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# Impact of Pre-Pregnancy Hemoglobin Level on the Association Between Pre-Pregnancy Body Mass Index and Gestational Diabetes Mellitus: A Retrospective Cohort Study in a Single Center in China

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**Aim:** To assess the impact of maternal pre-pregnancy body mass index (BMI) on gestational diabetes mellitus (GDM) based on different pre-pregnancy hemoglobin levels.

**Methods:** This retrospective cohort study included 1289 pregnant women between June 2020 and January 2022. Clinical data were collected by reviewing their medical and antepartum screening records between 24 and 28 gestational weeks, including pre-pregnancy BMI and pre-pregnancy hemoglobin (Hb) levels. The diagnosis of GDM mainly depended on oral glucose tolerance test (OGTT) during 24–28 weeks. Restricted cubic spline (RCS) was used to investigate the association between the pre-pregnancy Hb level and the risk of GDM. Univariate and multivariate logistic regression analyses were applied to evaluate the relative risk of GDM.

**Results:** Of the 1289 included pregnant women, 187 (14.5%) women were diagnosed with GDM in this study. The pre-pregnancy Hb level was significantly associated with GDM risk, and the pre-pregnancy Hb level of 123 g/L was identified as the threshold to stratify and assess the association between the GDM risk and the pre-pregnancy BMI. For women with a pre-pregnancy Hb level ≥123 g/L, the pre-pregnancy BMI showed a significant association with GDM risk, and the estimated incidence rate of GDM was 7.7%, 14.8%, 36.3% and 44% for underweight, normal-weight, overweight and obese pregnant women, respectively. After adjusting for potential influencing factors of GDM, the respective relative risk was 1.0 (reference), 2.04 (95% CI 0.84, 4.99), 7.06 (2.66, 18.61), and 10.77 (2.85, 40.63) (P for trend < 0.001).

**Conclusion:** In pregnant women with a pre-pregnancy Hb level ≥123 g/L, pre-pregnancy BMI showed a more significant association with GDM risk as compared with those with a pre-pregnancy Hb level <123 g/L.

**Keywords:** pregnancy, body mass index, hemoglobin, gestational diabetes mellitus, overweight, obese

## Introduction

Gestational diabetes mellitus (GDM) is a common complication during pregnancy, which may lead to maternal and neonatal mortality and morbidity, including delivery of large for gestational age (LGA) infants, preeclampsia, stillbirth and neonatal hypoglycemia.[1] Previous studies have reported that the prevalence of GDM was 22.94% in Southern China.[2] GDM has become an epidemic causing tremendous health and economic burdens in China. As GDM is usually diagnosed by oral glucose tolerance test (OGTT) at 24–28 gestational weeks, it is imperative to screen out modifiable risk factors to prevent GDM before pregnancy.



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The hemoglobin (Hb) level is a marker to evaluate anemia during pregnancy and before pregnancy. Anemia is diagnosed during pregnancy when the Hb concentration was lower than 110 g/L.[3] Numerous retrospective and prospective studies have reported the association between high Hb levels and GDM.[4–7] A Hb concentration value more than 130 g/L is an independent risk factor for GDM in Chinese women.[5] Besides, iron deficiency anemia even reduces the prevalence of GDM.[8] Actually, a high Hb concentration is a reflection of physical status nutrition, especially in GDM women. It is suggested that an increased incidence of GDM with high Hb may be related to their better nutritional status, but the question is which of them plays a predominant role in inducing a higher body weight and BMI. BMI is generally accepted as a risk of GDM, which could increase the cell oxidative stress, causing inhibition of insulin internalization and actions, then resulting in hyperinsulinemia and insulin resistance and increasing the risk of developing GDM.[9,10] Although Hb is an important index to assess anemia, a higher Hb level may be connected with higher BMI.[4] A prospective study showed that the mean BMI in the first-trimester of pregnant women in the high-Hb group was significantly higher than that of pregnant women in the low-Hb group, and Turkish women with high Hb levels were at increased risk for developing GDM.[11] In addition, the risk of obesity in women with high Hb levels (≥125 g/L) in the first trimester was at least twofold higher than that in women with normal Hb levels.[12] However, few studies have evaluated the association between pre-pregnancy BMI and GDM in pregnant women with high levels of pre-pregnancy Hb.

The aim of this retrospective study was to explore the possible association between pre-pregnancy BMI and GDM through stratified analysis based on the pre-pregnancy Hb concentration for the sake of providing more reasonable weight management guidance for women before pregnancy.

# Research Design and Methods

## Study Design and Population

Included in this study were all women who had regular prenatal care and maintained complete data of prenatal care in Shanghai Pudong Hospital (Shanghai, China) from June 2020 to January 2022, including 3625 nulliparity women who were scheduled to participate in antepartum screening at 24–28 gestational weeks. The antepartum screening records, including age, blood pressure (BP), lifestyle behaviors (smoking and alcohol use), family history of diabetes, menstrual history, due date, pre-pregnancy BMI, and pre-pregnancy Hb levels within 3 months before the last menstrual period, were obtained from the medical records. Of the 3625 women initially included, 929 were excluded due to the absence of the pre-pregnancy Hb data. Additional 1407 women were excluded due to pregestational diabetes, systemic lupus erythematosus (SLE), nephropathies, steroid administration, antiphospholipid antibody syndrome, hematological diseases, preeclampsia or other histories of adverse pregnancy outcomes. Finally, 1289 nulliparity women were included for analysis. The research protocol was approved by the institutional review board of the said hospital (Code No. WZ-14).

## Clinical Data and Laboratory Measurements Collection

At the first initial prenatal screening, the participants received a series of tests and examinations including physical examination, complete blood count, lifestyle behaviors (smoking and alcohol use), family history of diabetes, reproductive history, and menstrual history. Pre-pregnancy BMI was used as the measure of overall obesity within 3 months before pregnancy. Based on the criteria recommended by the WHO criteria, BMI was categorized into 4 groups: underweight (<18.5 kg/$m^2$), normal weight (18.5–24.9 kg/$m^2$), overweight (25–29.9 kg/$m^2$), and obesity (≥30 kg/$m^2$).[13] Pre-pregnancy Hb level was measured by using a XN-1000i autoanalyser (Sysmex, Hyogo, Japan).

GDM was diagnosed by 75-g OGTT at 24–28 gestational weeks, and the criterion of defined GDM was up to or exceeded 5.1 mmol/L at 0 h, 10.0 mmol/L at 1 h, or 8.5 mmol/L at 2h.

## Statistical Analysis

All analyses were accomplished by using SPSS 22.0 (IBM Corp., Armonk, NY, USA) and R x64 4.2.0 (R Foundation for Statistical Computing). Descriptive statistics included means and standard deviation (SD) for continuous variables and percentages for categorical variables. To compare the baseline characteristics by BMI, categorical variables were compared with the $\chi 2$ test and One-Way ANOVA for continuous variables. In addition, the restricted cubic spline

(RCS) regression model with assumed four knots at the 5th, 35th, 65th and 95th centiles were used to model the potential nonlinear relations of pre-pregnancy Hb levels with GDM. Categories of pre-pregnancy Hb levels were defined by the following quartiles: < 118, 118–122.9, 123–130, ≥130 g/L, and multivariable logistic regression analysis was performed to assess the potential associations of pre-pregnancy BMI with GDM risk, with adjustment for age, pre-pregnancy systolic blood pressure (SBP), pre-pregnancy diastolic blood pressure (DBP), smoking exposure, family history of diabetes, and alcohol consumption. Odds ratios (ORs) with 95% CI were generated as indicated. The level of significance was 0.05.

# Results

## The Comparisons of Baseline Characteristics

The baseline characteristics of the 1289 subjects included in this study are shown in Table 1. The mean pre-pregnancy BMI was 21.5 kg/m$^2$. Of the 1289 women, 187 (14.5%) developed GDM during pregnancy. The mean pre-pregnancy Hb level, maternal age, pre-pregnancy SBP and DBP were 123 g/L, 29.6 years, 112 mmHg and 70 mmHg, respectively. Moreover, pregnancy women with higher pre-pregnancy BMI tended to have higher rates of a family history of diabetes, alcohol consumption and smoking exposure, but there was no significant difference in smoking exposure between the groups stratified by pre-pregnancy BMI (P=0.09). There were statistically significant differences in fasting Plasma Glucose (FPG), 1h PG, 2h PG and HbA1c level at GDM screening between the four groups.

## Association of Maternal Pre-pregnancy Hb with GDM Risk

The result of logistic regression analysis showed that pre-pregnancy Hb levels were correlated with increased risk of GDM (Table 2). Women with a Hb level ≥130 g/L had 2.64-fold odds of GDM as compared with those with a Hb level <118 g/L (adjusted OR 2.64 [95% CI 1.66–4.19]; P <0.001). There was a strong increased risk trend between the pre-pregnancy Hb level and GDM risk ($P_{trend}$ < 0.001). In addition, there was a nonlinear relationship between pre-pregnancy Hb and GDM risk. According to the result of RCS regression model (Figure 1), a pre-pregnancy Hb level cutoff value =123 g/L showed an odds ratio value=1, which was selected as the threshold to stratify to assess the association between GDM risk and pre-pregnancy BMI.

**Table 1** Participants' Characteristics of the Total Sample Population and Subgroups Stratified by Body Mass Index

| | **Total n=1289** | **BMI<18.5 n=180** | **18.5≤BMI≤24.9 n=944** | **25.0≤BMI≤29.9 n=137** | **BMI≥30 n=28** |
|---|---|---|---|---|---|
| Age (years)** | 29.6±4.0 | 28.1±3.6 | 29.8±3.9 | 30.2±4.4 | 29.8±4.2 |
| Pre-pregnancy BMI (kg/m$^2$)** | 21.5±3.1 | 17.6±0.8 | 21.3±1.7 | 26.6±1.2 | 31.5±3.3 |
| Pre-pregnancy systolic blood pressure(mmHg)** | 112.0±11.1 | 109.9±12.2 | 111.4±10.6 | 116.6±11.2 | 121.1±11.8 |
| Pre-pregnancy diastolic blood pressure(mmHg)** | 70.0±8.8 | 69.5±9.0 | 69.7±8.5 | 71.5±10.4 | 76.4±8.8 |
| Smoking exposure** | 99(7.6) | 10(5.6) | 61(6.5) | 20(14.6) | 8(28.6) |
| Family history of diabetes** | 305(23.7) | 37(20.6) | 212(22.5) | 44(32.1) | 12(42.9) |
| Alcohol consumption* | 97(7.5) | 14(7.7) | 64(6.8) | 14(10.2) | 5(17.9) |
| Pre-pregnancy Hb levels (g/L)** | 123.3±9.3 | 120.3±8.8 | 123.4±9.2 | 126.2±9.2 | 128±11.4 |
| OGTT for GDM screening | | | | | |
| FPG (mmol/L)** | 4.5±0.5 | 4.3±0.3 | 4.4±0.4 | 4.9±0.9 | 4.8±0.7 |
| 1hPG (mmol/L)** | 7.2±1.7 | 6.8±1.5 | 7.1±1.6 | 8.1±2.2 | 8.0±1.8 |
| 2hPG (mmol/L)** | 6.4±1.4 | 6±1.2 | 6.4±1.3 | 7.1±1.8 | 6.7±1.6 |
| HbA1c at GDM screening(%) ** | 4.7±0.5 | 4.5±0.4 | 4.6±0.5 | 4.9±0.6 | 5.2±0.4 |
| GDM** | 187(14.5) | 11(6.1) | 120(12.7) | 47(34.3) | 9(32.1) |

**Notes**: Data are represented as the mean ± SD or n (%). The p-values refer to the overall differences across the BMI groups as derived from ANOVA (for continuous variables) or $\chi^2$ tests (for categorical variables). *P<0.05, **P<0.01.

**Abbreviations**: Hb, hemoglobin; BMI, body mass index; GDM, gestational diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; OGTT, oral glucose tolerance test; FPG, fasting plasma glucose; 1hPG, one-hour postprandial glucose; 2hPG, two-hour postprandial glucose.


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**Table 2** Association of Maternal Pre-Pregnancy Hemoglobin Levels with GDM Risk in the Overall Population

| Variables | GDM/Total (%) | Model 1† | | | Model 2‡ | | |
|---|---|---|---|---|---|---|---|
| | | OR | 95% CI | P | OR | 95% CI | P |
| Pre-pregnancy hemoglobin level (g/L) | | | | | | | |
| <118 | 33/362(9.1) | | Reference | | | Reference | |
| 118–122.9 | 45/310(14.5) | 1.69 | 1.05–2.37 | 0.031 | 1.705 | 1.05–2.76 | 0.03 |
| 123–130 | 51/337(15.1) | 1.78 | 1.12–2.83 | 0.015 | 1.709 | 1.07–2.73 | 0.025 |
| ≥130 | 58/280(20.7) | 2.60 | 1.64–4.13 | <0.001 | 2.64 | 1.66–4.19 | <0.001 |
| Trend test | | <0.001 | | | <0.001 | | |

**Notes**: †Univariate model. ‡Adjusted for age, pre-pregnancy BMI, pre-pregnancy systolic blood pressure, pre-pregnancy diastolic blood pressure, smoking exposure, family history of diabetes, alcohol consumption.

## Association of Pre-Pregnancy BMI with GDM Risk Based on Different Pre-Pregnancy Hb Levels

To investigate the relation between pre-pregnancy BMI and GDM risk based on different pre-pregnancy hemoglobin levels, we performed multivariable logistic regression analysis to assess the potential association of pre-pregnancy BMI alone with GDM risk. As shown in Table 3, pregnant women with pre-pregnancy BMI 25.0–29.9 kg/m$^2$ had the highest fold odds of GDM as compared with those with pre-pregnancy BMI <18.5 kg/m$^2$ (adjusted OR 5.96 [95% CI 2.84–12.47]; P <0.001), but not pre-pregnancy BMI ≥30 kg/m$^2$. We also found an increased risk trend across pre-pregnancy BMI groups with GDM risk ($P_{trend}$ <0.001).

The association between pre-pregnancy BMI and GDM risk based on different pre-pregnancy hemoglobin levels is shown in Table 4. It was found that pre-pregnancy BMI 25.0–29.9 kg/m$^2$ also had the highest fold odds of GDM in the subgroup of Hb level <123 g/L (adjusted OR 9.28 [95% CI 3.01–28.6]; P <0.001). However, when pre-pregnancy was BMI≥30 kg/m$^2$, no significant difference was observed as compared with the pregnant women with pre-pregnancy BMI <18.5 kg/m$^2$. In another subgroup of Hb levels ≥123 g/L, higher pre-pregnancy BMI was associated with a higher risk of GDM, and when pre-pregnancy BMI was ≥30 kg/m$^2$, the fold odds of GDM was the highest (adjusted OR 10.77 [95% CI 2.85–40.63]; P <0.001). In order to model and visualize the association of pre-pregnancy BMI with GDM risk based on different pre-pregnancy hemoglobin levels, we used restricted cubic splines to describe the nonlinear fashion in

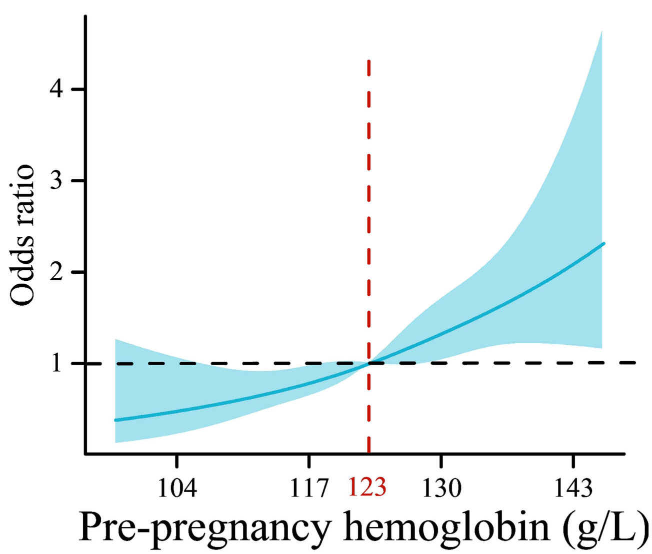


**Figure 1** The association of maternal pre-pregnancy Hb with GDM risk.
**Notes**: RCS regression analysis of pre-pregnancy hemoglobin levels with GDM risk. Hemoglobin 123 g/L was selected as the reference level. The lines indicate estimated ORs, and the light blue areas represent 95% CI.

**Table 3** Association of Pre-Pregnancy BMI with GDM Risk in the Overall Population

| Variables | GDM/Total (%) | Model 1† | | | Model 2‡ | | |
|---|---|---|---|---|---|---|---|
| | | OR | 95% CI | P | OR | 95% CI | P |
| Pre-pregnancy BMI (kg/m$^2$) | | | | | | | |
| <18.5 | 11/180(4.9) | | Reference | | | Reference | |
| 18.5–24.9 | 120/944(12.7) | 2.24 | 1.18–4.24 | 0.014 | 1.89 | 0.98–3.65 | 0.056 |
| 25.0–29.9 | 47/137(34.3) | 8.02 | 3.97–16.23 | <0.001 | 5.96 | 2.84–12.47 | <0.001 |
| ≥30 | 9/28(32.1) | 7.28 | 2.68–19.79 | <0.001 | 4.19 | 1.41–12.45 | 0.01 |
| Trend test | | <0.001 | | | <0.001 | | |

**Notes**: †Univariate model. ‡Adjusted for age, pre-pregnancy hemoglobin levels, pre-pregnancy systolic blood pressure, pre-pregnancy diastolic blood pressure, smoking exposure, family history of diabetes, alcohol consumption.

**Table 4** Association of Pre-Pregnancy BMI with GDM Risk Based on Different Pre-Pregnancy Hemoglobin Levels

| Variables | | GDM/ Total (%) | Model 1† | | | Model 2‡ | | |
|---|---|---|---|---|---|---|---|---|
| | | | OR | 95% CI | P | OR | 95% CI | P |
| Pre-pregnancy hemoglobin level (g/L)<123 | Pre-pregnancy BMI (kg/m$^2$) | | | | | | | |
| | <18.5 | 5/102(4.9) | | | Reference | | Reference | |
| | 18.5–24.9 | 41/411(9.9) | 2.15 | 0.83–5.58 | 0.116 | 2.13 | 0.82–5.55 | 0.123 |
| | 25.0–29.9 | 14/46(30.4) | 8.49 | 2.84–25.41 | <0.001 | 9.28 | 3.01–28.6 | <0.001 |
| | ≥30 | 1/10(10) | 2.16 | 0.23–20.51 | 0.504 | 2.09 | 0.21–20.65 | 0.530 |
| Pre-pregnancy hemoglobin level (g/L)≥123 | Pre-pregnancy BMI (kg/m$^2$) | | | | | | | |
| | <18.5 | 6/78(7.7) | | | Reference | | Reference | |
| | 18.5–24.9 | 79/533(14.8) | 2.09 | 0.88–4.95 | 0.960 | 2.04 | 0.84–4.99 | 0.117 |
| | 25.0–29.9 | 33/91(36.3) | 6.83 | 2.68–17.41 | <0.001 | 7.06 | 2.66–18.61 | <0.001 |
| | ≥30 | 8/180(44) | 9.60 | 2.76–33.45 | <0.001 | 10.77 | 2.85–40.63 | <0.001 |

**Notes**: †Univariate model. ‡Adjusted for age, pre-pregnancy systolic blood pressure, pre-pregnancy diastolic blood pressure, smoking exposure, family history of diabetes, alcohol consumption.

Figure 2A and B. The restricted cubic splines regression model revealed that higher levels of pre-pregnancy BMI were associated with an increased risk of GDM, especially when pre-pregnancy Hb level was ≥123 g/L.

## Discussion

In this study, we analyzed the relation between pre-pregnancy Hb and GDM risk and the association of pre-pregnancy BMI with GDM risk at different pre-pregnancy hemoglobin levels. Our data showed that pre-pregnancy Hb had an increasing tendency in GDM risk. More importantly, pre-pregnancy BMI had increased risk of developing GDM when pre-pregnancy Hb level was ≥123 g/L as compared with <123 g/L.

Some previous observational studies revealed that high Hb levels during pregnancy were related to a higher prevalence of GDM,[4,6,14] and that pregnant women with a Hb level ≥ 110 g/L in the first trimester and iron supplement in the second trimester had at least 1.53-fold odds of developing GDM.[6] A longitudinal study reported that pregnant women with Hb level> 108 g/L at gestational age of <14 weeks were at a higher risk of developing GDM in a Sudanese cohort. A Chinese retrospective study reported the similar result, saying that pregnant women with Hb level ≥150 g/L had 2.063-fold odds of developing GDM as compared with those with Hb level <110 g/L.[4] Although these data showed that high Hb concentrations during pregnancy were associated with increased odds of gestational diabetes, few studies had investigated the impact of pre-pregnancy Hb levels on the risk of GDM. Our result was similar to that reported by a large population-based cohort study,[15] which demonstrated that pre-pregnancy Hb levels ≥130 g/L was an independent risk

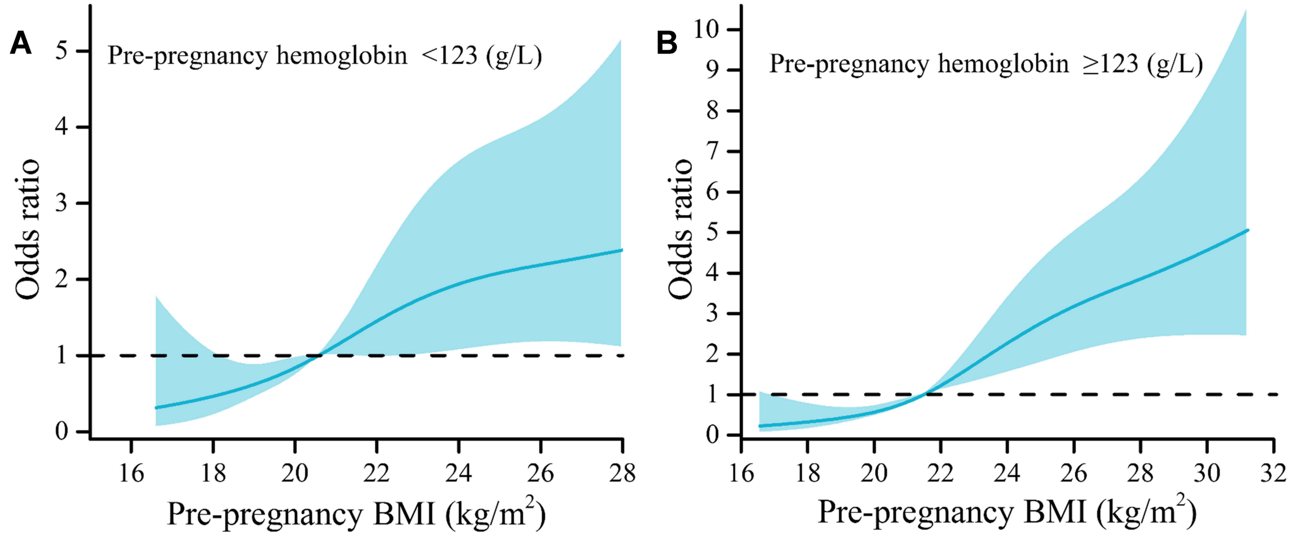


**Figure 2** The association of pre-pregnancy BMI with GDM risk based on different pre-pregnancy Hb levels.
**Notes**: RCS regression analysis of pre-pregnancy BMI with GDM risk through stratified analyses modified by pre-pregnancy hemoglobin levels < 123 g/L (**A**) and ≥ 123 g/L (**B**). The lines indicate estimated ORs, and the light blue areas represent 95% CI.

factor of GDM. They also found that pregnant women with pre-pregnancy Hb levels ≥130 g/L were associated with the need for insulin therapy during pregnancy. The aim of our study was not only to clarify the association between pre-pregnancy Hb levels alone with GDM but further explore the impact of pre-pregnancy BMI on this association. As shown in Tables 2 and 3, change in pre-pregnancy BMI had higher fold odds of GDM than change in pre-pregnancy Hb.

Overweight and obesity are generally accepted as major risk factors contributing to GDM.[16–19] Maternal pregnancy BMI is associated with the risk of GDM regardless of singleton or twin gestations.[20] A multicenter cohort study showed that overweight and obese pregnant women had at least twofold odds of developing GDM compared with nonobese women.[21] Furthermore, pre-pregnancy overweight is not only a risk factor of GDM but a greater risk for postpartum abnormal glucose tolerance compared with those with normal pre-pregnancy BMI.[22–24] Therefore, it is reasonable to suggest that pregnant women should do appropriate physical exercise and control diet during pregnancy to gain a reasonable gestational weight.[25] Some studies also have proved that gestational weight gain is a significantly independent risk factor for GDM.[26,27] However, it is often hard for obese women to change the incidence of GDM by controlling gestational weight gain.[28] Thus, how to reach an optimal weight before pregnancy is very important.

Unlike previous studies,[29,30] the present study not only investigated the association between pre-pregnancy BMI and GDM but further evaluated this association based on different pre-pregnancy Hb levels. Our result suggests that it is reasonable to control pre-pregnancy BMI around 18.5–24.9 kg/m$^2$, no matter pre-pregnancy Hb level was <123 g/L or ≥123 g/L. However, obese pregnant women showed at least 10-fold odds of developing GDM compared with nonobese women when pre-pregnancy Hb level was ≥123 g/L, revealing that pre-pregnancy Hb level is a more important risk factor for developing GDM than previously expected.[21] Knowing that the high Hb level is a reflection of the physical nutrition status, it could explain why the incidence of GDM in obesity group was lower than that in overweight group. After all, the physical status might be in a relative weak nutrition status at pre-pregnancy Hb level <123 g/L. Additionally, previous study had demonstrated that iron deficiency anemia could reduce the incidence of GDM, and the main reason may also be correlated with the weak nutrition status.[8] So, it seems that exploring the impact of pre-pregnancy BMI on GDM based on different pre-pregnancy Hb levels is more important than pre-pregnancy BMI alone or pre-pregnancy Hb level alone.

The biological mechanism underlying the association between pre-pregnancy high Hb level and increased GDM risk has not been defined. The main potential mechanism is that excess iron might disturb glucose homeostasis.[31–33] By and large, high Hb levels reflect high-level iron stores, which may generate reactive oxygen species (ROS) such as protein carbonyls, AGEs, Ox-LDL and malondialdehyde,[34] which could lead to oxidative stress, consequently resulting β-cell damage and apoptosis.[35] Furthermore, high-level iron stores may cause abnormal uptake or disposal of glucose in liver cells and muscles.[36–39]

Our study has some limitations. First, the pre-pregnancy HB level was obtained from a single spot and screened within 3 months before the last menstrual period, which may not precisely reflect the true pre-pregnancy Hb level. Second, China has a large population, and more data obtained from multiple centers are required to verify our findings and conclusions. Third, although we controlled for a series of most likely confounding variables, including age, pre-pregnancy SBP and DBP, smoking exposure, family history of diabetes, and alcohol consumption in the multiple regression analysis, some residual confounding cannot be ruled out, including physical activities and diets. Finally, we could not assess iron supplementations and dietary iron intake during pregnancy, especially in the first trimester.

## Conclusions

In this retrospective cohort study, we found a strong positive association between pre-pregnancy Hb and increased risk of GDM, and that pre-pregnancy BMI had higher risk of GDM when pre-pregnancy Hb level was ≥123 g/L as compared with <123 g/L. More investigations are required to verify our findings and conclusions. In addition, more studies are required to evaluate potential mechanisms that may be responsible for the association between pre-pregnancy Hb and GDM.

## Abbreviations

GDM, Gestational diabetes mellitus; BMI, body mass index; Hb, hemoglobin.

## Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

## Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Shanghai Pudong Hospital with the code (WZ-14).

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors have nothing to declare for this work.

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