Determining optimal strategies for primary prevention of cardiovascular disease: systematic review of cost-effectiveness analyses in the United Kingdom

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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/QOVK6659.

Primary conflicts of interest: none.

Published December 2022
DOI: 10.3310/QOVK6659

This report should be referenced as follows:

Mistry H, Enderby J, Court R, Al-Khudairy L, Nduka C, Melendez-Torres GJ, *et al*. Determining optimal strategies for primary prevention of cardiovascular disease: systematic review of cost-effectiveness analyses in the United Kingdom [published online ahead of print December 21 2022]. *Health Technol Assess* 2022. https://doi.org/10.3310/QOVK6659

Abstract

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Background: Cardiovascular diseases are the leading cause of morbidity and mortality worldwide. The aim of the study was to guide researchers and commissioners of cardiovascular disease preventative services towards possible cost-effective interventions by reviewing published economic analyses of interventions for the primary prevention of cardiovascular disease, conducted for or within the UK NHS.

Methods: In January 2021, electronic searches of MEDLINE and Embase were carried out to find economic evaluations of cardiovascular disease preventative services. We included fully published economic evaluations (including economic models) conducted alongside randomised controlled trials of any form of intervention that was aimed at the primary prevention of cardiovascular disease, including, but not limited to, drugs, diet, physical activity and public health. Full systematic review methods were used with predetermined inclusion/exclusion criteria, data extraction and formal quality appraisal [using the Consolidated Health Economic Evaluation Reporting Standards checklist and the framework for the quality assessment of decision analytic modelling by Philips *et al.* (Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al.* Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**(36)].

Results: Of 4351 non-duplicate citations, eight articles met the review's inclusion criteria. The eight articles focused on health promotion ($n = 3$), lipid-lowering medicine ($n = 4$) and blood pressure-lowering medication ($n = 1$). The majority of the populations in each study had at least one risk factor for cardiovascular disease or were at high risk of cardiovascular disease. For the primary prevention of cardiovascular disease, all strategies were cost-effective at a threshold of £25,000 per quality-adjusted life-year, except increasing motivational interviewing in addition to other behaviour change strategies. Where the cost per quality-adjusted life-year gained was reported, interventions varied from dominant (i.e. less expensive and more effective than the comparator intervention) to £55,000 per quality-adjusted life-year gained.

Future work and limitations: We found few health economic analyses of interventions for primary cardiovascular disease prevention conducted within the last decade. Future economic assessments should be undertaken and presented in accordance with best practices so that future reviews may make clear recommendations to improve health policy.

Conclusions: It is difficult to establish direct comparisons or draw firm conclusions because of the uncertainty and heterogeneity among studies. However, interventions conducted for or within the UK NHS were likely to be cost-effective in people at increased risk of cardiovascular disease when compared with usual care or no intervention.

Funding: This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in *Health Technology Assessment*. See the NIHR Journals Library website for further project information.

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CHEERS	Consolidated Health Economic Evaluation Reporting Standards	NICE	National Institute for Health and Care Excellence
CVD	cardiovascular disease	QALY	quality-adjusted life-year
ICER	incremental cost-effectiveness ratio	RCT	randomised controlled trial

Introduction

Cardiovascular disease (CVD) is a term used to describe disorders that affect the heart and circulatory system, and is a common ailment in the UK.[1–3] In the UK, in 2019/20, there were over 1.8 million inpatient episodes with a major diagnosis of circulatory system disorder and almost 480,000 people were diagnosed with coronary heart disease, also known as ischaemic heart disease.[4] In 2019, the UK's CVD mortality rate was 255 deaths per 100,000 people, with Scotland having the highest death rate of the devolved nations at 326 deaths per 100,000 people.[4] Furthermore, Scotland has the highest mortality rate for coronary heart disease, with 134 deaths per 100,000 people compared with the UK average of 108 deaths per 100,000 people.[4]

Cost–utility analyses have emerged as the dominant method for guiding health-care resource allocation decisions.[5,6] The effects of therapies are quantified in quality-adjusted life-years (QALYs), which is the product of health-related quality of life (anchored at 0 for death and 1 for perfect health) and the time spent experiencing that degree of health (in years).[7] When comparing a treatment with a less effective option, incremental cost-effectiveness ratios (ICERs) are employed, and a threshold value is used to assess whether or not a treatment is cost-effective. Varying countries have different willingness-to-pay thresholds for each QALY gained.[7] The National Institute for Health and Care Excellence (NICE) (London, UK) presently reimburses new medications in the NHS based on a cost-effectiveness threshold of £20,000–30,000 for every QALY gained.[5]

Numerous systematic reviews[8–43] of the clinical effectiveness of different interventions for the primary prevention of CVD have been conducted; however, we are not aware of any systematic review that has investigated the cost-effectiveness of different interventions for the primary prevention of CVD. Therefore, the aim of the study was to address this research gap. The objective of this systematic review was to review cost-effectiveness analyses conducted for or within the UK NHS, including any existing models for randomised controlled trials (RCTs) assessing the cost-effectiveness of any form of intervention aimed at adults for the primary prevention of CVD (e.g. lipid-lowering medications, blood pressure-lowering medications, antiplatelet agents, nutritional supplements, dietary interventions, health promotion programmes, physical activity interventions, and structural and policy interventions). Interventions may or may not be targeted at high-risk groups.

This publication on the systematic review of cost-effectiveness analyses in the UK of optimal strategies for the primary prevention of CVD is part of a series of publications on 'determining optimal strategies for primary prevention of cardiovascular disease' (NIHR Journals Library reference 17/148/05). Other publications in the series are forthcoming.

The findings from all the workstreams, including those from the systematic review of economic evaluation studies, are summarised in a synopsis paper.

Methods

Information sources and search strategy

A comprehensive systematic search of the evidence for published economic evaluations, including any economic models, was performed for the following electronic databases on 13 February 2020 (see *Appendix 1*):

- MEDLINE via Ovid (1946 to 12 February 2020)
- Embase via Ovid (1947 to week 6 2020).

The search included economic-, cost- and quality of life-related terms combined with CVD and primary prevention terms, and validated UK geographic search filters developed by NICE.[44–46] In addition, we checked weekly auto-alerts from MEDLINE and Embase until 31 December 2020 for any additional studies that could be included.

Inclusion criteria

Initial scoping searches were carried out in MEDLINE in February 2020 to assess the volume and nature of evidence relating to the cost-effectiveness of interventions for the primary prevention of CVD. The scoping searches informed the development of the final search strategies for the systematic review (see *Appendix 1*). Owing to the high volume of studies identified in the scoping searches, as well as the need to keep the searches applicable to studies conducted for or within the UK NHS setting, the following inclusion criteria were implemented.

Study type

- Fully published economic evaluations (including economic models) alongside a RCT.

Population

- Adult populations (aged $\geq$ 18 years).
- Interventions may or may not be targeted at groups with moderate/high risk of CVD, for example adults with hypertension, obesity, hyperlipidaemia, type 2 diabetes or a combination of these.

Intervention

- Any form of intervention aimed at the primary prevention of CVD, including, but not limited to, drugs (e.g. lipid-lowering medications, blood pressure-lowering medications and antiplatelet agents), diet (e.g. nutritional supplements and dietary interventions), physical activity or public health (e.g. health promotion programmes and structural and policy interventions).

Comparator

- Another form of intervention (e.g. a minimal intervention, active intervention or concomitant intervention), placebo, usual care or no intervention control group, or wait list control.

Outcomes

- Cost–utility studies reporting outcomes as QALYs.

Setting

- UK-based studies only.

Exclusion criteria

Studies meeting the following exclusion criteria were excluded from the review:

- non-English-language publications
- abstract/conference proceedings, letters and commentaries
- studies with quality of life reported without utility or QALYs
- studies that do not report cost per QALY.

Assessment of eligibility and data extraction

All retrieved records were collected in a specialist database (EndNote X9.3, Clarivate Analytics, Philadelphia, PA, USA) and any duplicate records were identified and removed. Two reviewers independently reviewed titles and abstracts to identify potentially relevant full-text papers for formal assessment. Full-text papers were assessed by two reviewers independently following predefined inclusion criteria (see *Inclusion criteria*). Discrepancies were resolved by discussion.

Independent data extraction was carried out by one reviewer using a standardised data extraction sheet in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) and was then checked by a second reviewer. The following data were extracted:

- study details (i.e. author names, title and source of publication)
- baseline characteristics (i.e. country, study design, population, intervention, comparators and outcomes)
- methods (i.e. study design, study population and subgroups, setting and location, type of economic analysis, study perspective, time horizon, measurement of outcomes, measurement and valuation of preference-based outcomes, resource use and unit cost data, currency and price year, discount rate and model type)
- results [i.e. results of the base-case (incremental costs and outcomes) and sensitivity analyses]
- discussion (i.e. study findings, limitations and generalisability)
- other details (i.e. sources of funding and conflicts of interest).

Quality assessment

The quality of studies was assessed by one reviewer, using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist,[47] and was then checked by a second reviewer. The CHEERS checklist comprises the following six dimensions: (1) title and abstract, (2) introduction, (3) methods, (4) results, (5) discussion and (6) other. Under these six dimensions, a series of questions check whether or not the criteria have been clearly reported. Any studies containing an economic model were further assessed using the framework for the quality assessment of decision analytic modelling by Philips *et al.*[48] The framework by Philips *et al.*[48] contains two main dimensions: (1) structure of the model and (2) data used to parameterise the model. Under these dimensions, several questions assess whether or not the criteria have been clearly reported.

Data synthesis

Data extracted from included studies were narratively summarised and tabulated. Findings from individual studies were compared narratively.

Results

The literature search identified 4351 records through the electronic database searches. After removing duplicates, 3075 records were screened to identify potentially relevant studies. Title and abstract screening excluded 3041 records. The remaining 34 records were included for full-text assessment, after which a further 26 records were excluded, as they did not meet the formal inclusion criteria (*Figure 1*). The majority of studies were excluded because they were not full economic evaluations (see *Appendix 2*). Two further[49,50] studies were identified from weekly auto-alerts and the full texts of these studies were obtained. However, both studies[49,50] were excluded as they were not primary prevention studies. Eight studies[51–58] met the inclusion criteria of this systematic review.

Overview of included studies

Full details of the overall characteristics of included studies are provided in *Table 1*. In summary, four studies[55–58] were conducted in the UK. The remaining four studies[51–54] were part of multicountry RCTs and we have reported the results from only the UK parts of these studies (i.e. data from UK centres in multinational studies). All studies were within-clinical trial economic evaluations; however, four studies[51–54] also developed an economic model using information from the clinical trial, alongside other published literature, databases and expert opinion. The majority of the populations in each study had at least one risk factor for CVD or were at high risk of CVD. Sample sizes ranged from 110 participants[55] to 9098 participants.[51] In two studies,[56,57] the intervention was a drug regimen (i.e. pravastatin and atorvastatin), which was compared with placebo. Two studies[56,57] compared a drug treatment with

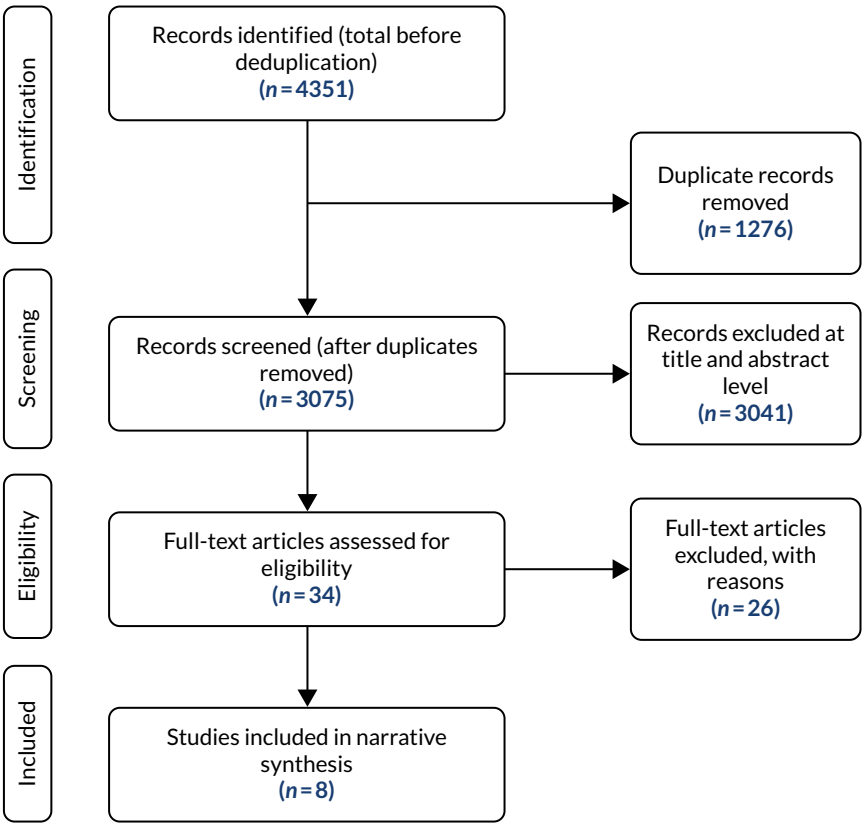

FIGURE 1 A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for cost-effectiveness studies.

TABLE 1 Summary of general characteristics of the studies

Study	Setting and location	Study design	Study population	Sample size	Intervention	Comparator
Barton *et al.*[55]	Five general practices in deprived communities (Liverpool, UK)	RCT. Within-clinical trial economic analysis	Patients aged ≥ 18 years with at least one risk factor for CVD (i.e. hypertension, raised cholesterol, diabetes, BMI > 30 kg/m^2 or current smoker)	72 patients in LHT group; 38 controls	In addition to what the control group received, the LHT provided patients with information, advice and support aimed at changing beliefs and behaviour. LHT support was available for 3 months, contact was made approximately every 2 weeks (six times in total), ideally via a face-to-face meeting, with additional telephone support, if required	Patients received health promotion literature, including British Heart Foundation (London, UK) patient booklets, and were asked to complete a food diary (at baseline and at 6-month follow-up)
Ismail *et al.*[58]	12 Clinical Commissioning Groups (South London, UK)	A three-arm single-blind parallel-group RCT. Within-clinical trial economic analysis	Patients aged 40–74 years with a QRISK®2 score ≥ 20.0% (the QRISK®2 indicates the probability of having a CVD event in the next 10 years)	1742 participants: (group intervention, $n = 697$; individual intervention, $n = 523$; UC, $n = 522$)	Motivational interviewing enhanced with behaviour change techniques delivered by health trainers. Intervention delivered in 10 sessions over 1 year, in a group or individual format	UC consisted of referrals to locally commissioned community-based weight loss, smoking cessation and/or exercise programmes
Lindgren *et al.*[51]	UK (and other European countries)	Open-label follow-up of a multicentre placebo RCT. Within-clinical trial economic model	Patients aged 40–79 years with no prior or current history of CHD, with either untreated hypertension or treated hypertension while not being treated with a statin or fibrate	9098 UK and Ireland patients	Amlodipine-based therapy or atenolol plus atorvastatin	Amlodipine-based therapy or atenolol-based therapy plus placebo
Lindgren *et al.*[52]	UK (and other European countries)	Open-label follow-up of a multicentre placebo RCT. Within-clinical trial economic model	Patients aged 40–79 years with no prior or current history of CHD, with either untreated hypertension or treated hypertension while not being treated with a statin or fibrate	4123 patients based on adherence (high, $n = 2415$; low, $n = 1708$)	Atorvastatin: high adherence defined as > 80% of days covered	Atorvastatin: low adherence defined as < 50% of days covered

Study	Setting and location	Study design	Study population	Sample size	Intervention	Comparator
McConnachie *et al.*[56]	UK	Placebo RCT. Within-clinical trial economic analysis	Men aged 45–54 years with hypercholesterolaemia who had no evidence of previous myocardial infarction	6595 patients (placebo, $n = 3293$; pravastatin, $n = 3302$)	Pravastatin (40 mg once daily): initial 5 years of treatment	Placebo
Mistry *et al.*[53]	Pairs of general practices in the UK (and six other European countries)	A matched paired cluster RCT. Within-clinical trial economic analysis and economic model	High-risk patients and their families to achieve recommended lifestyle and risk factor targets for CVD prevention in everyday clinical practice over 1 year	2024 patients (intervention, $n = 1019$; UC, $n = 1005$)	The programme was delivered by specialist nurses, working with general practitioners and supported by software programs, educational materials and group workshops	Patients in the UC arm did not receive any form of special care
Raikou *et al.*[57]	32 centres in the UK and Ireland	RCT. Within-clinical trial economic analysis	Patients aged 40–75 years who had type 2 diabetes without a documented history of CVD (but with at least one risk factor for CVD) and without elevated LDL cholesterol. The mean age of patients was 62 years, with the majority being white (94%) and male (68%)	2838 patients (atorvastatin, $n = 1428$; placebo, $n = 1410$)	Atorvastatin (10 mg) daily	Placebo
Simmons *et al.*[54]	Two UK centres (Cambridge and Leicester, UK, and other European countries)	Pragmatic multicentre cluster-randomised parallel-group trial. Within-clinical trial economic analysis and economic model	Patients aged 40–69 years with screen-detected diabetes	1024 participants were included in the within-clinical trial analysis and 999 participants were included in the economic model	Intensive treatment comprising screening and promotion of target-driven intensive management (i.e. medication and promotion of healthy lifestyles) of hyperglycaemia, blood pressure and cholesterol	Screening plus routine care

BMI, body mass index; CHD, coronary heart disease; LDL, low-density lipoprotein; LHT, lay health trainer; UC, usual care.

another drug treatment (i.e. amlodipine-based therapy or atenolol plus atorvastatin and high adherence to atorvastatin or low adherence to atorvastatin) and three studies[53,55,58] focused on interventions provided by health-care professionals that aimed to help change health behaviour or provide some form of educational support.

Review of economic evaluation methods and results

Table 2 presents the economic evaluation methods that were conducted in the included studies. Results of cost–utility analyses were presented in the form of ICERs, whereby the ICER was the cost per QALY gained. All studies presented economic evaluations alongside a RCT. The economic model was a simple decision-analytic model in one study,[54] whereas three studies[51–53] used a Markov model framework. We did not class Raikou *et al.*[57] as using an economic model per se, as this study used a non-parametric approach to extrapolate costs and effects over the lifetime using lifetables.

All studies except for one[58] adopted a health service (NHS) perspective. Ismail *et al.*[58] did not report the perspective adopted for the costs and outcomes analysis (see *Table 2*). The time horizon for the within-clinical trial analyses ranged from 6 months[55] to 15 years,[56] and one study[52] did not report the time horizon for the within-clinical trial analysis. For studies that included an economic model, the time horizon varied from 10 years[54] to a lifetime.[51,57] Furthermore, only two studies[51,53] provided the length of the model cycle.

In terms of resource use and costs, the majority of studies detailed cost components that contributed to the intervention arm, although the resource use and costs for the comparator arm were not reported consistently (see *Table 2*). For example, four studies[51,53,54,58] did not report any specific comparator costs. Other costs that were reported for both arms included hospital admissions, clinic visits, medications and, where appropriate for the economic model, health state costs. All studies except one[51] reported the costs in Great British pounds and one study[58] did not report the price year for the unit costs. Seven studies[51–54,56–58] reported that both costs and benefits were discounted at 3.5% per annum. One study,[55] which had a < 1-year time horizon, appropriately had no discounting of costs or outcomes.

The EuroQol-5 Dimensions instrument was used to obtain utility scores in seven studies[51–55,57,58] (*Table 3*). Only three[51,52,55] of these seven studies stated that the values that were used to calculate utility scores were obtained from the general public. One study[56] obtained utility values from a previous review.

All studies presented their results in terms of cost per QALY gained (see *Table 3*). Incremental costs ranged from £97 (where the intervention cost of lay health trainer was higher than the comparator cost of no intervention)[55] to £2505 (where atorvastatin daily was more expensive than the placebo comparator arm).[57] Incremental QALYs ranged from 0.0064 (where motivational interviewing enhanced with behaviour change techniques delivered by health trainers was more effective than usual care)[58] to 0.3871 (where atorvastatin daily was more effective than placebo arm).[57] For the majority of studies, the ICERs were below the NICE threshold of £20,000–30,000 per QALY.[59] The exception was the study by Ismail *et al.*,[58] in which behaviour change techniques were delivered by health trainers in an individual format and compared with usual care. Ismail *et al.*[58] reported a small difference in both the incremental costs and the incremental QALYs, leading to a large ICER of –£55,313 per QALY gained. Four studies[52,54,56,57] reported the probability of the intervention being cost-effective at the £20,000 and/or £30,000 willingness-to-pay threshold (or this could be deduced from the graphs on display in the articles) and four studies[51,53,55,58] did not report this finding.

All studies carried out some form of sensitivity or scenario analysis, the majority of which were one-way sensitivity analyses. The main parameters that varied were costs, discount rates and time horizons. Five studies[51–53,55,57] also undertook a probabilistic sensitivity analysis, namely to characterise uncertainty around key parameters.

TABLE 2 Detailed account of the economic evaluation methods and analysis: part 1

Study	Economic evaluation type	Model type	Study perspective	Time horizon	Resource use and costs	Currency (price year)	Discount rate
Barton *et al.*[55]	CUA	N/A	NHS and Personal Social Services	Within clinical trial: 6 months Model: N/A	Intervention: time spent by the study team on LHT advertisement, selection, training and supervision. Each LHT (a dietitian) recorded the number of face-to-face visits with each participant, plus time taken to contact the patient, visit preparation and travel Comparator: both groups received health promotion literature and were asked to complete a food diary Other: inpatient admissions, health-care professional and voluntary group visits, and medications	GBP (2008/9)	N/A
Ismail *et al.*[58]	CUA	N/A	NR	Within clinical trial: 12 and 24 months Model: N/A	Intervention: time spent by staff delivering sessions, including overheads and on-costs. For the group intervention, the costs were apportioned over attendees Comparator: NR Other: inpatient care, outpatient attendances, community contacts and prescription medication	GBP (NR)	3.5%

continued

TABLE 2 Detailed account of the economic evaluation methods and analysis: part 1 (*continued*)

Study	Economic evaluation type	Model type	Study perspective	Time horizon	Resource use and costs	Currency (price year)	Discount rate
Lindgren *et al.*[51]	CUA	Markov model	NHS	Within clinical trial: 3 years Model: lifetime (monthly cycles)	Intervention: drug costs (amlodipine-based therapy or atenolol plus atorvastatin) Comparator: drug costs (amlodipine-based therapy or atenolol-based therapy plus placebo) Other: inpatient admissions, outpatient visits, medications and other health states	Euros (2007)	3.5%
Lindgren *et al.*[52]	CUA	Markov model	NHS	Within clinical trial: NR Model: NR	Intervention: atorvastatin cost; dependent on adherence Comparator: NR Other: other health states	GBP (2007)	3.5%
McConnachie *et al.*[56]	CUA	N/A	NHS	Within clinical trial: 15 years (including follow-up) Model: N/A	Intervention: drug costs (pravastatin) Comparator: no cost for placebo Other: hospital admissions, coronary investigations and procedures, liver function and cholesterol tests, and statin treatment	GBP (2012)	3.5%

Study	Economic evaluation type	Model type	Study perspective	Time horizon	Resource use and costs	Currency (price year)	Discount rate
Mistry *et al.*[53]	CUA	Markov model	NHS	Within clinical trial: 1 year Model: 11 years (yearly cycles)	Intervention: EuroAction programme costs included the EuroAction nurses' costs, training costs, production of patient educational materials and any other costs associated with implementing the programme Comparator: NR Other: primary care contacts, cardiac-related drugs, cardiac-related procedures and tests, and other health states	GBP (2006/7)	3.5%
Raikou *et al.*[57]	CUA	No model per se, but extrapolation using a non-parametric approach and lifetables	NHS	Within clinical trial: 4.9 years (mean follow-up) Model: lifetime	Intervention: atorvastatin plus the use of any additional statin therapy for a cardiovascular event Comparator: the use of any additional statin therapy for a cardiovascular event Other: hospitalisations, clinic visits and tests	GBP (2003/4)	3.5%
Simmons *et al.*[54]	CUA	Decision-analytic model	NHS	Within clinical trial: 1–6 years Model: 10–30 years	Intervention: material design costs; meetings with health professionals, practitioner and patient; extra patient consultations; and treatments (including prescription of cardioprotective medication and glucometers with strips) Comparator: NR Other: routine cost of treating diabetes and diabetes-related events during trial follow-up (e.g. inpatient admissions and non-inpatient costs)	GBP (2009/10)	3.5%

CUA, cost–utility analysis; GBP, Great British pounds; LHT, lay health trainer; N/A, not applicable; NR, not reported.

TABLE 3 Detailed account of the economic evaluation methods and analysis: part 2

Study	Utility measure	Whose utility values?	Results (incremental costs and outcomes)	Key SA	Authors' conclusion
Barton *et al.*[55]	EQ-5D completed at baseline and at 6 months	The York A1 tariff was used to assign scores to each EQ-5D health state description	Incremental costs: £97.85 Incremental QALYs: 0.007 ICER: £14,480/QALY gained Probability of being cost-effective at £20,000/QALY: 0.395 Probability of being cost-effective at £30,000/QALY: 0.401	One-way SA: • Only LHT costs were included • Recruitment and training costs were excluded • A complete-case analysis was conducted • Only intervention participants known to have one LHT face-to-face visit were included PSA was also undertaken	LHTs' provision was estimated to be cost-effective for people at risk of CVD
Ismail *et al.*[58]	EQ-5D-3L completed at baseline and at 12 and 24 months	NR	The group arm was dominated by usual care (i.e. more expensive and less effective) Individual vs. usual care • Incremental costs: £354 • Incremental QALYs: 0.0064 • ICER: £55,313/QALY gained Individual vs. group • Incremental costs: £179 • Incremental QALYs: 0.0216 • ICER: £8287/QALY gained Probability of being cost-effective at £30,000/QALY • Individual: 0.381 • Group: 0.032 • Usual care: 0.587	SA around key costs: • Adjusting for therapist and general practice as random factors • Removing potential outliers • Including only patients with a BMI > 25 kg/m^2 • Adjusting for treatment compliance • Adjusting for the delay in intervention start • Adjusting for the unblinding of the research assistant at each follow-up appointment • Adjusting for the number of accelerometer wear-days at baseline and at follow-up • Adjusting for a BMI or QRISK®2 score • Adjusting for predictors of missing outcome data	Enhancing motivational interviewing with additional behaviour change techniques was not effective in reducing weight or increasing physical activity in patients with high CVD risk

Study	Utility measure	Whose utility values?	Results (incremental costs and outcomes)	Key SA	Authors' conclusion
Lindgren *et al.*[51]	EQ-5D: not stated when administered	Values were based on a representative sample of the UK population using the EQ-5D tariff	Atenolol-based therapy plus atorvastatin is eliminated through extended dominance Amlodipine-based therapy plus atorvastatin vs. amlodipine-based therapy alone • Incremental costs: €752 • Incremental QALYs: 0.063 • ICER: €11,965/QALY gained Amlodipine-based therapy vs. atenolol-based therapy alone • Incremental costs: €196 • Incremental QALYs: 0.021 • ICER: €9548/QALY gained Probability of being cost-effective at €20,000/QALY • Atenolol plus placebo: 0.00 • Atenolol plus atorvastatin: 0.00 • Amlodipine plus placebo: 0.10 • Amlodipine plus atorvastatin: 0.90	One-way SA: • Proportion of females • Starting age • Discount rate • Reduction of utility • Costs post event • Modified event costs PSA was also undertaken	A combination of amlodipine-based therapy or atorvastatin appears to be cost-effective in patients with hypertension and three or more additional factors
Lindgren *et al.*[52]	EQ-5D: not stated when administered	Values were based on a representative sample of the UK population using the EQ-5D tariff	Incremental costs: £366 Incremental QALYs: 0.02 ICER: £18,300/QALY gained Probability of being cost-effective at £20,000/QALY: NR Probability of being cost-effective at £30,000/QALY: NR	One-way SA: • Relative risk associated with high adherence • Drug cost • Starting age • Discount rate • Utility from events • Costs from events PSA was also undertaken	Given the higher risk of CVD events associated with low adherence, measures to improve adherence are an important part of the prevention of CVD

continued

TABLE 3 Detailed account of the economic evaluation methods and analysis: part 2 (*continued*)

Study	Utility measure	Whose utility values?	Results (incremental costs and outcomes)	Key SA	Authors' conclusion
McConnachie *et al.*[56]	No measures. Utilities were obtained from a previous review	Not known. Utilities were obtained from a previous review	Incremental costs: £710 Incremental QALYs: 0.136 ICER: £5221/QALY gained Probability of being cost-effective at £20,000/QALY: NR Probability of being cost-effective at £30,000/QALY: NR	SAs: • 25% reduction in admission costs • Reduction in the assumed health loss from a CVD event by 25% • Multiplying the prescribing and monitoring costs by five	Five years' primary prevention treatment of middle-aged men with a statin significantly reduces health-care resource utilisation, is cost saving and increases QALYs
Mistry *et al.*[53]	EQ-5D (during clinical trial) and utilities were obtained from a previous review	Not known. Utilities were obtained from a previous review and were based on UK population norms	Assuming no (0-year) duration of effect of the intervention beyond the end of the clinical trial (unadjusted results) Incremental costs: £419 Incremental QALYs: 0.076 ICER: £5539/QALY gained Probability of being cost-effective at £20,000/QALY: 0.95 Probability of being cost-effective at £30,000/QALY: 0.97	SAs: • Longer time frame PSA was also undertaken	Although the study achieved healthier lifestyle changes and improvements in management of blood pressure and lipids for patients at high risk of CVD, compared with usual care, it was not possible to show, using available risk equations, which do not incorporate diet and physical activity, that the intervention reduced longer-term cardiovascular risk cost-effectively

Study	Utility measure	Whose utility values?	Results (incremental costs and outcomes)	Key SA	Authors' conclusion
Raikou *et al.*[57]	EQ-5D scores from previous studies and quality-of-life tariffs owing to differences in non-fatal CVD event	Not stated	Incremental costs: £2505 Incremental QALYs: 0.3871 ICER: £6471/QALY gained Probability of being cost-effective at £20,000/QALY: NR Probability of being cost-effective at £30,000/QALY: NR	One-way SA: • Unit cost of atorvastatin • A different comparator treatment was considered by decreasing the event rates observed within the placebo population PSA was also undertaken	Primary prevention of CVD with atorvastatin is a cost-effective intervention in patients with type 2 diabetes
Simmons *et al.*[54]	EQ-5D. Not stated when administered in clinical trial and from previous studies	Not known. Utilities were obtained from a previous studies	Over a 5-year time period Incremental costs: £935 Incremental QALYs: −0.0040 ICER: dominated Probability of being cost-effective at £20,000/QALY: NR Probability of being cost-effective at £30,000/QALY: NR	One-way SA: • Treatment costs for events • Utility decrements • Discount rate	The intensive treatment was not cost-effective compared with routine care for screen-detected diabetes patients in the UK

BMI, body mass index; EQ-5D, EuroQol-5 Dimensions; EQ-5D-3L, EuroQol-5 Dimensions, three-level version; LHT, lay health trainer; NR, not reported; PSA, probabilistic sensitivity analysis; SA, sensitivity analysis.

In terms of overall results, the evaluated interventions were found to be a cost-effective use of resources, except for in two studies.[54,58] Ismail *et al.*[58] found that 'enhancing motivational interviewing with additional behaviour change techniques was not effective compared with the usual care in reducing weight or increasing physical activity in those at high CVD risk'. Simmons *et al.*[54] found that 'the intensive treatment was not cost-effective compared with routine care for screen-detected diabetes patients in the UK' and, instead, the intervention was dominated by routine care (i.e. the intervention was more expensive and less effective).

Quality assessment

Table 4 presents a summary of the scores of the quality assessment of the included studies. Using the CHEERS reporting tool[47] (see *Appendix 3*), the majority (75%) of studies fulfilled at least 20 of the 26 items. The study by Lindgren *et al.*[51] was the most comprehensively reported, scoring yes on 23 of the 26 items. When using the framework for the quality assessment of decision analytic modelling by Philips *et al.*[48] (see *Appendix 4*) for the studies that included an economic model, the least comprehensively reported study was by Lindgren *et al.*,[52] scoring yes on only 11 of the 57 items.

TABLE 4 Quality assessment

	CHEERS checklist		Phillips *et al.*[48] checklist	
Study	Item	Score	Item	Score
Barton *et al.*[55]	Yes	22	No model included	
	No	2		
	Partial	0		
	N/A	2		
Ismail *et al.*[58]	Yes	17	No model included	
	No	4		
	Partial	4		
	N/A	1		
Lindgren *et al.*[51]	Yes	23	Yes	23
	No	1	No	4
	Partial	2	Partial	22
	N/A	0	Unclear	8
			N/A	0
Lindgren *et al.*[52]	Yes	18	Yes	11
	No	3	No	7
	Partial	5	Partial	15
	N/A	0	Unclear	24
			N/A	0
McConnachie *et al.*[56]	Yes	22	No model included	
	No	1		
	Partial	2		
	N/A	1		

TABLE 4 Quality assessment (*continued*)

Study	CHEERS checklist		Phillips *et al.*[48] checklist	
	Item	Score	Item	Score
Mistry *et al.*[53]	Yes	21	Yes	25
	No	0	No	3
	Partial	5	Partial	13
	N/A	0	Unclear	16
			N/A	0
Raikou *et al.*[57]	Yes	20	No model included	
	No	0		
	Partial	5		
	N/A	1		
Simmons *et al.*[54]	Yes	22	Yes	27
	No	1	No	2
	Partial	3	Partial	14
	N/A	0	Unclear	10
			N/A	4

N/A, not applicable.

Discussion

To the best of our knowledge, this is the first systematic review investigating the cost-effectiveness of different interventions for the primary prevention of CVD. Eight studies[51–58] evaluating the cost-effectiveness of interventions for the primary prevention of CVD were included in this review. The eight studies[51–58] were published between 2007 and 2019. The studies focused on health promotion, lipid-lowering medicine and blood pressure-lowering medication. Seven[51–53,55–58] out of eight studies found therapies that were likely to be cost-effective within NICE cost-effectiveness threshold limits. The quality of the research included in the studies was variable, although quality improved with time, which is likely because of a consensus on reporting requirements for economic evaluations. All studies[51–58] included in this review, as part of our inclusion criteria, presented their findings in terms of QALYs. There was a lot of variation across the included studies[51–58] in terms of the interventions, the measure of benefit, the resources used and costs, and the time horizon. However, other features, such as intervention classes, could be used to group the interventions.

Implications for practice and research

There is an ever-increasing demand for cost-effective interventions in CVD primary prevention. We found few model-based health economic analyses of interventions for primary CVD prevention conducted within the last decade, suggesting that, despite significant investment in recent years, the cost-effectiveness of the primary prevention of CVD has received little attention. A better understanding of the cost-effectiveness of the primary prevention of CVD is an essential driver of optimal resource allocation.[60] The evidence obtained by health economics analysis makes it easier to deploy highly clinically effective and cost-effective primary CVD preventative strategies on a timely basis. As a result, in the health economics evaluation of primary CVD prevention, high-quality research is essential. Future economic assessments should be undertaken and presented in accordance with best practices so that future reviews may make clear recommendations to improve health policy.[60]

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 invited guidance and support from our patient and public involvement advisors at the preparatory phase of the project.

Conclusion

Establishing direct comparisons and drawing firm conclusions is challenging because of the uncertainty and variation across studies. However, interventions conducted for or within the UK NHS were likely to be cost-effective in people at increased risk of CVD, compared with usual care or no intervention control.

Acknowledgements

Contributions of authors

Hema Mistry (https://orcid.org/0000-0002-5023-1160) (Associate Professor, Health Economics) contributed to the protocol, study selection, validity assessments, synthesis of the included studies, the interpretation of the results and the writing of the report, and had overall responsibility for the economic evaluation study.

Jodie Enderby (https://orcid.org/0000-0002-1446-7512) (Research Associate) contributed to the protocol, study selection, validity assessments, synthesis of the included studies, interpretation of the results and to the writing of the report.

Rachel Court (https://orcid.org/0000-0002-4567-2586) (Information Specialist) contributed to the protocol development, developed the search strategies, conducted a range of searches to locate studies, wrote the sections of the report relating to the literature searches, contributed to the protocol and interpretation of the results, and commented on drafts of the report.

Lena Al-Khudairy (https://orcid.org/0000-0003-0638-583X) (Associate Professor, Evidence Synthesis) contributed to the protocol, study selection, validity assessments, synthesis of the included studies, interpretation of the results and to the writing of the report.

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Ethics statement

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

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.

Funding

This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in *Health Technology Assessment*. See the NIHR Journals Library website for further project information.

Article history

The research reported in this article was funded by the HTA programme under project number 17/148/05. The contractual start date was in February 2019. This article began editorial review in December 2021 and was accepted for publication in June 2022. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and production house have tried to ensure the accuracy of the authors' article and would like to thank the reviewers for their constructive comments on this article document. However, they do not accept liability for damages or losses arising from material published in this article.

Disclaimer

This article presents independent research funded 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, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

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Appendix 1 Search strategies for cost-effectiveness studies

Summary of bibliographic database searches

TABLE 5 Bibliographic database searches

Database	Date of search	Number of records
MEDLINE (Ovid)	13 February 2020	1648
Embase (Ovid)	13 February 2020	2703
Total number of records from database searches: 4351. Total number of records after deduplication: 3075.		

MEDLINE (via Ovid)

Actual database searched: Ovid MEDLINE® ALL.

Search date: 13 February 2020.

Date range searched: 1946 to 12 February 2020.

Search strategy

1. exp Primary Prevention/ (148,860)
2. primary prevention.ti,ab,kf. (18,711)
3. 1 or 2 (163,009)
4. exp Cardiovascular Diseases/ (2,342,767)
5. exp Stroke/ (129,744)
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. (3,176,762)
7. 4 or 5 or 6 (4,133,451)
8. 3 and 7 (17,743)
9. cardiovascular diseases/pc (32,957)
10. exp coronary disease/pc (20,241)
11. exp myocardial ischemia/pc (38,097)
12. exp heart failure/pc (3966)
13. exp heart arrest/pc (7169)
14. exp stroke/pc (16,705)
15. exp carotid stenosis/pc (288)
16. exp arteriosclerosis/pc (12,274)
17. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (102,314)
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. (232,585)

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. (672,451)
20. (((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. (29,399)
21. 8 or 17 or 18 or 19 or 20 (802,115)
22. Quality-Adjusted Life Years/ (11,825)
23. quality adjusted life year*.mp. (17,633)
24. (QALY or QALYS).mp. (10,200)
25. (utilit* adj2 (score* or value* or health)).mp. (5494)
26. (EuroQol or Euro Qol or Euro-Qol or EQ 5D* or EQ-5D* or EQ5D*).mp. (10,533)
27. (health utilities index or health-utilities-index or health-utilities index or health utility index or HUI).mp. (1753)
28. (SF 6D* or SF-6D* or SF6D* or SF-12* or SF 12* or SF 12* or short form health survey).mp. (10,403)
29. (short form 36* or SF36* or SF-36* or SF 36*).mp. (25,644)
30. Cost-Benefit Analysis/ (79,525)
31. (cost effective* or cost utilit* or cost benefit* or cost consequence*).mp. (178,346)
32. (pharmacoeconomic* or pharmaco-economic* or economic analy* or economic evaluation*).mp. (21,348)
33. (ICER* or incremental cost-effectiveness ratio*).mp. (8359)
34. (cost adj2 (evaluation* or analy* or study or studies or effective* or benefit* or utili*)).mp. (233,991)
35. (economic adj2 (evaluation* or analy* or study or studies)).ti,ab,kf. (20,353)
36. ((markov or decision or economic) adj3 model*).mp. (34,645)
37. 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 (307,088)
38. 22 or 23 or 24 (18,532)
39. exp united kingdom/ (360,716)
40. (national health service* or nhs*).ti,ab,in. (186,480)
41. (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (93,720)
42. (gb or “g.b.” or britain* or (british* not “british columbia”) or uk or “u.k.” or united kingdom* or (england* not “new england”) or northern ireland* or northern irish* or scotland* or scottish* or ((wales or “south wales”) not “new south wales”) or welsh*).ti,ab,jw,in. (2,011,610)
43. (bath or “bath’s” or ((birmingham not alabama*) or (“birmingham’s” not alabama*) or bradford or “bradford’s” or brighton or “brighton’s” or bristol or “bristol’s” or carlisle* or “carlisle’s” or (cambridge not (massachusetts* or boston* or harvard*)) or (“cambridge’s” not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or (“canterbury’s” not zealand*) or chelmsford or “chelmsford’s” or chester or “chester’s” or chichester or “chichester’s” or coventry or “coventry’s” or derby or “derby’s” or (durham not (carolina* or nc)) or (“durham’s” not (carolina* or nc)) or ely or “ely’s” or exeter or “exeter’s” or gloucester or “gloucester’s” or hereford or “hereford’s” or hull or “hull’s” or lancaster or “lancaster’s” or leeds* or leicester or “leicester’s” or (lincoln not nebraska*) or (“lincoln’s” not nebraska*) or (liverpool not (new south wales* or nsw)) or (“liverpool’s” not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or (“london’s” not (ontario* or ont or toronto*)) or manchester or “manchester’s” or (newcastle not (new south wales* or nsw)) or (“newcastle’s” not (new south wales* or nsw)) or norwich or “norwich’s” or nottingham or “nottingham’s” or oxford or “oxford’s” or peterborough or “peterborough’s” or plymouth or “plymouth’s” or portsmouth or “portsmouth’s” or preston or “preston’s” or ripon or “ripon’s” or salford or “salford’s” or salisbury or “salisbury’s” or sheffield or “sheffield’s” or southampton or “southampton’s” or st albans or stoke or “stoke’s” or sunderland or “sunderland’s” or truro or “truro’s” or wakefield or “wakefield’s” or wells or westminster or “westminster’s” or winchester or

"winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in. (1,359,981)
44. (bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in. (53,255)
45. (aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in. (202,500)
46. (armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in. (25,051)
47. 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 (2,588,203)
48. (exp africa/or exp americas/or exp antarctic regions/or exp arctic regions/or exp asia/or exp australia/or exp oceania/) not (exp united kingdom/or europe/) (2,809,225)
49. 47 not 48 (2,444,827)
50. 21 and 37 and 49 (1669)
51. limit 50 to english language (1648)

Embase (Ovid)

Actual database searched: Embase Classic plus Embase.

Search date: 13 February 2020.

Date range searched: 1947 to week 6 2020.

Search strategy

1. primary prevention/ (39,911)
2. primary prevention.ti,ab,kw. (28,624)
3. 1 or 2 (53,201)
4. exp cardiovascular disease/or exp cerebrovascular accident/ (4,341,232)
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. (4,519,286)
6. 4 or 5 (6,250,137)
7. 3 and 6 (27,199)
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 (38,096)
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. (322,379)
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. (971,868)
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. (46,849)
12. 7 or 8 or 9 or 10 or 11 (1,104,950)

13. quality adjusted life year/ (25,666)
14. quality adjusted life year*.mp. (28,653)
15. (QALY or QALYS).mp. (19,438)
16. (utilit* adj2 (score* or value* or health)).mp. (9679)
17. (EuroQol or Euro Qol or Euro-Qol or EQ 5D* or EQ-5D* or EQ5D*).mp. (20,064)
18. (health utilities index or health-utilities-index or health utilities index or health utility index or HUI).mp. (3596)
19. (SF 6D* or SF-6D* or SF6D* or SF-12* or SF 12* or SF 12* or short form health survey).mp. (15,587)
20. (short form 36* or SF36* or SF-36* or SF 36*).mp. (47,782)
21. economic evaluation/ (15,337)
22. cost benefit analysis/ (83,353)
23. cost effectiveness analysis/ (147,711)
24. cost utility analysis/ (9425)
25. (cost effective* or cost utilit* or cost benefit* or cost consequence*).mp. (315,249)
26. (pharmacoeconomic* or pharmaco-economic* or economic analy* or economic evaluation*).mp. (112,824)
27. (ICER* or incremental cost-effectiveness ratio*).mp. (15,431)
28. (cost adj2 (evaluation* or analy* or study or studies or effective* or benefit* or utili*)).ti,ab,kw. (226,088)
29. (economic adj2 (evaluation* or analy* or study or studies)).ti,ab,kw. (29,362)
30. ((markov or decision or economic) adj3 model*).mp. (41,674)
31. or/13-30 (497,035)
32. exp United Kingdom/ (443,429)
33. (national health service* or nhs*).ti,ab,in,ad. (336,697)
34. (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (43,535)
35. (gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jx,in,ad. (3,253,878)
36. (bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in,ad. (2,501,645)
37. (bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in,ad. (99,953)

38. (aberdeen or “aberdeen’s” or dundee or “dundee’s” or edinburgh or “edinburgh’s” or glasgow or “glasgow’s” or inverness or (perth not australia*) or (“perth’s” not australia*) or stirling or “stirling’s”).ti,ab,in,ad. (346,979)
39. (armagh or “armagh’s” or belfast or “belfast’s” or lisburn or “lisburn’s” or londonderry or “londonderry’s” or derry or “derry’s” or newry or “newry’s”).ti,ab,in,ad. (46,508)
40. or/32-39 (4,040,180)
41. (exp “arctic and antarctic”/or exp oceanic regions/or exp western hemisphere/or exp africa/or exp asia/) not (united kingdom/or europe/) (3,023,117)
42. 40 not 41 (3,841,327)
43. 12 and 31 and 42 (3512)
44. limit 43 to english language (3466)
45. limit 44 to conference abstract status (763)
46. 44 not 45 (2703)

Appendix 2 Studies excluded at full-text stage

Study	Reason for exclusion
Briggs *et al.*[61]	Secondary prevention of CVD
Calvert *et al.*[62]	Secondary prevention of CVD
Caro and Klittich[63]	Paper not available and no abstract
Cowie *et al.*[64]	Secondary prevention of CVD
Dalton and Bull[65]	A letter
De Smedt *et al.*[66]	Countries do not report separate data. Costs are in Euros
De Smedt *et al.*[67]	Secondary prevention of CVD
Fletcher *et al.*[68]	Model is based on a review; not a within clinical trial analysis
Griffin *et al.*[69]	A full economic evaluation was not conducted, the study looked at the feasibility of conducting a cost-effectiveness analysis in a future clinical trial
Griffiths *et al.*[70]	Treatment and not primary prevention
Mihaylova *et al.*[71]	Secondary prevention of CVD
Ismail *et al.*[72]	This is the full report; the later study was included and is the cost-effectiveness paper
Jacobs *et al.*[73]	Study was conducted in Belgium
Jones *et al.*[74]	Secondary prevention of CVD
Jönsson *et al.*[75]	Presents only methods, there are no results
Kashef *et al.*[76]	Not a full economic evaluation, no QALY data
Kim *et al.*[49]	Secondary prevention of CVD
Lee *et al.*[77]	Secondary prevention of CVD
Lindgren *et al.*[78]	Not a full economic evaluation, no QALY data
Lowres *et al.*[79]	Excluded as study conducted in Australia, but used treatment/outcomes data from a UK study
McInnes *et al.*[80]	Secondary prevention of CVD
Mihaylova *et al.*[81]	Secondary prevention of CVD
Rawles and Light[82]	Not a full economic evaluation, no cost data
Remak *et al.*[83]	Not primary prevention and data are pooled and not from one main trial
Rinciog *et al.*[84]	Secondary prevention of CVD
Taylor *et al.*[50]	Secondary prevention of CVD
Thom *et al.*[85]	Secondary prevention of CVD
Wonderling *et al.*[86]	Not a full economic evaluation, no QALY data

Appendix 3 Critical appraisal of the economic evaluation studies using the CHEERS checklist

CHEERS item	Study							
	Barton *et al.*[55]	Ismail *et al.*[58]	Lindgren *et al.*[51]	Lindgren *et al.*[52]	McConnachie *et al.*[56]	Mistry *et al.*[53]	Raikou *et al.*[57]	Simmons *et al.*[54]
Title and abstract								
Title	Y	Y	Y	Y	Y	Y	Y	Y
Abstract	Y	Y	Y	Y	Y	Y	Y	Y
Introduction								
Background and objectives	Y	Y	Y	Y	Y	Y	Y	Y
Methods								
Target population and subgroups	Y	Y	Y	P	Y	P	Y	Y
Setting and location	Y	Y	Y	P	P	Y	Y	Y
Study perspective	Y	N	Y	Y	Y	Y	Y	Y
Comparators	Y	Y	Y	Y	Y	Y	Y	Y
Time horizon	Y	P	Y	N	Y	Y	Y	Y
Discount rate	N/A	N	Y	Y	Y	Y	Y	Y
Choice of health outcomes	Y	Y	Y	Y	Y	Y	Y	Y
Measurement of effectiveness	Y	Y	Y	Y	Y	Y	Y	Y
Measurement and valuation of preference-based outcomes	Y	N	Y	Y	N	P	P	P
Estimating resources and costs	Y	Y	Y	P	Y	Y	Y	Y
Currency, price date and conversion	Y	P	Y	Y	Y	Y	Y	Y
Choice of model	N/A	N/A	Y	Y	N/A	Y	N/A	Y
Assumptions	Y	Y	Y	P	Y	Y	P	P
Analytical methods	Y	Y	Y	P	Y	Y	P	Y

CHEERS item	Study							
	Barton *et al.*[55]	Ismail *et al.*[58]	Lindgren *et al.*[51]	Lindgren *et al.*[52]	McConnachie *et al.*[56]	Mistry *et al.*[53]	Raikou *et al.*[57]	Simmons *et al.*[54]
Results								
Study parameters	Y	Y	P	Y	Y	Y	P	P
Incremental costs and outcomes	Y	Y	Y	Y	P	Y	Y	Y
Characterising uncertainty	Y	P	Y	Y	Y	Y	Y	Y
Characterising heterogeneity	N	N	N	N	Y	P	Y	N
Discussion								
Study findings	Y	Y	Y	Y	Y	Y	Y	Y
Limitations	Y	Y	Y	N	Y	P	Y	Y
Generalisability	Y	P	P	Y	Y	P	P	Y
Other								
Source of funding	Y	Y	Y	Y	Y	Y	Y	Y
Conflicts of interest	N	Y	Y	Y	Y	Y	Y	Y
Total (*n*)								
Y	22	17	23	18	22	21	20	22
N	2	4	1	3	1	0	0	1
P	0	4	2	5	2	5	5	3
N/A	2	1	0	0	1	0	1	0

N, no; N/A, not applicable; P, partially completed; Y, yes.

Note

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Appendix 4 Philips *et al.*'s quality assessment checklist for studies that included an economic model

Philips *et al.*'s[48] criterion	Study			
	Lindgren *et al.*[52]	Lindgren *et al.*[51]	Mistry *et al.*[53]	Simmons *et al.*[54]
Structure				
1. Is there a clear statement of the decision problem?	Y	Y	Y	Y
2. Is the objective of the model specified and consistent with the stated decision problem?	Y	Y	Y	Y
3. Is the primary decision-maker specified?	N	Y	Y	Y
4. Is the perspective of the model stated clearly?	Y	Y	Y	Y
5. Are the model inputs consistent with the stated perspective?	Y	Y	Y	Y
6. Has the scope of the model been stated and justified?	Y	Y	Y	Y
7. Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	P	Y	Y	Y
8. Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	Y	Y	Y
9. Are the sources of the data used to develop the structure of the model specified?	P	P	Y	Y
10. Are the causal relationships described by the model structure justified appropriately?	UNC	P	P	P
11. Are the structural assumptions transparent and justified?	UNC	P	P	P
12. Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	UNC	P	P	P
13. Is there a clear definition of the options under evaluation?	Y	Y	Y	Y
14. Have all feasible and practical options been evaluated?	P	Y	Y	Y
15. Is there justification for the exclusion of feasible options?	UNC	UNC	UNC	UNC
16. Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Y	Y	Y	Y
17. Is the time horizon of the model sufficient to reflect all important differences between the options?	UNC	Y	Y	Y
18. Are the time horizon of the model, the duration of treatment and the treatment effect described and justified?	UNC	Y	Y	Y
19. Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Y	Y	Y	Y
20. Is the cycle length defined and justified in terms of the natural history of disease?	N	Y	Y	N/A

Philips *et al.*'s[48] criterion	Study			
	Lindgren *et al.*[52]	Lindgren *et al.*[51]	Mistry *et al.*[53]	Simmons *et al.*[54]
Data				
21. Are the data identification methods transparent and appropriate given the objectives of the model?	P	P	P	P
22. Where choices have been made between data sources are these justified appropriately?	UNC	UNC	UNC	P
23. Has particular attention been paid to identifying data for the important parameters of the model?	UNC	P	P	P
24. Has the quality of the data been assessed appropriately?	UNC	UNC	UNC	UNC
25. Where expert opinion has been used are the methods described and justified?	N	UNC	UNC	UNC
26. Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	P	P	Y	Y
27. Is the choice of baseline data described and justified?	P	P	P	Y
28. Are transition probabilities calculated appropriately?	UNC	Y	Y	N/A
29. Has a half-cycle correction been applied to both costs and outcomes?	N	N	N	N/A
30. If not, has the omission been justified?	N	N	N	N/A
31. If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	P	Y	Y	Y
32. Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	UNC	P	P	Y
33. Have alternative extrapolation assumptions been explored through sensitivity analysis?	P	Y	Y	Y
34. Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	UNC	Y	Y	Y
35. Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis	UNC	P	P	Y
36. Are the costs incorporated into the model justified?	P	Y	Y	Y
37. Has the source for all costs been described?	P	Y	Y	Y
38. Have discount rates been described and justified given the target decision-maker?	Y	Y	Y	Y
39. Are the utilities incorporated into the model appropriate?	P	P	Y	Y
40. Is the source of utility weights referenced?	Y	Y	P	Y
41. Are the methods of derivation for the utility weights justified?	P	P	P	P
42. Have all data incorporated into the model been described and referenced in sufficient detail?	P	P	P	P
43. Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	UNC	UNC	UNC	UNC
44. Is the process of data incorporation transparent?	UNC	UNC	UNC	UNC
45. If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	UNC	P	UNC	UNC
46. If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	UNC	P	UNC	UNC
47. Have the four principal types of uncertainty been addressed?	UNC	P	UNC	UNC

Philips *et al.*'s[48] criterion	Study			
	Lindgren *et al.*[52]	Lindgren *et al.*[51]	Mistry *et al.*[53]	Simmons *et al.*[54]
48. If not, has the omission of particular forms of uncertainty been justified?	UNC	N	N	N
49. Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	UNC	P	UNC	P
50. Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	UNC	P	UNC	UNC
51. Has heterogeneity been dealt with by running the model separately for different subgroups?	N	N	P	N
52. Are the methods of assessment of parameter uncertainty appropriate?	UNC	UNC	UNC	UNC
53. If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	P	P	UNC	P
54. Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	UNC	P	UNC	P
55. Are any counterintuitive results from the model explained and justified?	UNC	P	UNC	P
56. If the model has been calibrated against independent data, have any differences been explained and justified?	N	UNC	UNC	P
57. Have the results been compared with those of previous models and any differences in results explained?	P	P	P	P
***Total* (n)**				
Y	11	23	25	27
N	7	4	3	2
P	15	22	13	14
UNC	24	8	16	10
N/A	0	0	0	4

N, no; N/A, not applicable; P, partial; UNC, unclear; Y, yes.

Note
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