Cost-effectiveness Analysis of Diabetic care in India

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A dissertation submitted for the partial fulfilment of BS-MS dual degree in Science

Under the guidance of
Prof. Sarang Deo, ISB

Indian Institute of Science Education and Research Mohali
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Certificate of Examination

This is to certify that the dissertation titled "Cost-effectiveness Analysis of Diabetic care in India" submitted by Mr. Saswat Pattnaik (Reg. No. MS16109) for the partial fulfilment of BS-MS dual degree programme of the Institute, has been examined by the thesis committee duly appointed by the Institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

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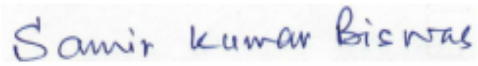

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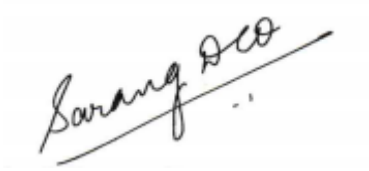

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Dated: May 30, 2021

Declaration

The work presented in this dissertation has been carried out by me under the guidance of Prof. Sarang Deo at the Indian Institute of Science Education and Research Mohali. This work has not been submitted in part or in full for a degree, a diploma, or a fellowship to any other university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgement of collaborative research and discussions. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

Saswat Pattnaik
(Candidate)
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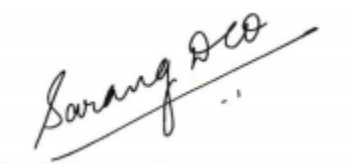
In my capacity as the supervisor of the candidate's project work, I certify that the above statements by the candidate are true to the best of my knowledge.



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I would like to express my gratitude to my parents and close friends who have been dependable pillars of strength for me throughout my time here.

— Saswat Pattnaik

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Notations

- ACCORD = Action for Community Organisation, Rehabilitation and Development
- aHR = Adjusted Hazard Ratio
- CEA = Cost Effectiveness Analysis
- CL = Confidence Level
- GNI = Gross National Income
- HbA1c = Haemoglobin A 1c
- ICER = Incremental Cost Effectiveness Ratio
- MI = Myocardial Infarction
- NCD = Non Communicable Disease
- RECODe = Risk Equations for Complications of type 2 Diabetes
- T2DM = Type 2 Diabetes Mellitus
- UKPDS OM2 = United Kingdom Prospective Diabetes Study Outcome Model 2

Contents

Abstract

In India, diabetes represents one of the major contributors to healthcare expenditure and overall disease burden. Being a lower-middle-income country, in India, this health condition has an immense effect on the average Indian population. The objective of this research work was to conduct a cost-effectiveness analysis of type 2 diabetes mellitus (T2DM) treatment using medications compared to a hypothetical 'no treatment' strategy in India using microsimulation. We simulated the sample based on the Indian demography, and the risks of macrovascular complications were calculated for them using previously validated RECODe equations. The average cost of hospitalization and medication incurred per patient receiving medications was $3054.93 {95% CL, ($3043.25 - $3066.61)}, whereas for those who were deprived of any medication was $20.43 {95% CL, ($19.65 - $21.23)}. The DALYs incurred per patient in both of these strategies were 17.15 DALYs {95% CL, (16.98 - 17.31)} and 20.97 DALYs {95% CL, (20.75 - 21.15)} respectively. From these results, the incremental cost-effectiveness ratio was calculated to be $795.32/ DALY averted. This ICER implies that the use of medication strategy is highly cost-effective as it lies below half of the per-capita GDP of India. The present study indicates the socio-economic value of diabetes intervention strategy in India. On a broader spectrum, this positively favors a path for resource allocation and health policy update in India based on economic evaluation at its core.

Chapter 1

Introduction

1.1 Non-communicable Diseases

Non-communicable disease is a health condition that is caused due to factors like physiology, genetics, lifestyle, environment, or a combination of all of them that can not be spread from person to person. It is non-infectious and lasts for an extended period. Unhealthy dietary intake, lack of physical activity, excess smoking, and alcohol consumption can be considered some of the risk factors associated with NCDs. 71% of all mortality cases worldwide are reported to be caused because of NCDs.[29] However, low or middle-income countries are affected the most, like around 75% of all NCD deaths and 82% of all 16 million premature deaths (before 70 years of age) worldwide occur in these countries.[28] As per the current fiscal year 2021, low-income countries are defined as those with a per capita GNI (gross national income) of $1,035 or less. For lower-middle-income countries, this number was 1,036 and $4,045. According to the World Bank, India is a lower-middle-income country in its latest classification with a per capita GNI of $2,120 for the year 2019.[11] NCDs are responsible for almost 60% (5.87 million) of all deaths in India.[18]

This highlights the gravity of the situation and demands urgent health interventions by the state, including policy changes, educational programs, health campaigns, using a drug/treatment, or combining these factors. The goal is to evaluate, revamp, sustain, boost and reform health as a whole.[7] Before or after a medical issue, effective healthcare interventions ensure scientific management of disease privately and publicly. Though every

intervention available at disposal is desired to be implemented, each intervention has an associated cost which means that a carefully calculated "Resource allocation" has to be made since the resources are limited. The resources used for one intervention might force us to forego another intervention and its benefits.[21] Thus, an intervention has to be chosen that provides the most value for the available resources. This is done by cost-effectiveness analysis which assesses different interventions in terms of cost per year of healthy life added. More and more studies are focusing on cost-effectiveness analysis of healthcare interventions in low and middle-income countries in recent years. However, there have not been many studies showing the cost-effectiveness of diabetic care in India.

1.2 Cost-effectiveness Analysis (CEA)

CEA is a way to examine both the costs and health outcomes of one or more interventions. In this, the incremental cost per standardized unit of health gain is measured and analyzed. This could be the added cost per death averted.[12] The intervention to be assessed is compared with another identified course of action which may be a standard practice like visiting doctors or a relatively less expensive or less intensive intervention. It is also important to note that the cost-effectiveness ratio, the cost per standardized unit of health gain, is the inverse of health gain per increment of spending. If we get more added health per increment of the expenditure, then we are spending less per added unit of health. The critical outcome metric for CEA is the incremental cost-effectiveness ratio: the ICER. This is the difference in costs divided by the difference in health outcomes. The differences are between two possible actions (say A and B).

Thus, $ICER = \frac{Cost\ A - Cost\ B}{Life\ Years\ A - Life\ Years\ B}$.

The ICER numerator is the net cost, and this is different from the cost of implementation. Net costs are the program costs adjusted for the resulting changes in medical costs. Medical costs can fall if the disease is averted with a prevention strategy. We can save the cost of treatment for a health condition if that condition is prevented. On the other hand, sometimes intervention can increase healthcare costs as well. Added or earlier care will increase the healthcare costs. Putting all these factors together and comparing the program costs to the

health care costs, we arrive at the difference between the net cost of A (the cost of the program adjusted for induced costs or savings) and the same type of net cost for B which is the numerator. This is also referred to as incremental cost.

The denominator is the difference between options A and B in terms of several possible health measures. In one cost-effectiveness report, multiple outcomes can be examined. It is essential to present the program's effectiveness in terms of results that people can understand, particularly when given to clinicians and other economists. For example, statements like '$1000 to avert a new infection or $500 to prevent a death or $50 per added life year' make sense to all the people associated with the healthcare services. However, there are limits to what kind of comparisons can be made when natural health events (e.g., new infections, deaths averted, life-years, or disease episodes) are used. It's hard to compare a measles episode prevented to an added life year. This is why metrics like DALYs and QALYs are used. DALYS (Disability-adjusted Life Years) is a measure of disease burden. By definition, they are undesirable, and we want to avert DALYs.

On the other hand, QALYs are a measure of health status, and therefore they are desirable and want to gain them. If we look only at the life years, we capture only the reduced mortality benefits of intervening, which is not enough to capture all the effects of the disease. So, we go an extra step and find DALYs and QALYs, which also capture the impact of reducing morbidity.

When we put the numerator and the denominator together, we get the ICER, the incremental costs divided by the DALYs averted. It compares an intervention to another intervention (or the status quo) by estimating how much it costs to gain a unit of a health outcome, i.e., a life-year gained or death prevented.

CEA could be divided into three parts, i.e., analyzing the cost, health outcomes and thereby calculating ICER (Incremental cost-effectiveness ratio). For the convenience of our analysis, we can proceed by answering specific questions to all three parts:

1: Cost: What is the cost of delivering screening/management of diabetes per patient compared with no screening/ management?

2: Health Benefits: How many DALYs will be averted per individual screened/managed for diabetes in this population over ten years vs. no screening/management of diabetes?Method to proceed:

Both cost and health outcomes are achieved by building a decision analysis model incorporating NCD projections with and without screening/ management.

Health outcomes are represented by using Disability Adjusted Life Years (DALYs) as they are the standardized quantitative measure of disease burden. DALYs, on the other hand, are the total morbidity and mortality.

DALY =Years of life lost (YLL) + Years of a life lived with disability (YLD)

3: ICER: What is the Incremental cost per DALY averted in this population vs. no screening/management of diabetes?

Method to proceed:

ICER can be calculated by dividing the difference of net costs (program costs adjusted for changes in the future NCD medical + care costs) in the numerator, and DALYs averted in the denominator.

Chapter 2

Background & Related works

2.1 Markov models

Markov chains are a mathematical construct in which transition from one state to another occurs based on some simple probabilistic rules. The transition from one state is dependent on the present state only, not on any other previous steps through which the process has reached the current state. This property is 'memorylessness' and is referred to as the Markov property.

Definition: A markov chain can be defined as a sequence on random variables $X_1, X_2, \ldots, X_n$ satisfying the property

$$Pr(X_{n+1} = x \mid X_1 = x_1, X_2 = x_2, \ldots\ldots, X_n = x_n) = Pr(X_{n+1} = x \mid X_n = x_n)$$

, where $Pr(X_1 = x_1, X_2 = x_2, \ldots\ldots, X_n = x_n) > 0$.

In clinical/ healthcare settings, Markov models are used to estimate risks as in such cases; a decision problem involves a risk that is ongoing over time. This could be the uncertain time of the event and multiple occurrences of an event. Most analytic issues involve at least one of these considerations. Modeling such problems with conventional decision trees may require unrealistic or unjustified simplifying assumptions and may be computationally intractable. Thus, the use of Markov models can permit the development of decision models that more

faithfully represent clinical problems. Here, there are some assumptions to be considered, such as

a. A patient is always in one of a finite number of states of health referred to as Markov states
b. The time horizon of the analysis can be divided into Markov cycles
c. Only a single state transition allowed during a cycle
d. Transition to the next state depends only on the current state, not on the previous state (memoryless system)

Markov processes may be represented by;

1. Cohort simulation (one trial, multiple subjects)
2. Microsimulation (many trials, a single subject for each)
3. Matrix algebra solution – Markov chain/ constant transition probability

For our study, we will be performing microsimulation, which determines the prognosis of a large number of individual patients.[22] Microsimulation is a form of economic modeling where modeled individuals are passed through the model one by one. Their results are then stored, and the experience of a cohort is obtained by aggregating the individual results. This contrasts with the Markov cohort model, where the cohort's experience is considered in a single pass through the model. Microsimulation models are advantageous when individuals have a mix of interrelated risk factors that influence their experience of a disease over time or where interactions between individuals are essential (e.g., chronic disease, infectious disease). Although more complex to create, they may have a more general application (than cohort models), particularly applying to cohorts with different characteristics (risk factor mix) at the start of the modeled period.[16]

2.2 Prognosis of CVD

A Markov cycle tree models the prognosis of a patient subsequent to the choice of a management strategy. Figure 1 depicts the tree representation of a patient having macrovascular diabetic complications. Consider a patient who has a diabetic situation may

develop complications such as MI and stroke at any later part of his/ her life. Either kind of event causes morbidity(short-term or chronic or both), resulting in the patient's death.

The health states (indicated by boxes) comprise:

a. Well (no past CVD event).
b. Occurrence of a CVD event.
c. Surviving after a myocardial infarction (post-MI).
d. Surviving after a stroke (postStroke)
e. deceased state.

The branches from each heath state lead to another health state based on the probability of the intermediate event. The (b) CVD Event is a transitionary Markov state and comprises either an occurrence of MI or stroke.

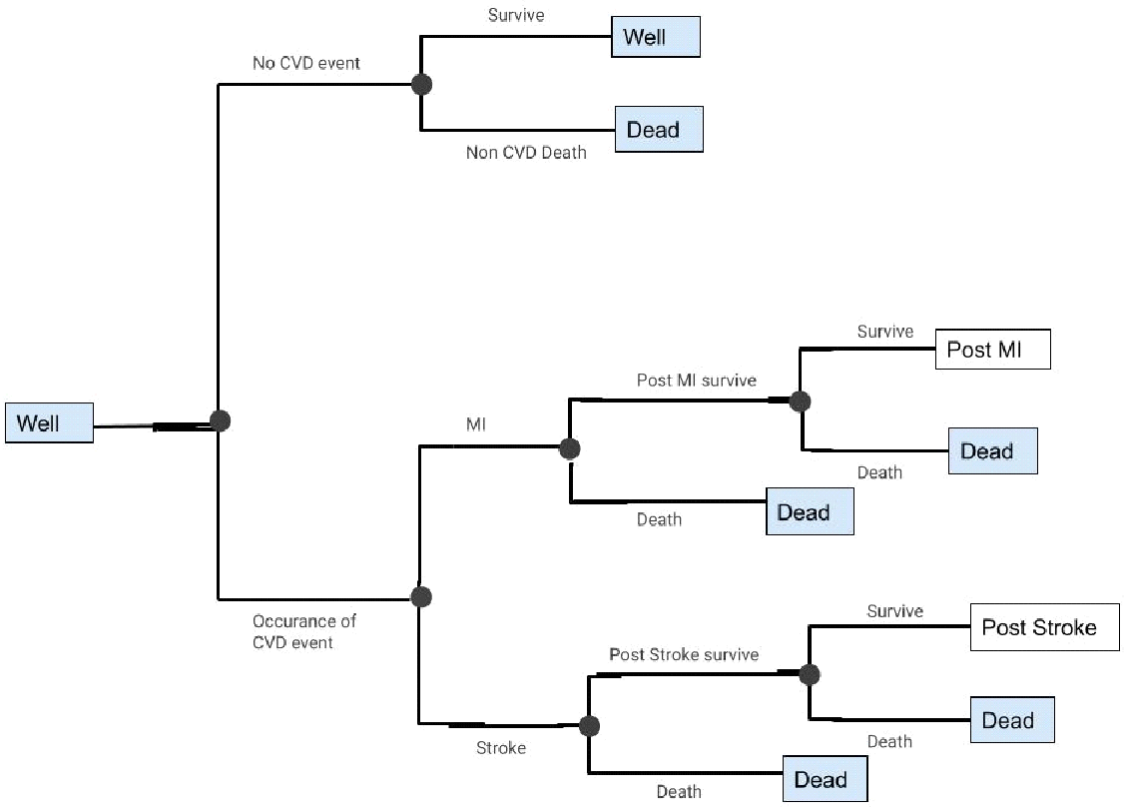

Figure 1: Schematic representation of Markov cycle tree diagram for diabetes complication

Chapter 3

Methodology

Overview

The first step of our methodology involves generating a random dataset that can represent the distribution of Indian patient profiles. All these generated sample data have been passed through 2 types of interventions (A. No one is taking medication, B. Everyone is taking medication). The risk of macrovascular complications was calculated using patients' risk factor values in both the intervention modes. Prior available risk equations, namely Risk Equations for Complications of type 2 Diabetes (RECODe) and risk reduction factors (hazard ratios) of the medications, were used for this purpose. Finally, using all these data and cost and disability weights of each state, microsimulation resulted in an ICER value. ICER was helpful in understanding and analyzing which intervention is more cost-effective as compared to the other.

3.1 Dataset generation

The simulated sample consisted of 1000 individuals of Indian origin with Type 2 diabetes mellitus (T2DM) based on the age and sex-specific distribution of the Indian population.[2] Then each of those individuals was assigned baseline risk factor values individually. The risk factors taken into account can be divided into four categories:[2]

1. Demographics

a. .Age (years) – cohorts with a range of 5 years

b. Sex (M/F) – based on the % of male/female in the specific age group

c. The prevalence rate of diabetes – based on the age and sex-specific data

2. Clinical Features

(Considered as Y when risk status is observed and N when it is absent)

a. Status of current Tobacco smoking (Y/N)

b. Status of Diabetes (Y/N)

c. BMI (kg/m2)

d. Systolic Blood pressure (mm Hg)

e. Heart rate (beats/min)

f. History of cardiovascular disease (Y/N)

g. Status of albuminuria (Y/N)

h. Status of atrial fibrillation (Y/N)

i. Status of Congestive heart failure (Y/N)

j. Status of Peripheral vascular disease (Y/N)

3. Drug use

(Considered as Y when intervention is taken and N when there is no intervention)

a. Blood pressure-lowering drugs (Y/N)

b. Oral diabetes drugs (Y/N)

c. Statins (Y/N)

d. Anticoagulant use (Y/N)

4. Biomarkers

a. HbA1c (%)

b. Haemoglobin (g/dL)

c. White blood cell (x10^9/L)

d. Total cholesterol (mg/dL)

e. HDL cholesterol (mg/dL)

f. LDL cholesterol (mg/dL)
g. Serum creatinine (mg/dL)
h. Glomerular filtration rate (ml/min/1.73m^2)
i. Urine creatinine (mg/dL)
j. Urine albumin:creatinine ratio (mg/g)

Those cohorts were defined by ten-year age groups, starting from 40 years old individuals to 70 years old individuals including both the sex. Range of mean values among age-, sex-, and urban/rural-specific cohorts used to simulate Indian populations were taken from the literature study.[2]

Now, customarily distributed risk factors were created using those ranges of the mean. For this, first, the sample mean was calculated by using the highest and lowest mean value for each risk factor.

Risk factor mean = $\frac{Highest\ Mean + Lowest\ Mean}{2}$

The standard deviation was also calculated by dividing the standard deviation by three as per the empirical rule or the three-sigma rule, which states that almost all observed data will fall within three standard deviations of the mean or average for a normal distribution.[14]

Risk factor standard deviation = $\frac{Highest\ Mean - Lowest\ Mean}{6} = \frac{Standard\ Deviation}{3}$

There are some risk factors with known correlation data among each other (as per the previously available literature), such as[1]

1. Systolic Blood pressure
2. LDL cholesterol
3. Tobacco smoking
4. Diabetes – Based on the prevalence for specific sex and age

3.2 Calculation of risk using RECODe

The annual risk for diabetes complications like myocardial infarction (MI) and stroke was calculated for each individual in each annual time step of the simulation. This was estimated from previously published Risk Equations for Complications of type 2 Diabetes (RECODe). The equations had been previously developed and validated using data from the Action to Control Cardiovascular Risk in Diabetes study (ACCORD, n=9635; 2001–09) and validated the equations for microvascular events using data from the Diabetes Prevention Program Outcomes Study (DPPOS, n=1018; 1996–2001), and for cardiovascular events using data from the Action for Health in Diabetes (Look AHEAD, n=4760; 2001–12) using individual participant data from randomized trials.[4] The reason to choose RECODe equations is due to the study that states it outperformed the UKPDS OM2 and ACC/AHA PCE risk equations based on metrics for discrimination and calibration. In contrast, the latter two risk equation sets exhibited substantial overprediction of both macrovascular and microvascular events in the studied cohorts.[3]

To compare the cost-effectiveness of two interventions (A. No one takes medication, vs. B. Everyone takes medication), the risk for MI and stroke was calculated using the RECODe equations for each scenario for the created sample profiles.

For Intervention A, where no one is taking medication,

The 10-year risk of MI = $1 - \lambda^{(\Sigma(\beta \times x) - Mean(\Sigma(\beta \times x)))}$;[4] where

β are the equation coefficients (refer to table 1)

x are the values for each covariate for an individual patient within the cohort under study.

λ value was 0·93 for fatal or non-fatal MI,

mean(Σ(β×x))) value was 2·92 for fatal or non-fatal MI

The 10-year risk of stroke is the same as that of MI, with different β and λ.

λ value was 0·98 for fatal or non-fatal stroke, and

mean(Σ(β×x))) value was 6·96 for fatal or non-fatal stroke.[4]

Table 1: Coefficients for outcomes of RECODe for macrovascular outcomes

Risk Factors	MI (fatal or non-fatal)	Stroke (fatal or non-fatal)
Demographics		
Age, years	0·04363	0·02896
Women	–0·20660	–0·00326
Clinical features		
Tobacco smoking, current	0·23580	0·16650
Systolic blood pressure, mm Hg	–0·00514	0·01659
History of cardiovascular disease	0·96180	0·41380
Drug use		
Blood pressure-lowering drugs	–0·12480	0·15980
Statins	0·04699	–0·18870
Anticoagulants	0·54400	–0·13870
Biomarkers		
HbA1c, %	0·21350	0·33650
Total cholesterol, mg/dL	0·00019	0·00171
HDL cholesterol, mg/dL	–0·01358	–0·00639
Serum creatinine, mg/dL	0·08027	0·59550
Urine albumin:creatinine ratio, mg/g	0·00042	0·00030

But in the case of Intervention B, where everyone is taking medication, the risk will be reduced as an outcome of the treatment. The medications used were Metformin and Gliclazide. Metformin is an anti-diabetic drug, helps lower plasma glucose levels [15], whereas gliclazide being a sulfonylurea, helps stimulate insulin secretion from pancreatic cells.[20] Both of these drugs are widely used to treat diabetes due to their benefits. But to understand and measure the effects of these medication choices, hazard ratios are found, which describes the outcomes of therapeutic trials and quantifies to what extent these drugs can shorten the illness duration analyzed by Cox proportional hazards regression.[23] Table 2 represents the adjusted hazard ratio values for these drugs, which are found from previously performed studies that suggest risk reduction due to metformin,[10] stroke risk reduction using metformin,[5] risk reduction due to gliclazide and metformin.[6]

Table 2: Adjusted Hazard Ratio for medications

Medication	**aHR for MI**	**aHR for Stroke**
Metformin	0.87	0.468
Gliclazide	1.01	0.914

Relative Risk Reduction through treatment :

To estimate the risk averted by treatment, the baseline risks associated with each individual for each condition were adjusted by the relative risk reduction attributable to each treatment. As we have two medications for our treatment group, their combined effect in terms of hazard ratio must be found. Hazard ratios are obtained by exponentiating the Cox regression coefficients. So by the laws of exponents, summing coefficients means multiplying hazard ratios.

This suggests us that the effective hazard ratio of MI = $0.87 \times 1.01 = 0.8787$

And of Stroke = $0.486 \times 0.914 = 0.444204$

The reduced 10 year risk of MI = 10 year risk of MI × (1-effective HR of MI)

= 10 year risk of MI × (1-0.8787)

= 10 year risk of MI × (0.1213)

The reduced 10 year risk of Stroke = 10 year risk of Stroke × (1-effective HR of Stroke)

= 10 year risk of Stroke × {1-0.444204)

= 10 year risk of Stroke × (0.555796)

The equations account for the risk of complications given a simulated individual's biomarker values, incorporating co-dependencies among complications such as the increased risk of cardiovascular complications given renal disease. We used a binomial probability function to

simulate whether a person experienced a complication that year given their RECODe risk that year for each complication and similarly computed mortality following a complication.

Now to perform the microsimulation, other types of probability values are needed as well. Monthly probabilities of age and sex-specific deaths from non-CVD causes, deaths due to fatal MI and stroke, deaths post-MI, and Stroke (non-fatal MI/Stroke) were used from previous study results.[8] All these probabilities represent cohorts defined by a five-year age group, starting from 40 years old individuals to 80 years old individuals, as they are specific to their sex.

Now, as we have all the transition probabilities in terms of monthly probability except for the likelihood from well to MI and well to stroke (10-year probability), we have to convert it into monthly probability. When changing the Markov-cycle duration yearly to monthly, one cannot simply divide the calculated transition probabilities by 12 to arrive at the appropriate transition probabilities for the shorter cycle.

Now, as we have only the 10-year transition probability and not the rate, the transition probability can be converted to a rate by solving the equation for r:

r = -($\frac{ln(1-p)}{t}$); where p is the 10 year transition probability and t = 10 years.

Or, r = -($\frac{ln(1-p)}{10}$) .[22]

Then using this calculated yearly rate the monthly transition probability can be re-calculated by using the equation,

p = 1 - $e^{-(rt)}$; where r= yearly transition rate and t =$\frac{1}{12}$.

Or, p = 1-$e^{-(\frac{r}{12})}$. [22]

Considering the cycle length of transitions as one month, the Markov state transition diagram can be depicted (refer to figure 2).

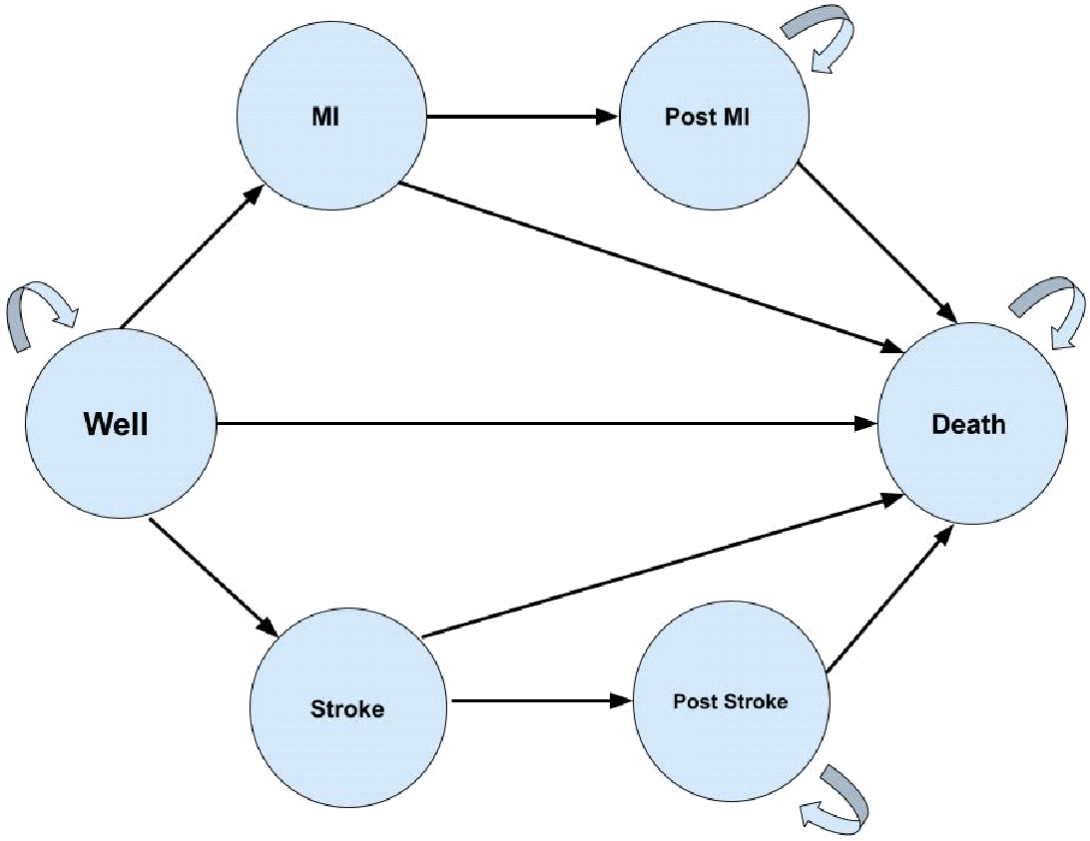

Figure 2: Markov state transition diagram (cycle length = 1 month)

This figure shows a commonly used representation of Markov processes, called a state transition diagram, in which a circle represents each state. Here, there are six definite Markov states, i.e., Well, MI, Stroke, Post-MI, Post-Stroke, Death. Arrows connecting two different states indicate allowed transitions. Arrows leading from a state to themselves suggest that the patient may remain in that state in consecutive cycles. Only specific transitions are allowed. The transitions happen, as shown in the image above.[22]

Till now, we have the following monthly transition probabilities.

1. Calculated using RECODe

a. Well to MI

b. Well to Stroke

2. From literature [8]

a. MI to Death

b. Stroke to Death

c. Post MI to Death

d. Post Stroke to Death

3. Death to Death (always 1 as once a person dies, he/she remains in the Dead state)

With all the available monthly transition probabilities from one state to another, the monthly probability of transition from MI to Post MI, Stroke to Post Stroke and probability of staying in the same state of Well, Post MI, Post Stroke for the next consecutive transition can be calculated by using simple rules of probability:

1. $MI\ to\ Post\ MI\ =\ 1\ -\ (Monthly\ transition\ probability\ of\ MI\ to\ Death)$
2. $Stroke\ to\ Post\ Stroke\ =\ 1\ -\ (Monthly\ transition\ probability\ of\ Stroke\ to\ Death)$
3. $Well\ to\ Well\ =\ 1\ -\ (Monthly\ transition\ probability\ of\ Well\ to\ MI)\ -\ (Monthly\ transition\ probability\ of\ Well\ to\ Stroke)\ -\ (Monthly\ transition\ probability\ of\ Well\ to\ Death)$
4. $Post\ MI\ to\ Post\ MI\ =\ 1\ -\ (Monthly\ transition\ probability\ of\ Post\ MI\ to\ Death)$
5. $Post\ Stroke\ to\ Post\ Stroke\ =\ 1\ -\ (Monthly\ transition\ probability\ of\ Post\ Stroke\ to\ Death)$

Although our analysis could have been done using monthly transition probabilities. Yet, we have done our cost-effectiveness analysis for annual cycle lengths for the ease of computation and error handling. So, now we have to consider some differences and assumptions than the time when cycle length was one month:

Assumption: Transitions occur in the first month of the year. For example, a transition from Well → Post MI over a year means a transition from Well →(MI) → Post MI in the 1st month followed by Post MI → Post MI for the rest of the 11 months.

Difference: In annual cycles, MI and Stroke are to be considered events, not as states. As there are only 4 Markov states, the yearly Markov-state diagram can be depicted (refer to figure 3).

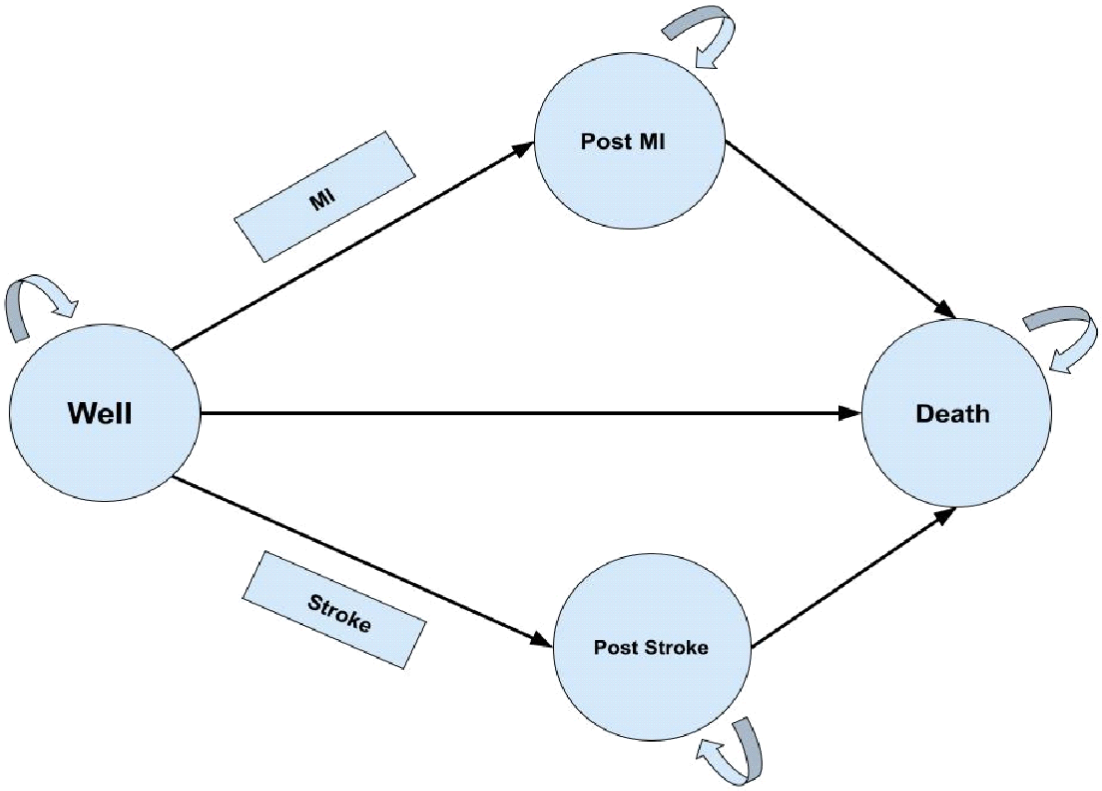

Figure 3: Markov state transition diagram (cycle length = 1 year)

Now, we can find the annual transition probabilities using the earlier calculated monthly transition probabilities using simple rules of probability.

The annual transition probability of

1. $Well\ to\ Post\ MI\ =\ (Well\ to\ MI) \times (MI\ to\ Post\ MI) \times (Post\ MI\ to\ Post\ MI)^{11}$
2. $Post\ MI\ to\ Post\ MI\ =\ (Post\ MI\ to\ Post\ MI)^{12}$
3. $Post\ MI\ to\ Death\ =\ 1\ -\ (Post\ MI\ to\ Post\ MI)^{12}$
4. $Well\ to\ Post\ Stroke\ =\ (Well\ to\ Stroke) \times (Stroke\ to\ Post\ Stroke) \times (Post\ Stroke\ to\ Post\ Stroke)^{11}$
5. $Post\ Stroke\ to\ Post\ Stroke\ =\ (Post\ Stroke\ to\ Post\ Stroke)^{12}$
6. $Post\ Stroke\ to\ Death\ =\ 1\ -\ (Post\ Stroke\ to\ Post\ Stroke)^{12}$
7. $Well\ to\ Well\ =\ (Well\ \ to\ Well)^{12}$
8. $Well\ to\ Death\ =\ 1\ -\ annual\ (Well\ \ to\ Well)\ -\ annual\ (Well\ to\ Post\ MI)\ -\ annual\ (Well\ to\ Post\ Stroke)$

9. $Death\ to\ Death\ =\ 1$

3.3 Microsimulation

By this time, we have created our input sample data and the probabilities of their transitions from one state to another. Now we perform the cost-effectiveness analysis between the two interventions that we have already defined in previous section 3.2:
Intervention A: Everyone takes medication
Intervention B: No one takes medication

For our analysis, we have performed our microsimulation for 1000 individuals. Each individual is passed through the model one by one 1000 times (everyone starts from the 'Well' state) for ten years. We can track all the individual transitions using the annual transition probability values as to which next state they are transitioning after a year, the following year, and so on. It should be noted that the transitions can be different for different interventions for every individual as due to medication, the risk might get reduced.
Every state in our study has some costs associated with it, which is found from previously conducted study results and is presented in table 3.[9] We subsequently calculated the total expenses from diabetes complications accounting for healthcare service availability.

Table 3: Associated costs

Cost of CVD medication ($)	
Retail cost per 1.5 pill of Aspirin 75 mg (dose 1.5/day)	0.0057
Retail cost per 1.5 pill of Atenolol 50 mg (dose 1.5/day)	0.036
Retail cost per 1.5 pill retail cost of Simvastatin 20 mg (dose 1.5/day)	0.3
Retail cost per 1.5 pill of Lisinopril 10 mg	0.255
Total Cost of CVD medication ($) per day	0.5967
Total Cost of CVD medication ($) per month	17.901
Total Cost of CVD medication ($) per year	217.7955
Cost of diabetes medication ($)	
Retail cost per pill of Metformin 1000 mg/person/month	0.69
Retail cost per pill of Gliclazide 80 mg/person/month	1.43
Retail cost per pill of NPH insulin + supplies*/person/month	28.02
Total Cost of diabetes medication ($) per month	30.14
Total Cost of diabetes medication ($) per year	361.68
Cost of medical care ($)	
Cost of MI acute care/event	664.35
Cost of MI post-event annual care/person/month	6.78
Cost of stroke acute care/event	909.49
Cost of stroke post-event annual care/person/month	68.24
Discount Rate (monthly)	0.0025

Similarly, every state will also have a disability weight associated with it and is presented as in table 4 .[9]

Table 4: Disability weights associated with each state

State	**Disability Weight**
MI	0.432
Stroke	0.57
Post MI	0.08
Post Stroke	0.135
Dead	1

We subsequently calculated disability-adjusted life-years (DALYs) and total deaths from diabetes complications accounting for healthcare service availability using the following formulae mentioned in earlier published literature.[1]

$$YLLs = \frac{Ce^{ra}}{(r+\beta)^2}\{e^{-(r+\beta)(L+a)}[-(r+\beta)(L+a) - 1] - e^{-(r+\beta)a}[-(r+\beta)a - 1]\}$$

and

$$YLDs = D\frac{Ce^{ra}}{(r+\beta)^2}\{e^{-(r+\beta)(L+a)}[-(r+\beta)(L+a) - 1] - e^{-(r+\beta)a}[-(r+\beta)a - 1]\}$$

;where r = the annual discount rate (3% in our assessment),

C = 0.1658 (a constant set by the Global Burden of Disease to enhance correspondence with DALY estimates conducted before the Global Burden assessments),

a = age of the event,

β = 0.04 (age weight chosen by the Global Burden of Disease),

L = expected duration of life at age a, which by age and sex is given in the SRS BASED ABRIDGED LIFE TABLES 2013-17 (refer table 5)[20]

^{D} = disability weight given above based on the type of event.

Total DALYs averted in a given scenario was equal to the sum of YLLs and YLDs averted in that scenario.

Table 5: Life expectancy at an age (sex specific)

Age	Sex	Expectation of life at age
30	Male	42.2
	Female	45.2
40	Male	33.2
	Female	35.9
50	Male	24.8
	Female	26.9
60	Male	17.4
	Female	18.9
70	Male	11
	Female	12.1

Sensitivity Analysis:

There is a need for testing the robustness of our study results which we have achieved through sensitivity analysis. This has been done by changing key input parameters like medication cost and timeline of the study in a set of independent simulation runs. We ran our model 1000 times with values of input parameters drawn jointly from their respective distributions and calculated costs and DALYs. In the simulation, 30% of the population were getting medication, and this proportion was increased to 60%, 80%, and finally 100% for comparison. Similarly, the period for which this simulation was run was also changed in multiple steps starting from 3 years and then subsequently increasing to 6 years, followed by eight years and finally ten years.

Chapter 4

Results and Discussions

4.1 Results

The microsimulation consisted of 1000 participant data (table of their baseline characteristics in method section). Of those populations, the average age was 54.04510.30 years, 52.2% were male, and 48.8% were female. Average baseline HbA1C was 7.910.49% (63 mmol/mol). Participants were exposed to the simulation for a time of 10 years. Using the RECODe coefficients from table 1, the 10-year risk for MI and stroke has been estimated from the RECODe equations, shown as follows.

As per the microsimulation results, the average cost incurred per patient receiving medications was found to be $3054.93 {95% CL, ($3043.25 - $3066.61)}. The average cost incurred per patient that achieved control treatment (patients who were not receiving any medication) was $20.43 {95% CL, ($19.65 - $21.23)}. This presents us the incremental cost incurred per patient (difference in costs between intervention A and intervention B), which is $3034.54.

Similarly, the health outcomes of the interventions were also calculated in terms of DALYs associated with each of them. The measured average DALYs incurred for patients following medication was 17.15 DALYs {95% CL, (16.98 - 17.31)}, whereas, for the other intervention, it was found to be 20.97 DALYs {95% CL, (20.75 - 21.15)}. The difference in these DALYs gives us information regarding DALY averted per person, which was 3.81 DALYs.

Considering the incremental cost and DALYs averted, the incremental cost-effectiveness ratio was calculated using the formulae $ICER = \frac{Incremental\ cost}{DALYs\ averted}$, which was found to be $795.32 per DALY averted. These results of the cost-effectiveness analysis were presented in table 6, and FIgure 4 depicts the comparison of costs versus DALYs per person in both the interventions.

Table 6: Costs and Health outcomes comparing the treatment group and the control group

Cost and Cost effectiveness	**Treatment group**	**Control group**
Total costs incurred per person ($ US)	$3054.93 ($3043.25 - $3066.61)Ψ	$20.43 ($19.65 - $21.23)Ψ
Total DALYs incurred per person	17.15 (16.98 - 17.31)Ψ	20.97 (20.75 - 21.15)Ψ
Difference in costs incurred per person (B-A)	$3034.54	
DALYs averted per person (A-B)	3.81	
ICER (Difference in costs/ DALYs averted)	$795.32/ DALY averted	

The ranges with the superscript of ψ are 95% confidence intervals.

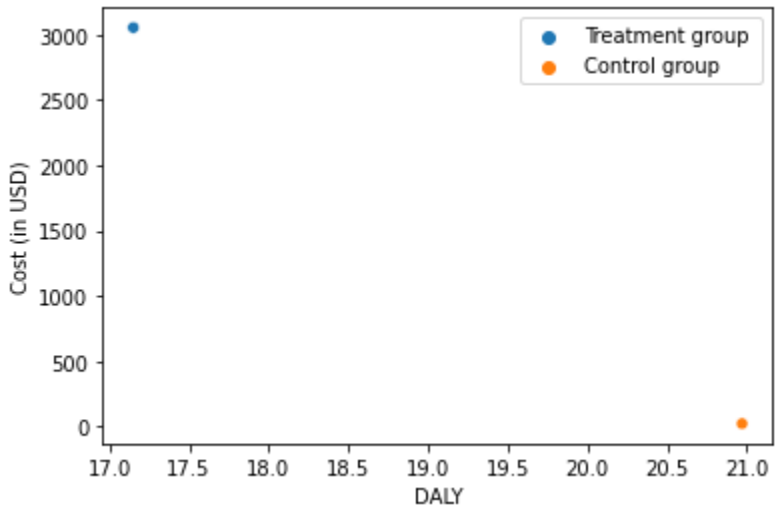

Figure 4: Comparison of Cost vs. DALY incurred per person

4.2 Discussions

All ICERs were reported in 2019 US dollars per DALY averted. An intervention is considered cost-effective when the ICER value resides below the per-capita GDP of India, i.e., US$ 2338. Intervention is regarded as highly cost-effective when the value of ICER goes below half of the per-capita GDP of India, i.e., US $1169.[8] This is the threshold for cost-effectiveness for an intervention. In our scenario, we obtained an ICER of US $795.32 per DALY averted, which is well under the point. This indicates that using medications like metformin and gliclazide is highly cost-effective compared to people without any medication strategies in the Indian demographic.

To deal with the growing burden of chronic diseases, there is a need to redesign primary care delivered to the common mass. This can be achieved mainly by three delivery models for screening and management of diabetes.

1. Community Health Worker
2. Telemedicine
3. Mobile Van

The choice of these programs should be based on their integrated care coordination system, accessible care provision, intensive training of the frontline health workers, follow-up care, and referral linkages; factors pertinent to provide effective long-term care for diabetes.[14] Various types of CHW program models vary depending on the community they serve, services provided, and the health program's aim. These community health workers could be people from the target population having prior specialized training or medical professionals working alongside. Their role might be to address health concerns in a community, help navigate patients with complex health conditions, screen & monitor, provide outreach & enrollment to the target population, provide health education, promote community action and build community support for new activities.[24] Telemedicine seems to be playing a crucial role nowadays as the internet connectivity issue is getting addressed effectively by private telecommunication organizations in an affordable manner. Also, there appears to be a shift in the mindset of an average consumer towards adopting mobile technologies during this pandemic, which makes it easier for an average Indian to gain access to a doctor virtually any time of the day. This is already becoming a widely used mode of delivery during the

COVID-19 days. Mobile van is another effective mode of delivering diabetic care, which involves active participation of the members in a small community using Mobile Medical Units (MMUs). Although we have discussed these three delivery models under this section, several other methods of providing diabetic care exist. To provide maximum benefits, many of these can be implemented simultaneously as well.

With the increase in the cost of diabetic care, ICER will also increase, giving lesser benefits than the current scenario. So, we should ensure the medication cost stays the same or even gets reduced in the near future. This could be achieved by leveraging new private players for nurturing innovations and extended promotion and awareness programs to use generic medicines as they are cheaper alternatives to the brands.

In our study, we are assuming that people are receiving medication for the entire duration of their life. But it doesn't happen in a real-world scenario. For the treatment period of 3 years, ICER was found to be US $2561.31/ DALY averted from the sensitivity analysis results. This value got reduced to US $1302.21/ DALY averted and US $976.71/ DALY averted with a subsequent increase in the intervention period to 6 years and 8 years, respectively (refer to table 7). That suggests a more negligible effect of our intervention. Scenarios where treatment was provided for ten years or even eight years became very cost-effective. In contrast, intervention is cost-effective when this duration is reduced to 6 years. However, the intervention didn't remain cost-effective anymore as the allocated period became 3 years.This clearly shows that better results are produced from the intervention by simply increasing the duration for which the treatment was implemented and this is depicted in figure 5.

Table 7: Effect of duration of treatment on ICER

Treatment Duration	**ICER ($/ DALY averted)**
3 years	2561.31
6 years	1302.21
8 years	976.71
10 years	795.32

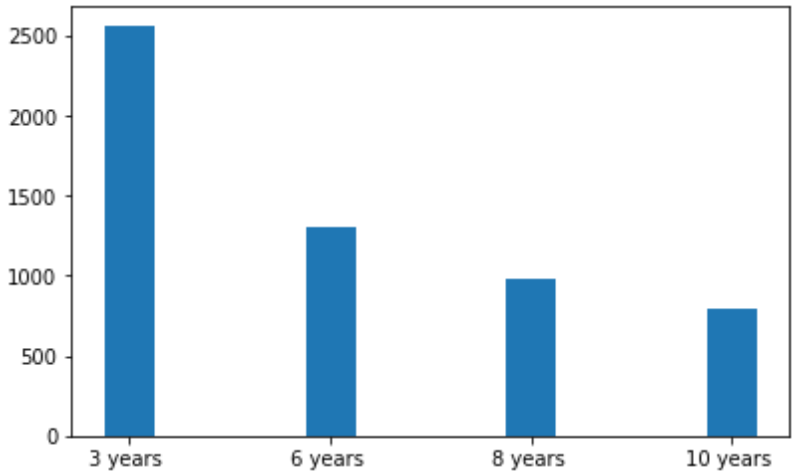

Fig 5: Comparison of ICERs due to difference in duration of treatment

We also assumed that everyone in the population received diabetes treatment, but that is not realistic to implement. So the analysis was performed at different levels of uptake of diabetic care, i.e., by allocating medication to 30%, 60%, 80%, and 100% of the population. Benefits are observed to be almost similar even if the proportion of the people treated were different. But in general, for better health outcomes and better performance, we need to increase uptake.

Table 8: Effect of allocating medication among the population on ICER

% of population with allocated medication	ICER ($/ DALY averted)
30%	794.45
60%	783.69
80%	788.89
100%	795.32

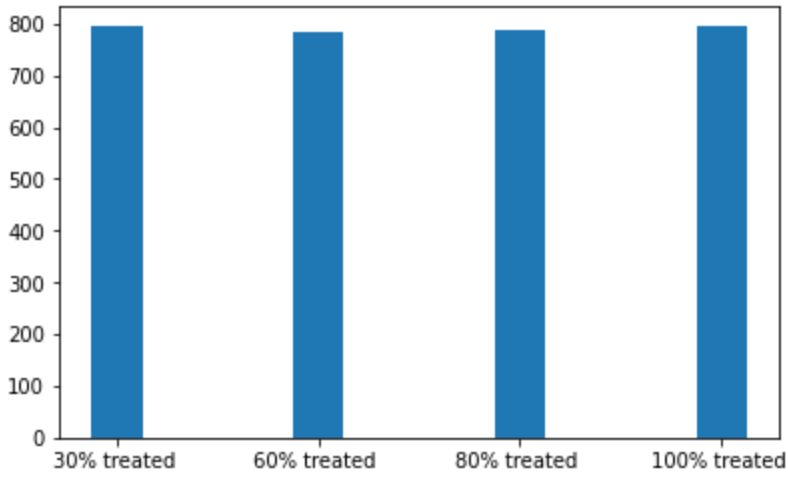

Fig 6: Comparison of ICERs due to difference in percentage of population allocated medication

Chapter 5

Conclusions

The present study indicates the benefits of diabetes intervention strategy in India. On a broader spectrum, this positively favors a path for resource allocation and health policy updating in India based on economic evaluation at its core. A financial assessment is crucial for the manifestation of fund disbursement by an organized health agency. For a significant public health intervention like diabetes treatment in India, economic evaluation represents whether the money from the public is well-spent or not. This also explains the effective use of allotted healthcare resources that are in short supply.

Based on the India-specific secondary data and following this line of thought mentioned above, we performed the cost-effectiveness analysis for diabetes treatment with and without medications, holding on to a ten-year-long time horizon. The analysis outcomes suggest that intervention A, in which everyone was getting drugs, was very cost-effective compared to intervention B (no one getting medications). Even after the sensitivity analysis results, this result remained relevant when the treatment was allocated for a long duration.

Limitations and Future works :

As with any such study that involves simulation techniques, this particular study also has some limitations that need to be addressed. First of all, the analysis was performed using previously available data from multiple secondary sources. So, the baseline population might not paint an exact picture of the average Indian population in a few cases. Our effect of the

medication is based on a small number of studies. There isn't sufficient literature for quantitatively allocating the effect of medicines for the Indian population.

Secondly, it should be acknowledged that there are insufficient published studies establishing the relationships among all the risk factors used in this present work. If it wasn't the case, it could have resulted in even more fruitful outcomes. However, correlations among risk factors could have been established using the copula function (used for multivariate correlations). On a positive note, this brings us to the future scope of works that could be performed to make this study more fruitful by addressing these shortcomings.

Thirdly, we have not explored the possibility of allocating the cost required for implementing this intervention itself, which may include someone going door-to-door, use of government shelters, integration of aadhar cards, and many more such strategies.

Fourth, the presence of other macrovascular complications would have an impact on the results of this study. But due to limited prior work in this domain, their effect is not considered.

In the context of the government sponsoring the diabetes care model, it could be a valuable investment in healthcare that can help release a heavy burden from the average Indian population in the long run. Also, with proper screening and management employing effective delivery models, the government could save a lot in segments like creating new infrastructure and diabetic care facilities on a large scale. Interests in insurance companies should also be an area of focus in such scenarios. Moreover, a national-level public health diabetes control program extended to both the public and private sector would ensure that effective treatment can be availed by patients irrespective of their choice of providers, be it a government or a private entity.

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