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EVALUATING COST-EFFECTIVENESS OF TREATMENT OPTIONS FOR DIABETES PATIENTS USING SYSTEM DYNAMICS MODELING

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ABSTRACT

The growing global diabetes epidemic is a serious public health problem. We developed a system dynamic model to study the cost-effectiveness of different diabetes treatment options. According to existing literature, we estimated dynamic costs and changes of hemoglobin A1c levels of two first-line monotherapies and a hypothetical innovation therapy for glycemic control over a 15-year horizon. Incremental cost-effectiveness ratios were expressed as dollars per HbA1c decrement from perspectives of the patient, insurance-payer, and society. Simulation results showed that better adherence with a more expensive and efficacious drug results in better control of HbA1c and cost-saving in the long-run. The results also showed that the cost-effectiveness ratio varied with patients' pre-determined out-of-pocket payment for health expenditure. The higher the rate of their out-of-pocket payment for extra health care expenditure to their household income, the more cost-effective it is for the innovative drug from the perspectives of the patient, insurance-payer, and society.

1 INTRODUCTION

Despite advances in clinic treatment and great efforts of public health programs on prevention and management, the global burden of diabetes is increasing. During recent years, the prevalence of type 2 diabetes mellitus (T2D) has reached almost 10% among adults in large countries like the U.S. and China (NDSR 2014; Yang et al. 2010; Xu et al. 2013). It is estimated that worldwide 382 million people were diagnosed with diabetes in 2013; and by 2035 the number will likely rise to 592 million with a worldwide medical cost of $500 billion, accounting for more than 10% of total health care expenditure globally (IDF 2013).

Many cost-effective pharmacological agents and diabetic prevention programs are available for glycemic control (Li et al. 2010; Tarride 2010). However, poor patients' compliance or adherence to treatment makes current diabetes care less effective than expected (Rozenfeld et al. 2008; Bailey and Kodack 2011; Ji and Hu 2013). Studies suggested that less than 50% of patients achieve the glycemic goals in both US and China (Bailey and Kodack 2011; Ji and Hu 2013). Among all factors that influence patients' adherence to medications, cost has been recognized as one of the key determinants (Kurland et al. 2009; Tunceli 2015). Poor adherence to medication also results in significant impact on health care costs, such as increasing hospitalizations and complications (WHO 2003; Encinosa et al. 2010; Golay 2011).

Simple models of treatment adherence cannot integrate all the information necessary to depict complex dynamic interactions governing adherence choices over time (Sterman 2000; Primozic et al. 2012). The information may include individual's preferences, and the evolving awareness of how adherence choices alter their financial situation, health, and co-morbidities. Thus, systems sciences perspectives and simulation modeling such as system dynamics model (SD), network analysis, and agent-based modeling have been used widely in the past decades (Homer and Hirsch 2006; Luke and Stamatakis 2012; Wang et al. 2015). SD is an approach to understand the nonlinear behavior of complex systems over time using stocks and flows and internal feedback loops and time delays. It has attracted increasing attention in public health field to evaluate the effectiveness of the health care system as a whole or specific intervention programs (Jones et al. 2006; Mahamoud et al. 2013). Regarding diabetes, most of the studies are conceptual frameworks while others simulate social and economic burdens based on population level data (Jones et al. 2006; Homer et al. 2004). Although a couple of models have incorporated individual's behavior with clinical consequences, very few economic evaluations integrate economic constraints and individuals' decisions with medical cost and clinical outcomes of hemoglobin A1c(HbA1c) simultaneously (Carson 1998; Eddy and UKPDS 1998).

To fill in this literature gap, we conducted cost-effectiveness analysis of diabetes interventions from a systems perspective. We developed a generic SD to evaluate the dynamic costs and health outcomes of diabetes interventions with considerations of multiple causalities, feedbacks loops, and delays of the system. This study will be helpful to understand cost-related non-adherence to medications, provide constructive input in policy design, intervention implementation, and guide multi-level decision making on the optimal allocation of resources.

2 METHODS

After integrating literature and insights from experts into a SD of costs and effectiveness of diabetes care, we established a set of plausible difference equations to simulate the dynamic changes of levels of HbA1c, as well as medical and non-medical costs for diabetes patients over a time horizon of 15 years.

2.1 System Boundary

For simplicity, we defined the system boundaries of the diabetes care model as resources, medication decision making, and HbA1c dynamics which proxies the progressive stages of diabetes (Figure 1). As shown in the framework, high levels of HbA1clead to progressive complications and decreased economic productivity, which results in constrained resources and medical choices. In addition to the available resources covering short- and long-term care cost, medical choices also depend on cost of interventions, and health insurance coverage as well as stage of diabetes and related risk of complications. In contrary, risk of complications can be reduced or controlled by interventions if the cost bellows the available resources. The dynamics of medical and non-medical cost also influence dynamics of resources reversely due to non-medical cost such as productivity losses.

2.2 Model Structure

Based on the above framework and health investment models, we developed feedback loops in causal loop diagram (Figure 2a). In the Figure, B1 is a balancing loop representing the counteracting effect of T2D interventions opposes the action of taking more medications. The negative feedback loop occurs because with higher adherence and higher efficacy of medications, will lower the level of HbA1c (Holman et al. 2008; Hoffmann and Spengler, 1997). Given the cost constraint of medication, balancing feedback loop B2opposes the action of taking more medications. In loop **B2**, taking more medicine means the increase of cost for medication, adding to the total health expenses, potentially resulting in higher insoluble health expenses. Ultimately with increased perceived financial burden, patients tend to reduce the intake of medicine.

Reinforcing feedback loop **R1** captures patients' decision of switching to use cheap medicine due to the cost constraints on medication. Because of the high perceived financial burden of using an effective medicine, patients switch to the less effective one with consequent increase in health cost although with a pace that is slower than that associated with the effective medicine. This cost gradually accumulates and increases patients' financial burden. Nevertheless, in order to maintain health, patients still have to adopt medications and choose inexpensive options.

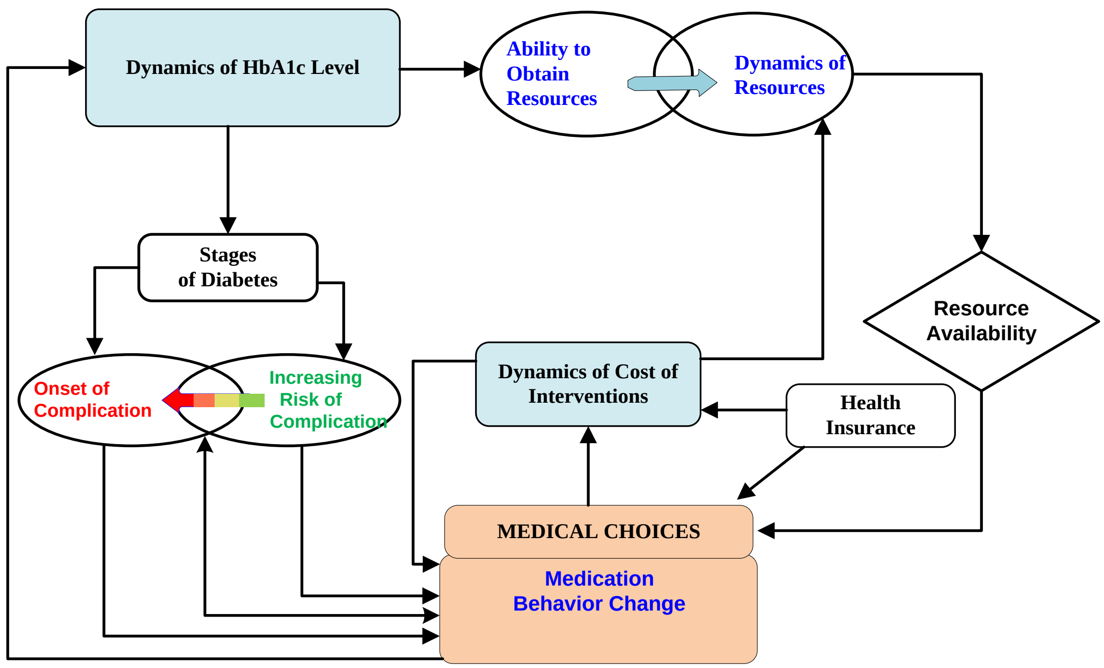

Figure 1: Macro-level system structure for type 2 diabetes (T2D) care.

Even though patients with limited resources tend to use less effective options to treat their T2D, this course of action is suboptimal possibly leading to higher risk of diabetes complication (Hoffmann and Spengler, 1997). This aforementioned case is captured in balancing feedback **B3**. Compared to effective medicine, taking less effective medicines reduces the efficacy of medication. The lower the efficacy of medication, the worse T2D control is as indicated by HbA1c.

Taking an inexpensive medicine increases the chance of complications of diabetes which eventually lowers income due to the high cost of interventions, and lower productivity. Using more of the cheaper medicine will sacrifice the efficacy of intervention and increase the odds of complication. As the complication occurs, financial resources become constrained forming a vicious cycle. This is represented in reinforcing feedback loop **R2**.

On the contrary, the decision of taking expensive medicine forms a virtuous cycle represented by reinforcing feedback loop **R3**. In the case of perceived financial burden, patient can afford to use more expensive medicine. With its high efficacy, better medicine can change the net increase rate of HbA1c to negative consequently reduce the level of HbA1c. As HbA1clevel is far away from the threshold for complication to occur, patient would spend less on the medical treatment and they have low perceived financial burden accordingly.

From the feedback loops, we further developed a stock and flow diagram to illustrate how patients' financial resource constraints and health insurance policies influence their decision-making for medications and the consequences of these decisions (**Figure 2b**). In the figure, stocks are shown as boxes representing accumulations and flows are depicted by faucet representing how fast a stock changes. Stocks are governed by a balance between inflows and outflows. For example, the level of HbA1c is determined by the accumulation on the difference between rate of glycolization of hemoglobin in the blood and the rate of clearance of HbA1c.The efficacy and adherence to the chosen medicine can reduce the glycolization rate by limiting the total amount of time the body is exposed to high glucose levels. The medication choice is based on the trade-off between the stage of diabetes and the stock of payment, which is the proportion of the amount spent on diabetes care exceeding average health payment to the total household income. The total cost is the sum of the total insurance expenditure and the total personal expenditure. Total insurance expenditure is the integral of expense paid by insurance provider for the complication treatment and the proportion of T2D medication expenses over time. The total personal expenditure is equal to the integral of the sum for income loss due to T2D and out-of-pocket health expenditure over time. The expected expenditure above average out-of-pocket is the integral for the difference between the health expense increase rate and payoff rate. Health expense increase rate is determined by the expenditure not covered by insurance for the complication treatment and T2D medication.

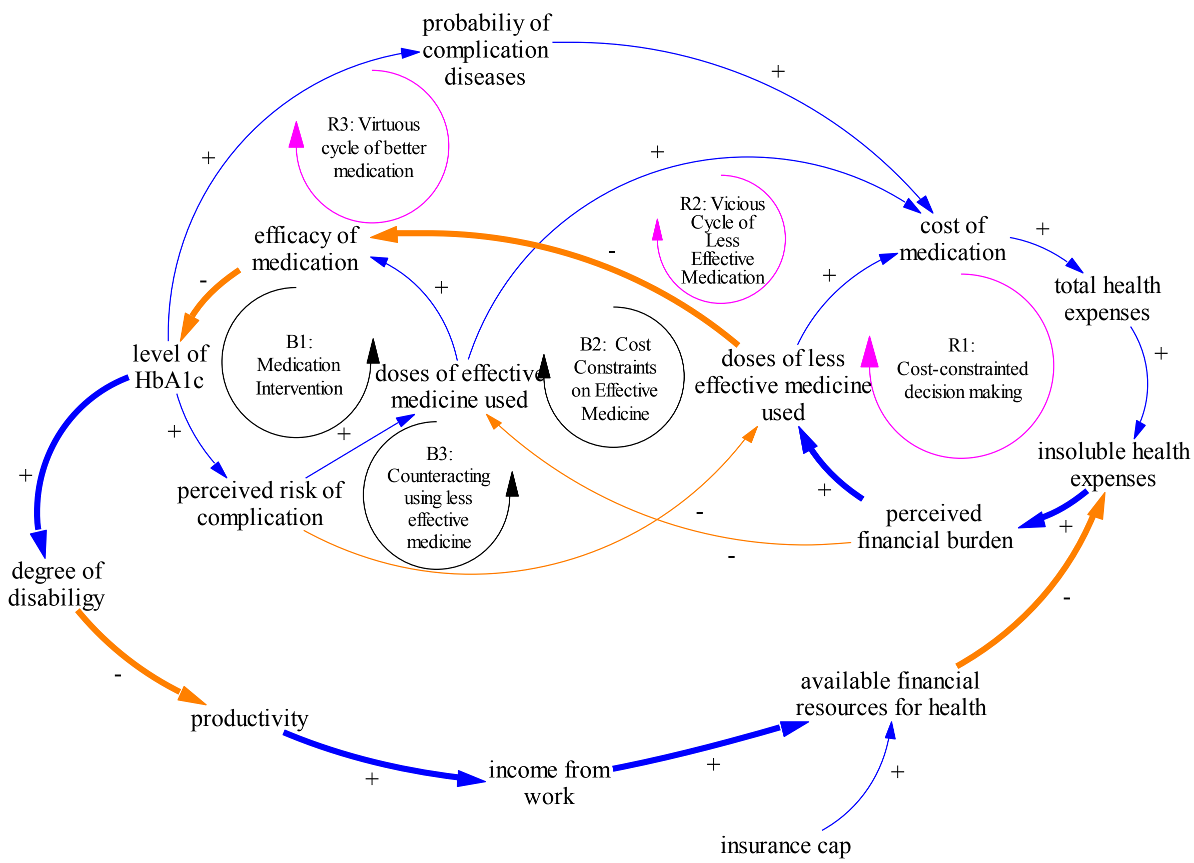

Figure 2a: Feedback loops capturing dynamics in T2Dintervention cost and impact on health outcomes.

2.3 Simulation Scenarios and Data Source Sensitivity Tests

To demonstrate, we assumed that two therapies were available on the market: One is M1 (Metformin), which helps patients to keep HbA1c <7.0. If patients' HbA1c>=7.0, then M2 (Acarbose) will be used. Patients do not need to take any medicine if HbA1c <6.5(Table 1). The intervention scenario is in addition to M1 and M2, there is a new hypothetical innovative therapy M3. We assume that M3is more expensive and has better efficacy than M2.

Costs and outcomes are simulated based on two different decision-making scenarios. For scenario 1 simulation, for status quo, when the HbA1c is high >7.0, and at the same time, the expected expenditure above average out-of-pocket is smaller than 7% of the patient's income, he/she would like to use M2. Otherwise, he/she will still use M1 because it is completed covered by insurance. For intervention status, if expected expenditure above average out-of-pocket is smaller than 7% of the patient's income, she/he would choose M3. Otherwise, he/she will use M1 as in status quo. Scenario 2 is similar to scenario 1 except that the cutting point for expected expenditure above average out-of-pocket is 10% instead of 7%.

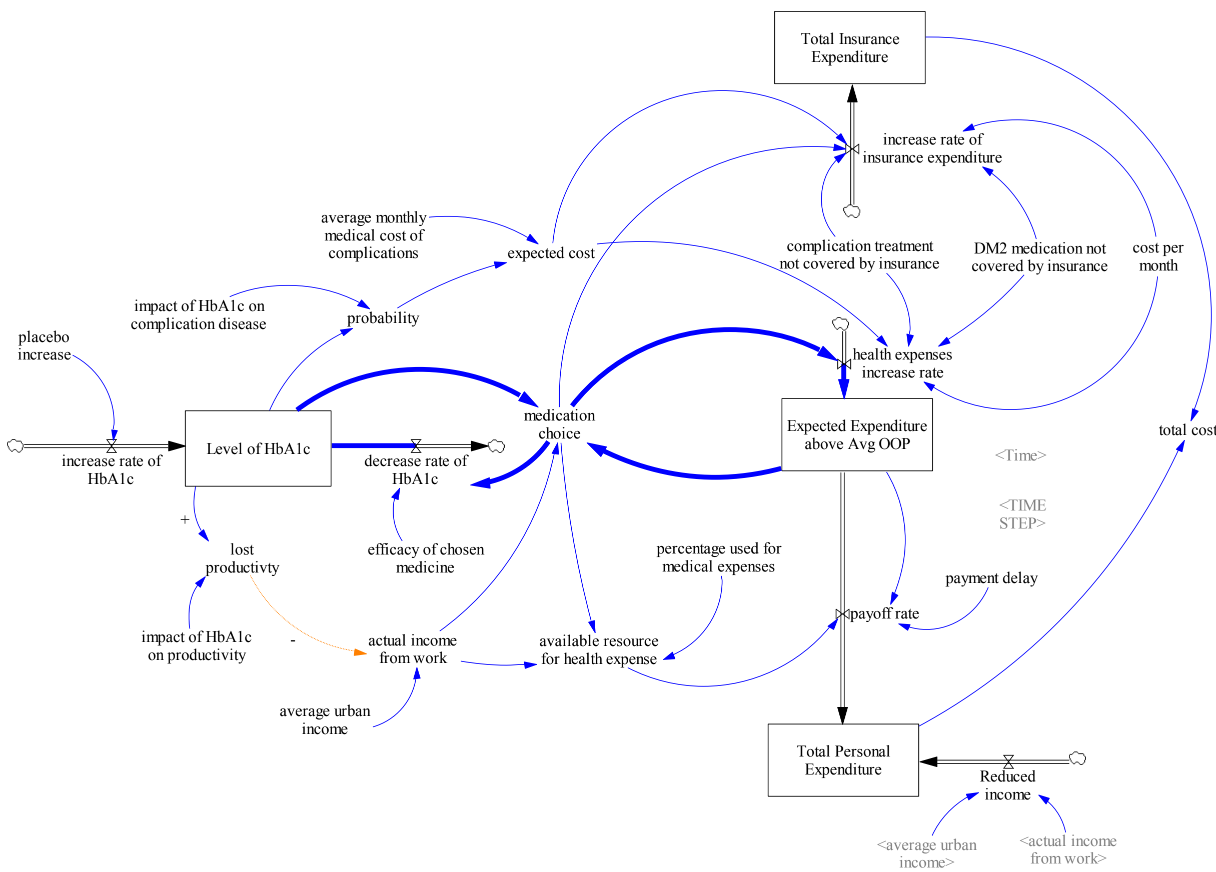

Figure 2b: Stock flow diagram of system dynamic model for T2Dintervention cost and impact on health outcomes.

The model's parameters were specified mainly from public available secondary data sources as well as estimates from international literature and opinions from diabetes clinicians and experts. The first-line diabetes therapies were based on 2013 Chinese Handbook for Diabetes Management. Their clinical efficacies, rates of complication risks, and diseases progression are mainly from previous literature (UKPD,

Table 1: Two scenarios.

Scenarios	**Expenses**	**HbA1c <6.5**	**6.5<=HbA1c <7.0**	**HbA1c>=7.0**
Scenario 1	Patients expected expenditure above average out-of-pocket is smaller than 7% of the patient's income	No Medicine	Metformin (M1)	Acarbose(M2) Or Hypothetical New Drug (M3)
Scenario 2	Patients expected expenditure above average out-of-pocket is smaller than 10% of the patient's income	No Medicine	Metformin (M1)	Acarbose(M2) Or Hypothetical New Drug (M3)

1998; Holman et al. 2008; Hoffmann and Spengler, 1997; Hirst et al. 2012; Eddy, Schlessinger, and Kahn, 2005).

We assumed the annual increase in HbA1c level with conventional treatment was about 0.14% per year over 10 y and 0.11% over 15 y and pharmacotherapy affects only HbA1c in the model and the multiplier on HbA1c is M1: 0.98, M2: 0.965 and M3: 0.9 (UKPDS, 1998; Yang et al. 2014). Medical expenditures and insurance coverage were based on the market available data in China. Specifically, based on the market prices and common dosage used, we assumed monthly expenditures for M1, M2, and M3 were $110.8, $150.5, and $205.3. M1 is 100% covered, but M2, M3 and other insurance coverage for complications (catastrophic disease from diabetes) were 80%. According to Chinese statistic year book, we also assumed that salary increase rate and inflation rate was5% as supported by recent averages of inflation in China. Dynamic cost-effectiveness analysis for the above two scenarios were as conducted as the following:

$$ICER_t = (\textit{Cost of intervention}_t - \textit{Cost of status quo}_t) / (\textit{HbA1c of status quo}_t - \textit{HbA1c of intervention}_t)$$

Where,

1) *t* is from month 1 to month180;
2) *intervention scenario* is when M1, M 2 and M 3 are available, patients choose nothing, M1, M2 or M3 based on their clinical needs and predetermined budget on out-of-pocket payment for medical care at each time period;
3) *status quo scenario* is when only M1 and M 2 are available, patients choose nothing, M1 or M2 based on their clinical needs and predetermined budget on out-of-pocket payment for medical care;
4) *Cost of intervention* $_t$ is the accumulated cost from time 0 to t of intervention scenario
5) *Cost of status quo* $_t$ is the accumulated cost from time 0 to t, of status quo scenario
6) *HbA1c of intervention* $_t$ is the HbA1c at time t in intervention scenario
7) *HbA1c of status quo* $_t$ is the HbA1c at time t in status quo scenario

2.4 Sensitivity Tests

In order to understand the whole system better, we evaluated the robustness of our results by doing univariate and multivariate sensitivity analysis. We chose payment delay and proportion of insurance coverage because initial explorations of the model showed there was some sensitivity to these two parameters. The payment delay affects how fast the unpaid expenditure is paid off and the original value was 1 month. In the simulation, we set a range of {0.1,3}. The variable, "complication treatment not covered by insurance", represents the proportion of medical charges that are not covered by the "insurance for catastrophic disease" with the baseline value set at 0.2. In the sensitivity analysis, we allowed it to range from {0.15, 0.25}. We also applied Monte Carlo methods assuming these two designated parameters are each distributed normally with standard deviation of 25% of their base case values.

3 RESULTS

3.1 Results of Dynamic Accumulated Costs and Outputs

Figures 4a-4d present projected dynamic accumulated costs and outputs for 15 years for status quo and intervention of scenario 1. As expected, the HbA1c level is lower over time for intervention group than status quo for both scenario 1 and scenario 2, and intervention treatment in scenario 2 have a better glycemic control (HbA1c <7.0) over time (Figure 3a). The total cost trends for two treatments in scenario 1 are similar (Figure 3b). For scenario 2, although the costs for intervention group scenarios are higher than those of the status quo in the first 8 years, its cumulated cost over 15 years is only $ 63,000 compared to $78,000 for status quo.

To illustrate different costs for patients and insurance decision makers, we divided the total cost into insurance coverage cost and personal out-of-pocket cost. We can see that the insurance cost trends for interventions in scenario 1 and scenarios 2 are slightly higher than status quo, especially in the short-run (Figure 3c). However, patient's out-of-pocket costs is much lower for intervention groups than groups of status quo in both scenarios (Figure 3d). For example, for scenario 2, the cumulated cost of out-of-pocket over 15 years is $11,000 less for intervention than for status quo.

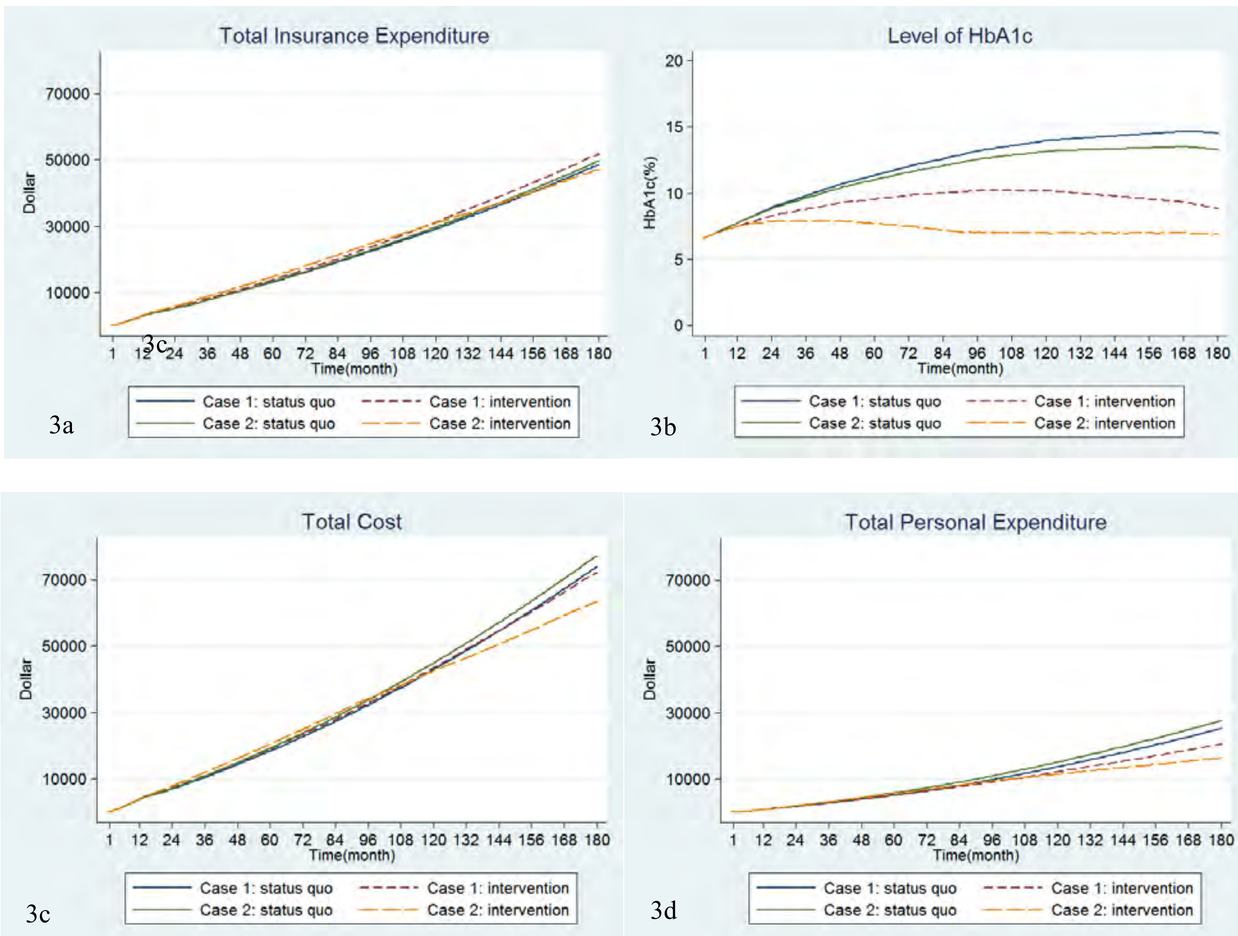

Figure 3: Projected costs and level of HbA1c for status quo and intervention for scenarios 1 & 2 (3a-3d).

3.2 Results of Projected Incremental Cost-effective Ratios (ICERs)

Figure 4a-c presents the projected incremental cost-effective ratios (ICERs) based on total cost, personal cost, and insurance cost regarding the change of HbA1c under intervention scenarios 1 and 2. These ICERs represent the cost for lowering one unit of HbA1c from the societal, insurance, and personal perspectives. The lower the ratio, the more cost-effective it is for intervention when M3 is available on the market. Negative ICER means that it costs less when M3 is available, but HbA1c is under better control. In general, the ICERs are decreasing over time and the decreasing rate is higher for scenario 2.

Figure 4a shows that the ICERs from societal perspective (i.e., total cost) starts at 782 dollar per HbA1c decrement for both scenarios. As the interventions go on over time, ICERs gets negative after 8 years (96 months) under scenario 2 and 12 years (144 months) under scenario 1. From insurance perspective, ICERs starts at 704 dollars per HbA1c decrement and decreases gradually and gets the value below zero after 12 years under scenario 2 (Figure 4b). Under scenario 1, ICERs decreases during year 2 to 4 to 344 dollar per HbA1c decrement and keeps stable until year 7, then increases to 595 dollar per HbA1c decrement from year 7 to15 under scenario 1. From the personal perspective, since most of the costs are covered by insurance, ICER is only 500 dollar per HbA1c decrement for both scenarios 1 and 2 during year 1 and begins to be negative in year 3.5 (Figure 4c).

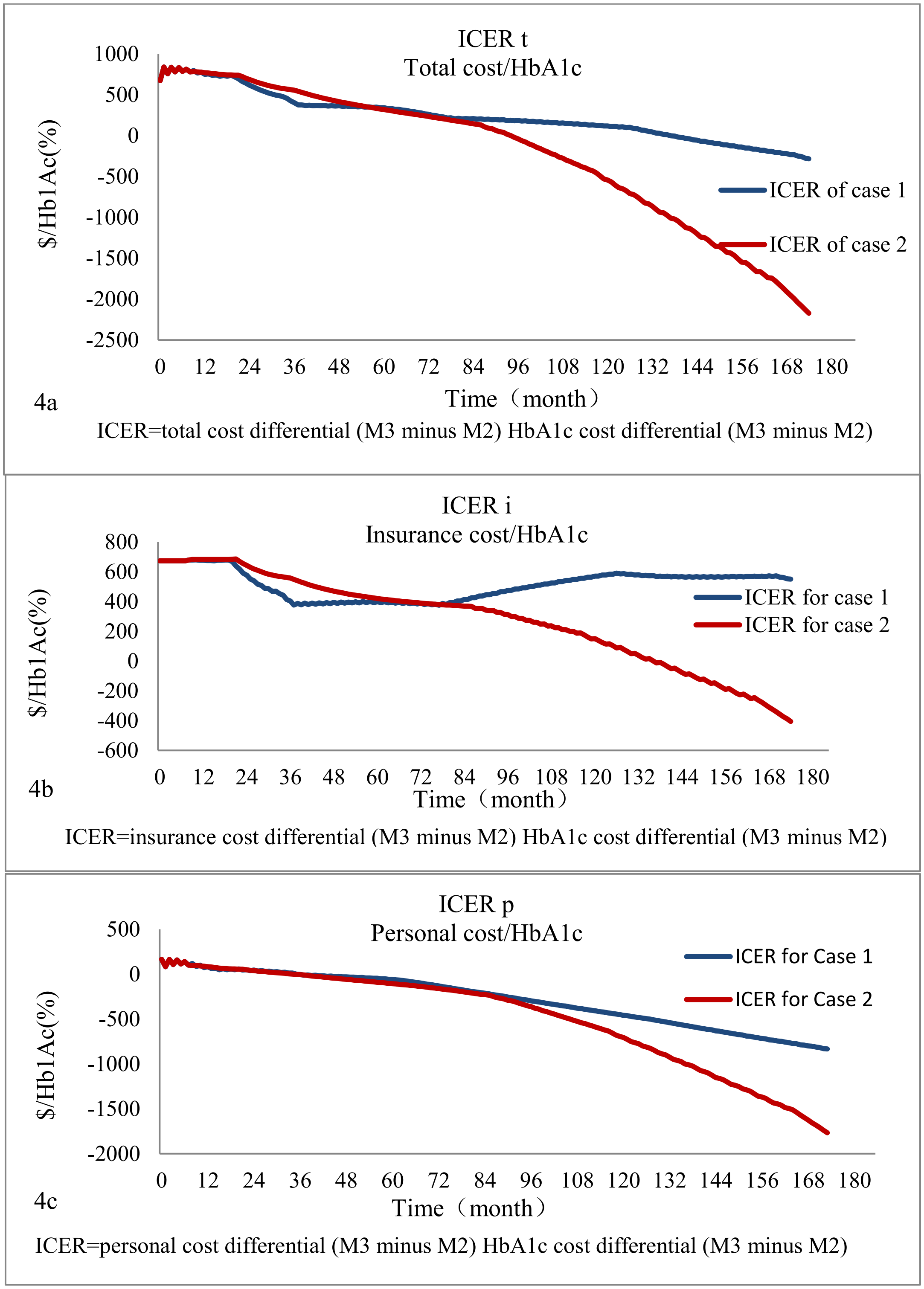

Figure 4: Projected ICERs based on total cost, personal cost, insurance cost and HbA1c for scenarios 1 and 2 (4a-4c).

4 DISCUSSIONS

If diabetes patients want to and can afford to pay more out-of-pocket for medical treatment for their health condition, they are more likely to be adherent to recommended medications. Our results showed that although a more expensive and effective drug might cost more in the short-run, in the long-run it would cost less and have better glycemic control. It also suggested that the more patients were willing to pay out-of-pocket for medical treatment, the more cost-effective an innovative therapy could be from both patients and societal perspectives. This may be due to the better adherence to the therapy and achieve its full cost-effectiveness and reduce non-adherence to therapy costs including the cost of treatment for complications.

Conventional health economic theory assumes that patients invest in their health by purchasing medical care and obtain optimal amount of care while maximize their utility under budget constraint. However, recent behavior economics and system sciences all demonstrated that due to bounded rationality of human mind, it is almost impossible for an individual to handle so many dynamically interacting variables in a complex system, such as diabetes care. As we can see from our framework, patients or even clinicians cannot handle those complex non-linear interactions among economic resources and health status factors. Thus, their individual decision-makings are usually limited to experiences and judgment for short-run and may not be optimal from either personal or societal perspectives.

Health insurance exists in almost all countries in the world to reduce patients' financial risks of health problems. On the one hand, many theoretical and empirical studies have shown that health insurance also makes medical care market inefficient. It reduces patients' income and price elasticity of medical care which leads to moral hazard of overusing health care. Thus, out-of-pocket payment is designed by most of the insurance programs to reduce moral hazard. On the other hand, recent literature points out that out-of-pocket payment, patients may underuse medical care due to their bounded rationality (Williams et al. 2013). Thus, they argue to cancel out-of-pocket payment for certain treatment, such as chronic conditions like diabetes.

At present, approximately 10% of Chinese adults have diabetes, and the rate has been growing steadily in recent years with the increase in obesity rates.[2] Diabetes, especially pool treatment of the condition, is very costly to patients, their families and the society. Therefore, effective prevention and management of diabetes is becoming an important public health priority in China and many other countries (Wang et al. 2007).

By compressing time and space, our SD framework offers decision makers a clear picture on how certain assumptions or decision might affect their choices and the consequent costs and outcomes in the future. Our study indicates that an innovative more expensive and high efficacy drugs can be cost-effectiveness, especially when patients are more likely to pay certain amount of out-of-pocket. Thus, public health policy should not only allocate resources to health insurance, but also to patients' education including their knowledge on diabetes complications and adherence to their therapies.

Currently, many countries have adopted economic evaluation methods for national policy making. Our study indicates that ICER depends on patients' decision making of out-of-pocket payment for medical treatment. The feedback structure of patient intervention choices may endogenously influence the cost and effectiveness of diabetes care dynamically. Thus, when conducting health economic evaluations for treatment of complex chronic condition like diabetes, it is important to consider cost-related non-adherence as well as multi-medication treatment in the real world.

This study has few limitations. Given the availability of data, this research only provided very preliminary results on the economic evaluation of T2D care. With more data available, the model needs to be calibrated and validated to make it more valuable for multi-stakeholders. This model emphasizes patients' decision making in diabetes care. In the future model, we will explore different scenarios including integrating patients' exercise and diet behavior changes, physician's behaviors, and different public health policy and insurance policies in the model. Our sensitivity analysis shows that the main results are robust to reasonable variation of key parameter levels. A key strength of the study is the application of systems modeling to study the complex dynamics and interactions regarding patients' adherences to medications, economic resources and health outcomes.

5 CONCLUSIONS

This study provided a platform for patients, health providers and policy makers to understand the complexities of patients' adherence with medications in diabetes care. It suggested that systemic dynamic simulations can be a new vehicle for health economic evaluation to provide insights for multilevel stakeholders to make decisions. The results also suggested that cost-related non-adherence with medication should be considered while conducting health economic evaluations for treatment of complex chronic condition like diabetes in the real world.

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