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The Short-Term Health and Economic Burden of Gestational Diabetes Mellitus in China: A Modeling Study

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Abstract

Objectives Gestational Diabetes Mellitus (GDM) is associated with higher risk for adverse health outcomes during pregnancy and delivery for both mother and baby. We aimed to assess the short-term health and economic burden of GDM in China in 2015, estimating the incremental costs and quality of life loss due to GDM in comparison with a pregnancy without GDM from the 28th gestational week until and including childbirth.

Design A decision analytical model was built in Microsoft Excel 2013 and Tree-Age Pro 2015 and populated with probabilities and costs based on literature, clinical guidelines, price lists and expert interviews. Deterministic and probabilistic sensitivity analyses were performed to test the robustness of the results.

Participants Chinese population who gave birth in 2015.

Results A pregnancy with GDM cost on average RMB 6677.37 (in 2015 international \$ 1929.87) more than a pregnancy without GDM (+95%), due to additional expenses during both pregnancy and delivery: RMB 4421.49 (+9179%) for GDM diagnosis and treatment, RMB 1340.94 (+26%) for mother's complications and RMB 914.94 (+52%) for neonatal complications. In China 16.5 million babies were born in 2015. At a prevalence rate of 17.5%,

the number of pregnancies affected by GDM was estimated at 2.90 million. Therefore, the annual societal economic burden of GDM was equal to RMB 19.36 billion (international\$ 5.59 billion). Sensitivity analyses confirmed the robustness of the results. Health losses were estimated at around one million Quality Adjusted Life Years (QALY) for mothers.

Conclusions In China the GDM economic burden is significant even in the short-term perspective and deserves more attention and awareness. Our findings indicate a clear need to implement GDM prevention and treatment strategies at a national level, in order to reduce the economic and health burden for both society and individuals.

Strengths and limitations of this study

- This is the first study to estimate the health and economic burden of GDM in China.
- A conservative approach was adopted, including in the analysis only the most common GDM complications and the costs related to the last trimester of pregnancy.
- We relied on several different sources for probabilities and costs, based on literature and experts' opinion rather than data from real cases.
- In order to extend our results to a national level, we assumed equal medical facility quality in urban and rural areas across China, while in reality healthcare system is not homogeneous.

Introduction

Gestational Diabetes Mellitus (GDM) is a health condition in which women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy.[1] If not adequately managed may lead to serious adverse health outcomes not only during pregnancy and delivery,[2] but even in the long-term: both mothers and newborn babies are more likely to develop type 2 diabetes mellitus and babies to become obese.[3-4] GDM affects 9.8-25.5% of pregnancies all over the world.[5] The International Diabetes Federation (IDF) estimated that 16.8% of pregnant women had some form of hyperglycemia

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4 61 during pregnancy, and the majority (84%) was due to GDM.[6] In China, according to on a
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6 62 nationwide study including 13 hospitals and 17,186 pregnant women[7] and based on the
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8 63 International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria,[5]
9
10 64 the GDM incidence rate in China is about 17.5%. In 2015, China's population was equal to
11
12 65 1.37 billion people and its annual pregnancy rate was 12.08 births per thousand,[8-9] which
13
14 66 means 16.5 million total pregnancies and 2.90 million pregnant women suffering from GDM.
15
16 67 The aim of this study was to assess the short-term health and economic burden of GDM in
17
18 68 China in 2015, estimating the incremental direct medical costs and the health loss due to
19
20 69 GDM in comparison with a pregnancy without GDM from the 28th gestational week, when
21
22 70 GDM can be diagnosed, until and including childbirth. Neither post-partum nor longer-term
23
24 71 consequences (e.g. eventually diabetes type 2) were taken into consideration. These
25
26 72 differences in costs and health loss were then applied to the entire Chinese population to
27
28 73 estimate the national burden of GDM.
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30 74

30 **Methods**

31
32 75 A model was built in Tree-Age Pro software 2015. Three sub-models respectively represented:
33
34 76 1) the GDM diagnosis and treatment (Figure 1); 2) the maternal complications (Figure 2); 3)
35
36 77 the neonatal complications (Figure 3). Maternal and neonatal complications were selected
37
38 78 according to the literature and expert opinions. Probabilities and costs related to each
39
40 79 branch of the model were collected from the literature, clinical recommendation and price
41
42 80 guidelines, and confirmed by a panel of experts (gynecologists, nutritionists, pediatricians
43
44 81 and endocrinologist) who are hospitals practitioners. Costs included expenses for outpatient
45
46 82 physician visits, screening, diet and exercise consulting, drugs, medical tests and supplies,
47
48 83 expenses for hospitalization (e.g. caesarean section and NICU admission) and rehabilitation
49
50 84 center (e.g. brachial plexus training).[10-11] The unit prices of various medical treatments
51
52 85 were obtained from the Chinese Price Bureaus in seven provinces representing seven regions
53
54 86 in China: Northern China (Beijing), Eastern China (Zhejiang); Southern China (Guangdong),
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56 87 Central China (Hunan), Northwestern China (Shanxi), Southwestern China (Chongqing), and
57
58 88 Tibet.[12] The costs taken from the literature were all converted into 2015 prices according
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3 90 to the inflation rates published by China National Bureau of Statistics.[13] No discounting
4
5 91 was applied, as the time horizon was shorter than 1 year. Finally, results were translated into
6
7 92 a national level to have the overall GDM burden and deterministic and probabilistic
8
9 93 sensitivity analyses were run to confirm the robustness of results. Quality of life loss,
10
11 94 expressed in Quality Adjusted Life Years (QALY), was calculated to estimate the health burden
12
13 95 for mothers, for infants it was not possible due to the lack of data. Since no human subjects
14
15 96 were involved, this study was exempt from institutional review board approval.
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18

19 98 **Results**

20 99 *Diagnosis and treatment model*

21
22
23 100 According to the most recent Chinese GDM guideline,[14] all women who have not yet been
24
25 101 diagnosed with diabetes take the 75g Oral Glucose Tolerance Test (OGTT) at the 24-28th
26
27 102 weeks of pregnancy. In our model (Figure 1), for simplicity, we start from the 28th week.
28
29 103 Women with negative OGTT tests entered the Euglycemia branch, and those with positive
30
31 104 OGTT test entered the GDM branch.
32

33
34 106 Women diagnosed with GDM in China firstly received “lifestyle interventions” (including diet,
35
36 107 exercise, and health education), which in the 80% of cases were able to control the blood
37
38 108 glucose levels.[15] Whenever not enough (20% of cases), an additional insulin medication
39
40 109 was prescribed.[14] We considered as suffering from GDM all the women who received this
41
42 110 diagnosis, independently from the way they control it (lifestyle interventions only or
43
44 111 additional insulin).
45

46
47
48 114 All women diagnosed with GDM started one week of lifestyle interventions. The 80% of
49
50 115 women who managed GDM only with lifestyle interventions until the end of their pregnancy
51
52 116 cost, on average, RMB 3118.14; the 20% who relied on insulin to control their glucose level
53
54 117 faced more expenses due to additional medications and exams, equal to RMB 9875.74 per
55
56 118 person (Table 1).
57

58 119 If we sum these costs, weighted for the type of treatment followed (80% lifestyle
59
60

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4 120 interventions only, 20% insulin addition), we estimated for diagnosis and treatment a cost of
5
6 121 RMB 4469.66 per GDM case. Being the Euglycemia diagnosis and treatment cost equal to
7
8 122 RMB 48.17, which includes the OGTT and some other basic visits that all pregnant women
9
10 123 are supposed to do, the extra burden due GDM is equal to RMB 4421.49 per case (+9179%).

11 124 ***Maternal complications model***

12
13 125 Maternal complications included in the model are represented in Figure 2. Costs and
14
15 126 probabilities associated with the adverse health outcomes are listed in Table 1. Due to the
16
17 127 lack of data on how likely are the two type of delivery (vaginal or caesarean section) after the
18
19 128 different complications (e.g. fetal distress in uterus), we assumed all branches as
20
21 129 independent events ending up with the same probabilities of facing either a caesarean
22
23 130 section or a vaginal delivery, differentiating only by GDM status (e.g. caesarean section 38%
24
25 131 in case of GDM, 30.3% in case of Euglycemia).

26
27 132 The probability of having a vaginal delivery was complementary to the one of having a
28
29 133 caesarean section and the cost assigned to it is equal to 3275.39 RMB.[16] Caesarean section
30
31 134 is even a complication per se independently from other events. The probability of not having
32
33 135 any complication was obtained subtracting to one the sum of the other probabilities.
34
35 136 Maternal complications cost on average RMB 5253.57 in Euglycemia cases and RMB 6594.51
36
37 137 in GDM cases, for a cost difference of RMB 1340.94 (+26%).

38 138 ***Neonatal complications model***

39
40 139 Neonatal complications included are represented in Figure 3. They are exclusive: if, for
41
42 140 example, an infant suffers from hypoglycemia, we assumed him/her not having any other
43
44 141 complication. We did not include macrosomia, one of the most common consequences of
45
46 142 GDM, as we cannot address a direct medical cost to it, but only to its consequences (e.g.
47
48 143 brachial plexus injury).

49 144

50 145 Related costs and probabilities to happen of the adverse health outcomes are listed in Table
51
52 146 1. The probability of having a newborn with no complications is complementary to the
53
54 147 others and no cost is assigned to it, on the assumption that this is included in mother's
55
56 148 delivery expenses.

57 149 Neonatal complications cost on average RMB 1755.57 in Euglycemia cases and RMB 2670.51

150 in GDM cases, for a cost difference of RMB 914.94 (+52%).

151

152 **Table 1. Input parameters: probabilities and costs (RMB)**

153 **Diagnosis and Treatment Model [12]**

Resource	Frequency of consumption			Unitary cost	Total costs		
	Euglycemia	Lifestyle intervention	Insulin		Euglycemia (week 28)	Lifestyle interventions (week 28-40)	Insulin (weeks 28-40; insulin costs from week 30)
OGTT	once	once a week	once a week	35.43	35.43	425.16	425.16
Venous blood collection	once	once a week	once a week	2.4	2.4	28.8	28.8
Obstetric and gynecologist outpatient registration fee	once	once a week	once a week	1.91	1.91	22.92	22.92
Examination fee	once	once the first week + 3 times a week	once the first week + 3 times a week	8.43	8.43	286.62	286.62
First consultation fee		once	once	23		23	23
Nutrition outpatient registration fee		twice a week	twice a week	1.91		45.84	45.84
Glucometer and self-testing kit		yes	yes	Monitor=190, strips=5 each		730	730
Laboratory fees (urine, glycosylated albumin)		once a week	once a week	70.79		849.48	849.48
Fetal heart and B ultrasound		once a week	once a week	58.86		706.32	706.32
Routine blood test			once a week	20.75			207.5
Insulin shot			3 times a day	30			6300
Endocrinology outpatient registration fee			once a week	1.91			19.1
Doppler ultrasound			twice	115.5			231
Total					48.17	3118.14	9875.74

154 **Maternal Complications Model - Probabilities and costs**

Complication	GDM (%)	%	Euglycemia (%)	Difference (%)	Complication Cost	Reference
Cesarean section	38.64		30.3	8.61	6174	[17- 22]
Fetal distress in uterus	9.26		6.48	2.78	3994	[18]
Maternal Infection	5.67		2.7	2.97	512.01	[23]
Hypertensive Disorders Of Pregnancy	10.63		7.11	3.52		[17- 22]
Mild PIH		84.2			53	
Preeclampsia		15.7				
Successfully treated		99.9			6762	
Severe preeclampsia		0.1				

6

1						
2						
3	<i>Successfully treated</i>		99.99		8939	
4	<i>Maternal death</i>		0.01		8939	
5	Polyhydramnios	9.83		3.78	6.04	3994 [17-22]
6	Postpartum Hemorrhage	8.32		4.28	4.04	[17-22]
7						
8	<i>Successfully treated</i>		99.75		7610	
9	<i>Surgical treatment</i>		0.24		15939	
10	<i>Maternal death</i>		0.01		8939	
11	Premature birth	6.35		2.47	3.88	2943 [17- 22]
12						
13	Neonatal Complications Model - Probabilities and costs					
14	Neonatal Complication	GDM (%)	%	Euglycemia (%)	Difference (%)	Complication Cost
15						Reference
16	Premature infant (NICU)	6.35		2.47	3.88	2536 [17- 22]
17	Neonatal respiratory distress syndrome (NICU)	5.9		4.03	1.87	32480 [17-22]
18						
19	Macrosomia	8.7		6.31	2.39	3675.56 [18-22]
20	<i>Shoulder Dystocia</i>		14.5			3578
21	<i>Brachial Plexus Injury</i>		18			7316
22						
23	Neonatal asphyxia (NICU)	3.78		1.27	2.52	6652.44 [18]
24	<i>Mild</i>		53			6064
25	<i>Neonatal encephaloathy</i>		47			7316
26						
27	Neonatal hypoglycemia (NICU)	6		0.86	5.14	3578 [24]
28	Neonatal hyperbilirubinemia NICU	1.8		0.9	0.9	3504 [21]
29						

153

154 **Overall costs**

155 Every GDM case cost on average RMB 6677.37 (\$1929.87 in 2015 international dollars at
 156 International\$ 1= RMB 13.46 exchange rate)[25] more (+95%) than a gestation without GDM
 157 due to additional expenses during both pregnancy and delivery.

158 Therefore, given the 2.90 million women affected with GDM in China, the annual economic
 159 burden of GDM in 2015 equaled RMB 19.36 billion (international\$ 5.59 billion).

160 **Sensitivity analyses**

161 In order to quantify the uncertainty existing around the base case estimates, we performed
 162 both a deterministic and a probabilistic sensitivity analysis. In the deterministic sensitivity
 163 analysis (Tornado diagram, Figure 4), we applied a $\pm 20\%$ variation to all costs and major
 164 probabilities of each sub-model to find out which of those mostly affect the outcomes and
 165 could have the greater impact on the overall result when varying. The variables affecting the
 166 final cost the most were insulin in the diagnosis and treatment model, the caesarean section
 167 (CS) in the maternal complication model and the respiratory distress syndrome (RDS), which

168 imply the admission to the intensive care unit, in the neonatal complication model. The
 169 variation of all the other costs had a minor impact on the final outcomes. The results of
 170 Tornado diagrams were shown in the Appendix Figure 1 due to the limited space.

171
 172 In the probabilistic sensitivity analysis (Monte Carlo simulation), we applied a $\pm 20\%$
 173 variations to all costs, modeled using a gamma distribution,[26] of the Maternal and
 174 Neonatal complication models, distinguish between GDM and euglycemia cases. The
 175 possible values outcome of the simulation ranged around the basecase ones. The results
 176 were overall robust. The results of Monte Carlo simulation were shown in the Appendix
 177 Figure 2 due to the limited space.

178

179 Utilities

180 Besides costs, we aimed at calculating the health-related quality of life loss due to GDM
 181 (Table 2).

182

183 **Table 2. GDM-related health loss**

Health outcome	QALY (1 year)	Reference	Health loss (3 months)	Probability (%)	Total health loss (3 months)
Maternal diabetes	0.65	[27]	0.0875	17.5	252656.25
Insulin injection	0.96	[28]	0.01	3.5	577500
Pre-term birth	0.99	[27]	0.0025	0.679	28008.75
Cesarean section	0.99	[29]	0.0025	1.506	62153.4375
Hypertensive disorders	0.9625	[30]	0.0094	0.616	95287.5
					1015605.938

184

185 Given the lack of published studies with neonatal utilities in China, we considered only
 186 mother-related ones. Each adverse health event had a utility value expressed in Quality
 187 Adjusted Life Year (QALY) (e.g. 0.65 in case of maternal diabetes). We calculated the
 188 difference between this value and the full health status (1 QALY) and, since QALY are based
 189 on one year, we divided this figure by four to take into consideration the health loss of 3
 190 months only (0.0875 QALY, following the example on maternal diabetes). To be conservative,
 191 we therefore assumed that the quality of life effect is restricted to the observation period,
 192 meaning that after the delivery all possible negative longer lasting health effects were not
 193 taken into account. Given the 16.5 million births of 2015, we then multiplied the 3 months

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3 194 health loss for the appropriate probability to happen: the number of women with GDM in
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5 195 case of maternal diabetes, the 20% of those in case of insulin injections and, for delivery
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7 196 events (pre-terms, caesarean section and pre-eclampsia), the number of GDM women
8
9 197 weighted by the difference in risks between GDM and euglycemic women, assuming that
10
11 198 some women would have gone through the same adverse outcomes regardless GDM. The
12
13 199 total health loss at population level was equal to 1 million QALYs.
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16

17 **Discussion**

18
19 202 GDM prevalence is increasing worldwide with its serious consequences for mothers and their
20
21 203 babies.[2] The relevance of GDM as a priority for maternal health and its impact on the long
22
23 204 term communicable diseases is nowadays established, however, a real consensus is still
24
25 205 missing on how to prevent, diagnose, and manage GDM to optimize care and outcomes.[31]
26
27 206 For example, even if IADSPG criteria are internationally well accepted and adopted by some
28
29 207 Asian countries, they are not consistently implemented, especially in low-resource
30
31 208 settings,[32] therefore having harmonized data to compare studies from different countries
32
33 209 is still a challenge.

34 **Principal findings**

35
36 211 To our best knowledge, this is the first study to estimate the economic burden of GDM in
37
38 212 China. More at-risk births are expected in the next years due to increasing prevalence of
39
40 213 overweight/obesity and older age at pregnancy of Chinese women.[33] Moreover, since a
41
42 214 previous pregnancy with GDM is a well-established risk factor to experience it again,[6, 34]
43
44 215 as the Chinese law formalized in the early 2016 the end of the one-child policy GDM cases
45
46 216 are likely to increase even due to more high-risk pregnancies for a second birth. Adding an
47
48 217 economic point of view to the GDM burden estimation may help to increase social
49
50 218 awareness and to develop national health policies. The cost analysis here reported showed
51
52 219 that the economic burden of gestational diabetes in pregnancy may be substantial, even
53
54 220 limiting the analysis on short-term effects only. According to our findings, the total burden
55
56 221 due to GDM in 2015 was estimated at RMB 19.36 billion (international\$ 5.59 billion), which is
57
58 222 equal to the 0.5% of the whole public expenditure for medical, healthcare and family
59
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3 223 planning in China in the same year.[35] GDM lifestyle interventions, including diet, exercise,
4
5 224 and health education, were very effective and in 80% of cases could significantly reduce
6
7 225 GDM complications and their final costs: only 20% of GDM women needed additional
8
9 226 medication interventions.[15, 36] However, the costs for these 20% GDM women was more
10
11 227 than three times higher (RMB 3118.14 vs. RMB 9875.74), due to the price of insulin, which,
12
13 228 as confirmed by the sensitivity analysis, had the greatest impact on the final cost of diagnosis
14
15 229 and treatment.
16
17 230 Finally, due to different GDM adverse events during both pregnancy and delivery, around 1
18
19 231 million QALYs were lost over a 3-month period even accounting for maternal consequences
20
21 232 only. To give an idea of size, this health loss is eight times the worldwide untreated travelers
22
23 233 diarrheas (126,800 QALYs)[37] and half of the estimated loss (2.1 million QALYs) due to
24
25 234 injuries, causing pain, suffering and restricted ability to work, of 0-19 years old US children
26
27 235 and teenagers during the year 2000.[38]

28 236 **Comparison with other studies**

29
30 237 Our study is based on Chinese health care system. Studies from Australia,[39] Finland,[40]
31
32 238 and USA[3] reported that the mean difference in healthcare costs between a normal
33
34 239 pregnancy and women diagnosed with GDM was about \$462.02 (AUD 650), \$1438 (EUR
35
36 240 1289) and \$15,593 respectively, but the comparison of these findings from high income
37
38 241 countries' with this study in China may not be straightforward considering different nature of
39
40 242 healthcare systems.

41 243 **Strengths and weaknesses**

42
43 244 Strength of this study was the conservative approach we adopted. For simplicity, we included
44
45 245 costs only from the 28th week of pregnancy, but GDM can be normally diagnosed since the
46
47 246 24th week or even earlier in some cases.[41] moreover, minor GDM complications, such as
48
49 247 neonatal hypoxic-ischemic encephalopathy or hyaline membrane disease, were excluded as
50
51 248 there were no clinical studies about their probabilities and costs in China. Furthermore, we
52
53 249 did not include the price of food substitution in case of a change of diet to control GDM.
54
55 250 Finally, we considered only insulin as a drug cost, disregarding other medications that may be
56
57 251 prescribed.

58 252 The first limitation of this study is that we relied on several different sources for probabilities

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2
3 253 and costs. Some of those, based on local literature, were confirmed from experts' panels,
4
5 254 and experts might rely on personal experiences. Secondly, due to the lack of data, in the
6
7 255 maternal model we assumed the same probabilities of having a caesarean section or a
8
9 256 vaginal delivery after every event, differentiating only by GDM status, while in a real life
10
11 257 setting this could not be the case (e.g. caesarean section may be more likely than vaginal
12
13 258 delivery in case of fetal distress in uterus). Nevertheless, several scenario analysis run with
14
15 259 different probabilities confirm that there was no major impact on the final outcome.
16
17 260 Third, we assumed all women to exactly follow the clinical pathway and be fully complaint,
18
19 261 which may not be always the case. However, it can be assumed that non-compliant behavior
20
21 262 would increase the health and economic burden of GDM as the health consequences of an
22
23 263 uncontrolled GDM are higher. The fourth limitation is due to the non-homogeneity of the
24
25 264 Chinese healthcare system, which makes hard to estimate the overall GDM economic burden
26
27 265 for the whole country: we assumed equal medical facility quality in urban and rural areas.
28
29 266 Finally, we could not estimate which percentage of out of pocket expenses is paid by the
30
31 267 single individuals.

32 **Public health implications**

33
34 269 In China, the maternity insurance, born to cover expenses during pregnancy and delivery, is
35
36 270 not included in the regular health insurance and is used by employed women all over the
37
38 271 country and by unemployed women only in urban areas.[42,43] Unemployed women living
39
40 272 in rural areas are covered by the subsidies of the newly cooperative medicine scheme
41
42 273 (NCMS). The purpose of these subsidies is the same of the maternity insurance: to provide
43
44 274 basic economic and health aids to pregnant women. Both maternity insurance and subsidies
45
46 275 reimburse a lump sum amount per pregnancy and delivery (vaginal delivery or C-section).
47
48 276 Unfortunately, there is a huge variations between the two type of coverage and more in
49
50 277 general for the specific amounts received within the country: the maternity insurance
51
52 278 normally pays about RMB 3000, while subsidies from NCMS in the rural areas are about RMB
53
54 279 500-1,000.[42,43] In both cases, however, the actual pregnancy and delivery expenses are
55
56 280 much more than the amount covered by maternity insurances or subsidies and GDM does
57
58 281 not represent a separate voice of reimbursement, which means that a huge part on the GDM
59
60 282 burden falls on women and their families. According to You et al (2016),[44] 60% of cost of

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2
3 283 delivery in China are paid out of pocket, a share that was not significantly changed after the
4
5 284 introduction of the insurance system. This is even worse for the low-income group where,
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7 285 given an average income equal to RMB 4747,[45] paying RMB 10965 for GDM antenatal and
8
9 286 delivery cost is not sustainable and it means to enter the area of the catastrophic health care
10
11 287 expenditure.[46]

12 288 **Unanswered questions and future research**

13
14 289 In China, the increase of GDM incidence led to significant economic burden and deserves
15
16 290 more attention and awareness. Our study showed the magnitude of the problem, but
17
18 291 cost-effective GDM preventions treatments are needed to reduce the GDM morbidities and
19
20 292 complications and the consequent the economic burden which affects society, households
21
22 293 and individuals in China.

23
24 294

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27
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29
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31
32 299 co-authors. TX and HF were involved in the design and were responsible of the data
33
34 300 collection. TX and LD completed the analyses presented here. LM provided independent
35
36 301 clinical advice. TX and HF wrote the first draft of the paper with further iterations involving
37
38 302 LD. KY contributed to the interpretation of the data and the critical revision of the
39
40 303 manuscript. All authors contributed, reviewed and approved the final submitted version.

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43 306 **Data sharing statement** No additional data are available.

44 307 **Declaration of interests** We declare no competing interests.

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Figure 1: GDM diagnosis and treatment model

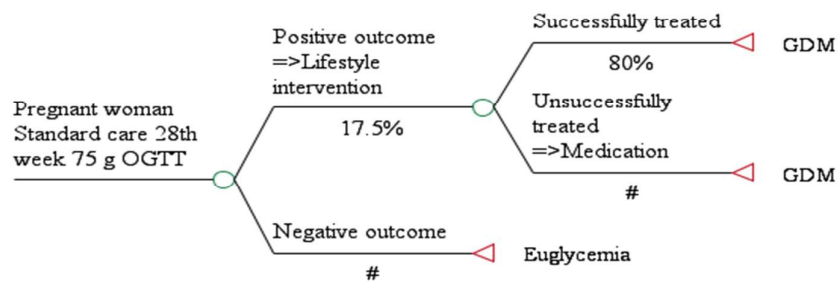


Figure 1 shows the generic framework of GDM screening path as recommended by Chinese guideline. Circles represent chance events, while triangles represent terminal nodes. The symbol # indicates that the probabilities of that branch are complementary with that of the other one.

Figure 2. Maternal complications model

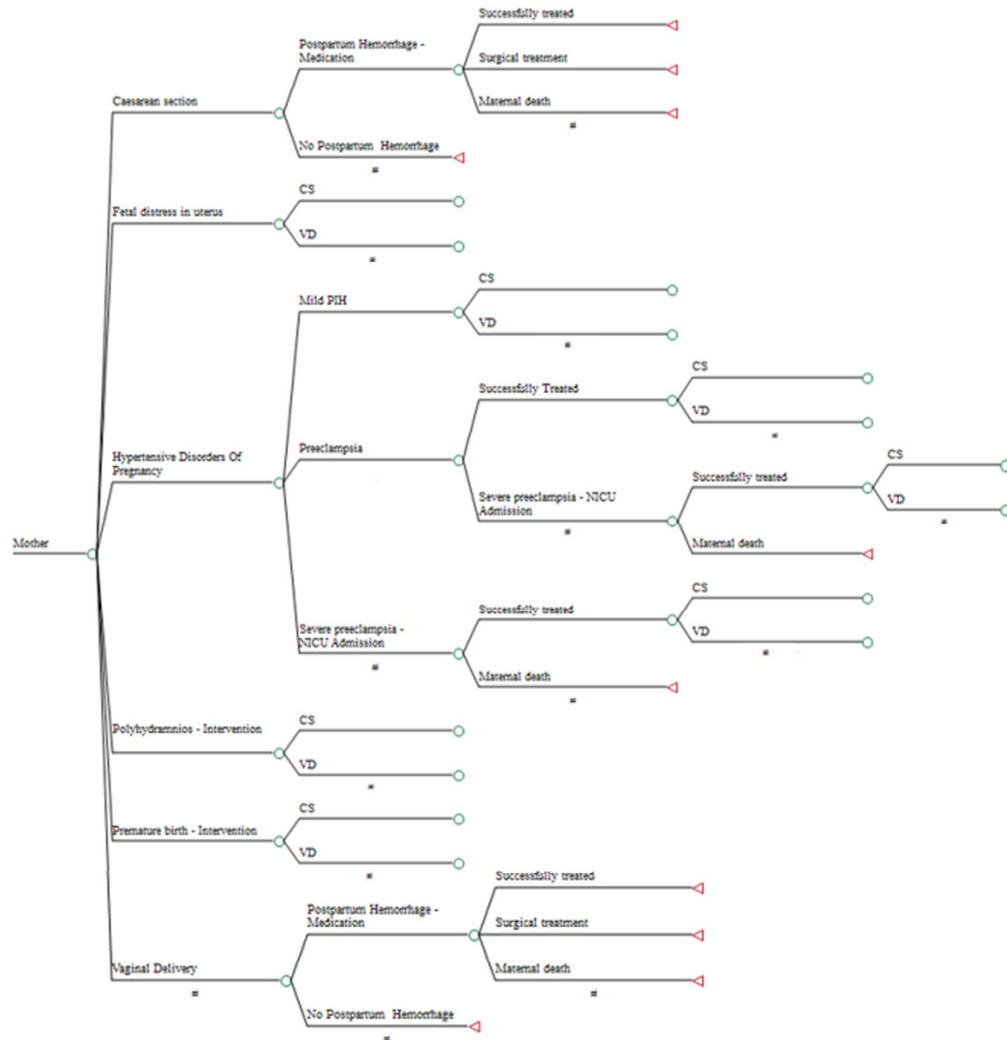


Figure 2 shows the mother complications model, which has the same structure for both GDM and Euglycemia branches. The symbol # indicates that the probabilities of that branch are complementary with that of the other one. Circles represent chance events, while triangles represent terminal nodes. Lines that do not terminate in a triangle are collapsed to facilitate display and are analogous to branches that are open.

Figure 3. Neonatal complications model

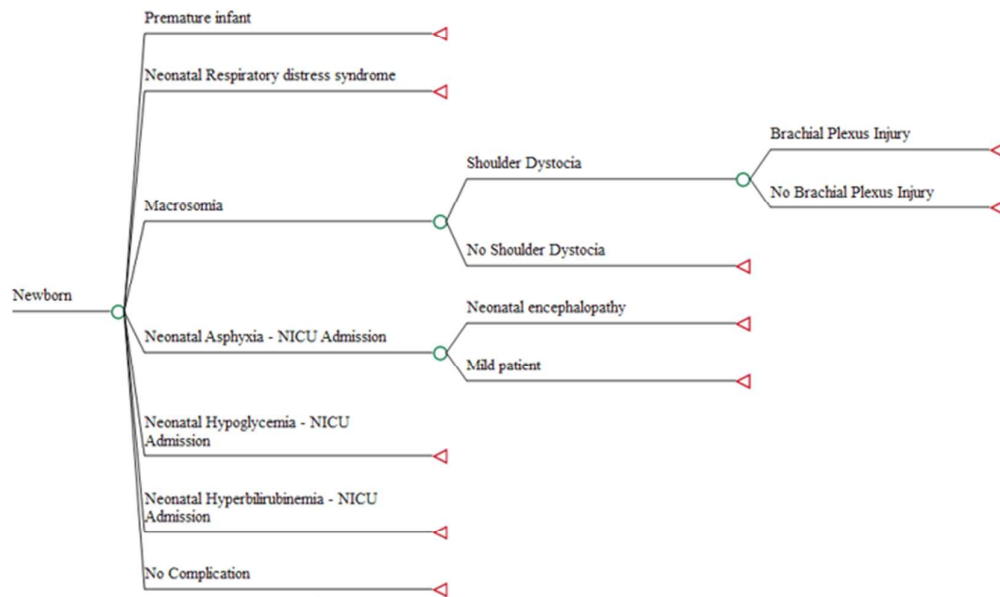
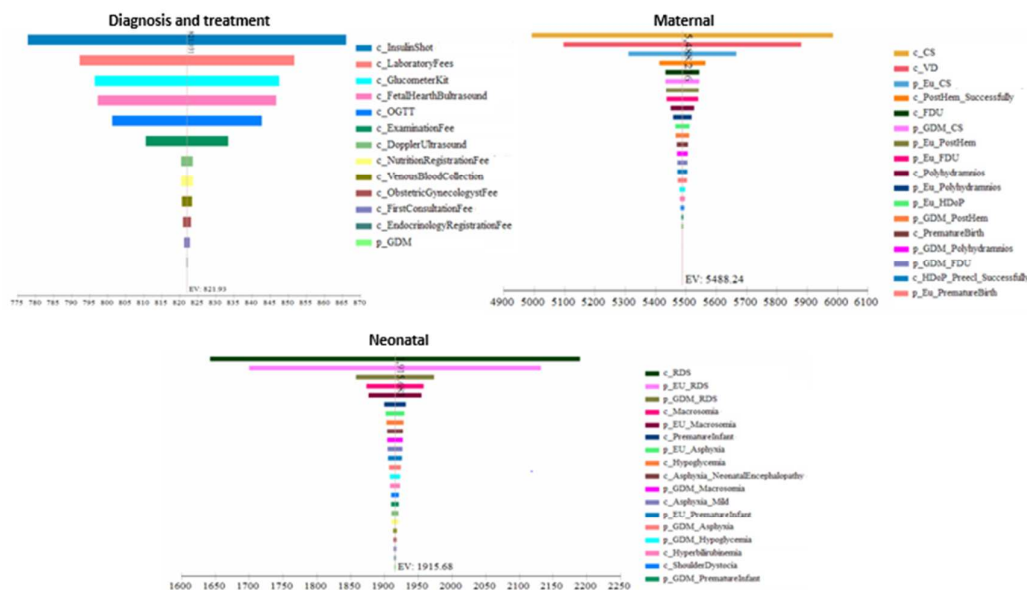


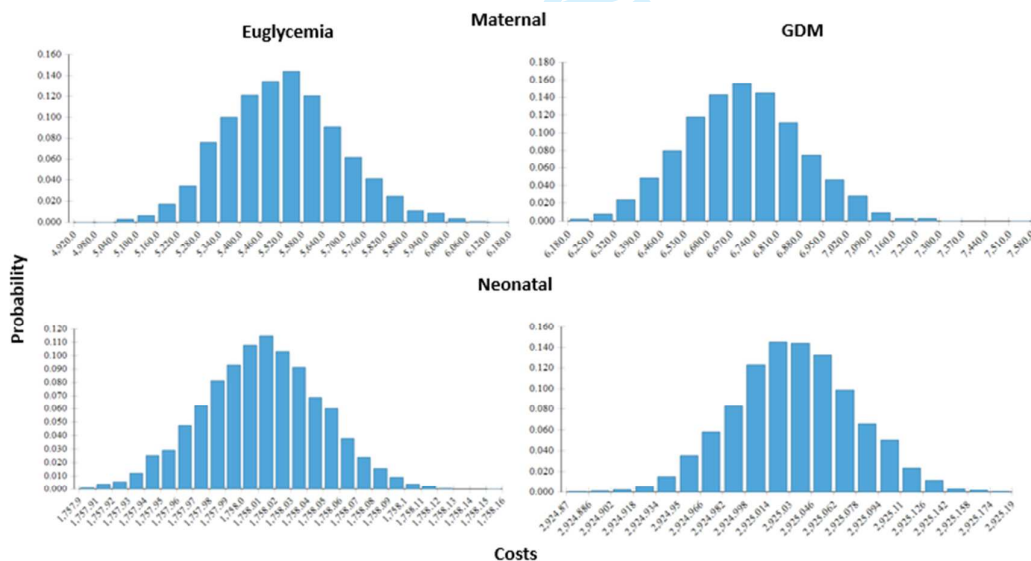
Figure 3 shows the neonatal complications model, which has the same structure for both GDM and Euglycemia branches. Circles represent chance events, while triangles represent terminal nodes.

Appendix Figure 1. Tornado diagrams.



The bars represent the relative importance of the variables on the expected value: the larger the bar, the higher the impact of that cost voice. CS, VD, PostHem, FDU and HDoP stand respectively for caesarean section, vaginal delivery, fetal distress in uterus, post partum hemorrhage and Hypertensive Disorders Of Pregnancy (Maternal complication model); RDS for Respiratory Distress Syndrom (Neonatal complication model).

Appendix Figure 2. Montecarlo simulations



Monte Carlo probability distribution (1000 iterations) of the Maternal (left) and Neonatal (right) complications models per case in both euglycemia (above) and GDM (below). The highest the bar in the histogram, the most likely the correspondent cost value.

EVEREST Statement: Checklist for health economics paper

	Study section (page)	Additional remarks
Study design		
(1) The research question is stated	Introduction (3)	
(2) The economic importance of the research question is stated	Introduction (2-3)	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Methods (3)	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	N/A	
(5) The alternatives being compared are clearly described	N/A	
(6) The form of economic evaluation used is stated	Introduction (3); Methods (3-4); Results (4-7)	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Introduction (3); Method (3-4)	
Data collection		
(8) The source(s) of effectiveness estimates used are stated	Methods (3-4,); Discussion (13)	
(9) Details of the design and results of effectiveness study are given (if based on single study)	Method (3-4); Results (4-7) Discussion (12-14)	
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	Methods (3-4); Discussion (12-13)	
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Results (4-11)	
(12) Methods to value health states and other benefits are stated	Results (4-7); table 1 (probabilities and costs) (8-9); table 2(health loss) (11)	
(13) Details of the subjects from whom valuations were obtained are given	N/A	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Method (3-4) Results (8-9)	
(17) Methods for the estimation of quantities and unit costs are described	Method (3-4)	Costs were not synthesised from individual units. Nominal

		cost were derived from published literature and official sources (e.g. the Chinese Price Bureaus and China National Bureau of Statistics)
(18) Currency and price data are recorded	Results (8-9); table 1(8-9)	
(19) Details of currency of price adjustments for inflation or currency conversion are given	Methods (3-4) Table1(8-9)	
(20) Details of any model used are given	Methods (3-4) Results (4-7)	A model was built in Tree-Age Pro software 2015. Three sub-models respectively represented: 1) the GDM diagnosis and treatment (Figure 1); 2) the maternal complications (Figure 2); 3) the neonatal complications (Figure 3). Maternal and neonatal complications were selected according to the literature and expert opinions.
(21) The choice of model used and the key parameters on which it is based are justified	Methods (3-7); Results (8-9); table 1 (8-9); table 2 (11)	
Analysis and interpretation of results		
(22) Time horizon of costs and benefits is stated	Introduction (3) Methods (3-4)	
(23) The discount rate(s) is stated	Methods (4)	No discounting was applied

(24) The choice of rate(s) is justified	Methods (4)	Justified with appropriate literature
(25) An explanation is given if costs or benefits are not discounted	Methods (4)	No discounting was applied, as the time horizon was shorter than 1 year
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods (4); Results (9-11); Figure 4; Figure 5;	
(28) The choice of variables for sensitivity analysis is justified	Results (9-11)	
(29) The ranges over which the variables are varied are stated	Results (9-10)	
(30) Relevant alternatives are compared	N/A	
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	table 1 (probabilities and costs) (8-9); table 2(health loss) (11)	
(33) The answer to the study question is given	Results (4-9); Discussion (12-13)	
(34) Conclusions follow from the data reported	Discussion (12-13);	
(35) Conclusions are accompanied by the appropriate caveats	Discussion (13-15);	

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The Short-Term Health and Economic Burden of Gestational Diabetes Mellitus in China: A Modeling Study

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Abstract

Objectives Gestational Diabetes Mellitus (GDM) is associated with a higher risk for adverse health outcomes during pregnancy and delivery for both mothers and babies. This study aims to assess the short-term health and economic burden of GDM in China in 2015

Design Using TreeAge Pro, an analytical decision model was built to estimate the incremental costs and quality of life loss due to GDM, in comparison with pregnancy without GDM from the 28th gestational week until and including childbirth. The model was populated with probabilities and costs based on current literature, clinical guidelines, price lists and expert interviews. Deterministic and probabilistic sensitivity analyses were performed to test the robustness of the results.

Participants Chinese population who gave birth in 2015.

Results On average, the cost of a pregnancy with GDM was RMB 6677.37 (in 2015 international\$ 1929.87) more (+95%) than a pregnancy without GDM, due to additional expenses during both the pregnancy and delivery: RMB 4421.49 for GDM diagnosis and treatment, RMB 1340.94 (+26%) for the mother's complications, and RMB 914.94 (+52%) for neonatal complications. In China, 16.5 million babies were born in 2015. Given a GDM

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3 32 prevalence of 17.5%, the number of pregnancies affected by GDM was estimated at 2.90
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5 33 million in 2015. Therefore, the annual societal economic burden of GDM was estimated to be
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7 34 RMB 19.36 billion (5.59 billion international\$). Sensitivity analyses were used to confirm the
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9 35 robustness of the results. Incremental health losses were estimated to be approximately
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11 36 260,000 Quality Adjusted Life Years (QALY).

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13 37 **Conclusion** In China, the GDM economic burden is significant, even in the short-term
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15 38 perspective and deserves more attention and awareness. Our findings indicate a clear need
16
17 39 to implement GDM prevention and treatment strategies at a national level in order to reduce
18
19 40 the economic and health burden at both the population and individual levels.

20 21 22 42 **Strengths and limitations of this study**

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24 43 • This is the first study to estimate the health and economic burden of GDM in China.
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26 44 • A conservative approach was adopted by including in the analyses only the most
27
28 45 common GDM complications and the costs related to the last trimester of
29
30 46 pregnancy.
31
32 47 • We relied on different sources for probabilities and costs based on the literature and
33
34 48 expert opinion rather than data from real cases.
35
36 49 • We assumed that all pregnant women received standard medical treatments
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38 50 recommended in the Chinese GDM guidelines.
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40 51 • In order to extend our results to a national level, the costs of medical treatments
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42 52 obtained from the literature and the Chinese Price Bureaus were adjusted by
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44 53 calculating average unit prices taking into consideration the different expenses for
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46 54 different levels of healthcare institutions.

47 48 49 56 **Introduction**

50
51 57 Gestational Diabetes Mellitus (GDM) is a health condition in which women without
52
53 58 previously diagnosed diabetes exhibit high blood glucose levels during pregnancy.[1] If not
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55 59 adequately managed, GDM may lead to serious adverse health outcomes not only during
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57 60 pregnancy and delivery,[2] but in the long-term as both mothers and newborn babies are

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4 61 more likely to develop type 2 diabetes mellitus and babies are more likely to become obese
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6 62 later on in life.[3-4]
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8 63 GDM affects 9.8-25.5% of pregnancies throughout the world.[5] The International Diabetes
9
10 64 Federation (IDF) estimates that 16.8% of pregnant women have some form of hyperglycemia
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12 65 during pregnancy, with the majority (84%) due to GDM.[6] According to a recent nationwide
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14 66 study in China that included 13 hospitals and 17,186 pregnant women,[7] the GDM incidence
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16 67 rate was approximately 17.5%, based on the International Association of the Diabetes and
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18 68 Pregnancy Study Groups (IADPSG) criteria.[5] In 2015, China's population was approximately
19
20 69 1.37 billion people and the annual pregnancy rate was 12.08 births per thousand
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22 70 individuals.[8-9] Therefore, China had a total of 16.5 million pregnancies and 2.90 million
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24 71 pregnant women suffered from GDM.
25
26 72 The aim of this study was to assess the short-term health and economic burden of GDM in
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28 73 China in 2015. Almost all of GDM cases were diagnosed by the 28th gestational week,
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30 74 therefore, we estimated the incremental direct medical costs and the health loss due to
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32 75 GDM in comparison with a pregnancy without GDM from the 28th gestational week until
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34 76 childbirth. These differences in costs and health loss were then applied to the entire Chinese
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36 77 population to estimate the national burden of GDM. Neither post-partum nor longer-term
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38 78 consequences (e.g. eventual development of type 2 diabetes) were taken into consideration,
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40 79 as data was not available from the literature.
41

42 **Methods**

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44 82 A model was built in Tree-Age Pro 2015. Three sub-models represented the cost of: 1) the
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46 83 GDM diagnosis and treatment (Figure 1); 2) the maternal complications (Figure 2); 3) the
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48 84 neonatal complications (Figure 3). Maternal and neonatal complications were selected
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50 85 according to published literature and expert opinions. Probabilities and costs related to each
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52 86 branch of the model were collected from the literature, clinical recommendations and price
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54 87 guidelines, and confirmed by a panel of hospital practitioners (gynecologists, nutritionists,
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56 88 pediatricians and endocrinologist). Costs included expenses for outpatient physician visits,
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58 89 GDM screening, diet and exercise consulting, drugs, medical tests and supplies, expenses for
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4 90 hospitalization (e.g. caesarean section and NICU admission) and rehabilitation center (e.g.
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6 91 brachial plexus training).[10-11] The unit prices of the GDM diagnosis and various medical
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8 92 treatments were obtained from the Chinese Price Bureaus in seven provinces representing
9
10 93 seven regions of China: Northern China (Beijing), Eastern China (Zhejiang); Southern China
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12 94 (Guangdong), Central China (Hunan), Northwestern China (Shanxi), Southwestern China
13
14 95 (Chongqing), and Tibet. An average unit price was calculated considering different expenses
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16 96 for the different levels of medical institutions (e.g. township/second-class/third-class
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18 97 hospital).[12] All the costs obtained from the literature were converted into 2015 prices
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20 98 according to inflation rates published by the China National Bureau of Statistics.[13] Costs
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22 99 were not discounted, as the time horizon was shorter than one year. Finally, the results were
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24 100 applied at the national level to estimate the overall GDM burden. Deterministic and
25
26 101 probabilistic sensitivity analyses were conducted to confirm the robustness of results.
27
28 102 Quality of life losses, expressed in Quality Adjusted Life Years (QALY), were calculated to
29
30 103 estimate the health burden caused by GDM for mothers; a QALY estimate was not possible
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32 104 for infants due to a lack of data. Given that human subjects were not directly involved, this
33
34 105 study did not require approval by an institutional review board .
35

36 107 **Results**

37 108 *Diagnosis and treatment model*

38
39 109 According to the most recent Chinese GDM guidelines,[14] all women who have not been
40
41 110 diagnosed with diabetes should take the 75g Oral Glucose Tolerance Test (OGTT) between
42
43 111 the 24-28th week of pregnancy. In our model (Figure 1), for simplicity, we started from the
44
45 112 28th week. Women with negative OGTT tests entered the Euglycemia branch, and those with
46
47 113 positive OGTT test entered the GDM branch.

48
49 114 Women diagnosed with GDM in China first receive one week of lifestyle interventions
50
51 115 (including diet, exercise and health education) and in 80% of cases the interventions
52
53 116 successfully controlled blood glucose levels.[15] When this was not enough (20% of cases), an
54
55 117 additional insulin medication was prescribed.[14] All of the pregnant women with a GDM
56
57 118 diagnosis entered the GDM branch, independently from the way they controlled the disease
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4 119 (lifestyle interventions only or additional insulin).
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6 120 The 80% of women who managed GDM with only lifestyle interventions until the end of their
7
8 121 pregnancy spent on average RMB 3118.14 per person; the 20% who relied on insulin to
9
10 122 control their glucose level needed additional medications and examinations, for a total
11
12 123 expense equal to RMB 9875.74 per person (Table 1).
13
14 124 Summing these costs, weighted for the types of treatments provided (80% lifestyle
15
16 125 interventions only, 20% additional insulin), the costs of diagnosis and treatment was equal to
17
18 126 RMB 4469.66 per GDM case. The costs of diagnosis and treatment for Euglycemia, which
19
20 127 included the OGTT and other recommended visits regardless of GDM status, was equal to
21
22 128 RMB 48.17. Therefore the extra burden due to GDM for diagnosis and treatment was equal
23
24 129 to the difference between GDM and Euglycemia women (RMB 4421.49 per case).

24 130 ***Maternal complications model***

25
26 131 Maternal complications included in the model are represented in Figure 2. The costs and
27
28 132 probabilities associated with the adverse health outcomes are listed in Table 1. Due to the
29
30 133 lack of data on probabilities of the two types of delivery (vaginal or caesarean section) after
31
32 134 different complications (e.g. fetal distress in uterus), we assumed all branches as
33
34 135 independent events ending up with the same probabilities of facing either a caesarean
35
36 136 section or a vaginal delivery. The difference was only by GDM status (e.g. caesarean section
37
38 137 38% in case of GDM, 30.3% in case of Euglycemia).

39
40 138 The cost assigned to vaginal delivery was equal to 3275.39 RMB.[16] All births following the
41
42 139 possible complications were classified as vaginal or caesarean section; however, a caesarean
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44 140 section was considered an additional complication independent of complications prior to
45
46 141 birth. The probability of not having any complication was obtained by subtracting the sum of
47
48 142 the other probabilities from one. The costs of maternal complications were on average RMB
49
50 143 5253.57 in Euglycemia cases and RMB 6594.51 in GDM cases, with a cost difference of RMB
51
52 144 1340.94 (+26%).

52 145 ***Neonatal complications model***

53
54 146 Neonatal complications are represented in Figure 3. A few rare neonatal complications (i.e.
55
56 147 abnormal fetus,) were excluded, as cost data was not available from the literature. We did
57
58 148 not include macrosomia, one of the most common consequences of GDM, because we could

149 not determine a direct medical cost for it, but only for its consequences (e.g. brachial plexus
150 injury).

151 Related costs and probabilities of the adverse health outcomes are listed in Table 1. The
152 probabilities of having a newborn with and without complications summed to 100%. Costs
153 were not assigned to newborns without complications, on the assumption that this should
154 be included in the mother's normal delivery expenses.

155 The costs of neonatal complications were on average RMB 1755.57 in Euglycemia cases and
156 RMB 2670.51 in GDM cases, resulting in a cost difference of RMB 914.94 (+52%).

157

158 **Table 1. Input parameters: probabilities and costs (RMB)**

159

Diagnosis and Treatment Model [12]

Resource	Frequency of consumption			Unitary cost	Total costs		
	Euglycemia	Lifestyle intervention	Insulin		Euglycemia (week 28)	Lifestyle interventions (week 28-40)	Insulin (weeks 28-40; insulin costs from week 30)
OGTT	once	once a week	once a week	35.43	35.43	425.16	425.16
Venous blood collection	once	once a week	once a week	2.4	2.4	28.8	28.8
Obstetric and gynecologist outpatient registration fee	once	once a week	once a week	1.91	1.91	22.92	22.92
Examination fee	once	once the first week + 3 times a week	once the first week + 3 times a week	8.43	8.43	286.62	286.62
First consultation fee		once	once	23		23	23
Nutrition outpatient registration fee		twice a week	twice a week	1.91		45.84	45.84
Glucometer and self-testing kit		yes	yes	Monitor=190, strips=5 each		730	730
Laboratory fees (urine, glycosylated albumin)		once a week	once a week	70.79		849.48	849.48
Fetal heart and B ultrasound		once a week	once a week	58.86		706.32	706.32
Routine blood test			once a week	20.75			207.5
Insulin shot			3 times a day	30			6300
Endocrinology outpatient registration fee			once a week	1.91			19.1
Doppler ultrasound			twice	115.5			231

Total		48.17	3118.14	9875.74		
Maternal Complications Model - Probabilities and costs						
Complication	GDM (%)	%	Euglycemia (%)	Difference (%)	Complication Cost	Reference
Cesarean section	38.64		30.3	8.34	6174	[17- 22]
Fetal distress in uterus	9.26		6.48	2.78	3994	[18]
Maternal Infection	5.67		2.7	2.97	512.01	[23]
Hypertensive Disorders Of Pregnancy	10.63		7.11	3.52		[17- 22]
<i>Mild PIH</i>		84.2			53	
<i>Preeclampsia</i>		15.7				
<i>Successfully treated</i>		99.9			6762	
<i>Severe preeclampsia</i>		0.1				
<i>Successfully treated</i>		99.99			8939	
<i>Maternal death</i>		0.01			8939	
Polyhydramnios	9.83		3.78	6.04	3994	[17-22]
Postpartum Hemorrhage	8.32		4.28	4.04		[17-22]
<i>Successfully treated</i>		99.75			7610	
<i>Surgical treatment</i>		0.24			15939	
<i>Maternal death</i>		0.01			8939	
Premature birth	6.35		2.47	3.88	2943	[17- 22]
Neonatal Complications Model - Probabilities and costs						
Neonatal Complication	GDM (%)	%	Euglycemia (%)	Difference (%)	Complication Cost	Reference
Premature infant (NICU)	6.35		2.47	3.88	2536	[17- 22]
Neonatal respiratory distress syndrome (NICU)	5.9		4.03	1.87	32480	[17-22]
Macrosomia	8.7		6.31	2.39	3675.56	[18-22]
<i>Shoulder Dystocia</i>		14.5			3578	
<i>Brachial Plexus Injury</i>		18			7316	
Neonatal asphyxia (NICU)	3.78		1.27	2.52	6652.44	[18]
<i>Mild</i>		53			6064	
<i>Neonatal encephalopathy</i>		47			7316	
Neonatal hypoglycemia (NICU)	6		0.86	5.14	3578	[24]
Neonatal hyperbilirubinemia NICU	1.8		0.9	0.9	3504	[21]

160

161 **Overall costs**

162 On average, women with GDM spent RMB 6677.37(equal to 2015 international\$ 1929.87
 163 (one international dollar=RMB 3.46)([25] more (+95%) than women without GDM, due to
 164 additional expenses during both pregnancy and delivery.

165 Therefore, given the 2.90 million women affected by GDM in China, the annual economic
 166 burden of GDM in 2015 equaled RMB 19.36 billion (international\$ 5.59 billion).

167 **Sensitivity analyses**

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168 In order to quantify the uncertainty, we performed both a deterministic and a probabilistic
169 sensitivity analyses. In the deterministic sensitivity analysis (Tornado diagrams, Appendix
170 Figure 1), we applied a $\pm 20\%$ variation to all costs and major probabilities of each sub-model
171 to determine which input variables had the largest impact on the outcomes and thereby had
172 a large impact on the overall results. The variables with the largest impact on the final costs
173 were insulin in the diagnosis and treatment model, caesarean section in the maternal
174 complication model, and respiratory distress syndrome, which included admission to the
175 intensive care unit, in the neonatal complication model. The variation of all the other costs
176 had a minor impact on the final outcomes.

177 In the probabilistic sensitivity analysis (Monte Carlo simulation, Appendix Figure 2) for the
178 Maternal and Neonatal complication models, we applied a $\pm 20\%$ variation to all costs,
179 modeled using a gamma distribution[26]. The possible outcomes of the simulation ranged
180 around the results from the basecase; the overall results were shown to be robust.

181

182 Utilities

183 In addition to the costs, we also calculated the health-related quality of life loss due to GDM
184 (Table 2).

185

186 **Table 2. GDM-related health loss**

187

Health outcome	QALY (1 year)	Reference	Health loss (3 months)	Probability (%)	N of women	Total health loss (3 months)
Maternal diabetes	0.65	[27]	0.0875	17.5	2887500	252656
Insulin injection	0.96	[28]	0.01	0.2*17.5	577500	5775
Pre-term birth	0.99	[27]	0.0025	0.0388 * 17.5	112035	280
Cesarean section	0.99	[29]	0.0025	0.0861* 17.5	248613.75	621
Hypertensive disorders	0.9625	[30]	0.0094	0.0352* 17.5	101640	953
Total						260285

188

189 Given the lack of published studies with neonatal utilities in China, we considered only
190 mother-related events. Each adverse health event had a utility value expressed in Quality
191 Adjusted Life Year (QALY) (e.g. 0.65 QALY in case of maternal diabetes). We calculated the

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4 192 difference between this value and 1 QALY, which corresponds to the full health status
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6 193 (following the example of maternal diabetes, $1-0.65=0.35$ QALY). Since QALYs were based on
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8 194 one year, we divided this amount by four to take into consideration the health loss of only 3
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10 195 months. This was the time horizon in the present study ($0.35/4=0.0875$ QALY). We then
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12 196 multiplied the 3 month health loss with the appropriate probabilities of occurrence
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14 197 corresponding to the entire population suffering from GDM (2.9 million women) in the case
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16 198 of “Maternal diabetes”, the 20% of those (577,000 women) in the case of “Insulin injection”,
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18 199 and the number of women with GDM weighted by the difference in probability between
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20 200 GDM and non GDM for “Pre-term birth”, “Caesarean section” and “Hypertensive disorders,”
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22 201 on the assumption that these adverse health events may occur even in non-GDM
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24 202 pregnancies. For example, the probability of having a pre-term birth was 6.35% for GDM
25
26 203 women and 3.47% for non GDM women (3.88% difference). Therefore, the pre-term birth
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28 204 health loss due to GDM was calculated as 0.0025 QALY (3 month health loss) multiplied by
29
30 205 112,000 women (2.9 million*3.88%). The total incremental health loss due to GDM in China
31
32 206 was equal to 260,000 QALYs.
33

34 208 **Discussion**

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36 209 GDM prevalence is increasing worldwide with serious consequences for mothers and their
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38 210 babies.[2] The importance of GDM as a priority for maternal health and its impact in the long
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40 211 term for communicable diseases has been established; however, a consensus on how to
41
42 212 prevent, diagnose, and manage GDM in order to optimize healthcare and minimize adverse
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44 213 outcomes has not been reached.[31] For example, although IADSPG criteria are
45
46 214 internationally well accepted and adopted by some Asian countries, criteria are not
47
48 215 consistently implemented, especially in low-resource settings,[32] therefore having
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50 216 harmonized data to compare studies from different countries remains a challenge.

51 217 **Principal findings**

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53 218 To our best knowledge, this is the first study to estimate the economic burden of GDM in
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55 219 China. More at-risk births are expected in the near future due to the increasing prevalence of
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57 220 overweight/obesity women and older age at pregnancy in China.[33] Moreover, in early 2016,

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3 221 the Chinese government officialized the end of the one-child policy, therefore, prevalence of
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5 222 GDM cases are likely to increase given that a previous pregnancy with GDM is a
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7 223 well-established risk factor for GDM in subsequent pregnancies.[6, 34] Adding an economic
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9 224 point of view to the GDM burden estimation may help to increase social awareness and to
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11 225 develop national health policies. The cost analysis showed that the economic burden of
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13 226 gestational diabetes in pregnancy may be substantial, even when limiting the analysis to only
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15 227 short-term effects. According to our findings, the total burden due to GDM in 2015 was
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17 228 estimated at RMB 19.36 billion (international\$ 5.59 billion), which is equal to 0.5% of the
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19 229 entire public expenditure for medical, healthcare and family planning in China in 2015.[35]
20
21 230 GDM lifestyle interventions, including diet, exercise, and health education, were very
22
23 231 effective. In 80% of cases, interventions were shown to significantly reduce GDM
24
25 232 complications and their final costs, and only 20% of women with GDM needed additional
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27 233 medications.[15, 36] However, the costs among the 20% of women with GDM requiring
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29 234 additional medications was more than three times higher (RMB 3118.14 vs. RMB 9875.74),
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31 235 due to the price of insulin, which had the greatest impact on the final cost of diagnosis and
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33 236 treatment.
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35 237 Finally, due to different GDM associated adverse events during both pregnancy and delivery,
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37 238 when only accounting for maternal consequences, around 260,000 QALYs were lost over a
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39 239 3-month period. To quantify the magnitude of this loss, the health loss due to GDM was
40
41 240 about 1/4 of 1,180,260 QALYs loss caused by squamous cell carcinoma (one lung cancer type),
42
43 241 or 1/18 of QALYs loss caused by all types of lung cancers in China.[37,38]

242 **Comparison with other studies**

243 Our study was based on the Chinese health care system. Studies from Australia,[39]
244 Finland,[40] and the USA[3] reported that the mean difference in healthcare costs between a
245 normal pregnancy and women diagnosed with GDM is about \$462.02 (AUD 650), \$1438
246 (EUR 1289) and \$15,593 respectively, however, comparing these findings from high income
247 countries with this study in China might not be straightforward considering the different
248 nature of healthcare systems between countries.

249 **Strengths and weaknesses**

250 A strength of this study was the conservative approach we adopted. For simplicity, we only

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4 251 included costs from after the 28th week of pregnancy, but GDM could be diagnosed at the
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6 252 24th week or even earlier in severe cases.[41] Moreover, minor GDM complications, such as
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8 253 abnormal fetus or hyaline membrane disease, were excluded as there were no clinical
9
10 254 studies to provide probabilities and costs in China. Furthermore, we did not include the price
11
12 255 of food substitutions in case of a change in diet to control GDM. Finally, we considered only
13
14 256 insulin as a drug cost, disregarding other medications that might be prescribed.

15
16 257 The first limitation of this study was that we relied on several different sources for
17
18 258 probabilities and costs. Some of those were based on local literature and confirmed by
19
20 259 expert panels, however, experts might rely on personal experiences. Secondly, due to the
21
22 260 lack of data in the maternal model we assumed the same probabilities of having a caesarean
23
24 261 section or a vaginal delivery after every event, differentiating only by GDM status, while in a
25
26 262 real life setting this would not be the case (e.g. caesarean section might be more likely than
27
28 263 vaginal delivery in case of fetal distress in uterus). Nevertheless, several scenario analyses
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30 264 with different probabilities confirmed that there was not a major impact on the final
31
32 265 outcome.

33
34 266 Thirdly, we assumed that all women followed exactly the clinical pathways and were fully
35
36 267 compliant, which might not always be the case. However, it could be assumed that
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38 268 non-compliant behavior would increase the health and economic burden of GDM as the
39
40 269 health consequences of uncontrolled GDM were higher. Finally, we could not estimate the
41
42 270 percentage of out of pocket expenses that were paid by each individual motherbirth.

43 271 **Public health implications**

44
45 272 In China, maternity insurance to cover expenses during pregnancy and delivery is not
46
47 273 included in regular health insurance and is only used by employed women.[42,43]
48
49 274 Unemployed women living in rural areas are covered by the subsidies of the newly
50
51 275 cooperative medicine scheme (NCMS). The purpose of these subsidies is the same as the
52
53 276 maternity insurance: to provide basic economic and health aids to pregnant women. Both
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55 277 maternity insurance and subsidies reimburse a lump sum amount per pregnancy and
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57 278 delivery (vaginal delivery or caesarean section). Unfortunately, there are huge variations
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59 279 between the two types of coverage and, in general, for the specific amounts received within
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280 the country, the maternity insurance normally pays approximately RMB 3000, while subsidies

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3 281 from NCMS in the rural areas are approximately RMB 500-1,000.[42,43] However, in both
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5 282 cases, the actual pregnancy and delivery expenses are much more than the amount covered
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7 283 by maternity insurances or subsidies. GDM is not reimbursed separately by any insurance or
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9 284 subsidies, so a large portion of the GDM burden falls on women and their families. According
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11 285 to You et al (2016),[44] 60% of the cost of deliveries in China were paid out of pocket, a share
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13 286 that did not significantly change after the introduction of the insurance system. This is even
14
15 287 worse for the low-income group where, given an average income equal to RMB 4747,[45]
16
17 288 paying RMB 10965 for GDM antenatal and delivery cost is not sustainable and could enter
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19 289 the area of the catastrophic health care expenditure.[46]

20 290 **Unanswered questions and future research**

21
22 291 In China, the increase of GDM incidence has led to significant economic burden and deserves
23
24 292 more attention and awareness. Our study showed the magnitude of the problem, and
25
26 293 cost-effective GDM preventions treatments are needed to reduce GDM morbidities,
27
28 294 complications from GDM, and the consequent economic burden which affects society,
29
30 295 households and individuals in China.

31 296 32 297 **Acknowledgments**

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44
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46
47 305 co-authors. TX and HF were involved in the design and were responsible of the data
48
49 306 collection. TX and LD completed the analyses presented here. LM provided independent
50
51 307 clinical advice. TX and HF wrote the first draft of the paper with further iterations involving
52
53 308 LD. KY contributed to the interpretation of the data and the critical revision of the
54
55 309 manuscript. All authors contributed, reviewed and approved the final submitted version.

56
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6

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- 41 434

435 **Figure Legend**

436 **Figure 1: GDM diagnosis and treatment model**

437 Figure 1 shows the generic framework of GDM screening path as recommended by Chinese
438 guideline. Circles represent chance events, while triangles represent terminal nodes. The
439 symbol # indicates that the probabilities of that branch are complementary with that of the
440 other one.

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4 442 **Figure 2. Maternal complications model**

5 443 Figure 2 shows the mother complications model, which has the same structure for both
6 444 GDM and Euglycemia branches. The symbol # indicates that the probabilities of that branch
7 445 are complementary with that of the other one. Circles represent chance events, while
8 446 triangles represent terminal nodes. Lines that do not terminate in a triangle are collapsed to
9 447 facilitate display and are analogous to branches that are open.
10 448

11 449 **Figure 3. Neonatal complications model**

12 450 Figure 3 shows the neonatal complications model, which has the same structure for both
13 451 GDM and Euglycemia branches. Circles represent chance events, while triangles represent
14 452 terminal nodes.
15 453

16 454 **Appendix Figure 1. Tornado diagrams.**

17 455 The bars represent the relative importance of the variables on the expected value: the larger
18 456 the bar, the higher the impact of that cost voice. CS, VD, PostHem, FDU and HDoP stand
19 457 respectively for caesarean section, vaginal delivery, fetal distress in uterus, post partum
20 458 hemorrhage and Hypertensive Disorders Of Pregnancy (Maternal complication model); RDS
21 459 for Respiratory Distress Syndrom (Neonatal complication model).
22 460

23 461 **Appendix Figure 2. Montecarlo simulations**

24 462 Monte Carlo probability distribution (1000 iterations) of the Maternal (left) and Neonatal
25 463 (right) complications models per case in both euglycemia (above) and GDM (below). The
26 464 highest the bar in the histogram, the most likely the correspondent cost value.
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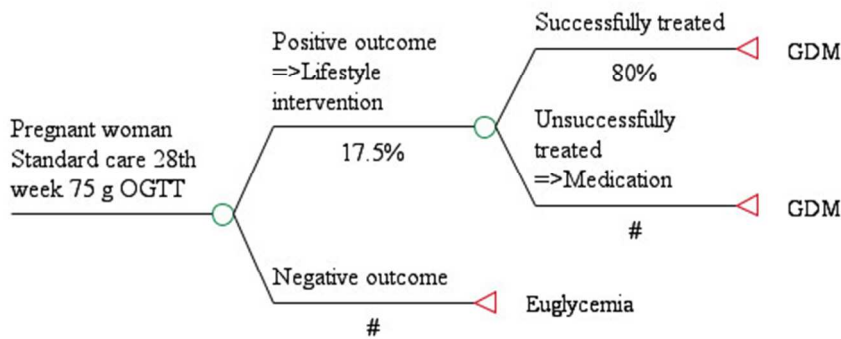


Figure 1: GDM diagnosis and treatment model

53x26mm (300 x 300 DPI)

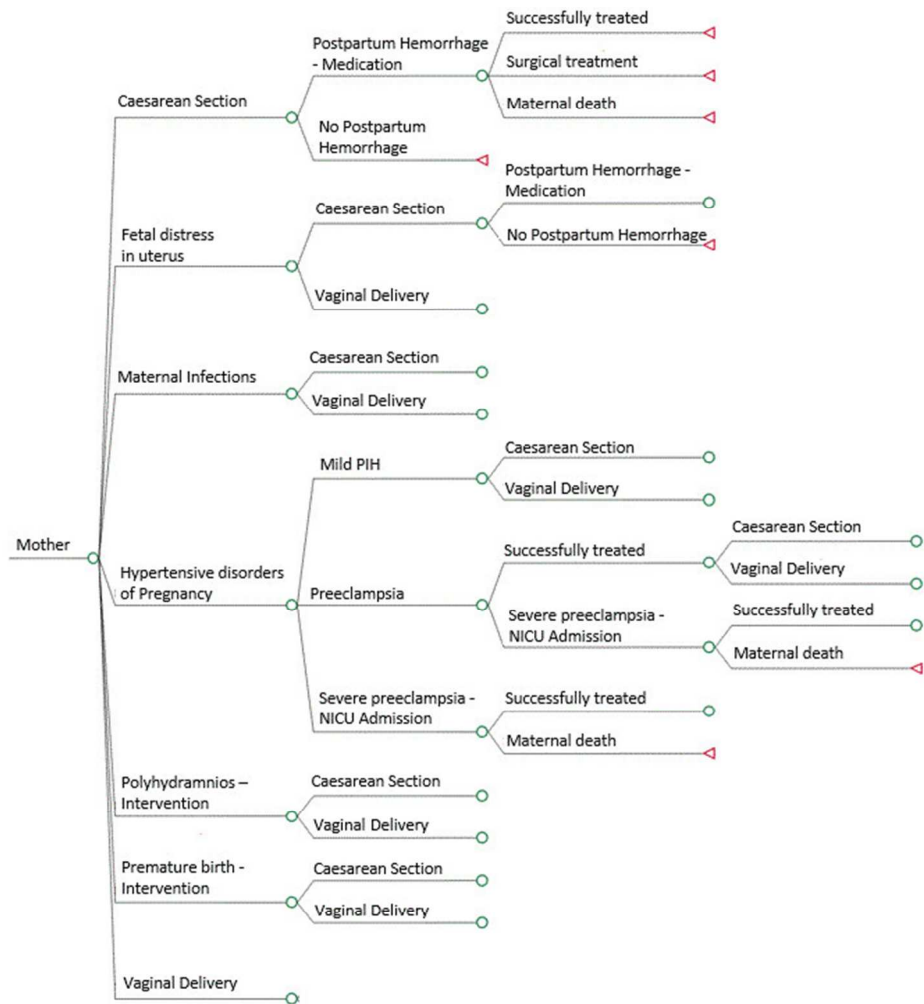


Figure 2. Maternal complications model

60x61mm (300 x 300 DPI)



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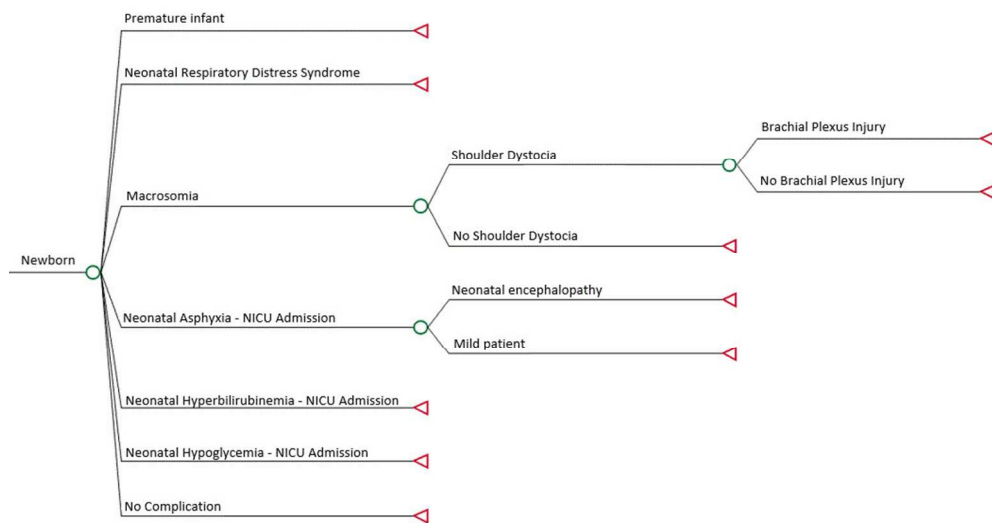
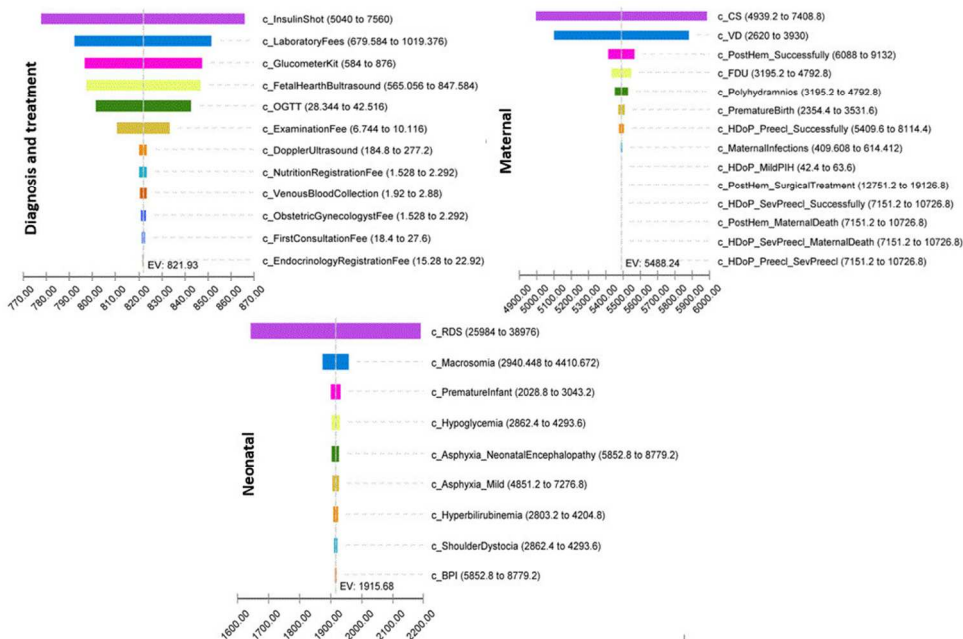


Figure 3. Neonatal complications model

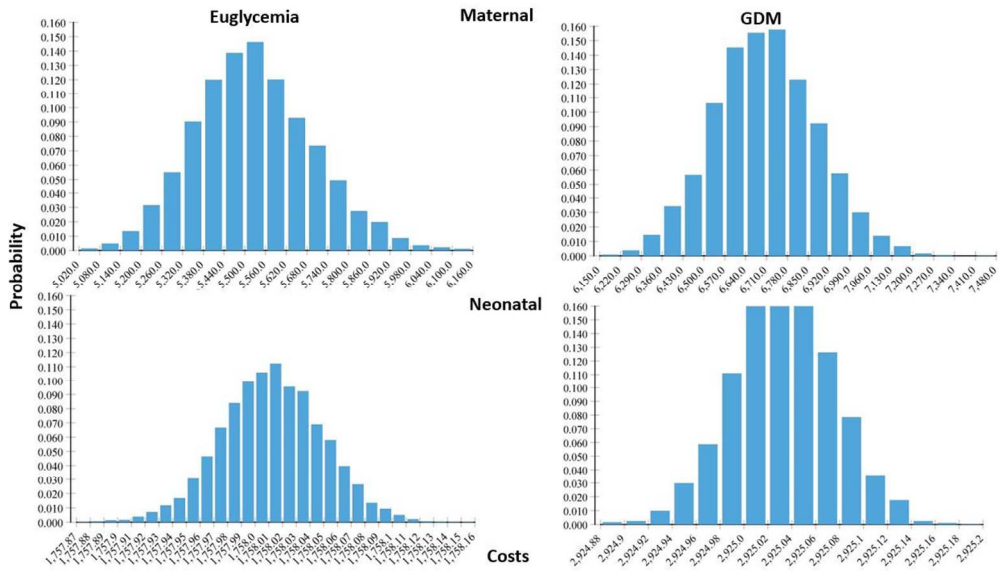
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92x60mm (300 x 300 DPI)

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CHEERS Checklist**Items to include when reporting economic evaluations of health interventions**

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24- item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

Section/item	Item No	Recommendation	Reported on page No/line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	<u>01/01</u>
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	<u>01-02/17-40</u>
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	<u>02-03/57-79</u>
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	<u>01/26</u>
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	<u>03/82-84</u>
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	<u>03-04/82-95</u>
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	<u>N/A</u>
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	<u>04/99</u>
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	<u>04/98-99</u>
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	<u>03-04/97-105</u>
Measurement of effectiveness	11a	<i>Single study-based estimates</i> : Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	



Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 2

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2				<u>N/A</u>
3		11b	<i>Synthesis-based estimates</i> : Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	<u>03/82-84</u>
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7	Measurement and	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
8	valuation of preference			
9	based outcomes			<u>04/102-104</u>
10	Estimating resources	13a	<i>Single study-based economic evaluation</i> : Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	<u>N/A</u>
11	and costs			
12				
13		13b	<i>Model-based economic evaluation</i> : Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	<u>03-04/84-100</u>
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20	Currency, price date,	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	<u>03-04/91-99</u>
21	and conversion			
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31	Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	<u>03/80-82</u>
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35	Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	<u>01/49-50</u>
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37	Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	<u>03/82-84</u>
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45	Results			
46	Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	<u>06-07/159</u>
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52	Incremental costs and	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	<u>06-07/159-166</u>
53	outcomes			
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57	Characterising	20a	<i>Single study-based economic evaluation</i> : Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	<u>N/A</u>
58	uncertainty			
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Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 3

		of methodological assumptions (such as discount rate, study perspective).	
	20b	<i>Model-based economic evaluation</i> : Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	07-08/167-180
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	09-11/217-241,250-271
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	12/310
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	12/313

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage:

<http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

The citation for the CHEERS Task Force Report is:

Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. *Value Health* 2013;16:231-50.