event outcomes or generic inverse variance outcomes, will be expressed as the logarithm of hazard ratio (HR).

If possible, we will use the intention to treat population for all analyses. When effect sizes are incompletely reported we will contact the corresponding author. When the SDs of absolute changes from baseline are not available from individual trials, we will impute them as described in detail in the Cochrane Handbook. In brief, we will assume a correlation of *r*=0.5 between baseline and follow-up to estimate SD for change from baseline. Using the imputed correlation coefficient values, we thereafter calculated SDs for the change from baseline for the studies with missing SDs using the following formula:

$$SD_{change} = \sqrt{SD^2{}_{baseline} + SD^2{}_{final} - (2 * r * SD_{baseline} * SD_{final})}$$

Unit of analysis issues

We will include cluster-randomised trials in the meta-analysis along with individually-randomised trials. Cluster-randomised trials will be labelled with a (C). For cluster-randomised trials to be included in the network meta-analyses, we will adjust for design effect using an 'approximation method' (Higgins 2011) if the trial did not use a cluster-adjusting analytical strategy. The 'approximation method' entails 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 intra-cluster correlation coefficient. For dichotomous data, we will divide both the number of participants and the number who experience the event by the same design effect, while for continuous data, only the sample size will be reduced (means and standard deviations (SDs) will be left unchanged).

Cost-effectiveness
For each identified study that meet the selection criteria, we will extract the following data: country, study design, population, intervention(s), comparator(s), type of economic analysis, perspective, model type (structure and key assumptions), time horizon, effectiveness data, primary outcome, resource use and unit cost data, price year, discounting and the results of the base case and sensitivity analyses. Data such as outcomes and characteristics will be synthesised quantitatively, where appropriate or narratively. For the primary outcome, the preferred measure will be cost per quality-adjusted life years (QALY) gained.

Risk of bias assessment

Clinical effectiveness
Two reviewers will independently assess risk of bias for each RCT using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions(4)*. We will resolve any disagreements by discussion or by involving another author. We will assess the risk of bias according to the following domains: (1) random sequence generation, (2) allocation concealment, (3) blinding of outcome assessment, (4) incomplete outcome data, (5) selective outcome reporting, and (6) other bias.

Cost-effectiveness
We will use the CHEERS checklist(5) to assess the quality of the economic evaluation studies and any economic models will be further assessed using the quality assessment of economic modelling checklist developed by Phillips et al (2004)(6).

Work stream #2: Determining optimal interventions

We will conduct network meta-analyses*(7, 8)* to compare effectiveness of the different types of dietary and physical activity 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 will use 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 will consequently increase our ability to rank these and to inform decision-making frameworks(9). The two-level hierarchical NMA (level 1: intervention type, and level 2: intervention class) will incorporate exchangeability between interventions of the same class to predict an effect estimate for each of the interventions individually(9).

We will calculate the probability of a given intervention having the largest beneficial effects as the proportion of simulations in which that intervention will be ranked as the 'best' according to the relative prevention effect estimate. In addition, we will calculate 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 will be 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. We will evaluate consistencies between direct and indirect comparison in the network of evidence using the method of 'node-splitting'(10), by calculating the difference for each pair of interventions and the probability of whether direct estimates surpass the indirect estimate.

Work stream #3: Reliability and conclusiveness of evidence

Accurate understanding of the strength of the evidence of interventions for primary prevention of CVD requires a systematic, comprehensive and unbiased assessment of the accumulated available

evidence. The reliability and conclusiveness of the evidence on interventions for primary prevention of CVD will be examined using trial sequential analyses (TSA)*(11-13)*. This analysis is similar to interim analyses in a single trial, where monitoring boundaries are used to decide whether a trial could be terminated early when a P value is sufficiently small to show the anticipated effect. On the basis of pre-determined criteria for minimal clinically important difference for primary outcomes (listed above), we will calculate the optimal information size required to yield "moderate" meta-analytic evidence, based on an alpha = 5% significance level, and beta = 20% (80% power). We will also calculate the optimal information size required to yield "strong" meta-analytic evidence based on an alpha = 1% significance level, and beta = 10% (90% power). The results of each trial sequential analysis will be classified into one of four mutual exclusive categories (superiority, inferiority, futility or inconclusive). These findings will help inform decision-making by illustrating which interventions have conclusive evidence of effectiveness (or ineffectiveness), where more evidence is needed, and where enough evidence has accumulated to permit a reliable conclusion.

Work stream #4: Between-study heterogeneity and prevention effects modifiers

We anticipate several sources of heterogeneity relating to the content of the intervention and study design. We will test effect modification of intervention effectiveness using sub-group analyses and meta-regression analyses. For example, where there are sufficient data, we will stratify our analyses (subgroup) by: population risk groups (healthy vs. high-risk), trial period (older versus recent), sex (male versus female) and age (young adult versus elderly population), by intervention components and by characteristics of outcome measures. Meta-regression analyses will be used to explore components of interventions, participant characteristics and outcome measures characteristics that can predict prevention effect estimates within and across different types of interventions. The network meta-regression will be performed by allowing for a common treatment-covariate interaction for each intervention in the network meta-analysis(14).

Work stream #5: Systematic Review of Cost-effectiveness Studies

In order to make different incremental cost-effectiveness ratios (ICERs) comparable, we will convert them from their currencies to pounds sterling (£) using online currency converter. Once converted to pounds sterling, the cost data will be inflated to 2017 prices using the NHS Executive Hospital and Community Services Pay and Prices inflation index. For studies that the did not report price year, the incremental cost-effectiveness ratios will be converted to pounds sterling using the rate in their study year.

Work stream #6: Transferability, Generalisability of interventions and production of lay summaries

For the five 'best' interventions identified from WS#2: Determining optimal interventions, we will assess the *'applicability'* -the extent to which an intervention *process* could be implemented in UK NHS setting; and '*transferability'* as the extent to which the clinical- and cost-*effectiveness* of an applicable intervention could be achieved in UK NHS setting (**Figure 2**)(15-17).

Figure 2: Comparison and contrast between applicability and transferability

Item	Applicability	Transferability
Meaning	Whether the intervention process could be implemented in the local setting, no matter what the outcome is.	If the intervention were to be implemented in the local setting, would the effectiveness of the programme be similar to the level detected in the study setting?
Synonym	Feasibility	Generalizability
Question to be answered	Is it possible to run this intervention in this local setting?	If the intervention is to be run in this local setting, can it achieve the same effectiveness as it did in the study setting?
Focus of appraisal	The *process* of the intervention	The *outcome* of the intervention

Broadly, the following characteristics will be considered: **Population (i.e. a**ge, sex, socioeconomic status, health status); **Setting** (i.e. country, geographical context, healthcare/delivery system, legislative approach, and policy, cultural, socioeconomic and fiscal context); **Intervention (i.e. f**easibility, acceptability, accessibility, and other practicalities); and **Outcomes (i.e.** appropriateness/relevance, follow-up periods, important health effects).

There are four possible results of an applicability and transferability appraisal. We will code these as:

1. Likely to be applicable across a broad range of populations and settings (directly applicable).
2. Likely to be applicable across a broad range of populations and settings, assuming it is appropriately adapted (partially applicable).
3. Possibly applicable only to the populations or settings included in the studies – the success of broader application is uncertain (partially applicable).
4. Applicable only to settings or populations included in the studies (not applicable).

5. Dissemination, Outputs and anticipated Impact

Findings from this study will be internationally relevant. Our findings will be widely shared with academics (as journal articles); policymakers, stakeholders, and key organisations such as the British Heart Foundation (executive summaries) and patient groups (lay summaries). Throughout our study we will work with our PPI team to ensure that our dissemination plan results in relevant and meaningful products that each user group can utilise. In order to have the widest possible reach, we will work with our PPI advisors and our university media team to develop a media strategy. This strategy would incorporate multiple media pathways such as press release, and social media platforms. Dissemination of key findings to Public Health England and British Heart Foundation and will be reviewed by PPI representatives within the advisory committee. We will disseminate key findings in plain English on their websites and via social media such as Facebook and Twitter.

6. Project timetable and milestones

The project will consist of six phases, including: literature search, study selection, data abstraction and critical appraisal, evidence synthesis, , and report writing. It is anticipated that the phases will be staggered with some overlaps between phases. The project will be completed within 24 months

Timescale (months)										
1-2	3-4	5-6	7-8	9-10	11-12	13-14	15-16	17-18	19-20	21-22	23-24
Trial search and retrieval											
Trial assessment and data preparation											

			Search & report retrieval							
					Network meta-analysis and cost-effectiveness review					
							Report and Dissemination Phase			
Quarterly meeting of steering/advisory group throughout the project										

7. Project management

OAU will be directly responsible for leading the research, the overall project management including financial management and will co-ordinate monthly core research team meetings, weekly contact with the review team, and the PPI. OAU will monitor the work plan and meeting milestones using a GANTT chart agreed by the core research team, including a risk analysis (the key dates are outlined above). All the core research team will attend the three Expert Clinical / Methodological Group meetings and contribute to the interpretation of the results, report writing and dissemination of the findings. A Project Advisory Group will be established to include a leading internationally-renowned researcher in this field, a policy lead, and our CLAHRC PPI representatives.

8. Ethics

This study does not require ethical approval as it will summarise published studies with non-identifiable data.

9. Patient and Public Involvement

Patient and public involvement (PPI) has informed and influenced the development of our project in several ways (advisors gave feedback on our proposed research questions and draft application), and we plan to embed PPI in each phase of the project (research/protocol development, contributing to research reporting, dissemination of findings. In the development of this project we worked with three dedicated PPI advisors as part of an existing research group holding grant funding for the West Midlands CLAHRC Theme 3 (Prevention and Detection). Drawing on INVOLVE guidance and support for best practice, we will work closely with three dedicated PPI advisors throughout this project, we will invite guidance and support from our advisors at the preparatory phase of the project, offering them the opportunity to opt out if appropriate. In terms of training our PPI advisors will be able to access training and support through our connection to the CLAHRC-WM and the University of Warwick as appropriate, i.e. the UNTRAP training materials.

10. Funding acknowledgement

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