ORIGINAL ARTICLE

Direct medical costs for patients with type 2 diabetes in 16 tertiary hospitals in urban China: A multicenter prospective cohort study

Xiang Li[1] [iD], Zhangrong Xu[1], Linong Ji[2], Lixin Guo[3], Jing Liu[4], Kun Feng[5], Yushan Xu[6], Dalong Zhu[7], Weiping Jia[8], XinWu Ran[9], Limin Chen[10], Shi Zhao[11], Bingying Shi[12], Jun Zhu[13], Zhongyan Shan[14] [iD], Zhiguang Zhou[15] [iD], Longyi Zeng[16], Jianping Weng[16]*, on behalf of the cooperative group on Direct Medical Cost Investigation of Diabetes in Chinese Urban Tertiary Hospitals, Chinese Diabetes Society[†]

[1]Diabetes Center, Department of Endocrinology, The 306th Hospital of PLA, [2]Department of Endocrine and Metabolism, Peking University People's Hospital, [3]Department of Endocrinology, Beijing Hospital, Beijing, [4]Department of Endocrinology, Gansu Provincial Hospital, Lanzhou, [5]Department of Endocrinology, Heilongjiang Provincial Hospital, Harbin, [6]Department of Endocrinology, First Affiliated Hospital of Kumming Medical University, Kunming, [7]Department of Endocrinology, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, [8]Department of Endocrinology, Shanghai Jiao Tong University, Affiliated Sixth People's Hospital, Shanghai, [9]Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu, [10]Key Laboratory of Hormones and Development (Ministry of Health), Tianjin Key Laboratory of Metabolic Diseases Hospital, Tianjin Medical University, Tianjin, [11]Department of Endocrinology, The Central Hospital of Wuhan Tongji Medical College, Huazhong University of Science & Technology, Wuhan, [12]Department of Endocrinology, The First Affiliated Hospital of Xi'an, Jiao Tong University, Xi'an, [13]Department of Endocrinology, First Affiliated Hospital of Xinjiang Medical University, Urumqi, [14]The First Affiliated Hospital of China Medical University, Shenyang, [15]Department of Endocrinology and Metabolism, The Second Xiangya Hospital of Central South University, Changsha, and [16]Department of Endocrinology and Metabolism, The Third Affiliated Hospital Sun Yat-Sen University, Guangzhou, China

ABSTRACT

Aims/Introduction: To investigate the direct medical costs for patients with type 2 diabetes in China and to examine the influencing factors.

Materials and Methods: In the present multicenter study, 1,070 patients with type 2 diabetes from 16 tertiary hospitals in 14 major cities of China were enrolled. Patient data and direct medical costs were collected during a follow-up period of 6 months at intervals of 1 month. The log-transformed direct medical costs were fitted by a generalized estimation equation to indicator variables for demographics, metabolic control, treatments, complications and comorbidities.

Results: Data of 871 participants were included in the analysis. The mean annual total direct medical costs and outpatient medical costs were $1,990.20 and $1,687.20 respectively. The average costs per inpatient per admission were $2,127.10. The share of out-of-pocket for total medical costs, outpatient costs and cost per inpatient per admission were 45.4, 46.3 and 26.0% respectively. Independent determinants of total medical costs were diabetes duration, dyslipidemia and diabetic complications, such as neuropathy and nephropathy, as well as diabetes treatment, such as the use of glucagon-like peptide-1 receptor agonists. Costs showed prominent variation across centers.

Conclusions: Diabetes is imposing a growing economic burden in patients with type 2 diabetes in China. Diabetes-related complications and comorbidities have a great impact on the medical costs. As different health policies, economic development and regional health inequalities also have an important influence on the direct medical cost, healthcare reform needs to optimize resource allocation in health service delivery systems, and provide more equitable and affordable healthcare.

INTRODUCTION

Diabetes mellitus is a chronic disease that lasts a lifetime, and imposes an enormous burden on patients, families, society and national healthcare systems. High blood glucose has become the third highest risk factor for premature mortality, after high blood pressure and tobacco use[1]. According to the International Diabetes Federation, 415 million people were estimated to have diabetes worldwide in 2015, and that number is expected to reach 642 million by the year 2040, with >55% of all diabetes cases occurring in Asia[2]. Globally, people with diabetes

generally spent two to three times more on medical care than people without diabetes[3–8]. Global healthcare expenditure was estimated to range from $673 billion to $1,197 billion in 2015, and this number will be projected to exceed $802 billion to $1,452 billion in 2040[2].

Over the past decade, the prevalence of diabetes in China has been increasing quickly as a result of rapid growth of the economy, urbanization, aging of the population and adoption of a Western lifestyle. The prevalence of diabetes has risen to 10.9%[9] in 2013 from 0.67%[10] in 1980. The estimated number of people with diabetes increased from 40 million in 2006[11] to 109.6 million in 2015[2]. China has become the country with the largest number of people with diabetes. In addition to the adults who currently have diabetes, a further 388.1 million people in China are estimated to have prediabetes, which greatly increases the risk of developing type 2 diabetes and is linked to the development of cardiovascular disease[9]. As a result, diabetes imposed a heavy economic, social and medical burden in China.

Over the past 20 years, the health expenditures associated with diabetes in China continued to rise significantly. There are several studies using data from the National Health Service Survey (NHSS) to estimate the direct medical costs of diabetes. Data from the first NHSS in 1993 showed the total direct medical costs of diabetes to be approximately $0.25 billion in that year, which accounted for 1.96% of the total health expenditures[12]. In 2003, data from the third NHSS showed that the number increased to approximately $2.29 billion[10]. In 2008, the estimated direct medical costs of diabetes based on the data of the fourth NHSS was approximately $8.65 billion[13]. As these studies used a top-down approach and the estimates were obtained by national statistics, only costs due to diabetes as the primary diagnosis were included. The costs attributed to complications where diabetes was the secondary diagnosis might not be fully included. Meanwhile, as diabetes contributes to many other diseases; for example, cardiovascular disease, the impact of diabetes on the cost of these diseases might also be omitted. Thus, these studies tend to underestimate the costs of diabetes. Actually, the NHSS in 2003 also showed that approximately 73% of people in rural areas who should have sought medical treatment chose not to do so because of cost[13]. Subsequently, a retrospective population-based study carried out by the International Diabetes Federation and Chinese Diabetes Society in 12 sites around China showed that China spent $25 billion a year on management of diabetes, which accounted for 13% of total health expenditures[14]. In 2009, China initiated a series of new health reforms and committed to spending an additional $125 billion in the ensuing 3 years, with the goal of provision of affordable and equitable basic healthcare for all by 2020[15]. The reforms focused on five major areas, including universal basic medical insurance coverage, the essential drug system, primary healthcare service provision, equitable public health services and public hospital improvements[16]. In the past 8 years, China has made big strides towards the goal of

achieving universal coverage of basic health services for all Chinese citizens by 2020, and achieved admirable achievements including the expansion of social health insurance, the reform of public hospitals and the strengthening of primary care. The share of the population covered by social health insurance schemes increased from 15% in 2000 to >97% in 2015[17]. Outpatient visits increased by 3.6 percentage points in rural China and by 7–13 percentage points in urban China. Individuals who require treatment would be more likely to seek treatment on time without underutilization[16]. Improved access to healthcare has also led to seeking treatment at higher-level facilities, longer inpatient stays, and prescription of newer and more costly drugs. These factors, along with the increased prevalence of diabetes in China, might accelerate the health expenditure of diabetes. Thus, it is becoming increasingly important for healthcare providers, policymakers and budget planners to know the health expenditure of diabetes after the reform. As type 2 diabetes is the most common type of diabetes and accounts for 95% of diabetes, we carried out a prospective, multicenter study of patients with type 2 diabetes to assess the direct medical costs for patients with type 2 diabetes in China and to examine the affecting factors. Estimates resulting from this approach are generally thought to be more precise, but because it is expensive and time-consuming, an approach like this has never been used in China.

METHODS
Study design
We carried out an observational, prospective, multicenter study with a bottom-up design to estimate the direct costs for patients with type 2 diabetes.

Study setting
Patient recruitment and data collection were carried out in 16 tertiary hospitals throughout China (eight in the east, three in the center and five in the west of China). The selected hospitals are all located in urban regions.

Study population and data collection
The study was approved by the ethics committee of the 306th Hospital of PLA. Participant inclusion criteria for enrollment were as follows: (i) diagnosed with type 2 diabetes according to the 1999 World Health Organization diagnosis criteria; (ii) aged ≥18 years; (iii) living in the city for at least 1 year; and (iv) willing and being able to give written informed consent and complete the study. The participating centers were asked to enroll 80 patients randomly. The recruitment period started in March 2015 and lasted for approximately 2 months. Patients were recruited consecutively from each center. For each day, the first five patients meeting the inclusion criteria were included. The enrollment flow chart is shown in Figure 1.

The patients were prospectively followed up by a face-to-face interview over a 6-month period at intervals of 1 month.
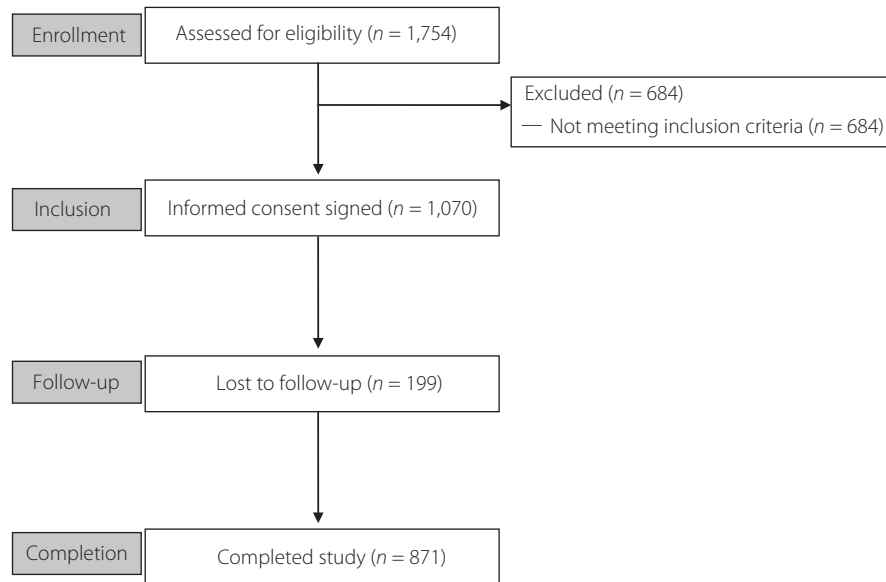
Figure 1 | Study patient enrollment flow chart.

Demographic data (age, sex, diabetes duration, body mass index, household income, type of medical insurance, education and cigarette smoking) and clinical data (diabetes treatment, glycated hemoglobin [HbA1c], retinopathy, nephropathy, neuropathy, cerebrovascular disease, cardiovascular disease, peripheral vascular disease, hypertension and dyslipidemia) were collected at baseline by investigative staff (diabetologist and/or diabetes educator) at each center using a dedicated electronic case report form.

Retinopathy was assessed by a fundus examination by independent ophthalmologists. Nephropathy was diagnosed if the participant had persistent proteinuria of 0.5 g, urine albumin:creatinine ratio >30 mg/g at least twice, estimated glomerular filtration rate <60 mL/min/1.73 m^2, was receiving renal dialysis or had a history of renal transplantation. Peripheral neuropathy was considered when the patients had the neuropathic symptoms and signs or objectively abnormal results with the Semmes–Weinstein 5.07/10 g monofilament or 128-Hz tuning-fork test and without other significant disease. The diagnosis of peripheral vascular diseases was made by a history of intermittent claudication, history of previous lower limb vascular surgery, absent or reduced pedal pulses, ankle brachial pressure index <0.9 or angiography showing significant stenosis in low extremity arteries. Coronary artery disease was defined as a history of myocardial infarction, angina, ischemic electrocardiogram change, or having undergone coronary bypass surgery or angioplasty. Cerebrovascular disease was defined as a history of stroke, transient ischemic attack or revascularization procedures.

All patients were asked to keep records of outpatient visits, hospital admissions and purchase of medicines from pharmacy during the follow-up period. At every contact, the investigative staff recorded data regarding the medical costs in the electronic case report form. All the investigative diabetologists had been trained in using the electronic case report form and practiced interviewing in a central location before the study. All the data were sent to the data collection center immediately after personal collection at each center. The data were regularly monitored by two independent researchers. All patients gave their written informed consent.

Estimation of costs

In the present study, we calculated the total direct medical costs including both diabetes-related and non-diabetes-related costs for patients with type 2 diabetes. Direct medical costs included outpatient and hospitalization costs. Outpatient costs consisted of costs associated with hospital outpatient visits, medications, laboratory tests, examinations, medical devices, such as glucose meters and test strips, and other medical supplies. Hospitalization costs covered payments for hospital treatments, hospitalizations, medications, and laboratory and medical services during the inpatient episode. Direct non-medical costs, such as transportation costs and indirect costs, were not included. The total direct medical costs were estimated by the total before-subsidy charges, which is the total medical bill before any deduction for government subsidies or insurance claims. Data on private healthcare costs for the patients themselves were also included in the total direct medical costs. All costs were recorded in Chinese Yuan, and then converted into $US at a currency exchange rate of $US 1.0 = CNY 6.2 (March 2015). As data were collected for a 6-month period, per patient cost was multiplied by a factor of two to obtain annual cost per patient.

Statistical analysis

The normality of the distribution of each continuous variable was assessed using the Kolmogorov–Smirnov test. If normality was established, results were presented as means ± standard deviation (SD), and Student's *t*-test was used to assess difference. As the distributions of costs were severely skewed, means and SDs together with medians and interquartile ranges (IQR) were used and were examined by the Mann–Whitney *U*-test and Kruskal–Wallis *H*-test. Categorical variables were calculated as a frequency, and expressed as numbers and percentages, and were compared by the Pearson χ^2-test.

Clinical practice and infrastructure differed according to the center. To assess influencing factors of raw medical costs (dependent variable), those factors with *P*-values <0.05 in the univariable analyses were further investigated using a generalized estimating equation[18] (GEE) model with gamma distribution and log link given the skewed nature of costs data. We further modeled annual direct medical costs as a function of a wide range of demographic characteristics, treatments and complications. All variables with coefficients significant at the *P* < 0.05 level were kept in the model. As the GEE with gamma distribution and log link model required original cost data to be log-transformed, coefficients and 95% confidence intervals from the model needed to be transformed back to the original scale in the form of multipliers.

For this model, the base case was determined to be the annual direct medical costs for a patient aged 58 years, diagnosed with type 2 diabetes for 8 years, treated with only diet and exercise, and with no diabetes complications and comorbidities. Because the costs for treating such a patient differed among centers, it was not appropriate to use a cost estimate from any of the centers as the base case cost. We decided to use the mean of the estimated base case costs among all of the centers. To do this, we included all of centers in the model and omitted the intercept to get the mean base case cost in each of the 16 centers, then computed the mean of the estimated mean costs in all the centers. That provided a modeled mean cost to use as the uniform direct medical cost for a base case patient. Then, to calculate cost for any other patient, the annual direct medical cost of the base case was multiplied by the cost multipliers calculated for each of demographic characteristic, treatments, complications and comorbidities for that patient. All statistical analyses were carried out using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

A total of 1,070 patients consented to be enrolled in the study. Among them, 199 (19.6%) were lost to follow up. A total of 871 patients completed follow up and were included for analysis. Table 1 summarizes the main demographics and clinical characteristics for study patients. The patients were equally distributed between the two sexes (54.8% male). The mean ± SD age of patients was 58.1 ± 11.3 years, and mean ± SD duration

Table 1 | Baseline characteristics of patients included in the analysis

Characteristics	
Mean age, years (SD)	58.1 (11.3)
Male, *n* (%)	477 (54.8)
Mean BMI, kg/m² (SD)	25.4 (3.6)
Mean diabetes duration, years (SD)	7.6 (7.2)
Mean systolic blood pressure, mmHg (SD)	130.0 (14.0)
Mean diastolic blood pressure, mmHg (SD)	80.1 (8.4)
Mean fasting blood glucose, mmol/L (SD)	8.2 (2.9)
Mean 2-h postprandial blood glucose, mmol/L (SD)	12.1 (4.7)
Mean HbA1c, % (SD)	7.8 (1.9)
Mean TC, mmol (SD)	4.7 (1.2)
Mean TG, mmol (SD)	1.7 (1.3)
Mean LDL-C, mmol (SD)	2.7 (0.9)
Mean HDL-C, mmol (SD)	1.3 (0.6)
Antidiabetic treatment	
Diet and exercise alone, *n* (%)	52 (6.0)
Oral antidiabetic agents alone, *n* (%)	456 (52.4)
Insulin alone, *n* (%)	83 (9.5)
Insulin in combination with oral agents, *n* (%)	269 (30.9)
GLP-1 RA, *n* (%)	11 (1.3)
Hypertension, *n* (%)	448 (50.4)
Dyslipidemia, *n* (%)	453 (52.0)
Macrovascular complications, *n* (%)	280 (32.1)
Microvascular complications, *n* (%)	351 (40.3)
Smoking habit, *n* (%)	282 (33.5)

GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TC, total cholesterol; TG, triglyceride.

of diabetes was 7.6 ± 7.2 years. Of the 871 patients, 282 (33.5%) were smokers; 448 (51.4%) had hypertension and 453 (52.0%) had dyslipidemia. Of the 94.0% patients who were taking antidiabetic medications, the majority used oral medications (52.4%), 9.5% were treated with insulin exclusively, 30.9% used both insulin and oral medications, and only 1.3% used glucagon-like peptide-1 receptor agonist (GLP-1 RA). Retinopathy, nephropathy and neuropathy were present in 180 (20.7%), 141 (16.2%) and 204 (23.4%) patients, respectively. The prevalence rates of cardiovascular, cerebrovascular and peripheral vascular disease were 21.5, 11.3 and 12.3% respectively.

Direct medical costs

Table 2 provides the unadjusted total direct medical costs and out-of-pocket (OOP) payments for over all, treatments, complications, comorbidities and demographic characteristics. During the study period, 54 (6.2%) patients had 62 hospital admissions. The mean annual total direct medical costs per patient were $1,990.20 (SD $2,849.60; median $1,409.60, IQR $690.00–2,393.20), and mean annual outpatient costs per patient were $1,687.2 (SD $1880.80; median $1,367.60, IQR $673.40–2,223.20). The averages cost per inpatient per admission were $2,127.10 (SD $3,149.50, median $1,335.90, IQR $665.50–

Table 2 | Differences in medical costs across demographic and clinical variables

	n	Unadjusted annual total direct medical costs per patient ($US)		Unadjusted annual OOP payments per patient for total direct medical costs ($US)	
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Overall	871	1,990.2 (2,849.6)	1,409.6 (690.0–2,393.2)	790.3 (1,719.2)	436.1 (182.4–866.4)
Sex					
Male	477	1,906.7 (2,626.9)	1,434.2 (758.3–2,338.2)	785.9 (2,039.3)	440.1 (1,78.2–843.5)
Female	394	2,091.4 (3,098.3)	1,398.5 (611.7–2,427.1)	795.6 (1,227.0)	429.9 (185.0–916.1)
P-value			0.607		0.809
Education level					
Illiteracy	17	1,400.7 (1,144.9)	1,148.3 (545.5–1,791.4)	701.9 (918.2)	410.1 (165.6–981.4)
Primary education	65	2,486.0 (5,310.4))	1,469.0 (921.0–2,727.1)	1,434.7 (4,907.1)	585.2 (334.4–1,190.2)
Secondary education	507	1,847.2 (2,400.6)	1,325.7 (607.4–2,215.9)	692.7 (1,000.6)	397.4 (151.8–802.1)
College and above	282	2,168.8 (2,849.5)	1,633.8 (845.3–2,540.7)	822.5 (1,304)	468.5 (204.5–886.9)
P-value			0.068		0.003
Hypertension					
Yes	448	2,302.5 (3,008.7)	1,595.4 (846.3–2,641.0)	785.6 (1,263.1)	448.3 (172.5–814.3)
No	423	1,659.6 (2,634.2)	1,200.5 (607.4–1,954.7)	795.2 (2,098.4)	418.7 (188.2–909.1)
P-value			<0.001		0.914
Dyslipidemia					
Yes	453	2,379.1 (3,413.5)	1,677.5 (972.8–2,642.5)	912.6 (2,214.1)	480.0 (207.5–1,009.6)
No	418	1,568.8 (1,992.2)	1,109.0 (560.9–1,923.0)	657.7 (904.8)	380.2 (148.5–777.8)
P-value			<0.001		0.003
Cardiovascular disease					
Yes	187	2,687.2 (3,423.9)	1,969.3 (1,246.1–2,968.1)	810.9 (1,317.1)	410.0 (175.5–790.6)
No	684	1,799.7 (2,639.1)	1,263.1 (608.6–2,143.9)	784.7 (1,814.4)	453.3 (183.9–891.4)
P-value			<0.001		0.422
Cerebrovascular disease					
Yes	98	2,748.4 (3,848.3)	1,671.1 (1,176.1–2,916.3)	1,037.5 (1,517.8)	497.6 (200.9–1,185.4)
No	773	1,894.1 (2,684.8)	1,363.1 (6,54.7–2,337.5)	756.0 (1,741.4)	420.1 (181.6–837.3)
P-value			0.003		0.115
Peripheral vascular disease					
Yes	107	2,484.5 (1,666.3)	2,260.6 (1,321.1–3,058.1)	688.4 (925.6)	417.8 (167.5–664.4)
No	764	1,921.0 (2,972.2)	1,348.5 (623.2–2,213.9)	804.6 (1,802.6)	439.2 (189.0–913.7)
P-value			<0.001		0.393
Retinopathy					
Yes	180	2,562.4 (4,212.9)	1,667.4 (845.1–2,778.5)	938.3 (3,061.5)	415.0 (125.0–875.0)
No	691	1,841.2 (2,350.9)	1,340.5 (655.6–2,288.3)	751.7 (1,134.8)	443.2 (195.8–866.4)
P-value			0.001		0.434
Nephropathy					
Yes	141	2,944.5 (3,531.7)	2,067.8 (1,391.8–2,975.4)	1,029.4 (1,531.1)	556.9 (290.9–1,238.5)
No	730	1,805.9 (2,661.8)	1,293.0 (608.3–2,197.5)	644.4 (751.9)	397.5 (167.3–744.2)
P value			<0.001		0.002
Neuropathy					
Yes	204	2,775.1 (4,140.8)	1,899.0 (1,184.8–2,847.1)	714.0 (948.5)	480.9 (160.5–909.2)
No	667	1,750.2 (2,266.0)	1,263.3 (599.1–2,220.1)	668.4 (9,31.6)	409.7 (188.4–802.1)
P-value			<0.001		0.053
Diabetic foot ulcer					
Yes	18	3,641.2 (5,905.8)	1,659.5 (627.2–3,800.4)	434.2 (390.2)	311.2 (138.0–698.8)
No	853	1,955.4 (2,745.4)	1,406.9 (690.2–2,358.6)	684.2 (942.8)	418.8 (182.5–843.2)
P-value			0.63		0.630
Smoking					
Non-smoker	579	1,926.7 (2,662.9)	1,370.1 (627.9–2,339.4)	701.4 (1,017.9)	421.6 (167.5–843.9)
Ex-smoker	123	2,191.7 (2,154.6)	1,888.9 (1,066.0–2,668.0)	683.2 (607.9)	483.2 (250.2–1,025.2)

Table 2 (*Continued*)

	n	Unadjusted annual total direct medical costs per patient ($US)		Unadjusted annual OOP payments per patient for total direct medical costs ($US)	
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Current smoker	169	2,061.2 (3,773.0.)	1,302.0 (673.3–2,126.7)	599.4 (829.7)	361.8 (155.2–752.6)
P value			0.009		0.063
Medical insurance					
None	39	1,263.7 (1,575.7)	857.3 (451.1–1,601.4)	1,263.7 (1,575.7)	857.3 (451.1–1,601.4)
Urban resident basic medical insurance	187	2,650.4 (034.7)	1,874.8 (1,202.0–2,773.6)	910.1 (3,000.0)	485.6 (215.4–809.2)
Urban employees basic medical insurance	503	1,781.5 (2,127.9)	1,343.0 (615.9–2,296.7)	571.7 (800.2)	346.2 (125.8–652.1)
New cooperative medical scheme	81	1,741.3 (2,005.2)	1,246.1 (721.6–1,902.2)	1,223.2 (1,265.3)	921.0 (288.2–1,656.9)
Other	61	2,482.9 (4,479.1)	1,409.6 (747.9–2,577.2)	1,348.4 (2,174.7)	630.8 (283.4–1,523.8)
P-value			<0.001		<0.001
Diabetes treatment					
Diet and exercise alone	52	1,065.6 (2,868.3)	487.8 (229.0–854.2)	566.7 (1,161.1)	249.5 (101.2–588.4)
Oral antidiabetic agents alone	456	1,733.4 (2,485.5)	1,263.1 (670.5–2,064.7)	824.7 (2,066.4)	470.9 (224.5–907.1)
Insulin alone	83	2,409.4 (4,453.9)	1,402.5 (755.8–2,423.5)	881.5 (1,178.9)	440.1 (167.5–1,374.3)
Insulin in combination with oral agents	269	2,436.8 (2,749.1)	1,908.9 (1,130.9–3,006.9)	737.3 (1,253.5)	401.8 (126.4–817.7)
GLP–1 RA	11	2,928.7 (1,722.7)	2,637.8 (1,934.8–4,124.2)	1,028.8 (1,394.8)	448.4 (213.2–1,517.7)
P-value			<0.001		0.004
Center					
1	67	3,235.0 (4,146.7)	2,477.6 (1,363.1–3,725.6)	1,178.2 (2,068.3)	540.0 (289.1–1,052.9)
2	64	2,988.8 (3,225.6)	2,423.1 (1,758.5–3,087.4)	677.9 (1,024.0)	419.8 (305.7–646.5)
3	73	2,232.4 (1,718.1)	2,000.0 (1,679.4–2,355.8)	433.2 (542.6)	197.8 (112.7–547.0)
	52	1,928.1 (3,143.4)	1,130.2 (514.6–1,874.1)	1,659.8 (1,896.7)	1,078.6 (514.6–1,765.2)
5	63	3,028.9 (2,933.8)	2,299.1 (1,373.0–3,183.1)	636.8 (650.1)	491.6 (299.4–738.6)
6	17	1,321.4 (1,179.2)	955.4 (632.3–1,380.6)	394.1 (459.1)	276.0 (209.2–3,84.1)
7	93	1,371.1 (1,635.5)	1,054.7 (807.3–1,460.2)	623.6 (419.8)	493.6 (308.4–901.3)
8	64	2,003.7 (3,889.6)	913.1 (418.1–2,110.1)	596.0 (605.7)	419.4 (155.5–796.6)
9	77	2,143.6 (4,974.1)	1,205.9 (628.6–1,957.1)	1,744.1 (4,553.7)	960.0 (511.2–1,585.0)
10	85	2,321.0 (1,531.6)	1,934.8 (1,349.2–2,917.9)	271.0 (356.9)	167.1 (79.0–336.2)
11	90	557.0 (435.3)	421.0 (303.4–668.5)	93.1 (146.1)	0 (0–161.3)
12	39	1,222.9 (897.1)	1,015.3 (514.3–1,727.1)	662.6 (652.9)	380.8 (205.5–998.5)
13[†]	1				
14	12	1,520.5 (953.1)	1,707.0 (633.1–2,413.2)	1,371.8 (979.7)	1,477.1 (454.3–2,193.5)
15	48	1,766.9 (1,676.4)	1,303.0 (637.2–2,319.7)	1,615.5 (1,340.2)	1,236.2 (637.2–1,960.1)
16	26	1,089.8 (536.4)	1,063.4 (592.6–1,355.7)	688.4 (480.2)	555.1 (403.8–876.4)
P-value			<0.001		<0.001

[†]As only one patient in the center completed the study, the annual total direct medical costs per patient could not be calculated. GLP-1 RA, glucagon-like peptide-1 receptor agonist; IQR, interquartile range; OOP, out of pocket; SD, standard deviation.

2,285.10). For annual total direct medical costs, mean OOP payments were $790.3 (SD $1,719.20, median $436.10, IQR $182.40–866.40) and the share of OOP was 45.4%. For annual outpatient medical costs, mean OOP payments were $679.1 (SD $935.20, median $418.70, IQR $180.80–831.40) and the share of OOP was 46.3%. For cost per inpatient per admission, mean OOP payments were $787.40 (SD $2,543.00, median $165.80, IQR $0–649.40) and the share of OOP was 26.0%.

Factors affecting the medical costs

At univariate analysis, annual total direct medical costs per patient were found to differ across enrolling centers, to increase with age and diabetes duration, and to be significantly higher in patients with hypertension or dyslipidemia, in those with macrovascular complications (cardiovascular disease, cerebrovascular disease or peripheral vascular disease), and in those with microvascular complications (retinopathy, nephropathy or neuropathy). To further evaluate the impact of complications, the annual total direct medical costs per patient according to the type of complications and the number of microvascular complications were analyzed. The annual direct medical costs for a patient with only nephropathy, two microvascular complications, only macrovascular or both macrovascular and microvascular complications were

significantly higher than the costs for patients without complications (Table 3).

Mixed results were found for costs by diabetes treatment, insurance type and education level, with no significant differences found in patients treated with oral antidiabetic agents alone when compared with patients treated with insulin alone. However, costs were higher in patients treated with insulin in combination with oral agents. No significant differences were found between patients with New Rural Cooperative Medical Scheme and patients without insurance. However, costs were higher in patients with Urban Resident Basic Medical Insurance and Urban Employees Basic Medical Insurance (UEBMI). Costs were higher in patients who had secondary education compared with patients who had college education or above. Costs were not significantly associated with sex.

For annual OOP payments per patient, similar to total direct medical costs per patient, costs increased with diabetes duration and were higher in patients with dyslipidemia, in those with diabetic nephropathy. Costs across each center also differed substantially. Costs were not significantly associated with age, sex, HbA1c, smoking status, hypertension, macrovascular disease, retinopathy or neuropathy.

Factors independently associated with annual total direct medical costs and the share of OOP costs are summarized in Table 4. Diabetes duration, diabetes-related complications (nephropathy and neuropathy), dyslipidemia and diabetes treatments (taking GLP-1 RA, insulin alone, and both oral medications and insulin) were associated with a significant increase of total direct medical costs. Taking center 1 as the reference center, except for center 5, all other centers were associated with a significant decrease of annual total medical costs. Age, smoking status, insurance types, education level, macrovascular disease, retinopathy, diabetic foot ulcers and hypertension were not independently associated with total direct medical costs. For the share of OOP, age and cardiovascular disease were significantly associated with a lower share of OOP payments. Neuropathy was significantly associated with a higher share of OOP payments. Taking center 1 as the reference, centers 4, 6, 7, 8, 9, 11, 12, 14, 15 and 16 were significantly associated with a higher share of OOP payments, and centers 2, 3 and 10 were significantly associated with a lower share of OOP payments. Insurance types were significantly associated with lower OOP payments. Diabetes duration, smoking status, HbA1c, diabetes comorbidities (dyslipidemia and hypertension), diabetes-related complications (cerebrovascular disease, peripheral vascular disease, retinopathy, diabetic foot ulcers, nephropathy and neuropathy), education level and diabetes treatments were not independently associated with the share of OOP payments.

Estimates of total direct medical costs by GEE model

A GEE model was used to further estimate the annual total direct medical costs for patients with type 2 diabetes by each patient's demographic characteristics, diabetes treatments, complications and comorbidities. The mean annual total direct medical cost for a patient aged 58 years, diagnosed with type 2 diabetes for 8 years, treated with only diet and exercise, and with no diabetes complications and comorbidities was $464.40. If a patient has any of the characteristics or complications listed in Table 5, the annual direct medical cost is then estimated by the cost multipliers for other characteristics, treatments, complications and comorbidities. Every 1-year increase in diabetes duration was each associated with annual total direct medical costs 1.7% higher than those of the base case patient. GLP-1 RA treatment resulted in an increment of 202% in total direct medical costs. Dyslipidemia, nephropathy and neuropathy were each associated with 14.3–30.1% higher total direct medical costs.

Difference in total direct medical costs across centers

As significant differences in total direct medical costs across centers were confirmed by multivariate analysis, further analyses were carried out to evaluate potential influencing factors of

Table 3 | Medical costs according to microvascular and macrovascular complications

	n	Unadjusted annual total direct medical costs per patient ($US)		P-value
		Mean (SD)	Median (IQR)	
No complications	414	1,414.0 (1,388.5)	1,086.1 (485.4–1,849.5)	
Microvascular complications	177	2,470.2 (4,396.0)	1,545.2 (841.1–2,431.0)	0.001
1 complication	123	2,046.7 (2,895.4)	1,343.0 (788.7–2,180.9)	0.144
Retinopathy	42	1,778.6 (3,245.6)	825.1 (448.8–1,574.6)	1.000
Neuropathy	49	1,716.9 (1,588.4)	1,443.7 (970.0–2,164.0)	0.630
Nephropathy	32	2,903.5 (3,758.5)	1,870.7 (1,244.3–3,128.1)	0.002
2 complications	43	3,792.3 (7,316.6)	2,115.4 (1,028.2–3,102.7)	0.011
3 complications	11	2,037.0 (1,751.9)	1,601.1 (1,193.5–2,379.5)	0.478
Macrovascular complications	106	2,248.7 (2,958.8)	1,594.3 (848.6–2,930.1)	0.001
Micro- and macrovascular complications	174	2,715.7 (3,107.9)	2,036.2 (1,362.1–2,971.7)	<0.001

IQR, interquartile range; SD, standard deviation.

Table 4 | Factors influencing the medical costs

Variable	Annual total medical costs			Share of OOP payments		
	Coefficient β	95% CI	*P*-value	Coefficient β	95% CI	*P*-value
Age (per year increase)				−0.010	−0.015 to −0.005	<0.001
Diabetes duration (per year increase)	0.017	0.008–0.026	<0.001			
Cardiovascular disease (absent reference)				−0.234	−0.354 to −0.113	<0.001
Diabetes complications (absent reference)						
Nephropathy	0.227	0.014–0.440	0.037			
Neuropathy	0.263	0.082–0.445	0.004	0.109	0.196–5.867	0.015
Dyslipidemia (Absent reference)	0.133	0.071–0.196	<0.001			
Diabetes treatment						
Diet and exercise alone (reference)						
GLP-RA treatment	1.106	0.087–2.125	0.033			
Medical insurance						
None (reference)						
Urban resident basic medical insurance				−0.925	−1.266 to −0.583	<0.001
Urban resident basic medical insurance				−0.833	−1.154 to −0.512	<0.001
Urban employees basic medical insurance				−0.638	−1.0.36 to −0.240	0.002
Center						
1 (reference)						
2	−0.180	−0.245 to −0.115	<0.001	−0.279	−0.390 to −0.169	<0.001
3	−0.549	−0.688 to −0.410	<0.001	−0.225	−0.324 to −0.127	<0.001
4	−0.371	−0.593 to −0.150	0.001	1.216	1.043–1.389	<0.001
6	−0.904	−1.107 to −0.702	<0.001	0.211	0.042–0.380	0.014
7	−0.882	−1.047 to −0.718	<0.001	0.573	0.429–0.717	<0.001
8	−0.260	−0.389 to −0.131	<0.001	0.541	0.443–0.638	<0.001
9	−0.386	−0.487 to −0.285	<0.001	1.105	0.892–1.137	<0.001
10	−0.427	−0.589 to −0.266	<0.001	−0.745	−1.000 to −0.490	<0.001
11	−1.701	−1.919 to −1.482	<0.001	0.299	0.140–0.457	<0.001
12	−0.638	−0.792 to −0.484	<0.001	0.597	0.461–0.733	<0.001
14	−0.672	−0.840 to −0.505	<0.001	0.951	0.811–1.090	<0.001
15	−0.296	−0.463 to −0.129	0.001	1.069	0.913–1.224	<0.001
16	−0.909	−1.071 to −0.747	<0.001	0.602	0.470–0.734	<0.001

95% CI, 95% confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; OOP, out of pocket.

such differences. The mean annual total direct medical costs incurred for each center differed approximately six times across centers ($557.00 in center 11 vs $3,235.00 in center 1). To

Table 5 | Total direct medical costs associated with demographic characteristics, treatments, diabetes complications and comorbidities

Characteristics	Multiplier	95% CI
Diabetes duration (per year increase)	1.017	1.008–1.027
Diabetes complications (absent reference)		
Nephropathy	1.255	1.014–1.553
Neuropathy	1.301	1.085–1.560
Dyslipidemia (absent reference)	1.143	1.073–1.217
Diabetes treatment		
Diet and exercise alone (reference)		
GLP-1 RA treatment	3.021	1.090–8.372

95% CI, 95% confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

remove the confounding effects of outliers, 24 individuals whose costs above the three standard deviations of the cohort mean cost were excluded and the annual month total direct medical costs per patient at each center was recalculated. Significant difference still occurred across centers ($557.00 in center 11 vs $2,625.40 in center 2).

Although significant differences in the share of OOP payments across centers were also confirmed by multivariate analysis, only centers 6, 8, 11, 12, 15 and 16 were significantly associated with a higher share of OOP payments compared with center 1 when the interaction effect of center and insurance type were entered into the GEE model. Hence, the insurance type could partially explain the discrepancy of OOP payments across centers.

DISCUSSION

The tremendous economic burden of diabetes makes the disease an important clinical and public health problem. A lot of

studies on the cost of diabetes have been carried out worldwide. Basically, either of two methodological approaches was used in most of these studies: a 'top-down' approach or a 'bottom-up' approach. The 'top-down' approach uses aggregated population data and is based on International Classification of Diseases codes. Although this method is broadly used in developed countries, it is not practicable for China, because of the lack of documented data on healthcare uses of the whole country. In contrast, the approach might considerably underestimate the healthcare costs of diabetes, because only costs where diabetes was listed as the primary diagnosis or reason for healthcare use will be included, and costs where diabetes was listed as a secondary or tertiary diagnosis were often not considered. In fact, many patients with diabetes were admitted into hospitals or died from other diseases, such as cardiovascular disease or cancer. The 'bottom-up' approach is based on costs of individuals with diabetes. Costs estimates resulting from this approach generally are more precise. Whichever approach is used, studies can be carried out either in a prospective or retrospective way. Although the retrospective approach is less costly and time-consuming, it can only be possible with sufficient observational datasets. In the prospective approach, however, complete consumption of healthcare resources and intervention can be made by the analysts from the questionnaires designed.

In the present prospective study, we examined the direct medical costs incurred over 6 months in 1,070 patients with type 2 diabetes and reported the annual costs per patient. The estimated annual direct medical costs per patient and outpatient cost per patient were $1,990.20 and $1,687.20 respectively. A retrospective cross-sectional study by Wang et al.[19] estimated a mean annual direct medical cost of $1,320.90 and a mean annual outpatients cost of $1030.10 in 2007. In the study by Wang et al.[18], based on the data from 15 hospitals in urban China, the direct medical cost was $891.70. Relying on participant recall of medical costs, Yang et al.[5] observed expenditures for medical care were $908.60 for patients with type 2 diabetes in 2008, which were 3.38-fold greater than people with normal glucose tolerance. The present results are much higher than prior studies' estimations of costs. The magnitude of the difference between the previous estimations and our estimate could be due to the methodology, enrollment of patients, inclusion of costs, increased diabetes prevalence, increased use of healthcare, increased price of new antidiabetic agents, such as GLP-1 RA, and increase in consumer price index. Actually, all the three studies were carried out in a retrospective manner. In the study by Wang et al.[19], 12.9% patients were enrolled from secondary hospitals, and in another study by Wang et al.[18], 41.3% patients were enrolled from secondary hospitals. However, all the patients in the present study were enrolled from tertiary hospitals. In China, the level of hospital also has an important influence on medical costs. Hospitals in China are classified into three tiers: tier-1 (primary), tier-2 (secondary) and tier-3 (tertiary) based on hospital service, size, management, quality, safety, facility, medical technology and so on. Regarding the

capabilities and medical resource availability in lower-level hospitals, and with no restriction in freedom to select hospitals for healthcare in China, patients often tend to seek care in tertiary hospitals. As tertiary hospitals can provide high-level specialist medical services, the charge for examination services and drugs are often higher than those in the lower level hospitals. It is thus reasonable to assume that patients' enrollment might partially explain the differences in costs between the present study and the studies of Wang et al. In the study by Yang et al.[5], patients from both urban districts and rural townships were included, but the present study only enrolled patients from an urban area. The difference in patient enrollments could lead to the disparity, because there is rural and urban inequality in health services utilization in China. Outpatient attendance and medication use is much lower in rural areas. The latest estimate of the average annual total costs per patients by Huang et al.[20] in patients with type 2 diabetes covered by the provincial UEBMI in Hangzhou city (a provincial capital city in east China) was $2,780 in 2011.

Compared with other Asian countries, our estimates appears to be higher than those in Singapore ($1,575.60)[21], Korea ($1,939)[22], Iran ($152)[23], Thailand ($551.20)[8], Bangladesh ($314)[24] and India ($525.50)[25]. Differences in the methodologies, infrastructure and financing of healthcare, a country's degree of economic development, and gross domestic product might account for the discrepancy in medical costs of diabetes among these countries. However, our estimates were far less than those in developed countries, such as the USA[26] ($11,167) and Germany ($4,713)[3]. This seems logical, as China is a rapidly industrializing middle-income country, and the healthcare facilities in China are of a lower standard compared with those in many developed countries. However, as China has the largest numbers of people with diabetes, the total spending for all people with diabetes is huge. The total diabetes-related health expenditure in China was estimated to be approximately 51 billion in 2015, which was the second highest expenditure for diabetes care in the world[2]. Thus, diabetes imposed a huge economic burden on the Chinese government, and there is an urgent need for prevention of diabetes in China. Indeed, a large body of evidence supports lifestyle interventions can prevent or delay type 2 diabetes and thus reduce the huge economic burden of diabetes. Furthermore, many of these interventions are cost-effective and/or cost-saving[2].

As expected, diabetes duration, diabetes complications, comorbidities and diabetes treatment were found to be associated with total direct medical costs. The present results have shown that macrovascular (cardiovascular disease and cerebrovascular disease) and microvascular complications (neuropathy and nephropathy) are associated with higher direct medical costs, which are consistent with findings from many other studies[3,18,22,27–33]. Diabetic complications are thought to be the key factors in determining quality of life and healthcare costs. Previous studies have shown that hospitalization costs account for the largest part of diabetes costs[4,34]. Patients who have

developed late complications might require extra inpatient hospital care and a longer hospital stay[35], which can result in an increase in diabetes costs. New data from UK Prospective Diabetes Study 84 also showed that diabetic complications are associated with substantial immediate and long-term healthcare costs, and that the largest average annual costs were attributable to amputation, followed by ischemic heart disease, myocardial infarction and stroke[36]. The costs were also reported to increase with the number of microvascular complications in patients without macrovascular complications[22]. In contrast, the present study found that the costs for patients with three complications were not significantly different from the costs for patients with two complications ($2,037.00 ± 1,751.90 vs $3,792.30 ± 7,316.6, $P = 1.0$). This difference could be due to a small sample size of patients with two and three complications (43 and 11, respectively), which might introduce potential bias to the cost analysis.

Long duration of diabetes was also shown to be associated with higher direct medical costs in the present study. Because of the chronic nature of diabetes, serious complications are always associated with long disease duration. An increase in diabetes duration can directly increase the risk of complications and then lead to higher costs.

Type of diabetes treatment was shown to have a strong impact on total direct medical costs. The earliest GLP-1 RAs, exenatide twice-daily and liraglutide once-daily, are available in China. As these newer agents have substantially higher drug acquisition costs compared with metformin and sulfonylureas, it is not surprising that GLP-1 treatment is associated with the higher medical costs of diabetes. However, long-term treatment with GLP-1 RA might have beneficial effects on glycemic control, lipids, body mass index and systolic blood pressure, which could be translated into reduced incidence of diabetic complications and improved life expectancy for patients with type 2 diabetes. The savings in complications-related medical costs could offset the higher pharmacy costs of GLP-1 RA, therefore the long-term treatment with GLP-1 RA might be cost-effective[37,38]. Recently the price of GLP-1 RA has reduced dramatically; for example, the price of liraglutide was reduced by >40%.

After adjusting for variability in patients' characteristics, diabetic complications and comorbidities, there persists significant intercenter cost variation for patients with type 2 diabetes. This suggests that although different centers might provide comparable quality of diabetes care, there is a wide divergence in the pathways used to achieve that level of care, with differing associated costs. In fact, the Chinese Diabetes Society has created clinical guidelines for type 2 diabetes management, and the National Health and Family Planning Commission of China has also issued clinical pathways for type 2 diabetes management to support the clinical guidelines to be carried out nationwide. Thus, compliance with diabetes clinical practice guidelines might ensure that hospitals consistently provide high-quality care and reduce healthcare costs.

Although the social health insurance coverage had reached 97% in 2015[17] in China, the present study found that just 54.6% of total direct costs were covered by health insurance, and the remaining 45.4% was OOP payments. This represents a significant burden for the individual diabetes patient. The basic health insurance in China consists of three schemes for different social groups. The rural areas are covered by the New Rural Cooperative Medical Scheme. The urban areas are covered by the UEBMI, which is for the employed, and Urban Resident Basic Medical Insurance, which covers the unemployed, children and elderly. The UEBMI aims at covering outpatients and inpatients services for urban employees. However, the other two schemes reimburse mainly on inpatient costs, though the coverage has gradually been expanded to outpatient costs. The share of OOP for patients covered by New Rural Cooperative Medical Scheme was 74.6% in the present study, which is more than twofold of the patients covered by UEBMI (37.2%) or Urban Resident Basic Medical Insurance (38.5%). This showed an inequality in affordability of healthcare services. Fortunately, recently announced reforms by the Chinese government will begin the process of integration of insurance programs both across policies and regions, aiming to minimize the differences in funding and functioning of the various insurance schemes, integrate the residence programs, diminish urban and rural differences, allow individuals to access benefits nationally, increase insurance mobility, and to lower barriers to insurance use[16].

Several strengths and limitations of the present study have to be taken into account. One of the main strengths was the use of a prospective cohort design and reflection of real-world clinical practice. In contrast to many previous studies based on retrospective data in this area, more confidence can be placed in the accuracy of the data collected in the present study, because patients were not required to recall events for long periods of time. Furthermore, the present study collected data across different regions of China and assessed a comprehensive set of cost items, allowing assessment of different contributors to direct medical costs, and the possibility of exploring factors associated with differences in costs across centers. Furthermore, the present study assessed variations in costs associated with different patient demographic characteristics, diabetic complications, comorbidities and diabetes treatments, allowing assessment of direct medical costs specific to patients with different characteristics.

However, the present study also had several limitations. First, the generalizability of the results could be a concern. Although our study is on a multicenter basis, the patients only came from 16 urban tertiary hospitals, which cannot be considered representative of all patients with diabetes in China and generalizable to patients in other settings. It would be preferable to carry out a community-based study and enroll rural patients in the future. Second, the present study focused on the direct medical costs of type 2 diabetes, and did not include the direct non-medical costs and indirect costs incurred. It has been

shown that the indirect costs might be higher than direct costs ranging from 30% to 56% of total costs[4,39–41]. Therefore, the present study might underestimate the total costs of type 2 diabetes. Third, because of the lack of a comparison group (i.e., individuals without diabetes), we were not able to accurately estimate the excess costs attributable to type 2 diabetes. Fourth, comorbidities were broadly defined in the present study and we did not distinguish the stage of each diabetic complication either, which might have affected the cost differences. Fifth, the cost data for the 6 months might not accurately reflect the cost data of 1 year (this method ignores any possible seasonal variation that might exist). Studies with longer duration of follow up are still required to evaluate the annual costs of type 2 diabetes more accurately. Sixth, as no death was noted during the study period and no clinical data (such as HbA1c, blood pressure and lipid profile) were collected by the end of the study, we were unable to assess the effects of death and these clinical parameters on medical costs. Indeed, death and management of patients of type 2 diabetes could cause a substantial increase in medical costs. Seventh, as all oral antidiabetic agents were classified to one group in the study, the different costs incurred by different oral antidiabetic agents could not be determined. Indeed, newer agents, such as dipeptidyl peptidase-4 inhibitors and sodium-dependent glucose transporters 2 inhibitors, might be more costly than older agents, such as metformin and sulfonylureas. Finally, the present study does not provide information on the association between costs and health outcomes, hence higher costs do not necessarily mean better services or outcomes.

The present study, despite some major limitations, confirms the high cost for patients with type 2 diabetes. As the prevalence of diabetes in China continues to increase in the years to come, the potential costs associated with prevention and management of diabetes are expected to be huge. Diabetes patients with poor glycemic control, diabetic complications and comorbidities incurred substantially higher medical costs. Therefore, in order to improve the patients' health and manage growth of medical costs in the long term, the health system has to shift from a disease-centered to a health-centered model, and give priority to prevention of type 2 diabetes and to primary healthcare[16]. As different health policies and regional health inequalities have important effects on direct medical costs, further efforts must be made to optimize resource allocation in health service delivery systems and provide more equitable healthcare. The present reform is seeking to establish a gatekeeper system for care-seeking to optimize resource allocation by adoption of a hierarchical diagnosis and treatment system, and downward allocation of tertiary hospital-based resources toward community-based primary care facilities. With implementation of the healthcare reform, patients with diabetes could be provided with affordable and equitable access to basic healthcare, and the care could also be substantially improved.

DISCLOSURE

The authors declare no conflict of interest.

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APPENDIX 1

The following contributed to the study. Investigators: Qian Ren, Peking University People's Hospital, Beijing (center 1). Yan Zhou, Beijing Hospital, Beijing (center 2). Suhong Wei, Gansu Provincial Hospital, Lanzhou (center 3). Lingfei Zhao, Heilongjiang Provincial Hospital, Harbin (center 4). Yanjun Liu, Wenfang Niu, The 306th Hospital of PLA, Beijing (center 5). Yan Jiang, First Affiliated Hospital of Kumming Medical University, Kunming (center 6). Guoyu Tong, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing (center 7). Xuhong Hou, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai (center 8). Hui Huang, West China Hospital, Sichuan University, Chengdu (center 9). Baocheng Chang, Tianjin Medical University Metabolic Diseases Hospital, Tianjin (center 10). Lan Yi, Tongji Medical College Huzhong University of Science & Technology, The Central Hospital of Wuhan, Wuhan (center 11). Xingjun Liu, The First Affiliated Hospital of Xi'an, Jiao Tong University, Xi'an (center 12). Shan Xiao, First Affiliated Hospital of Xinjiang Medical University, Urumqi (center 13). Chuyuan Wang, The First Affiliated Hospital of China Medical University, Shenyang (center 14). Yang Zhang, The Second Xiangya Hospital of Central South University, Changsha (center 15). Jing Lu, The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou (center 16).