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

Kavita Singh,1,2,3 Ambalam M Chandrasekaran,2 Soumyadeep Bhaumik,4 Kaushik Chattopadhyay,5,6 Anuji Upekshika Gamage,7 Padmal De Silva,8 Ambuj Roy,9 Dorairaj Prabhakaran,2,3,6 Nikhil Tandon1

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

For numbered affiliations see end of article.

Correspondence to Dr Kavita Singh; kavita@ccdcindia.org
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, 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. 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
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
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. and Evers et al. 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. 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, 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).
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

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.
| Source (author, year) | Country/Setting | Study population | Intervention | Comparison | Economic perspective | Methodology | Outcome measure studied | Risk of bias assessment |
|-----------------------|-----------------|------------------|--------------|------------|----------------------|-------------|------------------------|------------------------|
| Turi et al, 1991<sup>13</sup> | 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-effectiveness ratio between treatment groups not reported; long term outcomes not assessed; Decision model and assumptions appropriate: NA |
| Ahuja et al, 1997<sup>24</sup> | 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<sup>25</sup> | 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-effectiveness 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<sup>26</sup> | 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-effectiveness analysis was conducted; incremental cost-effectiveness ratio between treatment groups not reported; long-term outcomes not assessed; Decision model and assumptions appropriate: NA |

Continued
| Source (author, year) | Country/Setting | Study population | Intervention | Comparison | Economic perspective | Methodology | Outcome measure studied | Risk of bias assessment |
|-----------------------|-----------------|------------------|--------------|------------|----------------------|-------------|------------------------|------------------------|
| Murray et al, 2003<sup>57</sup> | 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<sup>58</sup> | 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<sup>59</sup> | 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<sup>60</sup> | 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/or treating 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 |
| Source (author, year) | Country /Setting | Study population | Intervention | Comparison | Economic perspective | Methodology | Outcome measure studied | Risk of bias assessment |
|----------------------|------------------|------------------|--------------|------------|----------------------|------------|------------------------|------------------------|
| Gaziano et al, 2006⁰ | 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, 2006⁰ | 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, 2006⁰ | 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, 2006⁰ | 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, 2006⁰ | 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 |
| Source (author, year) | Country/Setting | Study population | Intervention | Comparison | Economic perspective | Methodology | Outcome measure studied | Risk of bias assessment |
|----------------------|-----------------|------------------|--------------|------------|----------------------|-------------|------------------------|------------------------|
| Ramachandran et al., 2007 | 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 | 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 | 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 | 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. |
| Source (author, year) | Country/Setting | Study population | Intervention | Comparison | Economic perspective | Methodology | Outcome measure studied | Risk of bias assessment |
|----------------------|-----------------|------------------|--------------|------------|-----------------------|-------------|------------------------|------------------------|
| Sanmukhani, et al, 2010 | India | Patients at risk of CVD (primary prevention) Patients with history of CVD (secondary prevention) | Simvastatin—40 mg Pravastatin—40mg | 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 | South Asia region (India) | Population-based and individuals at high risk (BMI≥25 kg/m², 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 | 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 thrombolysis 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 |
| Source (author, year) | Country/Setting | Study population | Intervention | Comparison | Economic perspective | Methodology | Outcome measure studied | Risk of bias assessment |
|---------------------|-----------------|------------------|--------------|------------|---------------------|-------------|------------------------|------------------------|
| Donaldson et al, 2011 | 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 | 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: NA |
| Jafar et al 2011 | 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 | 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 | 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 |
### Table 1: Economic evaluations of prevention and treatment strategies for chronic non-communicable diseases in India

| Source (author, year) | Country/Setting | Study population | Intervention | Comparison | Economic perspective | Methodology | Outcome measure studied | Risk of bias assessment |
|-----------------------|-----------------|------------------|--------------|------------|----------------------|------------|--------------------------|------------------------|
| Brown et al, 2013     | India           | School students: aged 14 years and above | Project MYTRI; Four intervention components: 1. classroom activities/behavioural interventions 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   | 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: yes; Decision model and assumptions appropriate: yes; Decision model and assumptions appropriate: yes; Decision model and assumptions appropriate: yes; Decision model and assumptions appropriate: yes; Decision model and assumptions appropriate: yes; Decision model and assumptions appropriate: yes; Decision model and assumptions appropriate: yes; Decision model and assumptions appropriate: yes |
| Marseille et al, 2013  | 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)+metaanalysis 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 |
| Rachapelle et al, 2013 | 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: yes; Decision model and assumptions appropriate: yes; Decision model and assumptions appropriate: yes; Decision model and assumptions appropriate: yes; Decision model and assumptions appropriate: yes; Decision model and assumptions appropriate: yes; Decision model and assumptions appropriate: yes; Decision model and assumptions appropriate: yes; Decision model and assumptions appropriate: yes |

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  | 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 |
| Patel et al., 2014    | 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     | 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     | 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  | 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 |
| Source (author, year) | Country /Setting | Study population | Intervention | Comparison | Economic perspective | Methodology | Outcome measure studied | Risk of bias assessment |
|----------------------|------------------|------------------|--------------|------------|----------------------|-------------|------------------------|------------------------|
| Dukpa et al, 2015    | 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 |
| Basu et al, 2015     | 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 AarogyaYojana 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 (author, year) | Country/Setting | Study population | Intervention | Comparison | Economic perspective | Methodology | Outcome measure studied | Risk of bias assessment |
|-----------------------|-----------------|------------------|--------------|------------|----------------------|-------------|------------------------|------------------------|
| Basu et al, 2015       | 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 |
| Gupta et al, 2015      | 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 QALY's gained |
| Home et al, 2015       | 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 QALY's gained |
| Source (author, year) | Country/Setting | Study population | Intervention | Comparison | Economic perspective | Methodology | Outcome measure studied | Risk of bias assessment |
|-----------------------|-----------------|------------------|--------------|------------|---------------------|-------------|-----------------------|------------------------|
| Sengottuvelu et al., 2016 | 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 | 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 | India | Individuals aged 30–70 years at high CV risk (≥10%) | A treat-to-target strategy emphasizing lowering blood pressure to a target | 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; CABC, coronary artery bypass graft surgery; CCA, cost-sequences 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; CUDA, cost-utility analysis; CV, cardiovascular; CVD, cardiovascular diseases; C/E, Cost-effective; DALY, disability-adjusted life years; DOCT, Diabetes Control and Complications Trial; DOP2, Disease Control Priorities; DDD, a type of heart pacemaker 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; MYTH, Mobilizing Young 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; UFP, 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 \% 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 \( (2000) \). 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.
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 India31 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 India34 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, preventative multi-drug 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
| 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$, 1999 | RCT-based CEA | Hospital admission until discharge (5–7 days) | NA | Yes | No | + |
| Murray et al, 2003 | WHO-CHOICE | Not stated | Int$, 2000 | Standard multi-state 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 | WHO-CHOICE; University of Queensland, Australia; Centre for Addiction and Mental Health, Toronto, Canada | Not stated | Int$, 2004 | Static State Transition decision model (generalised CEA) | Not stated (assume: lifetime) | 3% for both costs and effects | Yes | Yes | + |
| Namboodiri et al., 2004 | PGIMER, Chandigarh, India | Not stated | Rupee, 2001 | Cost comparison/consequences analysis | NA | NA | NA | NA | − |
| Narayan et al., 2006 | DCP2 Chapter | Fogarty International Centre NIH, BMGF, WHO, World Bank | US$, 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 | DCP2 Chapter | Fogarty International Centre NIH, BMGF, WHO, World Bank | US$, 2001 | Population-based decision model; DALY weights taken from Mathers (2006) and costs data from McFayden (2003) | Not stated (assume: lifetime) | Not stated | Yes | Not stated | + |
| Willett et al, 2006 | DCP2 Chapter | Fogarty International Centre NIH, BMGF, WHO, World Bank | US$, 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 | DCP2 Chapter | Fogarty International Centre NIH, BMGF, WHO, World Bank | US$, 2001 | Population-based decision model; authors have used local costs data and interventions benefits from published literature sources | Not stated (assume: lifetime) | Not stated | Yes | Not stated | + |
| Jha et al, 2006 | DCP2 Chapter | Fogarty International Centre NIH, BMGF, WHO, World Bank | US$, 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 | PGIMER Chandigarh, India | Not stated | US$ and rupee, 2004 | RCT-based CEA | Within trial analysis (30-day follow-up) | NA | Yes | + |
| 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                      | IDRF, Chennai, India                                                                             | Not stated                                                                     | Rupee and US$, 2006            | RCT-based CEA                                                                    | Within trial analysis (3 years)     | No discounting             | Yes                         | Yes                      | ++                          |
| Zubair Tahir et al, 2009                      | Aga Khan University Hospital, Karachi, Pakistan                                                 | Not stated                                                                     | US$, 2007                      | Cost comparison/ consequences analysis                                            | NA                                  | NA                         | NA                          | NA                       | −                           |
| Habib et al, 2010                             | 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                             | 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                        | 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) | Yes                        | No                          | +                        |                             |
| Cecchini et al, 2010                          | WHO-CHOICE; University of Queensland, Australia; Economic Analysis Unit, Mexico                | None                                                                           | US$, 2005                      | Chronic disease prevention model — microsimulation                               | 50 years and lifetime horizon       | 3% for both costs and effects | Yes                        | Yes                      | ++                          |
| Schulman-Marcus et al, 2010                   | AIIMS, New Delhi; HSPH, New York York Cardiovascular Research Foundation, Fogarty International Centre NIH | Sarnoff                                                                       | US$, 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                         | PHFI and Johns Hopkins Bloomberg School of Public Health, Baltimore, USA                          | None                                                                           | US$, 2008                      | Details of model structure not provided, but assumptions and key parameters listed | 10 years and lifetime               | 3% for both costs and effects | Yes                        | Yes                      | ++                          |
| Lohse et al, 2011                             | Novo Nordisk Denmark and UCSF                                                                    | Novo Nordisk A/S.                                                             | US$, 2011                      | GDModel decision tree                                                            | Lifetime                            | 3% per year for costs; effects not discounted, neither justified | Yes                        | Yes                      | +                           |
| Jafar et al, 2011                             | AKU, Karachi, ICL, LSHTM                                                                         | Wellcome Trust award                                                          | US$, 2007                      | RCT-based CEA; benefits seen in BP reduction was converted to CV DALYs, using data from GBD study and using a linear regression model | 10, 20, 50 years and lifetime       | 5% for both costs and effects | Yes                        | Yes                      | ++                          |
| Ahmad et al, 2011                             | MGMC-Sitapura, Jaipur                                                                            | Not stated                                                                     | US$, 2010                      | Observational study                                                             | NA                                  | NA                         | Yes                        | No                       | +                           |
| Humaira et al, 2012                           | 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                             | University of Texas, Public Health Foundation of India                                            | NIH grant                                                                      | US$, 2006                      | RCT-based CEA and Markov model for long term cost-effectiveness                   | Lifetime, within trial             | No                          | Yes                        | Yes                      | +                           |
| Source (author, year)       | Institution(s) conducting the study                                                                 | Funding agency              | Currency, year | Choice of decision model and key parameters                                                                 | Time horizon                      | Discount rate used                                                                 | Incremental analysis reported | SeA done | Quality grading† (++, +, −) |
|-----------------------------|------------------------------------------------------------------------------------------------------|-----------------------------|----------------|-------------------------------------------------------------------------------------------------------------|-----------------------------------|-------------------------------------------------------------------------------------|-------------------------------|----------|--------------------------|
| Ortegón et al, 2012          | University of Columbia, University of Washington, WHO                                                | None                        | Int$, 2005     | Chronic disease prevention model — WHO software DisMod II                                                  | Lifetime                          | 3% for both costs and effects                                                        | Yes                           | Yes      | +                        |
| Marseille et al, 2013        | Chennai Corporation Maternity Hospital referred GDM cases to Diabetes Care and Research Institute for antenatal monitoring and treatment | Novo Nordisk A/S            | Int$, 2011     | Decision-analysis tool (the GeDiForCE) to assess cost-effectiveness                                       | Lifetime                          | 3% for both costs and effects                                                        | Yes                           | Yes      | +                        |
| Rachapelle et al, 2013       | Sankara Nethralaya, Vision Research Foundation, Chennai and LSHTM                                     | Sightsavers grant           | US$, 2009      | Markov model (TreeAge Pro 2009)                                                                          | 20 years, lifetime                 | 3% for costs                                                                      | Yes                           | Yes      | +                        |
| Megiddo et al, 2014          | 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$, 2014      | CHD cohort model                                                                                          | Lifetime                          | 3%                                                                                   | Yes                           | Yes      | ++                       |
| Patel et al, 2014            | Shrivath Centre of Excellence in Clinical Research, Ahmedabad, India; UN Mehta Institute of Cardiology and Research Centre, Ahmedabad, India; BJ Medical College, Ahmedabad, Gujarat, India | None                        | Rupee, 2007    | RCT-based CEA                                                                                             | Within trial analysis (8 weeks)    | No discounting                                                                     | No                            | No       | +                        |
| Lamy et al, 2014             | McMaster University, Canada; AIIMS and Centre for Chronic Disease Control, New Delhi, India            | Sanofi Aventis, Paris, France | US$, 2014      | Randomised trial-based cost-minimisation analysis                                                        | 6.2 years—median trial duration   | 3% for costs                                                                      | Yes                           | Yes      | ++                       |
| Lamy et al, 2014             | 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$, 2013      | Randomised trial-based cost-minimisation analysis                                                        | 1 year                            | Not applicable                                                                    | Yes                           | Yes      | ++                       |
| Anchala et al, 2015          | Public Health Foundation of India, New Delhi, India; Centre for Chronic Disease Control, New Delhi, India; University of Cambridge, UK; Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands | Wellcome Trust Capacity Strengthening Strategic Award to the Public Health Foundation of India and a consortium of UK universities | Rupee and US$ | RCT-based CEA                                                                                             | 1 year                            | 3% for costs                                                                      | Yes                           | No       | +                        |
| 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     | 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     | 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$, 2014 | Microsimulation model of myocardial infarction and stroke in India | 20 years | 3% for costs and effects | Yes | Yes | ++ |
| Basu et al, 2015     | Stanford University, USA; London School of Hygiene and Tropical Medicine, London, UK; Imperial College London, London, UK; Public Health Foundation of India; Veterans Affairs Hospital, Ann Arbor, Michigan, USA; University of Michigan, USA; University College London, London, UK | Various federal funding support* | US$, 2014 | Microsimulation model | 10-year implementation horizon | 3% for costs | No | Yes | ++ |
| Gupta et al, 2015    | 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$, 2013 | IMS CORE Diabetes Model | 1-year, 30-year time horizon | 3% for costs and effect measures | Yes | Yes | ++ |
| Home et al, 2015     | Newcastle University, Newcastle upon Tyne, UK; University Guro Hospital, Seoul, South Korea; Instituto Jalisciense de Investigacion en Diabetes y Obesidad, Guadalajara, Mexico; Internal Medicine Department, University Hospital Setif, Setif, Algeria; Market Access – Value Communication, Novo Nordisk A/S, Søborg, Denmark | Novo Nordisk | US$, 2013 | IMS CORE Diabetes Model | 24-week follow-up, 1-year time horizon | 3% for costs and effect measures | Yes | Yes | ++ |
| Sengottuvelu et al, 2016 | Apollo Hospitals, Chennai, India | Not stated | Rupee and US$, 2014 | Cost comparison/consequences analysis | NA | NA | NA | NA | − |
| Source (author, year) | Institution(s) conducting the study | Funding agency | Currency, year | Choice of decision model and key parameters | Time horizon | Discount rate used | Incremental analysis reported | SeA done | Quality grading† (++, +, −) |
|----------------------|--------------------------------------|----------------|---------------|------------------------------------------|--------------|-------------------|-----------------------------|----------|--------------------------|
| Limaye et al, 2016[7] | Hochschule Hannover, Hannover, Germany; Institute of Chemical Technology, Mumbai, India | Not stated | Rupee, 2016 | Cross-sectional study-based CEA | No details provided | No discounting | No SeA | No | − |
| Basu et al, 2016[8]  | Stanford University, Stanford, California, USA; Harvard Medical School, Boston, USA; University College London, London, UK; University of Michigan, Ann Arbor, USA; Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, USA; Imperial College London, London, UK; Public Health Foundation of India, New Delhi, India | Various federal funding support* | US$, 2015 | Decision modelling-based CEA | Lifetime | 3% for costs and effect measures | Yes SeA | 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; GR, general practitioner; HSPH, Harvard School of Public Health; ICL, Imperial College London; IDRF, India Diabetes Research Foundation; INR, 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†         |
|------------------------------------------------------------------------------|-----------------------------------------------|-------------------------|-----------------------------------|-----------------------------------------------|---------------------|
| **Primordial prevention**                                                    |                                               |                         |                                   |                                               |                     |
| Policy interventions                                                        |                                               |                         |                                   |                                               |                     |
| Tobacco control strategies (Ortegón et al²⁹)                                  |                                               |                         | 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                                        | 488                 |
| Tobacco control strategies (Jha et al⁶⁰)                                     |                                               |                         |                                   |                                               |                     |
| 33% price increase—low-end effect estimate                                  | No intervention                              | Lifetime                |                                   |                                               |                     |
| 33% price increase—high-end effect estimate                                 | No intervention                              | Lifetime                |                                   |                                               |                     |
| Non-price interventions: effectiveness                                       |                                               |                         |                                   |                                               |                     |
| 2%–10%—low-end estimate                                                     | No intervention                              | Lifetime                |                                   |                                               |                     |
| Non-price interventions: effectiveness                                       |                                               |                         |                                   |                                               |                     |
| 2%–10%—high-end estimate                                                    | No intervention                              | Lifetime                |                                   |                                               |                     |
| Complete smoking ban in public places (Donaldson et al³⁰)                     | 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 al³¹)                   | No intervention                              | 10 years               | 175 438.5                         | 4.52 (QALY/smoker averted)                     | 4501                |
| Promoting healthy diet strategies (Cecchini et al³²)                         |                                               |                         |                                   |                                               |                     |
| 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 al⁵⁷)                           |                                               |                         |                                   |                                               |                     |
| 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 al⁵)                           |                                               |                         |                                   |                                               |                     |
| Media campaign to reduce saturated fat content                               | No intervention                              | Lifetime                |                                   |                                               |                     |
| Substitute 2% of energy from trans fat with polyunsaturated fatty acid       | No intervention                              | Lifetime                |                                   |                                               |                     |

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                                            | Cost-saving                                                                                                 |
| Substitute 2% of energy from trans fat with polyunsaturated fatty acid (40% coronary artery disease reduction at $0.5 per adult) | No intervention                                 | Lifetime                |                                     | 376                                             | 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                |                                     | 3613                                            | Cost-saving                                                                                                 |
| Reducing salt content by means of legislation+public education             | No intervention                                 | Lifetime                |                                     |                                                 |                                                                                                               |
| Blood pressure-lowering strategies (Rodgers et al⁶⁹)                      |                                                 |                         |                                     |                                                 |                                                                                                               |
| Prevention by salt legislation                                             | No intervention                                 | Lifetime                |                                     | 49                                              |                                                                                                               |
| Alcohol control strategies (Chisholm et al⁷⁰)                              |                                                 |                         |                                     |                                                 |                                                                                                               |
| Taxation current+25% (alcohol use)                                        | No intervention                                 | Lifetime                |                                     |                                                 |                                                                                                               |
| Taxation current+50% (alcohol use)                                        | No intervention                                 | Lifetime                |                                     |                                                 |                                                                                                               |
| Breath testing                                                            | No intervention                                 | Lifetime                |                                     | 152                                             | Cost-saving                                                                                                 |
| Highest tax+advertisement ban                                              | No intervention                                 | Lifetime                |                                     | 5002                                            | Cost-saving                                                                                                 |

**Primary prevention**

**Policy interventions**

| Universal screening for diabetes and hypertension (Dupka et al⁷¹)          | 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 al⁷²)                            | No intervention                                 | Lifetime                | 26                                  | 2.33                                            | 16                                                                                                           |
| Screening to prevent GDM (Marseille et al⁷³)                               | No intervention                                 | Lifetime                | 194 358                             | 120                                             | 2317                                                                                                          |
| Expansion of national insurance to cover primary, secondary and tertiary treatment for CVD (Basu et al⁷⁴) | No intervention                                 | Lifetime                | 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 al⁷⁵)                                     |                                                 |                         |                                     |                                                 |                                                                                                               |
| Nicotine replacement therapy effectiveness                                  | No intervention                                 | Lifetime                | 142                                 |                                                 |                                                                                                               |
| Nicotine replacement therapy effectiveness                                  | No intervention                                 | Lifetime                | 1880                                |                                                 |                                                                                                               |
| To reduce alcohol use (Chisholm et al⁷⁶)                                    |                                                 |                         |                                     |                                                 |                                                                                                               |
| Brief physician advice                                                     | No intervention                                 | Lifetime                | 175                                 |                                                 |                                                                                                               |
| CVD prevention strategies (Ortega et al⁷⁷)                                  | 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 QALY=a-green; 1–3×GDP per capita per QALY=yellow |
|-----------------------------------------------------------------------------|------------|-------------------------|------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Combined home health education plus trained general practitioner for hypertension management (Jafar et al)<sup>36</sup> | No intervention | 2 years | 48 | | 48 |
| Diabetes prevention strategies (Narayan et al)<sup>34</sup>                  |            |                          |                                    |                                               |                                                                                                                  |
| 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)<sup>37</sup> | Number needed to treat to prevent a case of diabetes | 3 years | 164 | 6.4 | 2302 |
| Lifestyle modification                                                       | Standard healthcare advice | 3 years | 159 | 6.9 | 2396 |
| Metformin                                                                    | Standard healthcare advice | 3 years | 209 | 6.5 | 2973 |
| Secondary and tertiary prevention                                            |            |                          |                                    |                                               |                                                                                                                  |
| Policy interventions                                                         |            |                          |                                    |                                               |                                                                                                                  |
| 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 | 239 | |                                                                                                                  |
| 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)<sup>39</sup> | 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)<sup>29</sup>                        |            |                          |                                    |                                               |                                                                                                                  |
| 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 | 778.6 |
| Treatment of CHF with diuretics+exercise training+ACEi                      | Treatment of CHF with diuretics | Lifetime | 0.04 | 72 | 1236.7 |
| 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                                          | 790                                                                                                       |
| 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 with aspirin, BB, statin, ACEI | 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 | 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) | 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                 | 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 (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, 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 (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 acute myocardial infarction (aspirin, BB, ACEI, streptokinase)+post-acute ischaemic heart disease (aspirin, BB, statin) | 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 (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, statin) | Lifetime                 | 0.04                               | 178                                           | 524                                                                                                       |
| Continued                                                                 |                                                                            |                          |                                    |                                                |                                                                                                           |

Singh K, et al. BMJ Open 2018;8:e017809. doi:10.1136/bmjopen-2017-017809
## 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        |                                                                                                 |
| CVD treatment strategies (Murray et al45)                                   |                                                                           |                         |                                    |                                               |             |                                                                                                 |
| Treatment of SBP above 160 mm Hg with BB and diuretic                       | No intervention                                                            | Lifetime                |                                    |                                               |             |                                                                                                 |
| Treatment of SBP above 140 mm Hg with BB and diuretic                       | No intervention                                                            | Lifetime                |                                    |                                               |             |                                                                                                 |
| Treatment with statins for total cholesterol concentrations above education 6.2 mmol/L | No intervention                                                            | Lifetime                |                                    |                                               |             |                                                                                                 |
| Treatment with statins for total cholesterol concentrations above education 5.7 mmol/L | No intervention                                                            | Lifetime                |                                    |                                               |             |                                                                                                 |
| 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                |                                    |                                               |             |                                                                                                 |
| 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                |                                    |                                               | 94.8        |                                                                                                 |
| 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 al43)                    |                                                                           |                         |                                    |                                               |             |                                                                                                 |
| 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
| 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 al⁵⁹)                        |                                |                        |                                   |                                               |                                                                                                         |
| Multidrug regimen (aspirin, a BB, a thiazide diuretic, an ACEI and a statin) | No intervention                | Lifetime               |                                   |                                               | 1827                                                                                                    |
| Multidrug regimen (aspirin, a BB, a thiazide diuretic, an ACEI and a statin) | No intervention                | Lifetime               |                                   |                                               | 3408.6                                                                                                  |
| Multidrug regimen (aspirin, a BB, a thiazide diuretic, an ACEI and a statin) | No intervention                | Lifetime               |                                   |                                               | 5268.2                                                                                                  |
| Treat-to-target, benefit-based tailored treatment strategy vs hybrid strategy for lowering CVD risk (Basu et al⁷⁸) |                                |                        |                                   |                                               |                                                                                                         |
| 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 al⁴⁰) | No ECG-based referral in case of chest pain | Lifetime | 0.15                             | 0.012 (QALY gained) | 26.1                                                                                                    |
| Diabetes treatment strategies (Narayan et al⁵⁴)                             |                                |                        |                                   |                                               |                                                                                                         |
| 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 al⁶⁰)               |                                |                        |                                   | 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 | BIAsp 30 | 30 years | 868,496 | 2.52 | 412.9 |
| BIAsp 30±oral glucose-lowering drugs (Gupta et al)41 | BIAsp 30 | 30 years | −2524.192 | 2.82 | Cost-saving |
| Basal insulin vs oral glucose-lowering drugs (Home et al)75 | Basal insulin treatment with insulin detemir | Oral glucose-lowering drugs | 30 years | 3510.36 | 4.97 | 854.1 |
| Basal insulin vs oral glucose-lowering drugs (Home et al)75 | Basal insulin treatment with insulin detemir | Oral glucose-lowering drugs | 1 year | 338,796 | 0.322 | 1203.6 |
| Screen once in a lifetime | No screening | 25 years | 6.5 | 0.0049 | 2214.1 |
| Screen twice in a lifetime | No screening | 25 years | 5.3 | 0.0039 | 2252.7 |
| Screen every 5 years | No screening | 25 years | 19.6 | 0.0097 | 3400.1 |
| Screen every 3 years | No screening | 25 years | 17.4 | 0.0084 | 3411.8 |
| Screen every 2 years | No screening | 25 years | 18.4 | 0.0075 | 4084.5 |
| Screen once in a lifetime | No screening | 25 years | 13.2 | 0.0049 | 4515.6 |
| Screen twice in a lifetime | No screening | 25 years | 9.7 | 0.0039 | 4151.6 |
| Screen every 5 years | No screening | 25 years | 30.3 | 0.0097 | 5257 |
| Blood pressure-lowering strategies (Rodgers et al)59 | Prevention by salt legislation+health education | No intervention | Lifetime | 2562.7 |
| 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 | 9 |

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 | Incremental DALYs averted per million population |
|-----------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------------------|-----------------------------------|------------------------------------------------|----------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| 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)‡§¶                  |                                                                           |                         |                                   |                                                 |                                                                                                           |                                                  |
| 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, 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, 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, ACEI, statin) | Lifetime                | 0.04                               | 246                                             | 380                                                                                                       |                                                  |
| Expansion of national insurance to cover primary, secondary and tertiary treatment for CVD (Basu et al)§ | Incremental DALYs 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: –recommendation to protect from exposure to tobacco smoke –regulation of the contents of tobacco products –regulation of tobacco product disclosures –prohibition of tobacco advertising, promotion and sponsorship –education, communication, training and public awareness –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. 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 Database32 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 programme36 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. 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) 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. 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. But we preferred to present the findings based on WHO guidelines 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.

**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, International Society for Pharmacoeconomics and Outcomes Research, and the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine 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.

---

Singh K, et al. BMJ Open 2018;8:e017809. doi:10.1136/bmjopen-2017-017809
Author affiliations
1Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi, Delhi, India
2Clinical Trials Unit, Centre for Chronic Disease Control, New Delhi, Delhi, India
3Centre for Chronic Conditions and Injuries, Public Health Foundation of India, New Delhi, Delhi, India
4Health Promotion Division, Public Health Foundation of India, New Delhi, Delhi, India
5Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
6Division of Epidemiology and Public Health, School of Medicine, The University of Nottingham, Nottingham, UK
7Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
8Management and Development and Planning Unit, Ministry of Health, Colombo, Western, Sri Lanka
8WHO Collaborating Centre for Public Health Workforce Development, National Institute of Health Sciences, Kalutara, Sri Lanka
9Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India

Contributors KS, NT, DP and AR conceptualised and designed the study. KS, AMCS and SB designed the search strategy for the review. KS and AMCS performed the search strategy in electronic databases, screened, reviewed and extracted data from eligible studies included in this review, and performed data analysis. KS wrote the first draft of the manuscript. AMCS, SB, KC, PDS, AUG, AR, DP and NT contributed significantly to the revision of the manuscript. All authors have approved the submission of this version of the manuscript.

Funding This research has received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement In this paper, we report the results of a systematic review. KS has access to all the data extracted from published studies. However, there are no unpublished data linked with this systematic review.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

© Article author(s) (or their employer(s)) unless otherwise stated in the text of the article 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES
1. Ezzati M, Hoorn SV, Rodgers A, et al. Estimates of global and regional potential health gains from reducing multiple major risk factors. Lancet 2003;362:271–80.
2. Mendis S, Chestnott O, Costs, benefits, and effectiveness of interventions for the prevention, treatment, and control of cardiovascular diseases and diabetes in Africa. Prog Cardiovasc Dis 2013;56:314–21.
3. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998;317:703–13.
4. Yusuf S. Two decades of progress in preventing vascular disease. Lancet 2002;360:2–3.
5. Willett WC, Koplan JP, Nugent R. Disease control priorities in developing countries, 2nd edition. Chapter 44 prevention of chronic disease by means of diet and lifestyle changes. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, eds. Washington (DC): The International Bank for Reconstruction and Development / The World Bank. New York: Oxford University Press, 2006.
6. Wheeler ML. Translation of successful diabetes-related lifestyle interventions from research to practice. Curr Diab Rep 2005;5:365–6.
7. Webster R, Rodgers A. Polypharmacy and cardiovascular disease. Expert Opin Drug Deliv 2016;13:1–6.
8. Turnbull F, Neal B, Ninomiya T, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. BMJ 2008;336:1121–3.
9. Smith SC, Chen D, Collins A, et al. Moving from political declaration to action on reducing the global burden of cardiovascular diseases: a statement from the Global Cardiovascular Disease Taskforce. J Am Coll Cardiol 2013;62:2151–3.
10. Lee ES, Vedanthan R, Jeemon P, et al. Quality Improvement for Cardiovascular Disease Care in Low- and Middle-Income Countries: A Systematic Review. PLoS One 2016;11:e0157036.
11. Bhargava SK, Sachdev HS, Fall CH, et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. N Engl J Med 2004;350:865–75.
12. Truelsen T, Bonita R, Granbaek M, et al. Stroke incidence and case fatality in two populations: the Auckland Stroke Study and the Copenhagen City Heart Study. Neuroepidemiology 1998;17:132–8.
13. Ezzati M. Complexity and rigour in assessing the health dimensions of sectoral policies and programmes. Bull World Health Organ 2003;81:458–9.
14. Chisholm D, Sanderson K, Ayuso-Mateos JL, et al. Reducing the global burden of depression: population-level analysis of intervention cost-effectiveness in 14 world regions. Br J Psychiatry 2004;184:393–403.
15. Chisholm D, Rehm J, Van Ommeren M, et al. Reducing the global burden of hazardous alcohol use: a comparative cost-effectiveness analysis. J Stud Alcohol 2004;65:782–93.
16. Chisholm D, Doran C, Shibuya K, et al. Comparative cost-effectiveness of policy instruments for reducing the global burden of alcohol, tobacco and illicit drug use. Drug Alcohol Rev 2006;25:553–65.
17. Shrouf A, Chowdhury R, Anchala R, et al. Cost-effective interventions for the prevention of cardiovascular disease in low and middle income countries: a systematic review. BMC Public Health 2013;13:285.
18. Walker D, Fox-Rushby JA. Economic evaluation of communicable disease interventions in developing countries: a critical review of the published literature. Health Econ 2000;9:681–98.
19. Singh K, Chandra Sekaran AM, Bhauik S, et al. Cost-effectiveness of interventions to control cardiovascular diseases and type 2 diabetes mellitus in South Asia: protocol for a systematic review. BMJ Open 2015;5:e007205.
20. Drummond MF, Sculpher MJ, Torrance GW, et al. Methods for the Economic Evaluation of Health Care Programs. 3rd edn. Oxford, UK: Oxford University Press, 2005.
21. Evers S, Goossens M, de Vet H, et al. Criteria list for assessment of methodological quality of economic evaluations: consensus on health economic criteria. Int J Technol Assess Health Care 2005;21:240–5.
22. Philips Z, Ginnelly L, Sculpher M, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess 2004;8:i–iv, x–xi, 1–158.
23. Inflation Calculator India. Calculate India’s inflation between any two years from 1971 to 2017. http://inflation-calculator-india.php (accessed on 12 Aug 2017).
24. Inflation calculator. http://fxtop.com/en/inflation-calculator.php (accessed on 12 Aug 2017).
25. World Health Organization. WHO Guide to cost-effectiveness analysis. Geneva: World Health Organization, 2003.
26. Murray C, Lopez A, Mathers C, et al. The global burden of disease 2000 project: aims, methods and data sources. Geneva: World Health Organization, 2001.
27. Rachapelle S, Legood R, Alavi Y, et al. The cost-utility of telemedicine to screen for diabetic retinopathy in India. Ophthalmology 2013;120:566–73.
28. The World Bank Data. All countries and economies - GDP per capita. http://data.worldbank.org/indicator/NY.GDP.PCAP.PC (accessed on 20 Aug 2017).
29. Ortegon M, Lim S, Chisholm D, et al. Cost effectiveness of strategies to combat cardiovascular disease, diabetes, and tobacco use in sub-Saharan Africa and South East Asia: mathematical modelling study. BMJ 2012;344:e607.
30. Donaldson EA, Waters HR, Arora M, et al. A cost-effectiveness analysis of India’s 2008 prohibition of smoking in public places in Gujarat. Int J Environ Res Public Health 2011;8:1271–86.
31. Sharp HS, Sigler M, Perry C, et al. The cost-effectiveness of a school-based smoking prevention program in India. Health Promot Int 2013;28:178–86.
32. Cecchini M, Sassi F, Lauer JA, et al. Tackling of unhealthy diets, physical inactivity, and obesity: health effects and cost-effectiveness. Lancet 2010;376:175–84.
33. Dukpa W, Teararawattananon Y, Rattanavipapong W, et al. Is diabetes and hypertension screening worthwhile in resource-limited settings?
75. Home P, Baik SH, Gálvez GG, et al. An analysis of the cost-effectiveness of starting insulin detemir in insulin-naïve people with type 2 diabetes. *J Med Econ* 2015;18:230–40.

76. Sengottuvelu G, Chakravarthy B, Rajendran R, et al. Clinical usefulness and cost-effectiveness of fractional flow reserve among Indian patients (FIND study). *Catheter Cardiovasc Interv* 2016;88:E139–E144.

77. Limaye D, Todi K, Shroff J, et al. Cost-effectiveness study of antidiabetic drugs in type 2 diabetes mellitus patients from Mumbai, India. *Current Therapeutic Research* 2016;78:S2–S3.

78. Basu S, Yudkin JS, Sussman JB, et al. Alternative strategies to achieve cardiovascular mortality goals in China and India: a microsimulation of target- versus risk-based blood pressure treatment. *Circulation* 2016;133:840–8.

79. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3:e442.

80. McFayden JE. ed. *International drug price indicator reference guide*: Boston Management Sciences for Health, 2003.