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Cost-effectiveness of interventions to control cardiovascular diseases and diabetes mellitus in South Asia: a systematic review

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ABSTRACT

Objectives More than 80% of cardiovascular diseases (CVD) and diabetes mellitus (DM) burden now lies in low and middle-income countries. Hence, there is an urgent need to identify and implement the most cost-effective interventions, particularly in the resource-constraint South Asian settings. Thus, we aimed to systematically review the cost-effectiveness of individual-level, group-level and population-level interventions to control CVD and DM in South Asia.

Methods We searched 14 electronic databases up to August 2016. The search strategy consisted of terms related to 'economic evaluation', 'CVD', 'DM' and 'South Asia'. Per protocol two reviewers assessed the eligibility and methodological quality of studies using standard checklists, and extracted incremental cost-effectiveness ratios of interventions.

Results Of the 2949 identified studies, 42 met full inclusion criteria. Critical appraisal of studies revealed 15 excellent, 18 good and 9 poor quality studies. Most studies were from India (n=37), followed by Bangladesh (n=3), Pakistan (n=2) and Bhutan (n=1). The economic evaluations were based on observational studies (n=9), randomised trials (n=12) and decision models (n=21). Together, these studies evaluated 301 policy or clinical interventions or combination of both. We found a large number of interventions were cost-effective aimed at primordial prevention (tobacco taxation, salt reduction legislation, food labelling and food advertising regulation), and primary and secondary prevention (multidrug therapy for CVD in high-risk group, lifestyle modification and metformin treatment for diabetes prevention, and screening for diabetes complications every 2–5 years). Significant heterogeneity in analytical framework and outcome measures used in these studies restricted meta-analysis and direct ranking of the interventions by their degree of cost-effectiveness.

Conclusions The cost-effectiveness evidence for CVD and DM interventions in South Asia is growing, but most evidence is from India and limited to decision modelled outcomes. There is an urgent need for formal health technology assessment and policy evaluations in South Asia using local research data.

PROSPERO registration number CRD42013006479.

Strengths and limitations of this study

- This is the first systematic review to synthesise cost-effectiveness evidence on all types of interventions (policy, clinical or behavioural) to control cardiovascular diseases and diabetes mellitus in South Asia.
- This review used a rigorous and broad search strategy including a wide range of sources to ensure all published studies are included for review.
- This review used explicitly stated methods (protocol paper published) and standard checklists to assess methodological quality of studies.
- The search was confined to English language publications performed as of August 2016, and this review excluded unpublished and 'grey' literature domain as we wanted to include studies that have undergone peer review process.
- Significant heterogeneity in analytical framework and outcome measures used in these studies restricted meta-analysis and direct ranking of the interventions by their degree of cost-effectiveness.

INTRODUCTION

Evidence from randomised trials suggests that both pharmacological and non-pharmacological strategies are important in prevention and management of cardiovascular diseases (CVD) and diabetes mellitus (DM).[1–12] While there is strong evidence on cost-effectiveness of pharmaceutical and lifestyle interventions in reducing the CVD and DM risk in affluent settings,[13–16] little is known about the comparative cost-effectiveness of various interventions to control CVD and DM in South Asia. To generalise results from high-income countries to low and middle-income countries (LMICs) is not entirely justified because reasonable thresholds for cost-effectiveness will vary markedly—as will affordability. Also, setting specific cost-effectiveness information

is important because of the differences in healthcare infrastructure.

With the rapidly increasing prevalence of CVD and DM in South Asia and the consequent huge economic losses, coupled with ill-equipped health systems and scarce resources to tackle the burden of chronic conditions, it is imperative to promote the most cost-effective interventions in this region. While a large number of economic evaluations have been recently performed in context to LMICs, and some authors have reviewed the available literature on non-communicable diseases broadly,[17 18] no systematic attempt has been made so far to compile the evidence base and appraise the methodological quality of the economic evaluations of interventions to control CVD and DM in South Asia. To the best of our knowledge, no review has considered the cost-effectiveness evidence of interventions to control CVD and DM simultaneously, although these diseases share common risk factors.

We systematically reviewed the cost-effectiveness evidence on individual-level, group-level and population-level interventions to control CVD and DM in South Asia. The specific objectives were the following:

1. to summarise the incremental resource use, costs, consequences and cost-effectiveness of interventions versus comparators to control CVD and DM in South Asia
2. to describe the quality of economic evaluations considering key methodological issues.

Research design and methods

A protocol for the systematic review has been published previously and it provides a detailed description of the methodology, used for the current study.[19] The systematic review has been registered previously in PROSPERO (CRD42013006479).

Briefly, we searched for studies that met the following inclusion criteria:

1. type of studies: full economic evaluations (cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis) based on randomised trials or observational studies or decision models
2. type of participants: studies that included individuals with either established DM or CVD or at risk of developing these diseases in one of the South Asian countries: Afghanistan, Bangladesh, Bhutan, India, Pakistan, Maldives, Nepal and Sri Lanka
3. types of interventions: interventions or strategies for prevention and treatment of CVD or DM as documented in the previously published protocol[19]
4. types of outcome measures: we included several outcomes broadly under three domains—resource use, costs and cost-effectiveness as incremental cost per quality-adjusted life years (QALYs) gained, or disability-adjusted life years (DALYs) averted, or life years gained or intermediate outcomes; a detailed list has been presented in the previously published protocol[19]
5. studies published in the English language.

We searched 14 electronic databases and hand-searched for publications of the Disease Control Priorities Project 2 (DCPP2) and the WHO-Choosing Interventions that are Cost-Effective (WHO-CHOICE) to identify relevant studies. The details of the databases searched and a search strategy are provided in supplementary web appendix 1.

Critical appraisal of included studies

Checklists proposed by Drummond *et al*,[20] Evers *et al*[21] and Philips *et al*[22] were used for data extraction and to review methodological quality and strength of economic evidence. Also, we looked for funding sources of included studies.

Analysing, interpreting and reporting results

We extracted the incremental cost, incremental effect and incremental cost-effectiveness ratios (ICER) for interventions evaluated in the eligible studies. To adjust for cost and varying currencies over time, we used country-specific consumer price inflation rate to present value in 2017 and then used midyear currency conversion.[23 24] All costs were converted to US$ (2017). Data extraction and critical appraisal of included studies were conducted by two authors independently and differences if any were resolved by consensus.

We used country-specific gross domestic product (GDP) per capita threshold, as per WHO guidelines,[25] to interpret the ICER for all interventions evaluated in this review. We colour-coded ICER estimates as per the following scheme:

- green=ICER<1×GDP per capita per QALY gained (*highly cost-effective*)
- yellow=1–3×GDP per capita per QALY gained (*cost-effective*)
- red=ICER>3×GDP per capita per QALY gained (*not cost-effective*).

Interventions that resulted in a negative incremental effect were regarded as dominated strategy and no ICER was reported. Further, we synthesised the cost-effectiveness data and presented the ICER for policy or clinical interventions, separately in the following categories: primordial, primary, secondary and tertiary prevention.

Difference between protocol and full review

We have not planned to include economic evaluations based on observational studies in the protocol but we have included it in our review. The more inclusive criteria enabled us to provide a more comprehensive review of the evidence base surrounding the topic. Risk of bias assessment in randomised trials was not conducted using Cochrane methods as Drummond and Evers checklists are inclusive of methodological quality assessments of economic evaluations alongside randomised trials as well.

RESULTS

Search results

Our first search yielded 2949 items, titles and abstracts screening resulted in 85 articles, and full-text screening provided 42 articles that met full inclusion criteria (figure 1).

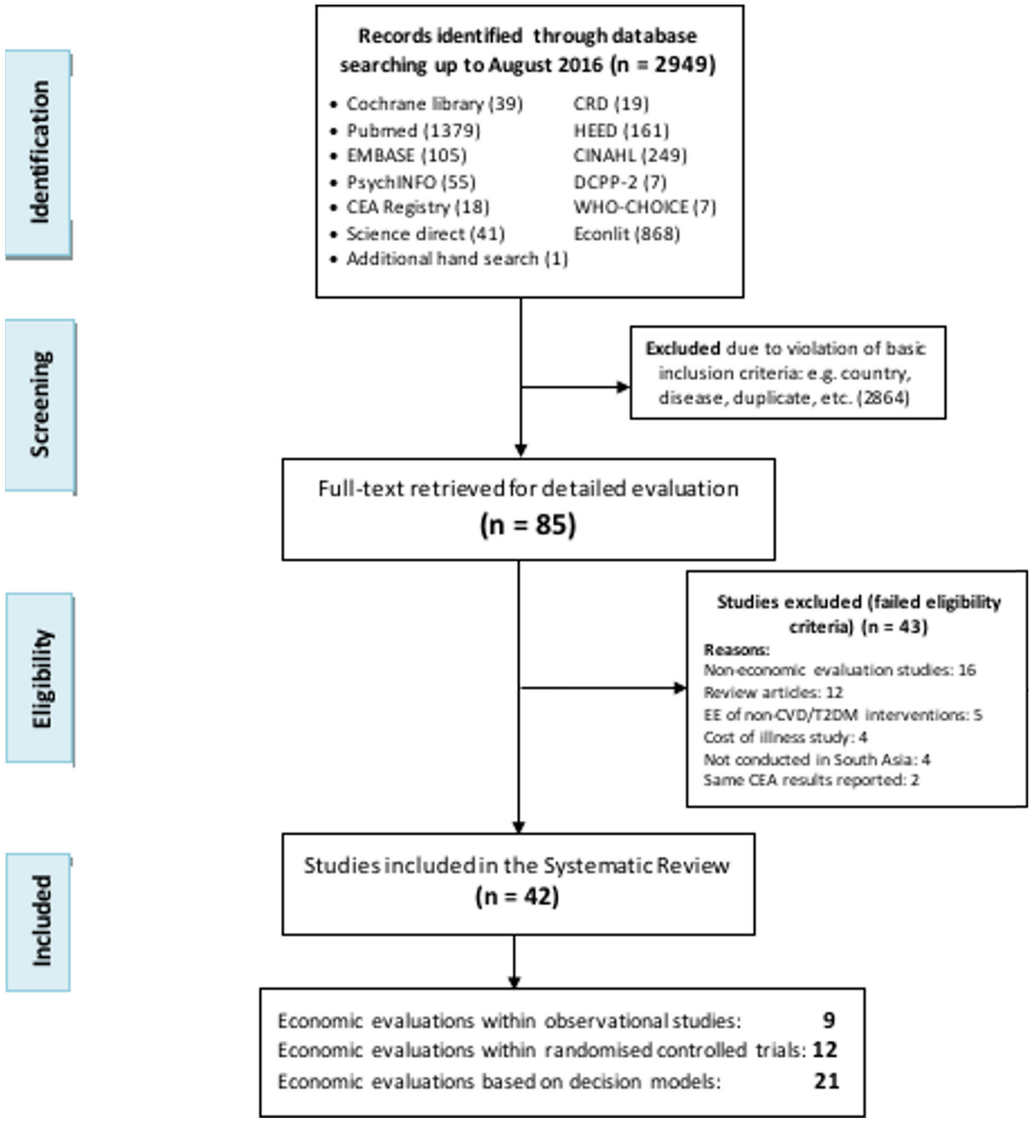

Figure 1 PRISMA flow chart for the selection of economic evaluations of interventions to control cardiovascular disease and diabetes mellitus in South Asia. CEA, cost-effectiveness analysis; CINAHL, Cumulative Index to Nursing and Allied Health Literature; CRD, Centre for Reviews and Dissemination; CVD, cardiovascular disease; DCPP2, Disease Control Priorities Project 2; EE, economic evaluation; HEED, Health Economic Evaluation Database; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; T2DM, type 2 diabetes mellitus; WHO-CHOICE, WHO-Choosing Interventions that are Cost-Effective.

Characteristics of included studies

Table 1 shows the detailed description of the studies (n=42) by country/setting, study population, intervention(s), comparator(s), economic perspective and type of analysis, and outcome measures.

Study design

The economic evaluations were based on observational studies (n=9), randomised controlled trials (RCT) (n=12) and decision models (n=21).

Study setting

Most studies were from India (n=37), followed by Bangladesh (n=3), Pakistan (n=2) and Bhutan (n=1). Decision modelling studies had used effectiveness data mostly from meta-analysis of RCTs that reported results from developed countries.

Study population

Individuals (or population) at risk or with established CVD or DM were included.

Intervention targets and comparators

Three hundred and one interventions (policy, clinical or behavioural) were evaluated against null scenario (no intervention) or active comparators.

Perspective

In two-thirds of the studies (n=28), the authors explicitly documented and justified the economic perspective of the study. The studies used '*health system*', that is, direct

Table 1 Description of the economic evaluations and risk of bias assessment in the included studies

Source (author, year)	Country /Setting	Study population	Intervention	Comparison	Economic perspective	Methodology	Outcome measure studied	Risk of bias assessment
Turi *et al*, 1991[53]	India	40 patients with severe rheumatic mitral stenosis	Percutaneous balloon commissurotomy	Surgical closed commissurotomy	Not stated (direct medical costs)	RCT-based CCA	Costs compared vs haemodynamic stability in both arms	Source of treatment effect: single-centre RCT Source of cost data: local hospital-level costs data collected Type of EE appropriate: cost-consequences analysis was conducted; incremental cost-effectiveness ratio between treatment groups not reported; long term outcomes not assessed Decision model and assumptions appropriate: NA
Ahuja *et al*, 1997[54]	India	Patients with mild hypertension	Antihypertensive regimens with diuretics	Antihypertensive regimens without diuretics	Patient	RCT-based CEA	Mean cost of control of BP to target levels per patient per day in control and study groups	Source of treatment effect: single-centre RCT Source of cost data: only drug costs included in the analysis Type of EE appropriate: no; only drug costs were compared for BP control; long-term outcomes not assessed Decision model and assumptions appropriate: NA
Nanjappa *et al*, 1998[55]	India	912 patients with symptomatic rheumatic mitral stenosis	Transvenous mitral commissurotomy: double-lumen (Accura) variable-sized single balloon	Triple-lumen (Inoue) balloon	Not stated (direct medical costs)	Observational study-based CCA	Costs compared vs haemodynamic stability in both arms	Source of treatment effect: hospital-based observational study, presurgery and postsurgery effects on haemodynamic stability reported Source of cost data: local hospital-level direct medical costs were included Type of EE appropriate: cost-consequences analysis was conducted; incremental cost-effectiveness ratio between treatment groups not reported; long-term outcomes not assessed Decision model and assumptions appropriate: NA
Malhotra *et al*, 2001[56]	India	Patients with unstable angina	Enoxaparin	UFH	Healthcare provider	RCT-based CCA	Mean cost per patient in UFH and enoxaparin groups	Source of treatment effect: single-centre RCT Source of cost data: local hospital-level costs data collected Type of EE appropriate: cost-consequences analysis was conducted; incremental cost-effectiveness ratio between treatment groups not reported; long-term outcomes not assessed Decision model and assumptions appropriate: NA

Continued

Table 1 Continued

Source (author, year)	Country /Setting	Study population	Intervention	Comparison	Economic perspective	Methodology	Outcome measure studied	Risk of bias assessment
Murray *et al*, 2003[57]	South Asia region (India)	High CV risk individuals	Behavioural interventions and treatment strategies to lower SBP and cholesterol	Various	Healthcare provider	Decision model-based CEA	DALYs averted by reduction in CVD risk	Source of treatment effect: systematic review and meta-analysis of RCT Source of cost data: WHO-CHOICE database Type of EE appropriate: yes Decision model and assumptions appropriate: state transition population cohort model
Chisholm *et al*, 2004[15]	South Asia region (India)	Individuals at risk of alcohol and tobacco use	Interventions to reduce use of alcohol and tobacco use	Various	Healthcare provider	Decision model-based CEA	DALYs averted by reducing use of tobacco, alcohol and illicit drug	Source of treatment effect: systematic review of observational study Source of cost data: WHO-CHOICE database Type of EE appropriate: yes Decision model and assumptions appropriate: state transition population cohort model
Namboodiri *et al*, 2004[58]	India	Patients awaiting pacemaker implant	DDD vs VDD pacemakers	–	Not stated (direct medical costs)	Observational study-based CCA	Costs compared vs clinical efficacy and complications between two arms	Source of treatment effect: hospital-based observational study, presurgery and postsurgery effects on haemodynamic stability and complications reported Source of cost data: local hospital-level costs data collected Type of EE appropriate: cost-consequences analysis was conducted; incremental cost-effectiveness ratio between treatment groups not reported; long-term outcomes not assessed Decision model and assumptions appropriate: NA
Narayan *et al*, 2006[34]	South Asia region (India)	Patients at risk of developing diabetes or patients with diabetes	Combination of treatment and screening strategies to prevent and manage diabetes	Various	Healthcare provider	Decision model-based CEA	QALYs gained by preventing and/ortreating diabetes and its complications	Source of treatment effect and cost data: extrapolated from developed countries; it was assumed that costs are eight times higher in developed countries than in low-income and middle-income countries; treatment effects (QALYs) were taken same as observed in the developed countries Type of EE/decision model appropriate: not much details provided to ascertain appropriateness of model fit Decision model and assumptions appropriate: no details provided

Continued

Table 1 Continued

Source (author, year)	Country /Setting	Study population	Intervention	Comparison	Economic perspective	Methodology	Outcome measure studied	Risk of bias assessment
Gaziano *et al*, 2006[43]	South Asia region (India)	Patients with high CV risk or established CVD	Interventions to manage CVD	Various	Healthcare provider	Decision model-based CEA	DALYs averted by treating and preventing CVD events	Source of treatment effect: derived from meta-analysis of RCT; disability weights taken from GBD study 2006 report Source of cost data: not clear Type of EE/decision model and assumptions appropriate: not much details provided to ascertain appropriateness of model fit
Willett *et al*, 2006[5]	South Asia region (India)	Population at risk	Dietary and LSM strategies	Various	Healthcare provider	Decision model-based CEA	DALYs averted by reducing CVD risk	Source of treatment effect: systematic review and meta-analysis of RCTs Source of cost data: no details provided Type of EE/decision model and assumptions appropriate: not much details provided
Rodgers *et al*, 2006[59]	South Asia region (India)	Population at risk	Multidrug regimen to reduce high blood pressure and cholesterol	Various	Healthcare provider	Decision model-based CEA	DALYs averted by reducing CVD risk	Source of treatment effect: derived from meta-analysis of RCTs of BP-lowering treatment; DALYs weight obtained from GBD 2000 study Source of cost data: annual medications cost derived from International Drug Price Indicator Guide Medical services: Xact Medicare Services 2003 + WHO-CHOICE Type of EE appropriate: yes Decision model and assumptions appropriate: no details provided
Jha *et al*, 2006[60]	South Asia region (India)	Population at risk	Interventions to reduce tobacco use	Various	Healthcare provider	Decision model-based CEA	DALYs averted by reducing tobacco use and preventing tobacco attributed deaths	Source of treatment effect: systematic review and meta-analysis of 139 observational studies Source of cost data: no details provided Type of EE appropriate: yes Decision model and assumptions appropriate: static cohort model
Shafiq *et al*, 2006[61]	India	Patients with unstable angina	Low molecular-weight heparins—enoxaparin, nadroparin and dalteparin	Active comparators	Patients and healthcare provider	RCT-based CEA	ICER per MACE outcomes (MI, recurrent angina, death)	Source of treatment effect: single-centre RCT Source of cost data: local hospital-level costs data collected Type of EE appropriate: no; since no difference in treatment effects was observed in the trial, an appropriate choice of economic analysis would be cost-minimisation analysis Decision model and assumptions appropriate: NA

Continued

Table 1 Continued

Source (author, year)	Country /Setting	Study population	Intervention	Comparison	Economic perspective	Methodology	Outcome measure studied	Risk of bias assessment
Ramachandran *et al*, 2007[37]	India	Individuals with impaired glucose tolerance	LSM, metformin	No intervention	Healthcare provider	RCT-based CEA	NNT to prevent or delay once incident case of diabetes	Source of treatment effect: single RCT Source of cost data: patients, health facility and program-level and societal costs included during the trial period Type of EE appropriate: yes Decision model and assumptions appropriate: NA
Zubair Tahir *et al*, 2009[62]	Pakistan	55 patients with aneurysmal subarachnoid haemorrhage	Endovascular treatment post subarachnoid haemorrhage	Surgical clipping post subarachnoid haemorrhage	Not stated (direct medical costs)	Observational study-based CCA	Costs compared vs circulation aneurysms between two arms	Source of treatment effect: hospital-based observational study, presurgery and postsurgery effects on haemodynamic stability reported Source of cost data: local hospital-level costs data collected Type of EE appropriate: cost-consequences analysis was conducted; incremental cost-effectiveness ratio between treatment groups not reported; long-term outcomes not assessed Decision model and assumptions appropriate: NA
Habib *et al*, 2010[63]	Bangladesh	Patients with diabetes nephropathy with at least 1 year of follow-up	Medical intervention for diabetic nephropathy	Late-detected vs early-detected diabetic nephropathy	Patients/ healthcare provider	Observational study-based CEA	Cost of treating early-detected and late-detected diabetes nephropathy was compared against the clinical outcomes: HbA1c, creatinine, BP, FBG, lipid profile	Source of treatment effect: hospital-based observational study Source of cost data: Local hospital-level costs data collected Type of EE appropriate: no; incremental cost-effectiveness ratio between treatment groups not reported; long-term outcomes not assessed Decision model and assumptions appropriate: NA
Habib *et al*, 2010[64]	Bangladesh	Patients with diabetes foot	Medical intervention for diabetic foot management	Late-detected vs early-detected diabetic foot	Patients/healthcare provider	Observational study-based CEA	Cost of treating early-detected and late-detected diabetes foot was compared against the clinical outcomes: HbA1c, creatinine, BP, FBG, lipid profile	Source of treatment effect: hospital-based observational study Source of cost data: local hospital-level costs data collected Type of EE appropriate: no; incremental cost-effectiveness ratio between treatment groups not reported; long-term outcomes not assessed. Decision model and assumptions appropriate: NA

Continued

Table 1 Continued

Source (author, year)	Country /Setting	Study population	Intervention	Comparison	Economic perspective	Methodology	Outcome measure studied	Risk of bias assessment
Sanmukhani, *et al*, 2010[65]	India	Patients at risk of CVD (primary prevention) Patients with history of CVD (secondary prevention)	Simvastatin—40 mg Pravastatin—40 mg	No therapy	Patient	Observational study-based CEA	Cost per major coronary event averted Cost per CHD death averted	Source of treatment effect: derived from published RCTs and observational studies* Source of cost data: local hospital-level costs data collected Type of EE appropriate: only average cost-effectiveness ratio was reported; incremental cost-effectiveness ratio between treatment groups not reported; long-term outcomes not assessed Decision model and assumptions appropriate: NA
Cecchini *et al*, 2010[32]	South Asia region (India)	Population-based and individuals at high risk (BMI≥25 kg/m^2, high BP, cholesterol, diabetes)	Dietary and physical activity interventions targeted at: 1. school level 2. worksites 3. mass media campaigns 4. fiscal measures 5. physician counselling 6. food advertising regulation 7. food labelling	No intervention	Healthcare provider	Decision model-based CEA	Reduction in BMI, cholesterol, SBP, fat intake and increase in fibre consumption	Source of treatment effect: distribution of risk factors in population obtained from WHO mortality database, UN statistics, US NHANES survey, Health Survey for England; treatment effects derived from Women's Healthy Eating and Living randomised trial and the Seven Countries Study Disability weights—GBD study 2006 Source of cost data: WHO-CHOICE database Type of EE appropriate: yes Decision model and assumptions appropriate: chronic disease prevention model
Schulman-Marcus *et al*, 2010[40]	India	Patients with acute coronary syndrome	Prehospital ECG performed by a GP to improve timely access to reperfusion by accurate referral to a hospital	ECG-based diagnosis vs no ECG tests in acute chest pain	Societal	Decision model-based CEA	QALY gained by accurate referral to hospital in patients with ACS	Source of treatment effect: relative risk reduction with thrombolytics derived from systematic review and meta-regression analysis of trials; QALY weight derived from DCP2, 2006 and GBD study 2006 reports Source of cost data: ECG cost—local Central Government Health Scheme rates in India Drug prices: International Drug Price Indicator Guide Medical services: cost derived from Disease Control Priorities Project Type of EE appropriate: yes Decision model and assumptions appropriate: Markov model

Continued

Table 1 Continued

Source (author, year)	Country /Setting	Study population	Intervention	Comparison	Economic perspective	Methodology	Outcome measure studied	Risk of bias assessment
Donaldson *et al*, 2011[30]	India	Individuals at risk of secondhand smoking	Prohibition of smoking in public places	No smoking ban	Societal	Decision model-based CEA	Life years saved and QALYs gained by complete smoking ban in public places and by averted AMI	Source of treatment effect: derived from systematic review and meta-analysis of observational study Source of cost data: local state records+WHO-CHOICE database Type of EE appropriate: yes Decision model and assumptions appropriate: model structure not described and ICER calculation looks ambiguous
Lohse *et al*, 2011[66]	India	Women with gestational diabetes	Screening programme for GDM to prevent T2DM	No screening	Societal	Decision model-based CEA	DALYs averted by preventing T2DM	Source of treatment effect: derived from two RCTs Source of cost data: primary cost data collected from four service delivery sites in India Type of EE appropriate: yes Decision model and assumptions appropriate: GDM model
Jafar *et al* 2011[36]	Pakistan	Individuals with high blood pressure	Community-based interventions for BP control: 1. combined HHE plus trained GP 2. HHE only 3. trained GP only	Usual care	Societal	RCT-based CEA	ICER per reduction in SBP and DALYs averted by reducing CVD events	Source of treatment effect: community-based cluster RCT Source of cost data: local hospital-level costs data collected Type of EE appropriate: yes Decision model and assumptions appropriate: NA
Ahmad *et al*, 2011[67]	India	Patients with diabetes undergoing surgery	Different insulin regimens for patients with diabetes undergoing surgery 1. pre-mixed regular/NPH (30:70) 2. split-mixed regular/NPH 3. split-mixed glargine/lispro 4. split-mixed detemir/aspart	Active comparators	Patient	RCT-based CEA	ICER for different insulin regimens for reduction in perioperative complications	Source of treatment effect: hospital-based RCT, although randomisation method is not clearly described Source of cost data: local hospital-level costs data collected Type of EE appropriate: yes Decision model and assumptions appropriate: NA
Humaira *et al*, 2012[68]	Bangladesh	Patients with DR with at least 1 year of follow-up	Medical intervention for diabetic retinopathy	Late-detected vs early-detected diabetic retinopathy	Patient/healthcare provider	Observational study-based CEA	Cost of treating early-detected and late-detected DR was compared against the clinical outcomes: HbA1c, creatinine, BP, FBG, lipid profile	Source of treatment effect: hospital-based observational study Source of cost data: local hospital-level costs data collected Type of EE appropriate: no; incremental cost-effectiveness ratio between treatment groups not reported; long-term outcomes not assessed Decision model and assumptions appropriate: NA

Continued

Table 1 Continued

Source (author, year)	Country /Setting	Study population	Intervention	Comparison	Economic perspective	Methodology	Outcome measure studied	Risk of bias assessment
Brown *et al*, 2013[31]	India	School students: aged 14 years and above	Project MYTRI Four intervention components: 1. classroom activities/ behaviouralinterventions 2. peer-led health activism 3. posters 4. parent cards	No intervention	Societal	RCT-based CCA	QALYs gained by averted smoking and medical costs	Source of treatment effect: single-cluster RCT Source of cost data: programme-level costs data collected during the trial period Type of EE appropriate: yes Decision model and assumptions appropriate: Markov model was used to project the short-term outcomes observed within the cluster RCT
Ortegón *et al*, 2012[29]	South Asia region (India)	Population-based and individuals at high CV risk	123 single or combination prevention and treatment strategies for CVD, diabetes and smoking	Various	Healthcare provider	Decision model-based CEA	DALYs averted by reducing CVD, diabetes and tobacco related disease	Source of treatment effect: tobacco interventions—derived from systematic review of observational study (cross-sectional and case–control study); tobacco tax effect—derived from US CDC, World Bank and WHO reports; salt reduction—analysis of observational data+data from trials of salt reduction; CVD drugs—derived from meta-analysis of RCTs; intensive glucose-lowering drugs derived from meta-analysis of RCTs; glycaemic control—UKPDS and DCCT studies Source of cost data: WHO-CHOICE database Type of EE appropriate: yes Decision model and assumptions appropriate: population-based cohort model used local epidemiological data
Marseille *et al*, 2013[35]	India	Women with gestational diabetes	Screening programme for GDM to prevent T2DM	No screening	Healthcare provider	Decision model-based CEA	DALYs averted by reducing perinatal complications and T2DM	Source of treatment effect: single RCT (IDPP-1 trial in India)+meta analysis of RCT; DALYs obtained from published literature sources (based on seven experts) Source of cost data: local hospital-level costs data collected Type of EE appropriate: yes Decision model and assumptions appropriate: GeDiForCE microsimulation model
Rachapelle *et al*, 2013[27]	India	Patients with diabetes aged 40 years who had not been previously screened for diabetic retinopathy (DR)	Telemedicine screening and hospital-based DR treatment	No screening	Healthcare provider and societal	Decision model-based CEA	QALYs gained by preventing DR	Source of treatment effect: single multicentre RCT (ETDRS study); baseline distribution of population obtained from population survey in India Source of cost data: local hospital-level costs data collected Type of EE appropriate: yes Decision model and assumptions appropriate: Markov model

Continued

Table 1 Continued

Source (author, year)	Country /Setting	Study population	Intervention	Comparison	Economic perspective	Methodology	Outcome measure studied	Risk of bias assessment
Megiddo *et al*, 2014[38]	India	Patients with acute myocardial infarction	Policies that expand the use of aspirin, injectable streptokinase, beta-blockers, ACE inhibitors, and statins for treatment and secondary prevention of AMI	Active comparators	Healthcare provider	Decision model-based CEA	DALYS averted by expanding use of CVD prevention drugs	Source of treatment effect: population distribution using World Bank population projection tables; life expectancy using WHO life tables; CHD incidence rates using published literature from India; baseline coverage of drugs for treatment of AMI obtained from CREATE registry and for secondary prevention of CVD therapy obtained from community-based survey PURE study in India; efficacy of aspirin obtained from ISIS-2; effectiveness of multidrug therapy obtained from prior literature sources (meta-analysis of RCTs); disability weights used from GBD 2006 report Source of cost data: Drug costs data obtained from cimsasia.com Type of EE appropriate: yes Decision model and assumptions appropriate: Markov model
Patel *et al*, 2014[69]	India	Patients with hypertension	Nebivolol (2.5 mg, 5 mg, 10 mg)	Sustained release metoprolol succinate (25 mg, 50 mg, 100 mg)	Patient	RCT-based CEA	ICER per unit reduction in blood pressure per day	Source of treatment effect: single RCT Source of cost data: local hospital-level costs data collected Type of EE appropriate: yes Decision model and assumptions appropriate: NA
Lamy *et al*, 2014[70]	Asia (India)	Patients at risk of CVD, with IGT/IFG, or type 2 diabetes mellitus	Insulin glargine	Standard management of hyperglycaemia and n-3 fatty acids or placebo	Healthcare provider and patient	RCT-based CMA	Cost per patient in insulin glargine arm vs standard care arm	Source of treatment effect: single multicentre RCT Source of cost data: local hospital-level costs data collected Type of EE appropriate: yes Decision model and assumptions appropriate: NA
Lamy *et al*, 2014[71]	Asia (India)	Patients requiring revascularisation procedure	Off-pump CABG	On-pump CABG	Healthcare provider and patient	RCT-based CMA	Cost per patient in the off-pump CABG vs on-pump CABG group	Source of treatment effect: single multicentre RCT Source of cost data: local hospital-level costs data collected Type of EE appropriate: yes Decision model and assumptions appropriate: NA
Anchala *et al*, 2015[72]	India	Patients with hypertension (30–64 years)	Decision support system for hypertension management	Chart-based support for hypertension management	Healthcare provider	RCT-based CEA	Cost per unit reduction in SBP	Source of treatment effect: single-cluster RCT Source of cost data: primary costs data collected from health centre Type of EE appropriate: yes Decision model and assumptions appropriate: NA

Continued

Table 1 Continued

Source (author, year)	Country /Setting	Study population	Intervention	Comparison	Economic perspective	Methodology	Outcome measure studied	Risk of bias assessment
Dukpa *et al*, 2015[73]	Bhutan	Population at risk of diabetes and hypertension	WHO Package of Essential Non-Communicable (PEN) disease interventions for primary healthcare—current PEN programme vs universal screening for diabetes and hypertension	No screening	Societal	Decision model-based CUA	Cost per DALYs averted	Source of treatment effect/model parameters: transition probabilities used from published literature sources, population risk profile for hypertension and diabetes obtained from local surveys; treatment effects with BP-lowering drugs (controlled hypertension) obtained from meta-analysis of RCT; intervention effectiveness with intensive glucose and hypertension control obtained from CDC diabetes cost-effectiveness group; disability weights obtained from GBD study, WHO 2004 Source of cost data: local primary data collected by the authors, from 16 key informants; both direct medical and non-medical costs included Type of EE appropriate: yes Decision model and assumptions appropriate: Markov model
Basu *et al*, 2015[39]	India	Population at risk of CVD and with existing CVD	Expansion of national insurance to cover primary prevention, secondary prevention and tertiary treatment for CVD	Active comparators	Healthcare provider	Decision model-based CEA	Cost of treatment/prevention strategies coverage per DALY averted	Source of treatment effect: current access to CVD therapy obtained from local survey in India (SAGE study); insurance coverage obtained from published literature (Rajiv Aarogyasri Community Health Insurance Scheme in Andhra Pradesh); disability weights obtained from GBD 2010 study; treatment effects of CVD drugs obtained from meta-analysis of RCTs Source of cost data: WHO-CHOICE database Type of EE appropriate: yes Decision model and assumptions appropriate: validated microsimulation model

Continued

Table 1 Continued

Source (author, year)	Country /Setting	Study population	Intervention	Comparison	Economic perspective	Methodology	Outcome measure studied	Risk of bias assessment
Basu *et al*, 2015[74]	India	Population at risk of diabetes	Alternative diabetes screening approaches: Chaturvedi risk score, Mohan risk score, Ramachandran risk score, random point of care glucose testing	Active comparators	Healthcare provider	Decision model-based CEA	Cost of implementing screening and confirmatory tests Cost per true positive case	Source of treatment effect: population demographics obtained from UN database, distribution of risk factors for diabetes among Indians obtained from IMS study and several other data sources and combined using regression models; to estimate health benefits of screening, UKPDS outcomes model 2 having South Asian-specific disease progression parameters (validated among South Asians in UK and India) were used Source of cost data: WHO-CHOICE database to include costs of personnel, operations and materials for screening Type of EE appropriate: yes Decision model and assumptions appropriate: validated microsimulation model used
Gupta *et al*, 2015[41]	India	Patients with type 2 diabetes mellitus	Biphasic insulin aspart 30±OGLDs	Biphasic human insulin 30±OGLDs, insulin glargine±OGLDs or NPH insulin±OGLDs	Healthcare provider	Decision model-based CEA	Incremental cost per life years gained Incremental cost per QALYs gained	Source of treatment effect: A_1chieve study—an observational 24-week study in insulin-naïve and insulin-experienced population; utility weights (QALY) were derived from the same study using EQ5D Source of cost data: existing literature, reviewed by experts; cost of insulin in OGLD obtained from local Novo Nordisk affiliates Type of EE appropriate: yes Decision model and assumptions appropriate: validated IMS CORE Diabetes Model used and C/E results projected for 30 years' duration
Home *et al*, 2015[75]	India	Type 2 diabetes mellitus	Basal insulin treatment with insulin detemir	No insulin detemir (all OGLDs)	Healthcare provider	Decision model-based CEA	Incremental cost per life years gained Incremental cost per QALYs gained	Source of treatment effect: A_1chieve study—an observational 24-week study in insulin-naïve and insulin-experienced population; utility weights (QALY) were derived from the same study using EQ5D Source of cost data: existing literature, reviewed by experts; cost of insulin in OGLD obtained from local Novo Nordisk affiliates Type of EE appropriate: yes Decision model and assumptions appropriate: validated IMS CORE Diabetes Model used and C/E results projected for 30 years' duration

Continued

Table 1 Continued

Source (author, year)	Country /Setting	Study population	Intervention	Comparison	Economic perspective	Methodology	Outcome measure studied	Risk of bias assessment
Sengottuvelu *et al*, 2016[76]	India	65 patients requiring angiogram followed by fractional flow reserve	Fractional flow reserve	Angiography	Not stated (direct medical costs)	Observational study-based CCA	Costs compared vs management decision	Source of treatment effect: hospital-based observational study, presurgery and postsurgery effects on haemodynamic stability reported Source of cost data: local hospital-level costs data collected Type of EE appropriate: no; incremental cost-effectiveness ratio between treatment groups not reported; long-term outcomes not assessed Decision model and assumptions appropriate: NA
Limaye *et al*, 2016[77]	India	Type 2 diabetes mellitus	Antidiabetic drugs (glimepiride, pioglitazone, metformin)	Active comparators	Patient	Observational study-based CEA	Cost per unit of effectiveness	Source of treatment effect: hospital-based observational study Source of cost data: local hospital-level costs data collected Type of EE appropriate: no; incremental cost-effectiveness ratio between treatment groups not reported; long-term outcomes not assessed Decision model and assumptions appropriate: NA
Basu *et al*, 2016[78]	India	Individuals aged 30–70 years at high CV risk (≥10%)	▶ A treat-to-target strategy emphasising lowering blood pressure to a target ▶ A benefit-based tailored treatment strategy emphasising lowering CVD risk ▶ A hybrid strategy currently recommended by the WHO	Active comparators	Healthcare provider	CEA	DALYS averted by reducing CVD deaths	Source of treatment effect: meta-analysis of RCTs; adherence to prescribed therapy was obtained from observational cohort studies Source of cost data: drugs costs derived from International Drug Price Indicator Guide; WHO-CHOICE cost estimates for medical services updated to 2015 dollars Type of EE appropriate: yes Decision model and assumptions appropriate: validated microsimulation model

*West of Scotland Coronary Prevention Study, the Air Force Coronary Atherosclerosis Prevention Study and the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm study for primary prevention; the Cholesterol and Recurrent Events Trial, the Long-term Intervention with Pravastatin in Ischaemic Disease Study and the Scandinavian Simvastatin Survival Study (4S) for secondary prevention; and two studies, the Heart Protection Study and the Pravastatin in elderly individuals at risk of vascular disease (PROSPER) study for high-risk patients.
ACEi, ACE inhibitors; ACS, acute coronary syndrome; AMI, acute myocardial infarction; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft surgery; CCA, cost-consequences analysis; CDC, Centers for Disease Control and Prevention; CEA, cost-effectiveness analysis; CHD, Coronary Heart Disease; CORE, Centre for Outcomes Research; CREATE, Treatment and outcomes of acute coronary syndromes in India; CUA, cost-utility analysis; CV, cardiovascular; CVD, cardiovascular diseases; C/E, Cost-effective; DALY, disability-adjusted life years; DCCT, Diabetes Control and Complications Trial; DCP2, Disease Control Priorities; DDD, a type of heart pacemake that is Dual pacing for both chambers, Dual chamber activity sensing, and Dual response; DR, diabetes retinopathy; ECG, echocardiogram; EE, economic evaluation; EQ5D, European Quality of Life 5 Dimension; ETDRS, Early Treatment for Diabetic Retinopathy Study; FBG, Fasting Blood Glucose; GBD, Global Burden of Disease; GDM, gestational diabetes mellitus; GP, general practitioner; HbA1c, glycated haemoglobin; HHE, home health education; ICER, incremental cost-effectiveness ratio; IDPP-1, Indian Diabetes Prevention Program trial 1; IFG, Impaired Fasting Glucose; IGT, Impaired Glucose Tolerance; ISIS-2, Second International Study of Infarct Survival; LSM, lifestyle modifications; MACE, major adverse cardiovascular events; MI, myocardial infarction; MYTRI, Mobilizing Youth for Tobacco-Related Initiatives in India; NA, not available; NHANES, National Health and Nutrition Examination Survey; NNT, Number Needed to Treat; NPH, neutral protamine Hagedorn; OGLD, oral glucose-lowering drugs; PURE, Prospective Urban Rural Epidemiology Study; QALYs, quality-adjusted life years; RCT, randomised controlled trials; SAGE, Study on Global AGEing and Adult Health; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; UFH, unfractionated Heparin; UKPDS,United Kingdom Prospective Diabetes Study; UN, United Nations; VDD, Ventricular Dual Chamber heart pacemaker; WHO-CHOICE, Choosing Interventions that are Cost-Effective.

costs incurred by the health system (n=26); '*patient*', that is, out-of-pocket payments by patient (n=6); or '*societal*', that is, inclusive of all direct and indirect costs, plus productive loss (n=6) perspectives. Five studies did not state any perspective.

Funding

Two-thirds of evaluations (n=29) provided statements on the funding source. Public sponsorship or charitable trust/foundation grant was most common (n=16), followed by pharmaceutical industry (n=6) or received no support (n=7). A large number of studies did not state their source of research funding (n=13).

Resource use and costs

Only 20% of the studies (n=8) reported types and quantities of resource use and unit costs separately. Of these, five were RCT-based economic evaluations and two were decision model studies, suggesting that RCT provides an advantage on the reporting of actual resource use data as it is being collected during the trial.

Mostly direct medical costs were considered, although the scope of this varied enormously. For instance, 14 studies included only cost of intervention (medicines, diagnostics), while others (n=28) included cost of training, delivery of intervention, associated healthcare visit costs and travel cost of patients to the healthcare facility. Most (n=27) appeared to use an 'ingredients' costing approach, where costs were broken down between the main cost components such as medications, healthcare visits, vehicles, salaries and consumables. Fewer (n=5) used an 'activity'-based approach, by identifying specific tasks such as programme and therapy costs. Two studies appeared to use some combination of the two, and it was not possible to discern the approach for eight papers. Few studies (n=6) also included 'productivity losses' (often termed 'indirect costs') in their assessment of costs, which were measured using the 'human capital approach'.

Regardless of the approach taken, most papers (n=21) presented aggregated cost information. Many studies used actual expenditure data (n=17) as their source of costs data. Seven studies used published sources to generate cost estimates sometimes supplemented with expert opinion. Currencies reported were mostly in US$ (n=25), international dollars (n=4) or local currencies (Indian rupees/Bhutanese rupees) (n=6). In addition, seven studies quoted costs in both US$ and the local currency.

Outcome measures (consequences)

Nearly half of the studies (n=21) used 'life years gained' or 'QALYs' or 'DALYs' in their analysis. The calculation of QALYs/DALYs was based on South Asian population life expectancies; however, the utility values (QALYs weight) were derived from developed countries. Disability weights used in the WHO-CHOICE-based decision model studies were derived from the Global Burden of Disease (GBD) study (2000).[26] The remaining studies reported intermediate outcome measures such as number needed to treat, length of hospital stay, hospitalisation rate, blood pressure (BP) reduction or CVD events avoided, which are easier to measure but harder to compare across interventions. None of the studies expressed outcomes (benefits) in monetary units.

Time horizon

Three-fourths of studies (n=31) explicitly stated their analytical time horizon. Eighty per cent of decision model studies adopted lifetime horizon and others reported cost-effectiveness estimates for 10, 20, 25, 30 or 50 years. RCT/observational studies-based economic evaluations had a median time horizon of 1 year.

Discounting

A discount rate of 3% was most often used for both costs and effects in decision model studies. RCT-based economic evaluations used a discount rate of 3% (n=3) and 5% (n=1). Further, 11 studies did not apply any discount rate.

Analytical approach

Cost-effectiveness analysis or cost-utility analysis were the main methods (n=34), followed by cost-consequences analysis (n=6) and cost-minimisation analysis (n=2). Although several of these papers (n=8) described themselves as cost-effectiveness analysis, they were in fact cost-consequences analysis or cost-minimisation analysis because an incremental analysis was not reported or there was no significant difference in the effectiveness of the intervention versus comparator, respectively. Most studies reported average cost-effectiveness ratio and interpreted it as ICER against the comparator as null scenario, that is, no intervention.

We found several different types of decision models used for cost-effectiveness analysis. A large majority of the studies used the WHO-CHOICE state transition model. Others used coronary heart disease (CHD) policy model, GeDiForCE, IMS Centre for Outcomes Research Diabetes Model, Centers for Disease Control and Prevention (CDC) model, Markov model or individual microsimulation model. Few studies provided details of model validation.

Sensitivity analyses and generalisability of study results

Nearly half of the studies (n=25) undertook some form of sensitivity analysis to assess the robustness of their findings to assumptions about input parameters. Of these, one-way sensitivity analysis was most often applied. Two studies used threshold analysis and one performed a multi-way sensitivity analysis. None considered the structural variations in the decision model for sensitivity analysis. Few studies described the model validation methods.

Three-quarters of the studies (n=32) discussed the generalisability issue. Efforts were largely confined to stating the limitations of the study, such as whether randomisation was employed or noting one or two facts

about the study site which might limit generalisability to other contexts. Another 12 studies discussed issues of affordability but in brief terms, for example, by noting that the available budget should be taken into account (most studies focused on the cost-effectiveness without considering the budget impact/constraint) or by questioning the sustainability of a novel service such as a mobile diabetic retinopathy services, where there are already existing health services.[27]

Risk of bias assessment

In our critical review of methods used in economic evaluations to assess risk of bias, we found that almost all economic evaluations based on observational study only presented costs and consequences of two treatment strategies separately, without reporting an ICER or employed sensitivity analysis to assess robustness of costs or treatment effect estimates. Also, estimates of treatment effects from the observational studies are not very reliable due to the limitations in the original study design. On the other hand, economic evaluations based on RCTs reported better economic outcomes, that is, ICERs; however, these studies were limited by short follow-up duration (30 days to 1 or 2 years), treatment effects assessed as intermediate clinical outcomes (BP reduction, number needed to prevent one DM case) and mostly direct medical costs from health system perspective or patient perspective were reported, which ignores the societal costs and productivity loss due to illness. Lastly, decision modelling studies reported ICER per QALY gained or DALY averted mostly using the WHO-CHOICE methods, Markov models or microsimulation models from societal or health system perspectives. Many of the decision model studies from DCPP did not report the source of costs data, source of QALY weights and details on decision model structure or validation methods. Further, most of the WHO-CHOICE-based generalised cost-effectiveness analysis used disability weights from an earlier version of the GBD study (2000). Therefore, findings from this review should be used with caution for local decision making, and there is an urgent need for more investment in local research to generate evidence/data on costs of treatment and health services and effectiveness of interventions (table 1).

Methodological quality: summary

Figures 2 and 3 report the overall quality of studies based on the key methodological issues and technical characteristics for decision model studies, respectively. In general, very few studies reported quantities of resource use data and unit costs separately, details of statistical tests used and CI around ICER estimates. Among decision model studies, none reported methods used to assess methodological, structural or heterogeneity uncertainties, and very few discussed model validation methods. Critical appraisal of studies revealed that there were 15 excellent (++), 18 good (+) and 9 poor quality studies (−) (table 2).

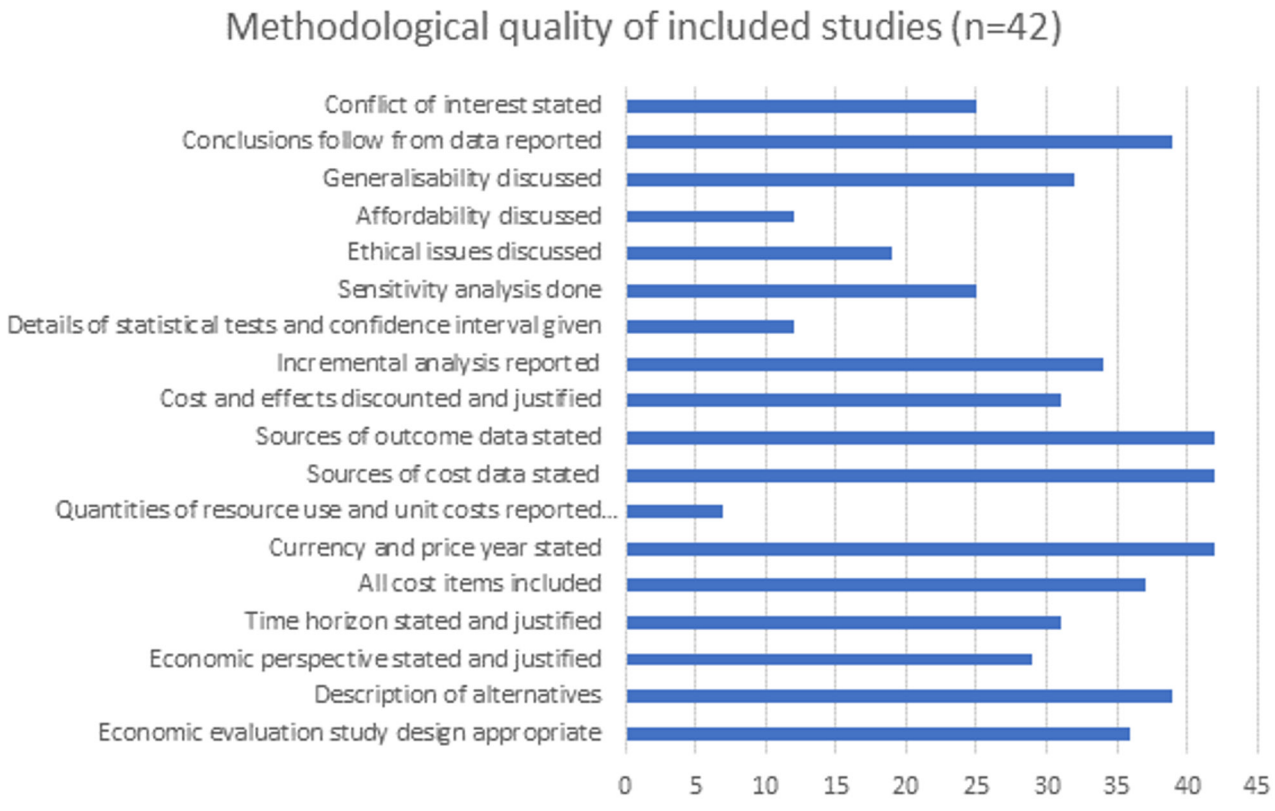

Figure 2 Methodological quality of included studies. This figure presents the number of studies meeting the key methodological quality metrics of economic evaluations as recommended in the standard checklists.

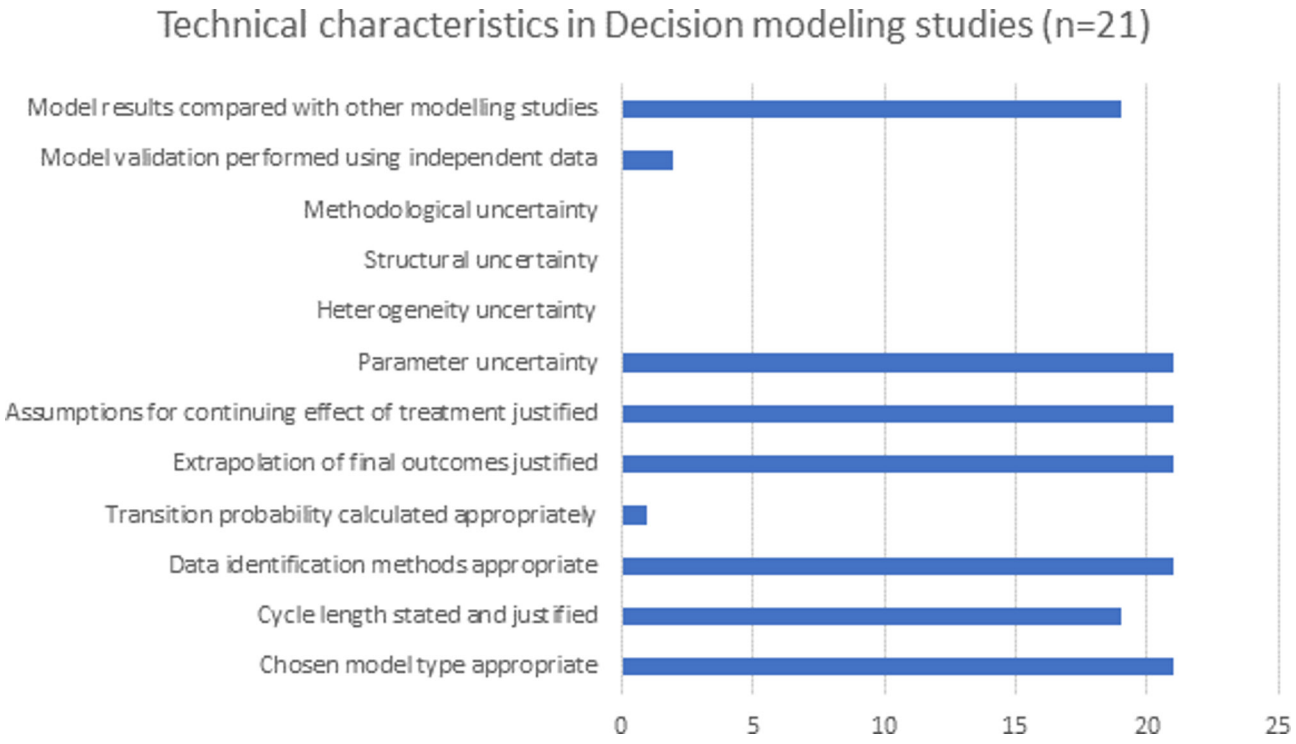

Figure 3 Technical characteristics of decision modelling studies. This figure presents the number of decision modelling studies meeting the key methodological criteria for decision modelling studies as proposed by Philips *et al*.[22]

Cost-effectiveness evidence

Interventions reviewed for their cost-effectiveness are grouped under the scheme of primordial, primary, secondary and tertiary prevention of CVD and DM (table 3). This flow is used to make information available in an accessible format for policy-level and clinical decisions. Cost-effectiveness results from observational studies have not been included in the final synthesis of cost-effectiveness data from South Asia due to poor quality of evidence. Cost-effectiveness data presented below are for India unless otherwise specified (the GDP per capita (in US$ 2016) for India, Pakistan and Bhutan are 1861.5, 1468.2 and 729.5, respectively).[28]

Primordial prevention

We found that a multicomponent population-level policy intervention consisting of increase in tobacco tax, clean indoor air law, advertisement ban and information/labelling are all highly cost-effective than increased tobacco tax alone (<1×GDP per capita per DALY averted).[29] Addition of 'nicotine replacement therapy', 'brief advice' or 'physician counselling' to the combination strategy for tobacco control was not cost-effective (>3×GDP per capita per DALY averted).[29] Complete smoking ban in public places is also highly cost-effective in terms of life years gained and acute myocardial infarction averted.[30] School-based smoking prevention programme as evaluated in a cluster randomised trial in India[31] was found to be cost-effective (1–3×GDP per capita per QALY gained). Salt reduction by legislation was cost-effective (1–3×GDP per capita per DALY averted).[29 32] Substitution of trans fat with polyunsaturated fatty acids was cost-effective compared with null scenario (no intervention) per DALY averted.[32] Media campaign to reduce saturated fat content was also cost-effective per DALY averted.[32] A combined intervention of salt reduction by means of legislation together with public education campaign is cost-effective too.[32] Alcohol taxation combined with advertisement ban was the most cost-effective strategy for alcohol control.[15]

Primary prevention

A 2015 modelling study conducted in Bhutan demonstrated that universal screening for diabetes and hypertension was highly cost-effective compared with no screening (<1×GDP per capita per QALY gained).[33] Another 2006 modelling study from India[34] showed that screening undiagnosed diabetes and treating those who test positive were not cost-effective, with an ICER of US$11 671 per DALY averted (ie, >3×GDP per capita for India), suggesting that screening for diabetes alone was not cost-effective and it should be supplemented with other risk factors, for example, hypertension. Other factors that could have influenced conflicting results include different health system-related cost, different model structure/model parameters, disease prevalence and time period.

Screening for gestational DM to prevent DM was also cost-effective compared with no screening.[35]

Among clinical interventions, preventive multidrug treatment provided to those at >35% cardiovascular risk vs 5% cardiovascular risk over 10 years was more cost-effective.[29] Combined strategy of home health education plus trained general physician for

Table 2 Technical characteristics of included studies and quality grading (strength of evidence)

Source (author, year)	Institution(s) conducting the study	Funding agency	Currency, year	Choice of decision model and key parameters	Time horizon	Discount rate used	Incremental analysis reported	SeA done	Quality grading† (++, +, –)
Turi *et al*, 1991[53]	Nizam's Institute of Medical Sciences Hyderabad, India	Not stated	US$, 1988	Cost comparison/consequences analysis	NA	NA	NA	NA	–
Ahuja *et al*, 1997[54]	King George's Medical College, Lucknow, India	Not stated	Rupee, 1997	RCT-based CEA	6 months	NA	Yes	No	+
Nanjappa *et al*, 1998[55]	Sri Jayadeva Institute of Cardiology, Bangalore, India	Not stated	US$, 1996	Cost comparison/consequences analysis	NA	NA	NA	NA	–
Malhotra *et al*, 2001[56]	Nehru Hospital, Chandigarh, India	Not stated	Rupee and US$, 1999	RCT-based CEA	Hospital admission until discharge (5–7 days)	NA	Yes	No	+
Murray *et al*, 2003[57]	WHO-CHOICE	Not stated	Int$, 2000	Standard multistate transition model tool with four states: PopMod was used to calculate DALY averted by reducing CVD risk	Lifetime	3% for both costs and effects	Yes	Yes	++
Chisholm *et al*, 2004[15]	WHO-CHOICE; University of Queensland, Australia; Centre for Addiction and Mental Health, Toronto, Canada	Not stated	Int$, 2004	Static State Transition decision model (generalised CEA)	Not stated (assume: lifetime)	3% for both costs and effects	Yes	Yes	+
Namboodiri *et al*, 2004[58]	PGIMER, Chandigarh, India	Not stated	Rupee, 2001	Cost comparison/consequences analysis	NA	NA	NA	NA	–
Narayan *et al*, 2006[34]	DCP2 Chapter	Fogarty International Centre NIH, BMGF, WHO, World Bank	US$, 2001	Cost-utility and cost-effectiveness analyses were based on published literature models; costs estimated from WHO-CHOICE resource	Not stated (assume: lifetime)	Not stated	Yes	Not stated	+
Gaziano *et al*, 2006[43]	DCP2 Chapter	Fogarty International Centre NIH, BMGF, WHO, World Bank	US$, 2001	Population-based decision model; DALY weights taken from Mathers (2006)[79] and costs data from McFayden (2003)[80]	Not stated (assume: lifetime)	Not stated	Yes	Not stated	+
Willett *et al*, 2006[5]	DCP2 Chapter	Fogarty International Centre NIH, BMGF, WHO, World Bank	US$, 2001	Population-based decision model; authors have used local costs data and interventions benefits from published literature sources	Not stated (assume: lifetime)	Not stated	Yes	Not stated	+
Rodgers *et al*, 2006[59]	DCP2 Chapter	Fogarty International Centre NIH, BMGF, WHO, World Bank	US$, 2001	Population-based decision model; authors have used local costs data and interventions benefits from published literature sources	Not stated (assume: lifetime)	Not stated	Yes	Not stated	+
Jha *et al*, 2006[60]	DCP2 Chapter	Fogarty International Centre NIH, BMGF, WHO, World Bank	US$, 2002	Population-based decision model; authors have used local costs data and interventions benefits from published literature sources	Not stated (assume: lifetime)	Not stated	Yes	Not stated	+
Shafiq *et al*, 2006[61]	PGIMER Chandigarh, India	Not stated	US$ and rupee, 2004	RCT-based CEA	Within trial analysis (30-day follow-up)	NA	Yes		+

Continued

Table 2 Continued

Source (author, year)	Institution(s) conducting the study	Funding agency	Currency, year	Choice of decision model and key parameters	Time horizon	Discount rate used	Incremental analysis reported	SeA done	Quality grading† (++, +, –)
Ramachandran *et al*, 2007[37]	IDRF, Chennai, India	Not stated	Rupee and US$, 2006	RCT-based CEA	Within trial analysis (3 years)	No discounting	Yes	Yes	++
Zubair Tahir *et al*, 2009[62]	Aga Khan University Hospital, Karachi, Pakistan	Not stated	US$, 2007	Cost comparison/consequences analysis	NA	NA	NA	NA	–
Habib *et al*, 2010[63]	Health Economics Unit, Diabetic Association of Bangladesh	None	US$ (year not stated)	Retrospective hospital medical records-based economic analysis	NA	NA	No	NA	–
Habib *et al*, 2010[64]	Health Economics Unit, Diabetic Association of Bangladesh	None	US$ (year not stated)	Retrospective hospital medical records-based economic analysis	NA	NA	No	NA	–
Sanmukhani *et al*, 2010[65]	Government Medical College, Gujarat, India; Postgraduate Institute of Medical Education and Research, Chandigarh, India	Cadila Pharmaceutical, Ahmedabad, Gujarat, India	Rupee, 2010	Published RCTs-based CEA	Not clear (variable as per the RCT selected for the CEA)	Not clear	Yes	No	+
Cecchini *et al*, 2010[32]	WHO-CHOICE; University of Queensland, Australia; Economic Analysis Unit, Mexico	None	US$, 2005	Chronic disease prevention model—microsimulation	50 years and lifetime horizon	3% for both costs and effects	Yes	Yes	++
Schulman-Marcus *et al*, 2010[40]	AIIMS, New Delhi; HSPH, New York	Sarnoff Cardiovascular Research Foundation, Fogarty International Centre NIH	US$, 2007	Markov model of urban Indian patients with acute chest pain presenting to a GP performing an ECG vs not performing one	Lifetime	3% for both costs and effects	Yes	Yes	++
Donaldson *et al*, 2011[30]	PHFI and Johns Hopkins Bloomberg School of Public Health, Baltimore, USA	None	US$, 2008	Details of model structure not provided, but assumptions and key parameters listed	10 years and lifetime	3% for both costs and effects	Yes	Yes	++
Lohse *et al*, 2011[66]	Novo Nordisk Denmark and UCSF	Novo Nordisk A/S.	US$, 2011	GDModel decision tree	Lifetime	3% per year for costs; effects not discounted, neither justified	Yes	Yes	+
Jafar *et al*, 2011[36]	AKU, Karachi, ICL, LSHTM	Wellcome Trust award	US$, 2007	RCT-based CEA; benefits seen in BP reduction was converted to CV DALYs, using data from GBD study and using a linear regression model	10, 20, 50 years and lifetime	5% for both costs and effects	Yes	Yes	++
Ahmad *et al*, 2011[67]	MGMC-Sitapura, Jaipur	Not stated	US$, 2010	Observational study	NA	NA	Yes	No	+
Humaira *et al*, 2012[68]	Department of Ophthalmology, BADAS, Bangladesh	None	US$ (year not stated)	Retrospective hospital medical records-based economic analysis	NA	NA	No	NA	–
Brown *et al*, 2013[31]	University of Texas, Public Health Foundation of India	NIH grant	US$, 2006	RCT-based CEA and Markov model for long term cost-effectiveness	Lifetime, within trial	No	Yes	Yes	+

Continued

Table 2 Continued

Source (author, year)	Institution(s) conducting the study	Funding agency	Currency, year	Choice of decision model and key parameters	Time horizon	Discount rate used	Incremental analysis reported	SeA done	Quality grading† (++, +, –)
Ortegón *et al*, 2012[29]	University of Columbia, University of Washington, WHO	None	Int$, 2005	Chronic disease prevention model—WHO software DisMod II	Lifetime	3% for both costs and effects	Yes	Yes	+
Marseille *et al*, 2013[35]	Chennai Corporation Maternity Hospital referred GDM cases to Diabetes Care and Research Institute for antenatal monitoring and treatment	Novo Nordisk A/S	Int$, 2011	Decision-analysis tool (the GeDiForCE) to assess cost-effectiveness	Lifetime	3% for both costs and effects	Yes	Yes	+
Rachapelle *et al*, 2013[27]	Sankara Nethralaya, Vision Research Foundation, Chennai and LSHTM	Sightsavers grant	US$, 2009	Markov model (TreeAge Pro 2009)	20 years, lifetime	3% for costs	Yes	Yes	+
Megiddo *et al*, 2014[38]	Centre for Disease Dynamics, Economics, and Policy, Washington, DC, USA; Public Health Foundation of India, New Delhi, India	Bill and Melinda Gates Foundation (Disease Control Priorities 3 Project)	US$, 2014	CHD cohort model	Lifetime	3%	Yes	Yes	++
Patel *et al*, 2014[69]	Shivrath Centre of Excellence in Clinical Research, Ahmedabad, India; UN Mehta Institute of Cardiology and Research Centre, Ahmedabad, India; BJ Medical College, Ahmedabad, Gujarat, India	None	Rupee, 2007	RCT-based CEA	Within trial analysis (8 weeks)	No discounting	No	No	+
Lamy *et al*, 2014[70]	McMaster University, Canada; AIIMS and Centre for Chronic Disease Control, New Delhi, India	Sanofi Aventis, Paris, France	US$, 2014	Randomised trial-based cost-minimisation analysis	6.2 years—median trial duration	3% for costs	Yes	Yes	++
Lamy *et al*, 2014[71]	McMaster University, Canada; University of Oxford, UK; AIIMS and Centre for Chronic Disease Control, New Delhi, India; Charles University, Prague, Czech Republic; Ankara University School of Medicine, Ankara, Turkey; and Unidade de Terapia Intensiva, Hospital do Coracao, Sao Paulo, Brazil	Canadian Institutes of Health Research grant	US$, 2013	Randomised trial-based cost-minimisation analysis	1 year	Not applicable	Yes	Yes	++
Anchala, *et al*, 2015[72]	Public Health Foundation of India, New Delhi, India; Centre for Chronic Disease Control, New Delhi, India; University of Cambridge, UK; Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands	Wellcome Trust Capacity Strengthening Strategic Award to the Public Health Foundation of India and a consortium of UK universities	Rupee and US$	RCT-based CEA	1 year	3% for costs	No	Yes	+

Continued

Table 2 Continued

Source (author, year)	Institution(s) conducting the study	Funding agency	Currency, year	Choice of decision model and key parameters	Time horizon	Discount rate used	Incremental analysis reported	SeA done	Quality grading† (++, +, –)
Dukpa *et al*, 2015[73]	Ministry of Health, Royal Government of Bhutan Health Intervention and Technology Assessment Program; Ministry of Public Health, Thailand; Mahidol University, Bangkok, Thailand	The Regional Office for South-East Asia of the WHO	Bhutanese ngultrum, 2013	Markov model	Lifetime	3% for costs and effects	Yes	Yes	++
Basu *et al*, 2015[39]	Stanford University, USA; London School of Hygiene and Tropical Medicine, London, UK; University of Southern California, USA; National Bureau of Economic Research, Cambridge, Massachusetts, USA	The World Bank, Rosenkranz Prize for Healthcare Research	US$, 2014	Microsimulation model of myocardial infarction and stroke in India	20 years	3% for costs and effects	Yes	Yes	++
Basu *et al*, 2015[74]	Stanford University, USA; London School of Hygiene and Tropical Medicine, London, UK; Imperial College London, London, UK; Public Health Foundation of India; Veterans Affairs Hospital, Ann Arbor, Michigan, USA; University of Michigan, USA; University College London, London, UK	Various federal funding support*	US$, 2014	Microsimulation model	10-year implementation horizon	3% for costs	No	Yes	++
Gupta *et al*, 2015[41]	Jaslok Hospital and Research Centre, Mumbai, India; Pharmacoeconomics Centre of KSMC, Riyadh, Saudi Arabia; Novo Nordisk A/S, Søborg, Denmark; Universiti Sains Malaysia, Penang, Malaysia	Novo Nordisk	US$, 2013 Rupee, 2013	IMS CORE Diabetes Model	1-year, 30-year time horizon	3% for costs and effect measures	Yes	Yes	++
Home *et al*, 2015[75]	Newcastle University, Newcastle on Tyne, UK; University Guro Hospital, Seoul, South Korea; Instituto Jalisciense de Investigacion en Diabetes y Obesidad, Guadalajara, Mexico; Internal Medicine Department, University Hospital Setif, Setif, Algeria; Market Access – Value Communication, Novo Nordisk A/S, Søborg, Denmark	Novo Nordisk	US$, 2013 Rupee, 2013	IMS CORE Diabetes Model	24-week follow-up 1-year time 30-year time horizon	3% for costs and effect measures	Yes	Yes	++
Sengottuvelu *et al*, 2016[76]	Apollo Hospitals, Chennai, India	Not stated	Rupee and US$, 2014	Cost comparison/consequences analysis	NA	NA	NA	NA	–

Continued

Table 2 Continued

Source (author, year)	Institution(s) conducting the study	Funding agency	Currency, year	Choice of decision model and key parameters	Time horizon	Discount rate used	Incremental analysis reported	SeA done	Quality grading† (++, +, –)
Limaye *et al*, 2016[77]	Hochschule Hannover, Hannover, Germany; Institute of Chemical Technology, Mumbai, India	Not stated	Rupee, 2016	Cross-sectional study-based CEA	No details provided	No discounting	No	No	–
Basu *et al*, 2016[78]	Stanford University, Stanford, California, USA; Harvard Medical School, Boston, USA; University College London, London, UK; University of Michigan, Ann Arbor, USA; Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, USA; Imperial College London, London, UK; Public Health Foundation of India, New Delhi, India	Various federal funding support*	US$, 2015	Decision modelling-based CEA	Lifetime	3% for costs and effect measures	Yes	Yes	++

*Various federal funding support—the US National Institutes of Health; the Veterans Affairs Health Services Research and Development Service; the Rosenkranz Prize for Healthcare Research in Developing Countries; the International Development Research Centre of Canada; the NIHR Research Professorship award; and the Wellcome Trust Capacity Strengthening Strategic Award.
†Quality grading: ++ studies meeting all criteria on the checklists used for critical appraisal and provides *strong CE evidence* on interventions evaluated; + studies that fulfils some of the checklist criteria and provides *supportive evidence on CE*, which needs to be confirmed by future studies; – studies not meeting most criteria from the checklists used and so the *CE estimates are uncertain*.
AIIMS, All India Institute of Medical Sciences; AKU, Aga Khan University; BADAS, Bangla Bangladesh Diabetic Somiti (The Diabetic Association of Bangladesh); BMGF, Bill and Melinda Gates Foundation; BP, blood pressure; CE, Cost-effective; CEA, cost-effectiveness analysis; CHD, Coronary Heart Disease; CORE, Centre for Outcomes Research; CV, cardiovascular; CVD, cardiovascular diseases; DALY, disability-adjusted life years; DCP2, Disease Control Priorities-2 book; GBD, Global Burden of Disease; GDM, gestational diabetes mellitus; GP, general practitioner; HSPH, Harvard School of Public Health; ICL, Imperial College London; IDRF, India Diabetes Research Foundation; Int$, international dollar; LSHTM, London School of Hygiene & Tropical Medicine; MGMC, Mahatma Gandhi Medical College; NA, not applicable; NIH, National Institutes of Health; PGIMER, Post Graduate Institute of Medical Education and Research; PHFI, Public Health Foundation of India; RCT, randomised controlled trials; SeA, sensitivity analysis; UCSF, University of California San Francisco; WHO-CHOICE, Choosing Interventions that are Cost-Effective.

Table 3 Cost-effective interventions to control CVD and DM in South Asia

Intervention	Comparator	Analytical time horizon	Incremental cost per capita (US$)*	Incremental effect (DALY averted/ QALY gained)*	ICER, 2017† Cost-effectiveness threshold: <GDP per capita per QALY=green; 1–3×GDP per capita per QALY=yellow
Primordial prevention					
Policy interventions					
Tobacco control strategies (Ortegón *et al*[29])				Incremental DALYs averted per million population	
Increased taxation (60%)	No intervention	Lifetime	0.27	3043	207
Tax increase+advertisement ban	Increased taxation	Lifetime	0.1	607.0	423
Tax increase+clean indoor air law	Increased taxation	Lifetime	0.09	574	366
Tax increase+information/labelling	Tax increase+clean indoor air law	Lifetime	0.11	485	529
Tax increase+advertisement ban+clean indoor air law	Tax increase+clean indoor air law	Lifetime	0.12	683	410
Tax increase+advertisement ban+information/labelling	Tax increase+advertisement ban+clean indoor air law	Lifetime	0.11	485	529
Tax increase+clean indoor air law+advertisement ban+information and labelling	Tax increase+advertisement ban+clean indoor air law	Lifetime	0.20	996.0	468
Tobacco control strategies (Jha *et al*[60])					
33% price increase—low-end effect estimate	No intervention	Lifetime			5
33% price increase—high-end effect estimate	No intervention	Lifetime			71
Non-price interventions‡ effectiveness 2%–10%—low-end estimate	No intervention	Lifetime			89
Non-price interventions‡ effectiveness 2%–10%—high-end estimate	No intervention	Lifetime			1132
Complete smoking ban in public places (Donaldson *et al*[30])	Current legislation for partial smoking ban in public places	10 years	–36 056 957	17 478 (acute myocardial infarction case averted)	732
School-based smoking prevention programme (Brown *et al*[31])	No intervention		175 438.5	4.52 (QALY/smoker averted)	4501
Promoting healthy diet strategies (Cecchini *et al*[32])					
Food labelling	No intervention	20 years			2220
Fiscal measure for 100% population	No intervention	50 years			Cost-saving
Food advertising regulation	No intervention	50 years			774
Food labelling	No intervention	50 years			1810
Promoting healthy diet strategies (Murray *et al*[57])					
Salt reduction through voluntary agreements with industry	No intervention	Lifetime			106
Population-wide reduction in salt intake legislation	No intervention	Lifetime			54
Health education through mass media	No intervention	Lifetime			40
Salt reduction via legislation+health education via mass media	No intervention	Lifetime			49
Promoting healthy diet strategies (Willett *et al*[5])		Lifetime			
Media campaign to reduce saturated fat content	No intervention	Lifetime			5086
Substitute 2% of energy from trans fat with polyunsaturated fatty acid (7% coronary artery disease reduction at $0.5 per adult)	No intervention	Lifetime			104

Continued

Table 3 Continued

Intervention	Comparator	Analytical time horizon	Incremental cost per capita (US$)*	Incremental effect (DALY averted/ QALY gained)*	ICER, 2017† Cost-effectiveness threshold: <GDP per capita per QALY=green; 1–3×GDP per capita per QALY=yellow
Substitute 2% of energy from trans fat with polyunsaturated fatty acid (7% coronary artery disease reduction at $0.6 per adult)	No intervention	Lifetime			2765
Substitute 2% of energy from trans fat with polyunsaturated fatty acid (40% coronary artery disease reduction at $0.5 per adult)	No intervention	Lifetime			Cost-saving
Substitute 2% of energy from trans fat with polyunsaturated fatty acid (40% coronary artery disease reduction at $0.6 per adult)	No intervention	Lifetime			376
Reducing salt content by means of legislation+public education	No intervention	Lifetime			3613
Blood pressure-lowering strategies (Rodgers *et al*[59])		Lifetime			
Prevention by salt legislation	No intervention	Lifetime			49
Alcohol control strategies (Chisholm *et al*[15])					
Taxation current+25% (alcohol use)	No intervention	Lifetime			Cost-saving
Taxation current+50% (alcohol use)	No intervention	Lifetime			Cost-saving
Breath testing	No intervention	Lifetime			152
Highest tax+advertisement ban	No intervention	Lifetime			5002
Primary prevention					
Policy interventions					
Universal screening for diabetes and hypertension (Dupka *et al*[73])§				DALY averted per person	
Current Package of Essential Non-Communicable (PEN) disease interventions programme	No screening	Lifetime	−77.2	0.038	Cost-saving
Universal screening	Current WHO-PEN programme	Lifetime	−33.1	0.016	Cost-saving
Screening for GDM to prevent DM (Lohse *et al*[66])	No intervention	Lifetime	26	2.33	16
Screening to prevent GDM (Marseille *et al*[35])	No intervention	Lifetime	194 358	120	2317
Expansion of national insurance to cover primary, secondary and tertiary treatment for CVD (Basu *et al*[39])				Incremental DALY averted per annum	
Insurance coverage for primary prevention of CVD	Status quo	20 years	1.19	2544.5	528
Clinical interventions					
Tobacco control strategies (Jha *et al*[60])					
Nicotine replacement therapy effectiveness 1%–5%—low-end estimate	No intervention	Lifetime			142
Nicotine replacement therapy effectiveness 1%–5%—high-end estimate	No intervention	Lifetime			1880
To reduce alcohol use (Chisholm *et al*[15])					
Brief physician advice	No intervention	Lifetime			175
CVD prevention strategies (Ortegón *et al*[29])				Incremental DALYs averted per million population	
Preventive multidrug treatment (>5% risk of CVD event)	No intervention	Lifetime	1.97	4542	4238
Preventive multidrug treatment (>35% risk of CVD event)	Preventive multidrug treatment (>5% risk of CVD event)	Lifetime	0.38	2582	341
Combination of individual-based drug therapy for hypertension and cholesterol control	Preventive multidrug treatment (>5% risk of CVD event)	Lifetime	1.8	1780	2358

Continued

Table 3 Continued

Intervention	Comparator	Analytical time horizon	Incremental cost per capita (US$)*	Incremental effect (DALY averted/ QALY gained)*	ICER, 2017† Cost-effectiveness threshold: <GDP per capita per QALY=green; 1–3×GDP per capita per QALY=yellow
Combined home health education plus trained general practitioner for hypertension management (Jafar *et al*[36])¶	No intervention	2 years			48
Diabetes prevention strategies (Narayan *et al*[34])					
Smoking cessation (physician counselling and nicotine replacement therapy)	No intervention	Lifetime			1990.6
Preconception care for women of reproductive age	No intervention	Lifetime			Cost-saving
Lifestyle interventions to prevent type 2 diabetes	No intervention	Lifetime			163.6
Metformin intervention to prevent type 2 diabetes	No intervention	Lifetime			4962.9
Lifestyle modification+metformin to prevent type 2 diabetes (Ramachandran *et al*[37])				Number needed to treat to prevent a case of diabetes	
Lifestyle modification	Standard healthcare advice	3 years	164	6.4	2302
Metformin	Standard healthcare advice	3 years	159	6.9	2396
Lifestyle modification+metformin	Standard healthcare advice	3 years	209	6.5	2973
Secondary and tertiary prevention					
Policy interventions					
Policies to expand use of drugs for acute myocardial infarction (Megiddo *et al*[38])					
Acute myocardial infarction treatment					
Aspirin to baseline	No intervention	Lifetime			0.6
Aspirin+injection streptokinase	Aspirin to baseline	Lifetime			693
Acute myocardial infarction prevention					
Aspirin to baseline	No intervention	Lifetime			299
Aspirin+BB	Aspirin to baseline	Lifetime			1960
Aspirin+BB+ACEi	Aspirin+BB	Lifetime			3120
Polypill to baseline	Aspirin+BB+ACEi+statin	Lifetime			1904
Expansion of national insurance to cover primary, secondary and tertiary treatment for CVD (Basu *et al*)[39]				Incremental DALY averted per annum	
Insurance coverage for secondary prevention of CVD	Status quo	20 years	0.36	147.9	2708
Insurance coverage for tertiary treatment of CVD	Status quo	20 years	4.68	2076.8	2538
Clinical interventions					
CVD treatment strategies (Ortegón *et al*[29])				Incremental DALYs averted per million population	
Treatment of CHF with diuretics	No intervention	Lifetime	0.03	402	188.9
Treatment of CHF with diuretics+exercise training	Treatment of CHF with diuretics	Lifetime	0.02	60	776.6
Treatment of CHF with diuretics+exercise training+ACEi	Treatment of CHF with diuretics	Lifetime	0.04	72	1296.7
Treatment of CHF with diuretics+exercise training+BB	Treatment of CHF with diuretics	Lifetime	0.08	95	1963
Treatment of post-acute ischaemic heart disease and stroke with aspirin, BB, statin	No intervention	Lifetime	0.03	609	114

Continued

Table 3 Continued

Intervention	Comparator	Analytical time horizon	Incremental cost per capita (US$)*	Incremental effect (DALY averted/ QALY gained)*	ICER, 2017† Cost-effectiveness threshold: <GDP per capita per QALY=green; 1–3×GDP per capita per QALY=yellow
Treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease with aspirin, BB, statin	No intervention	Lifetime	0.36	1047	799
Treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease with aspirin, BB, statin, ACEi	Treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease with aspirin, BB, statin	Lifetime	0.37	945	914
Treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease and stroke with aspirin, BB, statin	No intervention	Lifetime	0.04	263	354
Treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease and stroke with aspirin, BB, statin+CHF (diuretic, exercise)	Treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease and stroke with aspirin, BB, statin	Lifetime	0.26	1879	321
Individual-based prevention (hypertension and cholesterol control)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease (aspirin, BB, statin)	No intervention	Lifetime	2.57	5526	1084
Individual-based prevention (hypertension and cholesterol control)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease (aspirin, BB, ACEi, statin)	Individual-based prevention (hypertension and cholesterol control)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease (aspirin, BB, statin)	Lifetime	0.04	250	373
Individual-based prevention (hypertension and cholesterol control)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease and stroke (aspirin, BB, statin)	Individual-based prevention (hypertension and cholesterol control)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease (aspirin, BB, ACEi, statin)	Lifetime	0.04	201	464
Individual-based prevention (hypertension and cholesterol control)+treatment of post-acute ischaemic heart disease and stroke (aspirin, BB, statin)+CHF (diuretic, exercise)	Individual-based prevention (hypertension and cholesterol control)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease and stroke (aspirin, BB, statin)	Lifetime	−0.23	119	Cost-saving
Individual-based prevention (hypertension and cholesterol control)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease and stroke (aspirin, BB, statin)+CHF (diuretic, exercise)	Individual-based prevention (hypertension and cholesterol control)+treatment of post-acute ischaemic heart disease and stroke (aspirin, BB, statin)+CHF (diuretic, exercise)	Lifetime	0.26	437	1387
Combination drug treatment (>25% risk of CVD event)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+treatment of post-acute ischaemic heart disease (aspirin, BB, statin)	No intervention	Lifetime	1.16	4852	557
Combination drug treatment (>25% risk of CVD event)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+treatment of post-acute ischaemic heart disease (aspirin, BB, ACEi, statin)	Combination drug treatment (>25% risk of CVD event)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+treatment of post-acute ischaemic heart disease (aspirin, BB, statin)	Lifetime	0.04	237	394
Combination drug treatment (>25% risk of CVD event)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+treatment of post-acute ischaemic heart disease and stroke (aspirin, BB, statin)	Combination drug treatment (>25% risk of CVD event)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+treatment of post-acute ischaemic heart disease (aspirin, BB, ACEi, statin)	Lifetime	0.04	178	524

Continued

Table 3 Continued

Intervention	Comparator	Analytical time horizon	Incremental cost per capita (US$)*	Incremental effect (DALY averted/ QALY gained)*	ICER, 2017† Cost-effectiveness threshold: <GDP per capita per QALY=green; 1–3×GDP per capita per QALY=yellow
Combination drug treatment (>25% risk of CVD event)+treatment of post-acute ischaemic heart disease and stroke (aspirin, BB, statin)+CHF (diuretics, exercise)	Combination drug treatment (>25% risk of CVD event)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+treatment of post-acute ischaemic heart disease and stroke (aspirin, BB, statin)	Lifetime	−0.23	32	Cost-saving
Preventive multidrug treatment for >25% risk of CVD event+multidrug treatment of acute myocardial infarction or post-acute ischaemic heart disease and stroke+diuretics and exercise for CHF	Combination drug treatment (>25% risk of CVD event)+treatment of post-acute ischaemic heart disease and stroke (aspirin, BB, statin)+CHF (diuretics, exercise)	Lifetime	0.26	558	1086
Combination drug treatment (>35% risk of CVD event)+treatment of post-acute ischaemic heart disease and stroke (aspirin, BB, statin)+CHF (diuretics, exercise)	Combination drug treatment (>35% risk of CVD event)+treatment of post-acute ischaemic heart disease and stroke (aspirin, BB, statin)+CHF (diuretics, exercise)	Lifetime	−0.23	31	Cost-saving
Preventive multidrug treatment for >35% risk of CVD event+multidrug treatment of acute myocardial infarction or post-acute ischaemic heart disease and stroke+diuretics and exercise for CHF	Combination drug treatment (>35% risk of CVD event)+treatment of post-acute ischaemic heart disease and stroke (aspirin, BB, statin)+CHF (diuretics, exercise)	Lifetime	0.26	630	963
CVD treatment strategies (Murray *et al*[57])					
Treatment of SBP above 160 mm Hg with BB and diuretic	No intervention	Lifetime			103.2
Treatment of SBP above 140 mm Hg with BB and diuretic	No intervention	Lifetime			257.9
Treatment with statins for total cholesterol concentrations above education 6.2 mmol/L	No intervention	Lifetime			134.7
Treatment with statins for total cholesterol concentrations above education 5.7 mmol/L	No intervention	Lifetime			203.5
Treatment of SBP above 140 mm Hg with BB and diuretics and with statins for total cholesterol concentrations above 6.2 mmol/L	No intervention	Lifetime			240.7
Multiple drug therapy in >35% CV risk over 10 years	No intervention	Lifetime			Cost-saving
Multiple drug therapy in >25% CV risk over 10 years	No intervention	Lifetime			94.6
Multiple drug therapy in >15% CV risk over 10 years	No intervention	Lifetime			137.5
Multiple drug therapy in >5% CV risk over 10 years	No intervention	Lifetime			220.7
CVD treatment and secondary prevention (Gaziano *et al*[43])					
Medical therapy for acute myocardial infarction with aspirin	No intervention	Lifetime			25.8
Medical therapy for acute myocardial infarction with aspirin+BB	No intervention	Lifetime			31.5
Medical therapy for acute myocardial infarction with aspirin+BB+streptokinase	No intervention	Lifetime			1828.8
Medical therapy (aspirin+BB) for ischaemic heart disease, having hospital access	No intervention	Lifetime			Cost-saving
Medical therapy (aspirin+BB+ACEi) for ischaemic heart disease, having hospital access	No intervention	Lifetime			2049.5
Medical therapy (aspirin+BB+ACEi+statin) for ischaemic heart disease, having hospital access	No intervention	Lifetime			5214.2
Medical therapy (aspirin+BB) for ischaemic heart disease, limited hospital access	No intervention	Lifetime			1106.4

Continued

Table 3 Continued

Intervention	Comparator	Analytical time horizon	Incremental cost per capita (US$)*	Incremental effect (DALY averted/ QALY gained)*	ICER, 2017† Cost-effectiveness threshold: <GDP per capita per QALY=green; 1–3×GDP per capita per QALY=yellow
Medical therapy (aspirin+BB+ACEi) for ischaemic heart disease, limited hospital access	No intervention	Lifetime			2373.4
ACEi for CHF, hospital access	Baseline of diuretics	Lifetime			Cost-saving
ACEi, BB (metoprolol) for CHF, hospital access	Baseline of diuretics	Lifetime			627.7
ACEi for CHF, limited hospital access	Baseline of diuretics	Lifetime			71.6
ACEi, BB (metoprolol) for CHF, limited hospital access	Baseline of diuretics	Lifetime			782.5
Blood pressure-lowering strategies (Rodgers *et al*[59])					
Multidrug regimen (aspirin, a BB, a thiazide diuretic, an ACEi and a statin) in 35% CV risk over 10 years	No intervention	Lifetime			1827
Multidrug regimen (aspirin, a BB, a thiazide diuretic, an ACEi and a statin) in 25% CV risk over 10 years	No intervention	Lifetime			3408.6
Multidrug regimen (aspirin, a BB, a thiazide diuretic, an ACEi and a statin) in 15% CV risk over 10 years	No intervention	Lifetime			5268.2
Treat-to-target, benefit-based tailored treatment strategy vs hybrid strategy for lowering CVD risk (Basu *et al*[78])					
People treated identically by all three strategies	No intervention	10 years			383.7
People treated most intensively by treat-to-target	No intervention	10 years			432.1
People treated most intensively by benefit-based tailored treatment	No intervention	10 years			206.1
People treated most intensively by hybrid	No intervention	10 years			384.4
Prehospital ECG for accurate referral and timely access to reperfusion (Schulman-Marcus *et al*[40])	No ECG-based referral in case of chest pain	Lifetime	0.15	0.012 (QALY gained)	26.1
Diabetes treatment strategies (Narayan *et al*[34])		Lifetime			
Glycaemic control in people with HbA1c >9% (insulin, oral glucose-lowering agents, diet and exercise)	No intervention	Lifetime			Cost-saving
Blood pressure control in people with >160/95 mm Hg	No intervention	Lifetime			Cost-saving
Foot care in people with a high risk of ulcers	No intervention	Lifetime			Cost-saving
Influenza vaccination among elderly	No intervention	Lifetime			490.8
Annual eye examination	No intervention	Lifetime			954.4
ACEi use for people with diabetes	No intervention	Lifetime			1390.7
Intensive glucose control for people with HbA1c >8% (insulin, oral glucose-lowering agents or both)	No intervention	Lifetime			5453.7
Treatment of diabetes and its complications (Ortegón *et al*[29])				Incremental DALYs averted per million population	
Standard glycaemic control	No intervention	Lifetime	0.82	1717	1115
Retinopathy screening and photocoagulation therapy	No intervention	Lifetime	0.32	1891	396.4
Standard glycaemic control+retinopathy screening+neuropathy screening	Intensive glycaemic control+neuropathy screening	Lifetime	−0.65	213	Cost-saving

Continued

Table 3 Continued

Intervention	Comparator	Analytical time horizon	Incremental cost per capita (US$)*	Incremental effect (DALY averted/ QALY gained)*	ICER, 2017† Cost-effectiveness threshold: <GDP per capita per QALY=green; 1–3×GDP per capita per QALY=yellow
BIAsp 30±oral glucose-lowering drugs (Gupta *et al*[41])				Incremental QALY gained per annum	
BIAsp 30	BHI 30 or IGlar	30 years	868.496	2.52	412.9
BIAsp 30	NPH insulin	30 years	−2524.192	2.82	Cost-saving
BIAsp 30	IGlar	30 years	527.232	2.74	228.8
BIAsp 30	BHI 30 or IGlar	1 year	123.264	0.21	684.2
BIAsp 30	IGlar	1 year	93.984	0.23	487.2
Basal insulin vs oral glucose-lowering drugs (Home *et al*[75])				Incremental QALY gained per annum	
Basal insulin treatment with insulin detemir	Oral glucose-lowering drugs	30 years	3510.36	4.97	834.1
Basal insulin treatment with insulin detemir	Oral glucose-lowering drugs	1 year	338.796	0.322	1243.4
Telemedicine screening+diabetic retinopathy treatment (Rachapelle *et al*[27])					
Health system perspective				Incremental QALY gained per annum	
Screening once in a lifetime	No screening	25 years	6.5	0.0049	2214.1
Screening twice in a lifetime	No screening	25 years	5.3	0.0039	2252.7
Screening every 5 years	No screening	25 years	19.6	0.0097	3400.1
Screening every 3 years	No screening	25 years	17.4	0.0084	3411.8
Screening every 2 years	No screening	25 years	18.4	0.0075	4084.5
Societal perspective					
Screening once in a lifetime	No screening	25 years	13.2	0.0049	4515.6
Screening twice in a lifetime	No screening	25 years	9.7	0.0039	4151.6
Screening every 5 years	No screening	25 years	30.3	0.0097	5257
Combination of primordial, primary, secondary and tertiary prevention					
Interventions to reduce hazardous alcohol use (Chisholm *et al*[15])					
Highest tax+advertisement ban+brief advice	No intervention	Lifetime			2562.7
Blood pressure-lowering strategies (Rodgers *et al*[59])					
Prevention by salt legislation+health education	No intervention	Lifetime			87.2
Treatment with aspirin, BB, and a statin+salt legislation+health education in 35% CV risk over 10 years	No intervention	Lifetime			362.6
Treatment with aspirin, BB, and a statin+salt legislation+health education in 25% CV risk over 10 years	No intervention	Lifetime			1576
Treatment with aspirin, BB, and a statin+salt legislation+health education in 15% CV risk over 10 year	No intervention	Lifetime			3054
Intervention for CVD prevention and treatment (Murray *et al*[57])					
Combination of legislation for salt reduction, health education and treatment of individuals with combined CV risk of 35% with statin, diuretic, BB and aspirin	No intervention	Lifetime			63
Combination of legislation for salt reduction, health education and treatment of individuals with combined CV risk of 25% with statin, diuretic, BB and aspirin	No intervention	Lifetime			89

Continued

Table 3 Continued

Intervention	Comparator	Analytical time horizon	Incremental cost per capita (US$)*	Incremental effect (DALY averted/ QALY gained)*	ICER, 2017† Cost-effectiveness threshold: <GDP per capita per QALY=green; 1–3×GDP per capita per QALY=yellow
Combination of legislation for salt reduction, health education and treatment of individuals with combined CV risk of 15% with statin, diuretic, BB and aspirin	No intervention	Lifetime			132
Combination of legislation for salt reduction, health education and treatment of individuals with combined CV risk of 5% with statin, diuretic, BB and aspirin	No intervention	Lifetime			212
CVD prevention and treatment strategies (Ortegón *et al*[29])				Incremental DALYs averted per million population	
Population-based prevention (hypertension and cholesterol control)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease (aspirin, BB, statin)	No intervention	Lifetime	0.55	2376	538
Population-based prevention (hypertension and cholesterol control)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease (aspirin, BB, ACEi, statin)	Population-based prevention (hypertension and cholesterol control)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease (aspirin, BB, statin)	Lifetime	0.04	285	326
Population-based prevention (hypertension and cholesterol control)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease and stroke (aspirin, BB, statin)	Population-based prevention (hypertension and cholesterol control)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute ischaemic heart disease (aspirin, BB, ACEi, statin)	Lifetime	0.04	246	380
Population-based prevention (hypertension and cholesterol control)+treatment of acute myocardial infarction (aspirin, BB, ACEi, streptokinase)+post-acute Ischaemic heart disease and stroke (aspirin, BB, statin)+CHF (diuretic, exercise)	Population-based prevention (hypertension and cholesterol control)+treatment of post-acute ischaemic heart disease and stroke (aspirin, BB, statin)+CHF (diuretic, exercise)	Lifetime	0.26	646	937
Expansion of national insurance to cover primary, secondary and tertiary treatment for CVD (Basu *et al*)[39]				Incremental DALY averted per annum	
Insurance coverage for primary+secondary prevention of CVD	Primary prevention only	20 years	0.35	145.0	2739
Insurance coverage for primary+tertiary prevention of CVD	Primary prevention only	20 years	4.67	2084.6	2525

GDP per capita (US$, 2016) for India, Pakistan and Bhutan are 1861.5, 1468.2 and 729.5, respectively.
*Values refer to original study period.
†Conversion to current year, based on midyear consumer price index inflation rates.
‡Non-price interventions to reduce tobacco use:
–protection from exposure to tobacco smoke
–regulation of the contents of tobacco products
–regulation of tobacco product disclosures
–packaging and labelling of tobacco products
–education, communication, training and public awareness
–tobacco advertising, promotion and sponsorship
–demand reduction measures concerning tobacco dependence and cessation.
§Conducted in Bhutan.
¶Conducted in Pakistan.
ACEi, ACE inhibitors; BB, beta-blockers (blood pressure-lowering agents; BHI, biphasic human insulin; BIAsp 30, biphasic insulin aspart 30; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular diseases; DALY, disability-adjusted life years; DM, diabetes mellitus; GDM, gestation diabetes mellitus; GDP, gross domestic product; HbA1c, glycated haemoglobin; ICER, incremental cost-effectiveness ratio; IGlar, insulin glargine; QALY, quality-adjusted life years; NPH, neutral protamine Hagedorn; SBP, systolic blood pressure.

hypertension management was highly cost-effective per DALY averted than individual strategies or no intervention in Pakistan.[36]

Lifestyle modification (weight reduction, increased activity and healthy diet) was most cost-effective for prevention of DM, followed by metformin alone and

combination of lifestyle modification plus metformin (1–3×GDP per capita).[37]

Secondary and tertiary prevention

Policies to expand access of drugs for acute myocardial infarction prevention and treatment were cost-effective per DALY averted.[38] Also, expansion of national insurance to cover secondary or tertiary prevention of CVD was most cost-effective per QALY gained compared with status quo.[39] Clinical interventions for secondary prevention of CVD are mostly cost-effective per DALY averted.[29] ECG-based doctor referral to cardiac care unit versus no 'ECG use' was cost-effective per QALY gained.[40]

Many strategies for DM treatment and secondary prevention of macrovascular and microvascular complications were found to be highly cost-effective or cost-effective. Examples of highly cost-effective interventions are glycaemic control in people with glycated haemoglobin (A1c) >9% with insulin, oral glucose-lowering drugs, diet and exercise, BP control in people with >165/95 mm Hg, and foot care in people with high risk of ulcers (<1×GDP per capita per DALY averted).[34] Basal insulin treatment versus oral glucose-lowering drugs was highly cost-effective (<1×GDP per capita per QALY gained).[41] Diabetic retinopathy screening every 2–5 years versus no screening was cost-effective (1–3×GDP per capita per QALY gained).[27]

Combination of primordial, primary, secondary and tertiary prevention

Multicomponent strategies of salt reduction through legislation (increase tax), health education, plus treatment of individuals at 35% cardiovascular risk with statin, diuretic, beta-blockers and aspirin were highly cost-effective, followed by similar strategy in those at 25% or 15% cardiovascular risk over 10 years.[29] Policy measures such as expansion of insurance coverage for primary, secondary and tertiary prevention of CVD were also cost-effective (1–3×GDP per capita per DALY averted).[39]

Interventions that resulted in ICER>3×GDP per capita or were dominated by other highly cost-effective strategies are presented in online supplementary table 1. Significant heterogeneity in analytical framework and outcome measures used in these studies restricted meta-analysis and direct ranking of the interventions by their degree of cost-effectiveness.

DISCUSSION

This review finds that, with some exceptions, most interventions to control CVD and DM were cost-effective (<1–3×GDP per capita per QALY gained or DALY averted), although the strength of evidence (and risk of bias) varied across economic evaluations based on observational studies, RCTs and decision models. Most interventions were cost-effective because of the large benefits in DALY averted or QALY gained at a marginal increase in cost per capita ($). These results should motivate decision makers to invest in primordial prevention strategies (increased tobacco tax, salt reduction by legislation, food labelling and food advertising regulation), and primary and secondary prevention interventions: multidrug therapy for CVD prevention and treatment in high-risk groups, lifestyle modification and metformin for diabetes prevention, and screening for diabetes complications every 2–5 years. Although detecting and treating diabetes earlier can prevent future complications and their associated medical costs, such savings were shown to be relatively small.[34] An alternative to broad screening is to focus on targeted screening, that is, screening only persons with additional risk factors, such as hypertension and obesity. Such targeted screening was shown to be highly cost-effective or cost-saving when compared with no screening.[33]

Choice of comparator is an important decision when evaluating ICER of new interventions. In general, modelling studies that used the WHO-CHOICE method have reported average cost-effectiveness ratio against the null scenario (no intervention). In reality, however, this does not seem plausible because null scenario will not always reflect zero costs and zero effects. Also, these studies first identified the most cost-effective intervention among a group of strategies (eg, tobacco control, CVD prevention and treatment, or diabetes prevention and treatment) versus null scenario, then compared it with the next most cost-effective intervention.[29] In many of such analysis, because the description of comparator was not clearly specified, the reported ICERs look ambiguous and changing the 'comparator' might produce a different ICER.

In our formal appraisal of the methodological quality of studies, we observed limitations in documentation of main study details, for example, chosen study perspective, sources of cost data and analytical time horizon. In addition, significant number of studies failed to provide details on units of resource use, costing year, currencies and other economic aspects. Since the discount rate used has an impact on cost-effectiveness estimates, the zero-discount rate applied in some studies is deeply concerning. In reality, however, every economic evaluation will contain some degree of uncertainty or imprecision. While one-way sensitivity analysis is helpful in understanding the impact of assumptions about one input parameter, multi-way sensitivity analysis offers a robust method to explore the uncertainty concerning more than one input parameters, but few studies reported results using this technique.

In terms of comparing results of this review with other contemporary reviews, we found cost-effectiveness evidence on a large number of preventive strategies, which is inconsistent with a previous review that examined the economic evaluation from Health Economic Evaluation Database[42] and concluded that only 10% of all evaluations assessed preventive care. The greater number of preventive strategies found in our review could be due to the development of the WHO-CHOICE programme[26] and the release of the DCPP2 in April 2006.[43]

Although cost-effectiveness evidence is available for 301 interventions to control CVD or DM, most of this evidence is based on decision models, which used data (annual risk of disease progression and intervention benefits) from Western countries. Most decision model studies have derived treatment effects from either meta-analysis of RCTs if available for an intervention or single RCT if meta-analysis is not available. However, the limited representation of South Asian populations in those RCTs remains an important concern. Therefore, our review highlights an alarming paucity of local research data to conduct high-quality economic evaluations and reflect the concerns of others in the field that large research gaps do remain in the area of health economic analysis in South Asian countries.[44] Also, data from countries other than India are sparse. This is likely a reflection of research capacity in these countries, which needs to be addressed as a priority. Although the countries in South Asia are frequently grouped together, various countries in this region have substantially different health systems, health literacy, health indices, and hence healthcare needs. Understanding the differences be the countries is critical for policy makers, and therefore additional economic evaluations are urgently needed from other South Asian countries.

Strengths and limitations

This review has several strengths. This is the first study, to our knowledge, to include all types of interventions (policy, clinical and behavioural) that affect CVD or DM in South Asia. We considered all possible interventions (primordial, primary, secondary and tertiary prevention) to control CVD and DM together in this systematic review, primarily because policy makers have to choose between different options (competing priorities) for appropriate resource allocation, and as such a narrow economic research question is really not helpful for the systematic review, which intends to inform the process. We have used explicitly stated methods (protocol paper published)[19] and standard checklists to assess methodological quality of studies. Recently, new methods have been proposed by researchers that can be applied to review decision model studies.[45] However, use of new criteria would not change the findings of this review because these points have been covered broadly by the three popular checklists that we used in this review. Also, new methods have been proposed to estimate country-specific threshold for cost-effectiveness based on opportunity cost (health forgone) with investment in new intervention.[46] But we preferred to present the findings based on WHO guidelines[25] and for a lower threshold, that is, 1×GDP per capita. Moreover, the incremental cost and incremental benefits have been shown for all interventions (where available) so the decision makers or clinicians can make considerations based on their own willingness to pay threshold or budgetary constraints.

This review is not without limitations. First, the search was restricted to English-language publications performed as of August 2016. But this would not be a major problem because all the South Asian countries mostly publish research in English. Second, we excluded unpublished and 'grey' literature as we wanted to include studies that have undergone peer review process. We believe though that no major studies that can change the results of this review have been missed.

The review findings should be interpreted with caution because most of the cost-effectiveness studies were based on decision models. Although good-quality decision modelling study can provide information at a lower cost than RCT-based economic evaluations, models are based on assumptions and represent a simplification of—and therefore might depart from—reality. Furthermore, interventions that were highlighted as cost-effective (yellow) or highly cost-effective or dominant (green) analysed using the WHO-CHOICE framework could be reassessed by local agencies, particularly with regard to budget impact and also their cost-effectiveness, taking into account local costs and willingness to pay threshold value, similar to the work carried out by the Health Intervention and Technology Assessment Program in Thailand over the past decade.[47]

Future research directions

We have identified key research gaps in this review. Interventions involving multisectoral approach and policies for change in drug prices or devices (stents prices) have not been evaluated for their cost-effectiveness. The cost-effectiveness of these interventions should be assessed.

A few recommendations to advance the research on economic evaluations in the region are as follows. First, future studies need to take a broader societal perspective for analysis and present cost data in disaggregated form (resource consumption and unit costs, separately). Second, more research is needed to support the causes of variation among costs, effects and cost-effectiveness data on the universal screening of diabetes and/or hypertension. Third, research should focus on assessing the generalisability of cost-effectiveness analysis results within and between countries. Lastly, future cost-effectiveness analysis studies should adhere to international guidelines proposed by the WHO,[25] International Society for Pharmacoeconomics and Outcomes Research,[48–51] and the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine[52] as a benchmark for design, conduct and reporting.

CONCLUSION

The existing economic evidence base from South Asia should motivate policy makers to mobilise resource allocation towards the most cost-effective interventions identified in this review to curb the epidemic of CVD and DM in the region. Also, there is an urgent need to invest in health technology assessment and policy evaluations in South Asia using local research data.

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