Original Article

First-trimester Risk Score Model for Gestational Diabetes Mellitus based on a Systematic Review and Meta-analysis

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Abstract

Objective: To construct and confirm a risk model for predicting gestational diabetes mellitus (GDM) in the early stage of pregnancy. **Method:** Meta-analysis was employed to determine the factors contributing to GDM. Based on the findings of this meta-analysis, Rothman-Keller model was formulated. The model's effectiveness was then evaluated using actual clinical data from real-world settings. **Results:** After screening, 1,548,515 women were ultimately incorporated into our meta-analysis. Nine risk factors linked to the occurrence of gestational diabetes, including maternal age≥35, pre-pregnancy overweight or obese, family history of diabetes, history of GDM, polycystic ovary syndrome, parity≥1, history of abortion, conception by assisted reproductive technology, smoking before or during early pregnancy were identified and incorporated into the model. In the external validation, the area under receiver operating characteristic curve (AUC) of the model was 0.714 (95%CI 0.672~0.755). **Conclusion:** A first-trimester GDM prediction model was developed and validated through an extensive meta-analysis identifying risk factors. Although predictive accuracy of the model was promising, further refinement and validation were recommended to enhance its clinical utility.

Keywords: Gestational Diabetes Mellitus, Systematic Review, Risk Factors, Prediction Model.

Introduction

Gestational diabetes mellitus (GDM) is characterized as hyperglycemia first detected during the second or third trimester of pregnancy, in the absence of any prior history of overt diabetes before conception.[1] This disease is a prevalent complication encountered in obstetrics and its incidence may differ across regions, but it generally remains at a high level. The prevalence of GDM in 24 European countries stands at 10.9%,[2] in Asia, the cumulative incidence rate is 11.5%.[3] In the Middle East and North Africa, the incidence is reported to be 13.0%.[4] As the incidence of GDM increases, the negative effects on both mothers and fetuses also become increasingly severe. GDM elevates the likelihood of negative perinatal consequences for instance, preeclampsia, cesarean section, preterm birth, neonatal hypoglycemia and macrosomia.[5-7] Postpartum women face a higher risk of developing type 2 diabetes, and whereas their offspring have a greater likelihood of experiencing obesity.[8-10] Research indicates that early screening and intervention for GDM can lower its incidence and mitigate associated complications.[11,12] Given that women with GDM and their newborns require more frequent medical monitoring and management, along with higher healthcare costs, this contributes to a heightened financial strain on both families and society. Consequently, GDM is widely acknowledged as a major concern in public health that adversely affects maternal and neonatal health. To lower the prevalence of GDM and minimize the likelihood of unfavorable pregnancy outcomes along with long-term health complications, the prevention and management of GDM have become key areas of current research. Detecting expectant mothers who are at a significantly elevated risk for developing GDM in early

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gestation by predictive models that incorporate multiple risk factors and taking timely intervention measures might become a primary method for in preventing the condition.[12] In mainland China, the prevalence of GDM is as high as 14.8%,[13] and several researchers developed predictive models of GDM based on the Chinese population.[14] Systematic reviews and meta-analyses combine data from various studies, comprehensively analyze data from different studies, and enhance statistical power.[15] Research on developing predictive models through meta-analysis suggests that this approach may avoid potential limitations and biases of individual studies, such as small sample sizes and selection biases, potentially improving the model's predictive capacity for disease.[16] Rothman-Keller was created by Rothman and Keller in 1972 and was primarily used to predict and assess chronic diseases.[17] After meta-analysis of risk factors and combined RR, the risk of individual morbidity was calculated according to the Rothman-Keller formula, which had a high prediction performance.[18-20] In this study, a Rothman-Keller model was developed to assess GDM risk by conducting a meta-analysis of associated risky factors, and to validate model's predictive performance using clinical data.

Literature Review

Models Developed using Multivariable Logistic Regression Methods

Risk assessment and identification of high-risk populations are often facilitated by predictive models. These models analyze the relationships between numerous risk factors and specific health outcomes, assigning weighted significance to each factor. As a result, the application of risk prediction models enhances the precision of identifying individuals at elevated risk, providing a valuable reference for the early screening of disease. Many studies had developed models for predicting GDM based on populations in different countries and regions, and the risk factors incorporated into the models primarily consisted of maternal characteristics. By using statistics from a prospective study conducted in the Netherlands, the GDM risk was assessed using the formula 1/[1 + exp(-b)], b = -6.1 + 0.83 (non-Caucasian) + 0.57 (family history of diabetes)-0.67 (multiparous women without previous GDM) + 0.5 (multiparous women with prior GDM) + 0.13×body mass index (BMI) (kg/m^2) .The area under receiver operating characteristic curve (AUC) of the model was 0.77.[21] This risk model had been externally validated by populations in New Zealand, Canada and other countries, and has shown good prediction performance,[22-24] however, some studies suggested that this model may underestimate the probability of developing GDM.[25]

Another model was constructed using prospective cohort data from the UK, which included 11,464 pregnant women. The formula became b = -8.68947 + 0.05365×maternal age (year) + 0.10852 × BMI (kg/m^2) + 1.00312 (South Asian) + 0.88785 (East Asian) + 3.72259 (multiparous women with prior GDM) + 0.67673 (multiparous women with a history of having delivered large infants).[26] The model has good model performance in external validation in other countries.[22] During the external validation process, data from two prospective cohort studies were used to validate and compare the performance of twelve GDM prediction models, and the results showed that this model had the best prediction performance.[23] However, it had been suggested that this model uses older diagnostic criteria and may lead to an underestimation of its predictive risk when applied to populations using IADPSG diagnostic criteria.[25]

A retrospective analysis carried out at Shanghai International Peace Maternity and Child Health Hospital in China, involving 3,956 females, derived a formula for predicting probability of GDM , expressed as: P = 1/[1 + exp (-10.84 + 0.078×maternal age + 0.119×BMI + 0.893×fasting blood glucose + 0.491×if there is a family history of diabetes)]. The model had an AUC of 0.69 and was validated internally and externally by a prospective cohort including 6,572 women, demonstrating good calibration. But the external validation cohort was also derived from the same institution, so the data may be homogeneous, limiting the generalizability of its performance. Among 210 prenatal women from a hospital in Xi'an, China, this model performed limitedly.[27]

In addition to maternal characteristics, researchers began to explore the effects of laboratory biochemical indicators on GDM. In the study of involving singleton pregnant women at 11-13^{+6} weeks from a hospital in Australia, the initially developed model was founded on maternal characteristics for example, GDM history, family history of diabetes, parity, age, achieving an AUC of 0.88. In the external validation of the other populations, the discrimination performance decreased to 0.72, respectively,[23] 0.71.[25] A study reported that the model overestimated women's GDM risk.[23] Subsequently, the authors updated the model to include three new biological features: pregnancy-related plasma protein A, triglycerides, and lipid calmodulin, and the AUC of the new model reached 0.91.[28] Furthermore, a prospective multicenter cohort investigation conducted in Belgium screened 1843 women for GDM and developed two prediction models based on maternal clinical and biochemical variables.[24] The AUC of the model with the addition of biochemical variables was 0.76, and following cross-validation, the model's AUC decreased to 0.72. In external validation, the model attained an AUC of 0.77, exhibiting the best calibration among the models evaluated.[25] Also, the model performed well in the external validation of the Australian population.[25]

A training set consisting of 16,819 pregnant women was established, while a separate group of 14,992 women was designated for the test set, all selected from hospital electronic medical records. A logistic regression model was developed using a machine learning approach to identify key features, including maternal age, prior GDM, A family history of diabetes, multiple pregnancies, fasting blood glucose levels, glycosylated hemoglobin, and triglycerides.[29] It was reported that this model

achieved an AUC of 0.77, with a Hosmer-Lemeshow test P-value of less than 0.001. By using data of 22,302 pregnant women from Tianjin, China, the established model achieved an AUC of 0.663, and the risk of GDM may have been overestimated (Hosmer-Lemeshow test P = 0.099).[30] The model utilized a substantial sample size and incorporated easily obtainable, cost-effective predictors. Additionally, the model holds potential for validation in diverse populations in future research.

Models Developed using Machine Learning Algorithms

Apart from the logistic regression method, a few have explored the application of machine learning techniques in forecasting GDM. A retrospective study was carried out by using data from Israel's national electronic health record, which including 588,622 maternal populations. The dataset was separated into a training group consisting of 451,402 cases and three external validation samples, comprising 82,678 women from populations distinct from the training set.[31] The gradient boosting model for predicting GDM was constructed, and the model's AUC was 0.85, and the performance of the model, measured by AUC, was 0.875 and 0.863 in the geographic validation group and the geographic time validation set, respectively. The model was highly discriminative, but has not been externally validated in other populations. The extreme gradient boosting method (XG Boost) algorithm was used to establish a machine learning model of GDM.[30] Through cross-validation and grid search, 14 important risk factors associated with GDM were analyzed, which were fasting blood glucose, pre-pregnancy BMI, waist circumference, alanine aminotransferase, weight gain, age, hip circumference, income, systolic blood pressure, a history of diabetes in the family, educational qualifications, gravidity, diastolic blood pressure, and parity. A total of 200 decision tree structures were ultimately developed, and the predicted risk was calculated using the following method: GDM risk = 1+(1+exp (-(leaf1+leaf2+.....+leaf200))).[30] The AUC of the XGBoost model was 74.2%, and the calibration was acceptable. The XGBoost model has better prediction performance and better execution speed than multivariate logistic regression model. This study integrated it as the back-end of an online platform for risk assessment to enhance its applicability, but it has not been externally confirmed in other populations.

Application of Meta-analysis in Constructing Predictive Models

At present, most of the models for predicting disease occurrence are cohort studies or case-control studies based on population data, and limited studies have investigated the application of systematic reviews and meta-analyses in constructing disease prediction models, and then use clinical data to verify the predictive performance of the models. Meta-analyses were used to construct three types of models: disease risk scores, logistic regression models, and Rothman-Keller models. The risk factors of the disease and the corresponding pooled OR or RR values can be obtained by conducting a meta-analysis. The natural logarithm of the odds ratio (Ln [OR]) was equivalent to the regression coefficient (β). The score for each risk factor =β×10. A meta-analysis encompassing 20 cohort studies identified nine hazard factors. The total risk score for diabetic nephropathy was calculated by summing the individual risk factor scores, with a maximum possible score of 37. The model was externally validated by 380 patients from Metabolic Disease Hospital of Tianjin Medical University, as a result, the AUC of the model was 0.765. A similar approach has been applied in predicting terminal kidney disease in individuals suffering type 2 diabetes, achieving an AUC of 0.807, indicating good discriminatory ability. This method was also utilized to predict early diabetic foot, achieving an AUC of 0.798.[16] Besides, a meta-analysis was undertaken to examine risk factors of diabetic retinopathy in these individuals, and a predictive model was developed according to the optimized logistic regression formula. The study identified 12 risk factors, α = -0.949, substituting the above equation, Logit(P) = -0.949 + 0.548×gender (1 for males, 0 for no) -0.942×bariatric surgery (1 for yes, 0 for no) -0.375×myopia (1 for yes, 0 for no) + 0×without lipid-lowering drugs usage-0.994×the period of lipid-lowering drug administration less than 3 years +0.223×the period of lipid-lowering drug administration more than 3 years +0.223×fasting blood glucose +0.174×course of disease +0.372×glycosylated hemoglobin−0.400×intensive glycemic control (1 for yes, 0 for no) + 0.405×hypertension (1 for yes, 0 for no) + 0.688×insulin therapy (1 for yes, 0 for no) + 0.199×place of residence (1 for the countryside, 0 for the city) - 0.083×smoking (1 for yes, 0 for no). By using data from 60 patients with type 2 diabetes at Chongqing Sixth People's Hospital, the model underwent external validation, achieving an AUC of 0.912, demonstrating a high level of discrimination.

In a word, many reports have established models to predict GDM risk, commonly via methods such as multivariate logistic regression and machine learning.[28,32-35] However, several limitations remain. For instance, most studies are single-center, limiting population representativeness, and many models have not been confirmed externally. Moreover, systematic reviews and meta-analyses integrate findings of numerous studies, increasing sample size and enhancing result stability. Therefore, this study aims to estimate prediction performance of a GDM model developed through meta-analysis.

Methods

Search Approach and Study Selection

Four English and four Chinese databases, including PubMed, Web of Science, Embase, Cochrane library, CBM, Wangfang Data, CNKI, and Chongqing VIP, were searched for relevant studies. The search period covered from January 2010 to December 2023. The search strategy was conducted in

combination with subject headings and keywords, and a manual search of potentially eligible references was made according to the review's reference list. The following terms were used in the search of English database ("diabetes, gestational" OR "pregnancy-induced diabetes") AND ("risk Factors") AND ("China" OR "Chinese") AND ("Cohort Studies" OR "Case-Control Studies").

Inclusion criteria: (1) Studies focused on pregnant women living in mainland China; (2) Study design: cohort studies; (3) GDM diagnosis was made in agreement with the guidelines established by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) in 2010;[36] (4) Studies were required to include one or more of the following risk factors: maternal demographic variables (e.g., maternal age, race, educational attainment), medical history (e.g., a history of gestational diabetes mellitus in prior pregnancies, a familial predisposition to diabetes, the presence of polycystic ovary syndrome), obstetric history (e.g., gravidity, parity, history of abortion, conception through assisted reproductive technology, history of delivering a macrosomic infant), and nutrition and lifestyle factors (e.g., pre-pregnancy BMI, smoking or alcohol consumption before or during early pregnancy);(5) Studies reported risk ratios(RR) of risk factors along with their 95% confidence intervals (CI), or offered other available information to compute the above data.

Exclusion criteria:(1) Studies included women with pregestational diabetes and other severe chronic diseases;(2) Experimental studies, systematic review, conference abstracts, letters, guidelines and animal studies;(3) The sample size is less than 1000;(4) Repeated reports;(5) Studies published not in English or Chinese.

Data Extraction

Two independent reviewers were systematically given assess to all retrieved studies by reviewing their titles and abstracts. Each study was evaluated against the predefined eligibility criteria, which include both inclusion and exclusion factors, to determine its suitability for the systematic review. When a study satisfied the predefined selection requirements, its complete text was obtained for further assessment. Any disagreements were addressed and settled through deliberation and mutual agreement. Once the included literature was identified, data extraction was carried out by two researchers. One investigator used a standardized Excel to extract data from the included studies, and a second investigator independently examined the extracted data. The data to be extracted contained: the author's name, publication of year, research design, research period, number of participants, the number of GDM cases, identified risk factors, RR of each risk factor, and the corresponding 95% CI. Efforts were made to retrieve missing data from the authors. When the obtained information was inadequate, the study was omitted from the analysis.

Risk of Bias Assessment

After full-text screening, the Newcastle-Ottawa Scale (NOS) was employed to judge the potential risk of bias.[37] The scale assigns a maximum score of nine stars. Each study was rated on a star system, with the final score indicating the overall risk of bias for that study. Studies scoring 1-4 points, 5-6 points, and 7-9 points are assigned to groups of high, moderate, and low risk of bias, respectively. A higher score indicates higher study quality.

Data Analysis

A flow chart was used to illustrate the steps of literature selection. Data analysis was conducted using Stata 14.0, and a forest plot was used to depict the risk factors for GDM. Cochran's Q test and the I^2 indicator were applied to measure heterogeneity across the included studies. When I^2 value was below 50%, the fixed-effects model was adopted, whereas when it exceeded 50%, a random-effects model was applied. To assess stability of the pooled results, a sensitivity analysis was performed. This involved removing one study at a time from the analysis and re-estimating the pooled effect sizes based on the remaining data, allowing for an assessment of how each individual study influences the overall findings. When 10 or more studies were included, publication bias was examined through funnel plot and Egger's test.

Construction of Rothman-Keller Model

The meta-analysis yielded pooled RR values for the identified risk factors associated with GDM. After calculating exposure rates of risk factor in the population (P value), the model was constructed using the following formula.

(1) Population attributable risk percentage (PAR%)

$$PAR\% = \frac{P_i(R_i - 1)}{P_i(R_i - 1) + 1} \times 100\%$$

P_i: Prevalence of risk factor exposure within the general population; RR_i: relative risk of each risk factor

(2) Incidence ratio at baseline (*p)*

$$p = \frac{1}{\sum_{i=1}^{n} R_i \times P_i} = 1 - PAR\%$$

(3) Risk score (S)

$S = p \times RR_i$

(4) Combined risk score (Z)

$$Z = (M_1 - 1) + (M_2 - 1) + (M_3 - 1) \cdots (M_j - 1) + N_1 \times N_2 \times N_3 \cdots N_k$$

M_j: the risk score for S≥1; N_k: the risk score when S is less than 1

(5) Individual susceptibility to GDM (D)

$D = E \times Z$

E: the prevalence of GDM

Validation of Rothman-Keller Model

The validation sample consisted of women carrying a single fetus who delivered at the Second People's Hospital of Dali from December 2021 to December 2023. Those females who had a previous diabetes mellitus were not included in the study. Additionally, pregnancies that ended in miscarriage, were terminated before 24 weeks, or lacked complete

outcome information were not considered. Medical history and maternal characteristics were recorded at the time of enrollment for women. All participants were then subjected to a 75 g, 2-hour oral glucose tolerance test between 24 and 28 weeks during the gestational period for universal GDM screening, following IADPSG recommendations. SPSS 24.0 was employed to analyze the general features of the validation sample. Descriptive statistics were conducted on participants' demographic details, obstetric background and medical history.

For continuous variables, data is presented as the mean along with standard deviation or as the median with percentiles, whereas categorical variables are summarized using counts and percentages. Appropriate statistical tests were conducted according to the nature of the variables to assess differences in the validation population data. When the *p* value was below 0.05 that statistical significance was determined.

The data from the validation population was substituted into the model, and its predictive accuracy was assessed by calculating AUC. The receiver operating characteristic (ROC) curvature was formed by plotting the false negative proportion against the true positive proportion across several cutoff points for predictive score. The value of AUC was then applied to assess the model's capacity to differentiate between GDM and non-GDM cases. A higher AUC indicates greater discriminative power of the model.

Results

Literature Selection

A total of 4,234 records were retrieved through database searching and 56 studies were included. Figure 1 outlined the process of study selection. Among the 56 studies, including 10 case-control studies and 46 cohort studies, 46 cohort studies including 1,548,515 pregnant women were selected for model construction, because the RR of risk factors were necessary parameters in establishing Rothman-Keller model and RR values could be obtained from cohort studies, but not from case-control studies. Detailed information on the characteristics of these cohort studies, including author names, publication dates, study design, region, sample size, GDM case count, and relevant risk factors, were presented in Supplementary Table S1. The NOS results for 46 cohort studies were summarized in Supplementary Table S2.

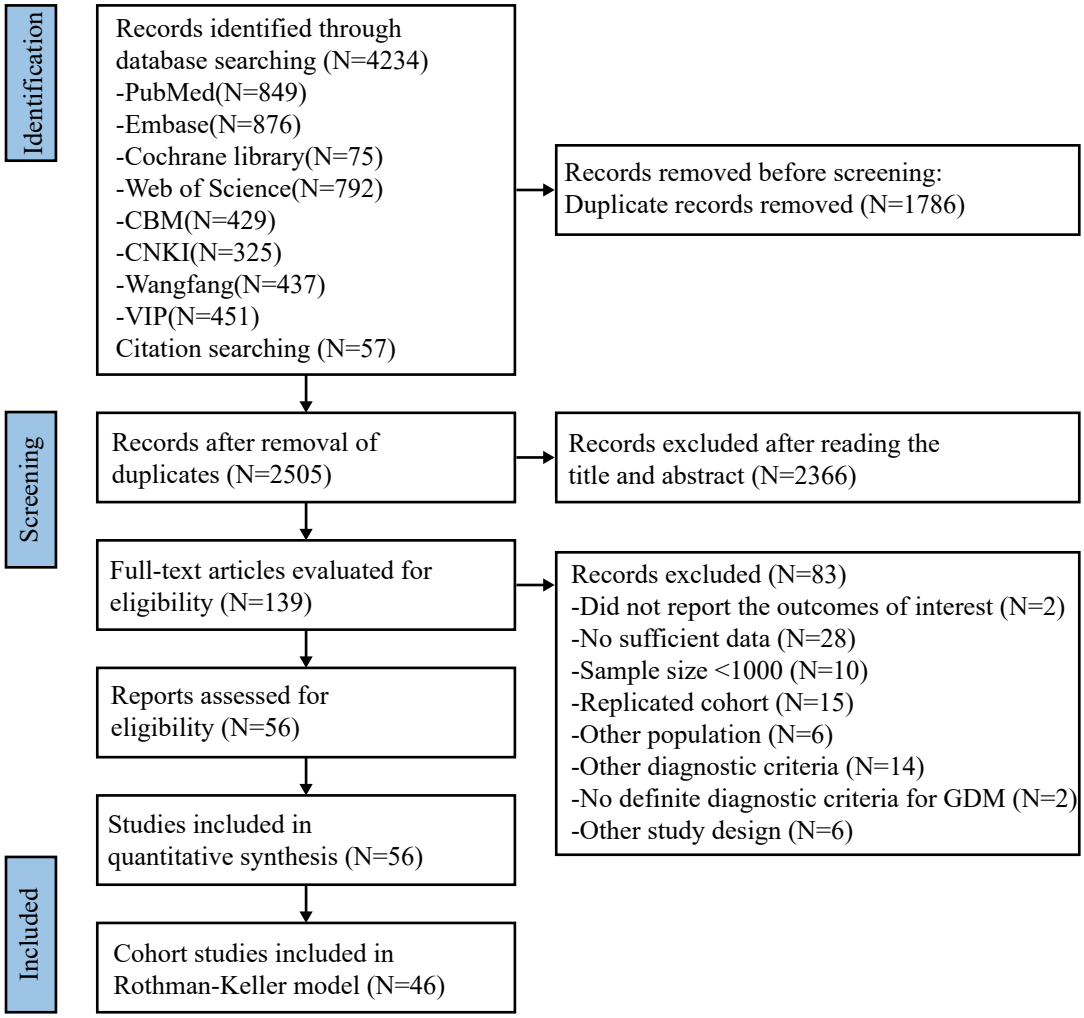


Figure 1: The process of Study Selection.

Risk Factors for GDM

Table 1 displayed the aggregated results about risk factors. Ten risk factors were identified as contributing to the GDM onset(P<0.05), including age≥35 years (Supplementary Figure S1), pre-pregnancy overweight or obese (Supplementary Figure S3), family history of diabetes (Supplementary Figure S4), previous GDM(Supplementary Figure S5), polycystic ovary syndrome(PCOS) (Supplementary Figure S6), parity≥1(Supplementary Figure S8),history of abortion(Supplementary Figure S9), assisted reproductive technology(ART) (Supplementary Figure S10), history of macrosomia (Supplementary Figure S11), smoking before or during early pregnancy(Supplementary Figure S12). But, educational level (Supplementary Figure S2), gravidity (Supplementary Figure S7) and alcohol consumption before or during early pregnancy (Supplementary Figure S13) were unrelated with GDM risk(P>0.05). Most pooled results were stable by conducting sensitivity analysis (Supplementary Figure S14-S22). The funnel plots of those studies(≥10) were showed in Supplementary Figure S23-S27.

Table 1: The Summary of Pooled Results.

Risk factor	Studies (n)	Sample Size	Number of Women with GDM	RR	95% CI	I2 (%)	Egger' test P Value
Maternal age	16	992191	100155	□	□	95.40	0.409
≥35	□	118517	20918	1.94	1.81~2.08	□	□
<35	□	873674	79237	1	/	□	□
Education level	16	218999	26862	□	□	94.70	0.010
High school or lower	□	94168	10561	1.08	0.96~1.20	□	□
College or higher	□	124831	16301	1	/	□	□
Pre-pregnancy overweight or obese	16	129504	21215	□	□	75.60	0.156
Yes	□	24632	6104	1.86	1.75~1.97	□	□
No	□	104872	15111	1	/	□	□
Family history of diabetes	16	164433	27634	□	□	75.90	0.545
Yes	□	10501	2518	1.67	1.54~1.82	□	□
No	□	153932	25116	1	/	□	□
History of GDM	6	44057	6716	□	□	87.50	/
Yes	□	784	434	3.25	2.49~4.25	□	□
No	□	43273	6282	1	/	□	□
PCOS	6	137780	15400	□	□	81.60	/
Yes	□	3635	1018	1.70	1.46~1.97		□
No	□	134145	14382	1	/	□	□
Gravidity	2	2951	533	□	□	29.30	/
1	□	1963	325	1	/	□	□
≥2	□	1048	208	1.10	0.94~1.30	□	□
Parity	19	220939	29027	□	□	72.80	0.201
0	□	136437	17361	1	/	□	□
≥1	□	84502	11666	1.23	1.16~1.29	□	□
History of abortion	4	390333	44263			79.20	/
Yes		118901	14727	1.33	1.27~1.40		
No		271432	29536	1	/		
ART	6	160649	13614	□	□	97.30	/
Yes		12521	2463	1.54	1.08~2.21	□	□
No		148128	11151	1	/	□	□
History of macrosomia	2	15381	4311	□	□	83.80	/
Yes	□	98	48	1.83	1.04~3.21	□	□
No	□	15283	4263	1	/	□	□
Smoking before or during early pregnancy	8	68644	10767	□	□	0.00	/
Yes	□	1521	215	1.23	1.09~1.38	□	□
No	□	67123	10552	1	/	□	□
Alcohol intake before or during early pregnancy	7	61644	7585	□	□	0.00	/
Yes	□	6510	574	1.02	0.93~1.11	□	□
No	□	55134	7011	1	/	□	□

Parameters of Rothman-Keller Model

There were insufficient studies available (N=2), so history of macrosomia was excluded from the analysis. Finally, 9 risk factors were used as predictors in the Rothman-Keller model, Proportion of risk factor (P_i) was calculated according to the count of women exposed to each hazard factor and the total number of population in cohort studies. The RR was obtained based on our meta-analysis. The parameters of GDM Rothman-Keller risk score were presented in Table 2.

Table 2: Parameters of Rothman-Keller Model.

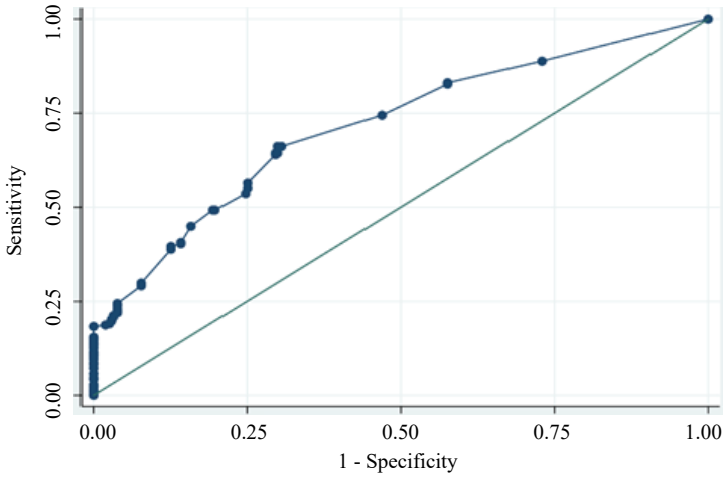
Risk Factor	P_i	RRi	PAR%	*p*	S
Maternal age					
≥35	0.1194	1.94	0.1009	0.8991	1.7442
<35	0.8806	1			0.8991
Pre-pregnancy overweight or obese					
Yes	0.1902	1.86	0.1406	0.8594	1.5985
No	0.8098	1			0.8594
Family history of diabetes					
Yes	0.0639	1.67	0.0410	0.9590	1.6015
No	0.9361	1			0.9590
History of GDM					
Yes	0.0178	3.25	0.0385	0.9615	3.1249
No	0.9822	1			0.9615
PCOS					
Yes	0.0264	1.70	0.0181	0.9819	1.6692
No	0.9736	1			0.9819
Parity					
0	0.6175	1			0.9191
≥1	0.3825	1.23	0.0809	0.9191	1.1305
History of abortion					
Yes	0.3046	1.33	0.0913	0.9087	1.2085
No	0.6954	1			0.9087
ART					
Yes	0.0779	1.54	0.0404	0.9596	1.4778
No	0.9221	1			0.9596
Smoking before or during early pregnancy					
Yes	0.0222	1.23	0.0051	0.9949	1.2238
No	0.9778	1			0.9949

Calculation of Individual Risk for GDM

Individual risk score for GDM (D) were predicted according to the parameters in Table 2. For example, information about a pregnant woman as followed: older than 35 years (S=1.7442), pre-pregnancy overweight (S=1.5985), with history of PCOS (S=1.6692), parity=1 (S=1.0685), and with history of abortion (S=1.2085), but without a family history of diabetes (S=0.9590), history of GDM (S=0.9615), ART (S=0.9596), and smoking before or during early pregnancy (S=0.9949). Next, the united risk score (Z) for this womaN=(1.7442-1) + (1.5985-1) + (1.6692-1) + (1.0685-1) + (1.2085-1) + 0.9590 × 0.9615 × 0.9596 × 0.9949 = 3.231. In mainland China, a study reported a GDM prevalence rate of 14.8%.[16] So, the likelihood of this woman for GDM (D) = 14.8% * 3.231 = 47.8%

Model Validation

Among the 585 validation samples, 278 developed GDM, while 307 maintained normal glucose tolerant (NGT). Table 3 showed the principal characteristics of these participants. The classification ability of the Rothman-Keller model was available in Figure 2. In our population, AUC for the Rothman-Keller model was recorded as 0.714(95%CI:0.672~0.755), demonstrating a moderate ability to differentiate cases. The sensitivity and specificity were 66.19% and 70.03%.



Area under ROC curve = 0.7135

Figure 2: The Model's ROC Curve.

Table 3: Principal Characteristics of Validation Population.

Characteristics	NGT Group	GDM Group	*P*
n	307	278	/
Maternal age	29.17±4.43	31.66±4.65	<0.001
≥35	35	80	<0.001
<35	272	198	
Pre-pregnancy BMI	21.51±3.22	23.62±3.61	<0.001
Pre-pregnancy Overweight or Obese			
Yes	66	132	<0.001
No	241	146	
Family history of diabetes			
Yes	0	16	0.05
No	307	262	
History of GDM			
Yes	0	17	<0.001
No	307	261	
PCOS			
Yes	2	15	0.001
No	305	263	
Parity			
0	154	126	0.138
≥1	153	152	
History of abortion			
Yes	138	149	0.022
No	169	129	
ART			
Yes	1	24	0.015
No	306	254	
Smoking before or during early pregnancy			
Yes	0	4	0.05
No	307	274	

Discussion

Principal Findings

This study established and confirmed a risk score model for evaluating GDM risk during early stage of gravidity, leveraging an inclusive systematic review and meta-analysis. Our findings identified nine key variables linked with the onset of GDM, including progressive maternal age (≥35 years), pre-pregnancy BMI indicating overweight or obesity, a family history of diabetes, a previous diagnosis of gestational diabetes mellitus, polycystic ovary syndrome, parity≥1, history of abortion, ART, and smoking before or during early pregnancy. The model demonstrated a moderate predictive performance in external validation (AUC =0.714,95% CI: 0.672~0.755).

Comparison with Previous Studies

Our meta-analysis identified nine key risk factors related with GDM risk. These results aligned with previous studies that had emphasized the role of demographic characteristics in GDM risk prediction. Some studies identified similar determinants for instance advanced maternal age,[52,53] pre-pregnancy overweight or obesity,[2,54,55] previous history of GDM,[3,56] and a familial predisposition to diabetes,[57] which were also significant predictors in our model. We observed that mothers diagnosed with polycystic ovary syndrome had a higher chance of suffering gestational diabetes, this finding demonstrated concordance with earlier research.[3,58] Additionally, in this study, the specific reproductive history such as previous abortion, parity ≥1, and ART conception might be related with a greater incidence of GDM, but gravidity≥2 was not linked to an increased probability of developing GDM. These factors demonstrated an inconsistent relationship with GDM, it was reported that history of abortion showed no correlation with GDM and being primigravida reduced GDM incidence.[56] Similarly, singleton pregnancies after ART remained to show an elevated likelihood of GDM.[59] Although we observed that smoking before or throughout early gestation could rise the risk of GDM, one research suggested that maternal smoking while pregnant did not show a significant correlation with the GDM probability.[60]

The Rothman-Keller model was employed to synthesize these risk factors into a comprehensive predictive score. This methodological choice was supported by its ability to handle multiple variables simultaneously while providing a clear framework for interpreting interactions between risk factors. The final model's performance was evaluated using actual clinical data externally. Although this AUC value indicated moderate predictive accuracy, it was slightly lower than some advanced models reported in other literature. A study focusing on early detection of gestational diabetes in Chinese females by means of machine learning approaches achieved a higher value (AUC=0.8).[39,41] It was indicated that while this model was useful, further refinement might be necessary to enhance its predictive power.

Strengths and Limitations

One of our study's strengths lied in substantial number of participants (1,548,515 women) included in the meta-

analysis, which provides robust statistical power and generalizability across diverse populations. Moreover, the model was externally validated using real clinical data, ensuring its generalizability across diverse populations. However, several limitations must be acknowledged. First, the model's performance could be improved by incorporating additional biomarkers such as fasting glucose levels or insulin resistance measures, which had shown promise in enhancing predictive accuracy in other studies. Second, the included populations in our study predominantly came from China mainland, limiting the applicability of our model to other ethnic groups.

Conclusion

In conclusion, in this study, a practical model aimed at predicting GDM during primary gestation was both developed and validated by utilizing data from a systematic review and meta-analysis. Integrating nine risk factors provided a comprehensive framework to detect individuals who exhibit an increased tendency for developing GDM timely. Although the model's predictive accuracy was moderate, it offered a practical tool for clinical practice that could be further refined through future research incorporating biochemical markers. Utilizing this model, healthcare providers could implement targeted interventions to reduce the harmful consequences of GDM for both mothers and newborns.

Supplemental Data

Supplemental Table S1: Characteristics and risk factors of the included cohort studies.
Supplemental Table S2: NOS results for cohort studies.
Supplemental Figures S1-S13: Forest plot of association between risk factors and GDM.
Supplemental Figures S14-S22: Sensitivity analysis of studies reported risk factors.
Supplemental Figures S23-S27: Funnel plot of studies.

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