Early prediction of gestational diabetes mellitus in the Chinese population via advanced machine learning

Yan-Ting Wu PhD\textsuperscript{1,2,3,}\textsuperscript{†}, Chen-Jie Zhang MD\textsuperscript{1,2,3}\textsuperscript{†}, Ben Willem Mol PhD\textsuperscript{4}, Andrew Kawai\textsuperscript{4}, Cheng Li PhD\textsuperscript{1,2,3}, Lei Chen\textsuperscript{1}, Yu Wang MD\textsuperscript{1,2,3}, Jian-Zhong Sheng PhD\textsuperscript{5}, Jian-Xia Fan PhD\textsuperscript{1,2,3}, Yi Shi PhD\textsuperscript{6,*}, He-Feng Huang PhD\textsuperscript{1,2,3,*}

\textsuperscript{1} International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 20030, China

\textsuperscript{2} Shanghai Key Laboratory of Embryo Original Diseases, Shanghai 20030, China

\textsuperscript{3} Research Units of Embryo Original Diseases, Chinese Academy of Medical Sciences, Shanghai 20030, China

\textsuperscript{4} Department of Obstetrics and Gynecology, Monash University, Clayton 3800, Australia

\textsuperscript{5} Department of Pathology and Pathophysiology, School of Medicine, Zhejiang University, Zhejiang, China

\textsuperscript{6} Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders, Shanghai Jiao Tong University, 1954 Huashan Road, Shanghai 200030, China.

\textsuperscript{†} Yan-Ting Wu and Chen-Jie Zhang contributed equally to this work.
* Co-corresponding author: He-Feng Huang, International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University, No.910, Hengshan Road, Shanghai, 200030, China

Tel: 86-21-64070434

Fax: 86-21-64474645

Email: huanghefg@sjtu.edu.cn

Yi Shi, Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders, Shanghai Jiao Tong University, 1954 Huashan Road, Shanghai 200030, China.

Email: yishi@sjtu.edu.cn
Conflict of Interest

The authors report no conflict of interest.

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Disclosure Summary

All of the authors declare that they have nothing to disclose.
Abstract

Context: Accurate methods for early gestational diabetes mellitus (GDM) (during the first trimester of pregnancy) prediction in Chinese and other populations are lacking.

Objectives: Establishing effective models to predict early GDM.

Setting: Pregnancy data for 73 variables during the first trimester were extracted from the electronic medical record system.

Main measures: Based on a machine learning (ML) driven feature selection method, 17 variables were selected for early GDM prediction. In order to facilitate clinical application, 7 variables were selected from the 17-variable panel. Advanced ML approaches were then employed using the 7-variable dataset and the 73-variable dataset to build models predicting early GDM for different situations respectively.

Results: 16,819 and 14,992 cases were included in the training and testing sets, respectively. Using 73 variables, the deep neural network model achieved high discriminative power, with area under the curve (AUC) values of 0.80. The 7-variable logistic regression (LR) model also achieved effective discriminate power (AUC = 0.77). Low BMI (≤ 17) was related to an increased risk of GDM, compared to a BMI in the range of 17 to 18 (minimum risk interval) (11.8% vs 8.7%, \( P = 0.0935 \)). TT3 and TT4 were superior to FT3 and FT4 in predicting GDM. Lipoprotein (a) was demonstrated a promising predictive value (AUC = 0.66).
Conclusions: We employed ML models that achieved high accuracy in predicting GDM in early pregnancy. A clinically cost-effective 7-variable LR model was simultaneously developed. The relationship of GDM with thyroxine and BMI was investigated in the Chinese population.

Keywords

GDM, early prediction, machine learning models, early pregnancy, BMI, thyroxine
Introduction

Gestational diabetes mellitus (GDM) is a common complication during pregnancy [1] that affects up to 15% of pregnant women worldwide [2]. Hyperglycemia is not, by itself, life-threatening for pregnant women, but can be harmful to the fetus, leading to complications, including stillbirth, premature delivery, macrosomia, fetal hyperinsulinemia, and clinical neonatal hypoglycemia [1]. The American Diabetes Association (ADA) and the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommend diagnosing GDM via a 2-h, 75 g oral glucose tolerance test (OGTT) at 24–28 weeks of pregnancy [3, 4].

There is accumulating evidence indicating that the exposure of embryos or fetuses to a hyperglycemic environment in the uterus can lead to chronic health problems later in life [5], including obesity, diabetes, and cardiovascular diseases [6-8]. Theoretically, GDM patients could have hyperglycemia for a long or short period of time before the GDM diagnosis, so the fetus will be more or less exposed to an intrauterine hyperglycemic environment in the second trimester (from 13 weeks of pregnancy to the day of the OGTT). Previous studies confirmed that fetal growth can already be abnormal preceding the diagnosis of GDM, including smaller fetuses at 24 weeks of gestation [9] and increased abdominal circumference growth rates compared with the non-GDM group [10]. Our previous study indicated that insulin therapy after GDM diagnosis cannot fully protect offspring from diet-related metabolic disorders in adulthood [11]. Therefore, a hysteretic diagnosis of GDM at 24–28 weeks of gestation might be too late for intervention and cannot completely reverse the adverse effects (including changes in epigenetics and abnormal fetal growth that occurred before 24 weeks of gestation) of the intrauterine hyperglycemia exposure on the offspring. It is thus essential to establish a prediction model to identify the high-risk group of GDM in the first trimester and provide an opportunity for interventions prior to diagnosis in the third trimester.
In GDM prediction, prior research has sought to find a threshold value of fasting plasma glucose (FPG) in the first trimester through large sample studies [12]. While elevating diagnostic criteria from FPG ≥ 5.1 mM to FPG ≥ 6.1 mM can obtain nearly 100% specificity, the corresponding low sensitivity (1%) greatly limits the feasibility [12]. In recent years, some novel biomarkers have been reported as potential GDM predictors, including angiopoietin-like protein 8, plasma fatty acid-binding protein 4, and various adipokines [13-15], but the low availability of these biomarkers in clinical practice limits its application. The exploration of prediction models based on multiple common risk factors, such as advanced maternal age, body mass index (BMI), and family history of diabetes, provides a new perspective in solving the problem [16]. Recently, artificial intelligence technology, particularly supervised machine learning (ML) methods, has been reported to demonstrate a powerful self-learning ability with improved GDM prediction accuracy [17]. However, GDM predictions are often made during the second trimester (20th week of gestation), creating a limited timeframe for doctors to intervene [17]. Therefore, in this study, we generated ML algorithms to predict GDM in the first trimester of pregnancy.

**Materials and Methods**

**Data source**

The training dataset included patients that were recruited from the 2017 obstetrical electronic medical record data from the International Peace Maternal and Child Health Hospital, Shanghai Jiao Tong University School of Medicine. Women with pre-GDM (FPG ≥ 7.0 mM or glycosylated hemoglobin A1c [HbA1c] ≥ 6.5%) were excluded. Samples that had a missing observation of greater than 20% were excluded from the dataset. Candidate variables including sociodemographic characteristics, clinical variables, and laboratory indexes in the
first trimester were collected. Following this, the 2018 obstetrical electronic medical record data were collected and curated, which served as the testing group to evaluate the prediction models. The details of the research subject selection are presented in Figure S1 [18]. The GDM diagnostic criteria followed the IADPSG guidelines (FPG ≥ 5.1 mM, 1 h ≥ 10 mM, and/or 2 h ≥ 8.5 mM). This study was approved by the Medical Ethical Committee of International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University (No. GKLW2019-05).

Variable selection

To ensure better model discrimination and create an efficient approach for clinical practice with fewer redundant variables, variable selection was conducted to select a panel of biomarkers with the most discriminative power for our outcome. All of the variables were sorted based on their absolute Spearman correlation coefficients and Pearson correlation coefficients with respect to the GDM and control groups, as demonstrated in Figures 1a and Figure S2a [18]. It can be seen from the figure that the indicators related to glucose and lipid metabolism have the strongest correlation with GDM, including FPG, HbA1c, lipoprotein (a), triglyceride (TG), and apolipoprotein-B. Total triiodothyronine (TT3) and GDM are also significantly correlated. Initial analyses using Spearman or Pearson correlation showed that several variables were highly correlated to each other and formed small clusters, as shown in Figures 1b–c and Figure S2b–c [18]. Correlation coefficient values are presented in Figure S5 [18]. This indicated that a representative small cluster of variables may provide enough discriminative power for a simplified model. The rationale of conducting correlation coefficient analyses before applying the model-free sequential forward variable selection is that in situations when many features exhibit at least weak correlation (e.g., |corr| > 0.05) with the outcome vector and when the features belong to multiple clusters, the sequential...
forward feature selection method tends to select representative features from each orthogonal cluster, spanning a more diverse feature space while excluding redundant information.

We applied a variable selection strategy that was previously successfully used in gene selection [19, 20]. In short, variable selection was completed using a cross-validation (CV) framework of 10-fold 100-repeat CV and leave-one-out (LOO) CV. The details of the CV method are shown in the Supplementary Text [18]. The variables were sorted using absolute correlation coefficients (both Pearson and Spearman correlation were tested and Spearman was chosen) with respect to the GDM and control group and an iterative approach of variable inclusion was utilized to assess the predictive power of each individual variable, using the average prediction accuracy or the area under the receiver operating characteristic (ROC) curve (AUC) as the indicator of model improvement. Figures 2a–b and 2e–f demonstrate the selected variable in each iteration. Figures 2c–d and 2g–h show the incremental trajectory of accuracy or AUC when including a contributing variable that remained in the selected variable pool in 10-fold and LOO CV, respectively.

**Prediction methods**

Using the selected variable panel, four ML methods were tested: logistic regression (LR) [21], k-nearest neighbor (KNN) [22], support vector machine (SVM) [23, 24], and deep neural network (DNN) [25, 26]. For the DNN classifier, a sequential model with two densely connected hidden layers and a single continuous output layer was devised (more details are shown in the Supplementary Text [18]). The LR classifier involved a linear combination of variables utilizing a sigmoid function. The SVM can identify classes by creating a hyperplane of decision within a higher feature space in a non-linear fashion [27]. For the SVM classifier, a radial basis function (RBF) (Gaussian) support vector model was used after considering the
linear kernel, polynomial kernel, and RBF kernels, where the default parameters were set as per the LIBSVM package [23]. For the KNN classifier, the hyperparameter \( k = 20 \) was chosen after testing \( k = 1, 5, 10, 15, 20, 50, \) and \( 100 \), such that the KNN’s majority voting was adopted as the prediction value.

**Model evaluation**

The discrimination of the models was assessed using the ROC curves and the AUC. The Hosmer–Lemeshow (HL) test was used to evaluate the calibration of each model. Finally, decision curve analysis (DCA) was introduced to evaluate the clinical application of each of the models. DCA is a useful method for evaluating the clinical net benefit of prediction models by comparing it to scenarios where all or none of the patients are treated.

**Results**

**Sample size**

In total, 16819 cases were included in the training dataset, and 15371 cases were included in the testing dataset. Sociodemographic characteristics are presented in Tables 1–3. The incidence of GDM between the training dataset and the testing dataset had no statistical difference (16.0% vs 14.4%, \( P = 0.0681 \)). The difference of multipara rates between the training dataset and the testing dataset showed statistically significance \( (P = 0.0043) \).

However, the difference in multipara rates between the two cohorts is very small (32.9% and 31.4%). A plausible explanation for this is that the large sample size magnifies the small difference between the two cohorts. Generally, the sociodemographic characteristics of the two groups are very similar. Good consistency in the data between the training dataset and the testing dataset is very important, because (i) this is in line with the real clinical setting (cohort data from the same hospital in adjacent years should be similar) and (ii) if the
sociodemographic characteristics of the training dataset and the testing dataset are too different, this will jeopardize the calibration of the model.

**Variable setting**

The 73 alternative variables, including sociodemographic characteristics, clinical variables, and laboratory indexes in the first trimester, are provided in Tables 1, 2, and S1 [18]. Six variables, namely, age, BMI, FPG, HbA1c, high density lipoprotein (HDL), and TG, were set as categorical variables apart from continuous variables. Previously, the ADA developed screening standards for women at high risk for gestational diabetes [28], which included BMI > 25 (> 23 if Asian American) and one or more of the following risk factors: HDL < 35 mg/dl (0.9 mM); TG > 250 mg/dl (2.8 mM); A1c > 5.7%. Therefore, in this study, the BMI, HDL, TG, and HbA1c binary classification threshold standards were adopted per ADA recommendations. The testing dataset was used to perform the optimal scaling regression analysis between age and gestational diabetes. With the increase of age, the risk of GDM gradually increases, but the increase is not linear; after the age of 38, the risk of GDM increases faster with age (Supplemental Figure A [18]). Therefore, we set the categorical age cutoff at 38 years old. The IADPSG uses 5.1 mM as the diagnostic criterion for early pregnancy gestational diabetes, but this has not been adopted in China because of high false positive rates. However, pregnant women with fasting blood glucose exceeding 5.1 mM in early pregnancy will receive nutrition and exercise intervention, and thus, the FPG classification standard was set at 5.1 mM herein [12]. The criteria for category are discussed in detail in the Supplementary Text [18].
Variable selection

To utilize as much as possible of the data, we considered two-by-two combinations of (10-fold CV or LOO CV) and (accuracy or AUC) to select feature sets. Specifically, when using the 10-fold CV to seek the optimal accuracy for predicting GDM (accuracy = sensitivity + specificity − 1) in the training dataset, 5 variables were selected and the accuracy was 0.9456. When using LOO CV to seek the optimal accuracy, 9 variables were selected and the accuracy was 0.9356. When using the 10-fold CV to seek the optimal AUC, 14 variables were selected and the AUC was 0.8503. For the combination of LOO CV and optimal AUC, 13 variables were selected and the AUC was 0.8503. Details are shown in Table 4. We merged all of the selected variables to obtain a 17-feature panel, namely, age, age†, FPG, FPG†, HbA1c, HbA1c†, lipoprotein (a), apolipoprotein-A, apolipoprotein-B, TG, TT3, total tetraiodothyronine (TT4), multiple pregnancy, multipara, smoking, family history of diabetes in a first-degree relative, and GDM history (categorical variables are denoted by †). BMI was not selected by our variable selection model. The statistics of these 17 variables in the GDM group and the control group are shown in Table 5. Compared with the control group, the GDM group is older and has higher FPG, HbA1c, apolipoprotein-A, apolipoprotein-B, TG, multiple pregnancy rate, multipara rate, and TT3 and lower TT4 (P < 0.0001). The incidence of previous history of GDM and family history of diabetes in the GDM group was significantly higher than that in the control group. The obvious difference in these variables between the two groups indicates that these variables have strong predictive potentials. There was no significant difference in smoking rate between the GDM group and the control group (0.5% vs 0.6% in the 2017 cohort, \(P = 0.8883\); 0.6% vs 0.5% in the 2018 cohort, \(P = 0.4392\)). Interestingly, smoking was still being screened out by ML as a potential GDM predictor. This agrees with a recent study which indicates that smoking is an independent risk factor for GDM [29]. Based on prior clinical experience and a close examination of each variable, the
selected variables were further narrowed to 7 variables, practically useful for clinical implementation. To validate the selected 7 features are of high discriminatory power, we performed a simulation test comparing the selected 7 features and 7 randomly selected features. We first enumerated all of the 7-feature combinations out of the 17 features using the nchoosek function in MATLAB. Specifically, the command “nchoosek ([1:17], 7)” generated 19448 combinations. Then, to randomly select combinations, we sequentially drew every 10th combination to obtain 1945 combinations (as detailed in Table S6 [18]). Based on each randomly generated feature set, we performed SVM, KNN, and LR prediction using the same parameters we used for the selected 7-feature based predictions. As demonstrated in Figure S3 [18], the average AUCs based on randomly selected features are significantly lower than the AUC computed based on the selected 7-feature based predictions, and in the best LR prediction model, the AUC based on the selected 7 features is higher than the maximum AUC of all randomly drawn feature combinations (0.77 vs 0.70, \( P < 0.0001 \)).

**Development of prediction models**

Eight prediction models were developed: KNN, SVM, LR, and DNN models were developed for both 7-variable and all-variable sets. The adjusted odds ratios (ORs) and coefficients from the LR model with 7 variables are shown in Table 6.

**Discrimination of different models**

The AUCs of different models are provided in Figure 3a and Table 7. The all-variable DNN, SVM, KNN, and LR models had AUCs and 95% confidence intervals (CIs) of 0.80 (95% CI, 0.79–0.81), 0.77 (95% CI, 0.76–0.78), 0.61 (95% CI, 0.59–0.62), and 0.77 (95% CI, 0.76–0.78), respectively. The 7-variable DNN, SVM, KNN, and LR models had AUCs and 95% CIs of 0.77 (95% CI, 0.76–0.78), 0.66 (95% CI, 0.65–0.67), 0.65 (95% CI, 0.63–0.66), and 0.77 (95% CI, 0.76–0.78), respectively. The discrimination effect of each model is shown
visually using violin plots (Figure 3b–c). The all-variable DNN demonstrated the best
discrimination ability, and the traditional LR models produced higher AUCs than the KNN
and SVM models. The optimal sensitivity and specificity of each model in certain threshold
probability (Pt) value ranges are given in Table 7. The accuracy of previous prediction
models has also been summarized; existing models do not exceed 0.70 and our model
achieved the highest discrimination (Table S2 [18]).

Calibration of different models

The HL test was used to test the calibration of the LR, SVM, and DNN models (Figure 4).
The HL test was not applied to the KNN models as the model did not provide individual risk
probabilities. The P values of six different models were < 0.0001 in the HL test. The 7-
variable models (Figure 4a–c) showed superior HL test performance compared to the all-
variable models (Figure 4d–f). The 7-variable LR model provided the most accurate
calibration among all of the prediction models.

Clinical use

The DCA results of the models are presented in Figure S4 [18]. Compared to treating all of
the patients or none of the patients, our prediction models provide a net benefit.

Discussion

Our paper explores prediction models based on a large sample of the Chinese population
using clinical data before 12 weeks of gestation, 2 months earlier than previous state-of-the-
art ML models. We used ML variable selection methods to screen for risk factors for early
development of GDM. Of the 73 extracted variables, 17 variables were selected for our
models, which included sociodemographic data (age, age†, smoking, and family history of
diabetes in a first-degree relative), clinical characteristics (multiple pregnancy, multipara, and
previous GDM history), glucose metabolism (FPG, FPG†, HbA1c, and HbA1c†), lipid metabolism (lipoprotein (a), apolipoprotein-A, apolipoprotein-B, TG), and thyroid function (TT3, TT4). Of these 17 variables, 7 were selected based on intra-variable correlation and clinical importance for our parsimonious model: age, family history of diabetes in a first-degree relative, multiple pregnancy, previous GDM history, FPG†, HbA1c, and TG. Details of how the 7 variables were selected are discussed in the Supplementary Text [18]. As shown in Figure 3, our all-variable DNN model achieved the highest accuracy in predicting GDM in early pregnancy, followed by SVM and KNN. Our parsimonious models using 7 variables performed similarly and with increased efficiency. The DCA of the different models also showed similar results (Supplemental Text, Figure S4 [18]).

Model comparisons

The advantage of DNN is its ability to capture subtle non-linear relationships between variables and outcomes. However, DNNs have a risk of overfitting, and as DNN is a black box to end-users, the individual weighted contribution of each variable can be difficult to explain [30]. On the other hand, LR highlights a clear contribution of each variable, making it useful for real-time clinical implementation. Our method of including only the important variables in each model resulted in a negligible running time difference between prediction models.

The HL test was adopted to evaluate the calibration of prediction models [31]. As KNN only results in a binary outcome rather than individual predicted probabilities, the HL test and DCA curve were not used to evaluate these models. The $P$ values of all of the models for the
HL test were < 0.0001, which implied that the model calibrations were not optimal. This shows that while the models were to be able to distinguish high-risk status of GDM in early pregnancy, the specific risk probabilities provided by these models can be further improved [32]. However, the 7-variable LR model revealed slightly better calibration than the DNN model. This may be due to the poor correlation between Pt and risk probability in DNN and SVM, indicating the HL test is not optimal to measure calibration for complex ML models. Furthermore, compared to existing LR prediction models (Table S2 [18]), our 7-variable LR and DNN models demonstrated very promising results in predicting GDM in early pregnancy.

There have been limited studies predicting GDM using ML algorithms. A retrospective electronic medical record study with 580,000 pregnancies in Israel reported an AUC of 0.85 using all variables and an AUC of 0.80 using only 9 variables [17]. However, the clinical data collected from studies in Israel were obtained at 20 weeks of pregnancy, unlike our prediction using variables only extracted from the first trimester. This allowed them to use variables that are only useful during the second and third trimesters to predict GDM, such as human placental growth hormone, human chorionic somatomammotropin, progesterone, and placental growth hormone [33].

**Risk factor evaluation**

The selected variables were found to be consistent with previous clinical studies. Advanced age, previous GDM history, family history of diabetes, and blood glucose are well-known risk factors of GDM [34]. Women with twin pregnancies have an increased risk of GDM, and higher rates of adverse pregnancy outcomes occur in GDM twin pregnancies [35]. HbA1c reflects the average blood glucose levels over the last 1–2 months [36, 37]. Previous studies
hypothesized that the link between higher parity and insulin resistance could be explained by the decreasing $\beta$-cell reserve in consecutive pregnancies [38, 39]. However, prediction models showed that parity plays a more complicated role, with multipara without previous GDM history reducing the risk of future GDM (OR = 0.5, $P = 0.05$), and multipara with previous GDM history increasing the risk of future GDM (OR = 1.6, $P = 0.55$) [40, 41]. We therefore believe that parity, when used with other selected variables, is conditionally correlated to GDM, and that its predictive power can be increased through such a combination.

Lipoprotein (a) was one of the 17 predictors and demonstrated high prediction power (AUC = 0.66, 95% CI, 0.65–0.68). Previous studies indicated that high levels of TGs and apolipoproteins are risk factors for GDM [42, 43]. However, lipoprotein (a) transports oxidized phospholipids that have pro-inflammatory activity, so the possible association of higher lipoprotein (a) levels with GDM remains controversial [44, 45]. For our model, the predicted effect of lipoprotein was better than that of apolipoproteins (Table S3 [18]). The reasons for this are not known.

Despite obesity being a well-known risk factor for GDM, our variable selection model did not choose BMI, instead highlighting biochemical indicators that reflect the level of lipid metabolism, such as TG. There are several explanations for this. First, compared to Europeans, Asians have more subcutaneous fat and higher s-leptin levels in early pregnancy, despite having lower BMI [46]. Second, the relationship between BMI and GDM is complex, with high BMI individuals having an insulin resistance mechanism and low BMI individuals having a defective insulin secretion mechanism in GDM [47, 48]. Our study showed that both
an increased BMI and a very low BMI (≤ 17) (n = 432) are related to an increased risk of GDM (Figure S5 [18]), compared to a BMI in the range of 17 to 18 (minimum risk interval) (n = 915), but this association was not statistically significant (11.8% vs 8.7%, P = 0.0935). Existing studies have not shown that extremely low BMI could increase the risk of GDM [17], but it has been found that BMI had J-shaped associations with overall mortality and diabetes mortality [48], supporting our findings.

A large portion of the selected variables were of a biochemical nature (Table S1 [18]). For example, TT3 and TT4 were selected as predictors of GDM, strongly suggesting the existence of a close relationship between thyroid function and GDM. In our training group, the GDM group had higher levels of TT3 (median, 2.1 nM vs 2.02 nM, P < 0.0001) and free triiodothyronine (FT3) (median, 4.80 pM vs 4.60 pM, P < 0.0001) and lower levels of TT4 (median, 114.2 nM vs 116.0 nM, P < 0.0001) and free tetraiodothyronine (FT4) (median, 13.6 pM vs 14.0 pM, P < 0.0001) compared to the non-GDM group. This result was consistent with previous studies [49, 50]. Current research findings remain divided with respect to the question whether high T3 or low T4 in early pregnancy is a risk factor for GDM, as this may be affected by variations between populations [49, 50, 51]. A study from a US cohort showed that FT4 was not associated with GDM, but high FT4–FT3 conversion efficiency (increased FT3/FT4 ratio) increased the risk of GDM [51]. Several studies noted that FT3 levels were positively associated with insulin secretion and hyperinsulinemia [52]. A study of the Chinese population suggested that increasing FT4 levels functioned as a protective mechanism against GDM, in that higher FT4 levels were associated with a lower incidence of GDM (P < 0.0001) [49]. Most of the prior research focused on the relationship between FT3 and FT4 and GDM, because FT3 and FT4 have much higher biological activity than TT3 and TT4 and can directly reflect thyroid function [51]. Interestingly, when we
included thyroxine in the prediction model, the TT3 and TT4 levels had better predictive power than FT3 and FT4 (Table S4 [18]). This suggests that the relationship between thyroxine and GDM is conditionally dependent on factors such as TT3 and TT4. However, further research on the relationships among total thyroxine, free thyroxine, and the risk of GDM in the Chinese population is needed.

Limitations

The limitations of this study include the limited sample size, the fact that all of the data were collected from a single center, and a lack of external verification. The prediction model is based on retrospective electronic medical data that many have inherent biases. However, electronic medical records are easily available clinical data resources, and predicting GDM based on electronic medical records is often the most feasible option. The diversity of laboratory testing between different hospitals caused by different laboratory instruments may also influence the effects of prediction and extrapolation. However, these shortcomings do not change the fact that the proposed variable selection and ML-based methodology itself are worthy of attention in early GDM prediction. In future work, we plan to collect multi-center clinical data to verify the extrapolation of these prediction models.
Conclusions

This study established state-of-the-art prediction models in early pregnancy for the early intervention of GDM in Chinese women. Using an ML-based variable selection approach, 17 important GDM predictive variables were selected. These 17 indicators are worthy of in-depth study in the GDM field; in particular, lipoprotein (a) may be closely related with GDM. A 7-variable LR model was developed for more practical clinical applications. Further research is required to clarify the relationship among total thyroxine, free thyroxine, and GDM and between excessively low BMI and GDM in the Chinese population.
Ethics approval and consent to participate

This study was approved by the Medical Ethical Committee of International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University (No. GKLW2019-05).

Disclosure of conflicts of interest

The authors declare that there are no conflicts of interest.

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Author contributions

Yan-Ting Wu contributed to the research idea and was the project coordinator. Chen-Jie Zhang contributed to the manuscript drafting. Ben Willem Mol and Andrew Kawai contributed to manuscript modification. Cheng Li contributed to figure production and modification. Lei Chen contributed to the data export from the hospital electronic medical record system. Yu Wang, Jian-Zhong Sheng, and Jian-Xia Fan provided useful suggestions.
Yi Shi contributed to the ML algorithm and statistical analysis. He-Feng Huang provided project guidance and financial support. All of the authors read and approved the final manuscript.

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Data availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.
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Table 1. Sociodemographic characteristics of the training group and the testing group.

| Characteristic                                      | 2017 training group | 2018 testing group | P value |
|-----------------------------------------------------|---------------------|--------------------|---------|
| Age (year), median (IQR)                            | 31 (28 to 34)       | 31 (28 to 34)      | 0.6847  |
| BMI before pregnancy (kg/m$^2$), median (IQR)      | 20.8 (19.3 to 22.6) | 20.5 (19.5 to 22.5)| 0.5114  |
| Smoking                                            | 95 (0.6)            | 74 (0.5)           | 0.3010  |
| Educational background                              |                     |                    |         |
| Primary school degree                               | 15 (0.1)            | 9 (0.1)            |         |
| Junior high school degree                           | 388 (2.3)           | 360 (2.3)          |         |
| High school degree                                  | 889 (5.3)           | 789 (5.1)          | 0.6981  |
| University degree and above                         | 15527 (92.3)        | 14213 (92.5)       |         |
| Family history of diabetes in a first-degree relative| 1202 (7.1)          | 1046 (6.8)         | 0.2296  |
| GDM                                                | 2696 (16.0)         | 2216 (14.4)        | 0.0681  |
| Personal history of GDM                             | 176 (1.0)           | 138 (0.9)          | 0.1752  |
| Natural pregnancy                                  | 14504 (86.2)        | 13258 (86.3)       | 0.9636  |
| Multiple pregnancy                                 | 489 (2.9)           | 466 (3.0)          | 0.5116  |
| Multipara                                          | 5539 (32.9)         | 4833 (31.4)        | 0.0043  |
Table 2. Sociodemographic characteristics of GDM and non-GDM cases.

| Characteristic                              | 2017 training group | 2018 testing group |
|--------------------------------------------|---------------------|--------------------|
|                                            | GDM cases | Controls | P value | GDM cases | Controls | P value |
|                                            | n = 2696    | n = 14123 |         | n = 2216  | n = 13155|         |
|                                            | n (%)       | n (%)     |         | n (%)     | n (%)     |         |
| Age (year), median (IQR)                   | 32 (29 to 36) | 30 (28 to 34) | < 0.0001 | 33 (30 to 36) | 30 (28 to 33) | < 0.0001 |
| < 38                                       | 2340 (86.8) | 13240 (93.7) | < 0.0001 | 1933 (87.2) | 12324 (93.7) | < 0.0001 |
| ≥ 38                                       | 356 (13.2) | 883 (6.3) | < 0.0001 | 283 (12.8) | 831 (6.3) | < 0.0001 |
| Weight before pregnancy, median (IQR)      | 56.0 (52.0 to 62.0) | 54.5 (50.0 to 59.0) | < 0.0001 | 58.0 (52.0 to 64.0) | 55.0 (50.0 to 59.0) | < 0.0001 |
| Height, median (IQR)                       | 161.0 (158.0 to 165.0) | 162.0 (159.0 to 165.0) | < 0.0001 | 161.0 (158.0 to 165.0) | 162.0 (160.0 to 165.0) | < 0.0001 |
| BMI before pregnancy (kg/m²), median (IQR) | 21.6 (20.1 to 23.6) | 20.7 (19.3 to 22.3) | < 0.0001 | 22.1 (20.1 to 24.4) | 20.8 (19.5 to 22.1) | < 0.0001 |
| ≤ 23                                       | 1620 (60.1) | 9926 (70.2) | < 0.0001 | 1386 (62.5) | 11064 (84.1) | < 0.0001 |
| Risk Factor | Control Group | Exposure Group | p-value | Odds Ratio (95% CI) |
|-------------|---------------|----------------|---------|--------------------|
| > 23        | 1076 (39.9)   | 4197 (29.7)    | 0.7902  |                    |
| Drinking    | 7 (0.3)       | 39 (0.3)       | 1.0000  |                    |
| Smoking     | 14 (0.5)      | 81 (0.6)       | 0.8883  |                    |
| Educational background | | | | |
| Primary school degree | 5 (0.2) | 10 (0.1) | 0.30 (1.1) | |
| Junior high school degree | 102 (3.8) | 286 (2) | 0.4392 | |
| High school degree | 162 (6) | 727 (5.1) | < 0.0001 | |
| University degree and above | 2427 (90.0) | 13100 (92.8) | 0.4392 | |
| Family history of diabetes in a first-degree relative | 439 (16.3) | 763 (5.4) | < 0.0001 | |
Table 3. Clinical features of GDM and non-GDM cases in the first trimester.

| Characteristic          | 2017 training group | 2018 testing group | 2017 training group | 2018 testing group |
|-------------------------|---------------------|---------------------|---------------------|---------------------|
|                         | GDM cases           | Controls            | P value             | GDM cases           | Controls            | P value             |
| n = 2696                | n = 14123           |                     |                     | n = 2216            | n = 13155           |                     |
| n (%)                   | n (%)               |                     |                     | n (%)               | n (%)               |                     |
| SBP (mmHg), median (IQR)| 114 (107 to 122)    | 110 (102 to 117)    | < 0.0001            | 115 (106 to 124)    | 110 (102 to 117)    | < 0.0001            |
| DBP (mmHg), median (IQR)| 71 (65 to 77)       | 68 (62 to 73)       | < 0.0001            | 71 (64 to 79)       | 68 (62 to 74)       | < 0.0001            |
| PCOS                    | 13 (0.5)            | 30 (0.2)            | 0.0195              | 30 (1.4)            | 65 (0.5)            | < 0.0001            |
| Personal history of GDM | 132 (4.9)           | 44 (0.3)            | < 0.0001            | 94 (4.2)            | 44 (0.3)            | < 0.0001            |
| Natural pregnancy       | 2180 (80.9)         | 12324 (87.3)        | < 0.0001            | 1796 (81.0)         | 11462 (87.1)        | < 0.0001            |
|                      | SBP     | DBP     | p-Value | SBP     | DBP     | p-Value |
|----------------------|---------|---------|---------|---------|---------|---------|
| Multiple pregnancy   | 110 (4.1) | 379 (2.7) | < 0.0001 | 80 (3.6) | 386 (2.9) | < 0.0001 |
| Multipara            | 1053 (39.1) | 4486 (31.8) | < 0.0001 | 825 (37.2) | 4008 (30.5) | < 0.0001 |

SBP, systolic blood pressure; DBP, diastolic blood pressure; PCOS, polycystic ovary syndrome
Table 4. Selecting variables by KNN.

| Selected variables | 10-fold (accuracy) | LOO (accuracy) | 10-fold (AUC) | LOO (AUC) |
|--------------------|--------------------|----------------|----------------|----------|
| FPG†               | Fasting plasma glucose | Fasting plasma glucose | FPG          |
| Lipoprotein(a)     | FPG†               | FPG†           |                | HbA1c    |
| Total triiodothyronine | Lipoprotein(a)  | Lipoprotein(a) |                | Family history of diabetes in a first-degree relative |
| Age†               | Total triiodothyronine | Total triiodothyronine | Triglyceride |
| Multiple pregnancy | Age                | Triglyceride   | Age            |          |
|                    | Total tetraiodothyronine | Age           | Total triiodothyronine |          |
| APO-A              | HbA1c†             | Lipoprotein(a) |                |          |
| Multipara          | Total tetraiodothyronine | Age†          |                |          |
| Multiple pregnancy | Age†               | Total tetraiodothyronine |          |          |
|                    | APO-B               | Multipara     |                |          |
| Multipara          | APO-A         |
|-------------------|---------------|
| Previous GDM      | Multiple pregnancy |
| Multiple pregnancy| Previous GDM |
| Smoking           |               |

†Categorical variable: age < 38: 0, age ≥ 38: 1; fasting plasma glucose < 5.1 mmol/L: 0, FPG ≥ 5.1 and < 7.0 mmol/L: 1; HbA1c ≤ 5.7: 0, HbA1c > 5.7 and < 6.5: 1

Using the 10-fold method, 5 variables were selected to obtain optimal accuracy; using the LOO method, 9 variables were selected to obtain optimal accuracy; using the 10-fold method, 14 variables were selected to obtain the optimal ROC area; using the LOO method, 13 variables were selected to obtain the optimal ROC area.
Table 5. Selected 17 variables in the training group and the testing group.

| Characteristic                              | 2017 training group | 2018 testing group |
|---------------------------------------------|---------------------|-------------------|
|                                             | GDM cases | Controls | P value | GDM cases | Control | P value |
|                                             | n = 2696 | n = 14123 |         | n = 2216 | n = 13155 |         |
| n (%)                                       |          |          |         |          |          |         |
| Age (year), median (IQR)                    | 32 (29 to 36) | 30 (28 to 34) | < 0.0001 | 33 (30 to 36) | 30 (28 to 33) | < 0.0001 |
| Age†, ≥ 38                                  | 356 (13.2) | 883 (6.3) | < 0.0001 | 283 (12.8) | 831 (6.3) | < 0.0001 |
| Smoking                                     | 14 (0.5) | 81 (0.6) | 0.8883 | 13 (0.6) | 61 (0.5) | 0.4392 |
| Family history of diabetes in a first-degree relative | 439 (16.3) | 763 (5.4) | < 0.0001 | 341 (15.4) | 705 (5.4) | < 0.0001 |
| Personal history of GDM                     | 132 (4.9) | 44 (0.3) | < 0.0001 | 94 (4.2) | 44 (0.3) | < 0.0001 |
| Multiple pregnancy                          | 110 (4.1) | 379 (2.7) | < 0.0001 | 80 (3.6) | 386 (2.9) | < 0.0001 |
| Multipara                                   | 1053 (39.1) | 4486 (31.8) | < 0.0001 | 825 (37.2) | 4008 (30.5) | < 0.0001 |
| Apolipoprotein-A                            | 2.01 (1.93 to 2.08) | 1.98 (1.94 to 2.02) | < 0.0001 | 2.15 (2.01 to 2.29) | 2.14 (2.01 to 2.27) | 0.1695 |
| Apolipoprotein-B                            | 0.89 (0.84 to 0.94) | 0.85 (0.84 to 0.88) | < 0.0001 | 0.79 (0.70 to 0.91) | 0.74 (0.65 to 0.85) | < 0.0001 |
|                                | Mean (95% CI)   | Mean (95% CI)   | p         | Mean (95% CI)   | Mean (95% CI)   | p        |
|--------------------------------|----------------|----------------|----------|----------------|----------------|----------|
| Triglyceride                   | 1.47 (1.15 to 1.89) | 1.22 (0.97 to 1.52) | < 0.0001 | 1.49 (1.16 to 1.93) | 1.24 (0.98 to 1.57) | < 0.0001 |
| Lipoprotein (a)                | 157.8 (101.5 to 185.9) | 191.2 (173.3 to 210.9) | < 0.0001 | 103.0 (46.0 to 216.3) | 123.0 (57.0 to 232.0) | < 0.0001 |
| FPG (mM)                       | 4.77 (4.49 to 5.13) | 4.50 (4.30 to 4.70) | < 0.0001 | 4.78 (4.50 to 5.14) | 4.54 (4.33 to 4.73) | < 0.0001 |
| FPG†, ≥ 5.1 and < 7.0 mM, n (%) | 766 (28.4) | 494 (3.5) | < 0.0001 | 614 (27.7) | 400 (3.0) | < 0.0001 |
| HbA1c (%)                      | 5.3 (5.1 to 5.5) | 5.1 (5.0 to 5.3) | < 0.0001 | 5.4 (5.2 to 5.6) | 5.2 (5.1 to 5.4) | < 0.0001 |
| HbA1c†, > 5.7 and < 6.5, n (%) | 179 (6.6) | 71 (0.5) | < 0.0001 | 241 (10.9) | 131 (1.0) | < 0.0001 |
| Total tetraiodothyronine (pM)  | 114.2 (106.6 to 119.0) | 116.0 (112.6 to 120.1) | < 0.0001 | 115.7 (99.4 to 132.9) | 118.9 (102.8 to 134.2) | < 0.0001 |
| Total triiodothyronine (nM)    | 2.10 (2.00 to 2.23) | 2.02 (1.97 to 2.08) | < 0.0001 | 2.10 (1.90 to 2.40) | 2.00 (1.80 to 2.30) | < 0.0001 |
Table 6. Multivariate analysis for the 7-variable LR model.

|                               | β     | Adjusted odds ratio (95% CI) | P value |
|-------------------------------|-------|-----------------------------|---------|
| Intercept                     | −14.2334 | -                           | < 0.0001|
| Age                           | 0.0681 | 1.070 (1.058 to 1.083)      | < 0.0001|
| Previous GDM                 | 2.6181 | 13.710 (9.532 to 19.718)    | < 0.0001|
| Family history of diabetes in a first-degree relative | 1.1062 | 3.023 (2.610 to 3.501)      | < 0.0001|
| Multiple pregnancy            | 0.4349 | 1.545 (1.208 to 1.976)      | 0.0005  |
| FPG†                          | 2.8165 | 16.718 (14.125 to 19.788)   | < 0.0001|
| Glycosylated hemoglobin A1c   | 1.6925 | 5.433 (4.472 to 6.600)      | < 0.0001|
| Triglyceride                  | 0.5005 | 1.650 (1.528 to 1.781)      | < 0.0001|

† Categorical variable: fasting plasma glucose < 5.1 mM: 0, FPG ≥ 5.1 mM: 1.
| Prediction model | AUC (95% CI) | Optimum Pt threshold | Sensitivity | Specificity | Youden index |
|------------------|--------------|----------------------|-------------|-------------|--------------|
| LR*              | 0.77 (0.76–0.78) | 0.13 | 59% | 82% | 0.41 |
| LR**             | 0.77 (0.76–0.78) | 0.02 | 58% | 86% | 0.44 |
| KNN*             | 0.65 (0.63–0.66) | - | 31% | 98% | 0.29 |
| KNN**            | 0.61 (0.59–0.62) | - | 23% | 99% | 0.22 |
| SVM*             | 0.66 (0.65–0.67) | 0.14 | 32% | 98% | 0.30 |
| SVM**            | 0.77 (0.76–0.78) | 0.15 | 32% | 98% | 0.30 |
| DNN*             | 0.77 (0.76–0.78) | 0.10 | 70% | 69% | 0.39 |
| DNN**            | 0.80 (0.79–0.81) | 0.15 | 63% | 82% | 0.45 |

*7-variable model; **all-variable model.
Figure legend

Figure 1. Variable selection results. (a) Spearman correlation coefficients between each variable and the GDM/non-GDM label vector, over all the samples. The bar plots from left to right represent absolute values from high to low. (b) Spearman correlation coefficients between all the variables over vectors of all the samples. Detailed correlation coefficient values can be found in Table S5 [18]. (c) Variable-way hierarchical clustering results using distance metrics based on Spearman correlation coefficients.

Figure 2. (a) and (b) Ten-fold CV based detailed prediction outcomes of each variable selection iteration. The yellow and blue elements represent predicted GDM cases and predicted non-GDM cases, respectively (a) Seeking optimal accuracy. (b) Seeking optimal AUC. (c) and (d) Variable selection trajectory guided by classification accuracy and AUC, respectively, under a 10-fold CV framework. (e) and (f) Leave-one-out CV based detailed prediction outcomes of each variable selection iteration. The yellow and blue elements represent predicted GDM cases and predicted non-GDM cases, respectively. (e) Seeking optimal accuracy. (f) Seeking optimal AUC. (g) and (h) Variable selection trajectory guided by classification accuracy and AUC, respectively, under a leave-one-out CV framework.
Figure 3. **Discriminative power comparison between different prediction models.** (a) ROC curves of different prediction models based on the 7-variable panel (*) and all-variable panel (**). (b) and (c) Violin plot comparisons of predicted score distribution using different prediction models with the 7-variable panel and the all-variable panel.

Figure 4. **Calibration of different models.** The $P$ values of all prediction models in HL tests are < 0.0001. The 7-variable models (a–c) show superior HL test performance as compared to the all-variable models (d–f). This is because if the model incorporates all of the variables without selection, it will inevitably over-fit, which will significantly affect the model calibration.
Sequential variable selection for seeking best accuracy (10-Fold)

Sequential variable selection for seeking best AUC (10-Fold)

Sequential feature selection (LOO)

Sequential feature selection (LOO)

Sequential feature selection (LOO)

Sequential feature selection (LOO)

Sequential feature selection (LOO)
