Mobile Phone Interventions for Adherence to Treatment for Diabetics in an Urban Area of Bangladesh

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Abstract

Background: Evidence suggests increasing prevalence of type 2 diabetes (T2D) in Bangladesh, imposing huge social and economic impacts. Mobile phone SMS have the potential to improve diabetes outcome. The research aimed to measure the clinical status and complications of T2D, mobile phone use and willingness-to-pay for diabetes SMS, effects of SMS on glycemic control, and healthcare use and expenditure for diabetes in Bangladesh.
Methods: We conducted a cross-sectional study among 515 patients with T2D in a tertiary hospital in Dhaka and selected 236 patients meeting the eligibility criteria for a randomized-controlled trial of an SMS intervention. We further conducted a matched case-control study including 591 additional individuals with diagnosed diabetes and 591 age, sex and residence matched controls without diabetes at the same hospital.
Results: The majority of patients with T2D had uncontrolled diabetes (71.3%) and self-reported complications (91.5%). In the randomized trial, the SMS intervention was effective with respect to the primary endpoint. Among the trial participants, the least squares mean difference of HbA1c from baseline to after 6 months was -0.85 (-1.05, -0.64) in the SMS group and -0.18 (-0.41, 0.04) in the control group. The difference between means was -0.66 (-0.97, -0.35; $p<0.0001$). In the case-control study, patients with diabetes had two times more days of inpatient treatment, 1.3 times more outpatient visits, and 9.7 times more medications than those without diabetes (all $p<0.005$). The total annual per-capita healthcare expenditure was 6.12 times higher for persons with diabetes than non-diabetics (USD 635 vs. 104, respectively).
Conclusion: This research provides evidence that diabetes management in Bangladesh is suboptimal even under best clinical settings and costly. It also demonstrates the effectiveness of an innovative automated SMS service as an addition to standard care in the management of T2D. As the mobile phone SMS setup is scalable and low-cost, it may be considered for diabetes care in Bangladesh and similar developing countries.

Key Words: Type 2 diabetes (T2D); Short Message Services (SMS); medication adherence; glycemic control; willingness to pay (WTP); health care use and expenditure; depression

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Abbreviations

BDT: Bangladesh Taka

BIHS: Bangladesh Institute of Health Science

BIRDEM: Bangladesh Institute of Research on Diabetes, Endocrine and Metabolism

BMI: Body Mass Index

BP: Blood Pressure CI: Confidence Interval

CI: Confidence Intervals

CVM: Contigent Valuation Method

CKD: Chronic Kidney Diseases

CVD: Cardiovascular Diseases

DM: Diabetes Mellitus

DMs: Persons with Diabetes Mellitus

HbA1c: Haemoglobin A1c or Glycated Haemoglobin

ICDDR,B: International Center for Diarrhoeal Diseases Research, Bangladesh

IDF: International Diabetes Federation

IQR: Intra-Quartile Range

LMU: Ludwig-Maximillians Universitat

LMICs: Low and Middle Income Countries

mHealth: Mobile Health (Mobile Phone Based Health Service)

NCDs: Non-Communicable Diseases

Non-DMS: Persons without Diabetes

OPD: Out Patient Department

SBP: Systolic Blood Pressure

SMS: Short Message Service

SPSS: Statistical Packages For Social Sciences

T2D: Type 2 Diabetes

WHO: World Health Organization

WTP: Willingness to Pay

1. Introduction

1.1) Global epidemiology of NCDs and diabetes

In recent years, non-communicable diseases (NCDs) such as diabetes, cardiovascular diseases, respiratory disease and cancers have increased in epidemic proportions globally. Around 80% of deaths due to NCDs occur in low-and-middle-income countries (LMICs), where the health systems are inadequate to provide the essential services [1]. The epidemiological transition and double burden of diseases in developing countries might be resulting from increasing age of the population, increase in average lifespan, decrease in childhood infections and death, rural-urban migration, and adoption of unhealthy lifestyle such as sedentary work habits, diets rich in fats, carbohydrate, and salt among others [1]. Diabetes is one of the leading causes of morbidity and mortality, affecting more than 382 million people globally and is projected to double by 2030 [2]. The global burden of disease study reported that over the last two decades NCDs have substantially increased in terms of absolute number of years of life lost and years lived with disability, and diabetes contributing to the largest increase in diseases burden [3].

1.2) Epidemiology of diabetes in Southeast Asia

Almost one-fifth of the world's total population with diabetes live in Southeast Asia region, where the prevalence of diabetes is estimated to increase by 71% by 2035 [2]. The International Diabetes Federation (IDF) Diabetes Atlas indicates that by 2030, 10.2% of the adult population in this region will have diabetes increasing the number of people with diabetes to 120.9 million [4]. Rapid urbanization and economic growth in many countries of Southeast Asia have lead to exposure to new risk factors, such as adverse dietary pattern, sedentary lifestyles, obesity, environmental exposure among others in addition to traditional risk factors of increasing age and genetic predisposition [5]. Southeast Asians develop type 2 diabetes at a lower body mass index (BMI) compared to Caucasians and have more central obesity [6]. Moreover, diabetes and its complications also develop at a relative younger age in South Asians compared to the Western population [7-9].

1.3) Epidemiology of type 2 diabetes in Bangladesh

According to the IDF Diabetes Atlas, there are an estimated 8.4 million people with diabetes in Bangladesh and a similar number of people with prediabetes. The IDF projected that the number of people with diabetes will increase to 16.8 million by 2030, placing Bangladesh among the top ten countries globally in terms of number of people living with diabetes [2]. A recent population-based study reported the overall age-adjusted prevalence of diabetes 15.2% in urban areas compared with 8.3% in rural areas in Bangladesh [10]. A scoping review of the increasing trend of diabetes prevalence in Bangladesh showed that the prevalence of diabetes varied from 4.5% to 35% with a pooled prevalence of 7.4% (95% CI 7.17-7.63) [11]. This study reported the increasing prevalence of diabetes in the urban and rural population at rate of 0.05% and 0.06% per year respectively in Bangladesh. Another systematic review of the risk factors for diabetes in Bangladesh identified the most common risk factors for diabetes in Bangladesh, namely increased age, obesity, social class, hypertension, family history, sedentary life style among others, which differed by urban-rural areas and by gender [12]. Diabetes is a complex condition and impacts on individuals, families, societies, health systems and the nation as a whole. The economic and human costs provoked by diabetes in a large population such as in Bangladesh will be substantial [13]. However, the social and economic impact of diabetes in Bangladesh, as well as its impact on individual, society and health systems level is largely not known.

1.4) Roles of mHealth in the management of type 2 diabetes

The growing epidemic of diabetes in Bangladesh and other developing countries suggest that traditional methods for diabetes management in hospital settings or clinics, might not be adequate to control the epidemic alone. Globally, mobile phone technologies have emerged as an essential tool for strengthening health systems and improving disease management in many countries [14]. In recent years, the Government of Bangladesh and the World Health Organization (WHO) have adopted information technologies for health to their strategic plans [15]. Previous studies showed the effectiveness of SMS for increasing medication adherence and behavior changes in developing countries [16-18]. Substantial evidence suggest that mobile phones might be a potential tool for addressing NCDs requiring life-long treatment in developing country settings [19, 20]. However, such innovative technologies for health interventions are complex and require solid evidence before they could be scaled up.

2. **Rationale and Objective**

A. The cross-sectional study: Substantial evidence suggests that in patients with type 2 diabetes (T2D) in Southeast Asian countries, diabetes starts relatively earlier in life and patients report higher number of complications as compared to Western populations. However, to the best of our knowledge, factors determining the clinical status and complications of patients with diabetes in Bangladesh have not been studied in detail. We therefore conducted this cross-sectional study in patients with T2D on oral therapy and with a time since diagnosis of less than 10 years to assess the current clinical status and complications. The results of this study will help clinicians and policy makers to further develop management plans for diabetes in Bangladesh and other developing countries.

B1. The Mobile phone use and Willingness to pay (WTP) for diabetes SMS study: During the last decades, there has been a dramatic increase in mobile phone penetration rates in Bangladesh, reaching all segments of the population [21, 22]. However, the use of mobile phones by patients with T2D and their willingness to pay for a diabetes SMS services are largely unknown. The objective of this study was to assess the mobile phone use and willingness to pay for a diabetes SMS service.

B2. The SMS intervention trial: Data to support a successful model of mobile phone SMS in disease management in Bangladesh are not available. In this trial, we therefore assessed whether the addition of an automated mobile phone SMS service to standard diabetes care would improve glycemic control in patients with type 2 diabetes in Dhaka city. If this intervention proves to be efficient and cost-effective in our trial, large-scale implementation of this care model could be undertaken for diabetes and, possibly for other NCDs in Bangladesh and potentially other countries.

C. The case-control study: Information on the availability, cost, and quality of medical care for diabetes is mostly not available for many low-and-middle-income countries, including Bangladesh. Complications from diabetes, which can be devastating, could largely be prevented by wider use of several inexpensive generic medicines, simple tests and monitoring and can be a cost saving intervention. There is a need for information on healthcare use and expenditure for diabetes to develop strategies and policies in Bangladesh. In this context, we conducted the first-ever comprehensive case–control study to measure the healthcare use and expenditure for diabetes in Bangladesh. This study will provide an in-depth and comprehensive picture of social and economic impacts of diabetes in Bangladesh and propose clear recommendations for improving prevention and management of diabetes.

3. Methods

A. The cross-sectional study:
Study population and settings: We conducted a cross-sectional study among 515 patients with T2D attending the outpatient department (OPD) of Bangladesh Institute of Health Science (BIHS) hospital in Dhaka from September to December 2013. The BIHS is a tertiary hospital of the Diabetes Association of Bangladesh. All registered patients with T2D are attended by certified diabetologists, receive a session of health education during registration and are referred to appropriate specialist at BIHS as necessary.

Data collection process: We collected data through face-to-face interviews using structured questionnaires, physical measurements, laboratory investigations and review of medical records. We obtained written informed consent from each participant. The ethical review committee of icddr,b approved the research protocol (PR#13068). The variables, measurements and case definitions are provided in details in the study protocol [23].

Statistical analysis: Data analyses were performed using SPSS version 20 (SPSS Corporation Inc., IL, USA). Data were expressed as mean ±SD and for non-normal data were as Median (IQR). Frequencies and percentages for independent variable were calculated. In simple logistic analysis, each independent variable was analyzed to look at any significant association with dependent variable (diabetes complications). The findings were presented with adjusted OR, its 95% CI and corresponding P-value. The level of significance was set at 0.05.

B1.Mobile phone use and WTP for diabetes SMS :
We conducted a WTP study as part of the randomized controlled trial on mobile phone SMS intervention. WTP was defined as the monthly amount of money each participant would be willing to pay if an SMS service for diabetes was available, in addition to regular medical care. We used contingent valuation methodology (CVM) to quantitatively measure patient WTP.

B2. The SMS intervention trial:
Study site and population: This was a six month, prospective, parallel-group, randomized controlled single-centre clinical trial designed to evaluate the effectiveness of mobile phone SMS in addition to standard care compared with standard care alone for glycemic control among patients with type 2 diabetes. The study protocol has been reported previously [24]. In brief, patients with type 2 diabetes (diagnosed within the last 5 years) attending the OPD of BIHS hospital in Dhaka, Bangladesh were recruited for this study between September 2013 and August 2014.

Patients were eligible for the study participation if they were over 18 years old, diagnosed as T2D patients by the BIHS attending physician according to WHO criteria, [24, 25] registered with the BIHS, taking oral antidiabetic medication, able to access a mobile phone on a daily basis and able to read SMS. Patients with insulin therapy, type 1 diabetes, gestational diabetes, other serious illness or co-morbidities requiring hospitalization, living outside Dhaka city and not having access to a mobile phone were excluded. The study protocol (PR#13068) was approved by the Research Review Committee and Ethical Review Committee of the ICDDR, B and received an Ethical Committee waiver from LMU and BIHS. This trial is registered in the German Clinical Trial Registry drks.de, DRKS00005188**. (Annex-3: Trial Profile)**

Randomization and masking: Of the 515 patients, 236 patients meeting the selection criteria were randomly assigned (1:1) by simple randomization to the SMS intervention plus standard of-care or standard-of-care alone (control group). The principal investigator generated the randomization numbers using a random number generating program (GraphPad Software, Inc., California, USA). Laboratory personnel and the principal and co-investigators were masked to the participants' group allocation until the end of the study. However, clinic staff and participants could not be masked because the intervention required active overt participation.

Procedures: All consecutive newly diagnosed patients with type 2 diabetes on oral medication were referred by the BIHS attending physician for the study. After screening for eligibility and obtaining written informed consent, data were collected through face-to-face interviews using a structured questionnaire, anthropometric measurements of weight, height, hip circumference, waist circumference, blood pressure, pulse and blood tests for HbA1c using standard procedures as mentioned in the study protocol [24]. Diabetes was diagnosed by BIHS attending physician according to WHO guidelines [25] and was validated by the study physician during recruitment through review of clinical and investigation records. Medication adherence was measured using Morisky 8-Item Medication Adherence Scale (MMAS) [26].

The SMS were developed by a team comprising of two general medical practitioners, an endocrinologist, two epidemiologists, a nurses and two undergraduate students. After developing the SMS in Bengali, we sent the SMS to several individuals in the pre-test stage including persons who can only read SMS and have no formal education qualifications. After receiving the feedback, we adopted the contents of the SMS for the general population. We ensured that all our participants in the study could read the SMS by themselves or someone in the family could read the messages to them. Most of the 90 SMS were developed based on the principles of behavioral learning theory and trans-theoretical model of behavioral change [27, 28]. All participants in the SMS intervention group received the 90 SMS randomly, once a day over a six month period. Some examples of the SMS are available in the study protocol published previously [24]. A SMS delivery manager website was created and SMS delivered in partnership with Telenor based Grameenphone Bangladesh.

The data collection team comprised of a physician, a research officer and three research assistants who were supervised by the principal investigator. The team was trained for two weeks by senior scientists and researchers at the Center for Control of Chronic Diseases, icddr,b on the study protocol, diabetes epidemiology, anthropometric measurements, research ethics and interview skills. All data were prospectively recorded on case report forms, which were forwarded to the study coordination center in icddr,b for data entry and analysis. Data that were missing, inconsistent, or both were obtained or clarified by direct communication of the data collectors. Data were unmasked when the six month clinical follow-up information from all patients had been obtained. All data were held at the study coordinating centre, but the principal investigator had full access to them.

Sample size: We based the sample size calculation on the hypothesis that the mobile phone SMS intervention is superior to standard care in reducing HbA1c by 0.5 points [29, 30]. Assuming a standard deviation of 1 and an alpha error level of 5%, the two-tailed calculation provided a power of over 90% with 90 participants in each arm of the study. To allow for a 20 % dropout rate, a total of 226 participants were required for the study.

Statistical analysis: We compared the baseline characteristics between the study groups with Chi-Square, Fisher's Exact, Mann Whitney-U test and t-tests. To test the primary hypothesis we used an intention to treat analysis based on all study participants with any follow-up information available. In accordance with the ICH E9 guideline [31], a total 36 participants with no data post randomization were excluded from the analysis. We calculated the least squares means of the HbA1c change between baseline and 6 month for the intervention and the control group and the difference between the two least square means using the SAS generalized linear model procedure. The same procedure was used to compare the two least squares means and to compute 95% confidence intervals (CIs). Baseline HbA1c, patient age, sex, education level, duration of known diabetes and the number of diabetes-related complications were included in the model to adjust for potential heterogeneities in the composition of the two study groups. The criterion for significance was set at α=0.05. The same method was used for the post-hoc subgroup analysis. Data were analyzed using SAS version 9.3 (SAS Institute Inc, NC, USA) and SPSS version 20 (IBM, New York, NY, USA).

C. The case-control study:

Study site and population: We conducted a matched, case-control study including 591 persons with diagnosed diabetes (DMs) and 591 age, sex and residence matched controls without diabetes (non-DMs) at the OPD of BIHS hospital between January and July 2014. Detailed methodology of the study design has been published elsewhere [13].

Sample size and selection: We considered a sample size of 500 cases and 500 controls to provide 90% power to detect a 5 percent difference in rates and proportions between cases and controls. Inclusion criteria for cases were: adults diagnosed with diabetes at BIHS OPD according to WHO criteria, provision of anthropometric measurements, and written informed consent. Controls were individuals without a self-reported history of diabetes matched on a 1:1 basis to cases by area of residence, age (within a 5 year band), and sex (male or female). We included all consecutive patients meeting the inclusion criteria waiting for consultation at the BIHS OPD. Controls were recruited within 48-hours of recruiting the index case, from either visitors of patients attending the OPD, or non-blood related visitors of index diabetes cases, in the same hospitals or the same geographical residence of cases. All controls underwent identical study questioning and examination as cases. One completed control interview was obtained for each case interview. (**Annex-4. Selection of participants**)

Data collection: The research tools and instruments used in this study were developed by the IDF Health Economic Group and translated into Bengali according to the WHO process of translation and adaptation of research instruments [32]. The questionnaires were field tested in a similar setting at the OPD of BIRDEM hospital before conducting the interviews among 25 cases and 25 control subjects. Feedback from the field tests was used to improve the language and the contents of the questionnaire and tools, as well as adapt them to local circumstances based on previous validated survey items [4]. Detailed methodology of data collection, including the questionnaire, variables, definitions and methods are published in the study protocol [13].

Ethics: The study was approved by the Research Review Committee and Ethical Review Committee of the International Center for Diarrheal Diseases Research, Bangladesh (PR-13062) and obtained ethical clearance waiver from Ludwig-Maximilians-Universität (LMU) and BIHS.

Data analysis: Descriptive analysis was performed for all variables and unadjusted comparisons between case and control were performed using t-tests (for continuous variables) or chi-square tests (for discrete variables). We estimated the impact of diabetes on healthcare use by calculating ratios and difference between DMs and non-DMs and tested for statistical difference using t-tests. All statistical analyses were performed using SPSS version 20 (IBM Corporation, USA).

4. Results

A. Socio-demographic and clinical characteristics of the study participants: A total of 515 patients participated in this study with a mean±SD age of 50.0±10.1 years and 55.9% were females. Majority of the participants were married (87.2%), completed secondary and higher level of education (71.5%) and had a family history of diabetes (68%). The median (IQR) income was 30 (34) thousands Bangladesh Taka (BDT). The median (IQR) time since diagnosis was 3 (6) years. The median (IQR) duration of hypertension was 5 (8) years. Almost 58% of the participants had diagnosed hypertension, 45% overweight and 18% obese according to BMI, 73% increased waist circumference and 97% high waist hip ratio. The mean HbA1c was 8.3±2.1%. The overall prevalence of dyslipidemia was 72.7%.

Complications: Among the 515 patients, only 44 (9.5%) reported no known complications. Most of the patients, had eye complications (68.9%), which was followed by chronic kidney disease (21.3%), cardiovascular diseases (11.8%), neurological problems (2.7%). About one third patients reported other chronic diseases such as bronchial asthma, tuberculosis, arthritis. We considered chronic kidney diseases according to eGFR. Other complications were recorded from patient's self-reported questionnaire and medical records. Eye complications were reported very frequently but funduscopy results were only rarely available. Therefore eye problems likely in many instances were unrelated to diabetes. There were significant associations between the complications and age, duration of diabetes and duration of hypertension in the univariate models. In the multivariate analyses, adjusting for other confounding variables, only SBP was significantly associated with complications [OR 0.809, 95% CI 0.666–0.981, p-value 0.031].

B1. Mobile phone use: All participants in this study owned a mobile phone. About half of the participants reported to be able to read/retrieve. SMS, while only 36.1% could send SMS. The median (IQR) years of mobile phone use among participants was 7 (6) years, which was significantly higher among males. A greater number of participants reported to read or send one SMS monthly (46.6%) and very occasionally (36.5%) than those who read or sent SMS more frequently. Half of the participants never read any SMS, one-fifth occasionally read and about one-third reported to read all SMS or only from known people. The use of SMS was significantly higher among males ($P<0.001$). The median (IQR) amount spent in a month for mobile bills was 300 (600) BDT. Males also reported spending significantly more on mobile phone bills compared with females. All participants in the study, except two females, reported their interest in receiving SMS for diabetes.

Willingness to pay (WTP) for diabetes SMS: Of the 515 participants, 268 (52.0%) expressed a positive WTP, 84 (16.3%) expressed a Zero WTP and 163 (31.6%) did not know how much to express or did not answer (missing). This left us with 352 (68.3%) for analysis of WTP. The median (IQR) WTP for SMS for diabetes in a month was 20 (45) BDT. The median WTP was around 36% of participants' monthly physician fees, 10% of mobile bill, 8% diabetic food costs and 3% of total monthly medication costs. In the multivariate analysis,

controlling for all other factors, WTP was significantly higher among males [OR 2.4, 95% CI (1.0–5.7)], those with household income. 50 000 BDT [4.6 (1.1–20.4)] and among those with primary education [5.6 (1.2–26.6)], secondary and higher education [5.2 (1.4–19.6)].

B2. Effects of SMS for glycemic control: The demographics and baseline characteristics of the study groups were generally well balanced, and similar to the general diabetic population in Bangladesh [10]. The mean±SD age of the participants was 48.1± 9.7 years, and 54.2% were females. The majority of the participants were married (89.4%), completed secondary education (70.3%) and had a family history of diabetes (65.7%). The median (Q1,Q3) duration of diabetes was 1 (0, 3) years. The mean±SD HbA1c at baseline was 8.4±2.6 % (68±28.4 mmol/mol).

Table 1. Difference in HbA1c (%) between baseline and 6 months

Primary outcome	**Least squares mean (95% CI)**	**p-value**
SMS group (n=106)	-0.85 (-1.05, -0.64)	
Control group (n=94)	-0.18 (-0.41, 0.04)	
Difference between means (95% CI)	-0.66 (-0.97, -0.35)	<0.0001

Table 1 shows the difference in HbA1c between baseline and 6 months. In a secondary analysis, the mean medication adherence score decreased significantly in both the SMS and the control group, indicating greater self-reported adherence to medication over time. There was no significant difference between the groups. Post-hoc subgroup analyses suggested that the SMS intervention worked better in females, those with a baseline HbA1c >8%, and those with a shorter duration of diabetes. (**Annex-4: Results of post-hoc the sub-group analysis**)

C1. The case-control study for healthcare use and expenditure for diabetes: Patients with diabetes had two times more days of inpatient treatment, 1.3 times more outpatient visits, and 9.7 times more medications than those without diabetes (all p<0.005). The total annual per capita expenditure on medical care was 6.12 times higher for persons with diabetes than non-diabetics (USD 635 vs. 104, respectively). Among persons with diabetes, 9.8% reported not taking any antidiabetic medications, 46.4% took metformin, 38.7% sulphonylurea, 40.8% insulin, 38.7% any antihypertensive medication, and 14.2% took anti-lipids over the preceding 3 months.

C2. Association between diabetes and depression: Further analysis of the case-control study showed that the prevalence of depression was 45.2% and 19.8% among persons with diabetes and persons without diabetes, respectively. In the multivariate analysis, mild as well as moderate to severe depression were significantly associated with diabetes and independent of sociodemographic factors and the number of diabetes-related complications (adjusted OR= 2.0, 95% CI= 1.4-2.9 and adjusted OR= 6.4, 95% CI= 3.4-12.3; with p=<0.001 for both).

5. Discussion

A. Clinical status and complications of diabetes: The majority of the 515 participants with T2D reported uncontrolled diabetes (71.3%) and self-reported chronic complications (91.5%). The prevalence of hypertension and dyslipidemia was 57.5% and 72.7%, respectively. Our results show that a great proportion of patients diagnosed with T2D in Bangladesh are relatively young and have a higher proportion of complications at diagnosis, compared to Western population. Central obesity was a common feature among most participants and

higher in females. The high rates of obesity along with unhealthy diet and lack of physical activity might lead to insulin resistance, beta cell dysfunction causing uncontrolled diabetes in this population. The findings suggest poor glycemic control and suboptimal diabetes management, which does not sufficiently reach the patients. Measures to improve clinic attendance, medication adherence, awareness and ability to manage diabetes are needed. In this study, eye problems were the most frequent complication followed by CVD, CKD, neurological problems and others.

Our study provides evidence that diabetes management in Bangladesh is suboptimal even under best clinical settings which might be similar in other areas of Bangladesh and many developing countries. As majority of patients in this study are relatively new cases of T2D presenting with high rates of complications, we can expect that for patients with longer duration, the number of complications will be much higher. Also it is expected that time of diagnosis is late and the T2D has probably been ongoing for years before it was diagnosed. Therefore a better screening for diabetes is necessary in Bangladesh. For prevention of complications, based on our data, there is a need for improving HbA1c, lowering BP and probably adding a statin to lower LDL cholesterol.

B1. Mobile phone use and WTP: This study, to the best of our knowledge, represents the first attempt to investigate the WTP for SMS-based service for any chronic, non-communicable diseases in Bangladesh. In this study, except for two participants, all expressed willingness to receive diabetes-related SMS and the median (IQR) WTP was 20 (45) BDT per month, which seems reasonable for such services compared with the current expenditure for physician fees. Results of this study demonstrate that a great majority of individuals with type 2 diabetes in an urban area of Bangladesh are willing to receive SMS for diabetes and to pay a small amount for such a service. Considering the huge number of diabetes patients and the low mobile phone rates in Bangladesh, a self-sustained business model for basic mHealth services for chronic diseases is therefore feasible in this and potentially other low-income countries.

B2. Effects of the SMS intervention: This study is the first in the developing countries, to the best of our knowledge, to measure the effectiveness of mobile phone SMS for glycemic control and medication adherence in patients with type 2 diabetes in clinical settings. Patients who received the additional SMS support were more likely to report higher adherence to diabetes medication and were more likely to have their blood glucose levels controlled compared to patients who received standard of care alone. Our primary analysis showed that the overall effect of mobile phone SMS was superior to standard-of-care alone in reducing HbA1c among newly diagnosed patients with type 2 diabetes in Bangladesh which support our primary hypothesis and was statistically significant. Our reported changes in HbA1c after 6 months intervention seem to be lower than reports other studies [33]. Results of the sub-group analyses showed that SMS intervention worked better in females and those with a higher HbA1c at baseline. Our finding is consistent with a previous systematic review, suggesting the benefit of individual education on glycemic control compared with the usual care in those patients with a baseline HbA1c >8% [34]. The design of SMS intervention and the objective measurement of HbA1c allowed us to isolate potential effects of the SMS intervention from other aspects of general practice care for patients with type 2 diabetes in the clinics.

This study demonstrates the effectiveness of an innovative model of care in the management of type 2 diabetes in Bangladesh. As mobile phone SMS is potentially scalable and likely to be low-cost, it might be considered as an additional technique for glycemic control in the clinics for patients with type 2 diabetes in Bangladesh and similar other developing countries. Further studies on potential benefits of SMS on cardiovascular risks factors, diabetes complications, physical activity and dietary adherence should be explored.

C1. Healthcare use and expenditure for diabetes: This study highlights the large economic burden of diabetes on individuals and healthcare systems in Bangladesh. To the best of our knowledge, this study is the first-ever published matched case-control study of healthcare use and expenditure for diabetes in South Asia. Our results show that the use of healthcare services and medicines was dramatically higher among persons with diabetes (DMs) than in matched controls without diabetes. DMs reported twice as many inpatient admissions and annual inpatient treatment days, 1.33 times more annual outpatient visits and 9.7 times more prescription medicines compared to non-DMs. Using the IDF estimates of 8.4 million DMs in Bangladesh, the total estimated healthcare expenditure for diabetes in Bangladesh is around 5.3 billion USD.

A greater number of patients with diabetes presenting at the clinics in Bangladesh have uncontrolled diabetes and underuse antihypertensive drugs and statins, as found in our previous study [7], which might result in expensive, disabling complications and higher use of medical service as found in this study. In Bangladesh, as in most developing countries, barriers to public-health facilities force the poor to pay for healthcare out-of-pocket, often driving them further into poverty [35, 36]. As a result, DMs may not seek required preventive care, which further increases the risk of complications and are more costly (if treated at all). This underuse of medical care by the general population is a third driver of the large diabetes-associated differences that we report. Medical care in Bangladesh is very costly relative to an average person's mean family income, often difficult to access, and leave a household vulnerable to the effects of catastrophic health expenses [35-37]. Bangladesh has an opportunity to reduce future healthcare costs by diagnosing diabetes earlier and by using inexpensive generic medicines much more widely and thus reducing hospitalizations, disability, mortality [38, 39]. Our data suggests that DMs in Bangladesh are less likely to receive preventive services and medication for proper management of diabetes and its complications, and therefore their high use of inpatient services might be the unfortunate result.

We estimated that healthcare expenditure were 6.12 times higher among DMs than among non-DMs. A similar study in China showed point-of-service payments was 3.97 times higher among DMs than Non-DMs [40]. The expenditure for diabetes in Bangladesh was much higher compared to China and other developed countries where the ratio of expenditure for diabetes ranged from 2.0-2.5 [41-43]. Thus, the social and economic impact of diabetes might be much higher in developing countries like Bangladesh compared to developed countries [40]. The IDF estimated the healthcare costs attributed by diabetes in developing countries to be USD 356 in 2013[44]. If the adjusted expenditure ratio of 6.12 that we observed had instead been used, the IDF estimate would have been much higher. The expenditure ratios reported here imply, that in Bangladesh the economic burden of diabetes may constrain the availability of medical resources for other health conditions and impede national economic growth in future.

C2. Association between diabetes and depression: This study, to the best of our knowledge, is also the first matched case-control study measuring the prevalence of depression and its association with diabetes. Our study showed that depression, particularly in a moderate to severe form, is more common in patients with diabetes than those without diabetes. In addition, we found that the association of depression and diabetes is independent of sociodemographic factors and diabetes-associated complications. Therefore, patients with diabetes should be routinely screened for depression in Bangladesh and probably in other developing countries as well. Management strategies and guidelines adequate for the country level need to be developed and further research to determine the pathophysiological role of depression in the development of diabetes in Southeast Asians is merited.

Limitations of the studies: Our study had several limitations. First, in the cross-sectional study, we collected data from the outpatient of a single hospital in Dhaka city among relatively new cases with access to mobile phones and on oral medications only. Thus, the results cannot be generalized to all diabetes patients in Bangladesh. Second, most of the complications were self-reported and based on patients medical records, which cannot be verified. Therefore, our reported complications might be higher and not always related to diabetes. Second, the WTP study was conducted among the participants of a trial, and thus WTP might be different from the general diabetes population in Bangladesh. Third, our RCT was open-label design, as blinding participants was not possible due to the nature of the intervention. Because no post-randomization data were available for the study participants lost to follow-up, we did not do a full intention-to-treat analysis with imputation of missing values. However, the proportion of lost subjects was small and most likely did not affect the primary outcome. The study population was representative of the general diabetic population in Bangladesh [10], but since access to a mobile phone was required generalizing the results to rural areas or even poorer parts of society may not be possible. Similarly, it remains to be determined whether the HbA1c-lowering effect of the intervention persists for periods longer than six months. Fourth, for the case-control study, we excluded undiagnosed cases of diabetes and pre-diabetes, therefore the results might overestimate medical services utilization for persons with undiagnosed diabetes and prediabetes. It is likely that DMs in our samples were mostly from urban areas, had more complications and were more likely to use and to be able to afford healthcare services than the general diabetes population. Fifth, a major limitation of this study is recall bias by cases and controls about different costs associated with disease and hospitalization. Finally, due to time constraints, we were not able to perform the socio-economic status (SES) analysis for diabetes and the cost-effectiveness analysis of the effectiveness of the SMS intervention for this thesis, which we will perform later.

6. Conclusion

The research project provides evidence that diabetes management in Bangladesh is suboptimal even under best clinical settings, which might be similar in many developing countries. We demonstrate the effectiveness of an innovative SMS model in addition to the standard of care management of T2D in Bangladesh. Automated mobile phone SMS represent a scalable and likely low-cost method to improve glycemic control for patients with T2D in Bangladesh and similar developing countries. The majority of our participants expressed willingness to receive diabetes-related SMS and pay a modest amount for such service, which seems reasonable compared with the current expenditure for physician fees. Considering the huge number of diabetes patients and the low mobile phone rates in Bangladesh, a self-sustained business model for basic mHealth services for chronic diseases is therefore feasible

in this and potentially other low-income countries. As diabetes is a costly condition, prevention and optimum management of diabetes should be a priority for all stakeholders.

7. Publications

1. **Shariful Islam SM**, Lechner A, Ferrari U, Froeschl G, Niessen LW, Seissler J, Alam DS: Social and economic impact of diabetics in Bangladesh: protocol for a case-control study. BMC Public Health; 2013; 13:1217.

2. **Shariful Islam SM**, Lechner A, Ferrari U, Froeschl G, Alam DS, Holle R, Seissler J, Niessen LW: Mobile Phone Intervention for Increasing Adherence to Treatment for Type 2 Diabetes in an Urban Area of Bangladesh: Protocol for a Randomized Controlled Trial. BMC Health Services Research. 2014; 14:586.

3. **Shariful Islam SM**, Alam DS, Wahiduzzaman M, Niessen LW, Froeschl G, Ferrari U, Seissler J, Rouf HMA, Lechner A: Clinical characteristics and complications of patients with type 2 diabetes attending an urban hospital in Bangladesh. Diabetes and Metabolic Syndrome Clinical Research and Reviews; 2015; 9:7-13.

4. **Shariful Islam SM**, Lechner A, Ferrari U, Seissler J, Holle R, Niessen LW: Mobile phone use and willingness to pay for SMS for diabetes in Bangladesh. Journal of Public Health. (Oxford, England). 2015. doi: 10.1093/pubmed/fdv009

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Manuscripts under review:

6. **Shariful Islam SM**, Niessen LW, Seissler J, Ferrari U, Islam A and Lechner A. Diabetes knowledge and glycaemic control among patients with type 2 diabetes in Bangladesh. Springer Plus. 2015.

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Author Contributions: Sheikh Mohammed Shariful Islam was responsible to design and develop the study protocol as the Principal Investigator, overall responsible to implement the studies, supervise data collection, data entry, perform data cleaning and data analysis, and write the first draft of the manuscripts and prepare the final manuscript for submission. Andreas Lechner, Uta Ferrari, Louis Niessen and Jochen Seissler were responsible for guiding the development of the study protocols, provided expert opinion and feedback, supported data collection, data analysis and reviewing the draft manuscripts for scientific improvements. Rolf Holle was involved in supporting the health economic component of the study protocol, provided data analysis support for economic analysis and reviewed the draft manuscripts. Other co-authors were involved mainly to review the draft manuscripts and provide scientific suggestions to improve the manuscripts.

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13. Islam SMS, Lechner A, Ferrari U, Froeschl G, Niessen LW, Seissler J, Alam DS: Social and economic impact of diabetics in Bangladesh: protocol for a case-control study. *BMC public health* 2013, 13(1):1217.
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Annex 1. Curriculum Vitae of Shariful Islam

EDUCATION:

- **PhD student (International Health):** Center for International Health, Ludwig-Maximilians University, Munich, Germany 2012-2015
- **MHR (Masters in Human Rights):** Dhaka International University. 2009-2010 (CGPA-3.84/4.00)
- **MPH** (Major in Epidemiology)**:** University of South Asia 2008-2009 (CGPA 3.75/4.00)
- **MBBS:** Bangladesh Medical College, Dhaka University, September 2000. (Passed)
- **Higher Secondary Certificate:** Notre Dame College, Dhaka, 1992 (First Division)
- **Secondary School Certificate:** Bangladesh Embassy High School, Jeddah, Saudi-Arabia, 1990 (First Division, Star Marks)

PROFESSIONAL EXPERIENCES:

- **Senior Research Investigator, Center for Control of Chronic Diseases, ICDDR,B: 01/ 2011 to Till-Date. [**I Completed several large scale epidemiological and clinical trial studies as Principal Investigator and Co-Investigator. Currently, involved as PI in developing a large scale implementation study with funding from the Government of Bangladesh (USD 6 Million). Also, working to develop clinical trials for diabetes and cardiovascular research.]

- Project Officer, German Technical Cooperation (GIZ) Bangladesh: 12/2009 - 12/2010
- Program Officer, Partners in Population and Development (PPD) Bangladesh: 05/2007- 04/2009
- Medical Officer, United Nations Development Programme (UNDP) Bangladesh:01/2006 -03/2007
- Research Investigator, ICDDR, B, Bangladesh: 10/2004 -01/2006
- Clinical Trial Physician: Texas Tech University Arsenic Project in Bangladesh: 01/2004 -10/ 2004
- Medical Officer and Center Manager, TARA Bangladesh: 11/ 2001 - 01/2004
- Resident Medical Officer, Bangladesh Medical College Hospital, Dhaka: 11/2000-11/2001

TEACHING EXPERIENCE:

1. Adjunct Faculty, James P. Grant School of Public Health, BRAC University, January 2013 to present. Courses: Epidemiology, Biostatistics-1 and Biostatistics-2
2. Faculty, CCCD, icddr,b Course on Advanced Research Methodology (CARM), for Post-MPH Research Fellows, January 2013 to till date

- **Student Thesis Supervised:** 4 MPH and 3 Post-MPH Fellows

- **Current Mentoring:** Currently mentoring three Masters students from Imperial College London, UK, Macquarie University, Sydney, Australia and Asian University for Women, Bangladesh.

- **Publications:** Total 17 including 12 as First Author (11 additional papers under review)

- **Journal Editorial and Review:** Sub-section Editor, Journal of Health, Population and Nutrition, Editorial Board Member, British Journal of Medical Practitioner and Reviewer, Bulletin of WHO

- **Awards:** Emerging Leader, World Heart Federation; DAAD Scholarship for PhD in International Health; Fogarty Fellowship (University of California, Berkeley, USA); WHO Fellowship, Packard Foundation Fellowship and Gold Medal for Academic Excellence (SSC).

- **Professional Membership:** Bangladesh Medical & Dental Council; Population Association of America; Asian Population Association; European Society of Cardiology; IUSSP.

Annex 2. List of publications of Shariful Islam

1. **Shariful Islam SM**, Niessen LW, Ferrari U, Seissler J, Ali L, Lechner A. Effects of mobile phone SMS to improve glycemic control among patients with type 2 diabetes in Bangladesh: A prospective, parallel-group, randomized controlled trial. Diabetes Care. 2015 (Press)
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17. **Shariful Islam SM**, Moreau A: Traditional healers in preventing HIV/AIDS: Roles and Scopes. Bulletin of Medicus Mundi International. 01/2009; 113.
18. **Books:** Dr. Sheikh Mohammed Shariful Islam: Health Rights in Bangladesh. 2011;VDM Publisher, Germany

Papers submitted in 2014-2015: (Under Review)

19. **Shariful Islam SM**, Lechner A, Ferrari U, Hossain MP, Laxy M, Seissler J, Niessen LW, Holle R. Healthcare use and expenditure for diabetes in Bangladesh: A matched-case-control study. Plos One. 2015.
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Annex-3. Trial Profile

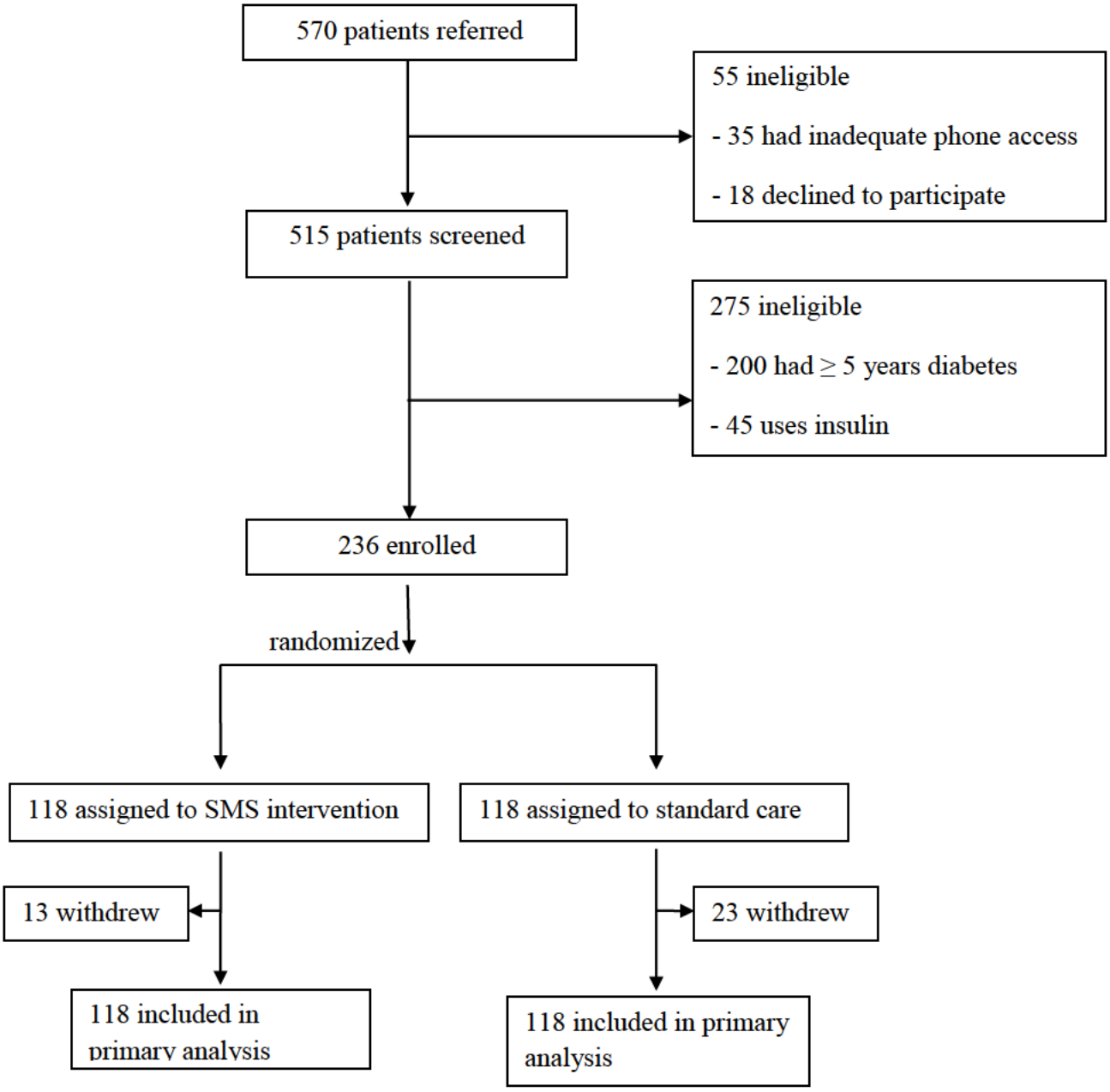
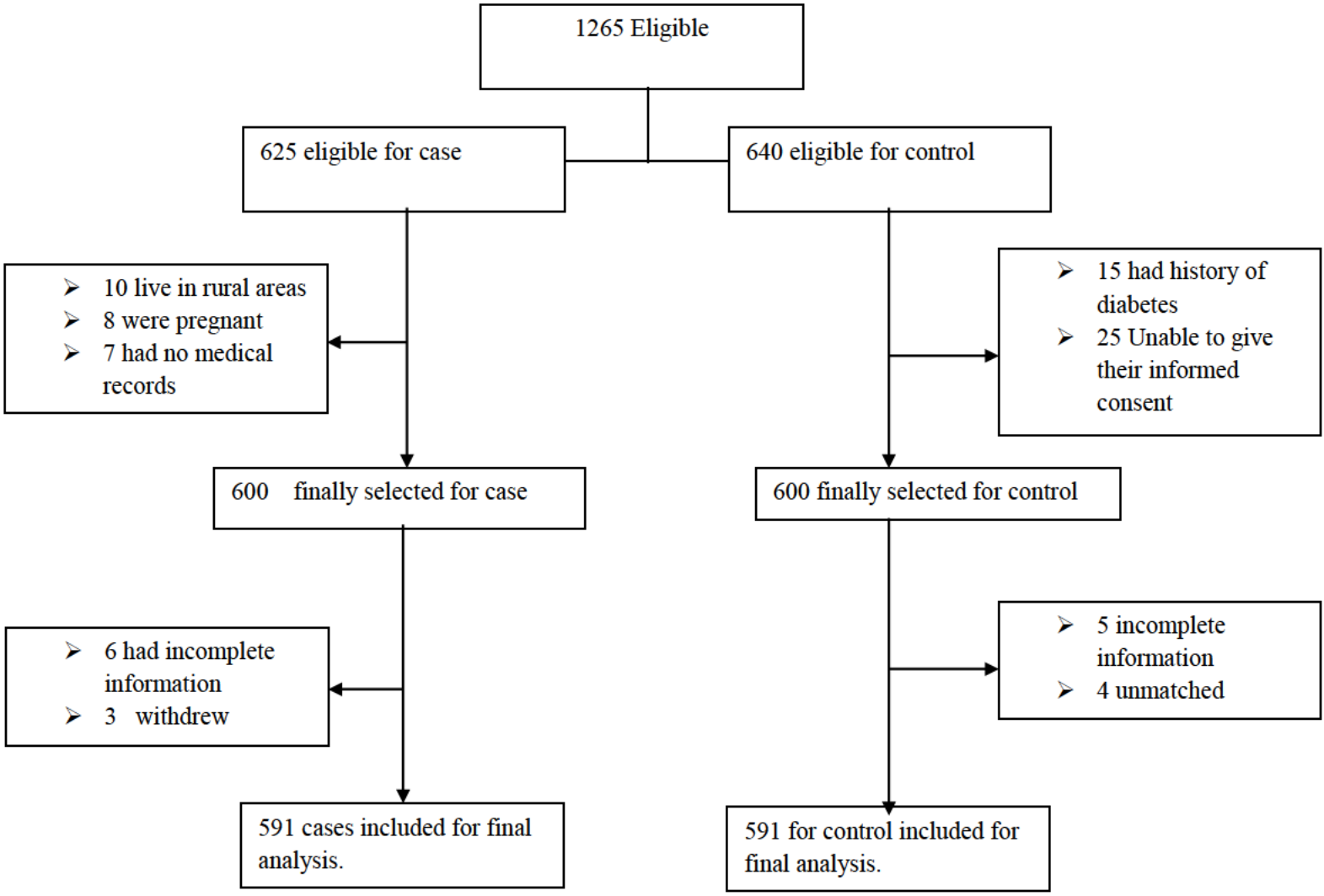


Figure 1: Trial profile

Annex-4. Selection of participants for the case-control study



Annex-4. Post-hoc subgroup analysis of the SMS intervention trial

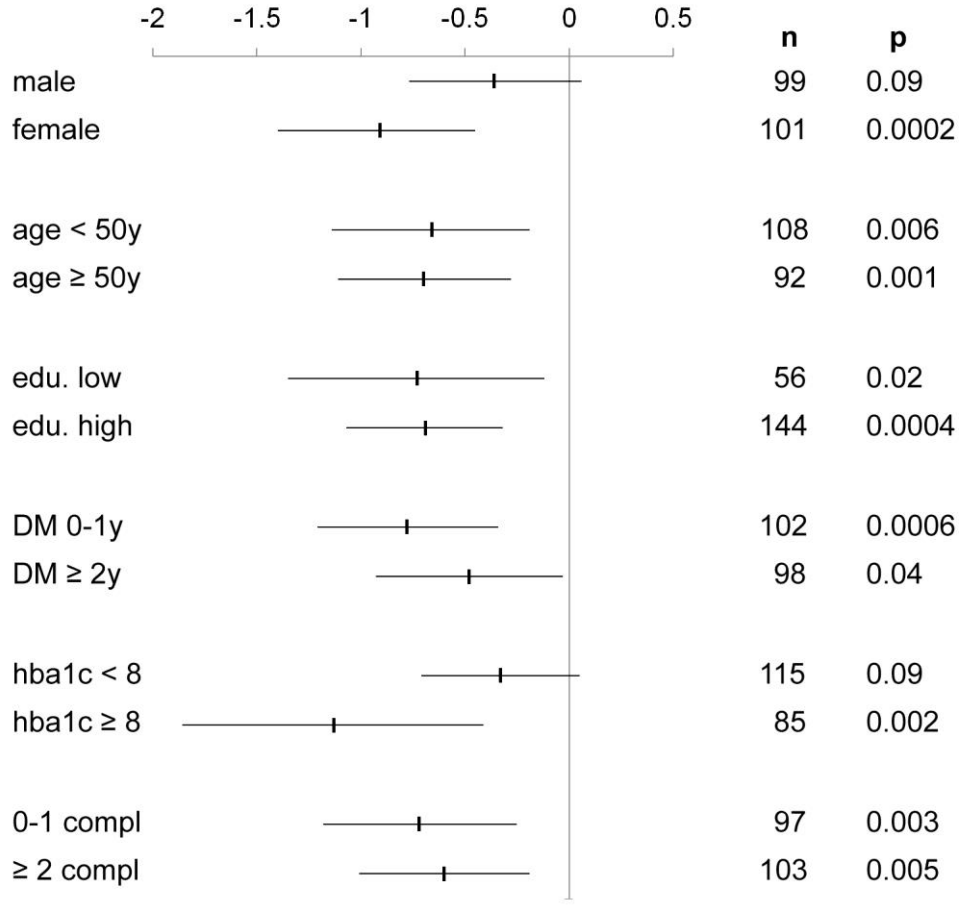


Figure. Post-hoc subgroup analysis of the HbA1c difference between the intervention and the control group

Annex-5. Acknowledgements

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