Cost effectiveness of interventions to prevent and control diabetes: A systematic review

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Abstract

By: Swati Jha

Background: Increasing prevalence of diabetes globally and thus increasing cost of diabetes calls for cost effective measures to combat and control this silent killer. We conducted a systematic review to gather updated cost-effectiveness data regarding of interventions for preventing or controlling diabetes and assessed their use in countries of all income brackets.

Methods: We systematically searched three electronic databases (Pubmed, Science Direct and Google Scholar) for articles published between May 2010 and June 1st, 2013 that included estimates of costs and incremental cost effectiveness ratio (ICER) of interventions to prevent and control diabetes. Estimates from these articles were standardized o 2010 International dollars using exchange rates and inflation rates. Using purchasing power parity adjusted gross domestic product (GDP) per capita for each country, we calculated ceiling ratios for spending levels considered to be cost saving (>GDP per capita), very cost-effective (1-2 times GDP per capita), cost-effective (2-3 times GDP per capita), and not cost-effective (>3 times GDP per capita. The median ICERs for each intervention were then assessed relative to calculated ceiling ratios for countries representing different country-income groups (high income [United States], upper middle [Mexico], lower middle [India] and low income [Kenya]).

Results: We included 27 manuscripts which focused on: lifestyle intervention for individuals with prediabetes or diabetes, metformin intervention prediabetes and blood pressure and blood cholesterol control for individuals with diabetes.

Lifestyle intervention (median ICER= Int$24,597.5/QALY) are cost saving in USA, very cost-effective in Mexico and not cost-effective in India as well as Kenya. Metformin therapy (median ICER = Int$7,638/QALY) is cost saving in USA and Mexico and very cost-effective in India whereas it is not a cost-effective intervention in Kenya. Glucose monitoring (median ICER= Int$40,938/QALY), hypertension and blood cholesterol controlling interventions (median ICER= Int$40,748/QALY) are considered cost saving in USA, cost-effective in Mexico but not cost-effective in India or Kenya.

Conclusion: Despite adjustments to standardize cost effectiveness data, further research and original studies from low-middle income and low-income countries will provide a far better understanding of cost effectiveness of diabetes interventions in these settings.

Key words: Cost-effectiveness, Diabetes prevention, Diabetes Control, Low-Middle income country, Low income country

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Introduction:

Diabetes is now a global epidemic[1]. The latest global estimates for the number of people with diabetes in 2012 was more than 371 million or 8% of all adult worldwide[2]. Due to the chronic and progressive nature of this disease that leads to disabling complications, the costs of managing diabetes and its morbidity are huge burdens on individuals, communities as well as the country's economy. In a low middle income country like India, median annual estimated cost of diabetes can range from $500 to $1,200 which may sum up to 60% of a household's income[3]. As a result, diabetes threatens economic development of many countries[2]. Diabetes is associated with huge losses of loss of productivity as well as direct and indirect costs. Due to low affordability and poor preventive health care accessibility, economic loss is relatively larger in poorer countries, arising from premature deaths, disability and increased expenditure on medications[4].

The cost of diabetes is steadily rising. The American Diabetes Association (ADA), estimates that the total costs of diagnosed diabetes in the United States (US) have risen to $245 billion in 2012 from $174 billion in 2007, when the cost was last examined[1]. This figure represents a 41 percent increase over a five year period[1]. The ADA report suggests that people with diagnosed diabetes, on average, have medical expenditures approximately 2.3 times higher than what expenditures would be in the absence of diabetes[1]. By 2034, 44.1 million Americans will be suffering from this disease, which is twice the current number and on accounting for inflation, the direct medical cost of treating them will rise from $113 billion annually to $336 billion, triple of the current diabetes-related costs[1].

Despite these daunting estimates, there is now extensive evidence regarding prevention and management interventions for diabetes, offering the opportunity of improving the immediate and long-term quality of life and reducing cost of care for those with prediabetes (people with higher than normal blood sugar who are not yet in diabetes range but at high-risk of converting of diabetes) or diabetes[2]. Early intervention and the avoidance or delay of progression to type 2 diabetes is of enormous benefit to patients in terms of increasing life expectancy and quality of life, and potentially in economic terms for society and health-care payers[2].

Various studies have been conducted in the past to assess cost effectiveness of interventions preventing and controlling diabetes. These studies are focused on a specific intervention, concentrating on a selected population. Also, though more than 80% of diabetes related deaths occur in low-middle income countries and low income countries[3], much of the research is done in high income countries like the USA. In our study, we accumulated data from multiple such studies, thus gathering data from all parts of the world, concerning different populations and interventions, to assess whether interventions to prevent and control diabetes are cost effective in all country-income groups.

In this systematic review we accumulated data regarding cost-effectiveness of diabetes prevention and control interventions from the published literature. We assessed whether these estimates of cost-effectiveness of diabetes interventions from the literature are applicable in four countries selected from four different country-income groups as defined by World Bank. These findings will provide a better understanding whether cost-effectiveness estimates can be transported in different settings and will also guide the implementation priority of different diabetes-interventions in different country income-groups.

Methods:

Search-

We conducted a systematic search of three databases to find data regarding cost effectiveness of interventions for diabetes published between May 1st 2008 and June 1st 2013. The last in-depth cost effectiveness analysis was conducted by Rui Li et al in 2010, which accrued data from 1985 to April 2008[5]. In order to collect recent data, we conducted literature review from May 2008 forwards.

Potential articles were selected from electronic data bases such as PubMed, Science Direct and Google Scholar. These articles were selected based on search conducted using a combination of the following key words: "diabetes", "impaired glucose tolerance"; "prevention", "control"; "cost" or "cost effectiveness" , "cost utility analysis", "cost benefit analysis", "cost of illness", "health care costs"; "quality adjusted life years", "disability adjusted life years".

Quality Assessment-

The quality of articles was tested using a 10-item check list by Drummond et al. This checklist of all quality assessment criteria are provided in *Table* 1. A point was given if the answer to the question was affirmative and a zero for each negative answer. In order for an article to be selected, it must have a score of 7 or higher out of 10. These criteria succinctly test for quality of contextualized matter (eg. whether the research question was well defined and posted in an answerable form), credibility of data (eg. whether cost were measured accurately in appropriate physical units) and usefulness of presented data (eg. whether presentation and discussion of the study results include issues of concern to users) in this systematic review.

Selection:

To be included in our study, articles had to meet the following criteria: The article must be published on or later than May 2008; must discuss cost, cost effectiveness or cost utility of diabetes prevention and control in terms of costs per unit of health; the article must have a counterfactual in order to assess the incremental benefits of an intervention; to ensure only high quality studies were included, we limited our inclusion to studies with a score of 7 or higher on the quality assessment as per the criteria defined by Drummond et al (*Table* 1). We selectively included interventions which are directed at prevention and control of diabetes, thus excluding interventions aimed at screening for diabetes or diabetes related complications (eg. foot checks, eye exams etc).

Lifestyle interventions included exercise and dietary programs. These interventions essentially comprise of sessions which promote weight loss through behavioral modification. Lifestyle programs based on diabetes prevention studies aim for a loss of 7% of body weight. Behavioral modification promotes modification of dietary choices, smoking cessation and adopting light to moderate exercise (for 150 minutes per week). Metformin Interventions include introduction of generic or non-generic metformin once or twice daily amongst individuals with prediabetes. Glucose monitoring interventions involve use of glucometers to self-monitor blood glucose levels while hypertension and blood cholesterol control include standard drug interventions such as beta-blockers, statins.

A single reviewer determined eligibility of studies and performed detailed data extraction to obtain costs and costs per unit health gained estimates from the studies selected.

Selection of Countries and their characteristics:

To test the feasibility of using cost-effectiveness estimates for different settings around the world we selected four countries, one from each country-income group. The World Bank, classifies countries into four country-income groups: High income, Upper-Middle income, Low-Middle income and Low income[6]. The four countries we selected to represent each of the respective income groups were: USA, Mexico, India and Kenya[6].

The countries selected for each income bracket are typical examples of their country-income group and have high burdens of diabetes. *Table* 3 illustrates the characteristics of the countries selected for each income bracket. These data were retrieved from the 2011 International diabetes federation Atlas and federal census reports[2]. The table outlines demographic traits such age distribution, diabetes prevalence and obesity prevalence of all the four countries. Age and weight are known to be high risk factors contributing towards increased risk for diabetes and diabetes related complications. As the population ages, risk of developing diabetes in that population greatly increases[2]. Diabetes prevalence accounts for both Type 1 and type 2 diabetes, these however do not account for impaired glucose tolerance (IGT a form of prediabetes) or unknown cases of diabetes.

In addition to demographic characteristics, we have described economic characteristics of each country. Major economic characteristics have been used as proxy measures in attempt to assess the feasibility of applying cost effectiveness estimates for interventions across the various income category countries. We have used country gross domestic product (GDP), purchasing power parity (PPP), mean exchange rate and inflation rate for cost-adjustment in order to make all cost comparable and to assess whether an intervention would be cost effective in the selected countries. Detailed explanation of how these proxy measures were used is provided in the data analysis section.

Data Analysis:

Analyses were carried out using data from all the studies selected for the review.

The unit of health in this study has been measured largely as quality adjusted life years or QALYs. QALY is a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health[7]. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a zero to one scale). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance[7]. QALYs offer a standard and comparable unit of health to compare cost-effectiveness estimates in different populations.

In economic analyses, cost per QALY is a useful value that is taken into account when deciding whether or not proposed new treatments are effective and incrementally better than the current option. This concept is implemented worldwide and is considered an indicator that supports decision-making regarding coverage or resource allocation for an intervention or treatment regimen or diagnostic test or health policy. To be able to compare the cost effectiveness of two interventions, tools or policies a comparison is made between the proposed intervention, tool or policy and a counterfactual scenario of no intervention, tool or policy or the standard intervention, tool or policy. This comparison generated an incremental cost effectiveness ratio or ICER. ICER compares the differences between the costs and health outcomes of two alternative interventions that compete for the same resources, thus it is be interpreted as additional costs per unit health outcome[8]. ICER is calculated as:

$ICER = (C1 – C2) / (E1 – E2)$[8];

Where C1 is cost of Intervention 1 (proposed);

C2 is cost of intervention 2 (counterfactual);

E1 is effectiveness of intervention 1 (proposed);

E2 is effectiveness of Intervention 2 (counterfactual)

Thus cost effectiveness of each intervention has been evaluated using ICERs reported by studies included in our review.

Cost and ICER standardization

Since this review includes 27 studies from multiple countries, we have attempted to make the ICERs and the costs comparable. Where costs of interventions are described in different currencies, we have used the currency exchange rate, and converted all costs and ICERs to International dollars. The exchange rate system is an indirect measure of a country's currency value, compared to a standard (the International dollar). An average exchange rate for the year the study was conducted has been used for calculation purposes in this study. All ICERs have been calculated and expressed in international dollars per QALY using the Federal Reserve Bank's annual foreign exchange rates and PPP[9]. These calculations have been done assuming unit health such as QALY remains unchanged. These ICERs calculated in international dollars have been used to assess cost effectiveness of an intervention based on ceiling ratios of each country[10].

An international dollar is a hypothetical currency that is used as a means of translating and comparing costs from one country to the other using a common reference point using purchasing power parity or PPP[10]. An international dollar would buy in the cited country a comparable amount of goods and services a US dollar would buy in the United States[10].

PPP is calculated as: $S = P_1/P_2$[10]

Where:

"S" represents exchange rate of currency 1 to currency 2

"P_1" represents the cost of good "x" in currency 1

"P_2" represents the cost of good "x" in currency 2

International dollar is calculated as:

Amount in national currency / PPP exchange rate = international dollar value[9,10]

Expressing values in International dollars thus adjusts the cost such that it compensates for different standards of living, thus allowing better comparisons across the various economic bracket countries. This adjustment assuming that PPP adjustment is adequate for adjusting for differences in costs of drugs or human resources etc. in various economic group countries.

Since most of the studies measure cost effectiveness over a long period of time or have reported findings in different years, adjustment for differences in time value of money is also important. Discount rates are traditionally used to account for costs incurred by ongoing studies whose costs have been projected in the future[11]. However, since we have historical values or costs in the past, we used mean annual inflation rates, of the country where study was conducted, in order to calculate the likely cost of each intervention in the year 2010 in international dollars. Over time as inflation occurs, every dollar will buy a smaller percentage of a basket of goods. The converse would occur if the inflation rate falls. Inflation rate in a country is a measure of the rate at which the general level of prices for goods and services is rising, and, subsequently, purchasing power of a single unit of currency is falling. The inflation rate gets added over and above the principal amount as compound interest. Inclusion of inflation rate will account for growing prices of goods and services over time.

Thus, using conversion rates and inflation rates, ICERs of interventions from various studies were standardized to international dollars per QALY. We calculated a median ICER of each intervention and used this median value to assess cost effectiveness of an intervention using the ceiling ratios.

Ceiling Ratio Calculation

Ceiling ratio can be interpreted as price that is acceptable to pay for a QALY[12]. To assess the benchmark cost-effectiveness estimate for an intervention in a given country, a ceiling ratio is calculated. In other words, it helps us decide, based on that country's wealth, whether an intervention would offer good "value for money". So the ICER is compared with monetary thresholds that are calculated considering the maximum willingness to pay and economic level of the country[12]. An intervention is considered cost effective if the ICER falls below these thresholds. Since each country falls into different income-groups, their willingness to pay varies considerably. Thus an intervention that is considered to be cost effective or cost saving in a high income country may be not cost effective in a low middle income country or low income country. To be able to account for these differences, the ceiling ratio for each individual country is calculated using the country's PPP adjusted GDP per capita. As per World Bank, GDP per capita is gross domestic product divided by midyear population. It is a useful tool when comparing two countries as it shows relative performance of the countries. GDP per capita is a representative of economic growth of the country.

The World Bank regards an intervention to be cost saving when the ICER < 1 times the GDP per capita; intervention is considered very cost-effective when ICER is higher than GDP per capita but less than twice the GDP per capita; intervention is considered cost effective when ICER is higher than twice the GDP per capita but less than three time GDP per capita; An intervention is considered not cost-effective when ICER is higher than three times the GDP per capita. These values for each country have been derived from World Bank database

Using this data at hand, we plotted the adjusted ICERs for each intervention against the estimated ceiling ratios of each country to assess their cost effectiveness.

Results:

Our search of electronic databases yielded 562 potential articles. A total of 84 studies were identified for detailed evaluation. On further evaluation, 19 studies were excluded due to poor quality, 34 were excluded due to foreign language, and 4 of the articles did not report comparable outcomes such as QALY or DALY or LY. 27 of the articles met the full-text inclusion criteria and were included in the final analysis, as depicted in *Figure 1*. Among the studies, there were eight randomized controlled trials, eleven non-randomized controlled studies and eight hypothetical model studies. Characteristics and quality assessment scores of the studies that qualified for this review have been illustrated in *Table* 4. This table enlists the sample population size, mean age, gender distribution, type and duration of intervention and description of counterfactuals comparison groups.

The studies have been disaggregated based on interventions that are focused on prevention of diabetes or prevention of diabetes related complications. These have been further sub-categorized into US and non-US based studies. Our systematic review contains four main intervention categories: twelve articles discussing lifestyle intervention and behavior modification for individuals with prediabetes or diabetes; five articles discussing metformin intervention for individuals with prediabetes; six articles discussing self-monitoring of blood glucose; and four articles discussing blood pressure and blood cholesterol control for individuals with diabetes.

Our systematic review revealed the costs of interventions in various countries which have been described in *Table* 5. The cost of lifestyle intervention in high income countries like USA ranges from $300 to $4,600 per participant per annum. Cost of metformin therapy ranges from $750 to $2,800 per patient per annum. Cost of self-monitoring of blood glucose ranges from $6,000- $48,000 per patient per annum, depending on frequency at which blood glucose is monitored. The average cost of SMBG once daily ranges from $6,000 to $10,000 per patient per annum and cost of SMBG three times per day ranges from $10,000 to $48,000. Cost of hypertension and blood cholesterol control ranges from $890 to $2,200 per patient per annum. These costs vary depending on the intervention setting, components of the intervention and whether generic or non-generic options are used, and cost of living in each country. The costs enlisted in *Table* 5 include direct cost of the intervention as well as overhead costs such as human resources, costs to record maintenance and other intangible costs associated with each intervention.

Characteristics and demographics of the four countries selected for this review have been described in *Table* 3. Diabetes burden in all four countries ranges between 2.7 to 14 percent of the entire population. In countries like Kenya, where reported diabetes prevalence is low, as per WHO, nearly 70-80 percent diabetics are un-diagnosed, thus, true burden is greater than the reported values. Obesity prevalence ranges from 4-37 percent, however these do not account for overweight population.

With the aim of assessing cost effectiveness of these interventions in all four countries, cost-effectiveness thresholds for each country have been calculated using country's GDP per capita. GDP per capita and calculated ceiling ratios have been presented in *Table* 6. Interventions with ICERs, measured as International dollars per QALY are considered cost saving when they fall below Int$49,965/QALY for USA, Int$15,312/QALY for Mexico, Int$3,830/QALY for India and Int$1,802/QALY for Kenya. An intervention is considered very cost effective when the ICERs range from Int$49,965- Int$99,930/QALY for USA, Int$15,312-Int $30,624/QALY for Mexico, Int$3,830-Int $7,660/QALY for India and Int$1,802-Int$3,604/QALY for Kenya. An intervention is considered cost effective when the ICERs range from Int$99,930-Int $149,895/QALY for USA, Int$30,624- Int$45,936/QALY for Mexico, Int$7,660- Int$11,490/QALY for India and Int$3,604- Int$5,406/QALY for Kenya. An intervention is considered not cost effective when the ICERs exceed Int$149,895/QALY for USA, Int$45,936/QALY for Mexico, Int$11,490/QALY for India and Int$5,406/QALY for Kenya.

These thresholds are used to assess if the given intervention is cost effective for a given country or not. Charts one to four illustrate ICERs in international dollars for each intervention (as derived from *Table* 5) and the calculated ceiling ratios for each country (derived from *Table* 6). Cost effectiveness of interventions in these countries was then interpreted by using the calculated ceiling ratios and median ICERs (in international dollars/QALY) derived from the systematic review *(Charts 1-4).*

Thus, at a median ICER of Int$24,597.5/QALY, lifestyle interventions are cost saving in USA, very cost effective in Mexico and not cost effective in India as well as Kenya. At a median ICER of Int$7,638/QALY metformin therapy is cost saving in USA and Mexico and very cost effective in India whereas it is not a cost effective intervention in Kenya. At median ICER of Int$40,938/QALY, glucose monitoring is cost saving in USA, cost effective in Mexico and not cost effective in India or Kenya. Finally, at median ICER of Int$40,748/QALY, hypertension and blood cholesterol control is cost saving in USA, cost effective in Mexico and not cost effective in India or Kenya.

Discussion:

Although multiple studies have been conducted to assess cost effectiveness of interventions to prevent and control diabetes, our systematic review uniquely utilizes these estimates to assess whether cost effectiveness of these interventions is applicable and feasible across various countries classified in different economic groups. As per our estimates, lifestyle interventions, metformin interventions, monitoring blood glucose as well as controlling hypertension and blood cholesterol are all cost saving interventions for high income countries (USA). Lifestyle interventions are very cost effective, metformin interventions are cost saving whereas monitoring blood glucose and interventions controlling hypertension and blood cholesterol are cost effective in upper mid-income countries like Mexico. Only metformin intervention is very cost effective whereas other interventions are not cost-effective in low middle income countries like India. None of these interventions are cost effective in a low income country like Kenya.

Previous cost effectiveness studies (for example Rui Li's cost effectiveness analysis[5]) indicate lifestyle intervention, metformin intervention, SMBG as well as controlling for hypertension and blood cholesterol are cost effective or marginally cost effective interventions. In our review we estimated whether these interventions are also cost effective in countries from other economic groups. Our cost effectiveness estimates are congruent with these studies for high income countries; however, very sparse data exists which assesses cost effectiveness of these interventions in low and middle income, and low income countries. Further research and original studies should focus on assessing short term as well as long term costs, cost effectiveness and benefits achieved through these interventions in low and middle income as well as low income countries. These would greatly aid in further improving our understanding of prevention and control of diabetes in low income settings and may serve as a guiding tool for potential future health investments.

Our study has certain limitations: Cost of delivery is adjusted only recognizing cost of living, we did not account for other variations in cost such as cost of labor. Interventions such as lifestyle modification, dietary or behavioral modification take in account cost of exercise equipment, cost of training and employing professionals and conducting group sessions. According to United States department of labor, man power can be up to 10-15 times cheaper in low and middle income countries when compared with USA. In addition, not all studies included in this review have used generic drugs for drug interventions. Generic drugs offer an average of 30% to 80% savings over their brand-name counterparts and their usage vary across cities let alone countries or globally. The wide variation in cost effectiveness may be attributed to difference in cost of goods, cost of labor and cost of drugs.

Another limitation of this study comes across when accounting for cost effectiveness of self-monitoring of blood glucose. Studies included in this analysis report costs and cost effectiveness of SMBG once daily, twice daily and/or thrice daily. SMBG once daily is a cheaper intervention when compared with twice or thrice daily SMBG. Mean ICER varies from Int$8,481/QALY- Int$78,768/QALY. Our study includes all estimates: once daily, twice daily as well as thrice daily SMBG. Inclusion of all estimates (once daily, twice daily and thrice daily) increase the mean and the median costs and ICERs of SMBG. In our study we used median ICER values to assess cost effectiveness of an intervention. Thus, our estimates for cost effectiveness of SMBG may differ from cost effectiveness estimates for SMBG only once a day or twice a day.

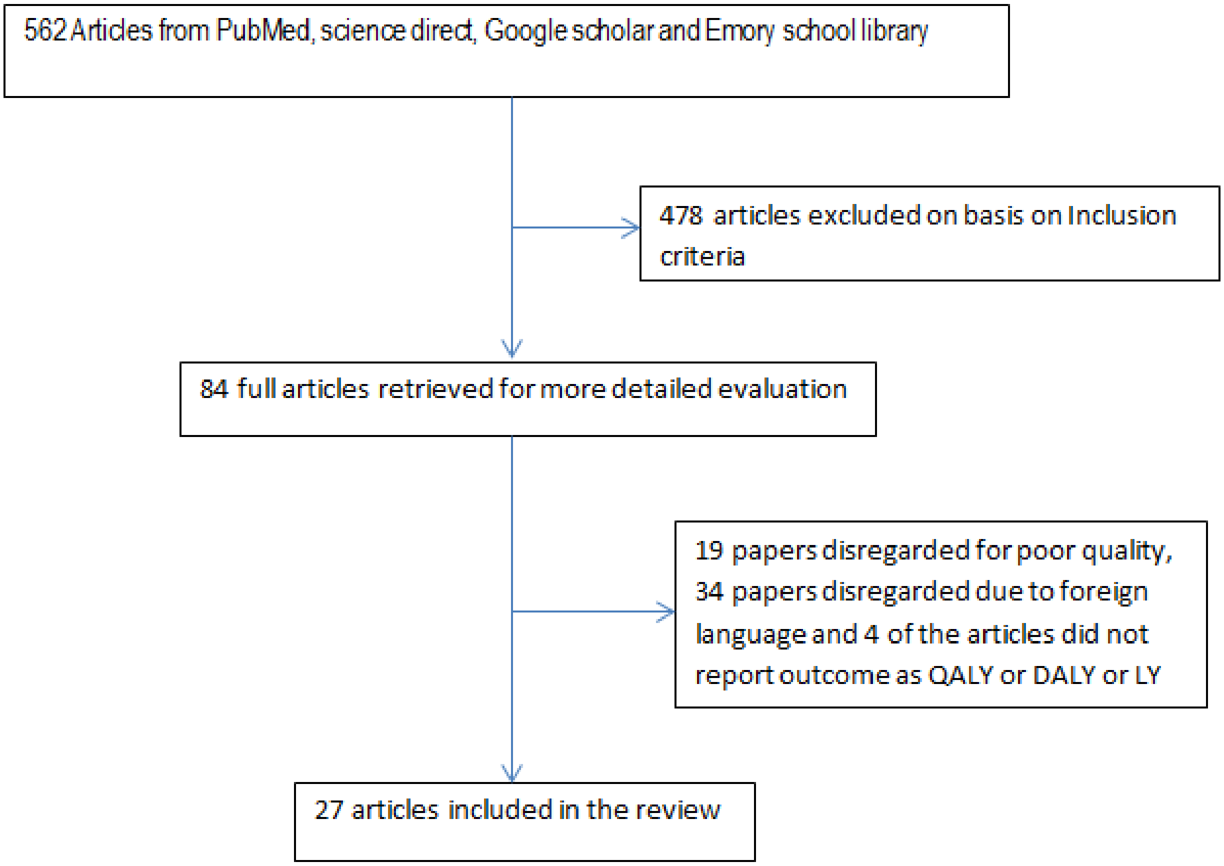
In this study, we assumed the effectiveness of an intervention remains the same and cost of delivery of each intervention does not change across different economic groups. Diabetes may affect a population more due to genetic or epigenetic factors and similarly an intervention may have more effectiveness in a specific group or population, which is not accounted for in our study. In addition, we assumed availability of basic health care facilities and drugs, which was received by the counterfactual groups in each study. Most of these groups received standard care as per ADA guidelines which are fairly high standards for low and middle income countries as well as for low income countries. These countries may not have primary health care clinics which would greatly interfere with our cost effectiveness estimates. This would increase initial cost of capacity building, which is not accounted for in our study. We have also not computed for organizations willing to finance for implementation of these interventions and their competing priorities which may reduce the necessary financial aid.

While calculating ICERs in international dollars, we assumed that QALYs do not vary. This may not be strictly be true since a number of factors are considered when measuring someone's quality of life, in terms of their health. They include, for example, the level of pain the person is in, their mobility and their general mood, which are relative terms and depend on how people value their health. However, various studies indicate minimal differences in QALY calculation across the world[7].

Our study uniquely accumulates data from around the world to understand cost effectiveness of interventions to prevent and control diabetes in countries from various economic groups. These estimates may serve as a guiding tool for potential health care investments. However, in our opinion, we need more data from low and middle income countries and low income countries, since their estimates may differ from high income countries on account of dissimilar infrastructure capacity, availability of drugs and human resources and competing priorities affecting financial aid for implementing the interventions.

Appendix:

Figure depicting selection of articles in this review:



Abbreviations:
DM = diabetes mellitus;
Pre-DM = prediabetes;
IGT = impaired glucose tolerance;
T2DM = type 2 diabetes mellitus;
BMI = body mass index;
RN = registered nurse;
CHE = certified health educator;
NR = not reported;
mths = months;
SMBG: self-monitoring of blood glucose;
CGM: continuous glucose monitoring;
GDP: gross domestic product;
CPI: consumer price index;
PPP: purchase power parity;
QALY: quality adjusted life years;
DALY: disability adjusted life years;
LY: life years;
ICER: incremental cost-effectiveness ratio;
NA: not applicable;
NR = not reported;
ADA: American diabetes association.

Table 1. The 10 item checklist for Quality assessment according to Drummond et al

1 Was a well-defined question posed in an answerable form?
2 Was a comprehensive description of the competing alternatives given?
3 Was the effectiveness of the programs or services established?
4 Were all the important and relevant costs and consequences for each alternative identified?
5 Were costs and consequences measured accurately in appropriate physical units?
6 Were costs and consequences valued credibly?
7 Were costs and consequences adjusted for differential timing?
8 Was an incremental analysis of costs and consequences of alternatives performed?
9 Was allowance made for uncertainty in the establishment of costs and consequences?
10 Did the presentation and discussion of study results include issues of concern to users?

Drummond et al criteria were employed for quality assessment purposes. A score of 7 of higher out of 10 was required for the article to be included in the review. Each point was given for an affirmative answer to each question.

Table 2. Proxy indices

Country	Income Group	GDP (Billions)	GDP per capita (Int$)	CPI (Index point)	Inflation rate (Mean)	PPP Exchange rate	Percent use of generic drugs
USA	High	15,597.0	49,965	111.7	1.6	1.0	78
Mexico	Upper-Middle	1155.3	15,312	124.2	4.2	0.6	17
India	Low-Middle	1857.9	3,830	151.9	12.1	0.4	48.7
Kenya	Low	33.6	1,802	180.1	11.8	0.5	NR

Data source: World Bank, Federal Reserve Bank's annual foreign exchange rates, Trading Economics data bank and International monetary funds;
Data have been derived for the year 2010;
GDP: gross domestic product; CPI: consumer price index; PPP: purchasing power parity
NR= not reported; NA = not applicable; Int $: International dollars (Amount in national currency / PPP exchange rate = Int$ value)

Table 3. Demographic characteristics of selected countries

Country	Population	Age distribution* (%)[13] 15-24yrs	25-54 yrs	55-64yrs	65+yrs	Diabetes prevalence (%)**	Obesity Prevalence (%)***
USA	308 million	13.7	40.2	12.3	13.9	8.3	35.7
Mexico	116.90 million	18.1	40.7	6.9	6.9	14	30.0
India	1.15 billion	18.2	40.0	6.9	5.7	12.1	3.8
Kenya	46.11 million	18.8	32.4	3.6	2.7	2.7	4.2

*Age distribution refers to percent adult population in the country in each age group category; yrs = years

**Diabetes prevalence accounts for known cases of diabetics, these do not account for IGT or unknown cases of Diabetes, thus, true burden of diabetes might be higher.

***Obesity suggests percentage of population with BMI≥30 kg/m². This does not account for overweight population (BMI 25-29.9 kg/m²).

Data has been retrieved from International diabetes federation and census reports

Table 4. Characteristics of Articles selected for the study

First Author's name	Study population	Setting	Mean Age	Gender (% Males)	Duration of study (Projected timeline)	Intervention	Counterfactual	Quality assessment Score
Diabetes Preventing Interventions								
USA based studies								
Zhuo X[14]	12.6 million	Community based	54 years	NR	1 yr (25 years)	Exercise, dietary and behavior modification	Standard of care	8
Herman W.H[15]	3,234	Community and home based	NR	32	1 yr (10 years)	Exercise and dietary modification with metformin	Only metformin intervention and placebo	7
DPP research group[16]	3,234	Community and home	51years	32	3yrs (10 years)	Exercise and dietary modification with metformin	Drug intervention	8
Non USA Based Study								
Wier M.F[17]	622	Community	43.5 years	41.6	24 months	Exercise and dietary modification	Standard of care	7
Irvine L[18]	660	Community and home based	58.9 years	52.5	13 months	Exercise and dietary modification	Standard of care	8
Diabetes Controlling Interventions								
USA based studies								

First Author's name	Study population	Setting	Mean Age	Gender (% Males)	Duration of study (Projected timeline)	Intervention	Counterfactual	Quality assessment Score
Anderson J.M.[19]	all people aged 65 years and older with prediabetes	Community based	67.2 years	NR	20 years	Exercise and dietary modification with metformin	No lifestyle modification	9
Brown H.S.[20]	6,551	Community based	52.06 years	NR	3yrs (5,10 and 15 years)	Exercise and dietary modification	Standard of care	9
McQueen R.B.[21]	Population level	Home based	40 years	NR	1 year (33 years)	CGM and SMBG	No CGM	8
Sandra L, Minshall M[22]	8,242	Home based	62.8 years	58	1yr (40 years)	SMBG	No SMBG	7
Ly D.[23]	3,000	Community based	25-65 years	NR	1yr (3 and 5 years)	Diabetes and Hypertension education	Standard of care	9
Brownson C.A.[24]	1,273	Clinical and Home	54.3 years	NR	3yrs (Lifetime)	Diabetes education	Standard of care	8
Sorensen S.V[25]	20,938	Home based	60 years	45	1 year (20 years)	Statin Therapy	Standard of care	8
Non-USA Based Studies								
Coyle D.[26]	3,642 patients	Community based	54.2 years	65.10	1 year (6 and 20 years)	Exercise interventions	No intervention	9
Palmer A.J.[27]	8,707	Community based	50.6 years	32.20	1 year (lifetime)	Exercise and dietary modification with metformin	No intervention	7

First Author's name	Study population	Setting	Mean Age	Gender (% Males)	Duration of study (Projected	Intervention	Counterfactual	Quality assessment Score
Bertram M.Y[28]	8,000	Community and home	NR	NR	1year (Lifetime)	Exercise and metformin	Compared with each other	7
Drabik A.[29]	86,968	Clinical based	66 years	47	4 yrs (30 years)	Diabetes education	Standard care	8
Xie X[14]	Overweight and diabetic population of Beijing	Home based	25-65 years	NR	1 year (11 years)	Intensive glycemic control	Standard care	7
Cameron C.[30]	3,642	Home based	61 years	48.9	1 yr (40 years)	SMBG	No SMBG	8
Sandra L. T[31]	2,270	Home Based	60 years	56	40-year	SMBG	No SMBG	8
Simon J[32]	453	Home based	59 years	NR	12 months	SMBG	No SMBG	9
Pollocka R.F[33]	1,000	Home based	62.8 years	57.5%	30 years	SMBG	No SMBG	9
Lafumaa A.[34]	2,800	Home based	63years	68	3.9 years	Statin therapy	Placebo tablet	8
L. Annemans[35]	2,838	Home based	64 years	49.1	5 years and 25 years	Statin therapy	Placebo tablet	7

NR= not reported;
Standard of care = current care guidelines as per American Diabetes Association;
SMBG: self-monitoring of blood glucose; CGM: continuous glucose monitoring; home based, community based and clinic based settings have been defined under definitions section.

Table 5. Cost components of interventions

First Author's name (Year at which cost is calculated)	Mean cost per person per year in Intervention arm	Mean cost per person per year in control arm	Mean Exchange rate (same year)	Cost in USD (same year)	Cost in 2010 USD	Unit Health Gained (ΔQALY)	ICER in currency/per QALY (value in 2010 Int$)
Diabetes Preventing Interventions							
USA based studies							
Zhuo X[14] (2011)	$300 for year 1 $150 for year 2 $50 thereafter	NR	NA	NA	$300 for year 1 $150 for year 2 $50 thereafter	0.3	NR
Herman W.H[15] (2010)	Lifestyle: $4,810 Metformin: $2,934	Placebo: $768	NA	Lifestyle: $4,810 Metformin: $2,934	Lifestyle: $4,810 Metformin: $2,934	Lifestyle vs placebo: 0.2; Metformin vs placebo:0.1; Lifestyle vs metformin: 0.1	Lifestyle vs placebo: $3235 (3235); Metformin vs placebo: CS*; Lifestyle vs metformin: $25,644 (25,644)
DPP research group[16] (2010)	Lifestyle: $4,601; metformin: $2,300	$2,823.6	NA	Lifestyle: $4,601 Metformin: $2,300	Lifestyle – $4,601 Metformin- $2,300	Lifestyle vs placebo: 0.1 Metformin vs placebo: 0.02 Lifestyle vs metformin: 0.1	Lifestyle vs placebo: $21,743 (21,743); Metformin vs placebo: CS*; Lifestyle vs metformin: $7,638 (7,638)
Non-USA based study							
Wier M F[17] (2008)	€2,356.5	€1,923.5	0.7	$2,705.4	$2,813.6	0.02	€50,273 (48,485.3)
Irvine L[18] (2009)	£574	£324.9	0.7	$874.0	$900.3	0.03	£67,184 (62,908.2)
Diabetes controlling Interventions							
USA based studies							

First Author's name (Year at which cost is calculated)	Mean cost per person per year in Intervention arm	Mean cost per person per year in control arm	Mean Exchange rate (same	Cost in USD (same year)	Cost in 2010 USD	Unit Health Gained (ΔQALY)	ICER in currency/per QALY (value in 2010 Int$)
Anderson J.M[19] (2007)	$9,713	$5,694	NA	$9,713	$10,613.7	0.4	NR
Brown S.H[20] 2010)	$143.6	NR	NA	$143.6	$143.6	394.9 (over 20 years)	$33,319 (33,319) (over 20 years)
McQueen R.B[21] (2007)	$494,135 (total lifetime cost/person)	$470,583 (total lifetime cost/person)	NA	$494,135 (total lifetime cost/person)	$539,955 (total lifetime cost/person)	0.5	$45,033 (49208.7)
Sandra L T, Minshall M[22] (2006)	OD 87,408 TID 88,761 (total lifetime cost/person)	No SMBG: 86,600 (total lifetime cost/person)	NA	OD 87,408 TID 88,761 (total lifetime cost/person)	OD: 98378.5 TID: 99901.3 (total lifetime cost/person)	QALY: No SMBG: 4.8 OD: 4.9 TID: 5.2	No SMBG vs OD: $7,856 (8,841.9); No SMBG vs TID: $6,601 (7,429.5)
Ly D[23] (2007)	$3,090	$3,337.6	NA	$3,090.0	$3,376.5	QALY HPM: 9 Control: 9	NR
Brownson C.[24] (2009)	$866 (For year 1 and 2. $433 thereafter)	Increased cost in control group: $3,385 over	NA	$866	$891.9	0.3	$39,563 (40,749.9)
Sorensen S. V[25] (2007)	$1,150	$131	NA	$1,150	1,294.3	0.2	$50,315 (54,980.5)
Non-USA based studies							
Coyle D[26] (2008)	Can$ 449 (lifestyle intervention); Can$ 250 (Group sessions)	Lifetime cost: $31,075	1.2	$ 404.9 (lifestyle intervention); $225.4 (Group sessions)	$429.52 (lifestyle intervention); $239.14 (Group sessions)	0.2	NR

First Author's name (Year at which cost is calculated)	Mean cost per person per year in Intervention arm	Mean cost per person per year in control arm	Mean Exchange rate (same year)	Cost in USD (same year)	Cost in 2010 USD	Unit Health Gained (ΔQALY)	ICER in currency/per QALY (value in 2010 Int$)
Palmer A.J[27] (2009)	Metformin- AUD 997.5 (yr 1) AUD 897.7 thereafter; lifestyle: AUD 154.1 (yr1) AUD 74.5 thereafter	Yr 1: AUD 154.0; Yr 2: AUD 74.5; Yr 3: AUD 74.5; total: AUD 303.1	1.3	Metformin- $750.0 (yr 1) $674.9 thereafter; lifestyle: $115.8 (yr1) $56.0 thereafter	Metformin-$772.5 (yr 1) $695.2 thereafter; lifestyle:$119.0 (yr1) $57.7 thereafter	ΔQALY: Metformin vs control: 0.1; lifestyle change vs control: 0.4	metformin vs control: AUD10,142 (6964.7); Lifestyle vs control: cost and lifesaving*
Bertram M.Y[28] (2003)	Diet plus exercise: AUD391; Exercise: AUD285; Diet: AUD220; Metformin: AUD258	NR	1.5	Diet plus exercise: $258.06; Exercise: $188; Diet: $145.2; Metformin:	Diet plus exercise: $317.4; Exercise: $231.2; Diet: $178.3; Metformin:$209.4	DALYs averted- Diet plus exercise:4,730; Exercise:4,000; Diet:2,290; Metformin: 4,290;	AUD/DALY Diet plus exercise:23,000 (18,858.1); Exercise: 30,000 (24597.5); Diet:38,000 (31,156.7); Metformin: 22,000 (18,038.2)
Drabik A.[29] (2003)	€3,318.2	€3,569.6	0.9	$3716.33	$4570.62	1 LYG in 18 years	€74 per patient per LYG (91.0)
Xie X[14] (2008)	RMB 4534	RMB 740	7.9	$572.33	$625.4	0.25	RMB 126,600 (191,871.3)
Cameron C[30] (2008)	Can$30,708	Can$27,997	1.2	$27,689.8	$29,376.1	0.02	Can$ 113,643 (100,469.89)
Sandra L T.[31] (2008)	No SMBG: Can$30,085; 1.29/day: Can$32,536 <1/day: Can$31,479 1-2/day: Can$32,528	Can$ 30,085	1.2	No SMBG: $27,128 1.29/day: $29,282.4 <1/day: $28,331 1-2/day: $29275.2 >2/day:	No SMBG: $28,780.1 1.29/day: $31,065.7 <1/day: $30,056.4 1-2/day: $31,058 >2/day: $34,689.2	No SMBG: 0.04; 1.29/day: 0.03; <1/day: 0.04; 1-2/day: 0.04; >2/day: 0.07	No SMBG: Can63,664 (56,284.3); 1.29/day: Can 46,306 (40,938.4); <1/day: Can 36,799 (32,533.5); 1-2/day: Can 61,698 (54,546.4); >2/day: Can89,096 (78,768.9)

First Author's name (Year at which cost is calculated)	Mean cost per person per year in Intervention arm	Mean cost per person per year in control arm	Mean Exchange rate (same year)	Cost in USD (same year)	Cost in 2010 USD	Unit Health Gained (ΔQALY)	ICER in currency/per QALY (value in 2010 Int$)
Simon J[32] (2007)	Less intensive SMBG: £940; More intensive SMBG: £868	£268	0.8	Less intensive: 1,128; More intensive: 1,041.6	Less intensive SMBG: 1,307.6; More intensive SMBG: 1,207.5	No SMBG 0.00; Less intensive -0.01; More intensive -0.04	NR
Pollocka R.F[33] (2006)	OD CHF2,479.4 BD CHF2,962.5 TID CHF3,445.5	CHF1,848.8	0.8	OD $3,099.2 BD $3,703.1 TID $4,306.9	OD $3,488.2 BD $4,167.9 TID $4,847.5	OD: 0.06; BD: 0.13; TID:0.17	OD: CHF 9,177 (6,885.8); BD: CHF 12,928 (9700.4); TID: CHF 17,342 (13,012.4)
Lafumaa A.[34] (2007)	€1,801	€1,636	0.8	2,161.2	2,361.60	0.067	€3,862/LY (3,836.5)
Annemans L.[35] (2009)	5 year: 1,598 per patient; 25 years: 9,164 per patient	5 year: 1,209 per patient; 25 years: 9,359 per patient	0.7	5 year: 2,237.2 per patient; 25 years: 12,829.4 per	5 year: 1,645.9 per patient; 25 years: 9,438.9 per patient	0.02	€16,681 (15619.5)

NR= nor reported; CS= cost saving; NA= not applicable;
QALY= quality adjusted life years; LY = life years; DALY= disability adjusted life years; ΔQALY = Difference in QALY between intervention and control group;
USD: US dollars; Can $: Canadian dollar; AUD: Australian dollar; CHF: Francs; RMB: Renminbi; Int$: International dollars; OD: once daily; BD: Bis die or twice daily; TID: ter in die or thrice daily.

Table 6. Ceiling ratio of Cost effectiveness for each country (in International dollars)

Countries	GDP per Capita* (Int$)	Cost saving (ICER in Int$/QALY)	Very Cost-effective (ICER in Int$/QALY)	Cost- effective (ICER in Int$/QALY)	Not cost-effective (ICER in Int$/QALY)
USA	49,965	<49,965	49,965-99,930	99,930-149,895	>149,895
Mexico	15,312	<15,312	15,312-30,624	30,624-45,936	>45,936
India	3,830	<3,830	3,830-7,660	7,660-11,490	>11,490
Kenya	1,802	<1,802	1,802-3,604	3,604-5,406	>5,406

*GDP per capita source: World Bank Database; Data derived for year 2010.

GDP: Gross Domestic Product

Cost Saving: ICER < GDP per capita; Very Cost-effective:1*GDP per capita ≥ ICER > 2*GDP per capita; Cost effective: 2*GDP per capita≥ ICER > 3*GDP per capita; Not cost-effective: ICER >3*GDP per capita.

Source: http://www.who.int/choice/costs/CER_thresholds/en/

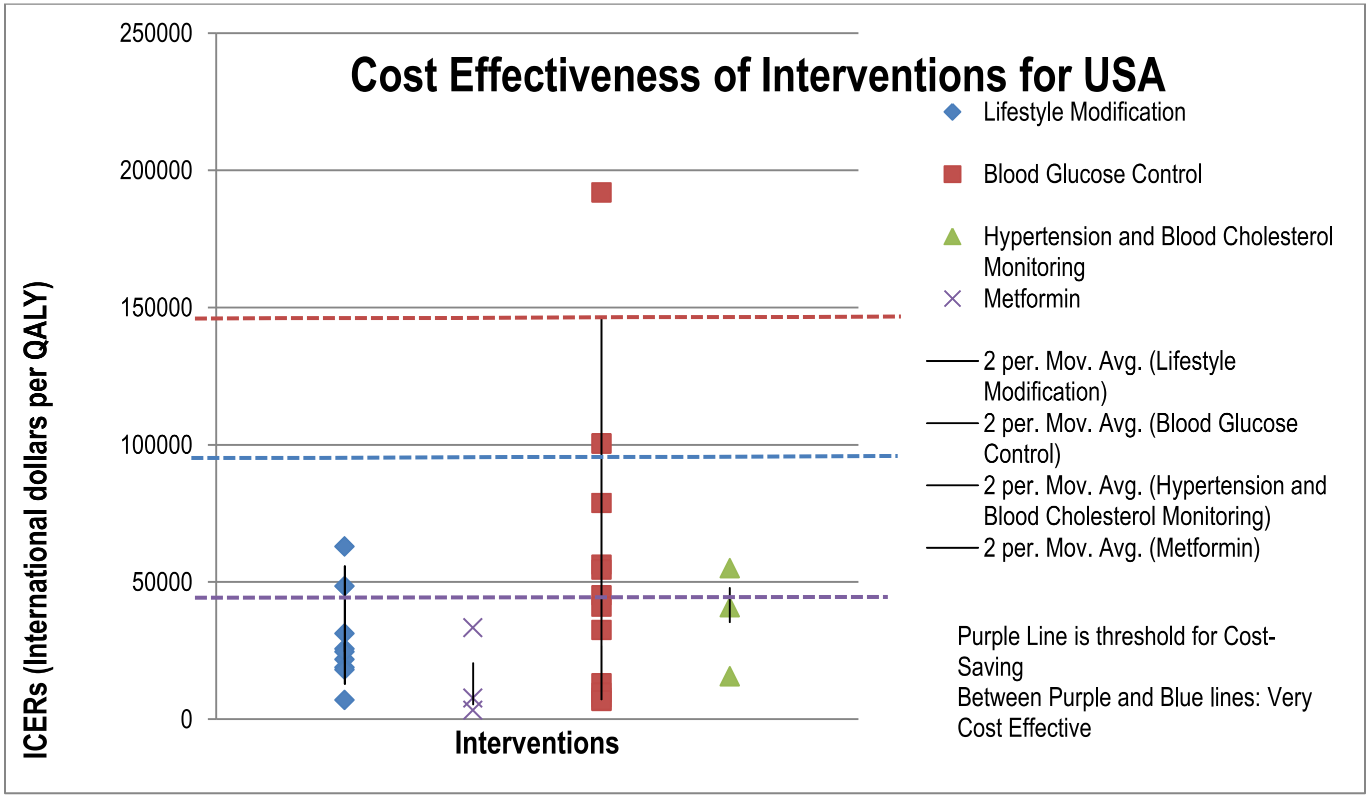
Table 7. Interpretation and Application of Ceiling Ratios

Intervention	ICER (Median)*	USA	Mexico	India	Kenya
Lifestyle Intervention	24,597.5	Cost Saving	Very Cost Effective	Not Cost Effective	Not Cost Effective
Metformin	7,638	Cost Saving	Cost Saving	Very Cost Effective	Not Cost Effective
Glucose Monitoring	40,938	Cost Saving	Cost Effective	Not Cost Effective	Not Cost Effective
Hypertension and Blood Cholesterol control	40,749	Cost Saving	Cost Effective	Not Cost Effective	Not Cost Effective

*ICER: Incremental Cost Effectiveness Ratio, expressed as International$/QALY
Cost Saving: ICER < GDP per capita; Very Cost-effective:1*GDP per capita ≥ ICER > 2*GDP per capita;
Cost effective: 2*GDP per capita≥ ICER > 3*GDP per capita; Not cost-effective: ICER >3*GDP per capita.
Data derived for year 2010
Source: http://www.who.int/choice/costs/CER_thresholds/en/

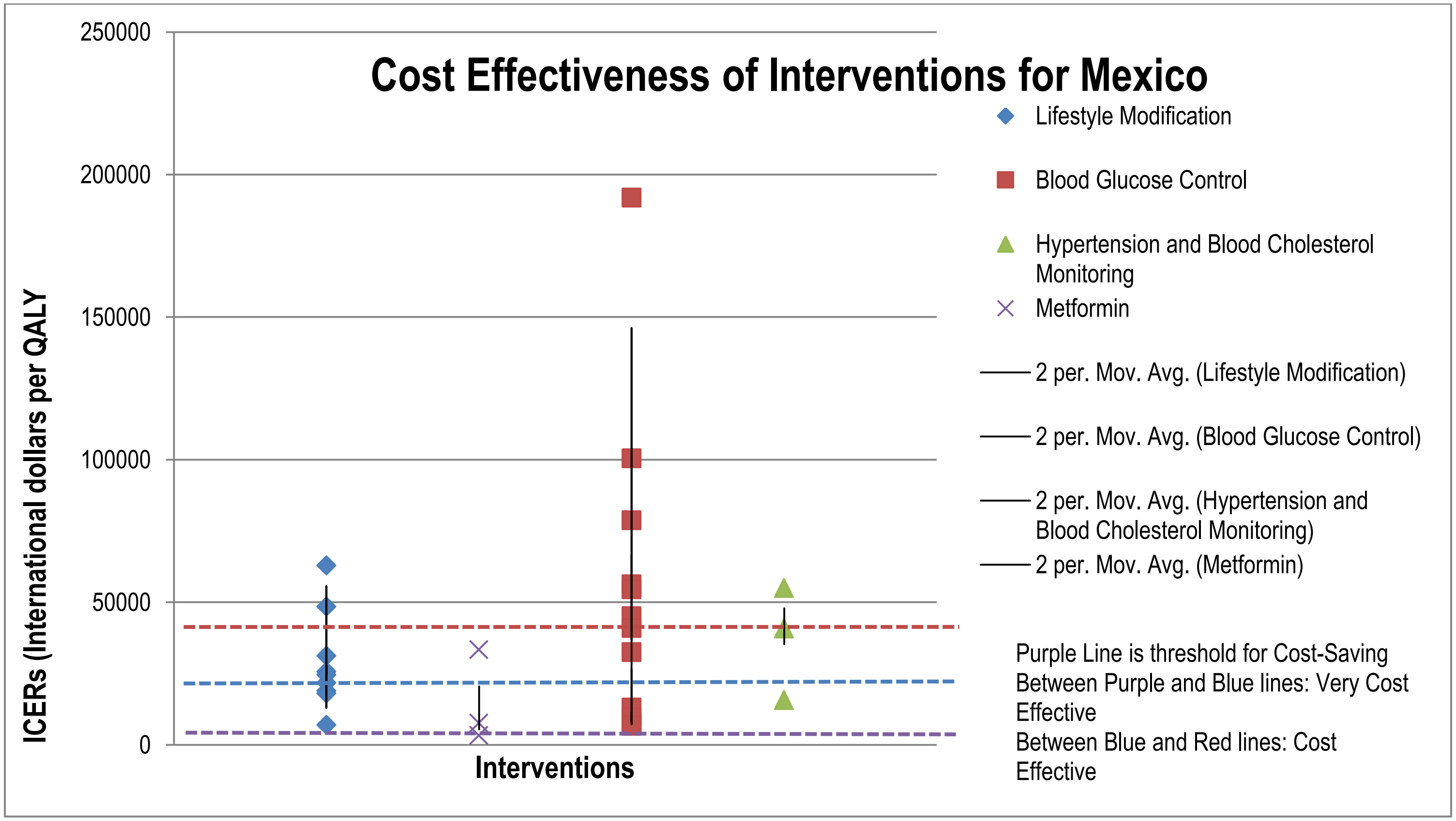
Charts:

Chart 1: Cost effectiveness of Interventions for USA



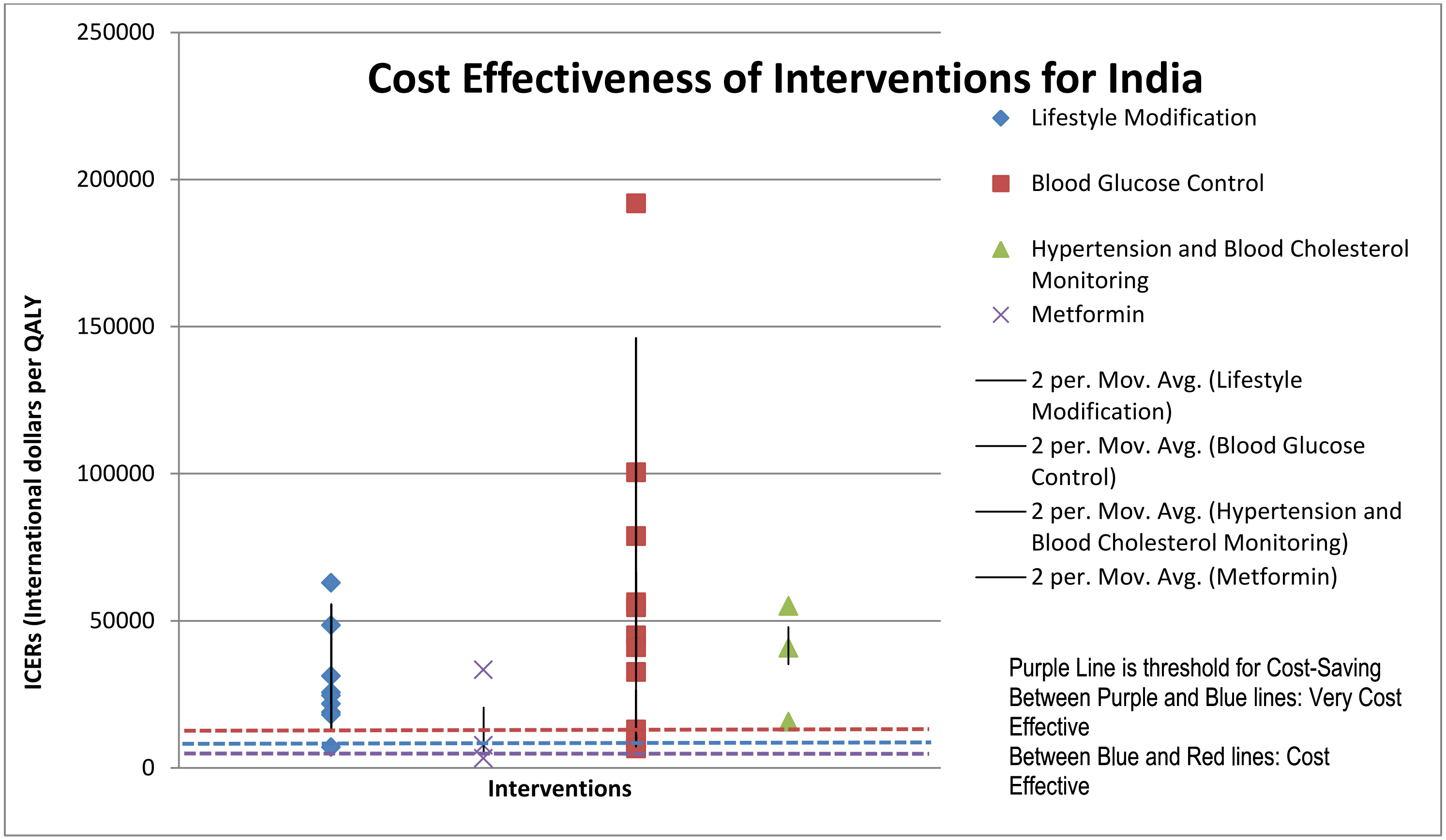
ICER: Incremental cost effectiveness Ratio, have been expressed in International dollar amounts (2010)
Purple line demarks threshold for ICER value to be cost saving for USA. Intervention is cost saving if ICER < GDP per capita i.e. ICER < Int$49,965/QALY
ICER values between purple and blue lines indicate intervention is very cost effective for USA. Intervention is very cost effective when 1*GDP per capita ≥ ICER > 2*GDP per capita, i.e. ICER is between Int$49,965/QALY-Int$99,930/QALY;
ICER values between blue and red lines indicate intervention is cost effective for USA. Intervention is very cost effective when 2*GDP per capita ≥ ICER > 3*GDP per capita, i.e. ICER is between Int$99,930/QALY-Int$149,895/QALY;
Red line demarks upper threshold for ICER value to be cost effective for USA. Intervention is considered to be not cost effective if ICER > 3*GDP per capita i.e. ICER >Int$149,895/QALY

Chart 2: Cost effectiveness of Interventions for Mexico



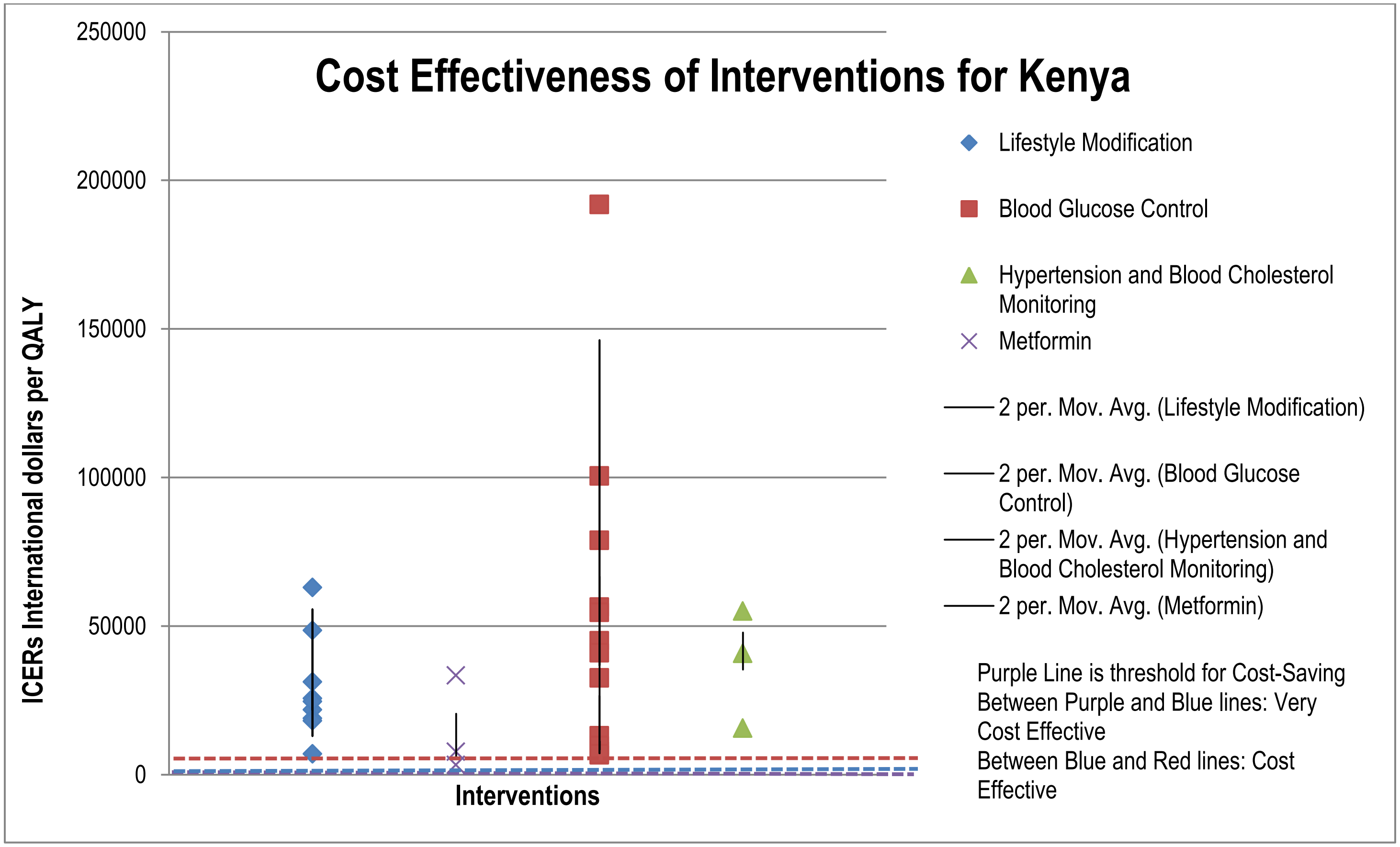
ICER: Incremental cost effectiveness Ratio, have been expressed in International dollar amounts (2010)
Purple line demarks threshold for ICER value to be cost saving for Mexico. Intervention is cost saving if ICER < GDP per capita i.e. ICER < <15,312
ICER values between purple and blue lines indicate intervention is very cost effective for Mexico. Intervention is very cost effective when 1*GDP per capita ≥ ICER > 2*GDP per capita, i.e. ICER is between 15,312-30,624;
ICER values between blue and red lines indicate intervention is cost effective for Mexico. Intervention is very cost effective when 2*GDP per capita ≥ ICER > 3*GDP per capita, i.e. ICER is between 30,624-45,936;
Red line demarks upper threshold for ICER value to be cost effective for Mexico. Intervention is considered to be not cost effective if ICER > 3*GDP per capita i.e. ICER > 45,936

Chart 3: Cost effectiveness of Interventions for India



ICER: Incremental cost effectiveness Ratio, have been expressed in International dollar amounts (2010)
Purple line demarks threshold for ICER value to be cost saving for India. Intervention is cost saving if ICER < GDP per capita i.e. ICER < Int$3,830/QALY
ICER values between purple and blue lines indicate intervention is very cost effective for India. Intervention is very cost effective when 1*GDP per capita ≥ ICER > 2*GDP per capita, i.e. ICER is between Int$3,830/QALY – Int$7,660/QALY;
ICER values between blue and red lines indicate intervention is cost effective for India. Intervention is very cost effective when 2*GDP per capita ≥ ICER > 3*GDP per capita, i.e. ICER is between Int$7,660V- Int$11,490/QALY;
Red line demarks upper threshold for ICER value to be cost effective for India. Intervention is considered to be not cost effective if ICER > 3*GDP per capita i.e. ICER > Int$11,490/QALY

Chart 4: Cost effectiveness of Interventions for Kenya



ICER: Incremental cost effectiveness Ratio, have been expressed in International dollar amounts (2010)
Purple line demarks threshold for ICER value to be cost saving for Kenya. Intervention is cost saving if ICER < GDP per capita i.e. ICER < Int$1,802/QALY
ICER values between purple and blue lines indicate intervention is very cost effective for Kenya. Intervention is very cost effective when 1*GDP per capita ≥ ICER > 2*GDP per capita, i.e. ICER is between Int$1,802V- Int$3,604/QALY;
ICER values between blue and red lines indicate intervention is cost effective for Kenya. Intervention is very cost effective when 2*GDP per capita ≥ ICER > 3*GDP per capita, i.e. ICER is between Int$3,604/QALY – Int$5,406/QALY;
Red line demarks upper threshold for ICER value to be cost effective for Kenya. Intervention is considered to be not cost effective if ICER > 3*GDP per capita i.e. ICER > Int$5,406/QALY

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