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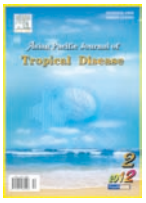

Document heading

Determination of the long term diabetes related complications and cardiovascular events using UKPDS risk engine and UKPDS outcomes model in a representative western Indian population

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ABSTRACT

Objective: To simulate and estimate the cardiovascular events associated with a representative Indian population of western India using UKPDS outcomes model and UKPDS risk engine. **Methods:** The data regarding the input variables was entered into the risk engine and the outcomes model. Projections for 1, 5 and 10 years was run on the engine and output determined. The data for each patient was processed using the diabetes risk engine to calculate an estimate of the forecasted value for the cardiovascular complications after a period of 10 years. **Results:**The absolute and relative risk along with 95% CI for CHD, fatal CHD, stroke and fatal stroke for 10 years for CHD, fatal CHD, stroke and fatal stroke was 2.65, 8.5, 5.95 and 1.15. The relative risk and 95% CI for CHD, fatal CHD, stroke and fatal stroke was 13.6, 4, 2.9 and 3.6. The mean and 95% CI of cases of ischemic heart disease, myocardial infarction, heart failure, cardiovascular disease, amputation and death for 1, 5 and 10 was 1.1, 8.3, 10.5; 2.2, 17.1, 27.2; 1.0, 7.1, 10.9; 0.9, 7.2, 11.2; 0.8, 3.9 and 6.8; 4.8, 31.4 and 55.5 respectively. **Conclusions:** The present investigation demonstrated that the co-morbid factors play a pivotal role in exacerbating diabetes and associated complications. Simulated projections of diabetic patients can predict serious life threatening cardiovascular consequences in the patients of diabetes in the representative cohort from western India.

1. Introduction

The most recent data from the International Diabetes Federation indicates that diabetes affects 246 million people worldwide and is expected to affect 380 million by 2025[1-2]. Diabetes has acquired the shape of an epidemic in India which is expected to escalate[3]. According to recent estimates, 32 million Indians suffer with diabetes. It is reported that 66% of Indian Diabetics are not diagnosed whereas 50% in Europe and 33% in USA are undiagnosed[3-4]. This makes the situation more complex and difficult. There is large pool of patients in Indian population which suffers with hypertension and cardiovascular diseases along with diabetes[5]. Diabetes progression is dependent upon a plethora of potential risk factors which contribute to the macrovascular and microvascular complications leading to serious cardiovascular events, neuropathic, nephropathic complications and premature death[6-9]. Amongst the patients suffering with these three diseases blood pressure, glycated hemoglobin, cholesterol, low density lipoproteins (LDL), very low density lipoproteins (VLDL) contribute to the complications in due course of time. These events are indispensable cascade which the patient follows once being detected with metabolic syndrome[10, 11].

International diabetic federation has laid down guidelines for defining a typical patient of metabolic syndrome. They include the particular physiological factors mentioned above, body weight, waist size, hip to waist ratio and BMI also help in identification of a patient of metabolic syndrome[12]. There are other factors like age, gender, family history are non-modifiable while others like smoking, diet, physical activity, anxiety, hypertension, diabetes etc. are modifiable[7]. An aging population with significantly improved life expectancy, presence of thrift genes, obesity and sedentary life style are some of the

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reasons for the increasing burden of diabetes[13].

Many efforts have been put into the development of mathematical simulation models of diabetes which bear significant similarity to natural progression of disease. It has been investigated that most of the diabetics suffer with one or more cardiovascular metabolic syndrome encompasses an umbrella of diseases such as diabetes, hypertension and cardiovascular diseases[14-16]. Metabolic Syndrome has been differently defined by National Cholesterol Education Program, World Health Organization, International Diabetes Federation, American Association Clinical Endocrinology, European Group of Insulin Resistance.

Computer simulation models are being used increasingly both to model the progression of Type 2 diabetes and to estimate lifetime outcomes associated with different disease management strategies. These models estimate the future occurrence of diabetes-related complications and quantify outcomes in terms of mean life expectancy or mean quality-adjusted life expectancy[17-20]. is a landmark clinical trial which provided mathematical biologists with insights to write risk equations to simulate diabetic complications and metabolic syndrome associated conditions. It was evident after the trial that long term diabetes has a close association with mortality due to cardiovascular events[21].

Eventually risk equations were written and fatal and non-fatal cardiovascular events were simulated using the UKPDS Diabetes Engine[22]. Various confounding factors like blood pressure, cholesterol, smoking habits etc. are the inputs required to forecast the risk of cardiovascular events in an individual[23, 24]. Time varying factors like HbA1c and blood pressure are also considered. The model makes the application of patient groups at different stages of diabetes. UKPDS Outcomes Model is a computer simulation that uses a set of risk equations to predict the occurrence and timing of severe diabetes-related complications (i.e. fatal or non-fatal MI (myocardial infarction), other ischemic heart disease, stroke, heart failure, amputation, renal failure and blindness) and death, to calculate life expectancy with Type 2 diabetes. It uses the equations and algorithms published in the UK Prospective Diabetes Study (UKPDS)[25]. The model results cannot be extrapolated to populations that differ significantly from that included in the UKPDS or that include ethnic groups other than White Caucasian, Afro-Caribbean or Asian-Indian[26]. The model was developed using data from patients with newly-diagnosed type 2 diabetes who participated in the UKPDS 2 and were followed up for between six and twenty years. It predicts likely outcomes using risk factors that include; age, sex, ethnicity, duration of diabetes, height, weight, smoking status, total cholesterol, HDL cholesterol, systolic blood pressure and HbA1c. By default, the model is able to forecast changes over time in smoking status, total cholesterol, HDL cholesterol, systolic blood pressure and HbA1c risk factor levels. However, if any or all of these risk factors have values available at any time points simulated, the model can incorporate them.

The objective of the present investigation was to simulate and estimate the cardiovascular events associated with a representative Indian population of western India using UKPDS outcomes model and UKPDS Risk Engine.

2. Material and Methods

2.1. methods

Permission for non commercial academic use of UKPDS risk engine and UKPDS outcomes model was obtained. The study was conducted using the clinical data accrued and recorded at the outpatient departments of Agarwal Hospital, Khenat Hospital, Dhekane Clinic and Prachiti Hospital located at various locations across Pune. Patient level data was recorded by a physician after examining the patient and getting the biochemical parameters measured at pathology laboratories. Continuous patients visiting the outpatient departments were carefully interviewed and the patient was asked to fill up a structured questionnaire bearing various baseline characteristics, socio-demographic factors, habits. The details regarding the blood levels of cholesterol, VLDL (very low density lipoprotein), LDL (low density lipoprotein) and HDL (high density lipoprotein) were recorded from the blood biochemical tests conducted at pathology laboratories. Cardiovascular events were captured from the patient history and past cardiovascular examinations and stress tests. These details were first recorded in patient files and later electronically captured. Thereafter the data was entered into the risk engine and the outcomes model. Projections for 1, 5 and 10 years was run on the engine and output determined. The numerical values pertaining to simulations and forecasted risk were documented from the output of the model.

2.2. Statistical analysis

Baseline characteristics are presented as means, median (interquartile range). Estimated 10-year first CHD risk was calculated for each participant using the UKPDS algorithms. Calibration of the model was visually checked by plotting the predicted probabilities estimated by the prediction models against the observed proportion of first CHD events (UKPDS) and fatal CHD events (SCORE). Participants were grouped into quintiles of predicted CHD risk within 10 years of follow-up.

3. Results

The results of the present investigation show that various factors vary with time and significantly govern the progression of the disease. The UKPDS risk engine output consisted of estimates of absolute and relative risk of CHD (congestive heart disease), fatal CHD, stroke and fatal stroke after a period of 10 years. The UKPDS outcomes model output consists of estimates of mean and 95% CI of IHD (ischemic heart disease), MI (myocardial infarction), HF

(heart failure), CVD (cardiovascular disease) amputation and death cases per 100 diabetics for one, five and ten simulated years (Figure 1). The baseline characters mentioned in Table 1 represent various parameters that correspond to subjects suffering with metabolic syndrome and are at an increasing risk of the development of severe cardiovascular symptoms. The hallmarks of metabolic syndrome like elevated glycated hemoglobin, fasting blood glucose, LDL, VLDL, systolic blood pressure, body mass index confirm that the subjects represented a population suffering from typical symptoms of metabolic syndrome. High percentage of alcoholics and smokers also confirmed prevalent metabolic syndrome amongst the subjects (Table 2).

Table 1.
Baseline characteristics of the patients.

Baseline Character	Mean	95 % CI
Age	56.5	53.5–59.5
Sex	Male = 176 (53.83 %)	
	Female = 151 (46.17 %)	
Duration of Diagnosis	11	8.5–13.5
BMI (kg/m^2)	25.5	24.2–26.8
Glycated hemoglobin	11.4	9.6–13.2
SBP	152	146.0–158.0
DBP	92	89.0–95.0
TC	5.85	4.2–7.5
HDL	2.35	1.3–3.4
LDL	4.1	2.9–5.3
Fasting Blood Glucose	10.5	8.7–12.3

The data for each patient was processed using the diabetes risk engine to calculate an estimate of the forecasted value for the cardiovascular complications after a period of 10 years. The absolute risk and 95% CI for CHD, fatal CHD, stroke and fatal stroke was 2.65 (1.6, 3.7), 8.5 (6.9, 10.1), 5.95 (4.8, 7.1) and 1.15 (0.6, 1.7) (Figure 1A). The relative risk and 95% CI for CHD, fatal CHD, stroke and fatal stroke was 13.6 (11.8, 15.4), 4 (2.7, 5.3), 2.9 (1.6, 4.2) and 3.6 (1.9, 5.3) (Figure 1B). It was evident from the UKPDS outcome model output that the mean and 95% CI of IHD cases per 100 diabetics in next 1, 5 and 10 years would be 1.1 (0.9, 1.4), 8.3 (7.1, 9.6) and 10.5 (7.5, 13.5) (Figure 2A).

Table 2.
Smoking and alcohol status of the patients.

Number of patients (n)	327
Current smoker	177 (54.13 %)
Previous smoker	43 (13.15 %)
Never Smoker	107 (32.72 %)
Current alcoholic	174 (53.21 %)
Previous alcoholic	50 (15.29 %)
Never alcoholic	103 (31.51 %)

It was evident from the UKPDS outcome model output that the mean and 95% CI of MI cases per 100 diabetics in next 1, 5 and 10 years would be 2.2 (1.5, 3.0), 17.1 (13.7, 20.5) and 27.2 (22.9, 31.5) (Figure 2B).

It was evident from the UKPDS outcome model output that the mean and 95% CI of CVD cases per 100 diabetics in next 1, 5 and 10 years would be 0.9 (0.3, 1.5), 7.2 (4.9, 9.5) and 11.2 (7.3, 15.2) (Figure 3A).

It was evident from the UKPDS outcome model output that the mean and 95% CI of HF cases per 100 diabetics in next 1,

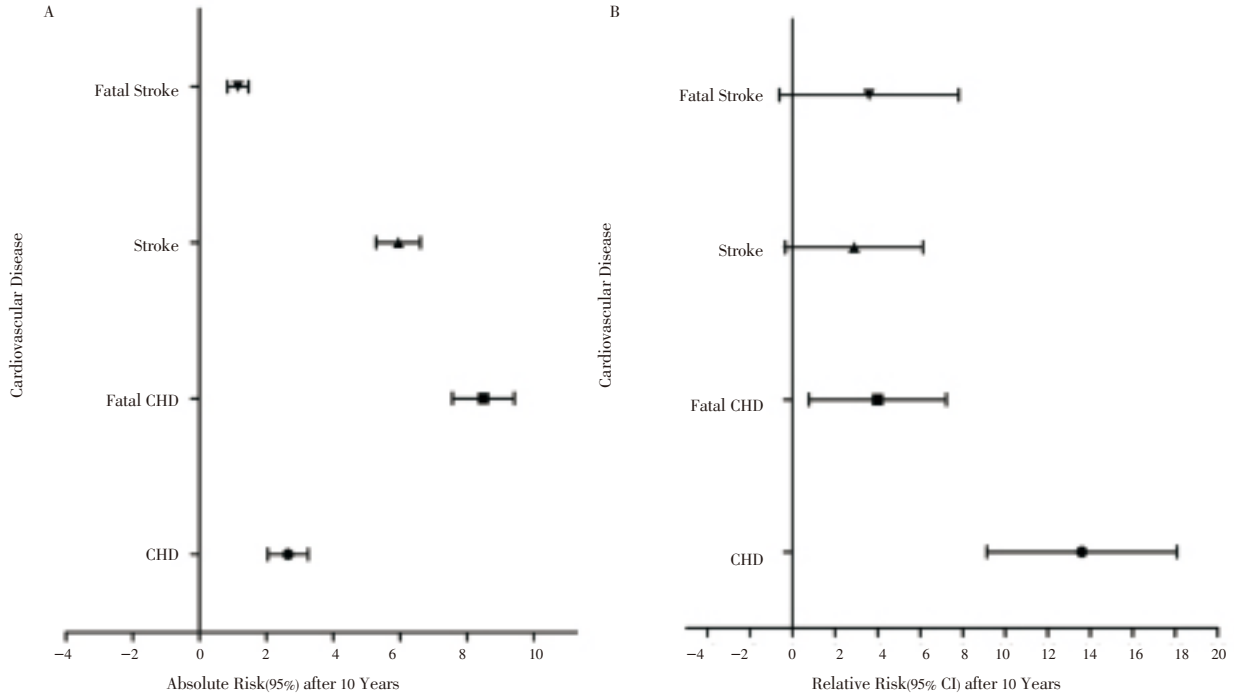

Figure 1. Modelled absolute risk (A) and relative risk (B) over period of 10 year with 95% confidence intervals of cardiovascular disease including CHD, Fatal CHD, stroke and fatal stroke using UKPDS risk engine.

5 and 10 years would be 1.0 (0.6, 1.5), 7.1 (5.2, 9.1) and 10.9 (7.3, 14.5) (Figure 3B).

It was evident from the UKPDS outcome model output that the mean and 95% CI of Amputation cases per 100 diabetics in next 1, 5 and 10 years would be 0.8 (0.3, 1.3), 3.9 (2.6, 5.3) and 6.8 (4.3, 9.3) (Figure 4A).

It was evident from the UKPDS outcome model output that the mean and 95% CI of Death cases per 100 diabetics in next 1, 5 and 10 years would be 4.8 (3.7, 5.9), 31.4 (28.4, 33.9) and 55.5 (51.7, 59.3) (Figure 4B).

The accumulated probability of the various diseases was also determined for 1, 5 and 10 forthcoming years. The accumulated probability for the occurrence of IHD for the next 1, 5 and 10 years was found to be 0.0011, 0.076 and 0.142

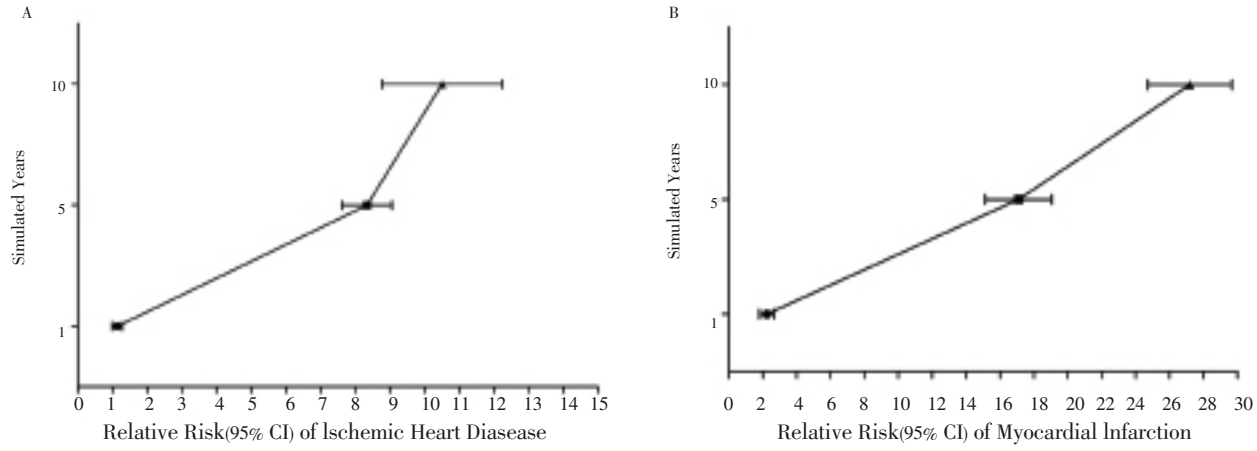

Figure 2. Simulated relative risk over period of 10 year with 95% confidence intervals of ischemic heart disease (A) and myocardial infarction (B) using UKPDS risk engine

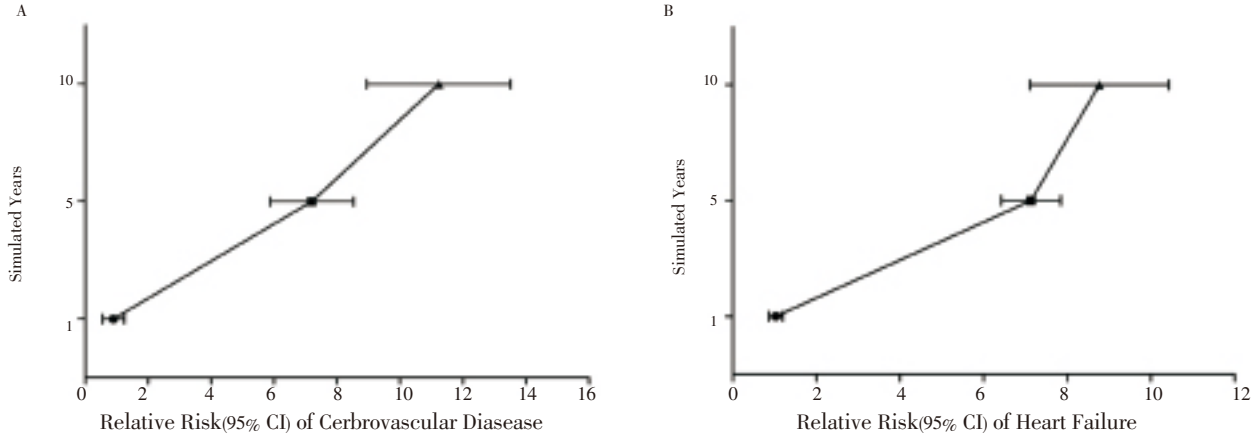

Figure 3. Simulated relative risk over period of 10 year with 95% confidence intervals of cardiovascular disease (A) and heart failure (B) using UKPDS risk engine

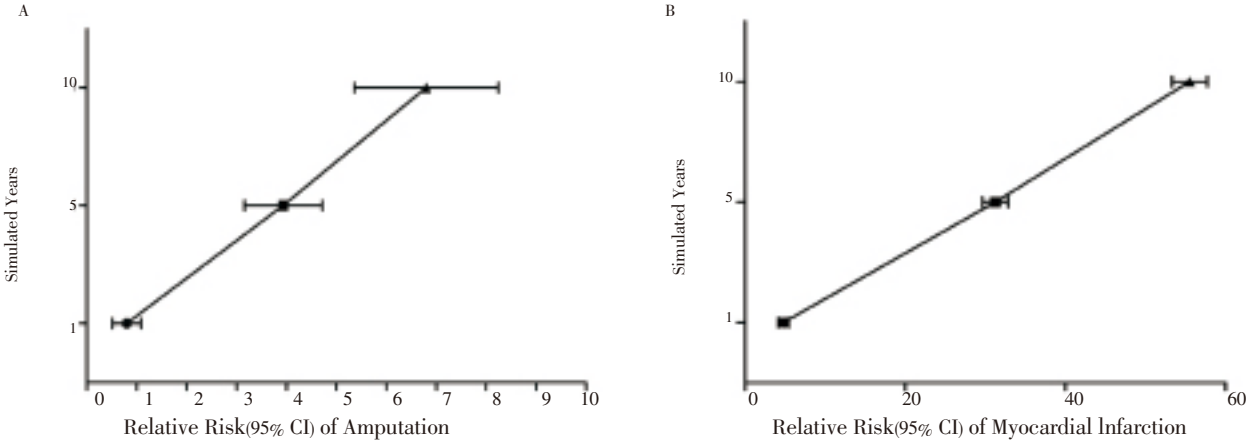

Figure 4. Simulated relative risk over period of 10 year with 95% confidence intervals of amputation (A) and death (B) using UKPDS risk engine

respectively. The accumulated poverty for the occurrence of MI for the next 1, 5 and 10 years was found to be 0.022, 0.179 and 0.289 respectively. The accumulated poverty for the occurrence of HF for the next 1, 5 and 10 years was found to be 0.019, 0.087 and 0.157 respectively. The accumulated poverty for the occurrence of CVD for the next 1, 5 and 10 years was found to be 0.0013, 0.087 and 0.121 respectively. The accumulated poverty for the occurrence of amputation for the next 1, 5 and 10 years was found to be 0.011, 0.059 and 0.092 respectively. The accumulated poverty for the occurrence of Death for the next 1, 5 and 10 years was found to be 0.056, 0.324 and 0.597 respectively (Figure 5).

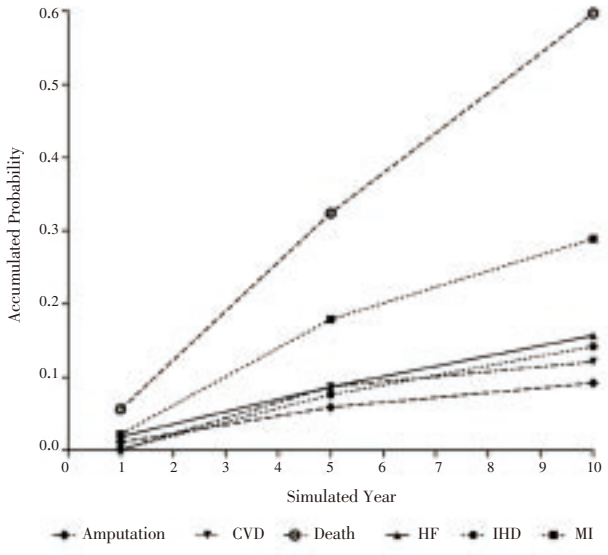

Figure 5. Accumulated probability of the various diseases over period of 10 year using UKPDS risk engine

4. Discussion

Mathematical modeling of various diseases has been carried out by many researchers[27, 28]. Diabetes is a long term disease where the slow progression is related with the micro and macrovascular complications affecting various organ systems[29-32]. Slowly various organ systems succumb to glycaemia induced pathologies[33, 34]. These include nephropathy, neuropathy, cardiomyopathy and dementia[35-38]. These changes or states can be mathematically expressed. The transformation of one state to the other follows a risk equation. These states are considered as mutually exclusive states and termed as Markov states. Recently, simulation based studies have been carried out which bears close similarity to the natural progression of diabetes[39-42]. These models involve mathematical expressions known as risk equations which relate the micro progression of diabetes. Assumptions are made and the transition probabilities are determined as per the landmark clinical trials. The patient level data is processed and transformed to mathematical formulae which in turn are coded into visual basic applications in excel sheet. These include the Cardiff long term model, CORE model, Michigan model, Archimedes model and UKPDS outcomes model and UKPDS diabetes risk engine[43]. This excel based executable model is immensely useful to simulate a patient cohort and the complications for a disease.

Diabetes has major impact on the health scenario in India[6, 32]. It is a non-communicable disease which has spread its claws across all the patient populations irrespective of age gender or region[44]. It is a lifestyle disorder which is not successfully controlled by other methods. It also corresponds to the spread of metabolic syndrome. Metabolic syndrome is spreading at an alarming rate across the world in all the populations including developing and developed countries[45, 46]. Sedentary life style, indiscriminate consumption of junk food, severe dependence on alcoholism elevated levels of anxiety and smoking are the major factors which contribute to the development and maintenance of metabolic syndrome in the Indian population[49-49]. Diabetes, hypertension and other cardiovascular diseases lead to metabolic disorders. A number of workers are currently working to evaluate novel moieties for diabetes amelioration[50, 51]. However, there is severe paucity of model based simulation and cost effectiveness studies using decision analytic model. However, model based simulation studies are being continuously performed in various parts of the world[52-57].

There are several shortcomings associated with UKPDS outcomes model which need to be considered while simulations are carried out using this model. The UKPDS outcome model calculates the probability of the occurrence of first event, but not the ones which follow the initial event. Factors like multiple amputation or two heart failures in the same individual are not considered.

Moreover, the UKPDS model considers that the cohort of the patients will receive the same medications and experience similar lifestyle changes as occurred in the UKPDS study. It needs to be born in mind that the individuals in India would behave differently and the disease may ideally follow a different progression pathway. Another factor that needs to be considered is that in UKPDS study the patients mostly belonged to newly diagnosed diabetes group whereas in the present investigation both newly diagnosed and long term cases of diabetics were included.

The findings of the present investigation demonstrate that there is an alarming forecast about the increasing risk of the patients of diabetes to develop cardiovascular diseases and mortality. The population is prone to severe cardiovascular disorders if suitable measures are not employed. However, UKPDS outcomes model has been reported by some authors to produce anomalous results which do not bear close association to the clinical progression of diabetes[58, 59]. The main disadvantage of simulation models is that estimates are not precise for patients who have characteristics different to that of patients who participated in the original trial. UKPDS was originally carried out on the Caucasian patient population in the UK. But the modelers of UKPDS risk engine and outcome model have provided an option to include the data of Asian Indians. The population of diabetes

patients of Pune who have been included in the study may be considered to be a representative of the general Asian Indian population.

The findings of the investigation draw a picture which inspires awe and establishes an urgent need to eradicate diabetes and related complications. Lifestyle changes are a must in the current scenario and the efforts are needed from the patients[60, 61]. The findings correlate well with the findings of Nagpal and Bhartia, 2006 who used similar techniques to evaluate the cardiovascular diseases in Indian population[62]. This is a pioneer study in India to use UKPDS outcomes model to determine the estimates for the long term diabetes complications. Similar studies have been carried out by other authors[17]. The estimated risk of the cardiovascular events for next one, five and ten years will contribute to better control of the rapid spread of diabetes and other metabolic disorders. Measures need to be taken to achieve better glycemic and cholesterol level control to halt the progression of diabetes into complications and mortality[63].

In India, there are a plethora of socio-demographic factors which affect the progression of various diseases. In the developed countries, expense on health care bears major economic and political issues. The methodology of cost-effectiveness (CE) analysis has evolved as an important instrument to assess the value of novel medical regimens, devices, formulations etc. by simultaneously determining incremental healthcare benefits in association with incremental costs[64]. The basic aim of CE research is to enable clinicians and medical decision makers to make suitable decisions regarding clinical care and allocation of resources. To conduct high quality cost effectiveness studies, suitable mathematical models need to be devised. Many cost effectiveness studies to simulate and project costs related with diabetes have been carried out across the world using various established disease models[53, 55]. But in India the scenario is not very encouraging. Only a few studies punctuate the entire database of cost effectiveness studies[65-67]. The need for model based studies may not be of concern in India at present but circumstances will compel researchers to device disease models specific to India in a few years. One basic flaw is the lack of epidemiological and landmark clinical studies which are intertwined with model based forecasted time event relations. It is encouraging that recent epidemiological work has elucidated that the role of factors like smoking, alcohol and life style have a grave impact on communicable or infectious[68-71] and non-communicable metabolic diseases[62, 72]. These two classes of diseases have a huge impact on the economic policies and health budget in India. The data regarding the factors influencing the infectious, communicable[73, 74] and non-communicable diseases[7, 75-78] are available but these have not been converted to well define mathematical models. There is severe paucity of modeling based studies in India. The basic reason for this seems to be inadequate technical knowhow about the entire model building process starting from conducting a landmark clinical study like UKPDS, writing risk equations bearing close resemblance to natural disease progression and coding in visual basic applications to construct a robust reproducible and disease centric model which simulates the progression of disease according to the variables of Indian scenario. These models will pave the way for model based cost effectiveness studies to ensure optimum health technology assessment submissions.

In recent past a number of preclinical as well as clinical studies were carried out to evaluate the cost effectiveness of medications before the launch of the formulation of a particular molecule[79-85]. Another overlooked facet is absence of high quality metanalytical and critical appraisal studies to educate the modeler regarding the important features and recent studies. Recent studies have been carried out where authors have applied metanalytical techniques to plot forest plots of diseases[86-88]. These studies are of immense help to the modeler who needs a step by step blue print of the micro progression of the disease. In India, a lacuna persists in this domain as HTA submission is not mandatory. As the government does not reimburse most of the medicaments at present, these submissions are not compulsory[89]. However, with the advent of better economic policies, the day is not far when sensitive disease models will be needed to conduct hypothetical cost effectiveness studies and clinical trials[90].

At such a juncture, disease models which have been developed for a different population and economic scenario may produce erroneous results ultimately affecting the budget allocated for health affairs. Hence, well designed disease models not only for diabetes but all the high burden diseases should be fabricated using the wide array of recent clinic-epidemiological and landmark clinical trials to gear up for the HTA era in India.

Conflict of interest statement

We declare that we have no conflict of interest.

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