Evaluating the Cost-Effectiveness of Metformin in Prediabetes Management: A Markov Model Analysis Combining Clinical and Real-World Data

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Background

- Prediabetes is defined as impaired fasting glucose (IFG), or impaired glucose tolerance (IGT), and a mixture of the two (IFG + IGT)[1].
- A 2015-2017 National Epidemiologic Survey revealed that the prevalence of prediabetes in China is 35.2% [1].
- The development of prediabetes is influenced by a number of factors, including the natural aging process, lifestyle modifications resulting from urbanization, excess body weight and obesity, dyslipidemia, and non-alcoholic fatty liver disease (NAFLD), which are becoming increasingly prevalent in China [1].
- A delay in the age of diagnosis of diabetes has been demonstrated to result in a reduction in mortality rates due to all causes, cardiovascular disease (CVD), and other factors[2].
- Patients with later-onset diabetes exhibit a reduced incidence of complications, a diminished risk of mortality, and a lower overall cost of treatment compared to patients diagnosed with diabetes at an earlier age.
- Lifestyle interventions alone or a combined approach with metformin proved to be effective to prevent or delay the onset of diabetes, reduce the incidence of complications, and ultimately lead to significant healthcare savings. However, the cost-effectiveness of such interventions remains unknown, which is essential for policy making and resource allocation.

Objective

- Our study aims to estimate the lifetime cost-effectiveness of metformin combined with lifestyle interventions versus lifestyle interventions alone among pre-diabetic subjects.

Methods

Research Design

- A Markov model was developed to conduct a cost-utility analysis (CUA) among adults with impaired glucose regulation.
- The model incorporated data from the China Diabetes Prevention Program（CDPP) and real-world evidence, to simulate the long-term health and economic outcomes of two intervention strategies.

Research Design Details	
Target population	• Adults with impaired glucose regulation in China
Interventions & comparators	• Metformin (850 mg/d 2 weeks later 1700 mg/d) + lifestyle intervention vs. lifestyle intervention
Outcomes	• Incremental QALY, incremental cost, incremental cost-effectiveness ratio
Model	• Long-term Markov model
Perspective	• Health system perspective
Starting age	• 53 years old (CDPP)
Time horizon	• Life-time
Cycle length	• One year
Discount rate	• 5%

Decision-Analytical Model

- The state-transition model has seven health states with annual transitions[3] (Figure 1):

  (1) NGT: Normal population; (2) IGR (initial state): Patients with IGF or IGT (without cardiovascular and other complications); (3) T-2D: Adults with diabetes (without cardiovascular and other complications); (4) IGR+: Patients with IGF or IGT (with cardiovascular and other complications); (5) T-2D+: Adults with diabetes (with cardiovascular and other complications); (6) Other-cause death; (7) Death

Figure 1. Overview of State-Transition Model Structure

Input Parameters:

- Health-state transition probabilities (or RR used to adjust incidence rates) were mainly obtained from published literature and publicly available sources (Table 1).
- Effect parameters: only the transition probability from IGR to T-2D was adjusted according to the CDPP study (HR=0.83)[4].
- Assumptions: (1) Patients with and without complications are equally likely to progress to T-2D; (2) Since the CDPP did not record patient course information it is assumed that all patients are diagnosed with IGR for the first time; (3) It is assumed that the probability of NGT progressing to IGR is 5.6%; (4) Only cardiovascular-related complications were considered for the occurrence of complications; (5) The mortality rate from the seventh census, minus mortality from cardiovascular and cerebrovascular diseases, represents the mortality from other causes
- Utility scores and health state costs for each health state were taken from published literature and real-world evidence (Table 2)[13].
- Metformin using pooled market share weighted average price: CNY1.42/850mg; Lifestyle intervention costs from expert research: CNY 234/year/person

Table 1. Transition Probabilities (RR used to adjust incidence rates) of the Model

From	To	Annual Transition Probabilities/ RR
IGR/IGR+	T-2D/T-2D+	5.6% (≤ 5 years）[5,6] 9.0% (> 5 years）
IGR	NGT	5.6% [7]
NGT	IGR	5.6% [7]
IGR	IGR+	RR_{IGR}=1.30 [8]
T-2D	T-2D+	RR_{T-2D}=2.00 [9]
IGR+	Death	RR_{IGR+}=1.34 [10]
T-2D	Death	RR_{T-2D}=2.00 [11]
T-2D+	Death	RR_{T-2D+}=2.78 [12]
NGT	Other-cause death	RR_{NGT}=1.00
IGR/IGR+	Other-cause death	RR_{IGR}=RR_{IGR+}=1.32 [8]
T-2D/T-2D+	Other-cause death	RR_{T-2D}=RR_{T-2D+}=1.89 [11]

Table 2. Utility Values and Health Service Costs

Health State	Utility Value	Health State Cost
NGT	0.768	NA
IGR	0.754	CNY 4990
T-2D	0.738	CNY 6336
IGR+	0.664[a]	CNY 5811
T-2D+	0.649[a]	CNY 10787

a. Reduced utility value by 12% for complication status [14]

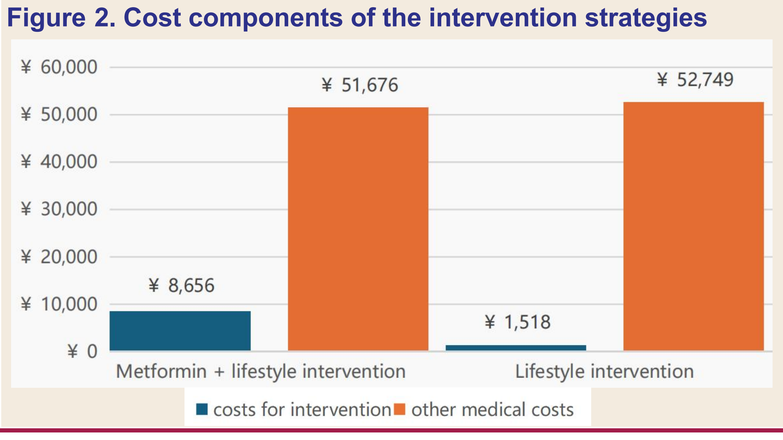
Results

- The study revealed that the group receiving both metformin and lifestyle interventions experienced a higher total QALY gain of 10.33 compared to 10.23 in the lifestyle-only group. The total cost for the combination therapy was CNY 59,095.24, while it was CNY 54,267.18 for the lifestyle-only intervention (Table 3).
- The incremental cost-utility ratio (ICUR) for the combination therapy was CNY 45,052.80 per QALY, equaling to 0.5 times per capita GDP of China in 2023, suggesting that the intervention is cost-effective (Table 3).
- The incremental cost-effectiveness ratio (ICER) for the combination therapy was CNY 45,344 per life-years (Table 3).
- The cost components of the different intervention strategies are shown in Figure 2

Table 3. Utility Values and Health Service Cost

Discounted Health Outcomes	Metformin + lifestyle intervention	Lifestyle intervention
Life-years	13.90	13.77
QALYs	11.38	11.25
Total Costs	CNY 60333	CNY 54267
Incremental Life-Years	0.13 Life-Years	
Incremental QALYs	0.12 QALYs	
Incremental Cost per LY Gained	CNY 45344 / LYs Gained	
Incremental Cost per QALY Gained	CNY 50593 / QALY Gained	

Figure 2. Cost components of the intervention strategies



- The results of the one-way sensitivity analysis are presented in Figure 3 and the results of probabilistic sensitivity analysis are presented in Figure 4.

Figure 3. The results of the one-way sensitivity analysis

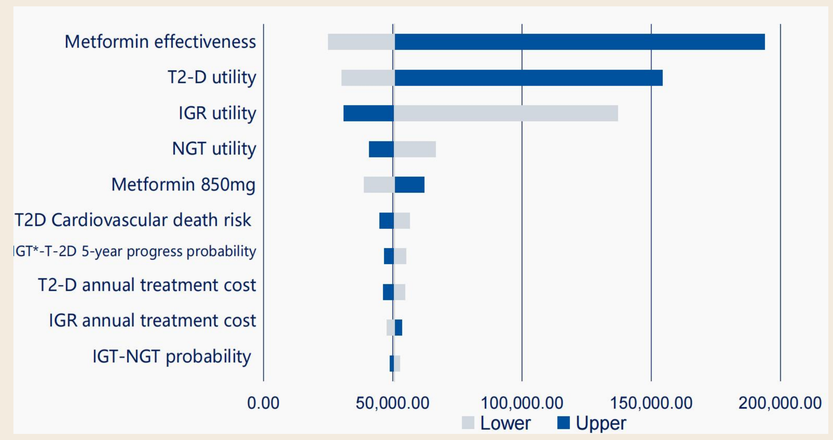
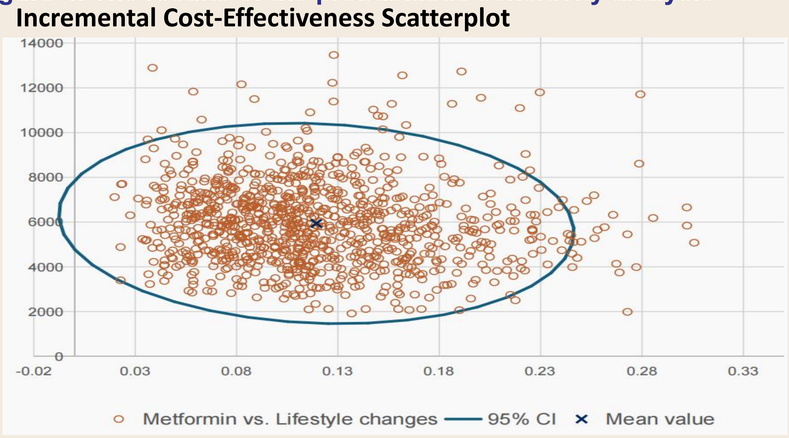
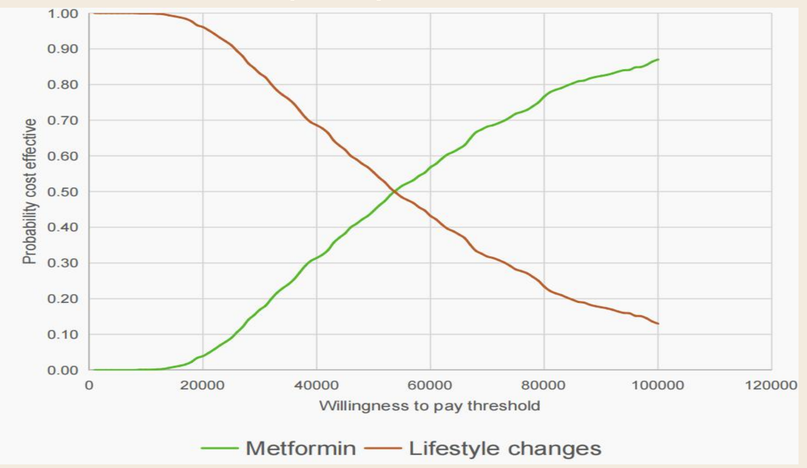


Figure 4. The results of the probabilistic sensitivity analysis

A. Incremental Cost-Effectiveness Scatterplot



B. Cost-Effectiveness Acceptability Curve



Limitations

- The field of prediabetes remains understudied, which has a negative impact on the classification of disease states in pharmacoeconomic evaluations.
- In China, there is a lack of evidence for both prediabetes and diabetes, leading to a large number of assumptions in this study.
- To date, no large prospective clinical cohort studies have been published on this topic. The UKPDS series of studies, which is commonly used in diabetes research, does not include patients with prediabetes. Furthermore, there are no health utility studies of patients with prediabetes in China.
- Adverse effects such as hypoglycemia and gastrointestinal reactions, which are common with metformin, were not considered in this study.

Conclusions

- In adults with impaired glucose regulation, the combination of metformin and lifestyle interventions is projected to be cost-effective. This study supports the integration of metformin therapy into prediabetes management protocols, emphasizing the economic viability and clinical benefits of early intervention with antidiabetic drugs.

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