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Economic Evaluation

Assessing the Burden of Type 2 Diabetes in China Considering the Current Status-Quo Management and Implications of Improved Management Using a Modeling Approach

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ABSTRACT

Background: Recent estimates from the International Diabetes Federation Diabetes Atlas have quantified the total annual expenditure for diabetes in China to be between 354 and 611 billion Chinese yuan (¥) (2015). **Objectives:** To use a modeling approach to assess the current and possible future diabetes burden in China on the basis of the current standard of type 2 diabetes (T2D) management (status quo [SQ]) and a series of hypothetical improved management strategies. **Methods:** The IQVIA CORE Diabetes Model was used to evaluate the economic burden of T2D in China on the basis of assumptions reflecting the current SQ of T2D management and a number of stepwise improvements. SQ was defined as a scenario in which T2D diagnosis is delayed by 4 years, treatment escalation to maintain glucose control occurs at a 9% glycated hemoglobin (HbA_{1c}) threshold, and there is an overall 60% adherence rate. Stepwise improvements considered immediate diagnosis, declining levels of HbA_{1c} escalation thresholds to 7.0%, and improvements in adherence rate to 80% and 100%. The CORE Diabetes Model was applied on per-capita level to project lifetime costs and clinical outcomes of newly diseased T2D individuals in the Chinese setting. Model outcomes were subsequently annualized and extrapolated to Chinese national level considering the total number of diagnosed individuals with T2D in China. **Results:** The total annual direct costs attributable to diagnosed T2D in China reflecting current SQ management were estimated at ¥621 billion. Scenarios exploring stepwise improvements from SQ estimated annual net savings of ¥35, ¥35, ¥60, ¥71, ¥75, and ¥106 billion for scenarios exploring immediate diagnosis, HbA_{1c} threshold reductions to 8.0% and 7.0%, adherence rate increase to 80% and 100%, and cardiovascular risk factor control in concordance with clinical guidelines, respectively. Net savings resulted from reduced costs to treat diabetes complications (¥38, ¥67, ¥124, ¥141, ¥161, and ¥212 billion) and excess treatment costs alongside stepwise management improvements (¥4, ¥32, ¥65, ¥69, ¥86, and ¥107 billion). Per-capita life expectancy was increased by 0.26, 0.68, 1.33, 1.47, 1.69, and 3.21 years, respectively. **Conclusions:** Improved T2D management strategies can help to decrease the financial burden of the disease and increase life expectancy of individuals with T2D.

Keywords: China, direct and indirect economic burden, healthcare costs, type 2 diabetes.

Introduction

The public health burden of diabetes in China is substantial. Diabetes prevalence has increased over the years. The total number of people with diabetes was 20.8 million in 2000 [1], which increased to 92.4 million in 2008 [2] and to 109.6 million in 2015 [3], representing 10.6% of the total population. Type 2 diabetes (T2D) accounts for approximately 95% of the total diabetes population [4], The economic burden of diabetes in China is staggering. Hu et al [5] reported that the estimated direct medical costs for T2D were $9.1 billion in 2008. More recently, the International Diabetes Federation (IDF) Diabetes Atlas [3] reported an annual expenditure between $51.1 and $88.4 billion for diabetes in 2015.

Diabetes-related complications represent a major driver of direct healthcare costs. Consequently, the optimal management of blood glucose and other macrovascular and microvascular risk factors is crucial.

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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The Chinese Diabetes Society guidelines for the management of T2D advocate treatment escalation algorithms designed to maintain glycated hemoglobin (HbA_{1c}) lower than 7.0% [6]. Nevertheless, in routine clinical practice, T2D diagnosis is often delayed (by up to 6 years) and therapy escalation typically occurs at higher HbA_{1c} thresholds than recommended [7]. Published data indicate that only 26% of patients with T2D in China receive treatment, and of these, only 40% have adequate glycemic control [8,9]. Furthermore, more than 75% of patients with diabetes have systolic blood pressure levels of more than 140/80 mm Hg or are taking antihypertensive medications simultaneously [10], and 72% of patients have either comorbid hypertension or dyslipidemia, or both [11]. An additional challenge relates to medication adherence with factors such as hypoglycemia and weight gain in China known to have a negative impact on adherence, thereby attenuating the potential effectiveness of glucose-lowering agents [12].

To formulate effective healthcare resource allocation plans, it is necessary to determine both the current and future expected economic burden of T2D across a spectrum of potential management strategies.

Consequently, the principal objective of this study was to estimate the economic burden of diabetes in China in terms of annual diabetes-related expenditures, life expectancy, and morbidity to reflect the local standards (status quo) of diabetes management. A secondary objective was to estimate the changes in expenditures as well as the improvements in morbidity and life expectancy for a number of hypothetical scenarios reflecting enhancements from current standards toward an optimized T2D management.

Methods

Model

This study used the IQVIA CORE Diabetes Model (CDM) [13,14]. The CDM is a widely published and validated [13,14] model for type 1 and type 2 diabetes. It is a non–product-specific diabetes policy analysis tool that performs real-time simulations designed to translate surrogate endpoints into long-term health and economic outcomes. The CDM represents the most widely adopted economic model by academia and the pharmaceutical industry, as well as healthcare payers and decision makers [15,16].

Data Collection

A number of pragmatic literature reviews using PubMed were conducted to define all model inputs required to populate the model for analyses in the Chinese setting. Literature searches focused on the collection of population characteristics, healthcare costs to treat diabetes-related complications, local T2D treatment modalities (treatment paradigms) to inform the most likely choices of glucose-lowering agents, long-term progression of HbA_{1c} to reflect the quality of glucose control, and importantly the current standards of T2D management in China, later called "status quo" (SQ). The full search strategies can be provided by the authors upon request. The information collected in the literature reviews was complemented by data collected from interviews with 5 local experts in the field. Interviews were carried out in the period between July 1 and July 26, 2016.

Population Characteristics

We simulated cohorts of individuals with T2D with recent disease onset across 3 age categories: (1) young onset (age $\leq$45 years), (2) intermediate onset (age between 46 and 64 years), and (3) late onset (age $>$65 years). The baseline characteristics were obtained from multiple literature sources [17-33] and approved by a local expert committee for validity (see Appendix Table S1 in Supplemental Materials found at 10.1016/j.vhri.2018.08.006).

Unit Cost

Direct medical costs were assessed as the sum of the cost of complications and treatment costs. Unit costs to treat diabetes-related complications in China were informed by a pragmatic literature review that identified 9 articles that report detailed cost data in the Chinese setting [34-42]. For those undiagnosed, we assumed that access to healthcare and associated costs to treat diabetes-related complications were the same as those in the diagnosed population. The costs of complications were accounted for by applying state and follow-up costs as appropriate to all events occurring during the simulation (see Appendix Table S2 in Supplemental Materials found at 10.1016/j.vhri.2018.08.006). Treatment costs were calculated on an annual basis as the sum of glucose-lowering medication costs and cardiovascular (CV) medication costs (angiotensin-converting enzyme inhibitors and statins). Annual medication costs were calculated on the basis of the unit cost of mostly prescribed pack type (data from 2015 IMS CHPA database) and daily dosage (recommended by treatment guideline or drug instruction) (see Appendix Table S3 in Supplemental Materials found at 10.1016/j.vhri.2018.08.006). Productivity loss associated with diabetes-related complications to assess indirect costs was obtained from multiple sources [43-48] (see Appendix Table S4 in Supplemental Materials found at 10.1016/j.vhri.2018.08.006).

Treatment Paradigms

We considered 4 treatment paradigms to best reflect patterns of care relevant to Chinese clinical practice on the basis of expert opinion, a survey including 1028 physician responses to inform the Chinese standard of care in T2D treatment [49], and 9872 outpatients with T2D [50]. The most frequently used insulin compositions in China represent premix insulin (65.6%), basal insulin (17%), and basal–bolus (7.9%) insulin [51].

HbA_{1c} Progression

HbA_{1c} progression was assumed to follow a natural progression trend (steady increase), being influenced by the effects of individual glucose-lowering agents included in the treatment paradigms. Natural HbA_{1c} progression was assessed via a random-effects panel equation from the UK Prospective Diabetes Study (UKPDS) [52] or, after escalation to fifth-line therapy, a steady increase of 0.04% points per year [53]. Undiagnosed individuals were considered to experience an "uncontrolled" HbA_{1c} progression. Following consensus agreement of the local expert committee, the annual HbA_{1c} progression in uncontrolled individuals was assumed at 0.32%, 0.24%, 0.2%, and 0.13% per year for time intervals of 1 to 5 years, 6 to 10 years, 11 to 15 years, and 16 years or more, respectively, after disease onset. Appendix Figure S1 in Supplemental Materials found at 10.1016/j.vhri.2018.08.006 presents the resulting HbA_{1c} trajectory curves as applied in our modeling analysis for no control (no Tx), SQ, and all scenarios considering improvements in HbA_{1c} levels (S1-S12).

SQ T2D Management in China

SQ management was defined across 4 domains including time (delay) from disease onset to diagnosis, HbA_{1c} thresholds considered by physicians in clinical praxis to change (escalate) treatments and achieve appropriate glucose control, average population adherence to glucose-lowering medications, and cardiovascular risk factor control (CV-RFC). A summary of the data obtained from the literature review [2,8,9,11,54-65] and local

expert estimates to inform SQ management is presented in Appendix Table S5 in Supplemental Materials found at 10.1016/j.vhri.2018.08.006. From these data we assumed an average delay of 4 years in T2D diagnosis [54-56], with therapy intensification occurring at an HbA_{1c} threshold of 9%. The average adherence rate to glucose-lowering medications was assumed at 60% [58-62]. The SQ of CV-RFC assumed that 22.9% of patients with hypertension are treated to guideline-recommended target values of systolic blood pressure and 11.6% of patients with dyslipidemia achieve guideline-recommended cholesterol targets [63]. Undiagnosed patients were considered to not receive any intervention.

Improved Management Scenarios

We considered 15 improved T2D management scenarios (S1-S15) based on stepwise enhanced conditions within the 4 domains that were selected to characterize SQ management. A summary of all the scenarios including SQ, no treatment in the undiagnosed (no Tx), and the 15 improved scenarios is presented in Table 1. Considerations for improved T2D management scenarios are outlined herein:

1. *Reduction in the delay in diagnosis of T2D*: We evaluated a 2-year and a 4-year reduction in the delay in diagnosis (from 4 years to 2 years and from 4 years to immediate diagnosis) (S1 and S6).
2. *Reduction in the delay in diagnosis of T2D in combination with improvements to glucose control*: A 2-year and a 4-year reduction in the delay in diagnosis were modeled with initiation and escalation of therapy occurring at 8.5%, 8.0%, 7.5%, and 7.0% HbA_{1c} thresholds (S2-S5 and S7-S10).
3. *Improvements from 1 and 2 and increased adherence to glucose-lowering medications*: In the base-case analysis, we assumed patients with overall adherence rates of 60%. Improved scenarios considered adherence rates of 80% and 100%. Each 20% improvement in adherence was associated with an overall 0.31% reduction in HbA_{1c} (average estimate from local experts) (S11 and S12).
4. *Improvements from 1, 2, and 3 in combination with advanced cardiovascular risk factor management (CV-RFM)*: Although the base-case analysis assumed that 22.9% of treated T2D individuals with hypertension reach guideline-recommended target values of systolic and diastolic blood pressure [63] and 11.6% of treated T2D individuals with dyslipidemia reach guideline-recommended lipid targets [63], we considered 3 levels of percentage improvements (L1, L2, and L3) from SQ assumptions until 100% (S13-S15). Corresponding CV risk factor levels representing L1 to L3 of CV-RFM are presented in Appendix Table S6 in Supplemental Materials found at 10.1016/j.vhri.2018.08.006.

Discounting

No discounting was applied because this analysis aimed to assess the annual disease burden for the year 2015 and no future scenarios were forecasted. Life expectancy outcomes were likewise not discounted.

Analytical Approach

1. A stepwise approach was used to estimate the 2015 annual disease burden reflecting the current SQ management of T2D in China and iterative improvements of the explored hypothetical scenarios.The model was applied to project the clinical course and associated costs of newly diseased T2D individuals over lifetime:

- In 3 age categories:
  - young disease onset (age $\leq$45 years)
  - intermediate disease onset (age between 46 and 64 years)
  - late disease onset (age $\geq$65 years)
- Across 4 treatment paradigms (A-D) aiming to represent the most commonly applied management strategies in Chinese clinical practice:
  - Four treatment paradigms representing a cascade of glucose-lowering agents applied from first- to fifth-line therapy

Table 1 – Summary of scenarios in base-case analysis.

Scenarios	Delay in treatment onset (y)	HbA_{1c} escalation threshold (% points)	Adherence rate (%)	CV-RFM (levels 0-3)
No treatment over lifetime				
Status quo	4	9.0	60	0
S1: 2-y diagnostic delay	2*	9.0	60	0
S2: 2-y diagnostic delay and 8.5% ESC	2	8.5*	60	0
S3: 2-y diagnostic delay and 8.0% ESC	2	8.0*	60	0
S4: 2-y diagnostic delay and 7.5% ESC	2	7.5*	60	0
S5: 2-y diagnostic delay and 7.0% ESC	2	7.0*	60	0
S6: Immediate treatment and 9.0% ESC	0*	9.0	60	0
S7: Immediate treatment and 8.5% ESC	0	8.5*	60	0
S8: Immediate treatment and 8.0% ESC	0	8.0*	60	0
S9: Immediate treatment and 7.5% ESC	0	7.5*	60	0
S10: Immediate treatment and 7.0% ESC	0	7.0*	60	0
S11: Immediate treatment and 7.0% ESC and 80% AR	0	7.0	80*	0
S12: Immediate treatment and 7.0% ESC and 100% AR	0	7.0	100*	0
S13: Immediate treatment and 7.0% ESC and 100% AR and level 1 improved CV-RFM	0	7.0	100	1*
S14: Immediate treatment and 7.0% ESC and 100% AR and level 2 CV-RFM	0	7.0	100	2*
S15: Immediate treatment and 7.0% ESC and 100% AR and level 3 CV-RFM	0	7.0	100	3*

AR indicates adherence rate; CV-RFM, cardiovascular risk factor management; ESC, escalation threshold; HbA_{1c}, glycated hemoglobin.
* Iterative improvement (step improvement) vs the previous scenario.

were defined on the basis of data from the literature review and suggestions from local experts.
  - Model projections in each age category and for each scenario considered (SQ and respective improvements) were applied for each paradigm separately.
  - Outcomes from the individual paradigm projections were combined by taking the arithmetic mean of the individual projections.

- Across 17 scenarios including the assumption of no treatment intervention over lifetime, SQ management, and 15 stepwise improvements from SQ until the most optimal T2D management approach; stepwise improvements from SQ management were assumed according to the following categories:
  - diagnostic delay
  - delay of treatment escalation aiming to maintain HbA_{1c} at controlled levels
  - adherence to glucose-lowering medications
  - CV-RFC

2. The model predicted per-capita lifetime outcomes (costs and complication incidence) for the aforementioned scenarios. By dividing the lifetime outcome by the mean life expectancy per scenario, the average annual cost (and complication incidence) per capita was calculated.
3. Annualized age-specific per-capita outcomes were extrapolated to national level by multiplication with the total number of diagnosed Chinese individuals with T2D in each age category.
4. Finally, total national outcomes representing all individuals with T2D in China, including young, intermediate, and late onset, were calculated as the sum of the individual age-specific national estimates.
5. Annual cost savings for improved management scenarios were calculated as the difference of total annual population-based costs in the SQ scenario and the total annual population-based costs in the improved scenario.

This approach to assess the annual population-based costs in China from per-capita model predictions is further illustrated in Appendix Figure S2 in Supplemental Materials found at 10.1016/j.vhri.2018.08.006.

Model Configuration

The CDM was applied using risk equations from the UKPDS 68 [52] to assess the risk of CV complications and mortality. The risk of non–diabetes-related death was sourced from China-specific life table data from the World Health Organization [66].

Sensitivity Analysis

Univariate sensitivity analyses were conducted to explore alternative assumptions for the definition of SQ management in China related to the following categories:

- The average diagnostic delay of 4 years in the SQ scenario was explored for 6, 8, and 10 years.
- The treatment escalation HbA_{1c} target of 9.0% in the SQ scenario was explored at 9.5% and 10.0%.
- The degree of HbA_{1c} progression during diagnostic delay (base case assumed 0.32% point increase per year) was increased and reduced to 0.4% and 0.26% points per year, respectively.

Furthermore, the model was evaluated using CV risk equations from the Hong Kong Diabetes Registry (HKRD) data [67,68].

Results

Population-Based Direct Costs

Annual population-based direct costs in 2015 for all evaluated scenarios including no treatment (no Tx), SQ, and S1 to S15 are presented in Figure 1. The total annual direct cost attributable to diagnosed T2D in China reflecting current SQ management was estimated at 621 billion Chinese yuan (¥) (Fig. 1A). Alongside improved scenarios, population-based net savings ranged from ¥19 billion (S1) to ¥106 billion (S15) (Fig. 1C). The relatively modest increase in net savings was directly driven by the predicted increases in treatment costs across scenarios, which ranged from ¥2 billion (S1) to ¥107 billion (S15) and competed against cost savings from prevented complications ranging from ¥20 billion (S1) to ¥212 billion (S15) (Fig. 1B). The total annual cost attributable to 55% of the T2D population that remains undiagnosed and untreated (no Tx) was estimated at ¥1122 billion.

Population-Based Indirect Costs

Figure 2 presents the annual indirect costs (2015) associated with lost productivity for all evaluated scenarios including no treatment (no Tx), SQ, and S1 to S15. Indirect costs were separately evaluated for undiagnosed and untreated individuals (¥114 billion) (representing 55% of the Chinese T2D population) as well as for diagnosed individuals (¥59 billion), adding to a total of ¥173 billion annual indirect costs for all T2D cases in China.

Scenarios representing improvement in T2D management considered that only diagnosed individuals (ie, 45% of the Chinese T2D population) would be subjected to improved management at a constant indirect cost burden of ¥114 billion from the undiagnosed population. Under this assumption, it was estimated that indirect costs could be reduced to ¥149 billion for optimal management according to S15 (Fig. 2).

Life Expectancy

Overall, life expectancy increased alongside projections representing improved management scenarios. In the most optimal scenario (S15) versus SQ, per-capita life expectancy was improved by 4.60, 3.64, and 1.97 years in the young-, intermediate-, and late-onset population, respectively. This resulted in an average life expectancy increase of 3.21 years in the total population (Fig. 3). In contrast, the assumption of no treatment intervention over lifetime resulted in a predicted average life-year loss of 2.85 years versus SQ.

Intuitively, life-year savings were the greatest in model projections of the young-onset population, with savings declining with more advanced age at disease onset. Average life expectancy savings attributable to a more timely diagnosis were relatively modest and ranged from 0.14 to 0.26 years in scenarios representing 2-year diagnostic delay (S1) and immediate diagnosis (S6) versus SQ, respectively. Projections exploring reductions in the HbA_{1c} treatment escalation threshold demonstrated substantially higher average life-year savings ranging from 0.31 to 1.25 years for threshold value assumptions from 8.5% to 7.0% (S2-S5), respectively, if T2D diagnosis was delayed by 2 years and 0.44 years to 1.33 years if immediate diagnosis was assumed (S7-S10). Scenarios reflecting improved adherence (S11 and S12) presented additional average life-year savings of 0.14 years and 0.36 years over lifetime if the overall adherence rate was assumed at 80% and 100% (vs 60% in SQ), respectively. Finally, model projections reflecting improved CV-RFM predicted additional life-year savings of 0.6, 1.08, and 1.51 years in scenarios assuming level 1, 2, and 3 of improved CV-RFM (S13-S15).

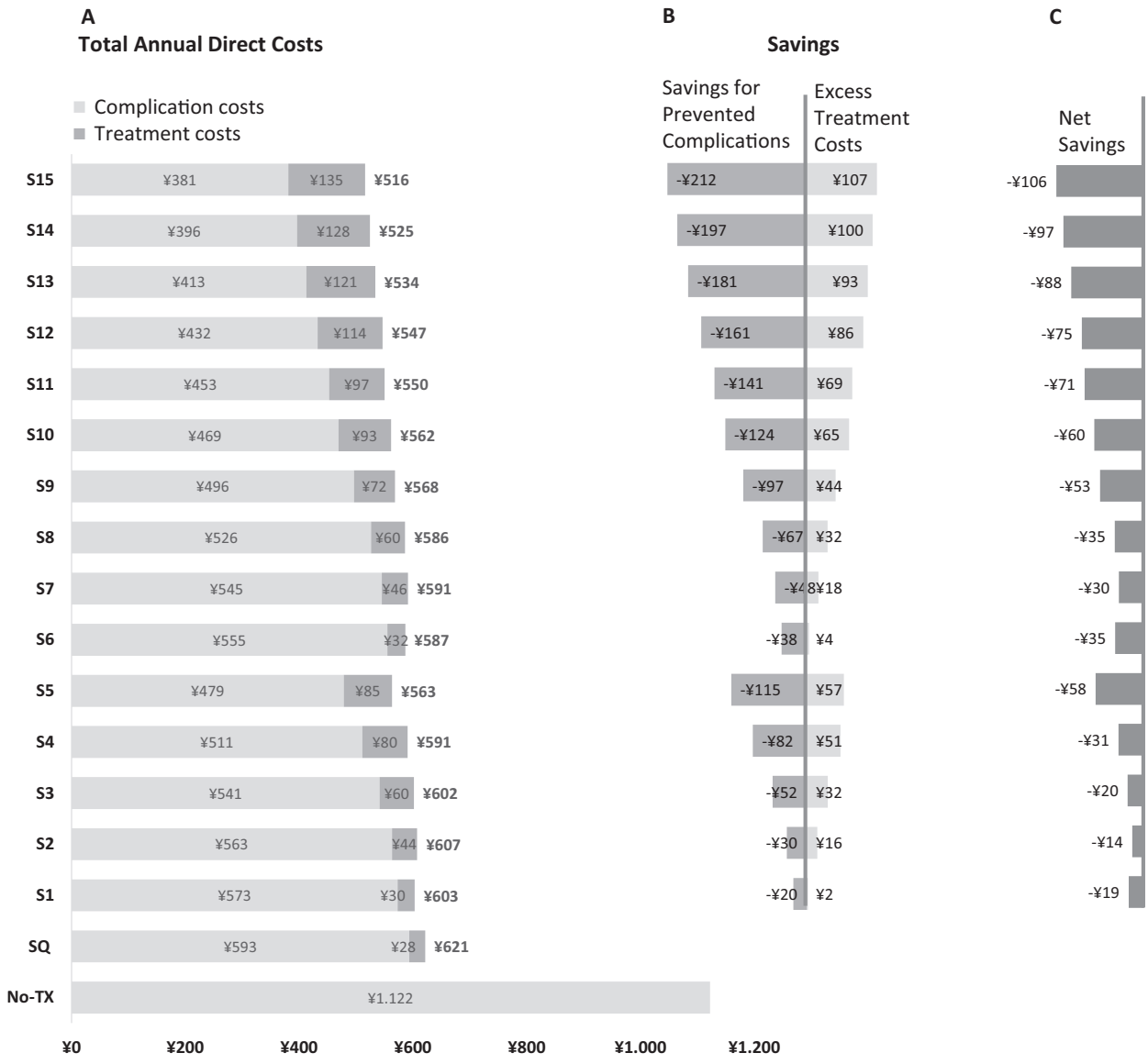

Fig. 1 – Population-based annual complication, treatment, and total direct costs; incremental expenses; and savings and net savings (¥, in billions). No Tx indicates no treatment; SQ, status quo.

Diabetes-Related Complications

The incidence of diabetes-related microvascular and macrovascular complications declined with improved T2D management, as expected. Overall, extrapolated model outcomes predicted that if all patients with T2D in China would be treated optimally alongside the definition of scenario S15, a total of 1.26 million microvascular complications (comprising blindness, renal failure, amputations, and neuropathy onset) and 1.33 million macrovascular complications (comprising myocardial infarction, stroke, heart failure, angina, and peripheral vascular disease) could be avoided annually in China in comparison with current SQ management (Fig. 4).

Assuming the currently undiagnosed 55% of the population were managed to existing SQ standards, the CDM estimates that 2.01 million microvascular and 0.89 million macrovascular complications would be avoided annually. Improvements in diagnostic delay resulted in an estimated reduction of 109 000 to 214 000 microvascular and 54 000 to 104 000 macrovascular events considering improvements to 2 years (S1) and immediate diagnosis (S6) versus SQ, respectively. Improvements in treatment escalation alongside HbA_{1c} threshold reductions translated into estimated 193 000 to 891 000 preventable microvascular complications reflecting threshold reductions from 8.5% to 7.0% (S2-S5) versus SQ, respectively, if diagnosis was delayed by 2 years, and 296 000 to 949 000 preventable cases considering immediate diagnosis (S7-S10). Corresponding cases of preventable macrovascular complications were estimated to range between 106 000 and 402 000 cases (S2-S5) and between 154 000 and 431 000 cases (S7-S10) considering 2-year diagnostic delay and immediate treatment versus SQ, respectively. Improvement in the adherence rate from 60% (SQ) to 80% and 100% (S11 and S12) translated into additional 85 000 and 239 000 prevented microvascular complications and 69 000 and 145 000 prevented macrovascular complications. The number of preventable

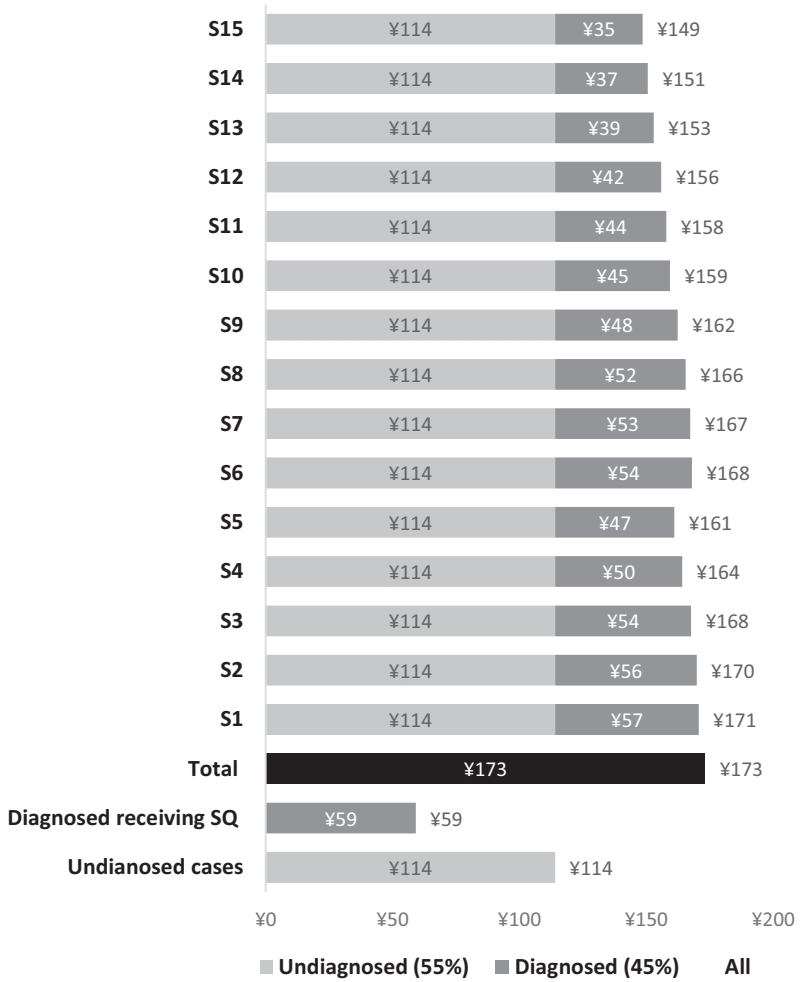

Fig. 2 – Population-based annual indirect costs associated with lost productivity. SQ indicates status quo.

complications associated with improvements in CV-RFM were minor in the microvascular disease section, with 24 000, 42 000, and 72 000 additional prevented cases in scenarios S13-S15, but considerable in the macrovascular disease section, with 303 000, 549 000, and 755 000 additional prevented cases per year reflecting level 1 to 3 CV-RFM improvements.

Sensitivity Analysis

All outcomes from the sensitivity analyses are presented in Table 2, which presents the population-based annual costs for T2D in China as well as per-capita life expectancy estimations for the alternative SQ definitions (SA1-SA7) and CDM projections using HKDR equations (SA8). Table 3 presents the population-based annual cost savings and life expectancy savings for optimal management (S15) (which remained unmodified in all sensitivity analyses) versus SQ.

Results of the sensitivity analyses demonstrated a remarkable increase in total population-based costs (and respective savings in S15 vs SQ) when diagnostic delay was assumed at 6, 8, and 10 years. Otherwise, outcomes supported the robustness of the base-case results, with direct population-based annual costs not varying by more than 4% versus base case in analyses S4 to S8.

Discussion

Executive Summary

This analysis used the IQVIA CDM to estimate the economic burden of diabetes in China and quantify the expected benefits and cost savings associated with improved strategies of T2D management in comparison with current standards of T2D patient management (SQ). Nationally, T2D-related direct annual costs were estimated at ¥621 billion ($90.5 billion) under current patient management conditions, which include ¥593 billion in diabetes-related complication costs and ¥28 billion attributable to glucose-lowering and CV risk factor regulating medications (treatment costs). Optimal management of T2D was estimated to save up to ¥212 billion of annual complication costs (assuming immediate diagnosis after disease onset, glucose-lowering treatment escalation at guideline-recommended target perfect patient adherence, and CV-RFC alongside guideline recommendations). Importantly, these savings are offset in part by increased treatment costs of ¥107 billion with optimal treatment versus the current management, but still result in an overall net savings of ¥106 billion. Improved management strategies also translated into considerable health benefit reflected by reduced complication rates and extended life expectancy. On average (across all age groups),

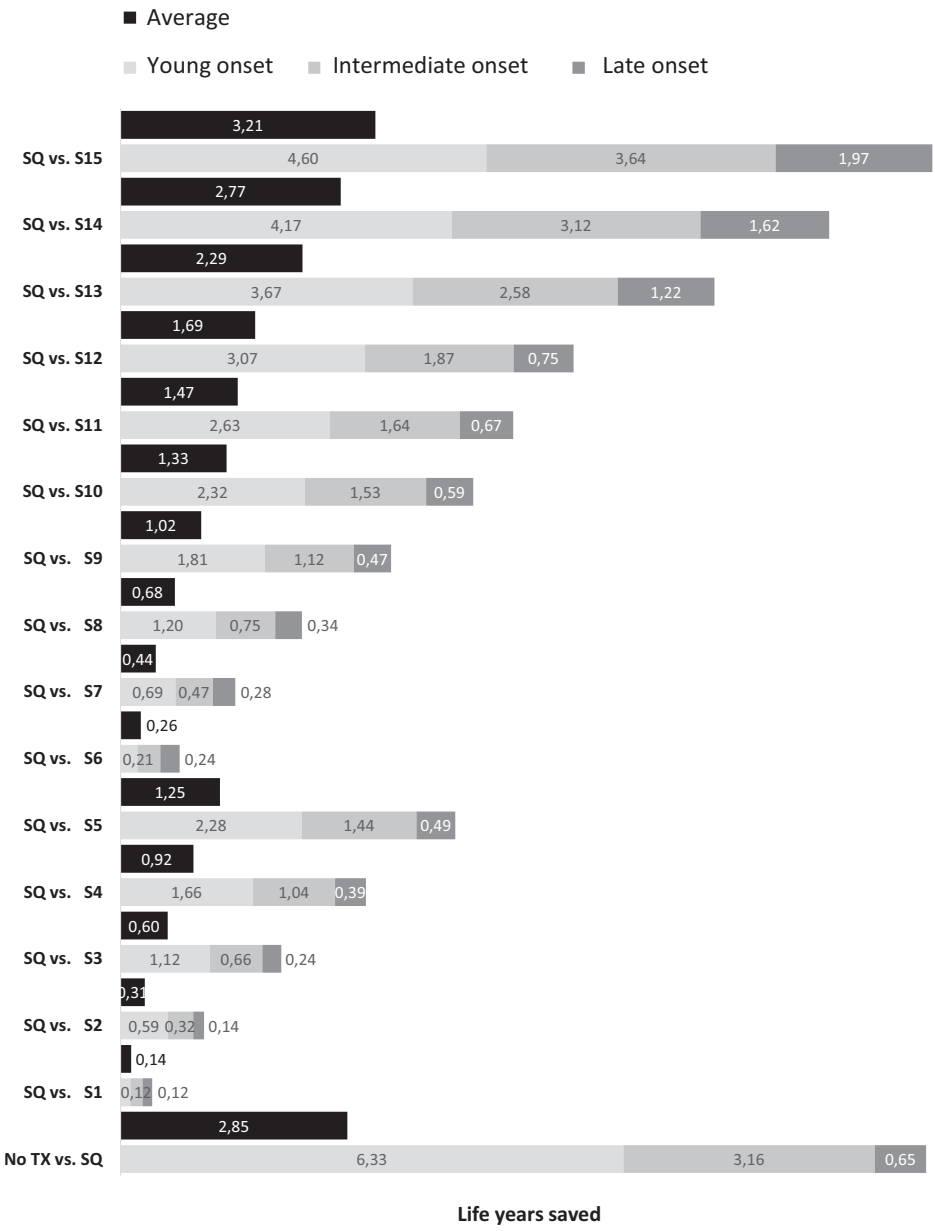

Fig. 3 – Per-capita life-year savings in SQ-managed patients vs those not receiving treatment and patients receiving improved management vs SQ. No Tx indicates no treatment; SQ, status quo.

per-capita life expectancy was increased by 3.21 years in individuals with optimal management versus SQ and the highest in individuals with young disease (4.6 years). Under optimal management conditions, a total of 1.26 million microvascular complications (comprising blindness, renal failure, amputations, and neuropathy onset) and 1.33 million macrovascular complications (comprising myocardial infarction, stroke, heart failure, angina, and peripheral vascular disease) could be avoided in China annually in comparison with current management.

Predicted Costs and Savings in Context

Our estimate of ¥621 billion (~$89 billion) of annual direct costs in China that are attributable to T2D compares with a wide range of T2D cost predictions from other studies that aimed to assess the economic burden of diabetes in China. A systematic review on the direct economic burden of T2D published estimated costs of $0.25 billion, $2.27 billion, and $9.1 billion direct medical costs incurred for T2D in the years of 1993, 2002, and 2008, respectively [5]. Another cross-sectional study based on hospital data from 1482 adults with diabetes from 4 major cities concluded on a much larger estimate of $26.0 billion in 2007 [69], and a global systematic review on the costs of T2D reported annual national costs of $73 billion for T2D in China for 2007 [70]. More recent estimates from the IDF Diabetes Atlas [3] report annual expenditures between $51.1 and $88.4 billion for diabetes for 2015, which lie much closer to the predictions of our study. Although there is an obvious trend toward increasing cost predictions that are related not only to increasing healthcare costs in China but also to an increasing prevalence of T2D,

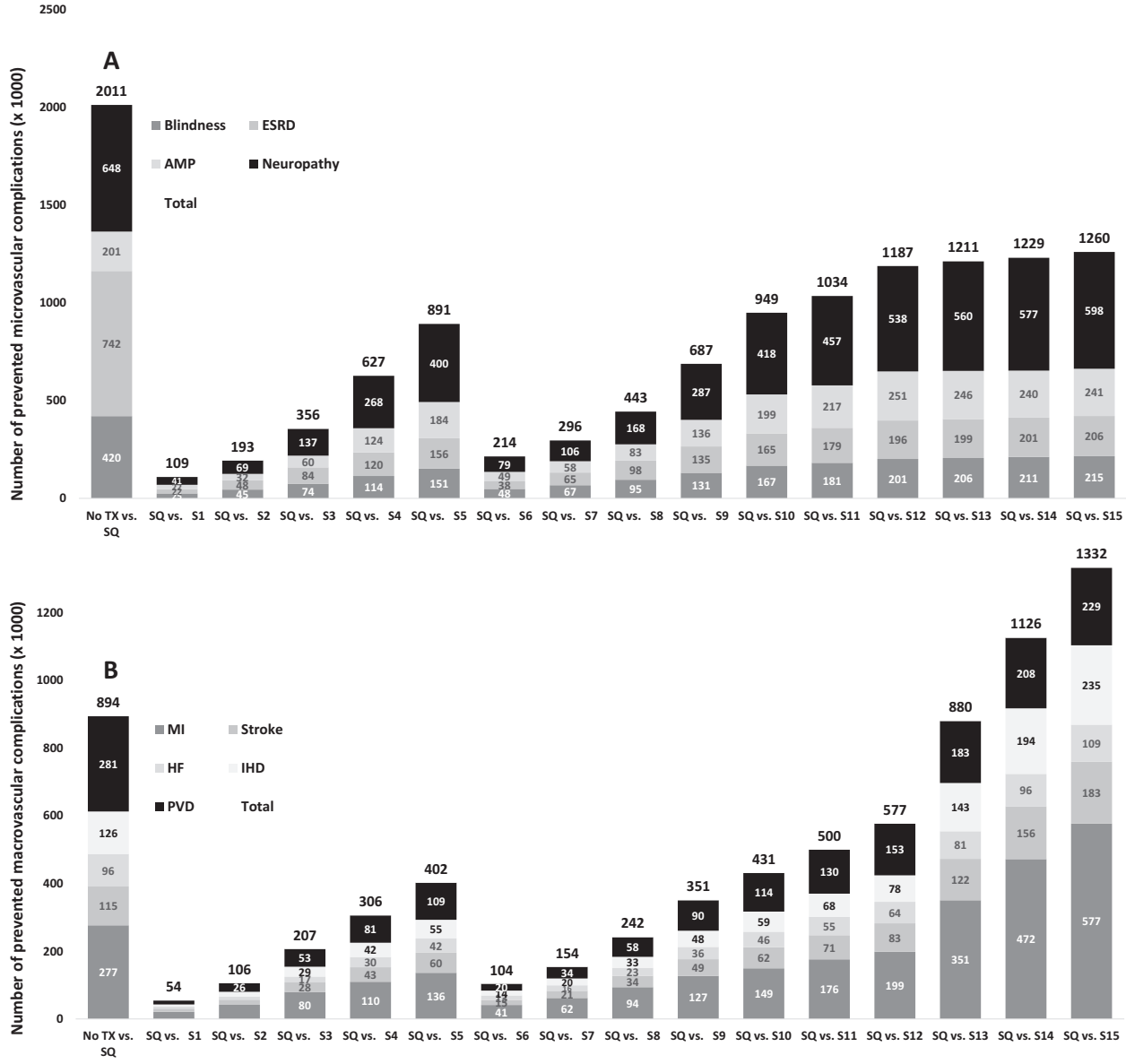

Fig. 4 – Number of preventable microvascular (A) and macrovascular (B) complications (× 1000) on a national level per year. ESRD indicates end-stage renal disease; HF, heart failure; IHD, ischemic heart disease; MI, myocardial infarction; No Tx, no treatment; PVD, peripheral vascular disease; SQ, status quo.

considerable differences in cost estimates exist between studies that may evolve from the methodological differences that were adopted across studies. Two alternative epidemiological approaches exist for the estimation of country-specific costs of a disease. The incidence approach assesses the per-capita costs associated with the disease over a specific time period, usually starting with disease onset until death, and extrapolates these numbers on a national level, whereas the prevalence approach estimates the costs of the disease for a cross section of people at a certain point in time, typically a year, who are at different stages of the disease. Because of these differential approaches, estimates from both may vary because of differences in time periods and data considered [70]. In our study, we used a mixture between the incidence and prevalence-based approaches insofar as we assessed the lifetime costs of newly diseased T2D individuals across 3 age ranges and subsequently annualized these lifetime costs by division through the average life expectancy in each age category. Finally, annual per-capita costs are extrapolated to the national level according to the prevalence of diagnosed T2D in each age category.

Differences may also arise because the inclusion or exclusion of expenditures not caused by diabetes is diversely handled across economic studies. For example, the IDF estimates exclude expenditures not caused by diabetes; that is, it evaluates only the excess direct costs for diabetes relative to the average costs in the general population [3]. Likewise, our modeling study considered only those costs for complications that are attributable to diabetes. Nevertheless, CV complications, which represent a major cost driver, also occur in the general population (at a lower rate) and this non–diabetes-related CV incidence is included in our evaluation. Hence, not all the non–diabetes-related costs are excluded from our evaluation.

Table 2 – Outcomes from sensitivity analyses.

Analysis	Outcome	Population-based annual costs (¥, in billions)				Life expectancy (per capita)
		Complication	Treatment	Direct	Indirect	
BC	SQ (4-y diagnostic delay, 9% HbA_{1c} escalation threshold)	594	28	622	59	21.03
SA1	SQ modified to assume 6-y delay in diagnosis and treatment	621	26	647	62	20.83
SA2	SQ modified to assume 8-y delay in diagnosis and treatment	660	48	708	66	20.63
SA3	SQ modified to assume 10-y delay in diagnosis and treatment	720	50	770	72	20.09
SA4	SQ modified to assume 9.5% HbA_{1c} escalation threshold	595	23	618	59	20.98
SA5	SQ modified to assume 10.0% HbA_{1c} escalation threshold	596	23	618	59	20.98
SA6	SQ modified to assume 25% reduced HbA_{1c} creep (0.25% points/y) during diagnostic delay	588	28	616	58	21.08
SA7	SQ modified to assume 25% increased HbA_{1c} creep (0.4% points/y) during diagnostic delay	602	28	630	60	20.96
SA8	SQ (and all other scenarios from S1 to S15) evaluated with risk equations from HKDR	569	29	598	51	22.45

BC indicates base case; HKDR, Hong Kong Diabetes Registry; SA, sensitivity analysis; SQ, status quo.

Predicted annual net savings amounted to ¥106 billion (17% of total direct national costs) for the most optimal scenario versus SQ. Considering the substantial improvements in T2D management that were assumed, these cost reductions may appear modest in relation but have to be viewed in perspective because improved management comes at a cost, which was predicted in our analysis at ¥107 billion.

Study Limitations

This study has several limitations. Although our study assessed the implication of management improvements in diseased individuals, it did not evaluate the implications of diabetes prevention. For the SQ scenarios, we considered therapy intensification occurring at an HbA_{1c} threshold of 9%. This estimate is based on expert opinion only because no data were identified in our literature review to inform HbA_{1c} threshold levels commonly applied in Chinese clinical practice. Nevertheless, data from other countries, for example, a retrospective study based on 81 573 people with T2D in the United Kingdom, suggest that our assumption of a 9.0% threshold value represents a conservative estimate. Clinical Practice Research Datalink reported that in the United Kingdom, mean HbA_{1c} at intensification with an oral antidiabetic drug or insulin for people taking 1, 2, or 3 oral antidiabetic drugs was 8.7%, 9.1%, and 9.7%, respectively [71].

A substantial proportion of the Chinese T2D population remains undiagnosed over lifetime. Evidence suggests that this proportion lies between 53% and 70% [3,8,57]. In our analysis we assumed this proportion to lie at 55%. Furthermore, we assessed the implications of SQ management and respective improvements from S1 to S15 for the 45% diagnosed cases only and assumed no treatment intervention in the 55% undiagnosed cases. Nevertheless, because we consider diagnostic delay in the diagnosed group (45% of cases), there is overlap between the groups (45% diagnosed and 55% undiagnosed), which may introduce some inaccuracy to our analysis.

Table 3 – Incremental outcome difference between SQ and optimal management (S15).

Analysis	Outcome	Population-based annual cost savings (¥, in billions)				Life expectancy savings (per capita)
		Complication	Treatment	Direct	Indirect	
BC	SQ (4-y diagnostic delay, 9% HbA_{1c} escalation threshold)	210	−103	107	24	3.16
SA1	SQ modified to assume 6-y delay in diagnosis and treatment	237	−105	132	28	3.36
SA2	SQ modified to assume 8-y delay in diagnosis and treatment	276	−83	193	32	3.56
SA3	SQ modified to assume 10-y delay in diagnosis and treatment	336	−81	255	38	4.10
SA4	SQ modified to assume 9.5% HbA_{1c} escalation threshold	211	−109	103	25	3.21
SA5	SQ modified to assume 10.0% HbA_{1c} escalation threshold	212	−109	103	25	3.21
SA6	SQ modified to assume 25% reduced HbA_{1c} creep (0.25% points/y) during diagnostic delay	204	−103	100	24	3.11
SA7	SQ modified to assume 25% increased HbA_{1c} creep (0.4% points/y) during diagnostic delay	218	−103	115	26	3.23
SA8	SQ (and all other scenarios from S1 to S15) evaluated with risk equations from HKDR	171	−104	67	16	1.67

BC indicates base case; HKDR, Hong Kong Diabetes Registry; SA, sensitivity analysis; SQ, status quo.

Our analysis considered that patients with complications have full access to healthcare and incur related costs to treat diabetes-related complications once they occur. Nevertheless, especially in rural areas of China, access to healthcare, even for diagnosed T2D, may be limited and/or other treatment measures may be preferred (ie, Chinese medicine). Therefore, the costs incurred but also the treatment and cure applied may be lower. This is in particular relevant for the estimation of costs in undiagnosed and untreated individuals for which overall annual national costs of ¥1122 billion were estimated. Actually, for this population, the costs can be assumed to be much lower because healthcare access may be minimal.

The SQ scenario in our analysis considered an average delay of 4 years between T2D disease onset and diagnosis. This estimate is based on literature observations [54-56] and consensus from our local expert committee. It may, however, be that the diagnostic delay in rural areas is considerably longer and our 4-year estimate represents an underestimation of the average situation in China, especially because most of the data sources refer to better controlled populations versus those that are residentiary in rural areas. For this purpose, a number of sensitivity analyses were conducted to explore assumptions of an elongated delay of 6, 8, and 10 years. Findings from these analyses suggested a substantial increase in the potential net savings for optimal (S15) versus SQ management, ranging from ¥107 billion in the base case (4 years) to ¥132, ¥193, and ¥255 billion for 6, 8, and 10 years of diagnostic delay, respectively.

In our analysis, indirect costs were estimated using the human capital approach by multiplying the estimated workdays lost to diabetes by the total number of workers with diabetes, valued in terms of the average salary for Chinese residents in 2015. Estimates of workdays lost to diabetes were obtained from absenteeism rates associated with diabetes-related complications. The burden of indirect costs, however, extends beyond absenteeism and includes other domains such as premature mortality (which was considered) and unemployment from disability, early retirement, and presenteeism (which were not considered in our evaluation of indirect costs). For this reason, our indirect cost predictions may represent an underestimation of the total indirect cost burden in China. Nevertheless, a recent global survey on the economic costs of T2D reported a direct to indirect cost relation of about 4.0 for China [70]. This compares with a direct to indirect cost relation of 3.6 in our study (¥621 direct costs/¥173 indirect cost = 3.6), which supports the plausibility of our estimate.

Although the CDM provides Asia-specific CV risk prediction models based on data from the HKDR equations [67,68], we used equations from the UKPDS 68 [52] to assess the risk of CV complications. The reason the Asia-specific equations were not adopted in the base-case analysis was that the CV risk factors (blood pressure and lipid parameters) as targeted in our analysis to explore improvements in CV-RFM are not considered by these equations. Yet, we explored the HKDR equations in the sensitivity analyses across all modeled scenarios, which showed only slightly reduced direct national costs (¥598 billion) versus the base case (¥621 billion) but more considerable reduction in overall cost savings (¥67 billion using HKDR equations vs ¥107 billion in the base case), which was primarily related to the fact that the HKDR equations did not pick up the CV risk factor improvements in scenarios S12 to S15.

An assessment of the likelihood of cost savings via probabilistic sensitivity analysis was not possible because of the applied approach to extrapolate per-capita outcomes to annual on national level.

Conclusion

The cost of treating diabetes in China is very important and will increase further due to increased prevalence of the disease. Improved T2D management strategies by treating patients earlier can help to decrease the financial burden of the disease and increase life expectancy of individuals with T2D.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.vhri.2018.08.006.

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