BMJ Open

Interventions for the prevention of cardiovascular diseases: a protocol for a systematic review of economic evaluations in low-income and middle-income countries

Leopold Ndemnge Aminde,[1,2] Lennert Veerman[1]

To cite: Aminde LN, Veerman L. Interventions for the prevention of cardiovascular diseases: a protocol for a systematic review of economic evaluations in low-income and middle-income countries. *BMJ Open* 2016;**6**:e013668. doi:10.1136/bmjopen-2016-013668

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-013668).

Received 29 July 2016
Revised 7 November 2016
Accepted 1 December 2016

[1]School of Public Health, Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia
[2]Non-communicable Diseases Unit, Clinical Research Education, Networking & Consultancy (CRENC), Douala, Cameroon

Correspondence to
Dr Leopold Ndemnge Aminde; l.aminde@uq.edu.au

ABSTRACT

Introduction: Low-income and middle-income countries (LMICs) are experiencing a growing disease burden due to cardiovascular and other chronic non-communicable diseases. Interventions for the control of these diseases are paramount; however, these countries are faced with competing health and financial needs. There is an urgent need for quality evidence on cost-effective strategies to address these chronic diseases. We aim to synthesise the current literature on economic evaluations of interventions for primary and secondary cardiovascular disease prevention in LMICs.

Methods and analysis: A systematic review of studies (published and unpublished) in LMICs up to 30 October 2016 will be conducted. The following databases will be searched: PubMed/MEDLINE, EMBASE, SCOPUS, CINAHL, Web of Science, EconLit, NHS Economic Evaluations Database (NHS EED). Data sources specific to African literature, such as the WHO AFROLIB, Africa Index Medicus and African Journals online (AJOL) as well as grey literature, will also be searched. 2 reviewers shall independently screen potential articles for inclusion and disagreements shall be resolved by consensus. Quality appraisal of studies shall be done using Drummond's checklist for economic evaluation of studies. A descriptive synthesis of the evidence obtained is planned. The primary outcomes will be costs per life years gained or unit of clinical outcome, cost per quality-adjusted life years or disability-adjusted life years. This systematic review protocol has been prepared according to the Preferred Reporting Items for Systematic reviews and Meta-analyses for Protocols (PRISMA-P) 2015 statement.

Ethics and dissemination: Ethics approval is not required considering that this is a protocol for a systematic review of published studies. Results from this review will be disseminated via conference presentations and peer-reviewed journal publications.

Trial registration number: CRD42016043510.

INTRODUCTION

Rationale

Chronic non-communicable diseases (NCDs) are a global health challenge and account for a major cause of morbidity and mortality.[1] The recent 2013 Global Burden of Disease (GBD) study estimated that NCDs accounted for 1.4 billion disability-adjusted life years (DALYs), which is almost a third of the global health burden.[2] Cardiovascular diseases (CVDs) are a major contributor to this NCD burden with over 17 million deaths worldwide. The situation is worrisome in low-income settings, and Africa in particular, as the bulk of premature deaths due to CVD (mostly from stroke and heart disease) occurs there.[3] Risk factors such as high blood pressure, dyslipidaemia, obesity, tobacco and physical inactivity are established drivers for this CVD epidemic globally.[3 4] The composite of these risk factors with the epidemiological transition and demographic changes explains this CVD burden.[5] Evidence from western countries suggests that interventions targeting these (modifiable) risk factors are beneficial in the fight against CVD.[6] The WHO Package for Essential Non-communicable (PEN) disease interventions highlighted that targeting these modifiable risk factors would be cost-effective due to their relative ease in implementation.[7] In 2006, the Disease Control Priorities Project (DCPP) for developing countries conducted economic evaluations of interventions for prevention of CVD.[8] This project appeared to be a turning point in low-income settings; following this DCPP, the past decade has seen a surge in studies on cost-effectiveness and economic evaluations of various interventions. According to the WHO, primary prevention refers to efforts geared at reducing the

incidence of cardiovascular events (ischaemic heart disease and strokes) in individuals at risk but who have not yet developed overt or clinical CVD. Efforts aimed at preventing recurrent clinical events (ischaemic heart disease, stroke) in individuals with established CVD is known as secondary prevention.[9] Studies have demonstrated the beneficial impacts of pharmacological interventions in primary and secondary prevention of CVD, though with caveats for population-based interventions. The need for economic assessment of these studies to identify those which have best value for money is paramount.[10 11] This is of particular significance for low-resource settings, especially Africa, with concomitant communicable, nutritional and neonatal diseases, relatively suboptimal healthcare systems and yet limited funds.[1 2] Owing to finite financial resources akin to these countries, and growing healthcare needs, it is almost inevitable for governments, health policy and decision makers to make choices via balancing costs and health benefits of intervention programmes geared towards addressing these health problems. Suhrcke and colleagues previously suggested that evidence for economic evaluation of CVD interventions was accumulating but still scarce in low-income and middle-income countries (LMICs). Efforts in a review later by Schroufi and colleagues concentrated on only cost-effectiveness studies conducted in low-income settings up to January 2011.[10 12] Preliminary searches suggest that since then, there have been more studies assessing costs and consequences of interventions for the prevention of CVD. We propose a systematic review which will synthesise all studies carried out thus far until October 2016 reporting economic evaluations of CVD in low-income and middle-income settings and hence provide overall updated evidence on which interventions provide maximum health benefits with limited costs.

Objectives

The objective of this review is to identify and provide a comprehensive synthesis of interventions for primary and secondary prevention of CVD delivered to populations in LMICs(as defined by the current World Bank classification[13]), all through until October 2016.

Review question

The proposed review will aim to address the following questions:

1. What are the costs and costs relative to the outcome measure of interventions for CVD prevention in LMICs from various perspectives (individual patients and their families, healthcare providers and society)?
2. What are the contexts that are conducive to lower cost and increase the effectiveness of interventions for CVD prevention?

METHODS

This review protocol is registered in the PROSPERO International Prospective Register of systematic reviews (Registration Number: CRD42016043510) and has been prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA-P) 2015 statement.[14]

Criteria for considering studies for the review

Inclusion criteria

A. Study population: studies involving adults (age ≥18 years) living in LMICs.
B. Intervention type: studies reporting on interventions for either primary or secondary prevention of CVD.
C. Setting: primary (randomised control trials and observational studies) or modelling studies conducted in LMICs.
D. Comparator: studies identifying how the interventions were compared, either with respect to current practice or the 'do nothing' scenario.
E. Outcome measures: the outcomes of interest would be: cost per life year gained or per unit clinical outcome, cost per quality-adjusted life years (QALYs) or cost per DALYs.
F. Study designs: studies reporting full economic evaluations (cost-effectiveness analysis (CEA), cost-benefit analysis (CBA), cost-utility analysis (CUA)) shall be considered. This would include empirical as well as modelling studies.
G. Language: studies reported in English and French.

Exclusion criteria

A. Study setting: any studies conducted in high-income countries and duplicate publications of the same material will be excluded. If a study has been published in more than one journal, only the most complete and recent version will be considered.
B. Study types: narrative reviews, letters to the editor, case reports, editorials or any other lacking explicit information and methods will be excluded.

Data sources and search strategy

The following databases will be searched: PubMed/MEDLINE, EMBASE, SCOPUS, Web of Science, EconLit, NHS Economic Evaluations Database, and Cochrane Library, Centre for Reviews and Dissemination (CRD) database, WHO AFROLIB and Africa Index Medicus (AIM). An elaborate and comprehensive search strategy will be designed for maximum sensitivity combining relevant terms, country and regional names to obtain the maximum possible number of studies. Table 1 shows the proposed PubMed search strategy which shall be adapted to other databases. If a country has changed its name over time, both names will be included in the search. We will also search the reference list of articles for potential articles of interest for inclusion.

Grey literature

We will contact authors, experts in the field, conference websites and research organisations for relevant material. This will be done via emails. In the event of no

Table 1 Suggested PubMed search strategy

	Search terms
#1	"Cardiovascular disease" OR "Coronary heart disease" OR "ischaemic heart disease" OR "coronary disease" OR "acute coronary syndrome" OR "heart attack" OR "heart disease" OR "atherosclerosis" OR "myocardial infarction" OR "myocardial ischaemia" OR "stroke" OR "cerebrovascular disease" OR "cerebrovascular accident" OR CVA OR "cardiovascular event"
#2	"prevention" OR "control" OR "primary prevention" OR "secondary prevention" OR "cardiovascular risk" "risk factor" OR "lifestyle" OR "behaviour" OR diet OR food OR "hypertension" OR "blood pressure" OR "smoking" OR "tobacco" OR alcohol OR "alcohol consumption" OR "physical activity" OR exercise OR salt OR "salt reduction" OR dyslipidaemia OR "lipid lowering" OR cholesterol OR fat OR "intervention" OR "strategies" OR "modification" OR improve OR "address*" OR tax OR "taxation" OR "advertising" OR "counselling" OR "diet advice" OR "health education" OR "patient education" OR
#3	"costs and cost analysis" OR "cost-effectiveness" OR "cost-effective" OR "cost-utility" OR "cost benefit" OR "economic evaluation"
#4	"Afghanistan" OR "Albania" OR "Algeria" OR "American Samoa" OR "Angola" OR "Armenia" OR "Azerbaijan" OR "Bangladesh" OR "Belarus" OR "Belize" OR "Benin" OR" "Bhutan" OR "Bolivia" OR "Bosnia and Herzegovina" OR "Botswana" OR "Brazil" OR "Bulgaria" OR "Burkina Faso" OR "Burundi" OR "Cabo Verde" OR "Cambodia" OR "Cameroon" OR "Central African Republic" OR "Chad" OR "China" OR "Colombia" OR "Comoros" OR "Democratic Republic of Congo" OR "Congo" OR "Costa Rica" OR "Cote d'Ivoire" OR "Ivory Coast" OR "Cuba" OR "Djibouti" OR "Dominica" OR "Dominican Republic" OR "Ecuador" OR "Egypt" OR "El Savador" OR "Equatorial Guinea" OR "Eritrea" OR "Ethiopia" OR "Fiji" OR "Gabon" OR "The Gambia" OR "Georgia" OR "Ghana" OR "Grenada" OR "Guatamela" OR "Guinea" OR "Guinea Bissau" OR "Guyana" OR Haiti" OR "Honduras" OR "India" OR "Indonesia" OR "Iran" OR "Iraq" OR "Jamaica" OR "Jordan" OR "Kazakhastan" OR "Kenya" OR "Kiribati" OR "Democratic People's Republic of Korea" OR "Kosovo" OR "Kyrgyz Republic" OR "Lao DPR" OR "Lebanon" OR "Lesotho" OR "Liberia" OR "Libya" OR "Macedonia" OR "Madagascar" OR "Malawi" OR "Malaysia" OR "Maldives" OR "Mali" OR "Marshall Islands" OR "Mauritania" OR "Mauritius" OR "Mexico" OR "Micronesia" OR "Moldova" OR "Mongolia" OR "Morocco" OR "Mozambique" OR "Myanmar" OR "Namibia" OR "Nepal" OR "Nicaragua" OR "Niger" OR "Nigeria" OR "Pakistan" OR "Palau" OR "Panama" OR "Papua New Guinea" OR "Paraguay" OR "Peru" OR "Philippines" OR "Romania" OR "Russian Federation" OR "Rwanda" OR "Samoa" OR "Sao Tome and Principe" OR "Senegal" OR "Serbia" OR "Sierra Leonne" OR "Solomon Islands" OR "Somalia" OR "South Africa" OR "South Sudan" OR "Sri Lanka" OR "St Lucia" OR "St Vincent and the Grenadines" OR "Sudan" OR "Suriname" OR "Swaziland" OR "Syrian Arab Republic" OR "Tajikistan" OR "Tanzania" OR "Thailand" OR "Timor-Leste" OR "Togo" OR "Tonga" OR "Tunisia" OR "Turkey" OR "Turkmenistan" OR "Tuvalu" OR "Uganda" OR "Ukraine" OR "Uzbekistan" OR "Vanuatu" OR "Vietnam" OR "West Bank of Gaza" OR "Yemen" OR "Zambia" OR "Zimbabwe" OR Africa OR "sub-Saharan Africa" OR "low and middle income countr*" OR "low income countr*" OR Low OR middle income countr* OR "developing country" OR "underdeveloped country" OR "resource limited"
#5	#1 AND #2 AND #3 AND #4

response after repeated attempts to contact authors via email for relevant information, the said study shall be excluded.

Study records

Data management

All studies identified shall be imported to EndNote V.7.4 software for de-duplication of records. After this, all studies shall be uploaded into Rayyan QCRI,[15] which is an internet-based program that facilitates collaboration between investigators during the screening and selection of studies to be finally included in the review. Prior to screening of studies, investigators shall develop a tool according to the eligibility criteria to guide the selection process.

Screening

Two reviewers (LNA and LV) will independently select studies that meet inclusion criteria. Titles and abstracts shall first be screened following inclusion criteria set a priori for relevance. Full texts of potentially eligible studies shall then be obtained and further screened for relevance using the predetermined tool for final eligibility for inclusion. Any disagreements shall be resolved by consensus. In case there is unclear or ambiguous information on studies, the corresponding authors shall be contacted via email to request clarification. The reasons for exclusion of any studies shall be documented and a flow chart shall be presented of the entire review process.

Data extraction

Two reviewers (LNA and LV) shall independently extract data from the final full texts of eligible studies using a predetermined data extraction sheet. Any disagreements or inconsistencies shall be resolved by consensus.

Data items

We shall extract the following data from included studies: author and year of publication, study setting,

Table 2 Drummond's checklist 1996

Item	Yes	No	Not clear	Not appropriate
Study design				
1. The research question is stated.	☐	☐	☐	
2. The economic importance of the research question is stated.	☐	☐	☐	
3. The viewpoint(s) of the analysis are clearly stated and justified.	☐	☐	☐	
4. The rationale for choosing alternative programmes or interventions compared is stated.	☐	☐	☐	
5. The alternatives being compared are clearly described.	☐	☐	☐	
6. The form of economic evaluation used is stated.	☐	☐	☐	
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	☐	☐	☐	
Data collection				
8. The source(s) of effectiveness estimates used are stated.	☐	☐	☐	
9. Details of the design and results of the effectiveness study are given (if based on a single study).	☐	☐	☐	☐
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	☐	☐	☐	☐
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	☐	☐	☐	
12. Methods to value benefits are stated.	☐	☐	☐	☐
13. Details of the participants from whom valuations were obtained were given.	☐	☐	☐	☐
14. Productivity changes (if included) are reported separately.	☐	☐	☐	☐
15. The relevance of productivity changes to the study question is discussed.	☐	☐	☐	☐
16. Quantities of resource use are reported separately from their unit costs.	☐	☐	☐	
17. Methods for the estimation of quantities and unit costs are described.	☐	☐	☐	
18. Currency and price data are recorded.	☐	☐	☐	
19. Details of currency of price adjustments for inflation or currency conversion are given.	☐	☐	☐	
20. Details of any model used are given.	☐	☐	☐	☐
21. The choice of model used and the key parameters on which it is based are justified.	☐	☐	☐	☐
Analysis and interpretation of results				
22. Time horizon of costs and benefits is stated.	☐	☐	☐	☐
23. The discount rate(s) is stated.	☐	☐	☐	☐
24. The choice of discount rate(s) is justified.	☐	☐	☐	☐
25. An explanation is given if costs and benefits are not discounted.	☐	☐	☐	☐
26. Details of statistical tests and CIs are given for stochastic data.	☐	☐	☐	☐
27. The approach to sensitivity analysis is given.	☐	☐	☐	☐
28. The choice of variables for sensitivity analysis is justified.	☐	☐	☐	☐
29. The ranges over which the variables are varied are justified.	☐	☐	☐	☐
30. Relevant alternatives are compared.	☐	☐	☐	☐
31. Incremental analysis is reported.	☐	☐	☐	☐
32. Major outcomes are presented in a disaggregated as well as aggregated form.	☐	☐	☐	
33. The answer to the study question is given.	☐	☐	☐	
34. Conclusions follow from the data reported.	☐	☐	☐	
35. Conclusions are accompanied by the appropriate caveats.	☐	☐	☐	

geographical region, study design, type of preventive intervention (primary vs secondary; pharmacological vs non-pharmacological), intervention target (individual vs population), time horizon of intervention, effect size (relative risk) associated with intervention, CVD risk factor targeted (single vs multiple), type of economic evaluation or method (CEA, CUA, CBA), modelling technique used, outcome measure (cost per unit of clinical outcome, QALYs or DALYs), economic perspective, uncertainty analysis.

Risk of bias and quality appraisal

The quality of included studies will be rated independently by two reviewers (LNA and LV) using the checklist (table 2) for economic evaluations produced by Drummond.[16] This checklist contains 35 questions (with *yes*, *no* and *not clear* as responses) divided into three sections. The quality rating will then be reported and ranked using the National Institute for Health and Care Excellence (NICE) scale from '++' for good-quality, '+' for moderate-quality, and '−' for low-quality studies, indicating

the lowest to highest risk of bias, respectively.[17] For decision modelling studies, we shall use Philip's checklist for critical appraisal.[18] Discrepancies will be resolved by consensus. Inter-rater agreement on screening, data abstraction and quality assessment will be assessed using Cohen's κ statistic. We plan to present a table showing risk of bias and quality rating of included studies.

Data synthesis

We plan to do an amalgamation of our findings while answering our research questions. In a descriptive fashion, we shall present and discuss the studies overall by geographical regions, according to type (primary vs secondary) of CVD prevention, intervention target, CVD risk factor (single vs multiple) assessed as well as perspective (patient, healthcare provider, societal) for economic evaluation. We shall classify studies according to economic evaluation (CEA, CUA, CBA) performed and also discuss the origin of data used in evaluation (intervention effect size and estimates of effectiveness, estimates of costs, resource usage, epidemiological data). For comparison, included studies shall be summarised (in tabular form) showing currency and year used for analysis, interventions assessed, their costs, incremental cost-effectiveness ratio and cost-effectiveness as reported by the authors in the study.

Reporting this review

The resulting systematic review will be reported according to the PRISMA 2009 statement.[19] Flow diagrams shall be used to demonstrate the study selection process detailing reasons for exclusion at each stage. The search strategy and quality appraisal tool will be published as online supplementary material.

Potential amendments

We do not envisage any further amendments to this protocol. However, in case of any changes, the amendment shall be detailed out in the final report.

Conclusion

Low-income settings are disproportionately affected by the current CVD epidemic, with the highest rates of premature deaths. Most of these countries similarly carry the largest burden of communicable diseases. With their mostly finite financial resources, and competing health needs, there is thus an urgent need for cost-effective strategies in these countries to address the disease burden. This review will update previous efforts by Shrouffi and colleagues and Suhrcke and colleagues by providing current evidence on economic evaluations of interventions for CVD prevention to inform policy and decision makers in LMICs.

Ethics and dissemination

Considering that systematic reviews are based on available published data, this review would therefore not need any formal ethical approval. Results of this systematic review will be disseminated via conference presentations and peer-reviewed publications.

Contributors LNA conceived the paper and wrote the first draft. JLV provided revisions to the manuscript. All authors read and approved the final manuscript. LNA is the guarantor of the review.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data for this manuscript are included in the submission.

REFERENCES

1. Mensah GA. Tackling noncommunicable diseases in Africa: caveat lector. *Health Educ Behav* 2016;43(Suppl 1):7S–13S.
2. Murray CJ, Barber RM, Foreman KJ, *et al*. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. *Lancet* 2015;386:2145–91.
3. World Health Organization (WHO). Cardiovascular disease (CVD) Fact sheet. 2016. (cited 2016 July 18). http://www.who.int/mediacentre/factsheets/fs317/en/
4. Echouffo-Tcheugui JB, Kengne AP, Erqou S, *et al*. High blood pressure in sub-Saharan Africa: the urgent imperative for prevention and control. *J Clin Hypertens (Greenwich)* 2015;17:751–5.
5. Mensah GA, Roth GA, Sampson UK, *et al*. Mortality from cardiovascular diseases in sub-Saharan Africa, 1990–2013: a systematic analysis of data from the Global Burden of Disease Study 2013. *Cardiovasc J Afr* 2015;26(2 Suppl 1):S6–10.
6. Harsha DW, Lin PH, Obarzanek E, *et al*. Dietary approaches to stop hypertension: a summary of study results. DASH collaborative research group. *J Am Diet Assoc* 1999;99(Suppl 8):S35–9.
7. World Health Organization (WHO). Package for essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings. 2010. (cited 2016 Jul 18). http://www.who.int/nmh/publications/essential_ncd_interventions_lr_settings.pdf?ua=1
8. Laxminarayan R, Mills AJ, Breman JG, *et al*. Advancement of global health: key messages from the Disease Control Priorities Project. *Lancet* 2006;367:1193–208.
9. World Health Organization (WHO). *Prevention of cardiovascular disease: guidelines for assessment and management of cardiovascular risk*. Geneva, Switzerland. 2007.
10. Suhrcke M, Boluarte TA, Niessen L. A systematic review of economic evaluations of interventions to tackle cardiovascular disease in low- and middle-income countries. *BMC Public Health* 2012;12:2.
11. Ortegón 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.
12. Shroufi 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.
13. World Bank Country and Lending Groups: Country classification. (cited 2016 October 23). https://datahelpdesk.worldbank.org/knowledgebase/articles/906519.
14. Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
15. Rayyan. The Systematic Reviews web app. (cited 2016 July 18). http://rayyan.qcri.org/.
16. Drummond F. Checklist for economic evaluations. 1996. (cited 2016 July 18). http://handbook.cochrane.org/chapter_15/figure_15_5_a_drummond_checklist_drummond_1996.htm
17. Methods for development of NICE public health guidance. *National Institute for Health and Clinical Excellence*. London. 2006. https://www.nice.org.uk/process/pmg4/chapter/reviewing-the-scientific-evidence
18. Phillips 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:iii—iv,ix-xi, 1-158.
19. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.