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Type 2 Diabetes Mellitus in Bangladesh: Cost-of-illness and Complications

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Notice 1

Table of Contents

List of abbreviations

ADA: American Diabetes Association

BADAS: Diabetic Association of Bangladesh

BDT: Bangladeshi currency, Taka

CAD: Canadian Dollar

CAD: Coronary Artery Disease

CKD: Chronic Kidney Disease

COI: Cost-of-Illness

CVD: Cardiovascular Disease

DED: Diabetes Eye Diseases

DME: Diabetic Macular Edema

ESRD: End Stage Renal Disease

GDM: Gestational Diabetes

GDP: Gross Domestic Product

HICs: High-Income Countries

ID: International Dollar

IDF: International Diabetes Federation

LMICs: Low- and Lower-Middle-Income Countries

NCDs: Non-Communicable Diseases

OHA: Oral Hypoglycaemic Agent

OOP: Out-of-Pocket

OPD: Outpatient Department

PAD: Peripheral Artery Disease

PALYs: Productivity-Adjusted Life Years

REDCap: Research Electronic Data Capture

SD: Standard Deviation

T2DM: Type 2 Diabetes Mellitus

UKPDS: United Kingdom Prospective Diabetes Study

US: United States

Abstract

Background

Diabetes, one of the top five non-communicable diseases (NCDs), contributes 1.6 million to the global death toll of 41 million people every year. Estimates for 2017 showed that 425 million of the global population are living with diabetes and are disproportionately spread in the low- and lower-middle-income countries (LMICs). In 2017, diabetes accounted for US$727 billion of the global health expenditure. Type 2 diabetes mellitus (T2DM) accounts for 90% of all the diabetes cases. Therefore, there has recently been an urgent call for sufficient scientific breakthroughs to combat the disease; however, there is still limited scientific evidence regarding T2DM, especially in LMICs, which include Bangladesh. The main objective of this thesis was to estimate the economic burden of T2DM, find the risk factors of T2DM complications and their impact on the economy, and explore the prevalence and determinants of glycaemic control. Furthermore, this thesis aimed to develop risk scoring tools for T2DM-related complications and evaluate the impact of diabetes on gross domestic product (GDP) of Bangladesh.

Methods

The study design was cross-sectional and retrospective. A prevalence-based approach with a bottom-up methodology was employed to calculate the cost from the patient's perspective. In 2017, 1,253 participants with T2DM were recruited from six diabetes hospitals providing primary to tertiary healthcare services, located in the northern and central regions of Bangladesh covering urban, semi-urban and rural residence. A structured questionnaire was used for face-to-face interviews via a web-based application to collect non-clinical data. Patients' medical records were reviewed for clinical data and hospital records were reviewed for hospitalisation data. The micro-costing approach was used to calculate the direct cost and the human capital approach was used to calculate the indirect cost. Descriptive statistics were used to summarise the data. The chi-square test, ANOVA, and simple and multiple regression analyses were also performed. Missing values were imputed using the iced chained equation (ICE) method and the bootstrap method was used to develop the models for risk scoring tools. The risk scoring systems for CAD and stroke were developed and translated into a web-based risk scoring tool. Using this tool, the absolute risk and additive scores of CAD and stroke can be calculated. Furthermore, based on the additive risk a patient can be classified into one of the following risk categories: very low, low, moderate, high and very high. Furthermore, a life table model was used to estimate the impact of productivity loss on GDP.

Results

1. The average annual cost for a person with T2DM was US$865 in Bangladesh, to which the medicine cost was the highest contributor followed by the hospitalisation cost. Patients who had a history of hospitalisation had a 4.2-fold higher average annual cost than those without hospitalisation.
2. Overall, 63.4% of participants had complications of which 14.8% had macro- and 20.7% had micro-vascular complications, while 27.9% had both. The outpatient department (OPD) cost was significantly higher for patients with the presence of coronary artery disease (CAD), nephropathy and retinopathy due to frequent OPD follow-ups. The hospitalisation cost was higher for patients with stroke and nephropathy due to higher treatment costs and prolonged hospital stays.
3. Among the study participants, 81.8% did not achieve the recommended HbA1c target level of lower than 7%, and 54.7% showed very poor control (≥9%). Being female, low education level, rural residence, unhealthy eating habits, smokeless tobacco consumption, insulin use, infrequent follow up check-ups, cognitive impairment and history of CAD were found to be associated with poor control of HbA1c level.
4. The prevalence of macrovascular complications of CAD, stroke and diabetic foot was 30.5%, 10.1% and 12%, respectively, while that for microvascular complications of nephropathy, neuropathy and retinopathy was 34%, 5.7% and 25.1%, respectively. Several modifiable and non-modifiable factors were identified to be associated with these complications.
5. In 2017, the prevalence of diabetes in Bangladesh was 6.9% (6.9 million people aged 20-59 years). Assuming a follow-up of this population until a retirement age of 60 years, an estimated 0.8 million excess deaths, loss of 4.0 million life years (5.5%) and 9.2 million productivity-adjusted life years (PALYs) (20.4%) were due to diabetes. The calculated loss in PALYs equated to a total of US$97.4 billion lost (US$16,987 per person) in GDP.

Conclusions

In Bangladesh, diabetes is a major public health issue with a high economic burden. Quantification of the economic burden of T2DM, in terms of both direct and indirect costs, highlighted the importance of prevention, treatment and adequate control of T2DM in Bangladesh. Optimisation of T2DM management through positive lifestyle changes is urgently required for prevention of comorbidities and complications, which, in turn, will reduce the cost. Having understood the modifiable and non-modifiable factors related to glycaemic control and complications among people with T2DM, policy makers, healthcare providers and patients should work together to combat this growing epidemic.

General Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signature: 

Print Name: Afsana Afroz

Date: 13/09/2019

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Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes six original papers published in peer reviewed journals. The core theme of the thesis is **Cost-of-illness of type 2 diabetes and its complications**. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Department of Epidemiology and Preventive Medicine under the supervision of Dr Baki Billah. The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapter 2 to chapter 7 my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
e.g. 2	*Waveforms in systemic arteries*	*Accepted*	*60%. Concept and collecting data and writing first draft*	*1) Albert Einstein, input into manuscript 25%* *2) Marie Curie, Data analysis, input into manuscript 15%*	*Yes* *No*
Chapter 2	Cost-of-Illness of Type 2 Diabetes Mellitus in Low and Lower-middle Income Countries: A Systematic Review	Published	Conducted literature search, quality assessment of the studies, compilation of the results, and drafted manuscript (70%)	30% of contribution by the co-authors below: 1. Mohammed J. Alramadan, 2. Md Nassif Hossain, 3. Lorena Romero, 4. Khurshid Alam, 5. Dianna J Magliano, 6. Baki Billah	No – for all but Mohammed J. Alramadan
Chapter 3	Cost-of-illness and its Determinants for Type 2 Diabetes Mellitus in Bangladesh: Protocol for a Cross-sectional Study	Published	Study design, ethics application, plan for participant recruitment, data collection and drafted the manuscript (80%)	20% of contribution by the co-authors below: 1. Khurshid Alam 2. Mohammed J. Alramadan, 3. Md Nassif Hossain, 4. Hasina Akhter Chowdhury, 5. Liaquat Ali,	No – for all but Mohammed J. Alramadan

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
				6. Dianna J Magliano, 7. Baki Billah	
Chapter 4	Study 1: Type 2 Diabetes Mellitus in Bangladesh: A Prevalence Base Cost-of-illness Study	Published	Study concept and literature search, data collection and statistical analysis, drafting of the manuscript (80%)	20% of contribution by the co-authors below: 1. Khurshid Alam, 2. Liaquat Ali, 3. Afsana Karim, 4. Mohammed J. Alramadan, 5. Samira Humaira Habib, 6. Dianna J Magliano, 7. Baki Billah	No – for all but Mohammed J. Alramadan
Chapter 5	Study 2: Macro- and Microvascular Complications of Type 2 Diabetes in Bangladesh - a Challenge for Healthcare	Published	Study concept and literature search, data collection and statistical analysis, drafting of the manuscript (80%)	20% of contribution by the co-authors below: 1. Khurshid Alam, 2. Md Nassif Hossain, 3. Animesh Biswas, 4. Liaquat Ali, 5. Dianna J Magliano, 6. Baki Billah	No – for all co-authors
Chapter 6	Glycaemic Control for People with Type 2 Diabetes Mellitus in Bangladesh - An Urgent Need for Optimization of Management Plan	Published	Study concept and literature search, data collection and statistical analysis, drafting of the manuscript (80%)	20% of contribution by the co-authors below: 1. Liaquat Ali, 2. Md Nazmul Karim, 3. Mohammed J. Alramadan, 4. Khurshid Alam, 5. Dianna Magliano, 6. Baki Billah	No – for all but Mohammed J. Alramadan
Chapter 7	7a: Macro- and Micro-vascular Complications and their Determinants Among People with Type 2 Diabetes Mellitus in Bangladesh	Published	Study concept and literature search, data collection and statistical analysis, drafting of the manuscript (80%)	20% of contribution by the co-authors below: 1. Wen Zhang, 2. Andre Jin Wei Loh, 3. Darryl Xing Jie Lee, 4. Baki Billah	No – for all co-authors

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

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The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor signature:  **Date:** 13/09/2019

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Chapter 1

INTRODUCTION

1.1 Background

Diabetes is a leading crisis of the twenty-first century for both medical science and the global economy (1, 2). The burden of diabetes continues to increase rapidly, especially in low- and lower-middle-income countries (LMICs) (3). Therefore, there has recently been an urgent call for sufficient scientific breakthroughs to combat the crisis. The greatest burden of the disease is mainly due to a variety of severe complications associated with long duration of diabetes (4, 5).

As estimated in 2017, globally, more than 425 million people had diabetes, and if the trend continues, the number is expected to be 629 million by 2045. The highest prevalence of diabetes with 11.1% was observed in the North America and Caribbean region, while the lowest was observed in the Africa region with 4.4% (3). According to the International Diabetes Federation (IDF), the Southeast Asia region is the epicentre of the diabetes crisis as about 80% of total diabetes deaths occurred here. Bangladesh belongs to South Asia, where all the countries are listed as LMICs. More than one third of diabetes cases are estimated to have resulted from population growth and ageing, 28% from an increase in age-specific prevalence, and 32% from the interaction of these two (3).

Diabetes places a significant burden on individuals, their families, society and overall on the economy of the country in addition to the human burden characterised by premature mortality and lower quality of life due to diabetes-related complications. In 2017, globally, US$727 billion was spent to treat and prevent diabetes and its related complications, representing an 8% increase compared to the 2015 estimate. A large disparity in the amount of healthcare expenditure can be observed across countries. Around the globe the United States (US) with international dollar (ID) 11,638, followed by Luxembourg and Monaco with ID8,941 and ID8634 respectively have the highest annual cost per person. Conversely, Central African Republic with ID47, the Democratic Republic of Congo with ID66 and Madagascar with ID87 have the lowest annual cost per person.

The burden of diabetes is mainly driven by its devastating complications, which are mainly grouped as macrovascular (coronary heart disease, cerebrovascular disease, peripheral arterial disease (PAD) contributing to diabetic foot, rheumatic heart disease, and congenital heart disease) and microvascular (retinopathy, nephropathy and neuropathy) complications. A number of modifiable and non-modifiable risk factors of macrovascular and microvascular complications have been identified by many epidemiological studies and randomised

controlled trials (6-9). The non-modifiable factors include advanced age, gender, use of insulin, duration of diabetes and other socioeconomic factors. The modifiable factors include lifestyle factors such as physical activity, diet, obesity and smoking and comorbidities such as hypertension and dyslipidaemia.

Optimal management of diabetes is highly related to glycaemic control to prevent diabetes complications. Therefore, it is considered as the main therapeutic goal for prevention of its injurious effects and the dire consequences. Results from many observational studies and randomised controlled clinical trials (10-13) revealed that strict glycaemic control helps to prevent complications, especially microvascular complications, and that these complications are directly related to quality of life (14, 15).

While there is a modest amount of information available from high-income countries (HICs) related to the economic burden of diabetes, factors related to glycaemic control and diabetic complications, there is a paucity of evidence from LMICs, which include Bangladesh. Therefore, the aim of this PhD research was to estimate the economic burden of T2DM, and to explore the risk factors of diabetic complications and glycaemic control among people with T2DM in Bangladesh.

This thesis consists of nine chapters. This first chapter is the introduction which defines diabetes and its complications and discuss the economic burden of diabetes and its complications, risk factors of diabetic complications, and the importance of glycaemic control. This chapter will conclude by presenting the outline and aims of this thesis.

1.2 Diabetes Mellitus: An Overview

Diabetes is no longer associated with affluence and has recently become the biggest health threat for both rich and poor. It is a group of metabolic disorders characterised by persistent hyperglycaemia with abnormal metabolism of carbohydrate, fat and protein resulting from impairment of insulin secretion, action or both (3).

Hyperglycaemia, if remains unchecked or uncontrolled over a long period of time, can cause long-term damage, including dysfunction and failure of multiple organs, resulting in cardiovascular disease (CVD), neuropathy, nephropathy and retinopathy (16). Diabetes can have a significant impact on quality of life and even reduce life expectancy, if not managed properly. To date, there is no cure for the disease; however, a person with diabetes can live an enjoyable life by learning about the condition and managing it effectively.

The commonly accepted classification of diabetes by the IDF includes three major types: type 1 diabetes, type 2 diabetes mellitus (T2DM) and gestational diabetes (GDM). Type 1 diabetes is caused by an autoimmune or idiopathic origin resulting in a relative or absolute deficiency of insulin in the body. T2DM is predominantly due to insulin resistance or insulin secretory defects or a combination of both conditions. Hyperglycaemia (high blood glucose level) that is first detected during pregnancy is classified as GDM (3).

Type 1 diabetes is more common in the developed world, usually in children and young adults and accounts for only 5-10% of people with diabetes worldwide (16, 17). Conversely, T2DM, which is associated with a number of modifiable (i.e. obesity, metabolic syndrome, sedentary lifestyle, unhealthy diet) and non-modifiable (i.e. ageing, ethnicity and genetics) risk factors, accounts for 90–95% of those with diabetes (3, 18-20). There is currently no effective intervention that can prevent type 1 diabetes, but lifestyle modification with physical activity (21) and/or a healthy diet (22-26) can delay or prevent the onset of T2DM.

1.3 Diabetes Complications

Diabetes is a lifelong condition that needs regular monitoring and proper management to live a healthy life. If not managed well, all types of diabetes can lead to severe life-threatening complications that affect many parts of the body, resulting in frequent hospitalisations, reduced quality of life and even early death. Continuous high blood glucose resulting from diabetes may cause damage to the blood vessels and nerves over time, causing CVD, blindness, kidney failure and lower-limb amputation.

Diabetes complications can be classified as acute and chronic complications. Acute complications include hypoglycaemia, diabetic ketoacidosis, hyperglycaemic hyperosmolar state, hyperglycaemic diabetic coma, seizures or loss of consciousness and infections (3). Chronic complications have two subgroups: microvascular complications (due to damage to small blood vessels) and macrovascular complications (due to damage to larger blood vessels) (3, 27). Microvascular complications include nephropathy, neuropathy and retinopathy (28). Macrovascular complication include coronary artery disease (CAD) leading to angina or myocardial infarction, cerebrovascular disease contributing to stroke, and PAD contributing to diabetic foot (3) grouped as CVD. Diabetes is also associated with increased rates of cancer (29), cognitive impairment, physical disability (30, 31), tuberculosis (32, 33) and depression (34).

1.3.1 Microvascular complications of diabetes

Hyperglycaemia is the main factor that leads to the development of microvascular complications such as retinopathy, nephropathy and neuropathy. Therefore, these complications only appear after a person has developed T2DM.

a. Diabetic retinopathy

Diabetic retinopathy is the most common microvascular complication of diabetes. In the US, it is responsible for more than 10,000 new cases of blindness every year (35). The risk of developing microvascular complications such as diabetic retinopathy depends on the duration and severity of hyperglycaemia and the presence of hypertension, according to the results of the United Kingdom Prospective Diabetes Study (UKPDS) (11). Retinopathy can affect the peripheral retina, the macula, or both. The development of retinopathy may begin as early as seven years before the diagnosis of T2DM (35).

Up to 21% of patients with T2DM have retinopathy at the time of first diagnosis of diabetes, and the rest develop some degree of retinopathy over time. The general classification of diabetic retinopathy includes non-proliferative and proliferative retinopathy (36). The prevalence of any retinopathy in people with diabetes is 35%, while it is 7% for proliferative retinopathy (37).

b. Nephropathy

Diabetic nephropathy, which is the leading cause of renal failure, is defined as proteinuria lead by microalbuminuria. Without intervention, people with T2DM and microalbuminuria typically progress to proteinuria and overt diabetic nephropathy. At the time of diagnosis with

T2DM, more than 7% of patients may already have microalbuminuria (38). Data from the US revealed that 40% of people with diabetes develop chronic kidney disease (CKD) and 19% of them have the signs of stage 3 or higher (39). There is a strong correlation between diabetes, hypertension and kidney failure. The CKD among patients with diabetes is called diabetic nephropathy. Hypertension is a risk factor for T2DM, which is the leading cause of CKD. In other words, hypertension can often precede T2DM and contribute to progression of CKD (40).

c. Neuropathy

Diabetic neuropathy is defined by the American Diabetes Association (ADA) as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes" (41). Diabetic neuropathy causes loss of sensation or dysfunction in the lower limbs. As a result of diabetic neuropathy, foot ulceration or injury occurs, which is subsequently responsible for more than 80% of amputations (42). The risk factors for people with diabetic foot often include older age, longer diabetic duration, hypertension, diabetes retinopathy and smoking (3).

1.3.2 Macrovascular complications of diabetes

Hyperglycaemia, insulin resistance and metabolic syndrome which are commonly observed in diabetic patients, are the factors that contribute significantly to atherosclerotic changes and the pathogenesis of macrovascular complications.

People with diabetes are 2- to 3-times more likely to have CVD than those without diabetes and CVD is the major cause of death and disability worldwide (43, 44). The increased risk of CVD in patients with diabetes has been demonstrated in numerous epidemiological studies (45, 46) conducted since the Framingham study (47). CVD is a group of disorders of the heart and blood vessels that include CAD, cerebrovascular disease, PAD contributing to diabetic foot, rheumatic heart disease and congenital heart disease (3). Hyperglycaemia adversely affects the cerebrovascular circulation by increasing the risk of intracranial and extracranial (e.g., carotid artery) atherosclerosis which leads to narrowing of arterial walls throughout the body, resulting in CVD (48).

The results of the UKPDS showed that a 14% reduction in the risk of CAD was associated with a 0.9% reduction in HbA1c level (11) and a 16% reduction for every 1% HbA1c level reduction (49). A 42% reduction in CVD risk and a 57% reduction in nonfatal myocardial infarction or death from CVD was found by the Diabetes Control and Complications Trial during a 17-year follow-up of the patients (50).

Reduced blood flow to the lower limbs causes PAD and increases the risk of amputation. The German Epidemiological Trial on Ankle Brachial Index study demonstrated that diabetic patients aged 65 or older have a 2-fold higher risk of PAD as well as a 2.5-fold higher risk of intermittent claudication (51). Furthermore, for patients diagnosed with PAD, the risk of developing ischemic ulceration is increased by more than 20% in ten years and among people with diabetes the likelihood is 3-fold higher (52).

The risk factors for the development of CVD includes high blood glucose; obesity; dyslipidaemia (i.e., elevated serum triglyceride, low-density lipoprotein, and free fatty acid levels and low high-density lipoprotein levels); hypertension (53, 54); unhealthy lifestyle characterised by high intake of sugar, salt and fat; low intake of fruit and vegetable; physical inactivity; and use of tobacco and alcohol (50, 55, 56).

1.4 Burden of Diabetes

1.4.1 Prevalence of diabetes and its complications

Diabetes has become one of the major global health emergencies. The prevalence of diabetes was estimated as 8.8% (95% CI 7.2-11.3%) in 2017 and is expected to be 9.9% (7.5-12.7%) by 2045 (3). In 2017, the highest prevalence of diabetes with 11.1% was observed in the North America and Caribbean region while the lowest was in the Africa region with 4.4% (3).

In Southeast Asia, 82 million adults live with diabetes which is the second-highest number of all IDF regions, and it is home to 19.3% of the total number of people with diabetes in the world. In 2017, 1.1 million people died due to diabetes, the second-highest number of deaths of all IDF regions. In the past two decades, the remarkable change in the prevalence was found in Nepal and China. The national prevalence has increased by two-fold or more within a decade in many countries of this region (57). In Bangladesh, the prevalence of diabetes was 9.7% in 2011 (58) and the number of adults with diabetes is projected to be 13.7 million by 2045 (3).

The estimated global prevalence of each complication for working-age adults aged between 20 and 65 years in 2017 showed that the prevalence of CAD ranged between 12% and 31.7%. The prevalence of diabetic foot was 6.4% (1) with a variation between 3% in Oceania and 13% in North America (1). The prevalence of nephropathy was 39% (19) and it varied between 16% and 66%. The prevalence of retinopathy, a leading cause of blindness was found to be 35%. Compared to Western populations, diabetes and its complications start relatively early among Southeast Asians with a higher magnitude and severity (59, 60).

1.4.2 Economic burden of diabetes and its complications

Diabetes is a global catastrophe that drains national healthcare budgets, reduces productivity, slows economic growth, and places a burden on vulnerable households and the economy of the country (61-63). For treatment and prevention of diabetes alone, US$727 billion was spent on healthcare in 2017, which corresponds to one of every eight dollars spent on healthcare (3). The economic burden of diabetes is expected to continue to grow with the growing incidence and prevalence of diabetes. The 2017 estimates showed that it would be US$776 billion by 2045, which represents 7% growth compared to the estimate for 2017 (3).

In addition to the direct cost, diabetes-related premature death and disability have a negative economic impact on the economy of countries, which is often called the indirect cost of diabetes. As estimated in 2017, approximately 4.0 (3.2-5.0) million people aged between 20 and 79 years died from diabetes, which is equivalent to one death every eight seconds (3). Among this age group, diabetes accounted for 0.7% of the global all-cause mortality, which was higher than the all-cause mortality from infectious diseases such as HIV/AIDS (64), tuberculosis (65) and malaria in 2015 (64). Diabetes also has an impact on the work productivity of the working-age population. Productivity loss occurs due to absenteeism (time lost from work due to illness) as well as presenteeism (time at work impaired due to illness) (3). A significant loss of productivity can result from the high prevalence of diabetes in a working-age population combined with high prevalence of diabetes complications and consequent disability. Lost productivity at work is an important concern for employees, employers and society as it places a significant economic burden on a country in terms of lost income earnings and tax revenue and diminished GDP.

Among the seven IDF regions, the North America and Caribbean region, the Europe region and the Western Pacific region were the top three regions with the highest expenditure on diabetes in 2017, which corresponds to 91% of the total global spending (3). The other four regions spent the remaining 9% on diabetes despite being home to 27% of the total population with diabetes (3). In the Africa region. on average, ID444 was spent on people with diabetes yearly. However, the expenditure was almost 20 times higher in the North America and Caribbean region, where ID8,396 was spent annually per person with diabetes (3).

People with diabetes have on average 2-fold higher medical expenditure than those without diabetes due to its chronic complications. Among the chronic complications, CVD consumes a significant part of diabetes resources nationally (66) and the economic burden as a percentage

of GDP was larger in LMICs than in HICs (67). Data from 23 LMICs showed that an estimated amount of US$84 billion of GDP was lost due to CVD between 2005 and 2015. China, India, and the Russian Federation were responsible for half of this GDP loss (68).

A survey conducted across 41 countries diagnosed 20% of adults with diabetes eye diseases (DED) and the prevalence of DED was the highest in the Southeast Asia with 41% (69). The burden of DED is also evident in the data from some developed countries: in Spain, the cost of diabetic retinopathy grew from €(euro)200 to €233 between 2007 and 2014 (70), while in Canada, the mean six-month cost of mild Diabetic Macular Edema (DME) was Canadian dollar (CAD) 2,092 and for severe DME it was CAD3,007 (71). In addition to the DED treatment, the cost is associated with productivity losses due to absenteeism and seeking the support of informal caregivers (72).

Nephropathy, the CKD in diabetes is associated with significant additional health expenditure and the costs vary depending on the severity of the disease. The associated health expenditure increases exponentially when nephropathy progresses to end stage renal disease (ESRD). The mean annual cost for nephropathy was US$6,826 in the US between 1999 and 2002, which is 49% higher than for people without nephropathy. Patients with ESRD experienced an annual mean cost of US$10,322 without dialysis, which it increased 2.8-fold with dialysis (73).

Diabetic foot complications due to neuropathy are among the most severe and costly complications of diabetes. One third of diabetes-related costs were estimated to be linked to foot ulcers in 2007. Among people with diabetes the cost of care is 5.4-fold higher for people with foot ulcers than those without foot ulcers. Furthermore, among patients with foot ulcers, the treatment cost of the highest grade foot ulcers was 8-fold higher than the cost of the lowest grade foot ulcers (74).

1.5 Glycaemic Control: An Important Aspect of Diabetes Management

Diabetes mellitus which is characterised by chronic hyperglycaemia, demands intensive management to achieve HbA1c of less than 7%, which is recommended by the ADA in standards of medical care in diabetes (75). Intensive control of hyperglycaemia reduces the development and progression of macrovascular and microvascular complications in both type 1 and T2DM.

The literature supports that glycaemic control (HbA1c less than 7%) is directly associated with the onset and progression of macro vascular and microvascular complications (76, 77). Results from the ten-year follow-up of the UKPDS found that newly diagnosed diabetes patients under

the intensive treatment (sulfonylurea, metformin or insulin) arm had reduced incidence of microvascular complications, myocardial infarction, and death from all causes than the control group (77). Results of the Action to Control Cardiovascular Risk in Diabetes and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation studies indicated that a lower HbA1c level is associated with a reduction in macrovascular complications of diabetes but failed to demonstrate conclusively that aggressive glycaemic control can improve the prognosis of macrovascular complications, especially for patients with existing CVD and long-standing diabetes (78, 79). However, newly diagnosed patients who have no notable microvascular or macrovascular complications can benefit from glycaemic control in the short term (to prevent microvascular complications) and in the long-term (to potentially prevent myocardial infarction and death from any cause) (76).

The ADA standards of medical care in diabetes recommended an individualised goal of glycaemic control, which means not all patients are candidates for an HbA1c goal of less than 7%. The goal individualisation should be based on duration of diabetes, age, comorbid conditions, known CVD or advanced microvascular complications, hypoglycaemia unawareness, and other individual patient considerations (75).

1.6 The Aims of This Thesis

Diabetes has become a global threat and in LMICs especially, it is a cause of greater concern as more than 80% of people with T2DM are living in these countries. Due to social, psychological, environmental, economic and lifestyle variations between HICs and LMICs, the factors related to the different aspects of diabetes and the cost of diabetes care vary enormously between them. Therefore, the scientific evidence that is mostly available in the context of HICs is rarely translatable to LMICs, which include Bangladesh. To generate research-based evidence in the context of Bangladesh, the main objective of this thesis was to estimate the economic burden of T2DM, find the risk factors of T2DM complications and their impact on the economy, and explore the prevalence and determinants of glycaemic control to support the management of T2DM in Bangladesh. This thesis was also aimed to develop a risk scoring tool for T2DM related complications and an economic model to estimate the impact of diabetes on GDP in Bangladesh.

Specifically, the aims were:

- To estimate the cost-of-illness (COI) for T2DM in Bangladesh
- To assess the economic burden of complications on total cost and hospitalisation for T2DM
- To find the prevalence and factors related to glycaemic control among people with T2DM
- To find the factors related to macrovascular and microvascular complications and develop a risk scoring tool for T2DM-related complications
- To model the effect of productivity loss on GDP in Bangladesh.

Chapter 2 presents the results of a systematic review to summarise the impact of the COI of T2DM in LMICs and to identify methodological gaps in measuring the COI of T2DM.

Chapter 3 of this thesis describes the methods and materials related to each of the studies mentioned above.

Chapter 4 of this thesis estimates the COI for people with T2DM in Bangladesh. The findings of this study highlight the major cost contributors and the cost determinants that will help both patients and the providers to manage and allocate scarce resources.

Chapter 5 outlines the burden of T2DM complications on hospitalisation and healthcare costs. Diabetes-related complications are the salient threat which is placing an enormous burden on the global economy, especially on the economy of a resource-limited country like Bangladesh. Identifying the complication with the highest impact will assist in making recommendations to advocate and develop a complication-specific diabetes management plan.

Chapter 6 estimates the prevalence of and identifies the factors related to glycaemic control among people with T2DM. It has been well established that intensive blood glucose control can reduce the incidence of complications and delay their onset and progression. However, keeping the blood glucose within the desired range is a challenging task without a clear understanding of the factors related to glycaemic control.

Chapter 7 assesses the prevalence of macrovascular and microvascular complications among people with T2DM. This chapter also identifies the plausible factors associated with each of the complications and describes the development of a risk scoring system for CVD related to T2DM.

Chapter 8 presents the economic model that was developed to assess the effect of productivity loss on GDP of Bangladesh to assist the healthcare providers and the policy makers of the country.

Chapter 9 provides a summary and the conclusion of this thesis.

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Chapter 2

LITERATURE REVIEW

Context of the study

A systematic review was conducted to serve the primary focus of this project that has been included in this chapter. The study performed a systematic search on the COI of T2DM in LMICs to summarise the previous study findings and their gaps and provided recommendations to appropriately measure the economic burden of T2DM in LMICs. This review was conducted by synthesising results from studies conducted in LMICs in English language covering the COI, healthcare cost or resource use for T2DM. The systematic search was conducted in the MEDLINE, EMBASE, CINAHL, PsycINFO and COCHRANE databases. Despite the substantial body of evidence on the COI of T2DM, most of the studies were conducted in HICs. At the time of this review, there was no synthesised evidence of the COI of T2DM in LMICs. Moreover, in HICs, the commonly used perspective was healthcare system, where insurance databases and healthcare providers were the main source of cost-related information. Therefore, the total medical cost approach is the most common in HICs as all the components of costs are available in the database for people with diabetes. Conversely, in LMICs, the choice of cost-estimation methodology was largely driven by the availability of data, which greatly influenced the magnitude of cost estimates. Therefore, this review aimed to summarise the COI of T2DM in LMICs to identify methodological gaps in studies conducted in these countries in measuring the COI of T2DM.

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RESEARCH ARTICLE Open Access

Cost-of-illness of type 2 diabetes mellitus in low and lower-middle income countries: a systematic review

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Abstract

Background: Diabetes is one of the world's most prevalent and serious non-communicable diseases (NCDs). It is a leading cause of death, disability and financial loss; moreover, it is identified as a major threat to global development. The chronic nature of diabetes and its related complications make it a costly disease. Estimating the total cost of an illness is a useful aid to national and international health policy decision making. The aim of this systematic review is to summarise the impact of the cost-of-illness of type 2 diabetes mellitus in low and lower-middle income countries, and to identify methodological gaps in measuring the cost-of-illness of type 2 diabetes mellitus.

Methods: This systematic review considers studies that reported the cost-of-illness of type 2 diabetes in subjects aged 18 years and above in low and lower-middle income countries. The search engines MEDLINE, EMBASE, CINAHL, PSYCINFO and COCHRANE were used form date of their inception to September 2018. Two authors independently identified the eligible studies. Costs reported in the included studies were converted to US dollars in relation to the dates mentioned in the studies.

Results: The systematic search identified eight eligible studies conducted in low and lower-middle income countries. There was a considerable variation in the costs and method used in these studies. The annual average cost (both direct and indirect) per person for treating type 2 diabetes mellitus ranged from USD29.91 to USD237.38, direct costs ranged from USD106.53 to USD293.79, and indirect costs ranged from USD1.92 to USD73.4 per person per year. Hospitalization cost was the major contributor of direct costs followed by drug costs.

Conclusion: Type 2 diabetes mellitus imposes a considerable economic burden which most directly affects the patients in low and lower-middle income countries. There is enormous scope for adding research-based evidence that is methodologically sound to gain a more accurate estimation of cost and to facilitate comparison between studies.

Keywords: Cost-of-illness, Direct cost, Indirect cost, LMICs, Systematic review, Type 2 diabetes mellitus

Background

Globally, diabetes is one of the most prevalent growing epidemics that causes premature death, disability, and economic loss; moreover, it is a significant threat to global development [1–4]. In 2015, 415 million people were diagnosed with diabetes mellitus (DM) and the number is predicted to be 624 million by 2040 [5]. This global increase in DM is attributed to population growth, ageing and an increasing trend towards unhealthy diets, sedentary lifestyles and obesity [6]. In 2013, about two-thirds of all individuals with diabetes lived in the lower-middle-income countries (LMICs) [4]. Its increased prevalence in the LMICs appears to be fuelled by rapid urbanisation, change in diet and increasingly sedentary lifestyles [7]. Diabetes is linked to macrovascular complications such as: cardiovascular, cerebrovascular, and peripheral vascular diseases, as well as microvascular complications such as: retinopathy, nephropathy and neuropathy [8, 9]. DM is a costly diseases due to its prolonged nature and associated complications [10]. Global

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healthcare expenditure to treat and prevent diabetes and its associated complications was USD376 billion in 2010; the expenditure is projected to be USD490 billion in 2030 [11].

Cost-of-illness (COI) studies include of the impact of a disease on individuals, community and the country as a whole from various aspects. The aim of a COI study is to identify and quantify all costs of a particular disease including direct, indirect and intangible costs. The output is the estimation of the total economic burden of a specific diseases to the society in monetary terms [12]. It is commonly accepted that estimating the total cost of an illness is a useful tool to national and international health policy decision making [13].

Development or improvement of cost-effective solutions for the management of type 2 diabetes mellitus (T2DM) depends on costs identification. A few studies addressed the COI of T2DM in LMICs, however no systematic review has been conducted. A systematic review helps to summarise the findings, discuss the methods used and identify the gaps in previous studies. Thus, the aim of this study was to perform a systematic review on COI of T2DM in LMICs which will summarise the previous findings and provide recommendations for appropriately measuring the economic burden of T2DM in future studies.

Overview of cost-of- illness studies

The COI typically stratifies costs into three categories: direct, indirect and intangible costs.

Direct cost

The direct costs associated with resources used to treat the disease including expenditure for medical care and treatment. The direct cost covers two sub categories: (a) direct medical costs which include hospitalisation costs, outpatient visits, medications, laboratory tests, medical supplies, emergency services, and traditional medicine services; and (b) direct non-medical costs includes travel and meal cost en-route to the hospital.

Indirect cost

The indirect cost includes the opportunity cost of productive time loss by patients and their accompanying persons due to morbidity, disability or premature death.

Intangible cost

The intangible cost includes social, emotional and human costs. Since the costs cannot be converted to money, they are unmeasurable. Intangible cost includes pain, suffering, loss of quality of life, lack of participation in social events or poor emotional health.

Perspective of COI studies

There are different perspectives to consider when undertaking a COI study, and each category includes marginally different sets of cost items. Thus, each perspective finally leads to different kinds of results for the same diseases. These perspectives can be societal, the health care system, third-party payers, business, the government, and participants and their families [12, 14, 15]. The societal perspective, which covers the maximum components of cost, is generally the most preferred. Table 1 presents the cost categories included in each perspective.

Approaches of COI studies

The approach of a COI study can be either prospective or retrospective. In a retrospective approach, all relevant cost components are followed up from previous records; thus, it is less expensive and less time consuming. On the other hand, in a prospective approach, all relevant cost components are followed up for the coming year means collecting data from patients over time; thus, it is quite expensive in terms of time and resources.

Types: Incidence-based vs. prevalence-based

There are two different types of COI studies—prevalence-based and incidence-based, depending on in which

Table 1 Costs included in cost-of-illness studies by perspective

Perspective	Medical cost	Morbidity cost	Mortality cost	Transportation/ Nonmedical cost	Transfer payment
Societal	All costs	All costs	All costs	All costs	–
Health care system	All costs	–	–	–	–
Third-party payer	Covered costs	–	Covered costs	–	–
Business	Covered costs (self-insured)	Productivity loses (absenteeism)	Productivity loses	–	–
Government	Covered (medical aid)	–	–	Criminal justice costs	Attributable to illness
Participants and families	Out-of-pocket costs	Wage losses/ Household production	Wage losses/ Household production	Out-of-pocket costs	Amount received

Source: Luce et al. 1996. 37 [15]

way the data are being used. The prevalence method estimates the economic burden of a diseases for a specific period, commonly six months to a year. Conversely, the incidence-based approach estimates the life-time cost, from the onset of diseases to cure or death. The prevalence-based method is the most common. Both the prevalence-based and incidence-based COI studies can be designed either in a prospective or retrospective way [16].

Methods

Criteria for selection of the studies

A systematic search was conducted in the MEDLINE, EMBASE, CINAHL, PHYCINFO and COCHRANE databases. The search (Additional file 1) has covered the period from date of their inception to September 2018. The search was limited to studies that addressed COI of T2DM in LMICs and published in English language. Furthermore, a manual search was conducted to identify relevant articles in the reference lists of the identified articles.

In the present review, a systematic search was conducted to screen for relevant articles following the pre-set inclusion and exclusion criteria. Results of original studies conducted in LMICs in English covering COI, healthcare cost, or resource use for T2DM were included in this review. The following studies were excluded from this review: studies conducted on other types of the diabetic population, studies that included a cost-effectiveness analysis of intervention, drug or treatments, studies performed on animals or in vitro studies, and studies conducted in high income countries. Also, review papers, conference abstracts, case reports, editorials and letters to the editor were excluded.

Screening and data extraction

A comprehensive search strategy developed with the help of an expert research librarian was implemented combining the three concepts: cost, T2DM and LMICs. A two-tire screening process was followed to retrieve the relevant articles from the literature search. Two trained, independent reviewers helped in the process of selecting relevant articles. Firstly, the titles of articles were screened under the following terms: for "**cost**" or similar words such as "cost or expenditure" or "costs and cost analysis" or "health care costs" or "cost of illness", and for "**diabetes**" similar words such as "type 2 diabetes," or "niddm or t2dm," or "non-insulin dependent diabetes mellitus" were included as a search term. The final search was conducted combining the three concepts using "AND". Secondly, two reviewers independently evaluated the abstracts and, if necessary, they read the full texts of all the articles which were selected considering the selection criteria. Any disagreement between the two reviewers was finalised upon discussion and additional consultancy with a third reviewer, if necessary. The reference lists of all the selected articles were screened manually for additional citations. Important information on the study methods and key findings were then retrieved from the articles and summarised in Tables 2 and 3. To compare different currencies that have been used in the studies, all costs were converted to PPP (Purchasing Power Parity). Local currencies were inflated applying the World Bank's consumer price index (CPI) [17] to make them equivalent to the cost in 2012, and then converted into US dollars (USD) using a conversion software [18].

Critical review of data and quality of studies

The quality of the studies was critically assessed following the previous reviews and guidelines [19–22]. The assessment tool (Additional file 1) had 15 indicators and each indicator was rated as high with a score of 1, partial with a score of 0.5 and low with a score of 0. The maximum obtainable score was 17. The quality assessment was also done by two independent authors; there was no significant disagreement between the authors.

Results

The initial search resulted in 5457 articles. Of these, 1802 were duplicates and were removed. Of the remaining 3655 articles, 3640 were excluded by screening of abstracts and titles, leaving 152 articles for full-text review. After screening the full-text articles, 147 were excluded leaving only five articles. Then the reference lists of these five articles were screened manually, and an additional three articles were included. Subsequently, eight articles were finally selected for inclusion in this systematic review (Fig. 1).

Characteristics of the studies

Table 2 summarises the methods and key findings of the eight articles included in the systematic review. Two-thirds (n = 6) of the studies were conducted in India [23–28], one (n = 1) in Pakistan [29] and one (n = 1) in Nigeria [30]. Four of the eight studies estimated both direct and indirect costs of T2DM [26–29] while the other half estimated only direct costs. Only one [26] study reported intangible costs. Furthermore, only three studies generalised the estimated cost for the national population [24–26]. All the studies were cross-sectional retrospective, except the study by Sadanandam et.al which was a prospective observational study. Only two [25, 26] of the eight studies recruited the study participants from the community while in the remaining studies data were collected from different levels of the hospitals.

Table 2 Characteristics of cost-of-illness studies for type 2 diabetes mellitus, arranged by year and reflecting costs incurred in the year stated

Sl no	Author (Year of costing)	Data source	Sample size	Study design	Country	Direct	%	PPP 2012	Indirect	%	PPP 2012
1	Shobana et al. [24] (1997)	Hospital (PHD & GGD)	596	Retrospective	India	Median annual direct cost for PHD Rs.4510 GGD Rs.247		PHD 218.7 GGD 11.9			
2	Ramachandran et al. [23] (2005)	Hospitals, clinics, (Rural & Urban)	556	Retrospective	India	Median annual direct cost for urban Rs 10,000, rural Rs 6260		Urban 323.5 rural 202.5			
3	Kumar et al. [25] (2005[1])	Community	819	Retrospective	India	Mean direct cost Rs. 6000		194.1			
4	Khowaja et al. [29] (2005)	Clinics (P,G&NGO)	345	Retrospective	Pakistan	Mean direct cost Rs 11,580		270.9	Meanproductivity loss by participants Rs. 113 and attendants was Rs. 208		2.6 4.8
5	Tharkar et al. [26] (2009)	Community	718	Retrospective	India	Median annual direct cost Rs. 25,391	83.70	605.3	The median annual indirect cost 4970 INR	16.3	118.5
6	Chandra et al. [27] (2012)	Hospital	219	Retrospective	India	Average annual direct cost Rs 8822	69.08	163.9	Average annual indirect cost Rs. 3949	30.9	73.4
7	Suleiman et al. [30] (2011–2012[1])	Hospital	321	Retrospective	Nigeria	Average annual direct cost NG 45531.19		284.5			
8	Akari et al. [28] (2012)	Hospital	150	Prospective observational	India	Average annual direct cost with complication US$293.79 without complication US$27.7	98.8 92.6	293.7 27.7	Average annual indirect cost with complication US$20.34 without complication US$2.21	1.1 7.4	20.3 2.2

Note: PPP = Purchasing Power Parity. Local currencies were inflated applying the World Bank's consumer price index (CPI) to make them equivalent to the cost in 2012, and then converted into USD as PPP applying the conversion rate on 3oth June 2012 using 1USD = 55.9 Indian Rupee, 94.9 Pakistan Rupee, and 160.0 Nigerian naira

Table 3 Components of direct healthcare costs for diabetes mellitus

Sl	Author	Year of Publication	Country	Hospital inpatient	Physician services	Emergency outpatient	Drugs	Laboratory tests	Other health professional/ allied health	Daily self-management	Transport	Food on the way to hospital	Dietary management	Surgery	Subsidized consultation and investigation cost	Informal care/caregiver	Indirect cost	Intangible cost	National estimation
1	Shobana et al. [24]	1999	India	√	√		√	√			√			√					√
2	Ramachandran et al. [23]	2007	India	√	√		√	√						√					
3	Kumar et al. [25]	2008	India		√		√	√		√									
4	Khowaja et al. [29]	2007	Pakistan		√		√	√			√	√			√		√		
5	Tharkar et al. [26]	2010	India	√	√		√	√		√	√	√				√	√	√	√
6	Chandra et al. [27]	2014	India		√		√	√						√			√		
7	Suleiman et al. [30]	2014	Nigeria		√		√	√			√								√
8	Akari et al. [28]	2013	India	√	√		√	√			√	√					√		

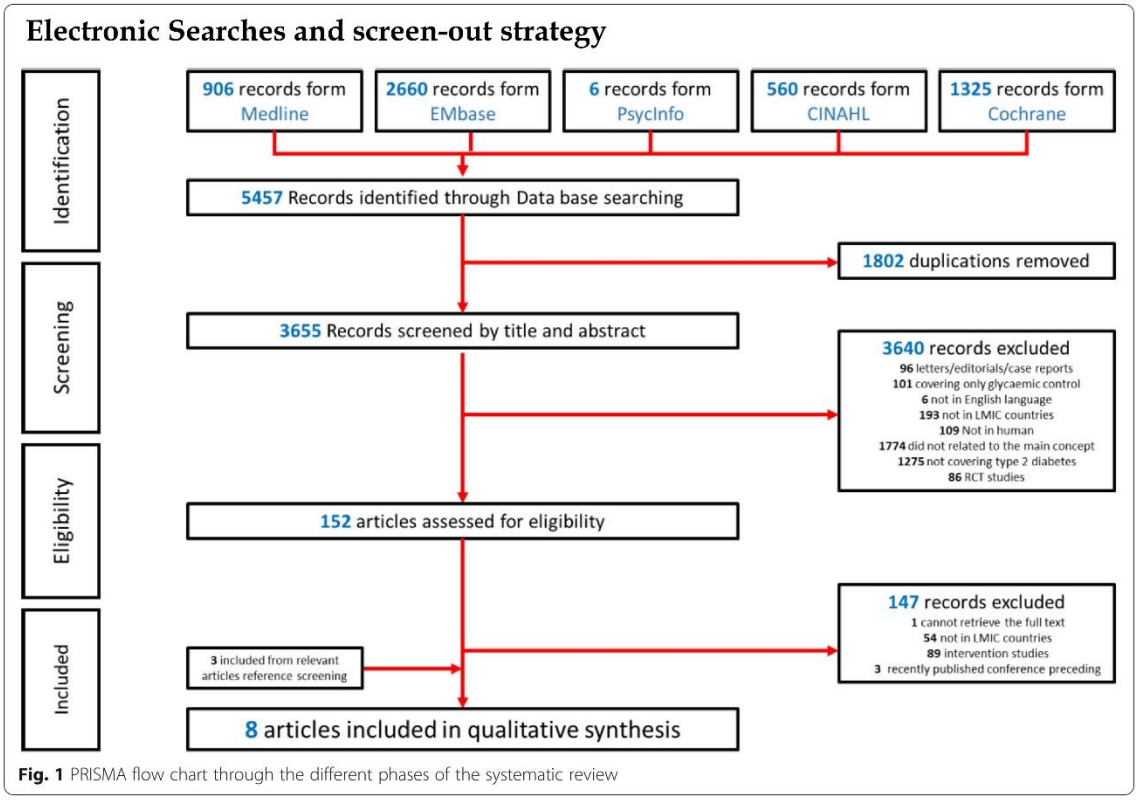

Fig. 1 PRISMA flow chart through the different phases of the systematic review

Cost components

There was a variation among the cost components that estimated the direct and indirect cost of the studies (Table 3). All the studies considered costs associated with hospitalisation, physician services, laboratory tests and drugs as components of direct cost. All reported direct costs were calculated from a patient's perspective and all indirect costs were measured using a human capital approach [31].

Total cost of T2DM

Of the eight articles in this review, 50% ($n = 4$) of the studies [26, 28–30] estimated the total cost (both direct and indirect costs). The annual average cost (both direct and indirect) per person for treating T2DM ranged from USD29.91 to USD237.38. However, Tharkar et al. [26] reported the annual average cost as USD672.6 per person, which included costs associated with complications.

Direct, indirect and intangible costs of T2DM

The reported costs components of T2DM varied by countries and year (Table 1). Most studies reported the average (mean) annual cost while three reported the median cost [23, 24, 26]. A clear trend of increment of the average annual direct and indirect costs per person per year (PPPY), respectively, from USD106.53 in PPP (Purchasing Power Parity) 2012 to USD293.79 and from USD2.6 in PPP 2012) to USD73.4 was observed between 1997 and 2012. Only one study reported intangible cost, which was USD41.1 PPPY. Furthermore, direct costs were higher compared to indirect costs for the four studies that estimate both direct and indirect costs. Hospitalisation costs were predominant among the contributors of direct costs, which were about half of the total costs. In the studies that did not consider hospitalisation costs, medication costs were the highest contributor of direct costs, which accounted for 26–66% of the total cost [26, 28]. The total direct costs ranged from approximately USD194.1 in PPP 2012 to USD314 (Fig. 2). Shobana et al. [24] reported that the minimum direct cost was USD5.8 in a government general hospital (GGH) setting. The minimum direct cost USD11.9 in PPP 2012 was low because 70% of the GGH subjects were unemployed and were from lower socio-economic groups. In contrast, in a private hospital setting the total direct cost was USD218.7 in PPP 2012 as most subjects were from middle, upper-middle and higher socio-economic

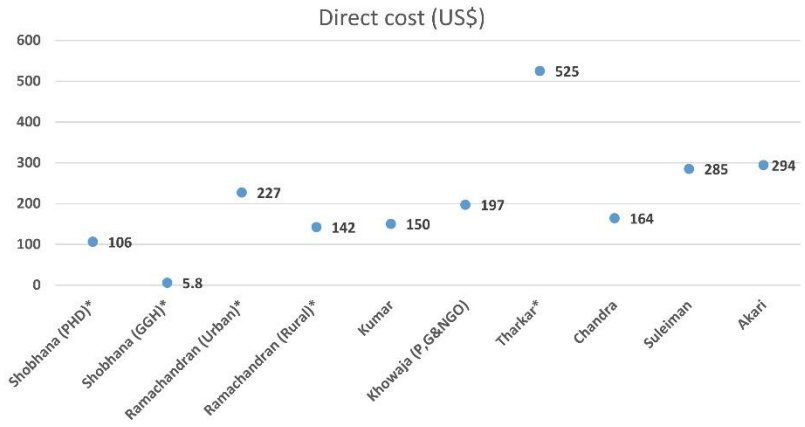

Fig. 2 Total direct cost of T2DM by reported studies

groups. Tharkar et al. reported [26] a median direct cost of USD605.3 in PPP2012, which may be reflected by the fact that this study considered the highest number of cost components among the studies in this review.

National burden of T2DM

The study by Shobhana et al. [24] in 1997 estimated an annual direct cost of USD2.2 billion (USD4.3 billion, in PPP 2012) for diabetes health care for approximately 20 million diabetic patients in India. Tharkar et al. [26] projected the total annual cost (direct and indirect costs) of USD31.9 billion (USD36.7 billion in PPP 2012) for type 2 diabetes in India in 2010. Ismail et al. [30] reported that in Nigeria, the annual average direct cost was USD284.56 PPPY for T2DM in 2012; this study also showed that without any complication the cost was USD1.64 billion.

Associated factors for costs

Of the eight studies in this review, two [27, 29] described the factors associated with the costs using bivariate analysis and three [23, 25, 26] described the factors associated with the direct cost using multivariable analysis. Results of the bivariate analysis showed that age, number of complications and duration of diabetes were associated with direct costs. In the multivariable analysis, education, income, number of complications, duration of diabetes, mode of treatment, hospitalisations and surgery were found to be associated with direct costs after adjustment for other potential variables.

Quality analysis

To execute a good COI analysis, it is necessary to perform quality assessment focusing on the important components. The studies included in this review were evaluated on a 17-point scale. The median score was 8.5 (range: 5 to 11.5). The studies in the review lacked precise definition and type of diabetes. Only three articles clearly defined diabetes and its type. No studies stated a clear definition of co-morbidity or complications they considered. Most studies were conducted over a satisfactory period of 6 months, however, two studies did not mention any timeline [27, 30].

Fifty percent of the studies included a reasonable number (n = 500 to 800) of participants while the remaining studies were based on samples which were either too small or limited to a specific group of people. Additionally, it is notable that the included studies commonly focused on the middle-income and high-income population. All the studies collected data from individuals based on self-assessment of costs using a questionnaire. Interestingly, half of the studies verified the self-assessment information by the actual bill or records collected from the care providers.

The quality assessment also considered the suitability of the different components of costs that were used. The suitability of cost components in each included study was evaluated against the study objectives and the minimum requirements of a comprehensive COI study: cost components, perspective, approach, data source and use of sensitivity analysis [22, 32]. Only four studies included the appropriate costs.

Considering the methods, most studies did not include enough details of the methods they used. Particularly, 50% of the studies did not refer to how they calculated the costs. None of the studies applied the incremental costs method and only two studies used the regression methods. The review of results indicates that the

prevalence-based bottom-up approach was common between the studies. Only two studies performed the uncertainty test via sensitivity analysis and three studies conducted linear or multivariable regression analysis.

Besides inconsistencies in the type and amount of information provided regarding methods, limitations were not discussed in some studies. Five studies comprehensively discussed limitation on data, components of cost, study assumptions and methods.

In terms of the statistical analysis that has been used, three studies performed all necessary statistical analyses. The remaining five studies employed the Student t-test, χ^2-tset, or the Kruskal Wallies or Mann Whitney U-test to determine the statistical significance. One study did not perform any statistical analysis. Seven studies presented the average cost either by mean along with standard deviation or median with range while one study included only the mean.

Discussion

Type 2 DM imposes a large economic burden on the health care system, society, and individuals. This is the first systematic review, which appraises the COI of T2DM in LMICs only. The most notable finding of this review is that a wide variation in methodology was used to estimate the COI and the cost components. This review shows that most studies have focused on a subset of the population or health-care expenditures. The quality of the studies reviewed were deemed to be fair.

The choice of cost-estimation methodology was largely driven by the availability of data which greatly influenced the magnitude of cost estimates. All the studies in this review were conducted on a relatively small sample and most of them were based on a single-centre. In the LMICs, self-administered surveys employing patients' perspective was the most popular method to accumulate data on the cost of diabetes and the sample-size, ranging from 150 [28] to 819 [25]. Hence, they were mostly limited to a specific group of people (a hospital or state), and were generally representative of that particular diabetes population only rather than at the national level. National or regional level databases are scarce in LMICs and collection of relevant data requires resources that are limited in these countries too. Conversely, in the high income countries (HICs), health-care system perspective was commonly used where insurance databases and healthcare providers are the main source of cost-related information [33–40]. Thus, the sum-all medical cost approach is the commonest in HICs as all the components of costs are available in the database for people with diabetes. In HICs, the sample-size mostly varies from 1000 to several millions. As a result, these studies are likely to be representative, either at a national or regional level.

In LMICs, individual and families with diabetes often suffer with the financial burden of the illness; consequently, they are in need of better health care coverage to deal with the issue. All the studies showed that the expenditure incurred for the direct costs was met by patients in LMICs, as health insurance is not yet common and there is a lack of publicly-available medical services. Conversely, in developed countries, health care facilities for diabetes are highly structured and almost fully funded by the state.

The magnitude of cost estimates was influenced by the cost components considered in a study. The costs of consultation, laboratory test and drugs were common between the studies. The magnitude of the cost increased as the number of cost components increased in a study. Studies that were limited to fewer categories of cost components are likely to have underestimated the actual costs of T2DM. In the studies of this review, the healthcare cost components including inpatient, outpatient and medication were similar to the cost reported by earlier reviews [10, 41]. Despite the fact that indirect costs far exceed direct costs [41], this review showed that the direct cost was higher than the indirect cost. This may be attributed due to accounting for hospitalisation cost which is consistent with other global COI studies [39, 42–45]. Studies which considered cost of hospitalisation showed that it consumed almost half [26, 28] of the total cost; these findings are similar to a study conducted in the U.S.A. [46].

Three of the eight articles in this review addressed the cost of comorbidities or complications and have shown that the cost was significantly higher for patients with comorbidity or complications [26, 28, 29]. Similarly, Ng et al. suggested that a considerable amount of DM accredited healthcare expenditure is related to complications. Further, it was reported that there was more than a two-fold increase in cost for patients with complications compared to patients without complications [41]. Thus, it is important to control the catastrophic spending due to complications to reduce the burden of high out-of-pocket expenditure.

Most of the studies in this review failed to achieve the aim of a COI study due to a poor study methodology. First of all, the studies had a lack of referring to a comprehensive list of unit costs. Secondly, the cost components and the sources of data were not clearly justified, and were not even discussed as limitations of the study which raises concern about the quality of the studies. The absence of these features has made these studies less accurate in terms of data collection and costs calculation [32].

The use of disease-attributable approaches via case matching or regression analysis would be more accurate to obtain the exact estimates of the costs as suggested by Ettaro et al. [10]. This type of analysis gives more precise estimates of the economic burden of type 2 diabetes in the absence of randomised clinical trials. None of the studies incorporated disease-attributable approaches and

only three studies [23, 25, 26] used regression analysis to identify the factors associated with cost.

The strength of the present study is that it incorporated a systematic search and used the recommended methodology for a review study. To avoid the potential bias in the selection of the study a dual search by two independent reviewers was done following a comprehensive inclusion and exclusion criteria. The present review provides the economic burden of T2DM in LMICs. As the focus and the methodologies of the studies reviewed were heterogeneous, we were unable to perform a meta-analysis. In addition, since the present review was limited to T2DM-related cost only, some information may differ from the studies that included both type 1 and type 2 diabetes.

Conclusion

It is anticipated that T2DM poses a significant financial burden on the healthcare system as well as on the individual and society as a whole. In LMICs, large scale national or sub-national level studies that involve methodologically sound economic analysis are required. Evidence of the studies will be helpful for public health policymakers to establish health care priorities and allocate scarce resources to assist people with type 2 diabetes. A COI study should consider a discussion referencing the issues that might affect the cost estimates.

The explanation of all data sources will be beneficial for the researcher to replicate and improve future COI studies. Partial inclusion of all affected cost components and a relatively small sample underestimate the COI and thus limit the generalisability of the findings. Disclosure of the year that costs were valued would help to interpret findings as it is important to compare findings between different studies or populations.

At the very least, researchers should disclose pertinent details (e.g., age group, type of diabetes, area of residence) in the method and follow the consensus opinion of the experts about what should ideally be included in a COI study [32, 47]. Standardised COI will permit public health policymakers and the general population to understand the magnitude of the financial burden, to derive decisions about future benefits, to control the disease, and develop programs to improve the health of people with type 2 diabetes.

Additional files

Additional file 1: Appendix 1. Search strategy. **Appendix 2.** Quality assessment tool. (DOCX 27 kb)

Abbreviations

COI: Cost-of-illness; DM: Diabetes mellitus; LMICs: Lower-middle-income countries; NCDs: Non-communicable diseases; T2DM: Type 2 diabetes mellitus

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Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Ethical approval and consent to participate

As this is a systematic review no ethical approval and consent to participate is required.

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Chapter 3

METHODOLOGY

This project was undertaken to address a number of key issues related to T2DM in Bangladesh. T2DM, which had become a major concern, should receive adequate attention with sufficient research-based evidence. To generate research-based evidence, some specific research questions were developed, and a cross-sectional survey was conducted from March to September 2017 in Bangladesh to address the research questions. There were some changes in the direction of the study project and the primary protocol of the study project that was published in the Bangladesh Journal of Medical Science. This chapter will provide the updated details of the study design, methods and statistical analysis.

3.1 Study Design and Study Population

The study design was a cross-sectional and retrospective study. A prevalence-based approach with a bottom–up methodology was employed to calculate the cost from patient's perspective.

Six hospitals located in the northern and central regions of the country were selected purposively to recruit the study participants. Two of these hospitals are in the central region, providing primary to tertiary healthcare, particularly to urban residents. The remaining hospitals are in the northern region, two of which provide primary and secondary healthcare and the other two provide primary to tertiary healthcare to people residing in semi-urban and rural locations. Patients attending hospitals providing primary and secondary healthcare but in need of tertiary care are usually referred to the tertiary care hospitals. Due to the similar social and economic status for people living in the northern and southern regions, the patients from the hospitals in the northern region are comparable to those living in the southern region of the country. Therefore, no hospitals were selected from the southern region. The Diabetic Association of Bangladesh (BADAS), a not-for-profit but mostly self-sustaining social welfare organisation, directly or indirectly (through affiliated local associations) owns all the selected hospitals. BADAS, the highest diabetes care provider, has 75 diabetes centres/hospitals that cover all 64 districts (second-highest tire of regional administration) across the country.

Bangladesh has both public and private healthcare sectors. The public health system is subdivided into four different levels according to their capacity of resolution and the internal organisation. However, except medical college hospitals (tertiary level), all other hospitals (community centres and primary- or secondary-level hospitals) are not well equipped to provide adequate treatment to people with diabetes. While private providers are more diverse in terms of the treatments provided, they are mainly money-driven and usually depend on out-of-pocket (OPP) and insurance money for every service provided. This makes them accessible

only to the middle- and high-income groups (1). However, diabetes-centred care is provided primarily by BADAS, which provides specialist clinics and tertiary-level specialist hospitals. BADAS also has a research institute, which has a main hospital providing specialist services in Dhaka and a network of specialist diabetes centres across Bangladesh (2).

The selection of hospitals in this study ensured the inclusion of rural-urban as well as professionally mixed populations (e.g. service holders, businessmen, farmers, day labourers, housewives, etc.) attending various levels of healthcare services. Furthermore, although the recruited 1,253 participants, selected using systematic random sampling, in our study may not be representative of the overall population with T2DM in Bangladesh, they are representative of a good majority of them.

3.2 Sample Size

The primary focus of this thesis was to estimate the COI of T2DM. The previous COI studies that were conducted in HICs usually considered the patient database and included the data from all eligible people for analysis. Conversely, in an LIMCs setting where a database is not available, studies usually consider a specific time period and recruit the maximum number of eligible participants within the time period. In this study, we followed the recruitment method of the studies conducted in an LMICs setting and recruited participants during a period of six months. The inclusion criteria were registered adults of either gender with a minimum one-year duration of T2DM. The study excluded people with other types of diabetes or women who were pregnant at the time of data collection.

To assess for power given the sample size, we used the statistical rule of thumb 'rule of 10'. Our studies in the thesis mainly used multivariable logistic regression model and multivariate linear regression models among other statistical methods to answer the research questions.

These two regression methods were used mainly for predictive purposes where statistical power is important. In the logistic regression modelling, we need at least 10 "yes" outcomes and at least 10 "no" outcomes per coefficient. Number of coefficients depend on the number of covariates in the model. For multivariable linear regression, we can use the simple rule of thumb i.e. 20 observations per coefficient. Statistically, bigger the sample size, the more power the study will have. In this study we recruited 1,253 patients, which is higher than the sample size required for regression analysis.

3.3 Information on the variables pertinent to the study

3.3.1 Socio-demographic and lifestyle characteristics

The socio-demographic characteristics included age, gender, marital status, education, profession and monthly household income. The lifestyle characteristics included smoking status, smokeless tobacco consumption status, eating habits and physical activity.

3.3.2 Clinical characteristics

The clinical characteristics included duration of diabetes, family history of diabetes, frequency of follow-up check-ups, mode of treatment and history of hypoglycaemic events.

3.3.3 Information related to cost-of-illness

All the information related to the COI of T2DM was collected using a questionnaire. The cost components are detailed in the table below:

Cost components	Details of the component
a. Direct cost	
i. Direct medical cost	
Outpatient visit	Consultancy fee paid per visit
Hospital care	Hospital care includes hospital stay, medicine and laboratory tests during stay
Medicine	Cost of medicine per day
Laboratory tests	Investigation test done during the previous year.
Other service utilisation[#]	Other service utilisation includes use of self-monitoring blood glucose and consumables during the previous year.
ii. Direct non-medical cost	
Transportation	Transportation cost en-route to the hospital.
Meal	Meal cost en-route to the hospital.
b. Indirect cost	
Productivity loss of patient	The productive time loss of the patient to attend out-patient visit and during hospital admission.
Productivity loss of accompanied person	The productive time loss of the attendant during out-patient visit and hospital admission of the patient.

3.3.4 Recognized tools used in the questionnaire

The questionnaire was tailored including several recognized tools to assess several known and alleged factors relating aspect of T2DM. The UK diabetes and diet questionnaire (UKDDQ) (3) was used with some minor modifications to make it suitable for Bangladeshi population. Selected six items from Global Physical Activity Questionnaire (GPAQ) (4) were used to assess the physical activity level. Patient Health Questionnaire-2 (PHQ-2) (5), Generalized Anxiety Disorder Scale (GAD-2) (6), Michigan Neuropathy Screening Instrument (7), and a Six-item Cognitive impairment test (6CIT) (8) were used without any modification. Permission was obtained from the respective authority to use the above-mentioned tools. Weight and

height of participants were measured in light clothes and taking the shoes off. Waist and hip circumference were measured against thin clothing. Body mass index (BMI) and waist-hip ratio (WHR) were calculated from the collected measurements. Research Electronic Data Capture (REDCap) was used to collect and manage data (9).

3.4 Cost Calculation

The total cost of T2DM was calculated from the patient's perspective for 2017, considering direct and indirect costs as the major components. The direct cost was estimated using a bottom-up approach for the primary data collection (10) and divided into two sub categories: (a) direct medical costs including costs of hospitalisation, outpatient visits, medicine, laboratory tests, and other service utilisation (includes use of self-monitoring blood glucose and consumables), and (b) direct non-medical costs including cost of transportation and meal en-route to the hospital.

3.4.1 Direct cost

The micro-costing approach was used to identify cost items in as much detail as possible to calculate the direct cost (11). Cost per daily dose (12) of each medicine and therapy was defined. Costs related to medicine, consultancy and laboratory tests were collected from respective hospitals. All hospitals under BADAS are homogeneous, and therefore there is negligible cost variation between the selected hospitals. For other components of direct medical cost and direct non-medical cost (transportation and meal), participants' responses to the questionnaire were considered as a reference. The calculation of unit costs was done for all components of direct cost and then multiplied by the quantities of medical services received during the previous year. The cost of hospitalisation (includes hospital stay, medicine and laboratory tests during stay) was retrieved for each patient from the hospital record that was provided by the accounts department of the respective hospital. The total direct cost was calculated by adding up all the components of direct medical and direct non-medical costs.

3.4.2 Indirect cost

The indirect cost was calculated for both patients and their attendants en-route to the hospital. The productive time loss to attend OPD visit and during hospital admission was recorded based on the information provided by the patients and their attendants. The human capital approach (13) was used to calculate the indirect cost for those who were productive and in the formal workforce or housewives but not for those who were unable to work (retired or due to ill health) or who chose not to work. The minimum wage rate (US$224/annum) (14) and the median

income of the participants who were in the formal workforce were used to calculate the indirect cost of housewives. The total cost was calculated by adding up the total direct and total indirect costs.

3.4.3 Currency exchange rates

All costs were calculated in the Bangladeshi currency, Taka (BDT). During the analysis, all costs were converted into US$ using the mid-year currency conversion rate for 2017 (US$1 = BDT80) (15).

3.5 Statistical Method and Techniques Applied for Data Analysis

To analyse the data for studies 1 to 5, the statistical software package Stata SE version 15.0 was used and a p-value of 0.05 or less was considered to be statistically significant.

Chapter 4 (Study 1) aimed to estimate the COI for people with T2DM in Bangladesh. The descriptive statistics include mean with standard deviation (SD) for numerical data and frequency with percentage for categorical data. A normality test of cost data was performed using a histogram, Q-Q plot and the Shapiro-Wilk test. Cost data was right skewed; therefore, mean, median with percentiles was used to report it. A median regression was performed to determine the factors related to average annual cost. A bootstrap method was used to calculate the 95% confidence interval (CI) of regression coefficients. Sensitivity analyses were performed to evaluate the assumption that the use of minimum wage to calculate the indirect cost of housewives may give the lowest estimate and to explore the change in average annual cost with assumptions of a 25% (+/-) change in the prevalence of insulin use and a 25% (+/-) change in the prevalence of T2DM-related complications.

Chapter 5 (Study 2) assesses the burden of T2DM complications on hospitalisation and healthcare costs. The mean with SD, median with percentiles and frequency with percentage were used as descriptive statistics. A normality test of cost data was performed using a histogram, Q-Q plot and the Shapiro-Wilk test. The nonparametric Mann-Whitney U-test and Kruskal-Wallis test were used respectively to compare two groups and more than two groups. A multiple logistic regression analysis was used to identify the factors related to hospitalisation. Furthermore, multiple non-parametric regression analyses (50th percentile (median), 75th percentile and 90th percentile) were performed to explore the relationship between average annual cost with macrovascular and microvascular complications. Sensitivity analyses were performed to investigate the robustness of the total estimated cost.

Chapter 6 (Study 3) aimed to estimate the prevalence of and find the factors related to glycaemic control among people with T2DM. Descriptive statistics were reported using mean with SD for numerical data and relative frequencies (percentages) for categorical data. To test the associations between risk factors and levels of glycaemic control, ANOVA, chi-square tests and simple logistic regression analysis were used as the univariate analysis. Risk factors with a p-value <0.05 in simple logistic regression analysis were considered for the multiple logistic regression model. Clinically plausible risk factors were included in the model even though they appeared as insignificant in the univariate analysis. Multicollinearity and the first order interaction effect between clinically relevant risk factors were investigated. The stepwise backward elimination method was used to select variables that are significantly related to the outcome measures. Multiple logistic regression analysis was mainly performed to identify the determinants for inadequate glycaemic level (HbA1c ≥7%) as well as for very poor glycaemic control (HbA1c ≥9%). To determine the duration-specific risk factors, the patients were stratified by T2DM duration of ≤5 years and >5 years.

Chapter 7 (Study 4 and Study 5) includes two studies, one (Study 4) that aimed to assess the prevalence and identify the associated factors of macrovascular and microvascular complications among people with T2DM, and another (Study 5) that described the developed risk prediction tools for CVD. In Study 4, data was summarised and presented as a mean (± SD) for numerical data and frequency and percentage for categorical data. The chi-square test was used to examine associations between each of the complications with patients' demographic and clinical characteristics. Any association was further examined using simple logistic regression analysis. Potential risk factors with a p-value of 0.1 or less in the simple logistic regression were included in the multiple logistic regression analysis. The stepwise variable selection method was used to identify the factors related to complications. Multicollinearity and first order interaction effect between covariates were also investigated.

In Study 5, we developed a risk scoring system. All missing values were imputed using the ICE method. The bootstrap method with multiple logistic regressions was used to identify predictors for cardiovascular complications of CAD and stroke. The selected predictors were then added to a mixed-effects multiple logistic regression to account for residential variation. The models were validated using the k-fold bootstrap method. Using the developed models for CAD and stroke, the absolute and additive scores were calculated and the risk of developing CAD or stroke for a patient was stratified into groups. The risk scoring systems for both CAD and stroke were translated into a web-based risk calculator.

Chapter 8 (Study 6) includes the economic model to estimate the impact of diabetes in Bangladesh in terms of mortality, years of life lost and PALYs lost. A life table model was developed using published demographic and mortality data to estimate excess mortality, years of life lost, quality-adjusted life years lost and PALYs lost among the Bangladeshi working-age (20 to 59 years) population with diabetes and each of them were simulated in a follow-up until a retirement age of 60 years. The health-related quality of life decrements and relative reduction in productivity attributable to diabetes were sourced from primary data of the cross-sectional survey conducted for this study in Bangladesh in 2017. A model was constructed for the people with diabetes and another model was developed for the same cohort on the assumption that they no longer had diabetes. The number of deaths, years of life lived and PALYs lived of the above two models were compared to evaluate the impact of diabetes. The standard annual discount rate of 3% by the World Health Organisation was applied to years of life lived and PALYs lived.

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Original article:

Cost-Of-Illness and its Determinants for Type 2 Diabetes Mellitus in Bangladesh: Protocol for a Cross-Sectional Study

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Abstract:

Background: Diabetes is one of the most prevalent non-communicable diseases (NCDs) all over the world and leading cause of death, disability, and economic loss. Diabetes imposes a heavy economic burden on individuals, their families and society as a whole. The aim of this study is to estimate the economic burden of type 2 diabetes mellitus (T2DM) in Bangladesh and to find association between glycemic control and Health Related Quality of Life with cost-of-illness (COI). ***Methodology:*** This will be an analytical cross-sectional cost-of-illness study. Within a specific time period participants aged ≥18 years, registered with Bangladesh Diabetic Somiti and having type 2 diabetes for more than one year will be recruited from selected hospitals inside and outside Dhaka to cover all level of health care services. A pre-tested electronic questionnaire will be used for data collection. The questionnaire will include demographic, clinical, behavioral information of the participants and all cost related information related to diabetes management during last one years. Descriptive statistics will include mean (±SD) or median (percentile) or relative frequencies (percentage) depending on the data. Two samples independent t-test or Mann-Whitney U-test, ANOVA or Kruskal-Wallis test and chi-squared tests will be used for univariate analysis. The multivariable regression analysis and bootstrap method will also be employed to analyze the relationship between the total cost of care (dependent variable) and several potential explanatory variables (independent variables). Logistic regression analysis will be performed to assess the factors affecting glycemic control and health related quality of life (HRQoL). The calculated total cost-of-illness will be projected for T2DM in Bangladesh by a mathematical modelling.***Discussion:*** The results of the study will be useful as background information to forecast the economic burden of type 2 diabetes mellitus in Bangladesh and will be beneficial to conceptualize health strategies at national level. Furthermore, recognizing the factors of cost-of-illness will help both patients and health care providers to improve the management plan and cost control and hence, to have better quality of life. Evidence about the magnitude of the burden of T2DM is important for public health policymakers who are involved in making health care priorities and allocating scarce resources to facilitate the greatest benefits for type 2 diabetic people in Bangladesh.

Keywords: *Bangladesh, Cost-of-illness, Direct and indirect cost, Economic burden, Type 2 diabetes mellitus*

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Background

Diabetes is one of the most prevalent non-communicable diseases (NCDs) globally. It is identified as a major threat to global development as it is the leading cause of death, disability and economic loss [1-4]. The burden of diabetes and its related mortality and disability has been rising around the globe, especially in South-East Asia. According to recent estimates by the International Diabetes Federation (IDF), the South East-Asia (SEA) region is home to more than 79 million adults (age group 20-79 years) with diabetes in 2017, and

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this number is projected to be 629 million in 2045 [5]. Results of several small-scale population-based studies in Bangladesh showed an increasing trend of diabetes prevalence in rural [6-12], semi-urban [12], and urban [8, 13] communities.

Diabetes is an expensive disease due to its chronic nature and its related complications. An estimated amount of US$727 billion of global healthcare expenditure was spent in 2017 to treat and prevent diabetes and its related complications, which represents an 8% increase compared to the 2015 estimate and the amount is projected to be USD 776 billion by 2045 means 7% growth [5]. People living in low- and middle-income countries pay a larger share of out-of-pocket health expenditures due to lack access to health insurance or publicly available medical services, compared with people living in high-income countries. Low- and middle-income countries which are home to 75.4 % of total population with diabetes, only 19% of global health expenditure on diabetes was spent on them [14]. An increasing trend of expenditure associated with diabetes was observed in developed [15-19] and developing [20-26] countries.

Maintaining the blood glucose level within the recommended range reduces the risk of diabetes complications and thereby reduce related cost. Thus, it has positive impact on economy. The role of improved glycemic control in the reduction of micro- and macrovascular complications of diabetes has been supported by many observational studies and randomized controlled clinical trials [10, 27-29]. Privation of optimal awareness of diabetes control may result in less-strict disease management, which in turn may lead to increase risk of diabetes-related complications [30] and associated higher healthcare costs [31]. Studies have shown that more intensive management of the disease, while initially costly, can be very cost-effective or can lead to long-standing cost savings by reducing the incidence or delay the progression of the costly complications [32-34]. To be able to assess the financial burden of diabetes and plan the future health care needs, estimation of the cost-of-illness of diabetes is an empirical need.

Among the south-east Asian countries, Bangladesh has the second-highest prevalence of diabetes. Therefore, diabetes and its related complications are placing a significant financial burden on individuals, the health care system and on the economy of the country as a whole. In order to allocate limited resources and to set healthcare priorities, it is important for public health policymakers to understand the magnitude of the burden of diabetes. However, in the context of Bangladesh, background data associated to the economic burden of diabetes is limited in the literature. The aim of the current study is to estimate the direct and indirect costs of type 2 diabetes and its association with glycaemic control and quality of life. Furthermore, to formulate a cost model to evaluate the economic burden of diabetes on individuals and at a country level.

Specific objectives

This study has three main objectives. Firstly, to estimate the cost-of-illness and to evaluate the determinants of cost-of-illness of type 2 diabetes mellitus in Bangladesh. Secondly, to find the determinants of glycaemic control and health-related quality of life. Thirdly, to assess the potential relationship of poor glycaemic level and health related quality of life with diabetes-related hospitalization costs. The secondary objective is to estimate the national economic burden of type 2 diabetes mellitus in Bangladesh by a mathematical modelling.

Outcome measures

The primary outcome measures will be cost-of-illness of T2DM in a descriptive manner. The determinants of cost will be assessed by an analytical operation. To evaluate the determinants of glycemic control and quality of life all potential variables including COI will be considered as independent variable.

The secondary outcome measure of the study is to estimate the economic burden of T2DM in Bangladesh.

Methodology

Ethical Approval

The project has been approved by the Monash University Human Research Committee and the Ethical Review Committee of the Bangladesh University of Health Sciences. The approval from the Diabetic Association of Bangladesh (BADAS) was also obtained.

Study Design

For primary outcome measure the study design will be observational analytic with a cross-sectional bottom–up prevalence-based approach. For secondary outcome the study will be based on mathematical modeling.

Study Population

The study population will consist of people with type 2 diabetic attending two tertiary level hospitals (BIRDEM and BIHS Hospitals) in Dhaka (the capital), two tertiary level hospitals in Dinajpur and Thakurgaon (two north-western districts in Bangladesh) and two secondary level health care centers in the same northern districts. All these

facilities are directly or indirectly (through affiliated local Associations) are owned by the Diabetic Association of Bangladesh (a not-for- profit but mostly self-sustained social welfare organization). All of these, in addition to tertiary or secondary health care, provide primary health services to the diabetic subjects. The comprehensive care, provided by these facilities, are fairly structured following policies and guidelines by the central Association.

The primary reason for choosing these facilities in the present study is their cost recovery approach which gives a fairly good idea about the cost of illness, to be explored in the present study, under an acceptable clinical management level. The selection of the specific facilities was done to create a rural-urban as well as professional mix and to get a population attending various levels of services. Data from the present facilities will also have the advantage of representing the mid-level costs which can be downscaled to the cost of public sector of facilities (with deduction of certain costs) and those can also be up scaled to the cost of the for-profit private sector facilities (by adding certain costs and profit). Thus the data will be useful for attaining the national economic burden of type 2 diabetes in Bangladesh by the mathematical modeling.

Sample Size

The present study is the first study which will estimate cost-of-illness of type 2 diabetes in Bangladesh, there is no sufficient background information to calculate a formal sample size for this study. Based on available budget and time, data will be collected from patients attending the selected hospitals. In order to attain a good power, we are aiming to recruit at least 1200 participants during a time period of six months.

Recruitment

A systematic random sampling method will be used to recruit participants. The expected number of participants that will be recruited every day is 10. Each day, the data collectors will start by randomly selecting a participant with type 2 diabetes from the first K participants attending the hospital and invite him/her to participate. The value of K will depends on the number of people attending the hospital every day. After that, every K-th patient will be approached. If the K-th person declines or he/she is not a type 2 diabetic, the next person will be invited. The recruitment will continue for a period of six months.

Patients' consent

At the beginning of the interview, the data collector will briefly inform each participant about the purpose of the study, the data collection procedure (interview, anthropometric measures and review of medical record), freedom of participation and the use of collected information. The eligible participants will be invited and an explanatory statement will be given with instructions to read and ask for clarification (if any). Upon their agreement to participate by signing the consent form, they will be interviewed.

Data collection instrument

A structured questionnaire has been developed based on published literature and using different standardized questionnaires. It has been developed in simple and plain English language and again have been translated into Bangla. Then, the Bangla version has been translated back into English to check the consistency of meaning between versions. A minor modification (vocabulary to ensure a better understanding) has done after the pilot survey. The approximate time for data collection using the questionnaire was about 35 minutes per participant.

Research Electronic Data Capture (REDCap) will be used to collect and manage the data [35]. REDCap is a secure web-based application for constructing electronic surveys and collecting data for research studies. It provides a user-friendly interface with validated data entry, audit trails for tracking data manipulation, and an automated export procedure for seamless data downloads into common statistical software packages.

Using the same questionnaire for all participants, the following information will be collected:

- Diabetes centre detail and participant's identification: hospital name, participant's name, contact details.
- Participant's socio-demographics and economic factors: age, gender, marital status, religion, education, professional status, personal income, household income and number of children.
- Anthropometric information: weight, height, waist circumference, hip circumference and neck circumference.
- Medical history: duration of diabetes, family history of diabetes, frequency of follow up, mode of treatment, self-monitoring blood glucose, hypoglycaemic events, and medical history of diabetes-related comorbidities and complications.
- Diabetes cost information: cost regarding treatment, duration of leave for each visit, information about the accompanying person, information about the treatment bearer due to cost, information about in-patient events.
- Adherence to management: medication, blood

glucose monitoring, diet, exercise.
- Family support for diabetes
- Lifestyle data including smoking status, dietary habits [36] and physical activity [37].
- Psychological aspects including depression (The Patient Health Questionnaire-2 (PHQ-2) [38] and anxiety (Generalized Anxiety Disorder Scale (GAD-2) [39]
- Patient's health-related quality of life (EQ-5D-5L) [40] and six-item Cognitive impairment test (6CIT) [41].
- Information from the patient's guide book: most recent blood pressure measures, fasting blood sugar measures, after-breakfast blood sugar measures, HbA1c, lipid profile, SGPT, serum creatinine, urine albumin, albumin/creatinine ratio, eGFR and currently prescribed medications.
- Anthropometrics: height, weight, blood pressure and waist and hip circumference. Information about height and weight will be recorded from patient's registered guide book. Waist and hip circumference of the patient will be measured using measuring tape following the procedures below:

Waist circumference: Participants will be measured against thin clothing (for cultural reasons), on exhalation, midway between the lower rib margin and the anterior superior iliac spine (hip bone), or the narrowest abdominal point. The subject should be relaxed with arms held loosely at their sides. The tape measure must be kept horizontal for a standing measurement. This will be done twice and if the measurements differ by more than 2 cm, a third measurement will be taken. The waist circumference will be recorded to the nearest 0.5 cm.

Hip circumference: Will be measured at the widest circumference around the hip bones, so that the tape passes over the greatest protrusion of the gluteal muscles. The tape measure must be kept horizontal for a standing measurement. This will be done twice, and if the measurements differ by more than 2 cm, a third measurement will be taken. The hip circumference will be recorded to the nearest 0.5 cm.

Data management and analysis

During the data-collection period, the data will be saved in the secure web-based application REDCap hosted by Monash University. The application will be accessible by the research team only. After completion of data collection, data will be exported to the IBM SPSS statistical package and will be saved on the secure network storage (Monash (S:) drive) allocated by School of Public Health and Preventive Medicine at Monash University. Participants' names will be removed from the database and each participant will be identified by a numeric code generated by REDCap. The database containing all information will be saved in a separate secure electronic folder, which will not be used for data analysis. Only the research team will have access to the identified and de-identified electronic databases.

Descriptive statistics will include either mean (±SD) or median (lower and upper quartiles) for continuous data, and relative frequencies (percentages) for categorical data. The t-test or Mann-Whitney U-test, and the ANOVA or Kruskal-Wallis test will be used for comparing two and multiple groups, respectively. Categorical variables will be compared using chi-squared tests. The liner regression analysis will be employed to analyze the relationship between the total cost of care (dependent variable) and several potential explanatory variables (independent variables). Multilevel logistic regression will be used to assess the factors affecting glycaemic control and health-related quality of life (HRQoL) as outcome variable, and to find its association with cost of care as independent variable. One-way sensitivity analysis will be used for analyzing the uncertainty of the results. The national economic burden of type 2 diabetes mellitus in Bangladesh will be estimated using a mathematical modelling.

Outcomes measures

Cost calculation method: The COI studies traditionally represents the earliest form of economic evaluation that stratify costs into three categories: direct, indirect, and intangible costs. Since the intangible costs have seldom been quantified in monetary terms due to the measurement difficulties, we mainly focus on the first two cost categories: direct and indirect costs.

The direct economic costs will reflect the resources used in treating or coping with the disease including expenditures for medical care and the treatment of diabetes. Direct cost will be calculated under two sub categories – (a) direct medical costs which will include costs of hospitalization, outpatient visits, drug, laboratory tests, materials, emergency services, and (b) direct non-medical costs will include cost of transportation to the health care providers, household expenditures, costs of meal and informal cares of any kinds.

To calculate direct cost the micro-costing approach will be used by identifying cost items as much detail as possible. Patients' demographic characteristics,

clinical status, quantities of medical services received, types and quantities of drugs and medical supplies used during last one year will be retrieved by reviewing patient's guide book. The drug cost will be calculated based on cost per defined daily dose (DDD) [42] of each drug and therapy duration. Costs of outpatient visits and laboratory testing will be calculated using the regular rate of BIRDEM or BIHS hospital. Drug cost will be calculated considering the regular rate of BIRDEM or BIHS pharmacy. Calculation of unit cost of medical services will employed the standard costing approach[43]. The calculation will be composed of four steps, i.e., calculation of the unit cost of medical services, direct cost determination, indirect cost determination, and total cost determination. The annual average costs on medical care will be estimated by multiplying the average per visit costs by the number of visit (records from patients guide book) per year.

The indirect costs will consist of opportunity cost of time lost due to morbidity (temporary disability). The morbidity related component includes the productivity losses of time invested by patients and their accompanying person. Indirect cost will be calculated using the human capital approach[44] for those who are currently working or keeping house but not for persons who are unable to work or who choose not to work.

All costs will be measured in Bangladeshi Taka (BDT); later will be converted to USD applying the current currency conversion rate.

Glycemic control: The proportion of glycosylated haemoglobin (HbA1c) measured as a percentage will be categorized as: good control (HbA1c $\leq$ 7.0%), fair control (HbA1c 7%-8%) or poor control (HbA1c >8.0%).

Quality of life: EQ-5D-5L health states scores will be converted into a single index value between 0 and 1, and the quality of life will be categorised as Good quality of life (0.67-1.00), fair quality of life (0.34-0.66) and poor quality of life ($\leq$ 0.33).

Personnel and training

Two interviewers who has completed university graduation and have prior experience with surveys will be recruited for data collection. The objectives of the study and contents of the questionnaire will be explained to the interviewers. They will be trained on approaching the potential participants, measuring anthropometrics, filling in the electronic questionnaire and obtaining information from the medical records. Training session will also include mock interviews between participants and field practice as a pre-test.

Quality assurance measures for data collection

To ensure the quality of data collection, the procedure will be monitored by the student investigator. In addition, the student investigator will carry out a random consistency check for at least 5% of the interviewed questionnaires.

Pilot study

The questionnaire was piloted on 31 participants attending Bangladesh Institute of Health Sciences Hospital over a period of one weeks. The questionnaire was found to be acceptable by most of the participants and practical by data collectors. The average time required to complete data collection from one participant was almost similar (around 40 minutes) as planned. The pilot study does not recommend any major change to the questionnaire.

Discussion

This study is a comprehensive multi-center study which will provide the most up-to-date in-depth information and a clear picture of economic burden of diabetes in Bangladesh. The study findings will serve as a research-based evidence to priorities and allocate scarce resources and will be beneficial to conceptualize national level health strategies. Furthermore, recognizing the factors of cost-of-illness and the relationship between glycemic control and quality of life with cost-of-illness will aid both patients and health care providers to improve the management, to control the cost and hence, to have improved quality of life. Evidence about the magnitude of the burden of T2DM will assist public health policymakers to develop programs and policies and cost-effective strategies for the better management of diabetes in the context of Bangladesh.

Author disclosure

All authors report no relation or financial interest with any entity that would pose a conflict of interest.

Authors' contribution

All authors were involved to the conception and design of the study. All authors critically review to improve the content and final approval of version to be submitted

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Chapter 4

COST-OF-ILLNESS OF TYPE 2 DIABETES MELLITUS IN BANGLADESH

Context of the study

Diabetes is a costly disease due to its chronic nature. It is a major public health concern in developing countries because of its rapidly increasing prevalence, related complications and the requirement for long-term care. Diabetes places a significant burden on individuals, their families, society and overall on the economy of a country. The economic burden of diabetes is well-acknowledged, investigated and evident in the literatures. The majority of the studies in the literature were conducted in the context of HICs. Therefore, information to support the burden of diabetes in LMICs is a significant limitation of the current literature. A limited number of studies addressed this in LMICs; however, there was a wide variation in the methodology that was used in these studies and the choice of methodology was mainly driven by the availability of data which greatly influenced the magnitude of cost estimates. Furthermore, it is difficult to generalise or compare the results of the studies conducted in different countries due to monetary issues such as fluctuating exchange rates and purchasing powers of currencies.

Diabetes is also an increasing economic threat in Bangladesh, however, studies on an adequate estimation of the COI for T2DM and the factors related to it are limited; which led to the aim of this paper. The results of this COI study will assist public health policy makers and the general population to recognise the magnitude of the up-to-date financial burden, to make decisions about future healthcare benefits, to place emphasis on controlling the disease, and to develop programs to improve the health of people with T2DM in Bangladesh.

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Type 2 diabetes mellitus in Bangladesh: a prevalence based cost-of-illness study

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Abstract

Background: The economic burden of type 2 diabetes has not been adequately investigated in many low- and lower middle-income countries, including Bangladesh. The aim of this study was to estimate the cost-of-illness of type 2 diabetes and to find its determinants in Bangladesh.

Methods: A cross-sectional study was conducted in 2017 to recruit 1253 participants with type 2 diabetes from six diabetes hospitals, providing primary to tertiary health care services, located in the northern and central regions of Bangladesh. A structured questionnaire was used for face-to-face interviewing to collect non-clinical data. Patients' medical records were reviewed for clinical data and hospital records were reviewed for hospitalisation data. Cost was calculated from the patient's perspective using a bottom-up methodology. The direct costs for each patient and indirect costs for each patient and their attendants were calculated. The micro-costing approach was used to calculate direct cost and the human capital approach was used to calculate indirect cost. Median regression analysis was performed to identify the determinants of average annual cost.

Results: Among the participants, 54% were male. The mean (±SD) age was 55.1 ± 12.5 years and duration of diabetes was 10.7 ± 7.7 years. The average annual cost was US$864.7 per patient. Medicine cost accounted for 60.7% of the direct cost followed by a hospitalisation cost of 27.7%. The average annual cost for patients with hospitalisation was 4.2 times higher compared to those without hospitalisation. Being females, use of insulin, longer duration of diabetes, and presence of diabetes complications were significantly related to the average annual cost per patient.

Conclusions: The cost of diabetes care is considerably high in Bangladesh, and it is primarily driven by the medicine and hospitalisation costs. Optimisation of diabetes management by positive lifestyle changes is urgently required for prevention of comorbidities and complications, which in turn will reduce the cost.

Keywords: Burden of diabetes, Cost-of-illness, Direct cost, Indirect cost, Management plan, Type 2 diabetes

Background

Diabetes is one of the most prevalent non-communicable diseases globally and, currently, the disease is a major public health issue in developing countries because of its chronic nature, rapidly increasing prevalence, related complications, and the requirement of long-term care. The higher prevalence of diabetes is related to an increased prevalence of obesity, population ageing, population growth, urbanisation and physical inactivity [1]. The International Diabetes Federation (IDF) estimated that, worldwide, approximately 425 million people had diabetes in 2017; the number is projected to be 629 million by 2045. For treating and preventing diabetes and its related complications, an estimated US$727 billion was spent in 2017, which represented an 8% increase from that estimated for 2015. The cost has been projected to be US$776 billion by 2045 [2]. The annual cost for people with diabetes is mainly related to direct (e.g. cost for medicine, hospital care, laboratory tests, etc.) and indirect costs (e.g. productivity loss from disability, premature mortality, etc.) [3].

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Compared to people living in high-income countries, people in low- and lower middle-income countries (LMICs) have a lack of access to health insurance or publicly available medical services. Thus, they pay a larger share of out-of-pocket (OOP) health expenditures. Furthermore, in some LMICs, people with diabetes and their families bear almost all of the expenditure related to diabetes care [4]. The prevalence of diabetes has escalated more rapidly in South East Asia than in any other large region in the world [2]. Literature showed that about 90 to 95% of all diagnosed diabetes cases of this region are type 2 diabetes [5, 6]. In Bangladesh, the estimated prevalence of diabetes among adults was 9.7% in 2011 [7] and the number is projected to be 13.7 million by 2045 [2]. According to the Bangladesh National Health Accounts, in 2010, Bangladesh spent US$2.3 billion on health (or US$16.20 per person per year) and 64% of this cost came from OOP payments [8]. However, according to the World Health Organization (WHO), in 2014, Bangladesh spent US$88 per person per year on health [9]. It has been observed that, on average, a household spent 7.5% of its total income on receiving health care, with the poorest 20% of the households spending approximately 13.5% of their income on it [8]. The per capita gross domestic product (GDP) of Bangladesh was US$1677 in 2018 [10], and nearly one-third (31.5%) of the population in the country was below the poverty line [11]. Hence, the OOP health care expenditure posed a notable economic burden on the Bangladeshi population.

In high-income nations, such as the USA [12–15] and in some European [16] and upper middle-income countries [17, 18], the economic burden of diabetes is well-acknowledged and investigated. Most of these studies have estimated the economic burden in terms of cost, while others [14, 15, 17] investigated the factors (e.g. patients' demographics, complications, payment methods and health care utilisation) correlated with the total cost. Low- and lower middle-income countries represent 80% of the global diabetic population [2]; however, research-based evidence on diabetes management-related cost is limited for most of these countries, including Bangladesh. A study [19] in Bangladesh that addressed the cost and its determinants recruited a relatively small sample from a single hospital located in the capital city, and thus covered mostly urban residents. Furthermore, the cost was calculated from the outpatient department only, which may underestimate the average annual cost.

Thus, the aim of this study was to estimate the average annual cost and to find its determinants, where the cost data included both outpatients and hospitalisation. This study's findings will provide the most up-to-date information on the economic burden incurred by people with type 2 diabetes mellitus (T2DM) in Bangladesh, which will be useful as an important aid in the planning of health care needs and allocation of scarce resources.

Methods

Study design and study population

A cross-sectional study was conducted with a prevalence-based approach [20]. Data was collected from six hospitals (specialising in diabetes) where patients' records were available for the previous years, located in the northern and central regions of the country. Two of these hospitals are from the central region, providing primary to tertiary health care, particularly to urban residents. The remaining hospitals are from the northern region, two of them providing primary and secondary health care and the other two providing primary to tertiary health care to people residing in semi-urban and rural locations. Patients attending hospitals providing primary and secondary but in need of tertiary care are usually referred to the tertiary care hospitals. Due to a similar social and economic status for people living in the northern and southern regions, the patients from the hospitals of the northern region are comparable to those living in the southern region of the country. Thus, no hospitals were selected from the southern region. The Diabetic Association of Bangladesh (BADAS), a not-for-profit but mostly self-sustaining social welfare organisation, directly or indirectly (through affiliated local associations) owns all the selected hospitals. BADAS, the highest diabetes care provider, has 75 diabetic centres/hospitals which cover all 64 districts (second highest level tire of regional administration) across the country. Due to lack of adequate services related to diabetes in public hospitals, particularly in peripheral areas, majority of the people with diabetes are treated and managed by the hospitals under BADAS. The hospitals were purposively selected to ensure that the study included patients from rural-urban as well as professionally mixed populations (e.g. service holders, businessmen, farmers, day labours, housewives, etc.) attending various levels of health care services. Between April and September 2017, 1253 participants were recruited using systematic random sampling and probability proportional to size (PPS) methods (Fig. 1). The target population comprised registered adults of either gender with a minimum one-year duration of T2DM. People with other types of diabetes or who were pregnant at the time of data collection were excluded as those people may have some additional expenses other than T2DM. A team of trained data collectors was involved in the data collection. At the beginning of the interview, the data collectors provided an explanatory statement to each participant and, upon his/her agreement to participate by signing the consent form, participants were interviewed face-to-face. Participants were recruited from the outpatient department of

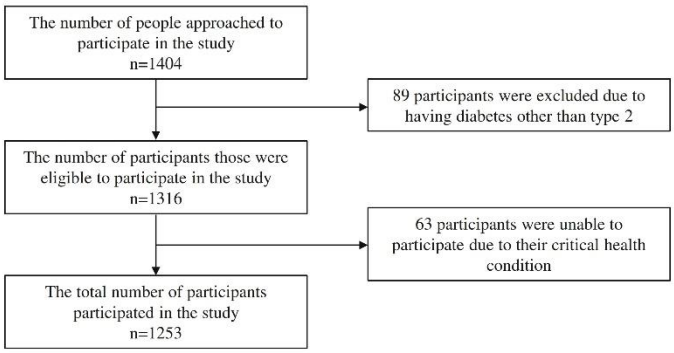

Fig. 1 Study participant's recruitment flowchart

the selected hospitals and those who were referred to hospital admission were followed-up to collect their hospitalisation information from the hospital inpatient department.

Data collection instrument

A structured questionnaire (Additional file 1) was developed and used in a secured web-based application, Research Electronic Data Capture (REDCap), for data collection [21]. Prior to the main survey, the content validity of the questionnaire was evaluated and pretested, using a pilot study conducted in a tertiary care hospital. The questionnaire gathered each patient's details and demographics, diabetes-related information, cost-related information and the patient's lifestyle behaviour. Patients' medical records (guide books) were also reviewed to retrieve information pertaining to clinical status and the number of medical services received during the previous year. To obtain information about the types and quantities of currently prescribed medicine, a copy of the prescription was kept in the REDcap application as an image for further use.

Calculation of costs

The total cost of T2DM was calculated from the patient's perspective for the year 2017, considering direct and indirect costs as the major components. Direct cost was estimated using a bottom-up approach for primary data collection [22] and divided into the two following sub-categories: direct medical costs, which comprise the costs of hospitalisation, outpatient visits, medicine, laboratory tests, and other service utilisation (including the use of self-monitoring blood glucose and consumables); and direct non-medical costs, which comprise the cost of transportation and meals en- route to the hospital.

The micro-costing approach was used to identify cost items in as much detail as possible for calculating direct cost [23]. Cost per daily dose [24] of each medicine and therapy was defined. Costs related to medicine, consultancy and laboratory tests that patients paid OPP were collected from a tertiary level hospital located in the central region. It should be noted that the health insurances support is literally non-exists in Bangladesh, thus all payments met by OPP. All hospitals under the BADAS are homogeneous; thus, there is a negligible cost variation between the selected hospitals. For other components of direct medical cost and direct non-medical cost, each participant's responses to the questionnaire were considered as a reference. Each component of direct cost was calculated by multiplying the unit cost with the quantities of medical services received during the previous year. The cost of hospitalisation (including hospital stay, medicine and laboratory tests during the stay) was retrieved for each patient from their hospital record, which was provided by the accounts department of the hospital. The total direct cost was calculated by adding up all components of direct medical and direct non-medical costs.

The indirect cost was calculated for both patients and their attendants' en-route to the hospital. The productive time lost to attend outpatient visits and during hospital admission was recorded based on the information provided by the patients and their attendants. The human capital approach [25] was used to calculate the indirect cost for those who were productive and in the formal workforce or housewives, but not for people who were unable to work (retired or ill health) or who chose not to work. The productivity loss of housewives was calculated using the minimum wage rate of Bangladesh (US$224/annum) [26] as well as the median income of the participants who were in the formal workforce. The total cost was calculated by adding up total direct and total indirect costs.

All costs were calculated in Bangladeshi currency, Taka (BDT) and then, to add an international perspective, they

Table 1 General characteristics of the study participants

Variables	*n* (%) (*n* = 1253)
Gender	
Male	681(54.4)
Female	572 (45.6)
Age (mean ± SD)	55.1 ± 12.5
≤ 40	176 (14.05)
41–60	669 (53.39)
61–80	380 (30.33)
≥ 80	28 (2.23)
Education	
Illiterate	161 (12.8)
Primary	239 (19.1)
Secondary	566 (45.2)
Tertiary	287 (22.9)
Work status	
Unemployed	36 (32.8)
Employed	411 (40.5)
Housewives	508 (23.8)
Retired	298 (2.9)
Area of residence	
Rural	174 (13.9)
Semi-urban	162 (12.9)
Urban	917 (73.2)
Monthly household income (US$)	
≤ 250	447 (35.7)
251–750	497 (39.7)
751 and above	309 (24.6)
Duration of diabetes (in year)	
≤ 5	360 (28.8)
6–10	348 (27.7)
≥ 11	545 (43.5)
Mode of treatment	
OHA	432 (34.5)
Insulin	87 (6.9)
Insulin + OHA	734 (58.6)
Family history of diabetes	734 (58.7)
Yes	433 (34.6)
No	820 (65.4)
HbA1c (%)	
Good (≤6.9)	182 (18.2)
Fair (7–7.9)	198 (19.8)
Poor (≥8)	621 (62.0)
Number of complication[a]	
None	458 (36.6)
One or two	613 (48.9)
Three or more	182 (14.5)
History of co-morbidity	
None	296 (23.6)
Hypertension	524 (41.8)
Dyslipidaemia	151 (12.0)
Hypertension + dyslipidaemia	283 (22.6)

OHA Oral hypoglycaemic agent
[a]Complications include coronary artery disease, stroke, diabetic foot, nephropathy, retinopathy and neuropathy

were converted into US$ using the mid-year currency conversion rate for the year 2017 (US$1 = BDT80).

Ethical approval

The study has been approved by the Monash University Human Research Ethics Committee (ID: 1469), the Ethical Review Committee of the Bangladesh University of Health Sciences (BUHS) and the Ethical Review Committee of the BADAS.

Statistical analysis

Descriptive statistics includes mean with standard deviation for numerical data and frequency with percentage for categorical data. A normality test of cost data was performed using histogram, Q-Q plot and the Shapiro-Wilk test. Cost data was right skewed; hence, mean and median with percentiles was used for reporting it. A median regression was run to determine the factors related to average annual cost. A bootstrapping method was used to calculate the 95% confidence interval (CI) of regression coefficients [27]. A one-way sensitivity analysis was performed to evaluate the assumption that the use of minimum wage to calculate the indirect cost of housewives may give the lowest estimate. A two-way sensitivity analyses were undertaken to explore the change in average annual cost with assumptions of a 25% (+/−) change in the prevalence of insulin use and 25% (+/−) change in the prevalence of T2DM related complications. The statistical software package STATA SE version 15.0 was used for data analysis and a *p*-value of 0.05 or less was considered to be statistically significant.

Results

General characteristics of the study participants

The general characteristics of the study participants are presented in Table 1. Among the 1253 participants with T2DM, 681 (54.3%) were male. The mean age of patients was 55.1 ± 12.5 years. Approximately 45% of participants

had a secondary level education and 23% had a tertiary level education. About two-fifths (40.5%) of the participants were employed and about a quarter (23.8%) were housewives. Three-quarters (73.2%) of the participants resided in urban areas and 51.2% of participants had a median monthly household income of US$375 (BDT30, 000). Mean duration of diabetes was 10.9 ± 7.7 years and 43.5% of the participants had diabetes for more than 10 years. More than half of the participants (58.6%) managed diabetes by a combination of an oral hypoglycaemic agent (OHA) and insulin, 34.5% by OHA only (merging 1.8% of people with lifestyle modification with OHA only), and 6.9% by insulin only. More than half (55.9%) of the participants moderately adhered to medication, followed by 37.2% with high adherence, with only 6.9% having poor adherence. About one-third (34.6%) of the participants had family history of diabetes; only 19.8% had fair (HbA1c 7–7.9%) and 62% had poor (HbA1c ≥ 8%) glycaemic control. About half (48.9%) of the participants had up to two diabetes-related complications (coronary artery disease, stroke, diabetic foot, nephropathy, retinopathy and neuropathy) and 14.5% had three or more complications. The study results showed that 41.8% had hypertension, 12% had dyslipidaemia, and 22.6% had both. The mean productive time lost during outpatient visits was 7.3 ± 1.5 h per month. For patients with a history of hospitalisation, productive time lost was 10.4 ± 8.8 days per year (data is not shown in the table).

Cost-of-illness by socio demographic and clinical characteristics

Cost-of-illness (total cost) by socio-demographic and clinical characteristics is presented in Table 2. The results showed that for each variable, direct cost is higher compared to indirect cost. The average annual cost increased with the increasing age, which ranged from US$588 for aged <=40 years to US$1434 for aged > = 80 years ($p < 0.001$). Illiterate people spent the lowest (US$637) and that was highest (US$962) for people with up to secondary level education ($p = 0.004$). The average annual cost was higher for retired people (US$1062, $p = 0.001$) compared to unemployed people (US$676). People residing in rural areas (US$422) spent less compared to people living in urban areas (US$1024, $p < 0.001$), and the high-income group spent more (US$1062, $p < 0.001$) than the low-income group. The average annual cost increased progressively with the increased duration of T2DM ($p < 0.001$) and people with diabetes duration of more than 10 years spent US$1160.8 per year. The average annual cost for insulin users with a combination of OHA was US$1042.8 compared to US$526.2 for only OHA users ($p < 0.001$). As the number of complications increased, the average annual cost increased ($p < 0.001$). People with the presence of three or more complications spent US$1351.5 annually compared to US$532.2 for people without any complication. Likewise, people with the presence of both hypertension and dyslipidaemia had an average annual cost of US$1022.6 compared to that of US$659.4 for those with no comorbidity ($p < 0.001$).

Annual cost-of-illness (COI) of diabetes care

Table 3 presents the estimated average annual cost per person by components of direct and indirect costs. The average annual cost of diabetes care was US$864.7, of which the direct cost was 90.5% with a mean of US$781.7 and the indirect cost was 9.5% with a mean of US$82.9. Without hospitalisation, the average annual cost was US$409.8, which increased to US$1705.2 with hospitalisation. Furthermore, Table 3 shows that of the overall direct cost, direct medical and non-medical costs were 96.9 and 3.1%, respectively. The medicine cost accounted for the largest share (60.7%) of overall direct cost followed by the hospitalisation cost (27.7%). Medicine cost was also the highest source of direct cost (83.5%) for patients without hospitalisation. For patients with hospitalisation, medicine cost contributed 50.7% of direct cost followed by a hospitalisation cost of 39.9%. The average annual indirect cost was approximately four times higher for patients with hospitalisation (US$158.9) compared to that of patients without hospitalisation (US$41.8).

Sensitivity analysis

The result of the one-way sensitivity analysis showed that use of the median income of the study participants instead of the minimum wage increased the indirect cost by 23%. However, the estimated average annual cost using the minimum wage rate of Bangladesh was US$853 (95% CI US$795.1-US$911.7), while it was US$864.7 (95% CI 806.5–922.9) using the median income of the study participants. The difference between these two estimates is insignificant as the CI overlapped each other.

The results of a two-way sensitivity analyses showed that the average annual cost increased by 2.9% (US$865 vs US$890) when insulin use was increased by 25% and that decreased by 4% (US$865 vs US$830) when insulin use was decreased by 25%. A 25% increase in prevalence of complications lead to a 5.3% (US$865 vs UD$898) increment of average annual cost, while it decreased by 3.9% (US$865 vs US$819) with a 25% reduction in complications.

Determinants of cost-of-illness

The results of simple and multiple median regression analyses are presented in Table 4. In the simple median regression analysis, age group 61–80 years (US$221.91, $p < 0.001$)

Table 2 Details of annual cost in US$ by socio-demographic and clinical characteristics of the study participants

Variables	Direct cost		Indirect cost		Total cost	
	Mean	Median (percentiles)	Mean	Median (percentiles)	Mean	Median (percentiles)
Gender[b]						
Male	795.2	456.1 (273.6, 893.4)	81.6	19.5 (0, 62.5)	876.9	497.9 (292.0, 977.3)
Female	765.7	446.6 (278.8, 905.2)	84.4	52.1 (16.1, 93.7)	850.1	516.89 (332.7, 988.3)
Age (years)[c]						
≤ 40	519.6	331.1 (205.4, 564.9)	68.8	41.6 (18.48, 72.91)	588.4	385.7 (241.0, 616.2)
41–60	738.7	421.1 (270.3, 784.7)	103.0	52.1 (19.5, 104.2)	841.8	476.2 (310.1, 860.1)
61–80	934.9	587.4 (337.1, 1168.9)	56.1	0 (0, 52.1)	991.0	613.7 (351.3, 1247.3)
> 80	1376.9	1052.1 (682.9, 1845.5)	57.1	0 (0, 0)	1434.1	1133.1 (712.2, 1936.1)
Education[c]						
Illiterate	575.3	421.1 (254.1, 705.5)	61.6	39.1 (3.6, 72.9)	636.9	437.2 (287.5, 775.3)
Primary	759.5	513.1 (291.3, 958.0)	59.3	31.2 (0, 72.9)	818.9	536.41 (323.5, 1036.1)
Secondary	874.1	483.1 (294.7, 989.4)	88.0	35.1 (0, 83.3)	962.1	529.2 (333.7, 1092.1)
Tertiary	733.9	409.4 (224.6, 831.8)	104.5	41.6 (0, 91.1)	838.4	452.0 (261.2, 913.5)
Work status[c]						
Unemployed	627.5	469.0 (298.7, 598.3)	48.0	0 (0, 0)	675.6	469.0 (298.7, 606.2)
Employed	598.9	343.1 (217.8, 607)	116.0	41.6 (18.7, 87.5)	715.0	393.3 (255.3, 700.7)
Housewives	798.9	488.3 (294.3, 936.7)	87.0	52.1 (20.8, 104.1)	885.9	533.6 (359.3, 1025.1)
Retired	1027.0	617.4 (369, 1189.9)	34.8	0 (0, 10.9)	1061.9	644.3 (374.2, 1298.3)
Area of residence[c]						
Rural	359.8	291.3 (202.4, 442.2)	61.7	47.9 (11.4, 83.3)	421.6	369.0 (239.6, 522.3)
Semi-urban	388.3	295.5 (228.1, 494.6)	48.1	33.2 (7.8, 70.3)	436.5	353.3 (253.7, 541.1)
Urban	931.3	545.3 (324.9, 1089.6)	93.1	34.3 (0, 87.5)	1024.4	590.3 (361.4, 1205.4)
Monthly household income (US$)[c]						
≤ 250	739.6	465.5 (258.1, 846.1)	65.2	31.2 (0, 78.1)	804.9	499.4 (289.5, 920.3)
251–750	692.1	407.9 (267.6, 757.3)	64.6	41.66 (1.30, 72.9)	756.8	456.5 (305.2, 810.7)
751 and above	986.8	571.8 (340.5, 1262.8)	138.0	41.6 (0, 125.0)	1124.9	499.4 (289.5, 920.3)
Duration of diabetes (in year)[c]						
≤ 5	526.3	325.8 (220.8, 539.2)	53.7	32.6 (10.4, 67.1)	580.1	378.9 (260.2, 589.0)
6–10	645.9	398.0 (258.3, 691.7)	61.4	41.6 (3.9, 72.9)	707.4	458.1 (292.5, 760.6)
≥ 11	1044.1	679.8 (378.8, 1251.3)	116.7	37.5 (0, 114.5)	1160.8	746.6 (418.3, 1442.5)
Mode of treatment[c]						
OHA	476.2	291.4 (209.6, 511.2)	49.9	31.2 (4.0, 62.5)	526.17	335.0 (238.7, 534.3)
Insulin	702.6	441.9 (224.3, 842.3)	67.2	41.6 (8.8, 83.3)	769.89	477.1 (259.8, 902.8)
Insulin + OHA	970.9	586.0 (368.9, 1129.6)	104.2	41.6 (0, 104.1)	1075.20	642.7 (412.4, 1223.7)
Family history of diabetes[b]						
Yes	818.4	487.3 (287.0, 964.3)	97.1	41.6 (9.8, 93.7)	915.6	524.3 (321.7, 1100.8)
No	762.4	441.4 (270.5, 879.9)	75.4	31.2 (0, 72.9)	837.9	493.1 (298.9, 954.2)
HbA1c (%)						
Good (≤6.9)	527.1	318.9 (205.9, 513.3)	84.5	31.2 (0, 65.1)	611.7	367.5 (234.2, 562.8)
Fair (7–7.9)	552.1	366.6 (242.3, 637.5)	53.2	26.0 (0, 62.5)	605.4	409.9 (277.8, 665.1)
Poor (≥8)	567.9	398.9 (267.2, 633.2)	58.5	36.4 (7.8, 72.9)	626.5	450.4 (300.7, 717.3)
Number of complication[a,c]						
None	466.8	295.9 (207.3, 507.0)	56.3	31.2 (15.6, 65.1)	523.2	347.9 (237.8, 549.2)

Table 2 Details of annual cost in US$ by socio-demographic and clinical characteristics of the study participants *(Continued)*

Variables	Direct cost		Indirect cost		Total cost	
	Mean	Median (percentiles)	Mean	Median (percentiles)	Mean	Median (percentiles)
One or two	657.5	379.9 (261.8, 670.7)	81.9	36.4 (0, 83.3)	739.4	437.1 (293.5, 739.7)
Three or more	1234.3	966.9 (511.1, 1519.8)	117.1	43.7 (0,130.2)	1351.5	1036.8 (547.8, 1718.5)
History of co-morbidity[c]						
None	595.5	354.2 (219.8, 580.7)	63.8	31.2 (10.4, 72.9)	659.3	418.2 (260.7, 632.8)
Hypertension	870.1	533.9 (317.5, 1041.9)	94.3	41.6 (0, 91.1)	964.4	582.4 (362.7, 1150.3)
Dyslipidaemia	566.8	332.6 (228.1, 561.9)	56.9	27.3 (9.1, 62.5)	623.7	376.1 (259.6, 608.8)
Hypertension + dyslipidaemia	926.9	534.0 (313.7, 1041.3)	95.7	41.6 (0, 91.1)	1022.6	587.6 (365, 1143.5)

OHA Oral hypoglycaemic agent, *HTN* Hypertension
[a]Complications include coronary artery disease, stroke, diabetic foot, nephropathy, retinopathy and neuropathy. [b]Mann Whitney U test and [c]Kruskal Wallis test were done for group comparison; *p*-value was considered significant at $p < 0.05$

and more than 80 years (US$741.58, $p < 0.001$), treated with insulin alone (US$140.69, $p = 0.042$) as well as with a combination of OHA (US$307.38, $p < 0.001$), duration of diabetes more than 10 years (US$368.68, $p < 0.001$), poor (HbA1c ≥8%) glycaemic control (US$79.41, $p = 0.009$), presence of any complication (US$201.54 for one or two and US$287.72 for more than two, $p < 0.001$), presence of hypertension (US254.89p < 0.001$) alone and hypertension with a combination of dyslipidaemia (US$169.07, $p = 0.001$) were significantly associated with higher costs.

Multiple regression analysis showed that the average annual cost was higher for females (US$44.85, $p = 0.036$). People treated with insulin with a combination of OHA (US$152.87, $p < 0.001$) also had higher costs compared to those treated with OHA only. Patients with a duration of diabetes of more than 10 years (US$66.93, $p = 0.025$) incurred a higher cost. Likewise, patients with the presence of any complication (US$63.69 for one or two and US$440.93 for more than two, $p < 0.001$) had higher costs compared to those without any complication.

Discussion

Diabetes has become a major global economic burden in recent decades, but proper management of the factors related to it can be useful for reducing this burden. Diabetes is also an increasingly economic threat in Bangladesh, yet studies on an adequate estimation of COI for T2DM and its key drivers are limited; hence, the aim of this paper. This study involved a large representative sample that adequately investigated the economic burden of type 2 diabetes in Bangladesh from the patients' perspective. The key finding of this study was that the average annual cost for T2DM patient is US$865 with the medicine cost being the highest contributor followed by the hospitalisation cost. The average annual cost for patients with hospitalisation was 4.2 times higher compared to those without hospitalisation.

The average annual cost for each person with T2DM in Bangladesh appears to be considerably higher than that reported in previous studies conducted in Bangladesh (US$314) [19] and other South Asian countries such as India (US$525) [28] and Pakistan (US$197) [29]. One possible explanation of this difference may be because the studies conducted in Bangladesh and Pakistan addressed only outpatient department cost, which underestimated the overall cost. In contrast, some high- or upper middle-income Asian countries, for example, China (US$1501.7) [30] and Singapore (US$1575.6) [18], reported higher cost for diabetes management.

This study finding showed that cost increased with age, which is supported by previous studies [14, 17, 31]. Additionally, female gender was a factor more likely to incur higher cost. A study conducted in Bangladesh by Shamima et al. showed that females had better awareness about diabetes and were more regular in receiving follow-up check-ups [7], which may be related to higher cost. A study conducted in Hawaii by Bhattacharyya et al. [14] showed a similar result, while Krop et al. [31] in Maryland and Chaikledkaew et al. [32] in Thailand showed that the cost of care was higher for males.

An important finding of this study was that 13.5% of participants had income less than the estimated average annual cost. Overall, a person with T2DM spent 9% of his/her annual household income on management, which is a notable financial burden for a family. In South Asia, health insurance is practically non-existent, and almost all expenses are met through OOP, which creates a significant burden and sometimes leads to family impoverishment. This study showed that urban residents spent more than the rural residents (mean cost for urban: US$1024.4, vs rural: US$421.6). This may be because of people residing in urban areas have better education and a higher income, and thus can better afford to receive adequate treatment and access to specialised doctors.

Table 3 Costs-of-illness of type 2 diabetes per person per year (in US$) by components of direct and indirect costs

Cost components	Mean	Median	25thp, 75th p	90th p	% of total	Total COI	% of total COI
Overall COI ($n = 1263$)							
a. Direct cost							
i. Direct medical cost					96.9		
Outpatient visit	11.8	6.3	2.2, 12.5	31.2	1.5	14,807.1	1.4
Hospitalisation[a]	216.7	496.6	0, 276.7	673.1	27.7	271,490.4	12.7
Medicine	474.5	331.0	205.3, 474.5	798.4	60.7	594,543.8	54.9
Laboratory tests	37.7	34.0	23.3, 47.2	62.1	4.8	47,311.9	16.8
Other service utilisation[#]	16.5	9.0	0, 18	54.0	2.1	20,718	1.8
ii. Direct non-medical cost					3.1		
Transportation	23.7	7.5	2.5, 27.5	62.5	3.0	29,748.7	2.8
Meal	0.7	0.0	0, 0	2.5	0.1	931.4	0.1
Total direct cost	781.7	453.6	276.6, 893.4	1705.0	100	979,551.3	90.5
b. Indirect cost							
Productivity loss of patient	67.8	26.0	0, 62.5	145.8	81.8	85,062.5	7.9
Productivity loss of accompanied person	15.1	0.0	0, 0	39.1	18.2	18,872.2	1.7
Total indirect cost	82.9	36.5	0, 82.8	187.5	100	103,934.8	9.5
Total cost	864.7	504.2	308.8, 982.7	1874.3		1,083,486.0	
Without hospital admission ($n = 813$)							
Direct cost							
i. Direct medical cost					93.9		
Outpatient visit	5.9	5.0	1.25, 8.75	12.5	1.6	4801.6	
Hospitalisation[a]	–	–	–	–	–	–	
Medicine	307.2	255.5	173.4, 387.8	520.1	83.5	249,827.3	
Laboratory tests	34.2	31.2	21.5, 41.8	53.9	9.3	27,828.6	
Other service utilisation[b]	10.5	9.0	0, 9	18.0	2.8	8523.0	
ii. Direct non-medical cost					2.8		
Transportation	9.4	3.7	2, 8.75	21.0	2.6	7662.6	
Meal	0.7	0.0	0, 0.6	2.3	0.2	524.5	
Total direct cost	367.9	320.1	227.9, 452.8	608.9	100	299,167.5	
Indirect cost							
Productivity loss of patient	34.7	24.7	0, 52.1	71.9	83.0	28,244.5	
Productivity loss of accompanied person	7.1	0.0	0, 0	20.8	17.0	5790.9	
Total indirect cost	41.8	31.3	3.9, 62.5	93.7	100	34,035.4	
Total cost	409.8	366.6	261.9, 505.7	662.7		333,202.9	
With hospital admission ($n = 440$)							
Direct cost							
i. Direct medical cost					96.7		
Outpatient visit	22.7	12.5	5, 37.5	51.3	1.5	10,005.5	
Hospitalisation[a]	617.0	419.4	247.3, 753.2	1303.9	39.9	271,490.4	
Medicine	783.4	469.9	346.7, 764.0	1455.4	50.7	344,716.5	
Laboratory tests	44.3	41.8	29.7, 56.9	71.6	2.9	19,483.4	
Other service utilisation[b]	10.0	9.0	9, 36	54.0	1.8	12,195.0	

Table 3 Costs-of-illness of type 2 diabetes per person per year (in US$) by components of direct and indirect costs *(Continued)*

Cost components	Mean	Median	25thp, 75th p	90th p	% of total	Total COI	% of total COI
ii. Direct non-medical cost					3.3		
Transportation	50.2	31.2	15, 62.5	112.5	3.2	22,086.1	
Meal	0.9	0.0	0, 0	2.5	0.1	406.9	
Total direct cost	1546.3	1121.1	806.3, 1845.9	2927.7	100.0	680,383.8	
Indirect cost							
Productivity loss of patient	129.1	35.1	0, 145.8	281.2	81.3	56,818.1	
Productivity loss of accompanied person	29.7	0.0	0, 0	104.1	18.7	13,081.2	
Total indirect cost	158.9	67.7	0, 182.9	345.1	100.0	69,899.4	
Total cost	1705.2	1247.4	876.9, 1996.6	3353.8		750,283.2	

[a]Hospitalisation includes hospital stay, medicine and laboratory tests during stay. [b]Other service utilisation includes use of self-monitoring blood glucose and consumables

The present results showed that direct cost had the largest share (90.5%) of overall cost. Among all the cost components of overall direct cost, medicine cost was the major contributor (60.7%). The studies conducted by Khowaja et al. [29] in Pakistan and Shobhana et.al [28] in India reported similar features. However, compared to these studies, the present study showed a much higher proportion of medicine cost. This difference may be related to many factors. Firstly, 93% of the participants in this current study had high or medium adherence to medication, which incurs a higher medicine cost. Secondly, among them, 65.6% used either insulin alone or insulin with a combination of OHA, which is higher than that reported in another study in Bangladesh [33].

Table 4 Median regression analysis of total cost

Variables	Unadjusted			Adjusted		
	Coefficients	*p*-value	95% confidence interval (CI)	Coefficients	*p*-value	95% confidence interval (CI)
Gender (ref: Male)						
Female	19.03	0.492	−35.32-73.37	44.85	0.036	3.02–86.68
Age (≤40 years)						
41–60 years	82.85	0.107	−17.79-183.49	21.13	0.419	−30.13-72.39
61–80 years	221.91	< 0.001	113.60–330.24	2.86	0.930	−60.70-66.41
≥ 80 years	741.58	< 0.001	499.87–938.30	170.76	0.708	− 723.11-1064.64
Mode of treatment (ref: OHA)						
Insulin	140.69	0.042	5.28–276.09	65.40	0.260	−48.28-179.07
Insulin + OHA	307.38	< 0.001	237.90–377.65	152.87	< 0.001	107.45–198.30
Duration of diabetes (ref: ≤5 year)						
6–10	78.36	0.080	−9.42-166.15	17.59	0.403	−23.68-58.82
≥ 11	368.68	< 0.001	289.32–448.04	66.93	0.025	8.55–125.32
HbA1c (ref: ≤6.9)						
Fair (7–7.9)	45.42	0.216	−26.60-177.43	−1.20	0.949	−63.50-59.51
Poor (≥8)	79.41	0.009	20.30–138.53	22.50	0.406	−30.58-75.58
History of co-morbidity (ref: None)						
Hypertension	164.89	< 0.001	76.10–252.79	30.13	0.213	−17.25-77.51
Dyslipidaemia	−42.17	0.494	− 163.00-78.66	2.88	0.924	−65.16-61.91
Hypertension+dyslipidaemia	169.07	0.001	68.60–269.55	53.07	0.098	−9.75-115.89
Number of complication (ref: None)						
One or two	210.54	< 0.001	134.48–28,660	63.69	0.003	21.70–105.68
Three or more	847.72	< 0.001	739.82–955.63	440.93	< 0.001	274.08–607.85

The guidelines for treatment and management of diabetes in Bangladesh follows lifestyle management as the first line care, metformin as second line care and then insulin, etc. depending on the health requirement (presence of comorbidity and complications) of the patients. Moreover, as all medical costs come from out of pocket payments, people usually visit doctor when diabetes makes obstacle to their daily living. This explained why a very low number of participants (1.8%) in this study were under lifestyle management. Thirdly, since insulin is very expensive in Bangladesh, it leads to a higher medicine cost. The result of other studies conducted in some developing countries [14, 34–37] also showed the medicine cost as a major contributor to direct cost.

Medicine was the highest source of direct cost (83.5%) for patients without hospitalisation. Furthermore, for patients with hospitalisation, medicine cost was 50.7% of the direct cost followed by a hospitalisation cost of 39.9%. However, a number of previous studies showed that the largest proportion of cost is attributable to hospitalisation followed by medicine cost. In the USA, hospitalisation cost accounted for 50% [38], while that was 55% in the Cost of Diabetes in Europe-Type II study [39].

In the present study, the cost of diabetes care substantially increased with the presence of comorbidities as well as complications related to T2DM. The cost was positively correlated with the increased number of comorbidities and complications leading to hospitalisation. This finding is supported by other studies in the developed [30, 37, 40–42] as well as in developing countries [43, 44]. In addition to complications and comorbidities, the duration of diabetes also accelerates cost; likewise, cost increased for patients who had poor glycaemic control compared to good control. Similar results were reported in previous COI studies [28, 29, 37, 45].

A Median regression analysis showed that female gender, use of insulin, longer duration of diabetes, and presence of complications are the factors related to a higher annual average cost per person. A majority of these variables also appeared as contributing factors in previous studies [14, 15, 17, 28, 42]. Thus, optimisation of the management of diabetes-related complications is an imperative need for people with T2DM in Bangladesh, which has also reflected in the results of sensitivity analyses of the current study.

The present study showed that in 2017 the annual average cost per T2DM was US$864.7, which is 52% of per capita GDP of Bangladesh [10] and 9.8 times higher than the general health care cost [9]. The burden of diabetes is influenced by many socio-economic and health care system factors, which consequently affects the cost of care. Early screening is one of the factors that may help to diagnose T2DM patients at an initial stage, thus avoiding complications. However, in developing countries, people often seek medical help when they have already developed some complications. In addition, inadequate awareness about diabetes-related complications, lack of access to medical care resulting from income disparities, lack of social supports, and heterogeneous quality of care are other societal factors that influence the diabetes-related cost of care [46]. Thus, this study finding will be useful for policy makers in planning future health care needs and allocating scarce resources. Furthermore, it will play a significant role for both patients and provider in identifying and quantifying the costs attributed to T2DM in Bangladesh.

A strength of this study was that it addressed all possible cost components of both direct (including hospitalisation) and indirect cost from the patients' perspective, and cost was calculated based on primary data. However, other recent COI studies have not addressed all cost components [3, 38], despite the cost being calculated from the societal perspective. Another strength was that a professional mix of patients residing in urban and rural locations was recruited randomly form six hospitals that provide primary to tertiary care.

Some limitations should also be noted. Firstly, in addition to direct and indirect costs, there are also intangible costs (e.g. pain, suffering, and loss of quality of life), which was not addressed in this study. Secondly, due to a lack of information, the calculation of indirect cost was done using the traditional human capital approach rather than the frictional cost approach [47]. Finally, as it was a descriptive cost-of-illness study, it did not provide information on the efficiency of resource use; thus, higher cost does not necessarily mean better services or value for money.

Conclusions

Diabetes is a major public health issue with a high economic burden in Bangladesh. The development and improvement of interventions toward better control of T2DM and the prevention of its complications are vital requirements for the country. Without these, in the near future, the private and public financing of diabetes treatment will be severely constrained, representing a health threat for the Bangladeshi population.

Additional file

Additional file 1: English language versions of the questionnaire (PDF 8 kb)

Abbreviations

BADAS: Diabetic Association of Bangladesh; BDT: Bangladeshi currency, Taka; BUHS: Bangladesh University of Health Sciences; CI: Confidence interval; COI: Cost -of-illness; GDP: Gross domestic product; IDF: International Diabetes Federation; LMICs: Low- and lower middle-income countries; OHA: Oral hypoglycaemic agent; OOP: Out-of-pocket; PPS: Probability proportional to

size; REDCap: Research Electronic Data Capture; T2DM: Type 2 diabetes mellitus; WHO: World Health Organization

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Authors' contributions
Concept and design (AA, BB), acquisition of data (AA, LA, SHH, AK), interpretation of data and drafting the manuscript (AA, KA, MJA, DJM, BB), critically review to improve the content and final approval of version to be submitted has done by all authors.

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Availability of data and materials
The data generated during and/or analysed during the current trial are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study has been approved by the Monash University Human Research Ethics Committee (ID: 1469), the Ethical Review Committee of the Bangladesh University of Health Sciences and the Ethical Review Committee of the Diabetic Association of Bangladesh. Informed written consent was obtained from all participants.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

Chapter 5

BURDEN OF TYPE 2 DIABETES RELATED COMPLICATIONS ON HOSPITALISATION AND HEALTHCARE COST

Context of the study

The increasing prevalence of uncontrolled diabetes leads to an increase in the prevalence of diabetes-related macrovascular and microvascular complications. People with diabetes have on average 2-fold higher medical expenditure than those without diabetes. The burden of this emerging pandemic is driven by its increased risk of complications and much of the burden, especially for people with T2DM, is related to microvascular and macrovascular complications. Each complication results in a different type of resource utilisation, which has an independent economic impact. The progression of complications results in frequent hospitalisations, which coupled with their ongoing treatment cost escalate the burden. To prioritise the resource allocation for the prevention of complications, policy makers need clear information about the individual impact of each complication on healthcare.

In Bangladesh, there is a paucity of research-based evidence regarding the burden of diabetes-related macrovascular and microvascular complications on hospitalisation and average annual cost of care, which led to the objective of this study. The findings of this study may help healthcare providers to intervene in improving patient management and possibly reduce healthcare costs in the near future.

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Original Article

Burden of macro- and micro-vascular complications of type 2 diabetes in Bangladesh

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ABSTRACT

Objective: The aim was to estimate the burden of macro- and micro-vascular complications on hospitalisation and healthcare cost among people with type 2 diabetes mellitus in Bangladesh.
Methods: A cross-sectional study was carried out in 2017. A total of 1253 patients were recruited from six hospitals. Information related to cost and complications of type 2 diabetes were collected. Multiple logistic and non-parametric regression analyses were performed to evaluate the effect of complications on hospitalisation and average annual cost.
Results: Overall, 63.4% of the participants had complications of which 14.8% and 20.7% had macro- and micro-vascular complications respectively and 27.9% had both. Use of insulin, presence of both hypertension and dyslipidaemia, coronary artery diseases, stroke, nephropathy, and retinopathy were significantly associated with hospitalisation. Further, use of oral hypoglycaemic agent with a combination of insulin, presence of coronary artery diseases, stroke, nephropathy, and retinopathy increased the average annual cost.
Conclusion: The prevalence of macro- and micro-vascular complications were very high in Bangladesh and majority of them are key drivers for hospitalisation and increased healthcare cost. An improvement of primary prevention strategy for complications is urgently needed which in turn will reduce the long-term healthcare cost for type 2 diabetes in Bangladesh.

1. Introduction

Diabetes mellitus and its related complications are a growing health and economic burden worldwide. The global prevalence of diabetes was estimated to be 8.8% among adults aged 20–79 years in the year 2017 [1]. About 79% of them were living in low- and middle income countries. It has been projected that by the year 2045 the global prevalence of diabetes will reach to about 9.9%. The largest increase will take place in regions where economies are moving from low income to middle income levels [1].

Diabetes is strongly associated with both macro- and micro-vascular complications [2]. The disease and its associated complications pose a severe economic burden on individuals as well as on the healthcare system. Expenditure on healthcare for people with diabetes are on average two-fold higher than that of people without diabetes [3]. To treat and prevent diabetes and its related complications, USD727 billion was spent in the year 2017 globally, which represents an 8% increase compared to that of the 2015 estimate [1].

A study conducted in the USA showed that the prevalence of uncontrolled diabetes increased from 35.8% to 44.5% between the year 1988 and 2000 [4]. The increasing prevalence of uncontrolled diabetes leads to an increase in the prevalence of diabetes related macro- and micro-vascular complications. This imposes a significant economic burden on healthcare systems, and above all, on individuals with diabetes and their families [1]. Detailed data on global estimates of diabetes related complications are limited. However, in some high income countries, where data are available,

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the prevalence of complications vary enormously [1]. A few studies [5–8] in Bangladesh investigated the prevalence of microvascular complications (nephropathy, retinopathy and neuropathy) of type 2 diabetes. However, none of the study investigated the macrovascular complications (coronary artery disease, stroke and diabetic foot).

Each complication results in different type of resource utilisation, thus have an independent economic impact. Poorly controlled diabetes leading to complications results in frequent hospitalisations [1] which escalates the cost further [9,10]. The Cost of Diabetes in Europe-Type II study [9] and study conducted in the USA [10] reported that the hospitalisation cost due to diabetes related complications ranges between 50% and 55% of the total cost of diabetes care. In order to prioritise the resource allocation for the prevention of complications, policymakers need a clear information about their individual impact on healthcare. In Bangladesh, there is a paucity of research-based evidence that addressed the burden of diabetes related macro- and micro-vascular complications on hospitalisation and average annual cost of diabetes care.

Thus, the aim of this study was to explore the association of hospitalisation as well as average annual cost with macro- and micro-vascular complications among people with type 2 diabetes mellitus (T2DM) in Bangladesh. This study findings will be useful to suggest recommendations in advocating and developing complication specific diabetes management plan.

2. Methodology

2.1. Study design and study population

This study has been approved by the Monash University Human Research Ethics Committee and the ethics committee of the Diabetic Association of Bangladesh (BADAS). The BADAS (a not-for-profit but mostly self-sustained social welfare organisation) has 61 affiliated hospitals and centres across Bangladesh that provide health services to majority of the people with diabetes in the country. Six hospitals were selected from the central and northern regions of the country which provide primary to tertiary level cares to rural-urban and professional mix population. Since the socio-economic status of people living in northern and southern regions in the country are very similar, no hospital were selected from the southern region.

2.2. Sample selection

A total of 1253 participants were recruited using probability proportional to size and systematic random sampling methods from April to September 2017. The target population was adults of either gender with a minimum one year duration of T2DM. People with other types of diabetes or pregnant women were excluded.

2.3. Data collection

Participant's socio-demographics and all information related to the cost of diabetes care were collected using a structured questionnaire in a secured web-based application known as Research Electronic Data Capture (REDCap) [11]. Clinical information related to T2DM and its complications in the previous year were retrieved from patient's medical records (guidebook) using a data extraction check-list. Patient's complication status was ensured by asking the patients and reviewing their documented medical records and prescribed drug list confirmed by the allocated medical doctor to the patient. A team of trained data collectors was involved in face-to-face interviewing of each patient. Before the interview, a signed consent was obtained from each patient. Data was collected from the out-patient department (OPD) of the selected hospitals. However, individual who were referred to hospital admission from the outpatient department, their hospitalisation related data was collected prospectively from record of the in-patient department (IPD).

2.4. Operational definition for identifying complications

Coronary artery disease (CAD) was defined by reviewing the medical records of documented diagnosis, prescribed medication or any procedure that was undertaken as a treatment of CAD. Stroke was defined by reviewing the documented diagnosis of an irreversible cerebrovascular accident as well as by asking the patient about any incidence in the previous years. Diabetic foot was defined by visual examination of ulcers or amputations and documented diagnosis of diabetic foot. Nephropathy was defined by an estimated glomerular filtration rate <60 ml/min/1.73 m^2 [12] and a documented diagnosis from the medical records. Neuropathy was defined using the Michigan Neuropathy Screening Instrument [13] and by the prescribed medication. Retinopathy was defined by documented diagnosis or a procedure undertaken for the treatment of retinopathy.

2.5. Cost calculation

The total cost of care was calculated using the standard micro-costing approach and considering societal perspective during the year 2017 [14]. Direct and indirect costs endured by the participants were taken into account in calculating the total cost. All costs attributed to resource utilisation were calculated in Bangladeshi Taka (BDT) and then converted into USD considering a mid-year currency exchange rate for the year 2017 (US$1 = BDT80).

In order to estimate direct cost, bottom-up methodology [15] was used for primary data collection. Direct cost was divided into direct medical and non-medical costs. Direct medical cost included costs of hospitalisation, out-patient consultancy, medicine, laboratory tests, and other services. Direct non-medical cost included costs of transportation and meal en-route to hospital. The unit cost of each direct cost component was multiplied by quantities of medical services that were used during the previous year and then the total direct cost was calculated adding up all the medical and non-medical cost components. The indirect cost included productive time loss of the patients and their attendants. The human capital approach [16] was adopted to estimate indirect cost for those who were currently in a formal workforce or housewives. In order to perform sensitivity analysis, minimum wage rate of Bangladesh [17] and then again median monthly income of the study participants were used to calculate the productivity loss of housewives. The total cost was calculated adding up total direct and total indirect costs.

2.6. Statistical analysis

The descriptive statistics included mean with standard deviation, median with percentiles and frequency with percentage. Normality test of cost data was performed using histogram, Q-Q plot and Shapiro-Wilk test. Nonparametric Mann–Whitney *U* test and Kruskal-Wallis test were used respectively for comparing two groups and more than two groups. A multiple logistic regression analysis was used to identify the factors related to hospitalisation. Furthermore, multiple non-parametric regression analyses (50th percentile (median), 75th percentile and 90th percentile) were performed to explore the relationship of average annual cost with macro- and micro-vascular complications. Sensitivity analyses were performed to investigate the robustness of total estimated

cost. All the statistical tests were considered significant at 5% level, and the presented p-values were two-tailed. Data was analysed using the statistical software package, Stata SE version 15.

3. Results

3.1. Socio-demographic and clinical characteristics

Table 1 showed the socio-demographic and clinical characteristics of the study participants (n = 1253). Among them, 54% were male with a mean age of 55.1 years (±12.5). Nearly half (46%) of participants had a secondary level education and 22.9% had a tertiary level education. About 41% of participants were employed and about a quarter (23.8%) were housewives. Three-fourths of participants resided in urban areas, 12.9% in semi-urban areas and 13.9% in rural areas. About a quarter (25.7%) of participants had a monthly household income of USD375 or less. The mean duration of T2DM was 10.7 years (±7.7), with 43.5% had a duration of more than 10 years. Nearly three-fifths of participants (58.6%) managed their glycaemic level using a combination of oral hypoglycaemic agent (OHA) and insulin, 34.5% using OHA only and 6.9% using insulin only. About two-thirds (62%) of participants had poor glycaemic control (HbA1c ≥ 8%) and 19.8% had fair glycaemic control (HbA1c 7–7.9%). More than half (55.8%) of participants were moderately adhering to medication, followed by 37.1% with good and only 6.9% with poor adherence. About a half (48.5%) of participants had one or two diabetes related complications, 15.2% had three or more and 36.3% had no complication. Hypertension (HTN) was presented among 41.8% of participants, 12% had dyslipidaemia and 22.6% had both HTN and dyslipidaemia.

3.2. Prevalence of complications

Fig. 1 shows the prevalence of T2DM related macro- and micro-vascular complications. Overall, 63.4% of patients had one or more macro- and/or micro-vascular complications. The prevalence of macrovascular complications of CAD, stroke and diabetic foot were respectively 30.5%, 10.1% and 12%, while that for microvascular complications of nephropathy, neuropathy, and retinopathy were 34%, 5.7% and 25.1% respectively.

3.3. Diabetes related complications and average annual cost (cost-of-illness)

Table 2 showed the OPD and IPD costs by complications, comorbidities and glycaemic control. The cost was higher for patients with the presence of CAD (USD33.3, p = 0.032), nephropathy (USD61.1, p = 0.010) and retinopathy (USD82.4, p = 0.001) in

Table 1
Socio-demographic and clinical characteristics of the study participants.

Variables		n (%) or mean ± standard deviation	
Age		55.1	±12.5
Gender	Male	681	54.3
	Female	572	45.6
Education	Illiterate	161	12.8
	Primary level	239	19.1
	Secondary level	566	45.2
	Tertiary level	287	22.9
Work status	Unemployed	36	32.8
	Employed	411	40.5
	Housewife	508	23.8
	Retired	298	2.9
Area of residence	Rural/Semi-urban	336	26.8
	Urban	917	73.2
Monthly household income (USD)	≤250	447	35.7
	251–750	497	39.7
	751 and above	309	24.6
Onset of diabetes	≤40 years	503	40.1
	40–60 years	644	51.4
	≥61 years	106	8.5
Duration of diabetes	Total	10.9	±7.7
	≤5 years	360	28.7
	6–10 years	348	27.8
	>11 years	545	43.5
Mode of treatment	OHA	432	34.5
	Insulin	87	6.9
	Combination	734	58.6
Family history of diabetes	Yes	433	34.6
	No	820	65.4
HbA1c (%)	Good control (≤6.9%)	182	18.2
	Fair control (7–7.9%)	198	19.8
	Poor control (≥8%)	621	62.0
Adherence to medication	Good	466	37.2
	Moderate	700	55.9
	Poor	87	6.94
Number of complication	No complication	458	36.6
	1 to 2	613	48.9
	3 or more	182	14.5
History of co-morbidity	No comorbidity	296	23.6
	HTN	524	41.8
	Dyslipidaemia	151	12.0
	HTN + Dyslipidaemia	283	22.6

OHA = oral hypoglycaemic agent; HTN=Hypertension.

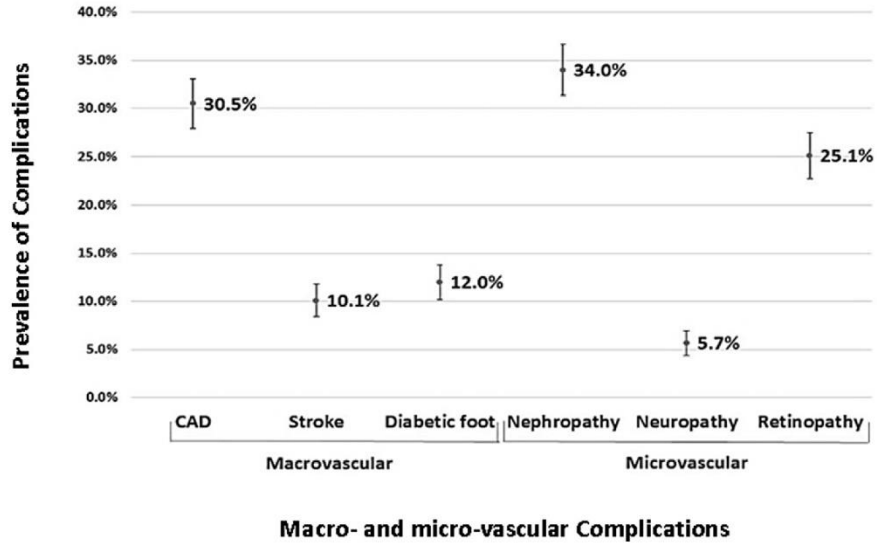

Fig. 1. Prevalence of major macro- and micro-vascular complications.

Table 2
Cost-of-illness (average annual cost) for diabetes related complications, comorbidities and glycaemic control.

Complications	Average annual cost Without hospitalisation (OPD)		Average annual cost With hospitalisation (IPD)	
	Median (25th p, 75th p)	p-value	Median (25th p, 75th p)	p-value
Macrovascular				
CAD				
No	359.9 (256.1, 509.1)	**0.032**	1189.9 (838.2, 1948.5)	0.272
Yes	393.2 (289.5, 509.1)		1281.1 (932.6, 2009.0)	
	CD 33.3		CD 91.2	
Stroke				
No	366.6 (265.3, 507.2)	0.513	1221.6 (857.7, 1856.2)	**0.006**
Yes	345.1 (233.7, 504.1)		1558.2 (1018.3, 2505.4)	
	CD 21.5		CD 336.6	
Diabetic foot				
No	364.1 (256.6, 505.7)	0.074	1179.8 (859.5, 1855.5)	**0.001**
Yes	425.8 (287.5, 516.8)		1130.2 (1130.2, 2958.4)	
	CD 30.9		CD 49.6	
Microvascular				
Nephropathy				
No	358.3 (255.7, 499.4)	**0.010**	1060.8 (727.7, 1652.9)	**0.001**
Yes	419.4 (295.5, 520.5)		1337.2 (953.7, 2043.8)	
	CD 39.8		CD 276.4	
Neuropathy				
No	366.6 (261.2, 504.2)	0.861	1277.6 (876.8, 1996.7)	0.503
Yes	356.4 (267.5, 559.4)		1022.0 (877.1, 1954.1)	
	CD 6.3		CD 255.6	
Retinopathy				
No	356.7 (255.9, 496.6)	**0.001**	1268.7 (897.9, 2097.6)	0.167
Yes	439.1 (321.2, 549.8)		1224.4 (857.5, 1902.6)	
	CD 65.3		CD 44.3	
Comorbidity				
None	324.3 (231.1, 502.8)	**0.001**	1283.4 (858.8, 1206.2)	0.994
HTN	387.5 (285.9, 526.9)		1230.8 (880.2, 1996.6)	
Dyslipidaemia	320.0 (237.0, 452.8)		1281.1 (876.5, 1630.2)	
HTN + Dyslipidaemia	387.1 (286.0, 503.3)		1227.2 (887.6, 2009.0)	
Glycaemic status (HbA1c %)				
Good control (≤6.9%)	307.3 (222.4, 466.5)	**0.001**	1198.3 (775.3, 1964.8)	0.612
Fair control (7–7.9%)	343.3 (264.8, 496.4)		1210.3 (893.1, 1658.7)	
Poor control (≥8%)	383.8 (275.7, 521.4)		1110.8 (858.7, 1551.1)	

CD = cost difference; Mann–Whitney *U* test and Kruskal-Wallis test were used respectively for comparing two groups and more than two groups.
p-values is significant ($p<0.05$).

comparison with those without these complications. Furthermore, the hospitalisation cost was higher for patients who had the event of stroke (USD336.6, p = 0.006) and nephropathy (USD276.4, p = 0.001). Participants with the presence of comorbidity as well as poor glycaemic control had higher (p = 0.001) OPD cost.

The cost ratio by the complication status presented in Table 3 showed that the ratio was 1.9-fold for patients with the presence of one or more complications compared to those without any complication. The ratio increased progressively as the number of complications increased. Patients with one, two and three or more complications (irrespective of macro- or micro-vascular) had 1.3-fold, 2.4-fold and 3.4-fold higher cost respectively. The presence of macro- and micro-vascular complications individually increased the cost ratio by 1.3-fold and 1.7 fold respectively and the ratio increased by 3.1-fold with the presence of both.

3.4. Relationship of hospitalisation with complications

Table 4 showed the results of multiple logistic regression analysis that identified the factors related to hospitalisation. The odds of hospitalisation increased by 6.1-fold (95% CI: 3.9–9.3) and 2.5-fold (95% CI: 1.5–3.8) for patients with the presence of nephropathy and retinopathy respectively. Furthermore, patients with stroke had 4.3-fold higher (95% CI: 2.1–8.7) odds (95% CI: 1.5–3.9) of hospitalisation and that was 2.5-fold higher for those with CAD. Patients with an onset of T2DM at aged 61 years or above had 2.3-fold increased odds to be hospitalised (95% CI: 1.1–4.9). The odds of hospitalisation was also higher for patients who were treated with insulin only (OR: 5.3, 95% CI: 2.1–13.1) or with a combination of OHA and insulin (OR: 2.9, 95% CI: 1.7–5.1). Compared to patients resided in urban areas, rural patients had 10% less odds to be hospitalised and compared to low income group that was 45% less for middle income group.

Table 4
Multiple logistic regression analysis: determinants of hospitalisation.

Variables	OR	p-value	95% CI
Gender (ref: male)rowhead			
Female	1.3	0.122	0.91–2.13
Onset of diabetes (ref: ≤40 years)rowhead			
41–60 years	0.8	0.433	0.53–1.32
≥61 years	2.3	0.031	1.07–4.92
Area of residence (ref: Urban)rowhead			
Rural/Semi-urban	0.1	0.001	0.02–0.12
Monthly household income (ref: USD≤250)rowhead			
USD251-750	0.45	0.002	0.27–0.74
USD751 and above	0.74	0.367	0.42–1.26
Mode of treatment (ref: OHA)rowhead			
Insulin	**5.3**	**<0.001**	2.17–13.1
OHA + Insulin	**2.9**	**<0.001**	1.71–5.06
HbA1c (ref: controlled ≤6.9%)rowhead			
Uncontrolled	1.3	0.363	0.72–2.37
Comorbidity (ref: no)rowhead			
HTN	1.4	0.293	0.75–2.57
Dyslipidaemia	0.6	0.328	0.25–1.57
HTN + Dyslipidaemia	1.3	0.349	0.71–2.62
Macrovascular complicationsrowhead			
CAD (ref: no)rowhead			
Yes	**2.5**	**<0.001**	1.59–3.97
Stroke (ref: no)rowhead			
Yes	**4.3**	**<0.001**	2.13–8.75
Diabetic foot (ref: no)rowhead			
Yes	1.7	0.144	0.87–3.32
Microvascular complicationsrowhead			
Nephropathy (ref: no)rowhead			
Yes	**6.1**	**<0.001**	3.94–9.35
Neuropathy (ref: no)rowhead			
Yes	1.2	0.770	0.45–2.92
Retinopathy (ref: no)rowhead			
Yes	**2.5**	**<0.001**	1.57–3.89

p-values is significant (p<0.05).

3.5. Relationship of average annual cost (or cost-of-illness) with complications

Multiple median (50th percentile) regression analysis results presented in Table 5 showed that patients with the presence of stroke and CAD had respectively USD241.8 (p < 0.001, 95% CI: 113.6–315.8) and USD83.3 (p = 0.009, 95% CI: 21.02–145.6) higher cost compared to those without these complications. Also, the presence of nephropathy increased the cost by USD215.1 (p < 0.001, 95% CI: 152.6–279.5) and it increased by USD84.3 (p = 0.015, 95% CI: 15.43–152.2) for patients who had retinopathy. Patients using a combination of OHA and insulin to control hyperglycaemia were subject to USD134.3 (p < 0.001, 95% CI: 76.70–191.6) higher cost in comparison with those using OHA only. Similarly, patients in a high income group spent USD74.5 (p < 0.034, 95% CI: 5.73–143.22) more than the lower income group.

The 75th as well as 90th percentile regression analyses were also performed to explore the key factors of cost for the patients within the top 25% and 10% of spending (Table 5). The 75th percentile regression analysis showed that patients with the presence of CAD, stroke and nephropathy spent respectively USD180.8 (p = 0.003, 95% CI: 61.6–300.0), USD332.1 (p = 0.001, 95% CI: 138.7–525.5) and USD537.7 (p < 0.001, 95% CI: 416.3–659.1) more

Table 3
Cost ratio by complications status.

Variable	Number (%)	Average annual cost		
		Median (25th p, 75th p)	p-value	Ratio
Complication statusrowhead				
Absent	458 (36.6)	359 (255.7, 524.3)	**<0.001**	1:1
Present	795 (63.4)	705 (393.1, 1360.4)		1:1.9
Number of complicationrowhead				
Absent	Reference			
One	352 (28.1)	473.4 (299.9, 806.5)	**<0.001**	1:1.3
Two	261 (20.8)	888.3 (475.9, 1432.8)		1:2.4
Three and more	182 (14.5)	1206.1 (723.8, 2043.8)		1:3.4
Types of complicationsrowhead				
Absent	Reference			
Macrovascular	186 (14.8)	451.6 (289.5, 810.7)	**0.001**	1:1.3
Microvascular	259 (20.7)	596.5 (364.1, 1088.8)		1:1.7
Micro and macrovascular	350 (27.9)	1048.4 (557.5, 1777.3)		1:3.1

Mann–Whitney *U* test and Kruskal-Wallis test were used respectively for comparing two groups and more than two groups.
p-values is significant (p<0.05).

Table 5
Multiple non-parametric regression analysis: determinants of overall average annual cost.

Variables	50th percentile (median) regression			75th percentile regression			90th percentile regression		
	Beta	p-value	95% CI	Beta	p-value	95% CI	Beta	p-value	95% CI
Gender (ref: male)									
Female	49.13	0.061	−2.25–100.53	32.44	0.518	−65.91–130.8	−12.77	0.902	−216.04–190.5
Onset of diabetes (ref: ≤40 years)									
41–60 years	−36.97	0.183	−91.3–17.43	−18.27	0.731	−122.3–85.8	−28.98	0.792	−244.16–186.2
≥61 years	−37.30	0.490	−143.2–68.67	−8.86	0.932	−211.6–193.9	110.88	0.604	−308.27–530.0
Area of residence (ref: Urban)									
Rural/Semi-urban	−54.03	0.068	−70.86–46.42	−52.48	0.354	−163.6–58.6	−132.01	0.260	−361.6–97.66
Monthly household income (ref: USD≤250)									
USD251-750	−12.21	0.683	−70.86–46.42	−8.23	0.886	−120.5–103.9	35.97	0.761	−195.9–167.9
USD751 and above	74.48	0.034	5.73–143.22	120.28	0.073	−11.27–251.8	218.4	0.115	−53.48–490.2
Mode of treatment (ref: OHA)									
Insulin	57.42	0.270	−44.76–159.6	**233.35**	**0.019**	37-79-428.9	309.65	0.133	−94.49–713.8
OHA + Insulin	**134.3**	**<0.001**	76.70–191.6	**170.78**	**0.002**	60.50–281.1	**312.7**	**0.007**	84-78-540.6
HbA1c (ref: controlled ≤6.9%)									
Uncontrolled	23.26	0.508	−45.71–92.24	−7.10	0.916	−139.1–124.9	11.12	0.936	−261.68–283.9
Comorbidity (ref: no)									
HTN	18.94	0.579	−48.12–86.02	29.18	0.656	−99.17–157.5	44.43	0.742	−220.8–309.7
Dyslipidaemia	−20.80	0.639	−107.9–66.30	−15.69	0.853	−182.3–150.9	−38.28	0.827	−382.7–306.2
HTN + Dyslipidaemia	10.12	0.799	−67.84–88.06	−6.71	0.930	−155.8–142.5	−27.85	0.859	−336.1–280.4
Macrovascular complications									
CAD (ref: no)									
Yes	**83.31**	**0.009**	21.02–145.6	**180.8**	**0.003**	61.60–300.0	**379.91**	**0.003**	133.5–626.3
Stroke (ref: no)									
Yes	**241.75**	**<0.001**	113.6–315.8	**332.14**	**0.001**	138.7–525.5	**466.09**	**0.022**	66.38–865.7
Diabetic foot (ref: no)									
Yes	41.23	0.357	−46.5–129.0	−6.85	0.936	−174.8–161.1	168.69	0.341	−178.4–515.8
Microvascular complications									
Nephropathy (ref: no)									
Yes	**215.11**	**<0.001**	152.6–279.5	**537.71**	**<0.001**	416.3–659.1	**1062.4**	**<0.001**	811.5–1313.3
Neuropathy (ref: no)									
Yes	−18.90	0.728	−125.6–87.8	−22.45	0.829	−226.7–181.8	−15.50	0.943	−437.6–406.6
Retinopathy (ref: no)									
Yes	**84.31**	**0.015**	15.43–152.2	59.47	0.369	−70.43–189.4	13.65	0.921	−254.8–282.1

p-values is significant (p<0.05).

than those without these complications. This differences were much higher for the 90th percentile regression, which showed that the presence of CAD, stroke and nephropathy increased the cost by USD379.9 ($p = 0.003$, 95% CI: 133.5–626.3), USD466.1 ($p = 0.022$, 95% CI: 66.38–865.7) and USD1062.4 ($p < 0.001$, 95% CI: 811.5–1313.3) respectively. Furthermore, both 75th and 90th percentile regression analyses revealed that patients treated with insulin only or with a combination of OHA and insulin had significantly higher cost compared to those treated with OHA only.

3.6. Sensitivity analysis

The results of sensitivity analysis confirmed that the estimated total average annual cost was robust between the use of minimum wage rate of Bangladesh and the median wage of study participants. Furthermore, the cost variation between the selected hospitals was homogeneous which demonstrates that the cost was not driven by a single hospital.

4. Discussion

Diabetes related complications are the salient threat on the global economy especially on the economy of the resource limited countries including Bangladesh. There is a dearth of evidence on the burden of macro- and micro-vascular complications of T2DM on hospitalisation and total healthcare cost in Bangladesh, hence the purpose of this study. This study results showed that overall 63.4% of participants had complications of which 14.8% had macrovascular complications, 20.7% had microvascular complications and 27.9% had both. The presence of CAD, stroke, nephropathy, and retinopathy increased the likelihood of hospitalisation in multi-fold and they had an independent impact on higher healthcare cost.

The estimated prevalence of each complication in this study was comparable to that of the global estimates for working people with diabetes aged between 20 and 65 years. The prevalence of CAD (30.5%) was within the range of the estimated global prevalence (12%–31.7%) [1] and that of diabetic foot (12%) was comparable with other Asian countries namely India [18] and Thailand [19], but higher than the global estimate of 6.4% [1]. It should be noted that the global prevalence of diabetic foot varied between 3% in Oceania to 13% in North America [1]. Poorly controlled blood glucose level causes damage to the nerves, which places the people with diabetes at 10 times higher risk of developing nephropathy [1]. In this study, the prevalence of nephropathy was 34% which resembles the estimated global prevalence of 39% [20]. This study showed that 5.7% of participants had neuropathy which was much lower than the estimated global prevalence (16%–66%) [1]. This may be due to the asymptomatic nature of this complication that keeps patients as undiagnosed. Furthermore, in Bangladesh, the healthcare cost is mostly out-of-pocket and hence, generally, people seek medical help when the complication incurs some obstacle to their daily living. Retinopathy is another microvascular complication which is commonly prevalent among people with T2DM and it is a leading cause of blindness for these people [1]. This study showed that the prevalence of retinopathy is 25.1%, which is less than the global prevalence of 35% [1]. This difference again may be due to the silent progression of retinopathy and unmet financial involvement for regular screening.

The cost of diabetes care is significantly associated with the level of complications that lead to hospitalisation. In this study, the OPD

cost was significantly higher for patients with the presence of CAD, nephropathy and retinopathy as they require frequent OPD follow-up. Hospitalisation cost was higher for patients with stroke and nephropathy which may be related to higher treatment cost and prolonged hospital stay. A study conducted in the USA also reported that nephropathy and cardiovascular diseases were the most prevalent among people with diabetes and were associated with predominantly higher costs [21]. The economic impact of managing T2DM with CAD and nephropathy is likely to be higher as the patients may require high resource treatment options.

Our study results showed that the patients who were treated with a combination of insulin and OHA were more likely to be hospitalised and had a higher cost which is supported by previous studies [22,23]. The higher spending for patients using insulin with a combination of OHA can be justified by the higher cost of insulin. Additionally, patients are generally prescribed for insulin in combination with OHA when the monotherapy fails to maintain the blood glucose level within the clinically recommended range. Furthermore, the progression of diabetes increases the likelihood of acquiring diabetes complications that require multiple modalities of treating hyperglycaemia.

The actual economic burden of diabetes remains underestimated if the cost of diabetes related complications had not been taken into account [24,25]. This study showed that patients with the presence of any complication experienced almost double healthcare cost compared to those without complication. Previous studies [26,27] also supported this finding where per patient cost increased between 2 and 3.5-fold with the presence of complications. Moreover, this study results showed that cost increased considerably as the number of complications increased and that was 3-fold higher with the presence of both macro- and microvascular complications compared to patients without complication. This finding is consistent with that of other studies [19,22,28,29].

Furthermore, this study results showed that patients with CAD, stroke, nephropathy and retinopathy were more likely to be hospitalised. These findings are similar to that in studies conducted by Williams et al. [28], Bhattacharyya et al. [22,30] and Chaikledkaew et al. [23]. As was evidenced by the multiple non-parametric regression analysis, each of the above complications increased the cost significantly and they are the key contributors for higher average annual cost per person. This can be due to the increased severity of the compilations and their resource-intensive treatment options. In addition, use of OHA in a combination with insulin appeared as an increased cost contributor which was similar to that of the previous studies [19,23,26,27,29,30]. The cost related to treating CAD, stroke and nephropathy progressively increased starting from the top 50% cost bracket, and this difference widens more towards the top 25% and 10% of patients. Early diagnosis and intensified treatment for these complications can be a way to avoid hospitalisation. This may result in a relatively large economic saving, thereby calling for tailored preventive interventions.

The International Diabetes Federation guidelines provide emphasis on comprehensive management plan including health education about the importance of positive lifestyle modification, effective monitoring for blood glucose and lipids, and regular screening for complications for people with T2DM [1]. In current practice, all the hospitals under the umbrella of the BADAS have health educators to educate patients on management plan including the benefits of positive lifestyle changes. Patients are also receiving advice for regular screening of complications. However, in general, patients are less likely to engage with this advice due to the out-of-pocket costs for screening and monitoring which lacks government subsidisation. Out-of-pocket access to healthcare is a factor that is closely related to household economic status. In Bangladesh, people have to pay out-of-pocket to secure their health and more than 12% of households have to borrow money or sell household assets to pay healthcare costs related to chronic diseases [31]. The healthcare financing in Bangladesh is still predominantly prioritised by maternal and child health programs [32] and NCDs especially diabetes and hypertension are being paid less attention. This study findings demonstrated that the economic burden of T2DM along with its complications will increase if preventive measures are not implemented. Hence, people with T2DM should be under the coverage of screening and monitoring programs on a regular basis. They should be advocated for positive lifestyle changes and better control of diabetes. Finally, these programs should be subsidised by the government so that every patients get an opportunity to access the service.

This study has some strengths and limitations. The strength of this study was that it has included a representative large sample covering professional mix patients living in urban, semi-urban and rural areas. Patients were recruited from multiple hospitals that provide primary to tertiary levels healthcare facilities and data collection using electronic questionnaire confirmed the data quality. Information regarding T2DM related complications was confirmed by the proper documentation of diagnosis and allocated medical doctors. This study captured all possible costs related to T2DM and its complications. At the same time, it has the limitation that this hospital based prevalence of complications may differ from a community-based study. Hence, generalizability of this study results may be limited to patients attending the hospitals under the BADAS and hospitals similar to this study hospitals. Due to cross-sectional study design, it was difficult to measure the severity of the complication that may influence the cost estimation.

5. Conclusion

While it is understood that prevention or a delayed onset of compilations for patients with T2DM leads to a reduction of healthcare cost on disease management, the findings of this study highlight the main cost contributors that require attention to maximise health outcomes for the T2DM population in Bangladesh. Access to robust monitoring and subsidised early screening programs for T2DM patients can help greatly to minimise the economic burden of macro- and micro-vascular complications related to this growing epidemic.

Author's contribution

Concept and design (AA, BB), acquisition of data (AA, AB, LA), interpretation of data and drafting the manuscript (AA, BB), critically review to improve the content and final approval of version to be submitted (AA, NH, BB, DM, KA, LA). All authors have read and approved the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.03.001.

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Availability of data

The data sets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Chapter 6

GLYCAEMIC CONTROL: AN IMPORTANT ASPECT OF DIABETES MANAGEMENT

Context of the study

Diabetes mellitus is a chronic disease for which there is no known cure, and it needs to be well managed to achieve better wellbeing. Management concentrates on keeping blood sugar levels as close to normal without having hyperglycaemia or hypoglycaemia. The detrimental consequence of hyperglycaemia is that it increases the likelihood of developing diabetes-related complications, which are a major concern. Long-term hyperglycaemia may affect many organs of a person's body and can lead to the development of disabling and life-threatening complications such as the macrovascular complication of CVD and the microvascular complications of neuropathy, nephropathy and retinopathy. Prevention of the injurious effects of hyperglycaemia is the most important aspect of the optimal management of patients suffering from diabetes. Glycaemic control is therefore considered an essential approach to prevent chronic complications in patients with T2DM.

Knowledge about the disease and actively participating in the treatment are important to prevent the onset and progression of complications since complications are far less common and less severe in people who have controlled blood sugar levels. Guidelines, interventions and lifestyle modification have focused on achieving optimal glycaemic control. However, without a clear understanding of the precise dynamics of poor glycaemic control, the achievement of optimal control of glucose is a daunting task for a person with T2DM. Factors related to poor glycaemic control have been investigated among the Western population; however, these are not translatable to the Bangladeshi population due to geographical, social and cultural variations.

Given the impact on patients, healthcare delivery, and policy making, the relationships between poor glycaemic control and all the potentially important factors, including compliance with management plans and the effects of lifestyle modification comparing their relationships with the body of evidence merits investigation. Therefore, this study aimed to estimate the prevalence of glycaemic control and to widen the investigation regarding its related factors among patients with T2DM in Bangladesh.

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Glycaemic Control for People with Type 2 Diabetes Mellitus in Bangladesh - An urgent need for optimization of management plan

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Aims: The objective of this study was to identify the determinants of glycaemic control among people with type 2 diabetes mellitus in Bangladesh. A cross-sectional study was carried out during March to September 2017, and 1253 adult patients with type 2 diabetes mellitus were recruited from six hospitals. Data were collected from patients via face-to-face interview, and their medical records were reviewed. Multiple logistic regression analysis was performed. Among the participants, 53.2% were male. Mean (±SD) age was 54.1 (±12.1) years and mean (±SD) duration of diabetes was 9.9 (±7.2) years. About 82% participants had inadequate glycaemic control (HbA1c ≥ 7%) and 54.7% had very poor control (HbA1c ≥ 9%). Low education level, rural residence, unhealthy eating habits, insulin use, infrequent follow up check-ups and history of coronary artery diseases found associated with inadequate and very poor controls. Being female and smokeless tobacco consumer appeared to be associated with inadequate control however cognitive impairment was associated with very poor control only. Prevalence of inadequate glycaemic level was very high in Bangladesh. Having understood relatable lifestyle modification factors, demographics and co-morbidities among people with type 2 diabetes, health care providers in conjunction with patients should work together to address the glycaemic control.

Diabetes is one of the biggest health threats of recent times for the global population, rich and poor alike. It was estimated that, in the year 2017, more than 425 million people globally were suffering from diabetes. The burden is increasing, predominantly in low- and middle-income countries, where about 80% of total diabetes deaths in the world occur[1]. In Bangladesh, the prevalence of diabetes was 9.7% in 2011[2], and the number of adults with diabetes is projected to be 13.7 million by 2045[1].

A major concern of diabetes is the complications that accompany it, which occur as detrimental consequences of hyperglycaemia. Long-term hyperglycaemia may cause damage in various organs and can lead to the development of disabling and life-threatening complications such as cardiovascular disease, neuropathy, nephropathy and retinopathy. In 2017, a total of US$727 billion was spent globally to treat and prevent diabetes and its related complications[1].

The most important aspect of the optimal management of patients suffering from diabetes is prevention of the injurious effects of hyperglycaemia. Glycaemic control is thus considered as the main therapeutic goal for prevention of these severe consequences. Results from many observational studies and randomised controlled clinical trials[3–6] have revealed that strict control of glycaemic levels helps to prevent complications, especially of the microvascular type, and that these complications are directly related to quality of life[7,8].

Optimal control of glucose is a daunting task without a clear understanding of the precise dynamics of poor glycaemic control in people with type 2 diabetes (T2DM). Epidemiological studies in different populations[9–14] have identified several factors that are related to poor glycaemic control. However, most of these studies have been conducted on patients in Western countries. A paucity of such evidence exists for resource-limited populations

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such as Bangladesh, where diabetes presents a huge burden that goes unnoticed to a large extent. Only one study[15] has been conducted in Bangladesh attempting to identify the risk factors related to poor glycaemic control; however, it addressed a limited number of factors compared to studies undertaken in Western countries. In order to provide effective research-based evidence, the relationships between poor glycaemic control and all potentially important factors, including compliance with management plans, the effects of lifestyle modification factors, family support, anxiety, depression, and cognitive function, need to be investigated. Thus, the objective of the current study is to estimate the prevalence of glycaemic control, and to widen the investigation regarding related factors, among patients with T2DM in Bangladesh.

Methodology

Study design and population. A cross-sectional survey was carried out in Bangladesh from March to September 2017. Data were collected from six hospitals across the country. The selected hospitals are all affiliated with the Diabetic Association of Bangladesh (BADAS), the largest diabetes care provider in the country. All of the hospitals provide various levels of care to people with diabetes. Hospitals affiliated with BADAS are located both inside and outside metropolitan areas across the country, covering rural, urban, and semi-urban settings. Within metropolitan areas, the selected hospitals are the central hospitals that provide primary to tertiary care services. The hospitals outside metropolitan areas usually provide primary to secondary care; hence, patients attending these hospitals but in need of tertiary care are usually referred to the metropolitan hospitals. Using a selection of these specific hospitals for this study allowed for recruiting a heterogeneous sample.

Using 95% confidence level and 5% significance levels, a margin of error of 2.5% for the prevalence of good glycaemic control of 18.8%[15] obtained from a previous Bangladeshi study on T2DM, a sample size of 938 patients was calculated. However, a total of 1253 patients, aged ≥18 years, all registered with BADAS and having been T2DM patients for a minimum duration of one year, were recruited for the study. The study excluded people suffering from other types of diabetes.

Data collection. Each patient was interviewed face-to-face using a pre-tested questionnaire after informed written consent was obtained prior to the interview. The questionnaire was pre-tested through a pilot survey in the Bangladesh Institute of Health Sciences hospital. The first section of the questionnaire consisted of questions about patients' socio-demographic and lifestyle characteristics, including age, gender, marital status, education, profession, monthly household income, smoking status, eating habits, and physical activity. The next section of the questionnaire consisted of clinical and diabetes-related information about the participants such as duration of diabetes, family history of diabetes, frequency of follow-up check-ups, mode of treatment, and hypoglycaemic events. A data extraction checklist was used to collect the data from patients' records, including laboratory test results, diagnosis, medications, history of complications, and comorbidities.

The final section of the questionnaire was tailored, including the use of several recognised tools to assess a variety of factors known and alleged to relate to aspects of diabetes control. The UK diabetes and diet questionnaire (UKDDQ)[16] was used, with some minor modifications to make it suitable for the Bangladeshi population. Six selected items from the Global Physical Activity Questionnaire (GPAQ)[17] were used to assess physical activity levels. Patient Health Questionnaire-2 (PHQ-2)[18], Generalized Anxiety Disorder Scale (GAD-2)[19], Michigan Neuropathy Screening Instrument[20], and a Six-item cognitive impairment test (6CIT)[21] were used, all without any modification. Permissions were obtained from the respective authorities to use the above-mentioned tools. The weight and height of participants were measured while they were wearing light clothes and no shoes. Waist and hip circumference were measured against thin clothing. Body mass index (BMI) and waist-hip ratio (WHR) were calculated from the collected measurements. Research Electronic Data Capture (REDCap) was used to collect and manage the data[22].

Operational definition. The patient's latest readings (within the previous three months) of glycaemic status were categorised as follows: good glycaemic control = HbA1c < 7%[23]; fair control = HbA1c 7–8%; and poor control = HbA1c > 8.0%[24]. An HbA1c cut-off value of ≥9% was used to represent very poor control[25]. BMI was categorised as: <18.50 = underweight; 18.50–24.99 = normal; >25.00 = overweight or obese[26]. The cut-off point for WHR was defined as a ratio of >0.90 for men and >0.80 for women[27]. Hypertension was defined by either a documented diagnosis of hypertension, the patient taking antihypertension medications, or the latest (within three months) blood pressure readings (either systolic ≥140 or diastolic ≥90)[28]. Dyslipidaemia was defined based on either a documented diagnosis of dyslipidaemia or the patient taking any lipid-lowering medications. Impaired cognitive function was defined as a score of more than seven using 6CIT[21]. Neuropathy was defined as a score of seven or more using the Michigan Neuropathy Screening Instrument[20]. Diabetic foot was confirmed by visual examination of ulcers or amputations and a documented diagnosis of diabetic foot. Physical activity was measured using the GPAQ, and >150 minutes of walking per week was considered as active. Dietary habits were assessed using the UKDDQ[16]. The dietary habit variable was measured on a scale between 0 and 48 and categorised using a cut-off at the first quartile (score 28). A score higher than 28 was considered to indicate healthy eating habits.

Ethical approval. The project was approved by the Monash University Human Research Ethics Committee and the Ethical Review Committee of the Bangladesh University of Health Sciences. Approval was also obtained from BADAS. All the study procedures were carried out in accordance with the principles of the Declaration of Helsinki as revised in 2013[19].

Data management and analysis. Descriptive statistics were reported using mean with standard deviation (SD) for numerical data and relative frequencies (percentages) for categorical data. To test the associations between risk factors and levels of glycaemic control, ANOVA, chi-square tests, and simple logistic regression

analysis were used for a univariate analysis. Risk factors with a p-value < 0.05 in simple logistic regression analysis were considered for a multiple logistic regression model. Clinically plausible risk factors were entered into the model even if they appeared to be insignificant in the univariate analysis. Multi-collinearity and the first-order interaction effects between clinically relevant risk factors were investigated. A step-wise backward elimination method was used to select variables that were significantly related to the outcome measures. Multiple logistic regression analysis was mainly performed to identify the determinants for an inadequate glycaemic level (HbA1c $\geq$7%) as well as for very poor glycaemic control (HbA1c $\geq$9%). In order to determine the duration-specific risk factors, the patients were stratified by the T2DM durations of: $\leq$5 years and >5 years[29]. Data were analysed using the statistical software package STATA SE version 15.

Results

Among the participants, 532 (53.2%) were male. The mean (±SD) age was 54.1 (±12.1) years and the mean (±SD) duration of participants' diabetes conditions was 9.9 (±7.2) years. The mean (±SD) BMI was 25.7 (±4.9) kg/m^2 and the mean (±SD) HbA1c was 9.0% (±2.2%). Only 18.8% of participants were classified as having good control, 19.78% had fair control, 62% had poor glycaemic control, and 54.7% had very poor control. Table 1 shows demographic and lifestyle characteristics for various glycaemic levels. The prevalence of poor control was higher among females ($p = 0.003$), participants with a lower level of education ($p = 0.001$), those living in rural areas ($p < 0.001$), and unemployed people or housewives ($p = 0.011$). Further, the prevalence of poor glycaemic control was higher among smokeless tobacco consumers ($p = 0.008$) and unhealthy diners ($p = 0.008$).

The associations between various clinical characteristics and glycaemic control are presented in Table 2. A higher prevalence of poor glycaemic control was present among people with more than five years' duration of diabetes ($p = 0.005$), insulin users ($p < 0.001$), those having irregular follow-up check-ups ($p < 0.001$), patients with a history of coronary artery diseases (CAD) ($p = 0.001$), and those with cognitive impairments ($p < 0.001$).

The results of multiple logistic regression analysis with step-wise removal for inadequate glycaemic control (HbA1c $\geq$7%) and very poor glycaemic control (HbA1c $\geq$9%) are presented in Fig. 1. The following variables presented an increased risk for both inadequate and very poor glycaemic controls: low level of education, residing in a rural area, unhealthy eating habits, use of insulin (either solely or in combination with an oral hypoglycaemic agent [OHA]), infrequent follow-up check-ups, and a history of CAD. However, the majority of these factors had more prominent effects among patients with very poor control. For example, patients living in rural areas showed 2.4-fold (95% CI: 1.1–3.4) higher odds of having inadequate control, compared to 4.1-fold (95% CI: 2.5–6.5) higher odds for very poor control. There were also some differences between risk factors for the two groups: female participants (OR: 1.7, 95% CI: 1.2–2.4) and smokeless tobacco consumers (OR: 1.7, 95% CI: 1.1–2.8) were at higher risk for inadequate control only, while for patients with impaired cognitive functions (OR: 3.2, 95% CI: 1.4–3.7), a higher risk was seen only in the category of very poor control.

The sub-group (duration of T2DM: $\leq$5 years, shorter and >5 years, longer) analysis results for inadequate and very poor glycaemic controls are presented in Tables 3 and 4 respectively. Table 3 shows that most of the variables in the multiple logistic model appeared as common risk factors between the two groups. However, smokeless tobacco consumption (OR: 2.9, 95% CI: 1.3–6.2) presented a risk only in the shorter duration group and female participants (OR: 2.5; 95% CI: 1.5–4.1) were at higher risk in the longer duration group only.

The sub-group analysis performed for very poor glycaemic control showed more differentiated risk factors than shared ones between the two groups, as shown in Table 4. Smokeless tobacco consumption (OR: 3.1; 95% CI: 1.2–8.1), use of insulin (solely or in combination with OHA) (OR: 6.1; 95% CI: 2.9–12.6), and history of CAD (OR: 3.5; 95% CI:1.1–10.8) were risk factors in the shorter duration group only, while patients aged above 60 years (OR: 0.5; 95% CI: 0.3–0.8) or suffering from cognitive impairment (OR: 3.2; 95% CI: 1.7–6.0) were at higher risk only in the longer duration group.

Discussion

Glycaemic control is the cornerstone of managing T2DM and is essential for the prevention of long-term diabetes complications. The key result of this study is that 81.8% of participants did not achieve the recommended HbA1c target of lower than 7%, and 54.7% showed very poor control (HbA1c $\geq$9%). In general, being female, a low level of education, rural residence, smokeless tobacco consumption, unhealthy eating habits, insulin use, history of CAD, and cognitive impairment were associated with inadequate glycaemic levels in the Bangladeshi T2DM population. Additionally, different sets of risk factors played pivotal roles in the two sub-groups formed based on different durations of T2DM. The cross-sectional nature of the study may not provide reliable insights on temporal relationships; however, the identified association between various factors and glycaemic control is certainly worthy of mention.

The prevalence of inadequate glycaemic control found among people with T2DM is consistent with previous studies conducted in Bangladesh by Selim *et al.*[15] and Latif *et al.*[30]. The proportion of people with inadequate glycaemic control is higher among females who have had the condition for a longer duration (>5 years), which is also similar to the findings of the previous studies[14,29]. This may be because the females who were in the longer duration group in the current study sample were comparatively older, less compliant with healthy eating, and were being treated with insulin. All of these factors pose individual risks for poorer control. The current study shows that the proportion of people with inadequate glycaemic control is higher among people with a low level of education and those living in rural areas, which is also supported by the previous studies[15,31,32]. People living in a rural area are likely to have a low level of education, and thus have lower levels of T2DM knowledge, low self-management behaviours, low self-efficacy, and low continuity of care. Furthermore, a low level of education increases the likelihood of being in a lower socio-economic class, which may limit their ability to access adequate health care facilities. Due to limited accessibility and affordability, they may not visit a diabetes specialist until they experience complications in the progression of their diabetes. On the other hand, people with a better

Variable	Glycaemic control (HbA1c)			p-value
	Good (<7%) n = 182	Fair (7–7.9%) n = 198	Poor (≥8%) n = 621	
Age in years (mean (±SD)	53.8 ± 12.7	55.9 ± 11.2	53.4 ± 12.2	**0.047**
Age % (n)				
≤40 years	20.5 (31)	13.9 (21)	65.6 (99)	**0.103**
41–60 years	16.7 (93)	19.6 (109)	63.7 (355)	
>60 years	19.8 (58)	23.2 (68)	57.0 (167)	
Gender % (n)				
Female	14.3 (66)	22.1 (102)	63.5 (293)	**0.003**
Male	22.2 (116)	17.4 (91)	60.3 (315)	
Education level % (n)				
Illiterate	14.6 (19)	18.4 (24)	66.9 (87)	**0.001**
Primary	12.1 (21)	18.9 (33)	68.9 (120)	
Secondary	16.5 (73)	20.3 (90)	63.1.(279)	
Tertiary	29.1 (69)	19.4 (46)	51.5 (122)	
Area of residency % (n)				
Rural	14.0 (24)	12.3 (21)	73.7 (126)	**<0.001**
Semi-urban	11.9 (19)	18.8 (30)	69.4 (111)	
Urban	20.8 (139)	21.9 (147)	57.3 (284)	
Working status % (n)				
Employed	233 (7)	26.7 (8)	50.0 (15)	**0.011**
Unemployed	21.9 (79)	15.6 (56)	62.5 (225)	
Homemaker	13.3 (55)	22.3 (92)	64.4 (266)	
Retired	20.9 (41)	21.4 (42)	57.7 (113)	
Income % (n)				
<=20000 tk	14.6 (50)	20.2 (69)	65.3 (223)	0.164
21000–60000 tk	20.1 (85)	17.9 (76)	61.9 (262)	
61000 tk and above	19.9 (47)	22.5 (53)	57.6 (136)	
Active smoking % (n)				
Never	17.2 (129)	21.1 (158)	61.7 (462)	0.336
In the past (>one year)	20.0 (34)	15.9 (27)	64.1 (109)	
Current smoker	23.2 (19)	15.8 (13)	60.9 (50)	
Passive smoking % (n)				
No	18.5 (158)	18.5 (158)	63.0 (537)	0.056
Yes	16.2 (24)	27.0 (40)	56.8 (84)	
Smokeless tobacco % (n)				
Never	20.4 (158)	19.7 (153)	59.9 (465)	0.008
In the past (>one year)	6.4 (4)	19.0 (12)	74.6 (47)	
Current consumer	12.3 (20)	20.4 (33)	67.3 (109)	
Eating habit				
Unhealthy	12.4 (28)	17.3 (93)	70.4 (159)	0.008
Healthy	19.9 (154)	20.5 (159)	59.6 (462)	
Fruits and vegetables % (n)				
Less frequent	17.1 (44)	22.9 (59)	60.1 (155)	0.344
Daily	18.2 (138)	18.7 (139)	62.7 (466)	
Physical Activity % (n)				
Inactive	16.6 (78)	18.5 (87)	64.9 (305)	0.211
Active	19.6 (104)	20.9 (111)	59.5 (316)	

Table 1. Demographic and lifestyle characteristics by glycaemic control.

education and living in urban areas usually have a higher income; thus, they are more likely to be able to afford to receive proper treatment and manage their condition.

The proportion of participants in the current study who are smokeless tobacco users was 22.35%, and the results of the sub-group analysis showed that smokeless tobacco consumers among the shorter duration group were at higher risk of having an uncontrolled glycaemic level. Smokeless tobacco consumption in the form of betel quid (pan) is very common in Bangladesh, especially among women living in villages. Tobacco usually raises blood sugar levels, and the adverse effects of smokeless tobacco on health are evident from previous studies[33]. However, the effect of smokeless tobacco on glycaemic control has not yet been documented in the literature.

Variable	Glycaemic control (HbA1c)			p-value
	Good (<7%) n = 182	Fair (7–7.9%) n = 198	Poor (≥8%) n = 621	
DM Duration years (mean ± SD)	8.1 ± 6.5	10.2 ± 7.5	10.4 ± 7.3	**0.001**
DM Duration % (n)				
≤5 years	24.0 (78)	20.3 (66)	55.7 (181)	**0.005**
6–10 years	17.6 (53)	17.6 (53)	64.8 (195)	
≥11 years	13.6 (51)	21.1 (79)	65.3 (245)	
Family history of DM % (n)				
No	18.4 (120)	19.4 (127)	62.2 (407)	0.921
Yes	17.9 (62)	20.5 (71)	61.7 (214)	
Mode of treatment				
OHA	30.2 (117)	22.4 (87)	47.4 (184)	<0.001
Insulin ± OHA	10.6 (65)	18.1 (111)	71.3 (437)	
Glucometer use % (n)				
Once or more a week	15.5 (38)	21.5 (53)	63.0 (155)	0.508
Less than once a week	18.0 (90)	18.6 (93)	63.3 (316)	
Hypoglycaemia events % (n)				
None	18.9 (149)	19.2 (151)	61.9 (487)	0.724
1–5 times	15.9(30)	21.7 (41)	62.4 (118)	
6 times and more	12.0 (3)	24.0 (6)	64.0 (16)	
Follow up check-up frequency % (n)				
Every 1–3 months	19.5 (144)	21.7 (160)	58.1 (434)	**<0.001**
Every six months	18.3 (17)	23.7 (22)	58.1 (54)	
Annually	12.4 (21)	9.1 (16)	78.2 (133)	
Hypertension % (n)				
No	18.6 (72)	16.0 (62)	65.4 (253)	0.058
Yes	17.9 (110)	22.2 (136)	59.9 (368)	
Dyslipidaemia				
No	17.1 (111)	18.7 (121)	64.2 (416)	0.162
Yes	20.1 (71)	21.8 (77)	58.1 (205)	
CAD % (n)				
No	20.8 (154)	18.3 (136)	60.9 (452)	**0.001**
Yes	10.8 (28)	23.9 (62)	65.3 (169)	
Stroke % (n)				
No	18.2 (169)	20.2 (188)	61.7 (574)	0.479
Yes	18.6 (13)	14.3 (10)	67.1 (47)	
Retinopathy % (n)				
No	10.1 (152)	19.4 (155)	61.5 (491)	0.361
Yes	14.8 (30)	21.2 (43)	64.0 (130)	
Nephropathy % (n)				
No	17.4 (129)	18.9 (140)	63.7 (472)	0.188
Yes	20.4 (53)	22.3 (58)	57.3 (149)	
Neuropathy % (n)				
No	18.5 (174)	19.3 (182)	62.2 (585)	0.301
Yes	13.3 (8)	26.7 (16)	60.0 (36)	
Diabetic foot % (n)				
No	18.4 (167)	19.2 (174)	62.4 (567)	0.304
Yes	16.1 (15)	25.8 (24)	58.1 (54)	
BMI % (n)				
Normal	18.9 (74)	18.2 (71)	62.8 (245)	0.471
Under weight	24.2 (8)	18.2 (6)	57.6 (19)	
Over weight	18.5 (72)	18.2 (71)	63.3 (147)	
Obese	16.9 (21)	26.6 (33)	62.5 (70)	
Family support % (n)				
No	11.5 (7)	13.1 (8)	75.4 (46)	0.085
Yes	18.6 (175)	20.2 (190)	61.2 (575)	

Continued

Variable	Glycaemic control (HbA1c)			p-value
	Good (<7%) n = 182	Fair (7–7.9%) n = 198	Poor (≥8%) n = 621	
Depression % (n)				
No	19.4 (135)	19.7 (137)	60.9 (424)	0.313
Yes	15.4 (47)	20.0 (61)	64.6 (197)	
Anxiety % (n)				
No	18.6 (167)	19.7 (177)	61.7 (555)	0.630
Yes	14.7 (15)	20.6 (21)	64.7 (66)	
Cognitive function % (n)				
Intact	21.5 (136)	21.4 (133)	57.4 (363)	**<0.001**
Partially impaired	14.7 (11)	22.7 (17)	62.7 (47)	
Impaired	11.9 (35)	16.3 (48)	71.8 (211)	
Waist/hip ratio (mean ± SD)	1.04 ± 0.07	1.10 ± 0.73	1.06 ± 0.08	0.156
Waist circumference (mean ± SD)	95.5 ± 9.1	96.5 ± 9.5	95.8 ± 10.0	0.660

Table 2. Clinical characteristics by glycaemic control. DM: Diabetes mellitus, OHA: Oral hypoglycaemic agent, CAD: Coronary artery disease, BMI: Body mass index.

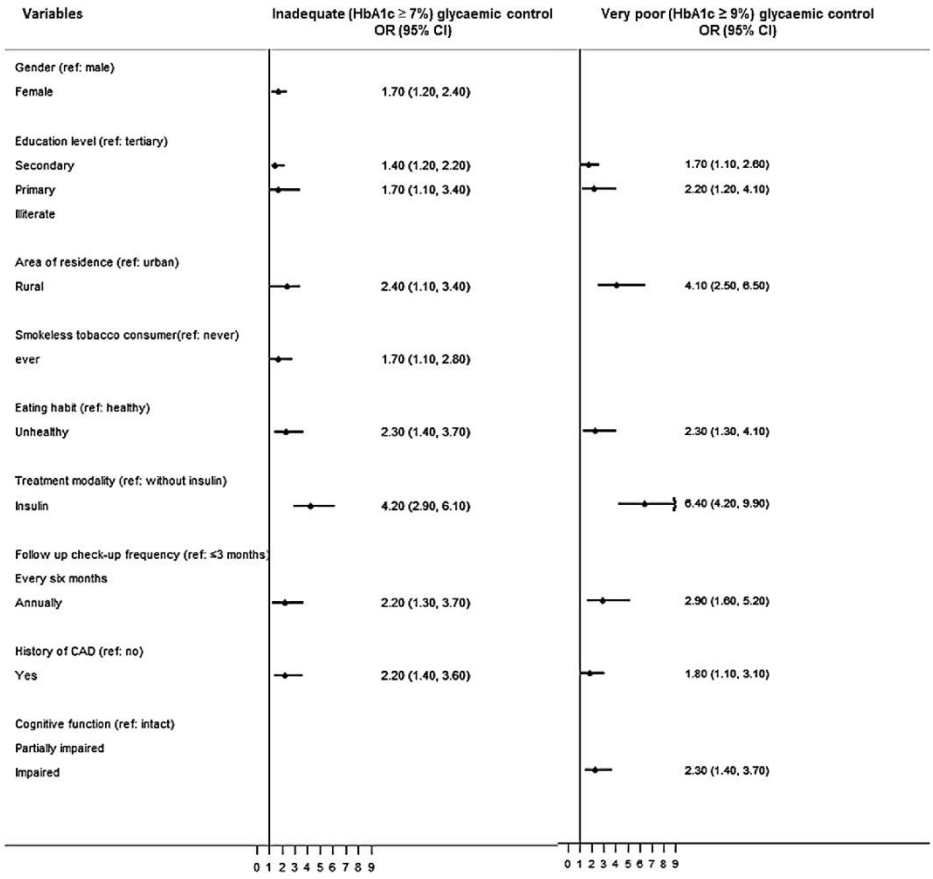

Figure 1. Adjusted association (odds ratio (OR)) between risk factors with inadequate glycaemic control (HbA1c ≥7%) and very poor glycaemic control (HbA1c ≥9%). Note: Variables introduced in to the multiple logistic regression analysis were age, gender, education level, location, work status, income, smokeless tobacco consumption, eating habit, duration of diabetes, modality of treatment, follow up check-up frequency, dyslipidaemia, history of CAD, family support and cognitive function.

Variables	Diabetes duration ≤5 years			Diabetes duration >5 years		
	OR	95% CI	p-value	OR	95% CI	p-value
Age (ref: ≤40 years)						
41 – 60 years						
>60 years						
Gender (ref: male)						
Female				2.5	1.5-4.1	0.001
Education level (ref: Tertiary)						
Secondary						
Primary						
Illiterate						
Location (ref: urban)						
Rural	2.5	1.3-4.5	0.002	2.6	1.5-4.7	0.001
Smokeless tobacco (ref: never)						
Ever consumer	2.9	1.3-6.2	0.007			
Eating habit (ref: healthy)						
Unhealthy	3.1	1.3-6.9	0.007	1.9	1.1-3.3	0.025
Modality of treatment (ref: without insulin)						
Insulin	3.8	2.1-7.1	<0.001	4.1	2.6-6.5	<0.001
Follow up check-up frequency (ref: ≤3 months)						
Every six months						
Annually	2.6	1.2-5.6	0.016	2.1	1.0-4.3	0.042
CAD (ref: no)						
Yes	3.9	1.5-10.3	0.005	1.9	1.1-3.2	0.022
Cognitive function (ref: intact)						
Partially impaired						
Impaired						

Table 3. Adjusted association (odds ratio (OR)) between risk factors and inadequate (HbA1c ≥ 7%) glycaemic control by duration of diabetes. Note: Variables introduced in to the multiple logistic regression analysis were age, gender, education level, location, work status, income, smokeless tobacco consumption, eating habit, duration of diabetes, modality of treatment, follow up check-up frequency, dyslipidaemia, history of CAD, family support and cognitive function.

Thus, an intensive investigation is urgently required in Bangladesh, as well as in other South Asian countries where smokeless tobacco consumption is a common practice. Further, education and awareness programs about the risks of smokeless tobacco consumption could be an option for the management of T2DM.

A healthy lifestyle with regular physical activity and healthy eating habits are very important factors for achieving and maintaining adequate glycaemic control. This study found that participants were active in following the recommended guidelines[28]. Conversely, a relationship was identified between unhealthy eating habits and both inadequate and very poor glycaemic control. Clinical trials[34] and epidemiological studies[14] have shown the positive effects of healthy diets on glycaemic control. The majority of the current study's participants responded that they had received dietary advice from health professionals; however, they also stated that they were unable to maintain the advice. This may be due to a lack of understanding or low affordability of healthy foods. Regular follow-up check-ups add an extra benefit in terms of better control and, similar to previous studies[35], our findings indicate that regular follow-up check-ups have a positive effect on glycaemic control. Thus, active and individualised education intervention is required to motivate patients towards healthy eating and frequent follow-up check-ups.

Treatment modality also influences the outcome of glycaemic control. In this study, the best glycaemic control was found among participants who used OHA only. Notably, none of the study participants were using insulin pumps or continuous glucose monitoring. A relationship between insulin use and glycaemic control was found in the study results, which is consistent with the findings of other studies[9–11]. Possible reasons for this could include the increasing difficulty of taking multiple medications, injection phobia, or inconvenience of insulin use. Additionally, the efficacy of insulin depends on storage conditions and its proper use, and appropriate dosage in response to different glycaemic levels depends on an individual's eating habits, exercise regimens, and other lifestyle factors. Insulin users may also have a more progressive disease condition that requires more aggressive treatment, and physicians may attempt dual therapies to achieve better control. Additionally, we found that only 37.6% of our participants used self-monitoring blood glucose devices; this indicates that a lack of proper monitoring, meaning that patients are likely to struggle with managing their insulin. In this context, further research is required to determine why a large proportion of insulin users were identified as having uncontrolled conditions.

Our results also show a relationship between glycaemic control and the presence of CAD. A systematic review investigating factors associated with glycaemic control showed a 48% increased risk of having poor condition control in the presence of CVD[14]. In general, patients with CVD are treated with multiple medications, and some

Variables	Diabetes duration ≤5 years			Diabetes duration >5 years		
	OR	95% CI	p-value	OR	95% CI	p-value
Age (ref: ≤40 years)						
41–60 years						
>60 years				0.5	0.3-0.8	0.003
Gender (ref: male)						
Female						
Education level (ref: Tertiary)						
Secondary						
Primary						
Illiterate						
Location (ref: urban)						
Rural	3.5	1.7-7.0	**0.001**	4.5	2.3-8.7	0.001
Smokeless tobacco (ref: never)						
Ever consumer	3.1	1.2-8.1	**0.010**			
Eating habit (ref: healthy)						
Unhealthy	3.1	1.2-8.1	0.017	6.5	3.8-11.2	<0.001
Modality of treatment (ref: without insulin)						
Insulin	6.1	2.9-12.6	<0.001			
Follow up check-up frequency (ref: ≤3 months)						
Every six months						
Annually	3.3	1.3-7.8	0.007	2.7	1.3-5.9	0.011
CAD (ref: no)						
Yes	3.5	1.1-10.8	0.028			
Cognitive function (ref: intact)						
Partially impaired						
Impaired				3.2	1.7-6.0	0.001

Table 4. Adjusted association (odds ratio (OR)) between risk factors and very poor (HbA1c ≥9%) glycaemic control by duration of diabetes. Note: Variables introduced in to the multiple logistic regression analysis were age, gender, education level, location, work status, income, smokeless tobacco consumption, eating habit, duration of diabetes, modality of treatment, follow up check-up frequency, dyslipidaemia, history of CAD, family support and cognitive function.

of these may have an adverse effect on glycaemic control. Thus, patients with CVD have a lower likelihood of controlling their condition. The identified relationship between CVD and glycaemic control reinforces the need to optimise the management of CVD.

Another important finding of this study is the association between impaired cognitive function and poor glycaemic control among patients with a longer duration of T2DM. Studies conducted previously in developed countries[36–38] have shown that there is a strong relationship between poorly controlled diabetes and greater decline in cognitive function. However, no similar study has been conducted in developing countries. Previous literature shows that the toxic effects of chronic hyperglycaemia may be related to slowly progressive functional and structural abnormalities in the brain[39], and thus could be one of the determinants of cognitive changes in people with diabetes[40,41]; which may not be confirmed by the current study due to its cross-sectional design. Additionally, insulin resistance, at least in the early stages of type 2 diabetes, is associated with compensatory hyperinsulinemia and the consequent accelerated cognitive decline[42], which supports the findings of our study.

This study has the strength of having a representative population, which increases the likelihood of the generalisability of the findings to people with T2DM attending hospitals associated with BADAS across the country. The study investigated all possible modifiable and non-modifiable factors affecting glycaemic control, which adds strength to the findings. The recruitment of participants and the information collection procedures ensured data quality. However, this study has the limitation of being cross-sectional in design, meaning that a temporal relationship between cause and effect cannot be established.

Conclusion

In conclusion, the proportion of people with uncontrolled glycaemic levels is considerably high in Bangladesh, which may contribute to an increasing prevalence of complications and thus may pose an extra burden on health care costs. This study has identified a number of modifiable predictors of inadequate glycaemic control: most importantly, different sets of risk factors were identified for participants who had been T2DM patients for different durations. The study's findings emphasise the importance of being compliant with follow-up check-ups, and of lifestyle modifications, including healthy eating and avoiding smokeless tobacco consumption. A comprehensive knowledge of modifiable and non-modifiable risk factors will help health care providers to individualise the choice of glycaemic goals in reference to duration, with the aim of improving care and outcomes for patients with T2DM.

Data Availability

The data sets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Author Contributions

Concept and design (A.A., K.A., D.J.M. and B.B.), acquisition of data (A.A. and L.A.), data analysis and interpretation of results (A.A., M.N.K., M.J.A. and B.B.), drafting the manuscript (A.A., M.N.K. and B.B.), critically review to improve the content and final approval of version to be submitted has done by all authors.

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Chapter 7

TYPE 2 DIABETES RELATED MACRO- AND MICRO-VASCULAR COMPLICATIONS: RISK FACTORS AND RISK SCORING SYSTEM

Context of the study (7a)

Diabetes is a leading cause of morbidity and mortality worldwide that affected 425 million or 8.8% of adults in 2017. In Bangladesh, the prevalence of diabetes is increasing in line with the epidemiologic transition that she is undergoing. This trend is also seen in the wider context of South Asia, where rapid urbanisation has led to an increasingly sedentary but more stressful lifestyle, change in eating habits including increased access to processed food, and reduced physical activity. Furthermore, biological factors have been found to predispose in the South Asians diabetes population. Therefore, both lifestyle and biological factors are related to higher prevalence of diabetes in South Asians than in Europeans.

Diabetes complications are another concerning issue in Bangladesh. Globally, the relative risk of microvascular and macrovascular complications among people with diabetes was estimated to be 10–20 times and 2–4 times higher respectively than in people without diabetes. Diabetes-related complications reduce the quality of life and life expectancy of the affected people and create an economic, physical, psychological and social burden. In Bangladesh, a limited number of studies have been conducted to study the prevalence of macrovascular and microvascular complications and identified factors associated with these complications among people with T2DM. However, due to the lack of a strong methodology, they might not be representative of all people with T2DM in Bangladesh. Therefore, this study aimed to estimate the prevalence of macrovascular and microvascular complications related to T2DM and to identify the various risk factors that influence these complications. The findings of this study may help in tackling the factors related to the complications early in treatment, which will help to prevent or delay the onset of complications.

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Original Article

Macro- and micro-vascular complications and their determinants among people with type 2 diabetes in Bangladesh

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ABSTRACT

Objectives: To identify the prevalence of micro- and macro-vascular complications and their associated factors for type 2 diabetes mellitus in Bangladesh.
Methods: This retrospective and cross-sectional study was conducted in six diabetes hospitals, covered urban and rural population. From April to September in 2017, a total of 1253 type 2 diabetes patients aged ≥18 years were recruited. Participants answered a pre-tested electronic questionnaire, and their medical records were reviewed for documented diabetes complications.
Results: Mean age was 55.1 (±12.6) years. Among macrovascular complications, the prevalence of coronary artery disease was found to be 30.5%, 10.1% for stroke and 12.0% for diabetic foot. Among microvascular complications, nephropathy was prevalent among 34.2%, retinopathy among 25.1% and neuropathy among 5.8% of patients. Risk factors found to be associated with one or more of the complications were female gender, higher age, lower education level, an urban area of residence, higher household income, smoking, physical inactivity, hypertension, poor glycaemic control, poor adherence to treatment, longer duration of diabetes, and insulin use.
Conclusion: Diabetes complications are highly prevalent among type 2 diabetes population in Bangladesh. Prevention strategies should focus on increasing physical activity, weight loss, smoking cessation, and more strict control of hypertension and glycaemic level.

1. Introduction

Diabetes mellitus is a growing problem worldwide, affecting 425 million or 8.8% of adults in 2017. The International Diabetes Federation (IDF) reports that a staggering 79% of adults with diabetes live in low- and middle-income countries [1]. By far the most prevalent type of diabetes, Type 2 Diabetes Mellitus (T2DM) constituted around 90% of all diabetic cases [2]. In Bangladesh, the prevalence of diabetes in adults aged 20–79 years was reported at 6.9%, affecting just below 7 million adults of the population and it is anticipated to increase to 13.7 million by 2045 [1]. The projected increase in prevalence is in line with the epidemiologic transition which Bangladesh is undergoing, whereby its burden of disease shifts from acute infectious and deficiency diseases to non-communicable chronic diseases, such as diabetes [3]. This trend is also seen in the wider context of South Asia, where rapid urbanisation has led to an increasingly sedentary lifestyle, increased intake of dietary fats and more stressful lifestyles. Biological factors have also been found to predispose South Asians to diabetes, and both lifestyle and biological factors are responsible such that South Asians have a 3-fold higher prevalence of diabetes compared to Europeans [4,5]. (see Table 1)

Diabetes mellitus is a disease characterised by either the lack of insulin (Type 1 Diabetes), or loss of insulin sensitivity (T2DM). This results in a chronic hyperglycaemic state, causing an increase in products of glycosylation. These molecules induce inflammation and injury to arterial walls, causing changes in vascular tissue, and promoting atherosclerosis. The resultant narrowing of arteries in turn increases the risk of coronary artery diseases, stroke and peripheral vascular disease, which are termed the macrovascular complications such as coronary artery disease (CAD), stroke and diabetic foot related to T2DM. Smaller blood vessels are also affected by atherosclerotic damage, leading to microvascular complications such as diabetic peripheral neuropathy, retinopathy

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Table 1
Demographic characteristics by type of macro and microvascular complications.

Variables	CAD 30.5% (n = 382)		Diabetic foot 12.0% (n = 150)		Stroke 10.1% (n = 127)		Neuropathy 5.8% (n = 72)		Nephropathy 34.2% (n = 429)		Retinopathy 25.1% (n = 315)	
	%	p-value	%	p-value		p-value	%	p-value	%	p-value	%	p-value
Age												
<60 years	23.7	**< 0.001**	12.4	0.475	6.8	**< 0.001**	5.5	0.687	23.9	**< 0.0001**	18.8	**< 0.001**
> = 61 years	44.4		11.0		16.9		6.1		55.6		38.1	
Gender												
Male	31.4	0.432	13.7	**0.045**	11.0	0.261	5.7	0.974	34.8	0.646	21.6	**0.002**
Female	29.4		10.0		9.1		5.8		33.6		29.4	
Education level												
Tertiary	25.4	0.064	12.2	0.863	6.6	**0.047**	4.2	0.218	33.5	**0.021**	25.1	0.295
Secondary	30.7		12.4		12.0		5.5		30.9		23.3	
Up to primary	33.7		11.2		10.0		7.2		39.5		27.7	
Area of residence												
Rural	16.7	**< 0.001**	10.4	0.305	3.5	**< 0.001**	5.6	0.119	13.3	**< 0.001**	11.1	**< 0.001**
Urban	19.1		12.5		12.5		7.4		41.9		30.4	
Household income												
< 20,000 tk	26.2	**0.016**	14.5	0.106	9.8	**0.026**	7.2	0.276	33.8	**< 0.001**	21.7	**< 0.001**
20,000–60,000 tk	31.0		10.9		8.1		5.0		29.2		22.9	
> 60,000 tk	35.9		10.0		13.9		4.9		43.0		33.7	
Active smoking												
Never smoker	29.0	**0.046**	10.7	**0.015**	9.2	**0.050**	5.7	0.916	33.7	0.491	26.6	**0.045**
Ever smoker	34.9		15.7		12.9		5.8		35.8		20.9	
Passive smoking												
No	30.5	0.983	11.5	0.176	10.0	0.639	5.6	0.566	34.8	0.339	25.0	0.745
Yes	30.6		15.0		11.1		6.7		31.1		26.1	
Smokeless tobacco consumer												
No	29.4	0.117	11.3	0.176	9.6	0.207	5.6	0.578	34.1	0.871	25.0	0.801
Yes	34.3		14.3		12.1		6.4		34.6		25.7	
Physical Activity												
Active (≥150 min/week)	23.7	**< 0.001**	10.5	0.107	5.1	**< 0.001**	5.9	0.840	25.3	**< 0.001**	19.4	**< 0.001**
Inactive (<150 min/week)	37.0		13.4		15.0		5.6		42.8		30.6	

and nephropathy [6].

In 2017, diabetes mellitus accounted for 976.9 disability-adjusted life years per 100,000 people in Bangladesh, making it the top 8th cause of death and disability [7]. The disease also costed Bangladesh approximately US$5.3 billion in 2014 [8]. The total annual per capita expenditure on medical care was 6.1 times higher for patients with diabetes than those without diabetes annually [9]. A recent Bangladeshi study further showed that the cost is 1.8–3.4 times higher for patients with the presence of one or more complications compared to those without any complications [10]. Another key challenge to the public health management of diabetes is that a large proportion of diabetics are unaware of their condition. Among Bangladeshi adults with diabetes, a worrying 56.0%, or 3.9 million, are undiagnosed [11]. Late diagnosis of diabetes could increase the risk of complications, and potentially leads to poorer prognosis and quality of life. The high economic burden on the Bangladeshi health care system coupled with the huge impact on the quality of life highlights the importance of early detection and management through the identification of risk factors of T2DM complications.

Globally, the relative risk of micro- and macro-vascular complications among people with diabetes was estimated to be at least 10–20 times higher and 2–4 times higher, respectively, than in people without diabetes mellitus [11]. Several studies have also noted that these complications result from a combination of genetic, metabolic and lifestyle factors [12,13].

More specifically, in South Asia, research showed that newly diagnosed South Asian patients have a higher prevalence of complications compared to Europeans. Macrovascular complications had a prevalence of 15.7% vs. 9.4% while microvascular complications had a prevalence of 27.3% vs. 16.5% [1414]. The significantly higher prevalence of diabetes and its complications has been attributed to various differing biological and lifestyle factors [14].

In Bangladesh, some studies have been conducted to study the prevalence of macrovascular and microvascular complications related to T2DM. Many of these studies observed an increasing trend in both types of complications and identified risk factors for these complications. Advanced age, longer duration of diabetes, hypertension, poor glycaemic control, and a lack of physical exercise were identified as risk factors of macrovascular complications, while increasing age, high hemoglobin A1c (HbA1c), fasting blood glucose (FBG), 2-h post load glucose concentrations (2-hBG) and high blood pressure were significant risk factors for any type of microvascular complications [11,12], where HbA1c, FBG and 2-hBG are markers of plasma glucose levels.

However, many of these studies had a small sample size, and were conducted within a single centre. Some studies were also only conducted on people with diabetes who have had the disease for a specific period of time, and therefore might not be representative of all people with diabetes in Bangladesh. Hence, this study aims to estimate the prevalence of macrovascular and microvascular complications related to T2DM among a sample of patients from urban, semi-urban and rural Bangladesh attending primary to tertiary health care services. We also aim to identify the various risk factors that influence these complications, so they can be tackled early on in treatment. This would lower the risk of developing diabetes-related complications, leading to better health outcomes in the long run.

2. Methods

2.1. Study design and study population

This retrospective and cross-sectional study was approved by the Monash University Human Research Ethics Committee, the Ethical Review Committee of the Bangladesh University of Health

Sciences (BUHS) and the Diabetic Association of Bangladesh (BADAS). Data was collected from two tertiary level diabetes hospitals located in the central region of Bangladesh, and two tertiary level diabetes hospitals and two secondary level diabetes hospitals located in the northern region of Bangladesh. These facilities covering professionally mixed patients residing in rural, semi-urban and urban areas.

2.2. Sample selection and data collection

A total of 1253 participants were randomly recruited using systematic random sampling during April to September, in 2017. The target population were adults of both gender and registered T2DM subjects with at least one-year duration of diabetes. People with other forms of diabetes, and pregnant women were excluded. Data was collected via face-to-face interview using a structured questionnaire in a secure web-based application, Research Electronic Data Capture (REDCap [15]). Details regarding sociodemographic which included age, sex, socioeconomic status, educational level, occupational history, physical activity (Global Physical Activity Questionnaire (GPAQ) [16]), smoking history, and diet were collected. Medical history (mental health status, and duration of diabetes) were also collected from all patients. Their anthropometrics (height, weight, hip and waist circumference) and blood pressure were measured and recorded in a standardized way [17].

Clinical information related to T2DM and its complications were retrieved from patients' medical reports which was recorded in their guide book. Documented medical records were used to assess their complications and confirmed both through physicians' notes and reviewing each patient's prescribed medication list. Information on the types and quantities of medication used by each patient were recorded in a copy of a prescription slip which was saved in the REDcap application as an image for future reference. A team of trained data collectors were involved in data collection and execution of each interview. Informed consent was obtained from each participant before their interview.

2.3. Operational definition for identifying complications

Participants were evaluated for CAD by reviewing their medical records, noting any documented diagnosis, prescribed medication or past procedures for CAD. A history of stroke was determined by past diagnoses of irreversible cerebrovascular accident. Additionally, the patient was asked about a possible incident in the previous years. Presence of diabetic foot was assessed by a visual examination of having ulcers or amputations and noting any documented diagnosis of diabetic foot. Nephropathy was defined by estimated glomerular filtration rate of <60 ml/min/1.73 m^2 (calculated from creatinine using the CKD-EPI creatinine equation [17]) and documented diagnosis. Neuropathy was defined using the Michigan Neuropathy Screening Instrument [18] and by the prescribed medication. Retinopathy was defined by documented diagnosis or a past procedure for the treatment of retinopathy.

2.4. Data analysis

Data analysis was carried out using Stata SE version 15.0. Data was summarised and presented as a mean (±standard deviation) for numerical data and frequency and percentage for categorical data. Chi-square test was used to examine associations between each of the complications with patients' demographic and clinical characteristics. Any association was further examined using univariate logistic regression analysis. Potential risk factors with a p-value of 0.1 or less in univariate logistic regression were entered into multiple logistic regression analysis [19]. Stepwise variable selection method was used to identify the factors related to each of the complications. A p-value of 0.05 or less was considered statistically significant. Multicollinearity and first order interaction effect between covariates were also investigated.

3. Results

3.1. General characteristics

The records of 1253 participants were used in the analysis. Of them, 54.3% (n = 681) were male and 45.7% (n = 572) were female. The mean age ±SD was 55.1 ± 12.6 years and 67.4% were in the below or equal to 60 years age group. About 12.8% of total study subjects were illiterate while the remaining were literate (primary = 19.1%, secondary = 45.2%, tertiary = 22.9%). In terms of area of residence, about three-quarters (73.2%) of participants lived in urban areas while 26.8% in rural areas. With respect to occupation, 2.9% were unemployed, 40.5% were home-makers, 23.6% were retired or of were ill health, and 32.8% were employed. Among macrovascular complications, CAD was present in 30.5%, stroke in 10.1% and diabetic foot in 12.0%. Among microvascular complications, nephropathy was prevalent among 34.2%, retinopathy among 25.1% and neuropathy among 5.8% (data not shown in table).

3.2. Univariate association between risk factors and complications

Inferring from Table 1, risk factors that were significantly associated with one or more diabetes complications include higher age, lower education level, an urban area of residence, higher household income, history of active smoking, history of being a smokeless tobacco consumer, and a low amount of physical activity. It is worthy to note that a history of passive smoking was not significantly associated with any diabetes complications. With regards to gender, the ma gender was significantly associated with diabetic foot while the female gender was significantly associated with retinopathy. Table 2 summarises the clinical characteristics for each macro- and microvascular complications. Poor glycaemic control (HbA1c) was only significantly associated with CAD and no other complications, while a negative family history of diabetes was associated with nephropathy. The prevalence of CAD, stroke, nephropathy and retinopathy is higher among people with hypertension. There was no significant association between waist hip ratio or body mass index and any diabetes complications. A history of dyslipidemia also showed no association with any micro- or macro- vascular complications. Among different modalities of treatment, people on oral hypoglycaemic agent and insulin treatment had a higher prevalence of CAD, stroke, nephropathy and retinopathy, while people on the insulin treatment alone had a higher prevalence of diabetic foot. Other risk factors which were associated with one or more complications include a DM duration of more than ten years and poor adherence with medication.

3.3. Multivariable association between risk factors and macrovascular complications

The results of the multiple logistic regression analysis with stepwise removal for the association between each of the macrovascular complications are shown in Table 3. Smoking, past or present and presence of hypertension increased the odds of CAD by 1.6-fold (95% CI, 1.1 to 2.3) and 3.6-fold (95% CI, 2.4 to 5.4) respectively. Patients with poor glycaemic control were also found to be at greater odds, 2.2-fold ((95% CI, 1.3 to 3.7), and those with education levels below tertiary standards were 1.8–2.1 times as likely to develop this complication. Increased odds of CAD were also observed among those with aged 61 years or above, with higher

Table 2
Clinical characteristics by type of macro and microvascular complications.

Variables	CAD 30.5% (n = 382)		Diabetic foot 12.0% (n = 150)		Stroke 10.1% (n = 127)		Neuropathy 5.8% (n = 72)		Nephropathy 34.2% (n = 429)		Retinopathy 25.1% (n = 315)	
	%	p-value	%	p-value	%	p-value	%	p-value	%	p-value	%	p-value
DM Duration												
≤ 5 years	20.1	< **0.001**	10.6	0.316	5.7	< **0.001**	4.9	0.703	16.6	< **0.001**	12.2	< **0.001**
6–10 years	26.8		11.0		7.5		6.1		26.5		19.0	
≥ 11 years	40.0		13.6		14.9		6.1		51.3		37.9	
Family history of diabetes												
No	32.0	0.121	11.7	0.692	9.6	0.418	5.7	0.976	36.6	**0.016**	25.4	0.800
Yes	27.7		12.5		11.1		5.8		29.8		24.7	
Modality of treatment												
Oral tablet	22.2	< **0.001**	8.6	**0.025**	7.2	**0.006**	4.9	0.459	20.8	< **0.001**	16.0	< **0.001**
Insulin	21.8		14.9		5.8		8.1		25.3		16.1	
Oral and insulin	36.4		13.6		12.4		6.0		43.2		31.6	
Medication adherence												
Adequate	27.0	**0.041**	10.5	0.222	5.6	< **0.001**	5.4	0.655	32.6	0.352	20.4	**0.003**
Inadequate	32.5		12.8		12.8		5.9		35.2		27.9	
Hypertension												
No	13.7	< **0.001**	10.5	0.245	3.8	< **0.001**	5.4	0.680	17.7	< **0.001**	12.6	< **0.001**
Yes	39.8		12.8		13.6		6.0		43.4		32.1	
Dyslipidaemia												
No	28.8	0.078	13.3	0.045	9.9	0.692	6.9	0.011	25.3	0.880	34.6	0.746
Yes	33.6		9.4		10.6		3.5		24.9		33.6	
Body mass index												
Normal	28.5	0.394	11.9	0.678	9.0	0.700	5.6	0.962	32.4	0.721	24.2	0.323
Overweight/Obese	31.1		11.1		8.3		5.5		33.5		27.1	
Waist/hip ratio												
Normal	7.1	0.098	7.1	0.803	0.0	0.289	21.4	0.004	14.3	0.297	28.6	0.607
High	26.8		9.1		7.5		4.7		26.7		22.8	
Glycaemic control (HbA1c)												
Control (≤6.9%)	15.4	< **0.001**	8.2	0.590	7.1	0.930	4.4	0.315	29.1	0.284	16.5	0.159
Uncontrolled (≥7%)	28.2		9.5		7.0		6.3		25.3		21.1	

income and with more than ten years of DM history. Only the two variables, being smoker and past or present insulin user in combination of oral hypoglycaemic agent were at 60% and 40% increased odds of diabetic foot respectively. In the context of stroke, patients staying in urban region had 2.3-fold higher odds (95% CI, 1.2 to 4.6) and that was 3.0-fold (95% CI, 1.6 to 5.5) higher among hypertensive patients. Furthermore, smoking (OR, 1.7; 95% CI, 1.1 to 2.8), being physically inactive (OR, 2.4; 95% CI, 1.5 to 3.8), and inadequate medication adherence (OR, 2.5; 95% CI, 1.5 to 4.3) were associated with stroke. Other variables, being aged 61 years and above, having attained a maximum of secondary education and having diabetes for more than ten years also increased the odds of stroke.

3.4. Multivariable association between risk factors and microvascular complications

Presented in Table 4 are the results of the multiple logistic regression analysis for risk factors of microvascular complications nephropathy and retinopathy. Having hypertension (OR, 2.6; 95% CI, 1.9 to 3.6) and being physically inactive (OR, 1.7; 95% CI, 1.3 to 2.3) were positively associated with diabetic nephropathy. Staying in urban region (OR, 3.2, 95% CI, 2.1 to 4.7) also increased the odds of having retinopathy. Other variables which were related to retinopathy includes being aged 61 years and over, having diabetes for more than ten years, and being on both oral hypoglycaemic agent and insulin. On the other hand, a positive family history of diabetes and having a monthly household income of 20,000 to 60000tk reduced the odds for nephropathy complications by 30% and 40% respectively. A series of factors were found to be associated with the development of diabetic retinopathy. Living in urban region (OR, 2.1; 95% CI, 1.3 to 3.2), being physically inactive (OR, 1.4; 95% CI, 1.0 to 2.1) and inadequate medication adherence (OR, 1.4; 95% CI, 1.0 to 2.1) were the factors associated with elevated odds of diabetic retinopathy. Further, female patients, patients older than 60 years, having diabetes for more than ten years and being on both oral hypoglycaemic and insulin were other associated factors to retinopathy.

4. Discussion

Diabetes is a major global health problem in the recent decades, and its complications, while very detrimental, have risks which can be reduced with proper measures. Diabetes is also an increasingly significant health issue in Bangladesh, but studies on prevalence of its microvascular and macrovascular complications, and their risk factors are relatively limited in Bangladesh, hence the purpose of this paper. This study results showed that, overall, complications were present in 63.4% of all participants. This is broken down into 14.8% of participants with only macrovascular complications, 20.7% with only microvascular complications, as well as 27.9% with both types of complications. Importantly, the study found that these complications had strong association with patients' demographics, lifestyle modification factors and co-morbidities.

Coronary artery disease was found to be the most prevalent macrovascular complication, with a prevalence rate of 30.5%. This is within the global prevalence range of 12%–31.7% [1]. Past studies conducted in Bangladesh also found CAD to be of highest prevalence, amongst all macrovascular complications [12,20]. Similarly, in rural India, a study found CAD prevalence to be the highest amongst macrovascular complications at 32.3% [21], while another study conducted in United Arab Emirates also found CAD to be the most prevalent macrovascular complication [22]. On the other hand, stroke was found to be the least prevalent macrovascular complication in our study group, with a prevalence of 10.1%. This falls within the global prevalence range of 4%–12% [23]. A study in

Table 3
Adjusted association between each of the macrovascular complications and potential risk factors.

Variables	CAD[a]			Diabetic foot[b]			Stroke[c]		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Age									
<60 years	Reference			Reference			Reference		
>= 61 years	1.6	1.1–2.3	0.009	–	–	–	1.8	1.1–2.8	0.009
Education level									
Tertiary	Reference			Reference			Reference		
Secondary	1.8	1.1–2.8	0.008	–	–	–	1.6	1.1–2.5	0.028
Up to primary	2.1	1.3–3.5	0.002	–	–	–	–	–	–
Household income									
< 20,000 tk	Reference			Reference			Reference		
20,000–60,000 tk	1.5	1.0–2.3	0.029	–	–	–	–	–	–
> 60,000 tk	2.3	1.4–3.7	<0.001	–	–	–	–	–	–
DM Duration									
≤ 5 years	Reference			Reference			Reference		
6–10 years	–	–	–	–	–	–	–	–	–
≥ 11 years	1.5	1.1–2.2	0.012	–	–	–	1.7	1.1–2.7	0.018
Area of residence									
Rural	Reference			Reference			Reference		
Urban	–	–	–	–	–	–	2.3	1.2–4.6	0.011
Modality of treatment									
Oral tablet	Reference			Reference			Reference		
Insulin	–	–	–	–	–	–	–	–	–
Oral and insulin	–	–	–	1.4	1.0–2.1	0.045	–	–	–
Active smoking									
Never smoker	Reference			Reference			Reference		
Ever smoker	1.6	1.1–2.3	0.015	1.6	1.1–2.4	0.008	1.7	1.1–2.8	0.017
Physical activity									
Active (>= 150 min/week) (ref)	Reference			Reference			Reference		
Inactive (<150 min/week)	–	–	–	–	–	–	2.4	1.5–3.8	<0.001
Hypertension									
No	Reference			Reference			Reference		
Yes	3.6	2.4–5.4	<0.001	–	–	–	3.0	1.6–5.5	<0.001
Medication adherence									
Adequate	Reference			Reference			Reference		
Inadequate	–	–	–	–	–	–	2.5	1.5–4.3	0.001
Glycaemic control (HbA1c)									
Control (≤6.9%)	Reference			Reference			Reference		
Uncontrolled (>7%)	2.2	1.3–3.7	0.002	–	–	–	–	–	–

[a] Adjusted for age, level of education, area of residence, household income, active smoking, smokeless tobacco, physical activity, duration of diabetes, medication adherence, modality of treatment, family history of DM, hypertension, glycaemic control, dyslipidaemia, and waist/hip ratio (area under the receiver operating characteristic curve: 73.6%, Hosmer-Lemeshow goodness-of-fit test p-value: 0.988).
[b] Adjusted for gender, household income, active smoking, smokeless tobacco, physical activity, modality of treatment, BMI, and dyslipidaemia (area under the receiver operating characteristic curve: 56.8%, Hosmer-Lemeshow goodness-of-fit test p-value:0.033).
[c] Adjusted for age, level of education, area of residence, household income, active smoking, smokeless tobacco, physical activity, duration of diabetes, medication adherence, modality of treatment, BMI, hypertension, and dyslipidaemia (area under the receiver operating characteristic curve: 78.3% and the Hosmer-Lemeshow goodness-of-fit test p-value:0.835).

Bangladesh also reported a similar prevalence of 11.0% [23]. While literature both within and outside of Bangladesh do not completely agree, it is consistent that the least prevalent macrovascular diabetes complication is one of either stroke or diabetic foot [12,20,21,24]. Our study showed that prevalence of diabetic foot was 12.0%. This is slightly higher than 6.4% global prevalence of diabetic foot among people with T2DM [25]. This is also slightly higher than other studies in Bangladesh and other parts of Asia, with prevalence ranging from 7.2% to 11.6% [12,22,26–28].

For microvascular complications, our study showed the prevalence of nephropathy to be highest at 34.2%. While this prevalence is within the global prevalence range of 12%–55% amongst all diabetic patients [1], past studies in Bangladesh reported a slightly lower prevalence of nephropathy [13,29]. Elsewhere in Asia, a study conducted on the Northwest Indian population found a nephropathy prevalence of 30.2% [28], while the prevalence of nephropathy was found to be 15% [27] in Saudi Arabia. Neuropathy was the least prevalent microvascular complication in our study, affecting 5.8% of our study's subjects, falling below the global prevalence range of 16%–66% [1]. Previous studies in Bangladesh reflected higher prevalence of neuropathy [13,30]. A study in Doha also showed results like our study, where neuropathy was the least prevalent microvascular complication, but with a higher prevalence of 15.3% [31]. The low prevalence of neuropathy reflected in our study was possibly due to the underdiagnoses of neuropathy, thus reflecting the need for improvements in neuropathy screening among people with T2DM in Bangladesh. In our study, diabetic retinopathy had a moderately high prevalence of 25.1%. This is slightly lower than the global prevalence of 35.0% [1], consistent with other studies in Bangladesh which also reported prevalence rates of diabetic retinopathy lower than the global prevalence [13,32]. The prevalence of diabetic retinopathy consistently falling below the global prevalence may be attributed to the finding that Asian countries typically have a lower prevalence of diabetic retinopathy than their Western counterparts, as reported by a review article by Lee et al. [33]. Furthermore, the asymptomatic nature of the complication means that people only seek medical help when their vision becomes significantly impaired, and their daily activities are affected [33]. This may also lead to underdiagnoses of retinopathy.

Among all the participants of this study, 25.9% had a smoking history. It was shown in our results that smokers, past and present, have a higher risk of all three macrovascular complications, with

Table 4
Adjusted association between each of the microvascular complications and potential risk factors.

Variable	Neuropathy[a]			Nephropathy[b]			Retinopathy[c]		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Age									
<60 years	Reference			Reference			Reference		
>= 61 years	–	–	–	2.4	1.8–3.3	<0.001	2.5	1.7–3.6	<0.001
Gender									
Male	Reference			Reference			Reference		
Female	–	–	–	–	–	–	1.7	1.2–2.4	0.003
DM Duration									
≤5 years	Reference			Reference			Reference		
6–10 years	–	–	–	–	–	–	–	–	–
≥11 years	–	–	–	2.3	1.7–3.2	<0.001	2.3	1.5–3.3	<0.001
Family history of diabetes									
No	Reference			Reference			Reference		
Yes	–	–	–	0.7	0.5–0.9	0.029	–	–	–
Area of residence									
Rural	Reference			Reference			Reference		
Urban	0.5	0.2–0.9	0.028	3.2	2.1–4.7	<0.001	2.1	1.3–3.2	0.001
Household income									
<20,000 tk	Reference			Reference			Reference		
20,000–60,000 tk	–	–	–	0.6	0.4–0.8	0.003	–	–	–
>60,000 tk	–	–	–	–	–	–	–	–	–
Modality of treatment									
Oral tablet	Reference			Reference			Reference		
Insulin	–	–	–	–	–	–	–	–	–
Oral and insulin	–	–	–	1.7	1.2–2.4	<0.001	1.4	1.0–2.1	0.039
Medication adherence									
Adequate	Reference			Reference			Reference		
Inadequate	–	–	–	–	–	–	1.4	1.0–2.1	0.035
Hypertension									
No	Reference			Reference			Reference		
Yes	–	–	–	2.6	1.9–3.6	<0.001	–	–	–
Physical activity									
Active (>= 150 min/week) (ref)	Reference			Reference			Reference		
Inactive (<150 min/week)	–	–	–	1.7	1.3–2.3	<0.001	1.4	1.0–2.1	0.031
Waist/hip ratio									
Normal	Reference			Reference			Reference		
High	0.2	0.1–0.7	0.015	–	–	–	–	–	–

[a] Adjusted for age, gender, area of residence, waist/hip ratio, and dyslipidaemia (area under the receiver operating characteristic curve: 60.1%, Hosmer-Lemeshow goodness-of-fit test p-value: 0.842).
[b] Adjusted for age, gender, level of education, area of residence, household income, active smoking, smokeless tobacco, physical activity, duration of diabetes, medication adherence, modality of treatment, family history of DM, BMI, and hypertension (area under the receiver operating characteristic curve: 80.9%, Hosmer-Lemeshow goodness-of-fit test p-value: 0.542).
[c] Adjusted for age, gender, level of education, area of residence, household income, active smoking, smokeless tobacco, physical activity, duration of diabetes, medication adherence, modality of treatment, BMI and glycaemic control (area under the receiver operating characteristic curve: 75.0%, Hosmer-Lemeshow goodness-of-fit test p-value: 0.759).

60–70% increased odds of CAD, diabetic foot and stroke. This is consistent with extensive literature worldwide [34–361]. Also, this study does not associate smoking as a significant risk factor for microvascular complications. Current literature differs across studies, but largely agree that smoking aggravates diabetic nephropathy [37,38]. It is however unclear if smoking is an independent risk factor for diabetic neuropathy and retinopathy [38,39]. While our study did not find an association between smoking and microvascular complications, it should nevertheless be discouraged by health practitioners as it is a major risk factor for macrovascular complications, which lead to high mortality rates.

The American Diabetes Association recommends adults with diabetes to engage in more than 150 min of moderate-to-vigorous intensity exercise over a week [40]. An alarming 51.2% majority of our participants did not reach this level of physical activity. The results in this study suggest that participants with inadequate physical activity are positively associated with stroke, nephropathy, and retinopathy, increasing the risk of each complication by 140%, 70%, and 40% respectively. This is supported by a meta-analysis conducted which showed that inactive individuals have 37% higher risk of stroke incidence or mortality compared to active individuals [41]. A Finnish study on diabetes also corroborated our findings that physical inactivity was more common in patients with nephropathy and retinopathy [42]. However, such findings may be in part due to the patients' diminished ability to exercise with complications present. Thus, patients should be educated regarding the benefit of exercise for prevention of diabetes complications, and they should be motivated to maintain a minimum of 150 min physical exercise per week.

In this study, hypertension was shown to be an independent risk factor for CAD, stroke, and nephropathy, with poor hypertension control increasing the risks of these complications by 3.6-fold, 3.0-fold and 2.6-fold respectively. The study also showed that 64.4% of all the participants were clinically hypertensive, suggesting poor control within the diabetic population in Bangladesh. The relationship between hypertension and atherosclerotic complications like stroke and CAD is thoroughly explored in literature, with elevations in both diastolic and systolic blood pressure beyond normal ranges increasing the risks of CAD and strokes [43,44], a finding that was similarly reflected in our study. Thus, hypertension should be a key target for intervention amongst patients with diabetes in order to reduce the risk of further macro- and micro-vascular complications.

This study further showed that living in urban regions resulted

in a higher risk of stroke, nephropathy, and retinopathy compared to living in rural regions. Living in an urban environment is associated with a 2.3-, 3.2- and 2.1-fold increase in risk of stroke, nephropathy and retinopathy respectively. Studies outside and within Bangladesh have also shown similar results for stroke, retinopathy and nephropathy [13,45,46]. This result of increased prevalence of certain complications in urban areas has been attributed to the fact that urbanisation is associated with a higher calorie food intake and increased stresses, and these are risk factors for diabetes and its complications [47]. This shows that environmental factors have a strong influence on the prevalence of diabetes and its complications. Bangladesh is facing rapid urbanisation in recent times, and hence targeting environmental risk factors for diabetic complications in urban areas would be of relevance in Bangladesh.

In our study, longer duration of diabetes was found to be an important risk factor for CAD, stroke, nephropathy and retinopathy. Having a diabetes duration of more than ten years was associated with a 1.5-, 1.7-, 2.3- and 2.3-fold increase in the risk of CAD, stroke, nephropathy and retinopathy respectively over those with a disease duration of five years and under. This is supported by studies which have also shown that a longer duration of diabetes leads to increased prevalence of certain macrovascular and microvascular complications [48–50]. Patients with a long history of diabetes are more likely to be at advanced stages of the disease. They are subject to a longer duration of the atherosclerotic process, thus driving the increased development of both macro- and microvascular complications. This therefore reflects the importance of screening of complications in patients who have had a longer history of T2DM, by general practitioners.

Our study showed that poor medication adherence leads to a 2.5- and 1.4-fold increase in the risk of stroke and retinopathy respectively. Our results are corroborated by past studies, which show a significantly lower incidence of developing new macrovascular and microvascular complications in patients with good medication adherence [51]. In light of this, when faced with patients with poorly controlled T2DM, clinicians should first consider counselling them on improving medication adherence, before increasing their medication dosage. This would in turn lead to a lower risk of developing diabetes complications.

Advanced age was similarly identified as a risk factor for the development of diabetes complications. Being more than 60 years of age was associated with a 1.6- and 1.8-fold increase in the risk of macrovascular complications such as CAD and stroke, respectively. It was also associated with a 2.4- and 2.5-fold increase in the risk of microvascular complications such as nephropathy and retinopathy, respectively which is reflected in other studies [52]. Clinicians are hence recommended to place more importance on screening for diabetes complications in this group of patients.

However, in our study, a traditionally known risk factor of a high waist-to-hip ratio (WHR) was shown to have no association with micro- and macrovascular complications but was protective for neuropathy. While many studies have shown a link between obesity and neuropathy [53,54], some studies have suggested that WHR is not an independent risk factor of neuropathy. These findings probably suggest that WHR is a risk of neuropathy mainly through an influence on other complication risk factors.

4.1. Strengths and limitations

Having an extensive sample size, this is one of the largest studies conducted in Bangladesh across a wide social demographic range that was surveyed. Data was collected from all primary, secondary and tertiary levels of health care, covering patients residing in rural, semi urban and urban areas. This study also evaluates all the macro- and microvascular complications of diabetes across a wide range of modifiable lifestyle factors as well as non-modifiable risk factors, allowing the independent risk of each individual factor to be established. Our study has a few limitations. Firstly, a few data obtained were self-reported and hence subjective. A cross-sectional study also does not allow the establishment of causality.

5. Conclusion

Our study demonstrated that among macrovascular complications, CAD was the most prevalent while among microvascular complications, nephropathy was the most prevalent. We also found that numerous lifestyle factors such as smoking, level of physical activity, and poor medication adherence can be important risk factors for both microvascular and macrovascular complications. Certain social demographics such as age, rural or urban area of residence were also found to be risk factors associated with diabetes complications. Clinical risk factors for diabetes complications we explored included the duration of diabetes and a history of hypertension. We recommend that screening and investigation be implemented early during the diagnosis of diabetes to identify the above risk factors so that they can be targeted early with an individualised treatment and management strategy to prevent the onset of complications. Further studies are needed to verify the above findings and to explore effective tools to predict patients' risk profile in developing complications upon diagnosis as this will be helpful in the early prevention of these complications.

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Author's contribution

Concept and design (AA, BB), acquisition of data (AA), interpretation of data and drafting the manuscript (WZ, AJWL, DXJL), critically review to improve the content and final approval of version to be submitted (AA, BB). All authors have read and approved the manuscript.

Disclosure

The authors have not declared any conflicts of interest.

Availability of data

The data sets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.07.046.

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Context of the study (7b)

Diabetes is a major risk factor for CVD, which is a leading cause of morbidity and mortality worldwide and accounts for approximately one third of all deaths globally. Vascular disorders include CAD, PVD, stroke, and diabetic foot. The global economy is highly affected by diabetes with CVD. The healthcare costs for diabetes with CVD comprise the largest share of diabetes health expenditure. The likelihood of having CVD is 2 to 3-fold higher for people with diabetes compared to the general population.

The evaluation of an individual's risk of experiencing a future cardiovascular event increasingly forms the basis of clinical guidelines for the prevention of CVD. Risk prediction tools play an important role in identifying patients with a high risk of diabetes complications and their use has been recommended in the diabetes management guidelines on assessing individual risk factors. These tools also help in patient counselling and motivation, particularly to change patients' lifestyle behaviour and encourage them to adhere to their management plans, by identifying patients who are at high cardiovascular risk. A number of risk prediction models for CVD including CAD and stroke are available in the literature and in use for routine clinical practice. However, they are rarely applicable to the Bangladeshi population due to social, cultural and economic variations. Therefore, the aim of this study was to develop risk prediction models for CAD and stroke specific to the T2DM population in Bangladesh, which will serve as an evidence-based risk scoring tool for these complications.

This paper has been included in its manuscript format within this thesis.

Manuscript

Cardiovascular Risk Scoring System for People with Type 2 Diabetes – a Case Study in Bangladesh

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Abstract

Aims: This study aimed to develop a risk scoring system for evaluating risk of cardiovascular complications for people with type 2 diabetes in Bangladesh.

Materials and Methods: A cross-sectional and retrospective study was conducted between April and September 2017. Using a systematic random sampling method, a total of 1,253 adults with type 2 diabetes were recruited from six hospitals, covering rural and urban residents. All missing values were imputed. The bootstrap method was used to identify plausible variables related to coronary artery disease and stroke. The mixed-effects multiple logistic regression was used to estimate the final model and the bootstrap method was used for model validation. The model was then translated to a risk scoring system.

Results: The variables age, female gender, hypertension and physical activity <150 minutes/week were selected as the predictors in both models. Glycaemic level, retinopathy, neuropathy, dyslipidaemia, ever smoking, and unhealthy eating habits were related to coronary artery disease only. Furthermore, education up to secondary level, duration of diabetes, and non-adherence to treatment were associated to stroke only. The discrimination and calibration powers of the models were very good.

Conclusions: The prevalence of coronary artery disease and stroke were high amongst people with type 2 diabetes in Bangladesh. The developed risk scoring system is parsimonious and easy to use. We recommend this to people with type 2 diabetes and clinicians as an evidence-based risk stratification tool.

Key word: Bangladesh, Coronary artery disease, Risk scoring tool, Stroke, Type 2 diabetes mellitus

Introduction

Diabetes is one of the major global health threats of the twenty-first century. It affected more than 425 million people across the world in 2017 and this number has been projected to rise to 628 million by 2045 [1]. The burden of this emerging pandemic is driven by its increased risk of complications and much of the burden, especially for people with type 2 diabetes mellitus (T2DM), is related to micro- and macro-vascular complications [2, 3]. Globally, 12.7% and 18.8% of people with T2DM suffer from macro- and micro-vascular complications, respectively [4].

Cardiovascular disease (CVD) is a macrovascular complication and is an umbrella term that includes coronary artery disease (CAD), stroke, diabetic encephalopathy and diabetic foot [1]. Diabetes with CVD poses a remarkable burden for the global economy as its related healthcare costs represent the largest proportion of diabetes health expenditure. The likelihood of having CVD is 2 to 3-fold higher for people with diabetes compared to those without diabetes [5, 6]. A higher prevalence is being observed in low- and middle-income countries (LMICs) compared to high-income countries [5]. In LMICs, an estimated US$84 billion of gross domestic product was lost due to diabetes with CVD between 2005 and 2015 [7]. Among the subclasses of CVD, CAD and stroke lead to the worst health outcomes including decreased quality of life, disability and mortality [5, 8]. The prevalence of CAD among people with T2DM ranges between 5% and 36% in different settings (population/hospital based) and that of stroke ranges from 4% to 12% in hospital-based studies and between 4% and 5% in population-based studies [9]. A multinational study showed the prevalence of CVD in South Asia was 23.3% among people with type 2 diabetes [10]. However, in Bangladesh, a study reported a prevalence of 25.8% for CAD and 11% for stroke, which was higher than the regional prevalence [11].

International guidelines for the management of diabetes suggest risk-stratified interventions based on a predicted risk profile of the disease, rather than individual risk factors [12-14]. A risk scoring tool can be used to screen and identify individuals who are at an increased risk of having a disease, and hence is potentially important in clinical decision making regarding the management of the disease and patient counselling.

A number of previous studies developed risk prediction models for CVD including CAD [15-18] and stroke [19-22], which are frequently used in clinical decision making. However, they are exclusive to either western populations [16-18, 20] or populations from upper-middle- or high-income countries in Asia such as China and Hong Kong [15, 19, 21, 22]. In addition to common risk factors such as age, gender, and duration of diabetes, these models considered some clinical variables including atrial fibrillation [20] and some biomarkers [18, 23, 24], which are not routinely collected in clinical practice. Furthermore, only a few of the previous models considered lifestyle factors such as smoking and physical activity

as potential risk factors, and none of them used eating habits or adherence to treatment as a risk factor of CAD and stroke. Furthermore, due to variations in environmental factors and economic conditions that affect lifestyle behaviours, risk scoring system adopted from one population may limit its accuracy when applied to another population.

An overall risk assessment tools for CAD and stroke among T2DM in Bangladesh are currently unavailable in the literature. Thus, the aim of this study was to develop risk scoring system for CAD and stroke specific to the Bangladeshi T2DM population, which will serve as an evidence-based risk stratification tool for these complications.

Materials and Methods

Study Design and Data Source

The project protocol was approved by the Monash University Human Research Ethics Committee and the Diabetic Association of Bangladesh (BADAS). A cross-sectional and retrospective study was carried out between March and September 2017 in six diabetes hospitals located in the central and northern regions of Bangladesh. The selected hospitals are under BADAS, which has the largest network of specialist diabetes hospitals/centres across the country providing primary to tertiary levels of healthcare services. Due to minimal variation between people attending hospitals in the northern and southern regions of the country, no hospitals were selected from the southern region. Bangladesh has also public and private healthcare sectors. In the public health system except medical college hospitals (tertiary level), all other hospitals (community centres, and primary or secondary level hospitals) are not well equipped to provide adequate treatment to people with diabetes. While private providers are mainly money driven thus accessible only to the middle- and high-income groups [25]. In this study, 1,253 participants were recruited from rural, semi-urban and urban locations which may not be representative to the overall population with T2DM in Bangladesh but represent a good majority of them. The inclusion criteria were adult subjects of either gender with a minimum one-year duration of T2DM. The study excluded patients with other types of diabetes such as gestational diabetes and type 1 diabetes. Participants were selected randomly and interviewed face-to-face using a structured questionnaire after obtaining informed consent from each of them. The questionnaire comprised questions about the patient's socio-demographics, lifestyle characteristics and clinical information. Participants' medical records were reviewed to collect the data regarding laboratory investigation, prescribed medicines and documented diagnoses of complications and comorbidities. All the study procedures were carried out in accordance with the principles of the Declaration of Helsinki as revised in 2013.

Definitions of Outcome Variables

The primary outcomes were CAD and stroke among people with T2DM. Information about CAD was obtained following a comprehensive review of the participant's medical record, prescribed medicine, and questionnaire survey. Stroke was defined by reviewing the documented diagnosis of an irreversible cerebrovascular accident as well as by asking the patient about any incidence in the previous years.

Description of Independent Variables

Patients' socio-demographics (including age, gender, marital status, education, professional status, and monthly household income) and medical histories (including duration of diabetes, family history of diabetes, frequency of follow up, mode of treatment and hypoglycaemic events) were derived from the administered questionnaire. Participants' complications and comorbidities were confirmed by the patient's response, a comprehensive review of the prescription for pharmacotherapy and by reviewing the record of documented diagnoses.

Mode of treatment was categorised as users of an oral hypoglycaemic agent (OHA) only, and users of insulin with or without an OHA. Glycaemic status was categorised using HbA1c <7% as good control and HbA1c ≥7% as poor control [26]. Body mass index was categorised into normal/overweight (<27.5 kg/m2) and obese (≥27.5 kg/m2), adhering to the World Health Organization guidelines for Asians [27]. The cut off for waist-hip ratio was defined as >0.90 for men and >0.80 for women [28]. Hypertension was defined as either a documented diagnosis of hypertension, taking antihypertension medications, or following the latest (within three months) blood pressure readings (either systolic ≥140 or diastolic ≥90) [29]. Dyslipidaemia was defined as either a documented diagnosis of dyslipidaemia or taking any lipid-lowering medicine. Nephropathy was defined by an estimated glomerular filtration rate <60 ml/min/1.73m² [30] or a documented diagnosis from the medical records. Neuropathy was defined as a score of seven or more using the Michigan Neuropathy Screening Instrument [31]. Retinopathy was defined by a procedure undertaken for the treatment of retinopathy or documented diagnosis. The diabetic foot was defined by documented diagnosis of diabetic foot and visual examination of ulcers or amputations. Physical activity was defined as active if the person had >150 minutes of physical activity measured by the Global Physical Activity Questionnaire [29]. Dietary habits were assessed by the UK Diabetes and Diet Questionnaire [32]. The dietary habit variable was measured as a scale between 0 and 48 and categorised using a cut off at first quartile (score 28). A score of more than 28 was considered to show healthy eating habits. Smoking status and smokeless tobacco consumption were the categories of ever and never being a smoker/consumer.

Statistical Analysis

Using an extensive literature review and clinical assessments, a set of potential variables was identified and then entered into the simple logistic regression analysis to examine the univariate association between outcomes and each of these variables. Then the bootstrap method with the receiver operating characteristics curve (BROC) was used to select the variables [33-35]. The selected variables were then entered into a multilevel mixed-effects logistic regression model to account for residential variation. The following steps demonstrate the development of the final model.

Imputation: Overall, 20.1% of data was missing. A multiple imputation using the ICE method was used for imputing the missing values [36, 37]. The missing values were imputed five times, i.e., five imputed samples were created, each the same size as the study sample (n=1,253).

Bootstrap model selection: The BROC method was used for variable selection [33]. From each of the five imputed samples, 5,000 bootstrap random samples were drawn using with replacement technique, which resulted in 25,000 bootstrap samples. For each of the bootstrap samples, a multiple logistic regression was run and variables that appeared significant were recorded. The percentage of times each variable appeared as significant were ranked from highest to smallest percentage of appearance. Then, a series of plausible models were developed and their corresponding receiver operating characteristic (ROC) was recorded. The first plausible model (M1) was developed by using the variable that appeared as significant in the highest percentage of times. Then, the variable that appeared as significant the second-highest percentage of times was added into the first model to develop the second model (M2). This procedure of entering one additional variable at a time to the preceding model was continued until all plausible models were developed. The variables with a percentage appearance of less than 20% were excluded from model development. The final model was selected by making a trade-off between the optimisation of ROC and the parsimony of the model [33]. The selected variables were then entered into multilevel mixed-effects logistic regression models in order to account for the residential variations (rural vs. urban). First-order interaction effect and multicollinearity between potential risk factors were also investigated.

Validation and calibration: The model's performance was evaluated using discrimination and calibration powers. The discrimination power of the model was evaluated using 1,000-fold bootstrap validation, where 1,000 random samples were drawn from the study sample, each of which was 90% of the size of the original sample [33-35]. The ROC was calculated for each sample and then averaged. Calibration was assessed by the decile-decile plot by comparing observed and predicted probability of the outcome of the deciles. A linear regression model was fitted with the deciles of the observed (dependent) and predicted (independent) values to measure the amount of variation in the observed

outcome explained by its predicted value. All statistical analyses were performed using the statistical software package Stata (version 15.0) and the imputation was carried out by the user-written program ICE in Stata [38].

Risk stratification

Using the beta coefficients of the respective variables related to CAD and stroke models, the absolute risk of these outcomes for a patient can easily be calculated using the following formula: absolute risk = exp(XB)/(1+exp(XB)), where 'X' is the set of variables related to outcome and 'B' is their corresponding beta coefficients, and 'XB' is the added of value of these beta coefficients and the constant term in the model. Furthermore, these beta coefficients can easily be translated into a risk scoring tool, which describes a points-based risk-scoring for each individual patient [39]. The higher the risk score, the worse the risk. The calculation of risk score has been described below:

Step 1: From the calculated beta coefficients, the smallest absolute beta coefficient was selected. Then, each of the beta coefficients was divided by the absolute smallest beta coefficient, which gives a score corresponding to each variable.

Step 2: The total risk score for each patient can be calculated based on the risk factors the patient has presented.

Step 3: The calculated scores for all patients will be divided into quintiles (five groups) and rounded to the closest integer for risk stratification.

Step 4: If a patient falls into the 1st or 2nd or 3rd quintiles, he/she will be classified as very low or low or moderate risk category, respectively. However, will be classified as high or very high category if the patient falls into the 4th or 5th quintiles, respectively.

Finally, a web-based calculator will be developed to facilitate the risk calculation online.

Results

General Characteristics of the Study Samples

Participants' general characteristics are presented in Table 1. Among the 1,253 participants, 54.4% were male. The mean age was 55.1±12.5 years. Approximately 45% had a secondary-level education and 23% had a tertiary-level education. About two-fifths (40.5%) were employed and about a quarter (23.8%) were housewives. Three-quarters (73.2%) resided in urban areas and 51.2% had a median monthly household income of US$375 (Bangladeshi currency taka (BDT) 30,000). The mean duration of diabetes was 10.9±7.7 years and 43.5% of participants had diabetes for more than ten years. About one-third (34.5%) managed their glycaemic level using only an oral hypoglycaemic agent (OHA), while the remaining 65.5% used insulin with or without OHA. More than one-third

(34.6%) had a family history of diabetes. Only 18.2% had good glycaemic control (HbA1c <7%). About two-thirds (62.8%) of participants did not adhere to treatment. Among the participants, 51.2% had physical activity levels of <150 minutes/week and 78.3% had unhealthy eating habits. About one-quarter (25.9%) were current smokers or had smoked in the past and 22.4% had a history of smokeless tobacco consumption. About two-thirds (64.4%) of participants had hypertension and one-third (34.6%) had dyslipidaemia. The prevalence of macrovascular complications of CAD, stroke and diabetic foot were, respectively, 30.5%, 10.1%, and 12%, while that for microvascular complications of nephropathy, neuropathy, and retinopathy were 34.2%, 5.7% and 25.1%, respectively.

Table 1 General characteristics of the study participants

Variables	n (%) **(n = 1253)**	**Variables**	n (%) **(n = 1253)**
Age (mean ± SD)	55.1±12.5	**Family history of diabetes**	
Gender		Yes	433 (34.6)
Male	681(54.4)	No	820 (65.4)
Female	572 (45.6)	**Physical activity**	
Education		≥150 minutes/week	612 (48.8)
Illiterate	161 (12.8)	<150 minutes/week	641 (51.2)
Primary	239 (19.1)	**Eating habit**	
Secondary	566 (45.2)	Healthy	272 (21.7)
Tertiary	287 (22.9)	Unhealthy	981 (78.3)
Work status		**Smoking status**	
Unemployed	36 (32.8)	Never-smoker	929 (74.1)
Employed	411 (40.5)	Ever-smoker	324 (25.9)
Housewife	508 (23.8)	**Smokeless tobacco consumption**	
Retired	298 (2.9)	Non-consumer	973 (77.6)
Area of residence		Consumer	280 (22.4)
Rural	336 (26.82)	**Hypertension**	
Urban	917 (73.2)	No	446 (35.6)
Monthly household income (USD)		Yes	807 (64.4)
≤250	447 (35.7)	**Dyslipidaemia**	
251-750	497 (39.7)	No	819 (65.4)
751 and above	309 (24.6)	Yes	434 (34.6)
Duration of diabetes (in year)		**CAD**	
≤5	360 (28.8)	No	871 (69.5)
6-10	348 (27.7)	Yes	382 (30.5)
≥11	545 (43.5)	**Stroke**	
Mode of treatment		No	1126 (89.9)
OHA	432 (34.5)	Yes	127 (10.1)
Insulin±OHA	821 (65.5)	**Diabetic foot**	
Adherence to treatment		No	1103 (88.0)
Adhere	466 (37.2)	Yes	150 (12.0)
Not-adhere	787 (62.8)	**Nephropathy**	

Variables	n (%) (n = 1253)	Variables	n (%) (n = 1253)
BMI (kg/m^2)		No	824 (65.8)
Normal (<23)	290 (25.3)	Yes	429 (34.2)
Over weight (23-27.4)	530 (46.3)	**Neuropathy**	
Obese (≥27.5)	325 (28.4)	No	1181 (94.3)
HbA1c (%)		Yes	72 (5.7)
Good (<7)	182 (18.2)	**Retinopathy**	
Poor (≥7)	1071 (81.8)	No	938 (74.9)
		Yes	315 (25.1)

SD= Standard deviation, OHA = Oral hypoglycaemic agent

Risk Prediction Models

The variables with the percentage of appearance as significant in the bootstrap analysis for CAD and stroke, along with ROC for each of the plausible models, are presented in Table 2. The ROC for the plausible models for each complication are plotted and presented in Figure 1. There was no first-order interaction effect or multicollinearity between the risk factors in the selected final model. Table 3 shows the beta coefficient and its corresponding odds ratio (OR) for the selected risk factors. Figure 2 illustrates the slope calibration for the final models.

Risk Prediction Model for CAD

The bootstrap results presented in Table 2 show that hypertension appeared as significant in all bootstrap samples, while poor glycaemic control and retinopathy appeared as significant in 99% and 95.8% of the samples respectively. Age ≥60 years was significant in 77.6% of the time and the variables of unhealthy eating habits, physical activity <150 minutes per week, and being an urban resident were significant between 60% and 70% of the time. Ever smoking, nephropathy and dyslipidaemia appeared as significant in between 45% and 55% of the samples, while the remaining variables were significant in less than 45% of the samples. Finally, after trading off between parsimony and discrimination powers of the plausible models, the variables age in years, glycaemic level (HbA1c %), hypertension, retinopathy, nephropathy, dyslipidaemia, ever smoking, physical activity <150 minutes/week, unhealthy eating habits, and urban area of residence (shown in M10 in Figure 1), were selected as the predictors for CAD. The variable gender was added to the final multilevel mixed-effects model irrespective of their significance status in bootstrapping.

Table 2: The average percentage of appearance and ROC in bootstrap-ROC analysis

Coronary artery diseases (CAD)			
Variable	**% of appearance as significant**	**Model**	**ROC (%)**
Hypertension	100.0	M1	64.1
Poor glycaemic control (HbA1c ≥7%)	99.0	M2	67.2
Retinopathy	95.8	M3	70.8
Age ≥60 years	77.6	M4	72.6
Unhealthy eating habit	67.9	M5	73.5
Physical activity (<150 minutes/week)	66.7	M6	73.7
Urban resident[§]	63.7	M7	74.5
Ever smoker	54.6	M8	75.1
Nephropathy	48.7	M9	75.4
Dyslipidaemia	46.4	M10*	75.6
High WHR	42.8	M11	75.8
Stroke	30.4	M12	75.9
Duration of diabetes >10 years	27.9	M13	76.0
Up to secondary level education	23.8	M14	76.0
Non-adherence to treatment	22.8	M15	76.1
BMI ≥27.5 kg/m^2	20.3	M16	75.9
Family history of diabetes	20.0	M17	76.1

Stroke			
Variable	**% of appearance as significant**	**Model**	**ROC (%)**
Physical activity (<150 minutes/week)	97.4	M1	63.5
Non-adherence to treatment	95.3	M2	67.4
Hypertension	90.5	M3	72.3
Urban resident[§]	80.2	M4	74.7
Up to secondary level education	61.2	M5	75.0
Duration of diabetes >10 years	53.2	M6*	77.2
Family history of diabetes	43.5	M7	77.1
Age ≥60 years	41.4	M8	77.0
Female gender	39.6	M9	77.9
Retinopathy	36.9	M10	78.4
Unhealthy eating habit	35.5	M11	78.8
Ever smoker	25.1	M12	79.0
History of CAD	22.6	M13	79.2
Diabetic foot	22.0	M14	79.3

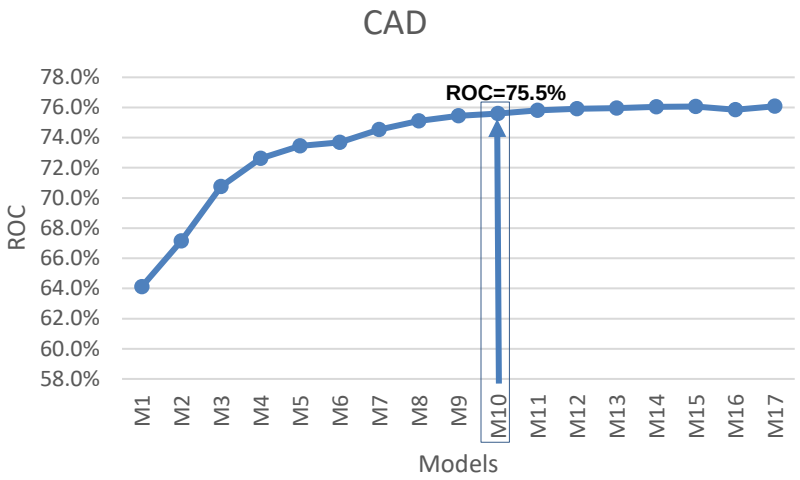
* The selected model for coronary artery disease (CAD) and stroke based on both the ROC and the percentage of appearance, [§]Area of residence was adjusted for both of the models using as multilevel variable.

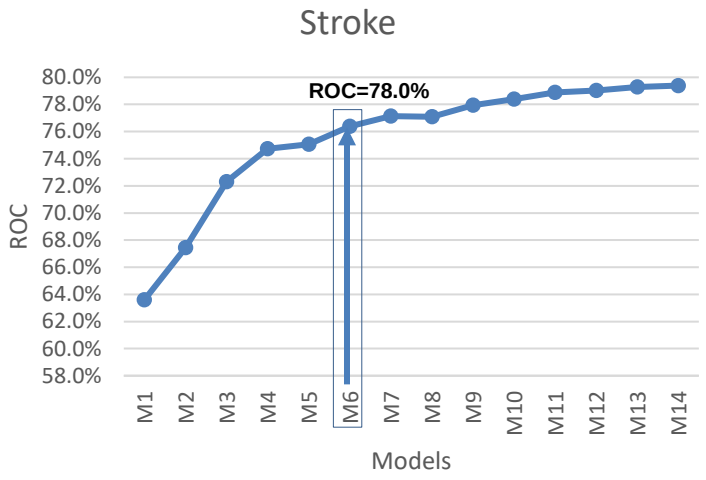
Table 3 Beta coefficient and OR (95% CI) for the predictors of coronary artery disease (CAD) and stroke

Coronary artery diseases (CAD)*			
Variables	**Beta Coefficient**	**OR**	**95%CI**
Female gender	-0.07	0.9	0.5-1.2
Age (in years)	0.03	1.0	1.1-2.3
Glycaemic level (HbA1c %)	0.05	1.1	1.5-9.3
Hypertension	1.09	2.9	2.2-4.7
Retinopathy	0.74	2.1	1.5-3.2
Nephropathy	0.20	1.2	0.9-2.0
Dyslipidaemia	0.42	1.5	1.2-2.1
Ever smoker	0.18	1.2	0.8-1.9
Physical activity (<150 minutes/week)	0.39	1.5	1.1-2.1
Unhealthy eating habit	0.35	1.5	1.1-2.5
Constant	-5.06		

Stroke *			
Variables	**Beta Coefficient**	**OR**	**95%CI**
Female gender	-0.38	0.7	0.4-0.9
Age (in years)	0.03	1.0	1.1-2.6
Up to secondary level education	0.58	1.7	1.1-3.1
Duration of diabetes (in years)	0.03	1.0	1.1-2.6
Hypertension	0.97	2.6	1.6-4.9
Non-adhere to management	0.79	2.2	1.4-3.6
Physical activity (<150 minutes/week)	0.86	2.4	1.6-3.9
Constant	-6.90		

* Accounts for residential variation in multiple mixed-effect logistic regression





Note: M1: model 1, comprised of one variable; M2: model 2, comprised of two variables; M3: model 3, comprised of three variables; and so on. The variables appearing as significant in bootstrapping were added into the model, starting from the highest to the lowest. A variable upon deletion that does not change the ROC of a model might be useful in the risk stratification of patients. Therefore, importance should be based on a model's parsimony and the clinical importance of the variable in question.

Figure 1 The selection of the variables into the final model for CAD and stroke (highlighted)

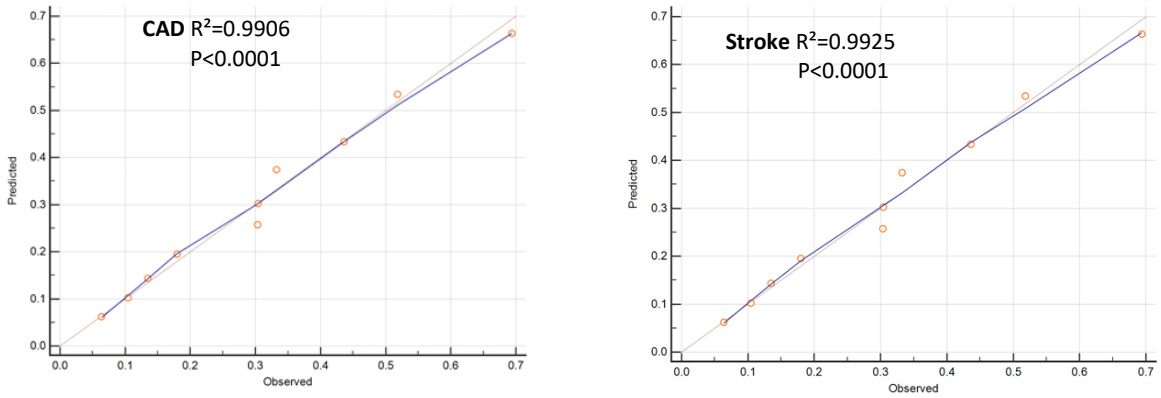


Figure 2 Decile-decile plot for coronary artery diseases (CAD) and stroke

Females had 90% (95% CI 0.5-1.2) lower odds of developing CAD, while the odds of CAD increased by 20% (95% CI 0.8-1.9) among people who had ever been smokers, and 50% for both who had physical activity <150 minutes/week (95% CI 1.1-2.1) and unhealthy eating habits (95% CI 1.1-2.5). The odds of CAD increased by 1% with every additional increase in both age (95% CI 1.1-2.3) and HbA1c% (95% CI 1.5-9.3). History of retinopathy, dyslipidaemia and nephropathy increased the odds of CAD by 2.1-fold (95% CI 1.5-3.2), 1.5-fold (95% CI 1.2-2.1) and 1.2-fold (95% CI 0.9-2.0), respectively. People with hypertension had 2.9-fold (95% CI 2.2-4.7) higher odds of having CAD compared to those without hypertension. The model has the bootstrap ROC value of 75.3% and calibration power of 99.0% (p-value < 0.001) (Figure 2).

Risk Prediction Model for Stroke

The results in Table 2 also show that physical activity <150 minutes per week, not adhering to treatment, and hypertension had a significant appearance in 97.4%, 95.3% and 90.5% of the bootstrap samples respectively. Residing in an urban area was significant in 80.2% of the times. Education up to secondary level and duration of diabetes >10 years were significant in more than 50% but less than 70% of the samples. The remaining variables were identified as significant in less than 50% of the bootstrap samples. The six variables, shown in M6 in Figure 1, were considered as the predictors for stroke. These variables are education up to secondary level, duration of diabetes >10 years, hypertension, not adhering to treatment, physical activity <150 minutes per week, and residing in an urban area. Irrespective of significance status in bootstrapping, age and gender variables were considered to the final multilevel mixed-effects model. The results of the final model presented in Table 3 showed that females have 70% (95% CI 0.4-0.9) lower odds of developing stroke. With each year increase in age, the odds of stroke (95% CI 1.1-2.6) increased by 1%. Education up to secondary level had increased odds of stroke of 70% (95% CI 1.1-3.1). The odds of stroke increased by 2.2-fold (95% CI 1.4-3.6), 2.4-fold (95% CI 1.6-3.9) and 2.6-fold (95% CI 1.6-4.9), respectively for non-

adherence to treatment, physical activity <150 minutes per week, and hypertension. The stroke model had a bootstrap ROC value of 76.7% and calibration power of 99.2% (p-value < 0.001) (Figure 2).

Example - a Case Study for CAD

Let us consider a male (beta = 0, additive score = 0) patient, who was 65 years old (beta = 0.03, additive score = 0.86) and had a recent HbA1c measurement of 13.2% (beta = 0.05, additive score = 4.4). The patient was a smoker (beta = 0.18, additive score = 1), physically inactive (beta = 0.39, additive score = 2.1), and has a healthy eating habit (beta = 0, additive score = 0). Furthermore, the patient presented with hypertension (beta = 0.1.09, additive score = 5.6), retinopathy (beta = 0.74, additive score = 4.1), nephropathy (beta = 0.2, additive score = 1.6) and dyslipidaemia (beta = 0.42, additive score = 2.2). The calculated absolute risk of this patient is 63.9% and the approximate risk score is 22, and based on the risk stratification presented in Table 4, the patient falls in the 5th quintile of risk groups, hence classified as having a very high-risk of developing CAD.

Table 4 The stratified additive risk score for patients presented CAD and stroke.

Risk quintiles	Risk groups	Additive score category for CAD	Additive score category for stroke
1st (0-20% of the patients)	Very low	0-9	0-3
2nd (21-40% of the patients)	Low	10-12	4-5
3rd (41-60% of the patients)	Moderate	13-14	6-8
4th (61-80% of the patients)	High	15-17	9-10
5th (81-100% of the patients)	Very high	Above 17	Above 10

Online Risk Calculator

The risk scoring system for both CAD and stroke were translated into a web-based risk scoring tool (calculator), which is available online using the following link:

http://projects.fimaruf.com/rc/

Discussion

Type 2 diabetes prevalence is increasing globally and it is related to CAD and stroke, which are major cost incurring among all diabetes related complications. These complications can be prevented or delayed by stratifying patients' risk of having the disease. A risk scoring tool is commonly used to stratify and evaluate the overall risk of a disease, monitor individual's progress to control the risk factors and provide objective risk estimates that can assist the decision making of health professionals. To the best of our knowledge, this is the first attempt to develop risk scoring tools for CAD and stroke

for T2DM population in Bangladesh. The developed tools are parsimonious, easy to apply and have high discrimination and calibration power.

In this study, the prevalence of CAD and stroke was 30.5% and 10.1%, respectively, which is comparable to the global prevalence that ranges from 14.8% to 40.5% for CAD and from 3.5% to 10.4% for stroke [40]. A limited number of studies in Bangladesh that confer the prevalence of CVD including CAD and stroke [41-44], show an increasing trend of CVD. These studies showed that factors including rapid urbanisation, habituation of a sedentary lifestyle, change in eating habits, and reduced physical activity [43, 44] are related to CVD. An upward trend in the prevalence of CVD shows the importance of development of a risk scoring tool specific to the Bangladeshi population to identify the patients at risk before onset of complications or in the early stage of complications.

Similar to previous risk prediction models for CAD and stroke [15-21], this study investigated the common risk factors such as age, gender, education, duration of diabetes, glycaemic control, smoking, hypertension, and dyslipidaemia. In addition, this study included life-style factors in the risk scoring tool. The positive effect of lifestyle behaviour factors such as healthy diet [45] and adherence to treatment [46] were evident in literature. Adherence to treatment was found to be significantly associated with good glycaemic control, which in turn may be related to reduced risk of diabetes complications [44]. However, their effect on CVD was not investigated adequately in the previously developed risk prediction models. Furthermore, several studies showed that nephropathy, assessed by eGFR, is strongly associated with the incidence of CVD and should be considered for the prediction of CVD risk [47-49]. It is also evident that the prevalence of nephropathy is higher among Asian T2DM population compared to others [50]. This current study investigated the effect of all T2DM related macro- and micro-vascular complications as potential risk factors for CAD and stroke.

Inclusion of some non-traditional biomarkers such as b-type natriuretic peptide, osteopontin, and β-2 microglobulin may improve the prediction performance of complications related to people with T2DM [18, 23, 24]. However, this study did not consider them as they are not usually collected in routine clinical practice and hence, their inclusion may limit the use of the risk scoring tool. The variables age ≥60 years, female gender, education up to secondary level, duration of diabetes >10 years, poor glycaemic control, hypertension, retinopathy, nephropathy, dyslipidaemia, ever smoking, physical activity <150 minute/week, unhealthy eating habits, and non-adherence to treatment were selected as significant risk factors in one or both of the tools.

The bootstrap method was used for developing and validating the underlying model of the risk scoring tools as opposed to the traditional split-sample method. The bootstrap method, which uses the entire data set for both model development and validation, is preferable over the split-sample method [51].

This is due to the fact that splitting the data can decrease the model's predictive accuracy and precision, particularly when the sample size is relatively small [52]. In this current study, the risk scoring tools for CAD and stroke were developed using the BROC method, which improves parsimony and performance of the tools compared to automated and other variable selection methods [33-35]. A selection of ten variables for CAD and seven variables for stroke in this study confirmed the parsimony of the proposed tools. Furthermore, high discrimination and calibration powers of both the CAD and stroke models confirmed their classification power. Guidelines for primary prevention often use risk scoring tools [16, 53-55] for CVD which combine CAD and stroke. However, a complication-specific tool is always preferable over a case-mix tool [20], which highlights the importance of individual risk scoring tool for CAD and stroke in this current study.

This study has several limitations and strengths to mention. A professionally mixed population recruited from six different hospitals covering rural and urban population, and the collection of primary data added strength to this study. Furthermore, use of the bootstrapping method for developing parsimonious risk scoring tools increased the potential for their use. Conversely, the cross-sectional design of this study lacks temporality. Some of the continuous variables were converted into categorical variables, which may subject to minor information loss, but a categorical variable is clinically more meaningful in a logistic regression model.

Conclusions

To conclude, the proposed risk scoring system for CAD and stroke was developed as a simple and easily applicable tool in daily practice. This tool, with its high calibration and discrimination powers, may increase the screening and lower the diagnostic thresholds related to CAD and stroke for people with T2DM in Bangladesh. This tool will support clinicians in patients' counselling and education for planning a primary prevention of CAD and stroke.

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Disclosure Statement

The authors declare no conflicts of interest.

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Chapter 8

EVALUATION OF THE IMPACT OF DIABETES ON THE ECONOMY OF BANGLADESH

Context of the study

Diabetes places an enormous economic burden on the global population, irrespective of whether people are rich or poor. The burden of the disease can be defined under two major subgroups: direct cost and indirect cost.

The direct cost affects the public health finance as an expenditure resulting from treatments, medicine and hospitalisations. Furthermore, the economy faces a loss related to the indirect cost of diabetes. Productivity losses that can be measured through absenteeism (work day lost due to illness), presenteeism (impaired work time due to illness), productivity (work day lost due to illness plus impaired work time due to illness) and labour force dropout (retirement before the official retirement age due to illness) are considered as indirect costs. They have an impact in terms of lost income earnings and tax revenue and reduced GDP of the country.

The impact of diabetes on work productivity has been addressed adequately in the context of HICs but there is a lack of studies in LMICs, which include Bangladesh. To make a trade-off between the direct costs of prevention initiatives, health services for diabetes and net economic consequences taking future productivity gained into account, quantification of the economic burden of diabetes in terms of lost productivity is imperative. Therefore, this study aimed to estimate the impact of diabetes on productivity in Bangladesh in terms of years of life lost and PALYs lost due to diabetes by using a life table model.

This paper has been included in its manuscript format within this thesis.

Manuscript

The Impact of Diabetes on the Productivity and Economy in Low and Lower-middle Income Settings: Bangladesh Perspective

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Abstract

Aims: Diabetes in the middle ages combined with loss of productivity has the potential to cripple countries such as Bangladesh. The loss of productivity due to diabetes has not been well described in low and lower-middle income countries which include Bangladesh. Thus, the aim of the present study was to estimate the impact of diabetes in terms of mortality, years of life lost, and productivity-adjusted life years (PALYs) lost in Bangladesh.

Methods: A life table model was developed using published demographic and mortality data to estimate excess mortality, and years of life, and PALYs lost among the Bangladeshi population of working age (20 to 59 years), with simulated follow-up until a retirement age of 60 years. Quality of life decrements and relative reduction in productivity attributable to diabetes were sourced from a cross-sectional survey conducted in Bangladesh in 2017. Two models were constructed; one for the individuals with diabetes, and another for the same cohort assuming that they did not have diabetes. Differences in the number of deaths, and years of life, and PALYs lived between the two models reflected the impact of diabetes. The World Health Organisation standard annual discount rate of 3% was applied to YLL and PALYs lived.

Results: In 2017, 6.9 million (6.9%) people aged 20-59 years in Bangladesh had diabetes. Assuming a follow-up of this population (aged 20-59 years) until age 60 years, an estimated 0.8 million excess deaths, and loss of 4.0 million life years (5.5%), and 9.2 million PALYs (20.4%) were attributable to diabetes. This was equivalent to 0.7 years of life, and 1.6 PALYs lost per person. The loss in PALYs equated to a total of US$97.4 billion lost (US$16,987 per person) in gross domestic product (GDP).

Conclusions: In Bangladesh, the impact of diabetes on productivity and the broader economy looms large, and poses a substantial risk to the country's future prosperity. This highlights the critical importance of health strategies aimed at the control of diabetes.

Keywords: Bangladesh, Cost, Diabetes, Gross Domestic Product, Productivity, Productivity Adjusted Life Years

Introduction

Diabetes is a leading cause of morbidity and mortality across the globe (1, 2). According to the International Diabetes Federation (IDF), the cluster of low-middle income countries which make up South-East (SE) Asia is home to 82 million people (aged 20-79 years) living with diabetes (3). In Bangladesh, the prevalence of diabetes has been steadily rising, reaching 6.9% in 2017 (3, 4). Compounding the problem, compared to Caucasian populations, Asian populations experience more severe complications and greater risk of premature mortality (4, 5). Furthermore, develops at an earlier age, meaning the absolute burden of disease is higher among younger populations in Asia (6).

In addition to the direct (healthcare-related) costs of diabetes, the indirect costs of diabetes are also significant. Indirect costs include work productivity losses, which can be measured through absenteeism (work day lost due to illness), presenteeism (impaired function at work due to illness), or labour force dropout (retirement before the official retirement age due to illness or premature death) (7, 8). The economic impact of productivity loss poses a burden to individuals, society and the country as a whole in terms of lost income earnings, tax revenue, and reduced gross domestic product (GDP) (9, 10). In 2017, an estimated US$89.9 billion was lost due to diabetes-related productivity losses in the US, including diabetes-related absenteeism (US$3.3 billion), presenteeism (US$26.9 billion), reduced labour force participation (US$37.5 billion), and diabetes related premature deaths (US$19.9 billion) (9). In Bangladesh in 2017, diabetes was the 8th highest cause of death and disability in the country (11). Diabetes also cost Bangladesh approximately US$5.3 billion in direct healthcare costs in 2014 (12).

A number of studies have examined the impact of diabetes on work productivity in high income countries (13), but not in low- and lower-middle income countries, which include Bangladesh. This information will inform investment in strategies to control diabetes and its complications. Thus, the aim of this study was to estimate the health impact of diabetes in the context of years of life, as well as the broader economic burden in terms of productivity-adjusted life years (PALYs) lost and their implications on GDP (13, 14) in low- and lower-middle income setting such as Bangladesh.

Research Design and Methods

Age (in five-year age groups) and sex specific life table models were constructed for the Bangladeshi population aged 20 to 59 years, with a follow-up until the official retirement age of 60 years (15), with estimation of years of life and PALYs lived. First, a life table model was developed to estimate these parameters for the Bangladeshi population of working age with diabetes. Then, the cohort was re-simulated with the hypothetical assumption that subjects did not have diabetes, with relevant changes to mortality, labour force participation and relative productivity (see below). The differences

between the two cohorts in terms of total years of life, and PALYs lived reflected the impact of diabetes. The key model inputs and their data sources are shown in supplemental Table S1. The World Health Organisation (WHO) standard 3% annual discount rate was applied to all future years of life and PALYs lived (16).

Population and mortality rates

The demographics of the model population were profiled using IDF estimates for 2017 (3). Data regarding diabetes prevalence, stratified by sex and five-years age groups were also derived from the 2017 IDF Diabetes Atlas (3). Sex and age specific mortality data for 2017 were retrieved from the Institute for Health Metrics and Evaluation (IHME)-Global Health Data Exchange (GHDx) database (17). Age and sex-specific mortality data for 2017 were extrapolated from the Urban Rural Epidemiology Study (CURES - 150) (18). These were attributed to those with and without diabetes was based on diabetes prevalence and the relative risk (RR). Based on an assumption that the mortality rate for a five-year age group applied to people in the midpoint of that age band, mortality rates for age in single years were derived using exponential functions (EMS Table 2). Temporal trends in population mortality across the model time horizon was projected using the average annual proportional reduction in adult mortality in Bangladesh (1.0% per year) from the United Nations World Population Prospects (UN WPP) forecast (19). Annual age and sex specific mortality rates were applied to the model in yearly cycles, with deaths assumed to have occurred at the mid-point of the year.

Labour force participation

Sex and age-specific labour force participation in Bangladesh were sourced from International Labour Organisation (ILO) estimates for 2017 (20). Labour force participation was lowest in men aged 20-24 years (74.5%) and in women aged 55-59 years (30.7%). The participation was highest in men aged 30-34 years (97.9%) and in women aged 35-39 years (49.2%).

Utility and productivity indices

Diabetes-related productivity loss was quantified in terms of productivity indices, which reflect relative work productivity impairment, and range from 0 (entirely unproductive) to 1 (entirely productive) (13, 14). Productivity indices were derived from estimates of labour force participation and absenteeism in people with diabetes compared to those without (21). Diabetes-related labour force drop-out was expressed as labour force participation percentage shortfall, and ranged from 7.0% in women and 5.2% in men with diabetes aged 20-29 years to 12.8% in women and 8.3% in men with diabetes over 40 years (21). These relative reductions were applied to 2017 the ILO gender and age-group specific population labour force participation rates to estimate labour force participation in

those with and without diabetes. All workers were assumed to be in equivalent full-time (EFT) employment due to the absence of data on division of the labour force into full and part-time employment.

To estimate PALYs lived by the cohorts, each year lived in the labour force by the cohort was multiplied by a productivity index derived from estimates of diabetes-related absenteeism (13, 14). This is akin to multiplication of years of life lived by utilities to derive QALYs (22). Absenteeism was defined as the number of lost work days per year due to diabetes and was expressed as a percentage of the total working days per year. These inputs were derived from primary data collected through a cross-sectional study in Bangladesh in 2017 (23), stratified by gender and five-year age groups. Absenteeism was estimated to be on average 4.1 days per year in men and 4.9 days in women. These represented 1.7% and 2.0%, respectively, of the 240 maximum working days per year in Bangladesh. Hence the productivity indices for men and women with diabetes were 0.983 and 0.980, respectively.

Data on GDP per worker were drawn from the World Bank database for 2018 and the figure was Tk701,062 (US$8,763) in Bangladesh in 2017 (24). We assumed that the economic value of each PALY was equivalent to annual GDP per worker, as per other studies (13, 14). We projected temporal trends in GDP across the model time horizon using the Organisation for Economic Co-operation and Development (OECD) long-term GDP forecasts (25). The World Health Organisation standard annual discount rate of 3% was applied to YLL and PALYs lived.

Sensitivity and scenario analyses

First, the individual contribution of absenteeism, labour force drop-out and premature mortality to productivity loss were calculated. Secondly, to assess the impact of uncertainty around diabetes-related mortality risk, productivity indices, and economic data inputs, deterministic sensitivity analyses were performed on the model to calculate PALYs lost in the Bangladeshi population with diabetes. These estimates included upper and lower 95% confidence intervals (CIs) around estimates of all-cause mortality associated with diabetes (26), and varying estimates of absenteeism and labour force drop out by 25% (21). Finally, scenario analyses were undertaken to explore other model assumptions: doubling the average annual reduction in mortality risk from the UN WPP (1.0% per year) to a 2% reduction per year; removing the temporal trend in mortality risk; doubling the annual GDP growth rate from 1.8% per year (OECD forecast average annual GDP growth rate) to 3.6% per year; removing the temporal trend in GDP per worker (24) ; and varying the annual discount rate of to 5% and 1.5% (16).

Results

In 2017, an estimated 6.9 million people (6.9%) aged between 20 years and 59 years in Bangladesh had diabetes. The prevalence of diabetes was 7.0% in women and 5.7% in men (Table 1).

Table 1: The age and gender-specific population and number of people living with diabetes in Bangladesh in 2017

	Men			Women		
Age group	**Population [a]**	**Prevalence of diabetes (%) [a]**	**Number of men with diabetes**	**Population [a]**	**Prevalence of diabetes (%) [a]**	**Number of women with diabetes**
20—24	7,862,660	1.8	142,542	7,621,330	3.1	235,700
25—29	7,312,030	2.7	197,467	7,357,770	4.2	308,150
30—34	6,796,110	3.9	267,674	7,028,330	5.6	391,801
35—39	6,118,590	5.5	339,234	6,367,610	7.2	458,686
40—44	5,211,850	7.4	387,166	5,294,190	8.9	472,611
45—49	4,626,430	9.4	433,997	4,591,970	10.5	482,417
50—54	4,012,750	11.1	445,988	3,923,260	11.7	458,192
55—59	2,962,960	12.3	365,906	2,818,620	12.3	345,557
Total	**44,903,380**	**5.7**	**2,579,975**	**45,003,080**	**7.0**	**3,153,114**

[a] Age and gender-specific population estimates and age and gender-specific prevalence of diabetes based on estimates by age and gender from the International Diabetes Federation Diabetes Atlas for 2017 (3).

Excess mortality and years of life lost to diabetes

The projected deaths in each five-year age and sex group are shown in Table 2. It was estimated that of the current working-age population followed up until retirement, there were 813,807 extra deaths due to diabetes, 304,682 among men and 509,125 among women. Over the modelled time horizon, 3.9 million years (5.5%) would be lost to diabetes, which equated to overall 0.7 years (for both in men and women) of life lost per person.

Table 2: Excess deaths and years of life lived in those with diabetes, and in the same cohort assuming no diabetes, over the working lifetime of the Bangladeshi population simulated from life table modelling

Age group	**Deaths in cohort with diabetes**	**Deaths in 'diabetes cohort' assuming no diabetes**	**Excess deaths in diabetes cohort**	**Years of life lived in cohort with diabetes**	**Years of life lived in 'diabetes cohort' assuming no diabetes**	**Years of life lost (%)**
Men						
20—24	30,555	14,932	15,623	3,220,724	3,274,155	53,431 (1.6)
25—29	43,782	21,160	22,622	4,096,295	4,186,292	89,997 (2.1)
30—34	61,053	28,957	32,096	4,984,404	5,132,967	148,563 (2.9)
35—39	78,945	36,266	42,679	5,492,587	5,722,470	229,883 (4.0)
40—44	90,752	39,439	51,313	5,193,160	5,514,858	321,698 (5.8)
45—49	90,204	40,391	49,813	4,610,903	4,870,686	259,784 (5.3)
50—54	76,201	35,218	40,982	3,306,543	3,458,901	152,358 (4.4)
55—59	33,603	15,868	17,735	1,339,258	1,372,462	33,204 (2.4)
Total	505,094	232,231	272,863	32,243,872	33,532,792	1,288,919 (3.8)

Age group	Deaths in cohort with diabetes	Deaths in 'diabetes cohort' assuming no diabetes	Excess deaths in diabetes cohort	Years of life lived in cohort with diabetes	Years of life lived in 'diabetes cohort' assuming no diabetes	Years of life lost (%)
Women						
20—24	51,703	17,955	33,748	4,948,710	5,021,949	73,239 (1.5)
25—29	69,989	23,854	46,135	5,822,208	5,938,666	116,458 (2.0)
30—34	91,734	30,327	61,407	6,454,351	6,634,683	180,332 (2.7)
35—39	109,996	34,592	75,404	6,277,909	6,535,570	257,660 (3.9)
40—44	114,967	33,217	81,750	4,950,391	5,275,494	325,103 (6.2)
45—49	103,412	30,790	72,622	3,432,044	3,649,764	217,720 (6.0)
50—54	77,001	22,168	54,833	3,395,268	3,397,913	2,645 (0.1)
55—59	31,236	8,575	22,662	1,696,908	1,738,891	41,982 (2.4)
Total	650,038	201,478	448,560	36,977,790	38,192,929	1,215,139 (3.2)
Total	**1,155,132**	**433,708**	**721,423**	**71,725,721**	**71,732,349**	**2,504,059 (3.5)**

Calculation of years of life lived were modelled in life tables with a half cycle correction and were subject to an annual discount rate of 3%.

Productivity-adjusted life years and quality-adjusted life years lost to diabetes

It was estimated that 9.2 million (20.4%) PALYs were lost due to diabetes, which equated to 1.6 PALYs lost per person (1.7 in men and 1.5 in women) (Table 3). Assuming a constant GDP per EFT worker of Tk701,062 (US$ 8763), the economic impact of productivity lost due to diabetes in Bangladesh would be Tk7.7 trillion (US$97.4 billion) loss in GDP. This is equivalent to an average GDP loss of Tk1,358,969 (US$16,987) per person with diabetes over the working lifespan.

Table 3: Productivity-adjusted life years (PALYs) lived in those with diabetes, and in the same cohort assuming no diabetes, over the working lifetime of the Bangladeshi population simulated from life table modelling

Age group	PALYs lived in cohort with diabetes	PALYs lived in 'diabetes cohort' assuming no diabetes	PALYs lost (%)	PALYs lost per person with diabetes
Men				
20—24	2,671,875	2,967,848	295,973 (10.0)	2.1
25—29	3,486,379	3,898,715	412,336 (10.6)	2.1
30—34	4,279,719	4,833,905	554,186 (11.5)	2.1
35—39	4,684,690	5,371,987	687,297 (12.8)	2.0
40—44	4,334,462	5,092,370	757,908 (14.9)	2.0
45—49	3,710,326	4,367,645	657,319 (15.0)	1.5
50—54	2,528,227	2,974,315	446,088 (15.0)	1.0
55—59	958,753	1,117,325	158,572 (14.2)	0.4
Total	26,654,431	30,624,110	3,969,679 (13.0)	1.5
Women				
20—24	1,456,552	1,936,201	479,649 (24.8)	2.0
25—29	1,765,396	2,390,714	625,318 (31.7)	2.0
30—34	1,954,412	2,713,980	759,568 (32.9)	1.9
35—39	1,842,080	2,650,325	808,245 (34.6)	1.8
40—44	1,360,367	2,068,313	707,946 (37.3)	1.5
45—49	840,444	1,339,904	499,460 (38.8)	1.0

Age group	PALYs lived in cohort with diabetes	PALYs lived in 'diabetes cohort' assuming no diabetes	PALYs lost (%)	PALYs lost per person with diabetes
50—54	672,063	1,108,213	436,149 (37.3)	1.0
55—59	389,432	618,867	229,435 (37.3)	0.7
Total	10,280,746	14,826,517	4,545,771 (30.7)	1.4
Total	**36,935,177**	**45,450,627**	**8,515,450 (18.7)**	**1.8**

Notes: Calculation of PALYs were modelled in life tables and subject to an annual discount rate of 3%.

Sensitivity and scenario analyses

Figure 1 shows the contribution of labour force drop out, mortality and absenteeism to diabetes-related productivity loss. Labour force drop-out (64.9%) was the major contributor to productivity loss followed by mortality (26.8%) and absenteeism (8.3%). Accordingly, the majority of costs associated with productivity losses were caused by diabetes-related labour force drop out (Tk5.1 trillion, US$63.2 billion) followed by mortality (Tk2.1 trillion, US$26.1 billion) and absenteeism (Tk648 billion, US$8.1 billion). The proportion of PALYs lost to diabetes-related mortality and absenteeism were higher in men (37.0% and 10.2%, respectively) than women (18.0% and 6.7%, respectively), while the proportion of PALYs lost to labour force drop-out was higher in women (75.2%) than in men (52.8%).

Figure 1: Economic burden of productivity loss in those with diabetes due to diabetes-related absenteeism, premature mortality and labour force drop out over the working lifespan in the Bangladeshi population

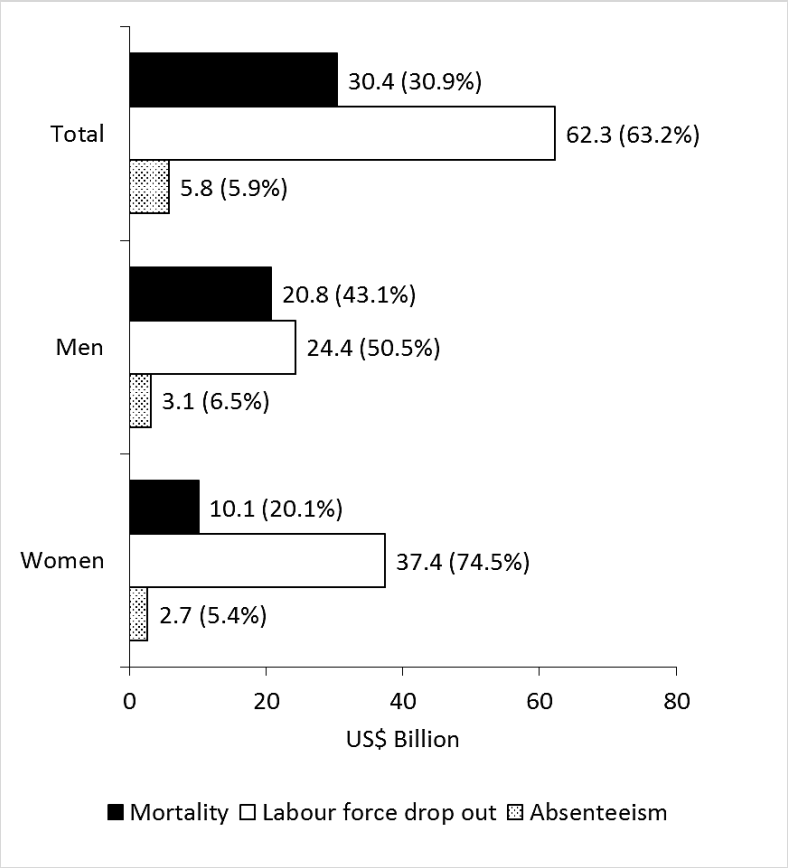

Table 4 includes sensitivity and scenario analyses. The model was sensitive to a number of inputs such as productivity indices, diabetes-related labour force drop-out, and mortality risk, and model assumptions including temporal trends in mortality risk and the annual discount rate. The PALYs lost to diabetes were reduced by 5.4% and increased by 1.6%, respectively using the upper and lower uncertainty bounds of absenteeism estimate compared to the base case. At the hypothetical 25% change of diabetes-related labour force drop-out, PALYs lost changed in the same direction by 16.7% Applying the upper and lower bounds of 95% CI around estimates of all-cause mortality risk associated with diabetes, PALYs lost were increased by 20.5% and decreased by 8.7%, respectively.

In scenario analyses, the annual reduction in population mortality risk to 2% and removal of the temporal trends in population mortality risk resulted +/-1.2% change in PALYs lost. Doubling the annual GDP growth rate to 3.6% lead to an increase in the estimate of GDP lost to Tk9.0 trillion (US$112.9 billion), while removing all temporal trends in GDP decreased the estimate of GDP lost to Tk6.6 trillion (US$81.9 billion). Finally, altering the annual discount rate to 5% and 1.5% corresponded to a 17.1% reduction in PALYs lost and a 17.3% increment in PALYs lost, respectively (Table 4).

Table 4: Sensitivity and scenario analyses to assess the impact of the uncertainties around productivity, mortality and economic data inputs on Productivity-adjusted life years (PALYs) lost in those with diabetes in the Bangladeshi population and the associated economic impact

	PALYs lost due to diabetes	% change in PALYS lost compared to base case	GDP lost (USD$ billion)	GDP lost per person with diabetes (USD$)
Base case	8,515,450		89.0	18,061
1. Productivity indices upper uncertainty bound [a]	8,006,695	-5.97	83.8	17,005
2. Productivity indices lower uncertainty bound [a]	8,662,166	+ 1.7	90.5	18,362
3. Labour force drop out upper uncertainty bound [b]	6,938,986	-18.5	73.1	14,835
4. Labour force drop out lower uncertainty bound [b]	10,091,914	+18.5	104.9	21,286
5. Upper uncertainty bound of all-cause mortality risk associated with diabetes [c]	11,159,921	+31.1	118.0	23,929
6. Lower uncertainty bound of all-cause mortality risk associated with diabetes [c]	8,466,438	-0.58	88.6	17,965
7. Temporal trend in population mortality risk is doubled to a 2% reduction per year [d]	8,432,686	-1.0	88.1	17,868
8. No temporal trend in population mortality risk [d]	8,610,128	+1.1	90.1	18,281

	PALYs lost due to diabetes	% change in PALYS lost compared to base case	GDP lost (USD$ billion)	GDP lost per person with diabetes (USD$)
9. Annual GDP growth rate is doubled to 3.6% per year [e]			102.8	20,846
10. No temporal trend in GDP [e]			75.3	15,275
11. Annual discount rate increased to 5% [f]	7,117,931	-16.5	72.8	14,762
12. Annual discount rate reduced to 1.5% [f]	9,923,170	+16.5	105.8	21,469

a Sensitivity analysis 1 & 2 apply (1) a 25% reduction and (2) a 25% increase in absenteeism estimate, holding all other model inputs constant

b Sensitivity analysis 3 & 4 apply (3) a 25% reduction and (4) a 25% increase in diabetes-related labour force drop out estimates, holding all other model inputs constant

[c] Sensitivity analysis 5 & 6 apply (5) the lower bound of the 95% confidence interval and (6) the upper bound of the 95% confidence interval around the estimate of relative risk of all-cause mortality associated with diabetes, holding all other model inputs constant

[d] Scenario analysis 7 & 8 apply (7) double the annual reduction in mortality risk to 2% per year and (8) no temporal trend in population mortality risk, holding all other model inputs constant

[e] Sensitivity analysis 9 & 10 apply (9) double the annual growth rate in GDP to 3.6% per year and (10) no temporal trend in GDP across the model, holding all other model inputs constant. These sensitivity analyses do not affect the number of PALYs lived but do affect their assumed value and therefore the resulting GDP lost

[f] Sensitivity analysis 11 & 12 apply an annual discount rate (11) increased to 5% (in line with the WHO standard annual rate) and (12) reduced to 1.5%.

Discussion

This study highlights that diabetes would lead to a significant reduction in years of life lived and productivity when projected among a cohort of working age Bangladeshi population with diabetes. Assuming a follow-up of this population until the retirement age an estimated 0.8 million excess death, loss of 4.0 million life years (5.5%) and 9.2 million PALYs (20.4%) were expected due to diabetes.

The productivity loss attributable to diabetes represents a combined effect of premature mortality, diabetes-related labour force drop-out and absenteeism during the working lifespan. Over the working lifespan of the diabetes cohort, higher all-cause mortality risk in those with diabetes resulted in a 5.5% reduction in years of life lived and was almost similar in men and women. This is consistent with the previous study conducted in India (18) but is contrary to the findings of a study conducted in China showing higher mortality risk in working age Chinese men than women (27). The relative impact of diabetes on years of life lost was higher among younger people due to their longer working lifespan, though the prevalence of diabetes among younger age groups was lower.

Traditional health economic analyses evaluate the cost-effectiveness of health interventions in terms of net costs per year of life saved or QALY saved (28, 29), but they have no inherent financial value. This study estimates showed that the loss of productivity, measured in terms of PALYs, among the working population has economic implications as it can be ascribed a financial value. The results of

our modelling estimate the loss of over 9.2 million PLAYs in those with diabetes, or 1.6 PALYs per person, over a working lifespan. The average number of PALYs lost (1.6) per person with diabetes in Bangladesh was higher than that reported in recent studies conducted in Australia (1.4) and China (1.3) (13, 30). The retirement age for men in Bangladesh is similar to men in China but for women it is five years higher than women in China (30). Compared to Australia, a high-income country, retirement age in Bangladesh is 10 years lower in both gender (13), people living with diabetes in Bangladesh incurred higher productivity losses over a shorter timeframe compared to the Australian population. Additionally, greater productivity loss would be borne by younger people as with years of life lost due to diabetes, in proportional terms, is greater for them. This reflects the higher mortality risk and labour force drop out in Bangladesh compared to Australia (13). Our model did not account the direct cost of diabetes and thus, if considered the broader economic burden of diabetes in Bangladesh could be multi-fold higher than the current estimates, which is mirrored in previous studies (9, 21).

The most recent study conducted in Bangladesh showed that 40% of people with type 2 diabetes had the disease before the age of 40 years (31). This study showed that the relative impact of diabetes on productivity loss was greater in younger people, reflecting the greater cumulative losses associated with early onset diabetes. The absolute number of PALYs lost was greater in men (1.7) than in women (1.5). This is because the higher labour-force participation of men than women in Bangladesh (20), that cause higher diabetes-related productivity losses among men. However, the relative reduction in productivity due to diabetes was higher in women (32.5%) than men (14.5%), driven by higher labour force drop outs (75.2% in women vs 52.8% in men). There is evidence of an employment shortfall in people with diabetes compared to those without diabetes (9, 32, 33). Results from studies in the US showed that diagnosis of diabetes was associated with approximately double the labour force participation shortfall and compared to men with diabetes, more work days lost in women with diabetes (34, 35).

We estimated an average GDP loss of Tk 1,358,969 (US$16,987) per person with diabetes over the working lifespan. According to Islam et.al, Bangladesh spends a much lower percentage (3.5%) of its GDP on health compared to neighbouring counties like Maldives (10.8%) or countries with similar economic status like South-Africa (8.9%) and Tanzania (7.3%) (36). Nevertheless, allocating funds to health care and money spent on prevention strategies may yield a better return on investment. If the amount representing GDP lost to diabetes over the working lifespan in the current diabetes cohort in Bangladesh was directed to prevention of diabetes, this could be viewed as an ‘investment’ rather than as an ‘expenditure’, as financial benefits would accrue not only from work productivity gains, but also reductions in direct costs of diabetes treatment and management. Acknowledging that

diabetes is not 100% preventable, if even 10% of diabetes was prevented, Tk 135,89 (US$1,698) could be spent per working age person as, at least, a break-even investment.

This study quantifies the macroeconomic burden of diabetes-related lost productivity using contemporary age- and gender-specific estimates of diabetes prevalence by the IDF, mortality risk, and labour force participation (3). The major strength of the study is, we used PALYs to calculate productivity losses. PALYs are able to ascribe a financial value in terms of GDP and net costs. PALYs represent a useful measure alongside QALYs which require the calculation of incremental cost-effectiveness ratios to estimate the impact of health interventions. Strengths of our study include the use of productivity indices and utility values which were stratified by age, gender, and the type of work that people undertake and were sourced from a study conducted on Bangladeshi population, thus, estimates of the impact of diabetes on the productivity of specific subgroups were more precise and are generalisable to the total Bangladeshi population. In addition, we used contemporary age-group and gender-specific estimates of diabetes prevalence, mortality risk, labour force participation and in-work productivity, which can inform the targeting of interventions. Life table modelling allowed us to capture the impact of diabetes-related productivity losses across the working lifespan.

Life table modelling is a well-recognized tool used in epidemiological and demographic studies but is subject to uncertainty and this is one of the limitations of the study. The uncertainty around productivity indices was explored in sensitivity and scenario analyses and found that the developed model was more sensitive to variation in labour force drop out (±16.7%) while varying absenteeism by 25% had a minimum effect on estimates of PALYs lost (+1.6%, -5.4%). Our model did not account for the large proportion of people (56%) who are unaware of the presence of diabetes (37). Thus, these results may be considered an underestimation of the effect of diabetes on work productivity as diabetes could still exert an impact in those with undiagnosed diabetes. We also assumed that current projections in temporal trends in mortality rates and GDP growth held true across the model time horizon. However, in scenario analyses, the doubling and removal of the trend in population mortality rates affected the model output by <2%, although estimates of GDP lost were more sensitive to the equivalent changes in GDP growth rate. The contribution of comorbidities of diabetes such as obesity and hypertension to productivity loss could not be distinguished from these estimates. Due to the absence of available data, an assumption was made that work will relate to paid employment and the population worked full-time, and no attempt was taken for unpaid and part-time workers. Furthermore, diabetes might impact on GDP in ways other than through productivity losses (8, 10). While these limitations may affect the current estimates of our model, the overall conclusion of the study is unlikely to be changed.

Conclusion

Diabetes creates a substantial burden on the Bangladeshi population, not only in terms of health and well-being, but also in terms of lost productivity. By quantifying the economic burden of diabetes in terms of missed production opportunities, rather than health expenditure only, our findings highlight the importance of prevention, treatment, and adequate control of diabetes in Bangladesh as an investment. An economic payoff through gains in productivity can be achieved by interventions aimed to prevent and adequately control diabetes. Future studies should aim to describe the dynamics of the balance between the economic benefits arising from productivity gains and the greater investment in prevention and health services for diabetes.

Conflict of interest

The authors declare that there are no conflicts of interest associated with this manuscript. The interpretation and conclusions contained in this study are those of the authors alone.

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Electronic Supplementary Material (ESM)

ESM Table 1: Description and source of data used as inputs for life table models.

Model input and description	Data source
Population:	
The 2017 population of Bangladesh, stratified by gender and 5-year age groups	International Diabetes Federation: IDF Diabetes Atlas (8th edition) (1).
Diabetes Prevalence:	
Prevalence of T2Dm in Bangladesh in 2017, stratified by gender and 5-year age group	International Diabetes Federation: IDF Diabetes Atlas (8th edition) (1).
Mortality rates:	
Mortality rate in the 2017 population of Bangladesh, stratified by gender and 5-year age groups	IHME-Global Health Data Exchange (GHDx) database (2)
Temporal trends in population mortality rate	Projected average annual proportional reduction in adult mortality in Bangladesh (1.0%) from the United Nations (UN) World Population Prospects (WPP) forecast.(3)
Relative risk (RR) of all-cause mortality associated with diabetes	The Chennai Urban Rural Epidemiology Study (CURES - 150) of adults with diabetes. (4)
Population Labour force participation: Labour force participation in Bangladesh in 2017, stratified by gender and 5-year age groups	International Labour Office: ILO Labour force estimates and projections: 1990-2030.(5)
Diabetes-related productivity losses:	
Productive time loss due to diabetes in 2017, stratified by gender and 5-year age groups	Primary data collected from a cross-sectional survey among Bangladeshi population with diabetes in 2017.
Labour force participation shortfall and absenteeism in those with T2DM	Bommer et al. The global economic burden of diabetes in adults aged 20–79 years: a cost-of-illness study. The Lancet Diabetes & Endocrinology 2017;5:423-430.(6)
Gross Domestic Product (GDP):	
The GDP and GDP per effective full-time (EFT) Bangladeshi worker in 2017.	International Labour Organization, ILOSTAT database. Data retrieved in September 2018. (https://data.worldbank.org/indicator/SL.GDP.PCAP.EM.KD?locations=BD&view=chart) The World Bank: World Development indicators, 2017.(7)

Temporal trends in GDP growth rate	Organisation for Economic Co-operation and Development (OECD) long-term GDP forecasts (8).

ESM Table 2: Annual mortality rate in the total population, those with diabetes and those without diabetes in Bangladesh in 2017 by age group and sex based on the GBD 2017 (1)**.**

Age group	Mortality rate in the total population per person year	Mortality rate among people without diabetes per person year	Mortality rate among people with diabetes per person year
Men			
20-24	0·00074	0.00067	0.00501
25-29	0·00088	0.00078	0.00451
30-34	0·00115	0.00100	0.00468
35-39	0·00142	0.00123	0.00474
40-44	0·00223	0.00191	0.00626
45-49	0·00382	0.00326	0.00925
50-54	0·00679	0.00583	0.01452
55-59	0·01131	0.00922	0.02617
Women			
20-24	0·00078	0.00058	0.00704
25-29	0·00087	0.00065	0.00599
30-34	0·00087	0.00064	0.00474
35-39	0·00119	0.00087	0.00526
40-44	0·00201	0.00147	0.00750
45-49	0.00253	0.00187	0.00818
50-54	0.00532	0.00400	0.01527
55-59	0·00748	0.00529	0.02315

Calculation of annual mortality rates in those with and without diabetes in the Bangladeshi population by age group and sex was based on the following formula:

*MortNon-diabetes = MortTotal / (DiabetesPrevalence*RR+(1-DiabetesPrevalence))*

The mortality rate for those with diabetes were based on the following formula:

*MortDiabetes = MortNon-diabetes*RR*

Where:
MortTotal = total deaths in population/total population

MortDiabetes = mortality rate in those with diabetes

MortNon-diabetes = mortality rate in those without diabetes

RR=relative rate of all-cause mortality in those with diabetes compared to those without diabetes

Average annual proportional reduction in adult mortality in Bangladesh (1.0% per year) from the United Nations (UN) World Population Prospects (WPP) forecast,[4] was applied progressively across the model time horizon.

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Chapter 9

DISCUSSION AND CONCLUSION

9.1 Overview of the Main Findings

This thesis has five main objectives: first, to estimate the COI for T2DM in Bangladesh; second, to assess the influence of complications on total cost and hospitalisation; third, to find the prevalence of glycaemic control and its associated factors among people with T2DM; fourth, to find the prevalence of macrovascular and microvascular complications and explore their associated factors, as well as to develop a risk scoring tool for CVD as it was found to be the most prevalent and cost-incurring complication among the Bangladeshi T2DM population; and finally, to use a life table model to estimate the impact of diabetes on lost productivity in Bangladesh. There are five individual chapters in this thesis, each of which presents the study findings related to each of the objectives. The key findings of each chapter are summarised below.

9.1.1 Cost-of-illness of type 2 diabetes mellitus in Bangladesh

Chapter 4 shows that of the average annual cost of US$865 for a person with T2DM in Bangladesh, the medicine cost was the highest contributor followed by the hospitalisation cost. Patients who had a history of hospitalisation had a 4.2-fold higher average annual cost than those without hospitalisation. The average annual cost for each person with T2DM in Bangladesh appears to be considerably higher than in the neighbouring countries (1, 2) but lower than in the high- or upper-middle-income countries (3, 4) in Asia.

We investigated the contribution of several demographic and clinical factors to the average annual cost. Consistent with a previous study (5), the finding of this study showed that older age and being female were more likely to incur higher cost. This may be due to the fact that females had better awareness about diabetes and attended more regular follow-up check-ups (6). Urban residents spent more than rural residents, which may be due to the fact that urban residents have higher income and therefore are more able to afford the cost of treatment. The results also showed that 13.5% of participants had income less than the estimated average annual cost, which creates a notable financial burden for a family as almost all expenses were OOP in Bangladesh.

Chapter 4 also shows that the direct cost had the largest share (90.5%) of the overall cost. Among all the cost components of the overall direct cost, the medicine cost was the major contributor (60.7%). This finding is similar to those of the studies conducted in Pakistan (2) and India (1). Better adherence to medication, higher percentage of insulin users and high cost of insulin may be the reasons for the high medicine cost, which makes it the main contributor. Furthermore, presence of comorbidity and complication were identified as significant cost contributors that emphasise the importance of optimisation of the management of diabetes-related complications and comorbidities. The cost of

diabetes care was found to be increased with the increasing duration of diabetes, which adds multiple complications and comorbidities, making the disease condition more critical.

The estimated average annual cost of US$864.7 per person with T2DM is 52% of per capita GDP of Bangladesh (7) and 9.8-fold higher than the general healthcare cost (8). Therefore, this chapter of thesis highlights the importance of the development and improvement of interventions for better control of T2DM and the prevention of its complications to avoid the threat to healthcare financing.

9.1.2 Burden of type 2 diabetes-related complications on hospitalisation and healthcare cost

Chapter 5 of this thesis reported the burden of macrovascular and microvascular complications on hospitalisation and healthcare cost among people with T2DM in Bangladesh. The key finding of this chapter was that 63.4% of participants had complications, of which 14.8% had macrovascular complications, 20.7% had microvascular complications and 27.9% had both. The cost of diabetes care is significantly associated with the level of complications that lead to hospitalisation. In this study, the OPD cost was significantly higher for patients with the presence of CAD, nephropathy and retinopathy as these patients required frequent OPD follow-ups. Furthermore, the hospitalisation cost was higher for patients with stroke and nephropathy, which may be due to the fact that these complications are related to higher treatment and prolonged hospital stay costs.

The findings of this study in chapter 5 also show that patients under the insulin mode of treatment were more prone to be hospitalised and thus incurred higher cost than those treated with an oral hypoglycaemic agent only. This may be due to the fact that the higher cost of insulin increases the spending for patients using insulin with a combination of OHA. Moreover, patients are generally prescribed insulin with or without a combination of OHA when the monotherapy fails to maintain the blood glucose that requires multiple modalities of treating hyperglycaemia or they have multiple complications that makes them prone to hospitalisation. As described in previous studies (9, 10), this study also shows that patients with the presence of any complication experienced almost double the healthcare cost of those without any complication. Furthermore, the cost increased considerably as the number of complications increased and it was 3-fold higher for patients with the presence of both macrovascular and microvascular complications than for patients without any complication. The number and severity of complications increased the likelihood of hospitalisation that boosts the cost increment, which is also evident in the literature (11-14).

All these findings indicate that people with T2DM in Bangladesh should be under the coverage of screening and monitoring programs on a regular basis to avoid T2DM-related complications. These programs should be subsidised by the government as the patients are paying all the costs OOP and

more than 12% of households in the country have to borrow money or sell household assets to pay healthcare costs related to chronic diseases (15).

9.1.3 Glycaemic control: an important aspect of diabetes management

Glycaemic control, which is considered as the main therapeutic goal for prevention of the injurious effects of hyperglycaemia and its consequences, has been described in chapter 6. The key results of the study in chapter 6 show that 81.8% of the study participants did not achieve the recommended HbA1c target of lower than 7% and 54.7% showed very poor control (HbA1c ≥9%). This finding is consistent with the findings of previous studies conducted in Bangladesh (16, 17).

In this chapter, we also widened the investigation to the factors related to poor glycaemic control and how the identified factors play a role in different durations of T2DM. Consistent with the literature (16, 18-21), the non-modifiable factors of female gender, low level of education and rural residence were found to be associated with uncontrolled glycaemic level.

Smokeless tobacco consumption, which is very common in South Asian countries, was found to be associated with uncontrolled glycaemic level for participants with shorter duration (≤5 years) of T2DM. Furthermore, a relationship was identified between unhealthy eating habits, infrequent follow-up check-ups and poor glycaemic control. These findings highlight the importance of active and individualised education intervention to motivate patients to eat healthily, attend frequent follow-up check-ups and avoid smokeless tobacco consumption.

The results of this study also showed that insulin use and history of CVD were associated with poor glycaemic control. The insulin users are expected to have better control, which is contradictory to our findings. This reinforces the need for further research to determine why a large proportion of insulin users have uncontrolled diabetes in Bangladesh. Furthermore, the findings highlight the need for optimisation of CVD management. Another important finding of this study was the association between impaired cognitive function and poor glycaemic control, which is evident in the context of developed countries (22-24) but no similar data was found in the context of developing countries, including Bangladesh.

The identified associated factors will help healthcare providers to individualise the choice of glycaemic goals in reference to duration of diabetes. This goal individualisation will significantly aid in improving patient care and health outcomes.

9.1.4 Type 2 diabetes-related macrovascular and microvascular complications: risk factors and risk scoring system

There are few studies on the prevalence of macrovascular and microvascular complications of T2DM in Bangladesh in the literature, which has been addressed in one (7a) of the studies included in chapter 7. Another study (7b) in which we developed a risk scoring tool for CVD for people with T2DM in Bangladesh was also included in chapter 7.

The key results of Study 7a showed that the prevalence of macrovascular complications of CAD, stroke and diabetic foot was 30.5%, 10.1% and 12% respectively, while the prevalence of microvascular complications of nephropathy, neuropathy and retinopathy was 34%, 5.7% and 25.1% respectively. Several modifiable and non-modifiable factors of female gender, higher age, lower education level, urban area of residence, higher household income, smoking, physical inactivity, hypertension, poor glycaemic control, poor adherence to treatment, longer duration of diabetes, and insulin use were identified to be associated with one or more of the macrovascular and microvascular complications.

Study 7b aimed to develop a risk scoring tool for CVD (CAD and stroke) in people with T2DM in Bangladesh. The bootstrap method was used for the model development and validation, which is recommended for a relatively small sample (25) as opposed to the traditional split-sample method (26). In this study, the risk scoring tools for CAD and stroke were developed separately using the BROC method, which improves the parsimony and prediction performance of the model compared to automated and other variable selection methods (27-29). The developed risk scoring systems with their high calibration and discrimination powers are the simplest and most easily applicable tools in daily practice.

The developed CVD risk scoring tool will support clinicians in motivating and educating the patients for better managing the disease. Furthermore, it could potentially assist policy makers in developing conservative health policies and risk prevention approaches such as diet and lifestyle modifications, which were identified to be associated with CAD and stroke in the Bangladeshi T2DM population.

9.1.5 Evaluation of the impact of diabetes on the economy of Bangladesh

The impact of diabetes in terms of mortality, years of life lost and PALYs lost in Bangladesh is described in the study included in chapter 8. In 2017, the prevalence of diabetes was 6.9% (6.9 million people aged 20-59 years) in Bangladesh. Assuming a follow-up of this population (aged 20-59 years) until a retirement age of 60 years, an estimated 0.8 million excess deaths, and loss of 4.0 million life years (5.5%) and 9.2 million PALYs (20.4%) were attributable to diabetes. This was equivalent to

0.7 years of life, and 1.6 PALYs lost per person. The loss in PALYs equated to a total of US$97.4 billion lost (US$16,987 per person) in GDP.

Bangladesh spends a much lower percentage (3.5%) of GDP on health than the neighbouring counties such as Maldives (10.8%) and countries with a similar economic status like South Africa (8.9%) and Tanzania (7.3%) (30). However, allocating funds to healthcare and money spent on prevention strategies should be perceived as an investment rather than expenditure.

The results of our study highlight that the prevention of diabetes and diabetes complications is vitally important from both an economic perspective and a health perspective. Investment in the management of disease such as diabetes, which is highly prevalent and consequential will be of paramount importance, especially in developing countries where the diabetes prevalence is rising at a much more rapid rate in the working-age population than in developed countries (31). An economic pay-off through gains in productivity can be achieved by interventions aimed at the prevention and adequate control of diabetes.

9.2 Strengths and limitations

The strengths and limitations pertaining to each of the studies presented as individual publications are summarised in the respective sections. Therefore, here, I will discuss the limitations and key strengths of this thesis in general, as all the studies were sourced from the same dataset except study eight, where some secondary data sources were used.

Chapter 4 to 7b are based on the cross-sectional survey that was conducted between March and September 2017 in Bangladesh. The cross-sectional nature of the study may not provide reliable insights on temporal relationships; however, it has uncovered many important aspects of T2DM in Bangladesh that helped to fill the gaps in the current literature. Furthermore, the developed risk scoring tool described in study 7b needs the inclusion of prospective measurements which may further refine the models that identified the associated factors of CVD. To find out potential risk factors for one complication; other complications (CAD, Diabetic foot, Stroke) from the same patients were used in the model. Therefore, there is a potential risk of multiplicity, which has not been addressed in this thesis. Study 8 was based on a life table model, a simple and recognised tool used in epidemiological and demographic studies that has its inherent limitation of uncertainty and was explored in sensitivity analyses.

In contrast, the recruitment of participants and the information collection procedures using web-based software ensured data quality. Data collection from six hospitals affiliated with BADAS, the largest diabetes care provider in the country, supported the recruitment of a heterogenous professional-mixed population residing in rural-urban locations. Furthermore, it increased the likelihood of the

generalisability of the findings to people with T2DM attending hospitals affiliated with BADAS across the country.

9.3 Implications and Future Research Directions

The studies that have been included in this thesis have several clinical and public health implications and, suggestions for future research directions, which are described below.

9.3.1 Clinical implications

This thesis has provided substantive evidence on the average cost of T2DM care, the clinical and economic burden of T2DM-related complications, factors associated with macrovascular and macrovascular complications and the current scenario of glycaemic control among the Bangladeshi T2DM population. The clinical implications specific to each study are listed below:

1. Study 4 provided the most up-to-date information on the economic burden incurred by T2DM in Bangladesh which is supportive for both patients and clinicians in identifying and quantifying the costs attributed to T2DM.
2. Study 5 highlighted the most cost contributing T2DM related complications that will help clinicians to be more focused on these complications while treating and managing patients with T2DM.
3. The high prevalence of inadequate glycaemic control estimated in study 6 emphasised the need for regular monitoring and counselling to prevent long-term diabetes complications. Furthermore, the identified modifiable factors of inadequate glycaemic control highlighted the importance of being compliant with follow-up check-ups and lifestyle modifications to control or delay the onset of long-term complications.
4. Study 7a demonstrated that CAD among macrovascular and nephropathy among microvascular complications were the most prevalent and thus need the highest attention of the clinicians during patient follow-up and treatment. Moreover, the findings of this study highlighted the need for lifestyle modification by identifying the modifiable factors of complications. The developed risk scoring tools for CAD and stroke, in study 7b, can aid clinicians to educate and motivate patients. Also, patients can use this tool to calculate their risk of complications and hence adapt better management strategies for prevention. This will help patients in reducing their long-term economic burden.
5. The substantial burden quantified through the life-table model in study 8 highlighted the importance of prevention, treatment, and adequate control of diabetes in Bangladesh.

9.3.2 Public health policy implication

The outcome of this thesis has important implications for health service planners and policy makers in Bangladesh regarding the prevention and control of T2DM. One of the major implications of this thesis is that the identified cost contributors of T2MD care will help public health policy makers to prioritise and allocate the scarce healthcare resources of a country like Bangladesh. We recommend that policy makers, the government and healthcare providers focus on improving the understanding of modifiable risk factors that are associated with various T2DM-related complications and glycaemic control. Thus, they may able to develop and improve tailored and complication specific strategies in advocating a diabetes management plan. They should pay special attention to the complications that are the highest cost contributors and develop cost-effective health strategies to maximise health outcomes for the T2DM population in Bangladesh.

The developed risk scoring tool will help to manage adverse disease progression and thus aid in reducing long-term treatment expenditure. Furthermore, the findings of the developed economic model will assist public health policy makers in designing effective public health strategies regarding the control and prevention of diabetes to avoid the burden in the long-term.

9.4 Future Research Directions

Bangladesh belongs to the IDF Southeast Asia region, which is considered as the epicentre of the diabetes epidemic. There is a huge gap in the literature regarding several important aspects of T2DM in Bangladesh. This thesis has been designed to fill the gaps in the literature and at the same time, to make some suggestions regarding future research directions to overcome its limitations. The cross-sectional design of this project may able to identify the plausible factors but unable to establish the temporal relationship with the outcome, which requires longitudinal cohort studies. We recommend the inclusion of prospective measurements in the development of a risk scoring system to refine the current developed tool for CVD and that complications of T2DM other than CVD should be considered in future risk prediction model development. Furthermore, future studies should aim to describe the dynamics of the balance between the economic benefits arising from productivity gains and the greater investment in prevention and health services for diabetes.

9.5 Conclusion

Prevention, treatment and adequate control of T2DM and its consequences are of paramount importance, especially in developing countries like Bangladesh where diabetes prevalence is rising much more rapidly than in developed countries. This doctoral thesis addressed several important gaps in the literature within the scope of cost-of-illness, the influence of complications on total cost, glycaemic control and its associated factors, the prevalence and factors related to macrovascular and

microvascular complications, risk scoring tool development and the impact of diabetes on the economy of Bangladesh. The insights drawn from this thesis may prove useful to policy makers, clinicians and patients alike to gain an understanding of the magnitude of the disease, effective policy development for better management of the disease and ideal use of scarce healthcare resources.

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APPENDICES

Appendix 1 Ethics Approval Certificate

Monash University Human Research Ethics Committee

Approval Certificate

This is to certify that the project below was considered by the Monash University Human Research Ethics Committee. The Committee was satisfied that the proposal meets the requirements of the *National Statement on Ethical Conduct in Human Research* and has granted approval.

Project Number: 1469
Project Title: COST-OF-ILLNESS AND ITS DETERMINANTS FOR TYPE 2 DIABETES MELLITUS IN BANGLADESH
Chief Investigator: Mr Md Billah
Expiry Date: 15/12/2021

Terms of approval - failure to comply with the terms below is in breach of your approval and the *Australian Code for the Responsible Conduct of Research*.

1. The Chief Investigator is responsible for ensuring that permission letters are obtained, if relevant, before any data collection can occur at the specified organisation.
2. Approval is only valid whilst your hold a position at Monash University.
3. It is responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by MUHREC.
4. You should notify MUHREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. The Explanatory Statement must be on Monash letterhead and the Monash University complaints clause must include your project number.
6. Amendments to approved projects including changes to personnel must not commence without written approval from MHUREC.
7. Annual Report - continued approval of this project is dependent on the submission of an Annual Report.
8. Final Report - should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected completion date.
9. Monitoring - project may be subject to an audit or any other form of monitoring by MUHREC at any time.
10. Retention and storage of data - The Chief Investigator is responsible fo the storage and retention of the original data pertaining to the project for a minimum period of five years.

Thank you for your assistance.

Professor Nip Thomson

Chair, MUHREC

CC: Assoc Professor Dianna Magliano, Ms Afsana Afroz, Dr Khurshid Alam

Appendix 2 Consent From

MONASH University

CONSENT FORM

(Participants with type 2 diabetes in Bangladesh)

Project: Cost-of-illness and its determinants for type 2 diabetes in Bangladesh

Chief Investigator:

Dr Md Baki Billah
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I have been asked to take part in the Monash University research project specified above. I have read and understood the Explanatory Statement and I hereby consent to participate in this project.

I consent to the following:	Yes	No
I agree to be interviewed to fill up a questionnaire which includes personal and health related information.	☐	☐
I agree to have my height, weight, blood pressure and circumference of neck, waist and hip to be measured and recorded.	☐	☐
I agree to have my medical records to be reviewed by the interviewer to collect information related to diabetes including laboratory investigations, diabetes related complications and medications.	☐	☐

I understand that my participation is voluntary, and I have the right to withdraw my participation at any stage of the interview without any penalty.

I understand that the information collected from me and from my medical records are confidential and will be kept in a secure storage accessible by the research team only. I also understand that the recorded information held by the university will be destroyed securely after 5 years from the completion of the study.

I understand that any report from this project will contain un-identifiable group data only and will not be disclosed in any report or to any other party.

Name of Participant _____

Participant Signature _____ Date _____

Appendix 3 Explanatory Statement

MONASH University

EXPLANATORY STATEMENT

(Participants with type 2 diabetes in Bangladesh)

Project: Cost-of-illness and its determinants for type 2 diabetes mellitus in Bangladesh

Chief Investigator:

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Student Investigator:

Afsana Afroz
Department of Epidemiology and Preventive Medicine
Faculty of Medicine, Nursing and Health Sciences
Monash University
Phone : +61 048 185 9004
Email: afsana.afroz@monash.edu

You are invited to take part in this study. Please read this Explanatory Statement in full before deciding whether or not to participate in this research. If you would like further information regarding any aspect of this project, you are encouraged to contact the researchers directly or via the phone numbers or email addresses listed above.

What does the research involve?

The purpose of this study is to estimate the economic burden of type 2 diabetes mellitus in Bangladesh and to find association between glycaemic control and Health Related Quality of Life with cost-of-illness.

The study results will help to forecast the economic burden of diabetes mellitus in Bangladesh which will be invaluable for policy makers to formulate strategies at a national level. Furthermore, the results can be used as a financial tool for cost control and disease management for individuals.

Upon your agreement to participate in this study, the interviewer will:

1- Request you to read and sign the consent form. If you are unable to read or sign, a data collector will communicate the information in this statement to you and a finger print will suffice as a replacement to signature.

2- Ask you some questions to fill up a questionnaire. The questions will aim to extract information pertaining to participant's demographics, contact information, adherence to management, medical history, lifestyle factors, cost of care and quality of life.

3- Measure your weight, height/waist/hip/neck circumferences and blood pressure.

4- Review your medical records to obtain information about your recent blood investigations, medical history and medications.

The interview will take around 45 minutes.

Why were you chosen for this research?

You were chosen randomly from adults who have type 2 diabetes for at least one year and presently visiting the hospital.

Consenting to participate in the project and withdrawing from the research

The consent process involves reading, signing and returning the consent form. It will take place after reading, addressing any queries (if any) and approval.

Withdrawing from the research

You have the right to withdraw your participation at any stage of interview without penalty. In the event of a withdrawal your information will not be used in this research and will be discarded securely.

Possible benefits and risks to participants

We cannot guarantee or promise that this survey will directly benefit you but we hope that this work will be beneficial in forecasting the economic burden of type 2 diabetes mellitus in Bangladesh. Furthermore, the results can be used as a financial tool for cost control and disease management for individuals and thus improve their quality of life.

This research does not impose any intervention on you and it is not expected to have any significant risk to you. However, as some information may be considered to be sensitive, your confidentiality will be maintained through de-identification of data. Your individual findings will be kept confidential and only group data will be reported.

Confidentiality

The collected information will be saved at Monash University secure web-based system and will be accessible by the research team only. Your name and contact information will be removed from the main database and will be saved in a separate secure electronic folder. The records in the database will be coded and identified by a number so that no one can relate the collected information to you. Your information will not be used for any other purposes other than those stated in this study.

The research findings will be shared through research article, conference proceedings or in other scientific media as group information. The published reports will include group data only and no individual data or information will be shared that may enable identification of any of the participants.

Storage of data

The collected information will be saved at Monash University secure web-based system and will be accessible by the research team only. Your records will be saved securely for 5 years after completion of the study for reference purposes, after which all your records will be discarded securely.

Results

Findings of the study will be published in recognized international journals within 5 years after the completion of data collection. Summary of the results will also be disseminated to participants and the public through reports in the national media.

Complaints

Should you have any concerns or complaints about the conduct of the project, you are welcome to contact:

Bangladesh

Prof Liaquat Ali
Director
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Thank you,

Dr Md Baki Billah

Appendix 4 Questionnaire

Confidential

Cost-of-Illness and its ddeterminants for Type 2 Diabetes Mellitus in Bangladish

Please complete the survey below.

Thank you!

A. Patient's details

A1. Patient ID _____

A2. Name of the hospital _____

A3. Patient contact number _____

A4. Patient's name _____

A5. Present address _____

Is permanent address is different than present address?
- ◯ Yes
- ◯ No

A6. Parmanent address _____

A7. Gender (by observation)
- ◯ Male
- ◯ Female

A8. Age (guide book record) _____ (years)

A9. What is your marital status?
- ◯ Single
- ◯ Married
- ◯ Divorced
- ◯ Widow

A10. What is your religion?
- ◯ Islam
- ◯ Hindu
- ◯ Buddhist
- ◯ Christianity

A11. What is your highest education level achieved?
- ◯ Illiterate
- ◯ Primary
- ◯ JSC
- ◯ SSC
- ◯ HSC
- ◯ Graduate and above

A12. What is your work status?
- ◯ Full-time paid work
- ◯ Part-time paid work
- ◯ Unemployed and looking for work
- ◯ Not working and not looking for work

A13. Which of the following best describes your main work status over the past 12 months?
- ◯ Government employee
- ◯ Non-government employee
- ◯ Self-employed
- ◯ Business owner
- ◯ Homemaker / caring for family
- ◯ Not working for pay

A14. What is the main reason you are not working for pay?

- ◯ Looked but can't find a job
- ◯ unpaid work / voluntary activities
- ◯ Studies / training
- ◯ Retired / too old to work
- ◯ Ill health
- ◯ Other

A15. What is your monthly income? _____

a. from salary/wage _____ (tk)

b. from business/firm _____ (tk)

c. property/rent _____ (tk)

d. others _____ (tk)

A16. Are you the only earning member of the household?

- ◯ Yes
- ◯ No

A17. What is your total monthly household income?

a. from salary/wage _____ (tk)

b. business/firm _____ (tk)

c. property/rent _____ (tk)

d. others _____ (tk)

A18. What is your monthly household expenditure?

a. food _____ (tk)

b. housing _____ (tk)

c. education _____ (tk)

d. health care _____ (tk)

e. others _____ (tk)

A19. In which year you have been diagnosed to have diabetes? _____ (years)

A20. Does anyone of your family have diabetes?
- ◯ Yes
- ◯ No

A21. How frequent are you following up for diabetes?
- ◯ Monthly
- ◯ Every 2 months
- ◯ Every 3 months
- ◯ Every 6 month
- ◯ 1 year
- ◯ Irregular

A22. How do you currently treat your diabetes?
- ☐ Diet plan/Exercise
- ☐ Oral hypoglycemic agent (OHA)
- ☐ Insulin
- ☐ OHA and insulin
- ☐ Tradition medicine

A23. Do you have self-monitoring blood glucose devise at your home?
- ◯ Yes
- ◯ No

A24. Do you monitor your blood glucose at nearby pharmacy?
- ◯ Yes
- ◯ No

A25. How often do you measure your blood glucose over the last month?
- ◯ Daily (once or more)
- ◯ 2 - 6 times every week
- ◯ Once weekly
- ◯ 1 - 2 times a month
- ◯ Did not use it

A26. Do you test both preprandial/ fasting and postprandial/ABF glucose level at a time?
- ◯ Yes
- ◯ No

A27. How many times in the last month have you had a low blood sugar reaction with symptoms such as sweating, weakness, anxiety, trembling, hunger, headache or passing out?
- ◯ 0 times
- ◯ 1-5 times
- ◯ 6-10 times
- ◯ More than 10 times
- ◯ Do not know

B. Information from patients guide book

B1. Fasting (FBG) (recent report during last year) _____

Frequency _____

B2. ABF (recent report during last year) _____

Frequency _____

B3. HbA1c (recent report during last year) _____

Frequency _____

B4. TG (recent report during last year) _____

Frequency _____

B5. TC (recent report during last year) _____

Frequency _____

B6. HDL (recent report during last year) _____

Frequency _____

B7. LDL (recent report during last year) _____

Frequency _____

B8. SGPT (recent report during last year) _____

Frequency _____

B9. Serum Creatinine (recent report during last year) _____

Frequency _____

B10. Urine Albumin (recent report during last year) _____

Frequency _____

B11. ACR (recent report during last year) _____

Frequency _____

B12. eGFR (recent report during last year) _____

Frequency _____

B13. Blood pressure _____

B14. How many times do you visit to doctor last year due to diabetes? _____

B15. Prescription

(Upload the current prescription image)

History of diabetes related comorbidities and complications

Have you ever been told by a doctor or a nurse that you have high blood pressure?
- ◯ No
- ◯ I do not know
- ◯ Yes

Have you ever been told by a doctor that you have high lipids or cholesterol?
- ◯ No
- ◯ I do not know
- ◯ Yes

Have you ever been told by a doctor that you have heart disease or coronary artery disease?
- ◯ No
- ◯ I do not know
- ◯ Yes

Have you been diagnosed by a doctor to have a stroke before?
- ◯ No
- ◯ I do not know
- ◯ Yes

Have you ever been told by a doctor that your diabetes have affected your eyes (retina) before?
- ◯ No
- ◯ I do not know
- ◯ Yes

C. Diabetes cost information

C1. In current visit how much money you spent for consultation? _____ (tk)

C2. In current visit how much money you spent for travel to hospital from your present address? _____ (tk)

C3. In current visit how much money you spent for travel to hospital from your permanent address? (if, different from present address) _____ (tk)

C4. In current visit how much money you spent for food on the way to hospital? _____ (tk)

C5. In current visit how much money you spent for any other reason? _____ (tk)

C6. How much money you spent for traditional medicine? _____ (tk)

C7. For how long you take leave from your employer for each visit?
- ◯ 1-2 hrs
- ◯ ½ day
- ◯ Full day

C8. Does anyone accompany you to the hospital?
- ◯ Yes
- ◯ No

C9. What is his / her job?
- ◯ Government employee
- ◯ Non-government employee
- ◯ Self-employed
- ◯ Business owner
- ◯ Housewife/ Homemaker
- ◯ Not earnable

C10. What is his/her monthly income? _____

C11. Because of cost, do you skip

	Yes	No
a) Medicine or insulin shot	◯	◯
b) Checking blood sugar	◯	◯
c) Consultation	◯	◯
d) Healthy diet	◯	◯

C12. In the last 12 months, which sources did you use to pay for any diabetes related health expenditures?
- ☐ current income
- ☐ savings
- ☐ sold items (e.g. furniture, animals, jewellery, furniture)
- ☐ loan/borrowing form family members or friends from outside the household
- ☐ loan/borrowing form from someone other than a friend or family
- ☐ Payment or reimbursement from a health insurance plan
- ☐ Bear by children
- ☐ other

C13. Do you have any extra cost in last year for dietary management? _____ (tk)

C14. Do you have any extra cost in last year for purchasing any exercise machine? _____ (tk)

C15. Do you have any extra cost in last year for purchasing monitoring devices? _____ (tk)

C16. Do you have any extra cost in last year for any issue related to diabetes?
- ◯ Yes
- ◯ No

Please specify the reason. _____

Cost _____

C17a. How much money do you spent for drug (monthly)? _____

C17a. How much money do you spent for insulin (monthly)? _____

In-patient event (if any, during last year)

C18. Have you been hospitalized due to diabetes or its complication in last year?
- ◯ Yes
- ◯ No

C19. What was the reason of admission? _____

C20. Where do you hospitalized?
- ◯ Public hospital
- ◯ Privet hospital

C21. What was the total length of stay? _____

C22. In total how much money you spent for hospitalization? _____

C23. How much money you spent for hospital stay? _____

C24. How much money you spent for investigation? _____

C25. How much money you spent for medicine? _____

C26. How much money you spent for food? _____

C27. How much money you spent for transportation? _____

C28. Does anyone accompany you to the hospital?
- ◯ Yes
- ◯ No

C29. What is his / her job?
- ◯ Government employee
- ◯ Non-government employee
- ◯ Self-employed
- ◯ Business owner
- ◯ Housewife/ Homemaker
- ◯ Not earn-able

C30. What is his/her monthly income? _____

C31. Was there any extra cost (food, transport, accommodation) for the accompanying person? _____ (tk)

D. Adherence to management

D1. Do you ever forget to take your medicine?
- ◯ Yes
- ◯ No

D2. Are you careless at times about taking your medicine?
- ◯ Yes
- ◯ No

D3. Sometimes if you feel worse when you take the medicine, do you stop taking it?
- ◯ Yes
- ◯ No

D4. When you feel better do you sometimes stop taking your medicine?
- ◯ Yes
- ◯ No

	No	Yes
D7. Have you been told to follow a schedule for your meals and snacks?	◯	◯
D8. Have you been told to weigh or measure your food?	◯	◯
D9. Have you been told to use exchange lists or food group lists to plan your meals?	◯	◯

	Never	Sometimes	Always
D10. How often do you follow the schedule for your meals and snacks?	◯	◯	◯
D11. How often do you weigh or measure your food?	◯	◯	◯
D12. How often do you (or the person who cooks your food) use the exchange lists or food group lists to plan your meals?	◯	◯	◯

E1. Lifestyle behaviour (Smoking)

E1a. Do you or did you smoke any tobacco products such as cigarettes or Shisha (water pipe)?
- ◯ No, never smoked
- ◯ Yes, in the past (more than 1 month)
- ◯ Yes, currently smoking

E1b. Does anyone at your house currently smoke cigarettes or Shisha (water pipe)?
- ◯ No
- ◯ Yes, away from you (not exposed to the smoke)
- ◯ Yes, in front of you (You are exposed to the smoke)

E1c. Do you consume any smokeless tobacco products daily?
- ◯ No, never
- ◯ Yes, in the past (more than 1 month)
- ◯ Yes, currently consuming

E2. Lifestyle behaviour (Diet)

Think of your diet over the last month

	3 or more times a day	1 - 2 times a day	5 - 6 times a week	2 - 4 times a week	Once a week or less	Never or very rare
1. How often did you eat a portion of fruit? Include fresh, frozen, tinned and dried fruit. Do not count fruit juices.	○	○	○	○	○	○
2. How often did you eat a portion of vegetables? Including fresh, tinned and frozen vegetables.	○	○	○	○	○	○
3. How often did you eat red meat? Including camel, lamb, beef, and veal.	○	○	○	○	○	○
4. How often did you eat rice?	○	○	○	○	○	○
5. How often did you eat bread?	○	○	○	○	○	○
6. How often did you eat cake, sweet pastry, biscuits, chocolate, halva or other types of sweet pastries or desserts?	○	○	○	○	○	○
7. How often did you drink sugary drinks? Including, non-diet soft drink (soda) and sugar sweetened fruit juice, tea, coffee or milk?	○	○	○	○	○	○
8. How often did you use butter or animal fat in your cooking? (for example for cooking rice, vegetables and pastries)	○	○	○	○	○	○

9. What amount of cooked rice do you eat in one meal?

- ○ 4 or more cups
- ○ 3 cups
- ○ 2 cups
- ○ One cup
- ○ Less than a cap

10. What amount of bread do you usually eat in one meal?

- ○ 4 or more slice of 30 gm bread
- ○ 3 slice of 30 gm bread
- ○ 2 slice of 30 gm bread
- ○ One slice of 30 gm bread
- ○ Less than a slice of 30 gm bread

E3. Lifestyle behaviour (Exercise)

E3a. Do you walk for at least 10 minutes continuously to get to and from places?	◯ Yes ◯ No
E3b. In a typical week, on how many days do you walk at least 10 minutes continuously to get to and from places?	_____ (number of days)
E3c. How much time do you spend walking for travel on a typical day?	_____ (minutes)
E3d. Do you do any sports, fitness or recreational (leisure) activities that cause increases in breathing or heart rate for at least 10 minutes continuously?	◯ Yes ◯ No (walking)
E3e. In a typical week, on how many days do you do this sports, fitness or recreational (leisure) activities?	_____ (Number of days)
E3f. How much time do you spend doing this sports, fitness or recreational activities on a typical day?	_____ (minutes)

F. Family support

Does your family help and support you to do the following?

	No	Sometimes	Yes, all the time
F1. Follow a diabetic diet	◯	◯	◯
F2. Take your medication	◯	◯	◯
F3. Do physical activity	◯	◯	◯
F4. Test your blood sugar at home	◯	◯	◯
F5. Follow up regularly with your physician(s)	◯	◯	◯

G. Depression (PHQ-2)

How often during the past 2 weeks were you bothered by the following problems?

	Not at all	Several days	More than half the days	Nearly every day
G1. Little interest or pleasure in doing things	◯	◯	◯	◯
G2. Feeling down, depressed, or hopeless.	◯	◯	◯	◯

H. Anxiety (GAD-2)

Over the last 2 weeks, how often have you been bothered by the following problems?

	Not at all	Several days	More than half the days	Nearly every day
H1. Feeling nervous, anxious, or on edge	○	○	○	○
H2. Not being able to stop or control worrying	○	○	○	○

I. Neuropathy screening (The Michigan Neuropathy Screening Instrument)

	Yes	No
I1. Are your legs and/or feet numb?	○	○
I2. Do you ever have any burning pain in your legs and/or feet?	○	○
I3. Are your feet too sensitive to touch?	○	○
I4. Do you get muscle cramps in your legs and/or feet?	○	○
I5. Do you ever have any prickling feelings in your legs or feet?	○	○
I6. Does it hurt when the bed covers touch your skin?	○	○
I7. When you get into the tub or shower, are you able to tell the hot water from the cold water?	○	○
I8. Have you ever had an open sore on your foot?	○	○
I9. Has your doctor ever told you that you have diabetic neuropathy?	○	○
I10. Do you feel weak all over most of the time?	○	○
I11. Are your symptoms worse at night?	○	○
I12. Do your legs hurt when you walk?	○	○

I13. Are you able to sense your feet when you walk?	◯	◯
I14. Is the skin on your feet so dry that it cracks open?	◯	◯
I15. Have you ever had an amputation?	◯	◯

J. Six-item Cognitive Impairment Test (6CIT)

	Correct	Incorrect
J1. What year is it?	◯	◯
J2. What month is it?	◯	◯
J3. About what time is it?	◯	◯

	Correct	One error	More than one error
J4. Count backward from 10 - 1	◯	◯	◯
J5. Say the month of the year in reverse	◯	◯	◯

J6. Repeat address phrase

◯ Correct
◯ 1 error
◯ 2 errors
◯ 3 errors
◯ 4 errors
◯ All wrong
(Ali, Hossain, 45, Mirpur Road, Dhaka)

K. Patients health related quality of life (EQ-5D-5L)

K1. Mobility

◯ I have no problems in walking
◯ I have slight problems in walking
◯ I have moderate problems in walking
◯ I have severe problems in walking
◯ I am unable to walk

K2. Self-care

◯ I have no problems washing or dressing myself
◯ I have slight problems washing or dressing myself
◯ I have moderate problems washing or dressing
◯ I have severe problems washing or dressing myself
◯ I am unable to wash or dress myself

K3. Usal activity
(e.g. work, study, housework, family or leisure activities)

◯ I have no problems doing my usual activities
◯ I have slight problems doing my usual activities
◯ I have moderate problems doing my usual activities
◯ I have severe problems doing my usual activities
◯ I am unable to do my usual activities

K4. Pain/discomfort

◯ I have no pain or discomfort
◯ I have slight pain or discomfort
◯ I have moderate pain or discomfort
◯ I have severe pain or discomfort
◯ I am extreme pain or discomfort

K5. Anxiety/depression

- ◯ I am not anxious or depressed
- ◯ I am slightly anxious or depressed
- ◯ I am moderately anxious or depressed
- ◯ I am severely anxious or depressed
- ◯ I am extremely anxious or depressed

K6. Compared with your general level of health over the past 12 months, your health state today is:

- ◯ Worse
- ◯ Much the same
- ◯ Better

K7. We would like to know how good or bad your health is TODAY.

_____

(This scale is numbered from 0 to 100. 100 means the best health you can imagine. 0 means the worst health you can imagine. Mark an X on the scale to indicate how your health is TODAY.)

Household information

L1. What is the main source of drinking water for members of your household?

- ◯ Piped water
- ◯ Deep Tubwell
- ◯ Well
- ◯ Water from spring
- ◯ Rain water
- ◯ Bottle water
- ◯ Surface water (River/Dam/Lake/Ponds/Stream/Canal/Irrigation channel)

L2. What is the main source of water used by your household for other purposes such as cooking and hand washing?

- ◯ Piped water
- ◯ Deep Tubwell
- ◯ Well
- ◯ Water from spring
- ◯ Rain water
- ◯ Bottle water
- ◯ Surface water (River/Dam/Lake/Ponds/Stream/Canal/Irrigation channel)

L3. What kinds of toilet facility do members of your household usually use?

- ◯ Flush/Pour Flush toilet
- ◯ Pit latrine
- ◯ Busket toilet
- ◯ Hanging toilet
- ◯ No facility/Bush/Field

L4. Do you share this toilet facility with other households?

- ◯ Yes
- ◯ No

L5. Does your household have the following items?
(Multiple responses)

	No	Yes
Electricity	☐	☐
A radio/television	☐	☐
A computer/ i pad	☐	☐
A mobile telephone	☐	☐
A land phone	☐	☐
A refrigerator	☐	☐
An almirah/wardrobe	☐	☐
A table	☐	☐
A chair	☐	☐
A watch	☐	☐
A bi-cycle	☐	☐
A motor cycle/motor scooter/tempo	☐	☐
An animal-drawn cart	☐	☐
A car/truck/bus	☐	☐
A boat with a motor	☐	☐

L6. Does your household own any livestock, herds, other farm animals or poultry?
◯ Yes
◯ No

L7. Does your household own any homestead?
◯ Yes
◯ No

L8. Does your household own any land (other than the homestead land)?
◯ Yes
◯ No

L9. What is the main material of

	Natural (Earth/Sand)	Rudimentary (Wood Planks, Palm/Bamboo)	Finished floor (Parquet or polished wood, Ceramic tiles, Cement, Carpet)
L9a. the floor of your house?	◯	◯	◯
L9b. the roof of your house?	◯	◯	◯
L9c. the wall of your house?	◯	◯	◯

M. Anthropometric measurements

M1. Weight

_____
((in kg))

M2. Height

_____
((in cm))

M3. Waist circumference

_____
((in cm))

M4. Hip circumference

_____
((in cm))

Appendix 5 Screenshot of the online risk calculator