

# Older Underweight Pregnant Women Beat Young Overweight/Obese Ones on Incidence of Gestational Diabetes

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**Objective:** This study aimed to compare the incidence of gestational diabetes mellitus (GDM) in older underweight pregnant women vs young overweight/obese ones.

**Methods:** A multiracial retrospective-cohort study was conducted in five hospitals of Shanghai on 7,485 women who had been pregnant during 2018–2020. Incidence of GDM was equal to the proportion of GDM cases in the total number of cases observed in the same period. Comparison of GDM incidence of older underweight pregnant women and young overweight/obese ones was done with  $\chi^2$  tests. ORs and 95% CIs for GDM were estimated using univariate and multivariate logistic regression across gestation age and prepregnancy BMI.

**Results:** Advanced age (OR 1.09, 95% CI 1.072–1.11;  $P=0$ ) and higher BMI (OR 1.57, 95% CI 1.112–2.212;  $P=0.01$ ) were found to be risk factors of GDM. The incidence of 13.33% of older underweight pregnant women (age  $\geq 35$  years, BMI  $< 18.5$  kg/m<sup>2</sup>) developing GDM was lower than that of young overweight/obese ones (age  $\leq 24$  years, BMI  $\geq 24$  kg/m<sup>2</sup>). For those aged  $\geq 35$  years, it is advised that BMI be kept to  $< 18.5$  kg/m<sup>2</sup>. For those aged  $\leq 24$  years, BMI control should not exceed 24 kg/m<sup>2</sup>.

**Conclusion:** Older underweight (age  $\geq 35$  years, BMI  $< 18.5$  kg/m<sup>2</sup>) pregnant women beat young overweight/obese ones (age  $\leq 24$  years, BMI  $\geq 24$  kg/m<sup>2</sup>) on incidence of GDM. Factors influencing obesity/overweight in GDM were high maternal age, though being young is a promising protective factor for GDM and tolerance of BMI is promoted, but should be limited to certain ranges. Being older increased the chances of developing GDM, but those with lower BMI still had lower GDM incidence than younger pregnant women.

**Keywords:** gestational diabetes mellitus, GDM, prepregnancy body-mass index, pre-BMI, pregnancy outcome

## Introduction

Gestational diabetes mellitus (GDM), the most common pregnancy complication, is defined as any degree of glucose intolerance with onset or first recognition during pregnancy, regardless of the degree of hyperglycemia. GDM affects approximately 14% of pregnancies worldwide, which represents approximately 18 million births annually,<sup>1</sup> and this trend is getting even worse with the escalating obesity epidemic. Well-known risk factors of GDM include overweight and obesity, advanced maternal age, and a family history or any form of DM,<sup>2–5</sup> though the specific pathophysiology or mechanisms underlying GDM are poorly defined. An ocean of studies have been performed to explore or demonstrate risk factors of GDM, while few have focused on

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looking for protective or counteractive factors can neutralize risk. Since advanced maternal age and obesity subsidize the process of GDM, being underweight and young press the development of GDM, what kind of BMI complicated with advanced pregnant women would offset the unfavorable impact of advanced age remains obscure, the same as maternal BMI. This article compares the incidence of GDM of older underweight pregnant women vs young overweight/obese ones and explore upper BMI limits in young pregnant women and BMI ranges that can counteract the adverse effect of advanced age.

## Methods

### Ethics

This multiracial retrospective-cohort study was conducted in five hospitals in Shanghai: Shanghai General Hospital, Shanghai Changning District Maternal and Child Health Care Hospital, Shanghai Jiading District Maternal and Child Health Care Hospital, Shanghai First Maternal and Infant Health Hospital, and the International Peace Maternal and Child Health Center.

The study was approved by the ethics boards of these hospitals and conducted in accordance with the Declaration of Helsinki, and participants provided written informed consent. The trial was registered with Chinese Clinical Trial Registry (ChiCTR2000036575).

### Diagnosis of GDM

GDM was diagnosed based on the International Association of Diabetes and Pregnancy Study Groups criteria.<sup>6</sup> Women not previously diagnosed with DM undergo a 75g oral glucose-tolerance test (OGTT) at 24–28 weeks of gestation, and plasma-glucose measurement was taken after the patient has fasted for 1 and 2 hours. The OGTT should be performed in the morning after an overnight fast of at least 8 hours. Diagnosis of GDM is made when any of the following plasma-glucose values are met or exceeded: fasting blood glucose (FBG) 92 mg/dL (5.1 mmol/L), and BG at 1 hour (BG<sub>1h</sub>) 180 mg/dL (10 mmol/L) and 2 hours (BG<sub>2h</sub>) 153 mg/dL (8.5 mmol/L).

### Study Population

The data came from the clinical cards of pregnant women who had attended antenatal clinics and delivered in the aforementioned hospitals. The information on these cards comprises but is not limited to age, height, gravida, parity, prepregnancy weight, weight at different gestational stages,

chronic disease complications, gestational complications, and previous GDM diagnosis. Prepregnancy body-mass index (pre-BMI) was divided into three groups: underweight (BMI <18.5 kg/m<sup>2</sup>), normal weight (BMI 18.5–23.9 kg/m<sup>2</sup>), and overweight or obese (BMI ≥24 kg/m<sup>2</sup>). Age was categorized into four groups: ≤24 years old, 25–29 years old, 30–34 years old, and ≥35 years old.

Eligibility criteria were singleton pregnancy, regular antenatal checkups during pregnancy, and complete medical history. Exclusion criteria were DM diagnosed before pregnancy, history of GDM or macrosomia delivery, complications with gestational hypertension, preeclampsia, or any other chronic diseases, and gestational weight gain<sup>7</sup> insufficient or excessive (<5 kg or >18 kg).

Based on these criteria, 7,485 women attending antenatal clinics were enrolled, of which 1,111 had been diagnosed with GDM, accounting for 14.84% of the whole group. Those aged 25–29 years with BMI 18.5–23.9 kg/m<sup>2</sup> were used as the reference group.

### Statistical Analysis

Data normality was evaluated using the skewness–kurtosis test. Binary outcomes are presented as relative risks with 95% CIs. Age, height, weight, BMI, FBG, BG<sub>1h</sub>, and BG<sub>2h</sub> were regarded as continuous variables, while times of gravida, parity, and complications with first family history were taken as categorical variables. Continuous variables were analyzed by means of ANOVA, and are expressed as means ± if they were normally distributed and as means of nonparametric tests if their distribution was abnormal. Age, height, weight, BMI, FBG, BG<sub>1h</sub>, and BG<sub>2h</sub> were distributed normally. The incidence of GDM was equal to the proportion of GDM cases in the total number of cases observed in the same period.  $\chi^2$  tests were used to compare disordered categorical variables between and among groups. ORs and 95% CIs for GDM were estimated using univariate and multivariate logistic regression, and confounders included gravida, parity, gestational age at OGTT examination, and maternal family history of DM and hypertension. Statistical significance was regarded as  $P < 0.05$ .

## Results

### Characteristics of Participants

Baseline characteristics for each group are outlined in Table 1. There were 7,485 pregnant women enrolled in this study. There were 1,111 GDM cases (14.84%). As presented

**Table 1** Characteristics of those Studied

	Non-GDM (6,374)	GDM (1,111)	SUM	P
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	29.33±4.02	31.22±4.53	29.61±4.16	0**
Height (cm)	161.58±4.86	161.2±5	161.53±4.88	0.07
Weight (kg)	54.7±7.89	58.55±9.43	55.27±8.26	0.35
BMI (kg/m <sup>2</sup> )	20.93±2.74	22.52±3.43	21.17±2.91	0.60
FBG (mmol/L)	4.48±0.36	5.03±0.87	4.56±0.51	0.75
BG <sub>1h</sub> (mmol/L)	7.57±1.29	9.93±2.04	7.92±1.66	0**
BG <sub>2h</sub> (mmol/L)	6.55±1.06	8.53±2.02	6.84±1.43	0**
Gestational age when taking OGTT	25.22±1.42	25.25±1.78	25.24±1.63	0.74
Birth weight	3,324.607	3,337.866	3,326.483	0.35
Cesarean/vaginal delivery	2,804/3,568	586/527	3,390/4,095	0**
First family history	183/6,372	114/1,113	232/7,485	0**

**Notes:** Fasting and 1- and 2-hour blood glucose are OGTT results. \*\* $P<0.01$ .

**Abbreviations:** BMI, body mass index, GDM, gestational diabetes, FBG, fasting blood glucose.

in Table 1, those with GDM were older and heavier than those without. Pregnant women with GDM had higher rates of cesarean delivery and a family history of DM (Table 1).

## GDM Risk Factors

On bivariate logistic regression analyses, factors significantly increasing the risk of GDM were age, gravida, parity, height, prepregnancy weight, and BMI. On multivariate logistic regression analysis, only age (OR 1.09, 95% CI 1.072–1.11;  $P=0$ ) and BMI (OR 1.57, 95% CI 1.112–2.212;  $P=0.01$ ) reached statistical significance (Table 2).

Age was classified into four groups:  $\leq 24$ , 25–29, 30–34, and  $\geq 35$  years. Based on classification criteria for the Chinese population, BMI was stratified into three layers:  $<18.5$  kg/m<sup>2</sup>, 18.5–23.9 kg/m<sup>2</sup>, and  $\geq 24$  kg/m<sup>2</sup>. After permutation and combination of the two subgroups, the entire population was categorized into 12 groups, listed in Table 3.

Age 25–29 years and BMI 18.5–23.9 kg/m<sup>2</sup> were set as reference group. ORs for the other groups were then calculated. Age  $\geq 35$  years and BMI  $\geq 24$  kg/m<sup>2</sup> (OR 6.458, 95% CI 4.74–

8.798;  $P=0$ ) topped the list, age 30–34 years and BMI  $\geq 24$  kg/m<sup>2</sup> (OR 3.564, 95% CI 2.743–4.63;  $P=0$ ) was second, and then followed by the branch of age  $\geq 35$  years and BMI 18.5–23.9 kg/m<sup>2</sup> (OR 3.113, 95% CI 2.497–3.88;  $P=0$ ). Interestingly, older underweight pregnant beat young overweight ones in terms of chance of developing GDM, because the OR for age  $\geq 35$  years and BMI  $<18.5$  kg/m<sup>2</sup> was only 1.414 (95% CI 0.664–3.014,  $P=0.037$ ) while that for age  $\leq 24$  years and BMI  $\geq 24$  kg/m<sup>2</sup> was 3.009 (95% CI 1.737–5.212,  $P=0$ ; Table 4).

## Crossover Analysis of Age and BMI for Incidence of GDM

GDM incidence in each group was calculated (Table 5). The lowest incidence (3.85%) was unsurprisingly in the age  $\leq 24$  years and BMI  $<18.5$  kg/m<sup>2</sup> group, while the highest incidence (41.26%) was in the age  $\geq 35$  years and BMI  $\geq 24$  kg/m<sup>2</sup> group. The rate of GDM in the age  $\leq 24$  years and BMI  $\geq 24$  kg/m<sup>2</sup> group was 22.5% versus

**Table 2** Risk Factors of GDM

	P	OR	95% CI	Adjusted P	Adjusted OR	Adjusted 95% CI
Age**	0	1.11	1.097–1.13	0	1.09	1.072–1.11
Gravida	0	1.23	1.169–1.297	0.90	1.00	0.928–1.068
Para	0	1.59	1.423–1.773	0.06	1.17	1.015–1.35
Height	0.02	0.98	0.971–0.997	0.19	1.07	0.968–1.173
Weight	0	1.05	1.044–1.059	0.09	0.90	0.786–1.019
BMI**	0	1.18	1.157–1.204	0.01	1.57	1.112–2.212
First-degree DM history**	0	1.89	1.484–2.411	0	1.78	1.375–2.296

**Notes:** \*\* $P<0.01$ .

**Abbreviations:** BMI, body-mass index; GDM, gestational diabetes mellitus.

**Table 3** Variables Based on BMI and Age

	Age	Height (cm)	Weight (kg)	BMI (kg/m <sup>2</sup> )	FBG (mmol/L)	BG <sub>1h</sub> (mmol/L)	BG <sub>2h</sub> (mmol/L)
Age ≤24, BMI <18.5 (156)	22.65±1.49	161.98±4.73	46.03±3.44	17.53±0.83	4.49±0.45	7.31±1.67	6.45±1.35
Age ≤24, BMI ≤18.5–≤23.9 (405)	22.92±1.46	162.04±5.04	54.36±5.26	20.68±1.47	4.52±0.49	7.37±1.63	6.52±1.35
Age ≤24, BMI ≥24 (80)	22.73±1.73	162.82±6.16	71.23±7.86	26.84±2.24	4.71±0.56	8.05±1.86	6.58±1.79
Age ≤25–≤29, BMI <18.5 (623)	27.2±1.36	161.73±4.87	45.83±3.32	17.51±0.79	4.44±0.37	7.56±1.45	6.68±1.28
Age ≤25–≤29, BMI ≤18.5–≤23.9 (2,319)	27.33±1.33	161.73±4.8	54.37±5.02	20.76±1.43	4.52±0.48	7.71±1.55	6.71±1.30
Age ≤25–≤29, BMI ≥24 (414)	27.35±1.32	161.5±5.11	69.38±7.91	26.57±2.47	4.68±0.75	8.32±1.99	7.06±1.80
Age ≤30–≤34, BMI <18.5 (289)	30±0.56	161.27±4.62	45.93±3.11	17.65±0.68	4.47±0.39	7.62±1.39	6.65±1.43
Age ≤30–≤34, BMI ≤18.5–≤23.9 (1,870)	31.37±1.06	161.47±4.86	54.5±5	20.89±1.45	4.55±0.46	8±1.58	6.87±1.33
Age ≤30–≤34, BMI ≥24 (383)	33.89±0.31	160.95±5.08	68.5±7.43	26.42±2.33	4.71±0.60	8.71±1.81	7.26±1.60
Age ≥35, BMI <18.5 (60)	36.78±2.58	160.93±4.76	45.78±3.25	17.66±0.67	4.58±0.51	7.92±1.37	6.87±2.28
Age ≥35, BMI ≤18.5–≤23.9 (680)	37±2.04	160.99±4.59	55.03±4.97	21.21±1.48	4.59±0.51	8.34±1.64	7.14±1.53
Age ≥35, BMI ≥24 (206)	37.22±2.39	160.77±5.45	67.76±7.03	26.19±2.17	4.89±0.79	8.96±1.93	7.61±1.75

**Notes:** Fasting 1- and 2-hour blood glucose are OGTT results. Units of age and BMI are years and kg/m<sup>2</sup>, respectively.

**Abbreviations:** BMI, body-mass index, FBG, fasting blood glucose.

**Table 4** ORs of GDM

	Wald	P	OR	95% CI
Age ≤24, BMI <18.5	5.617	0.018	0.368	0.161–0.841
Age ≤24, BMI ≤18.5–≤23.9	3.368	0.046	0.683	0.454–1.026
Age ≤24, BMI ≥24	15.436	0	3.009	1.737–5.212
Age ≤30–≤34, BMI <18.5	1.914	0.017	0.720	0.453–1.146
Age ≤30–≤34, BMI ≤18.5–≤23.9	35.385	0	1.750	1.455–2.104
Age ≤30–≤34, BMI ≥24	90.573	0	3.564	2.743–4.63
Age ≥35, BMI <18.5	0.806	0.037	1.414	0.664–3.014
Age ≥35, BMI ≤18.5–≤23.9	101.953	0	3.113	2.497–3.88
Age ≥35, BMI ≥24	139.776	0	6.458	4.74–8.798
Age ≤25–≤29, BMI <18.5	4.388	0.036	0.699	0.499–0.977
Age ≤25–≤29, BMI ≥24	54.756	0	2.738	2.097–3.575
Age ≤25–≤29, BMI ≤18.5–≤23.9			1	

**Notes:** Units of age and BMI are years and kg/m<sup>2</sup>, respectively.

**Abbreviations:** GDM, gestational diabetes mellitus, BMI, body-mass index.

13.33% for the age ≥35 years and BMI <18.5 kg/m<sup>2</sup> group. GDM rates in those aged ≤24, 25–29, 30–34, and ≥35 years were 8.11%, 10.94%, 16.80%, and 28.01%, respectively. When comparing the incidence of GDM based on BMI category, 7% was observed for <18.5 kg/m<sup>2</sup>, while 13.78% and 28.16% were found for 18.5–23.9 kg/m<sup>2</sup> and ≥24.0 kg/m<sup>2</sup>, respectively (Table 5).

## Discussion

Advanced maternal age, overweight, and obesity are widely accepted risk factors of GDM.<sup>8,9</sup> In this study, advanced age and high BMI again proved to be risk factors

of GDM. Based on our data, GDM incidence in older underweight pregnant women (≥35 years old, BMI <18.5 kg/m<sup>2</sup>) was lower than young overweight ones (≤24 years old, BMI ≥24 kg/m<sup>2</sup>).

To support the needs of a growing fetus, a mother's body undergoes a series of physiological changes during a healthy pregnancy, of which insulin sensitivity changes over the course of gestation. During the first trimester, insulin sensitivity increases, promoting glucose entry into adipose cells with the purpose of conserving energy for later stages of pregnancy.<sup>10</sup> However, as the pregnancy progresses, ever-growing levels of hormones, including human placental lactogen (also known as chorionmammotropin) and placental growth hormone mediated by placenta,<sup>11</sup> are released into the circulation and consequently insulin resistance is promoted. Mildly elevated BG is transported across the placenta to fuel the growth of the fetus, and this slightly elevated state of insulin resistance also stimulates endogenous glucose production and the breakdown of fat stores, inducing a further increase in BG and free fatty-acid concentrations. Increased glucose-stimulated insulin secretion and hypertrophy and hyperplasia of pancreatic β-cells tend to maintain glucose homeostasis and make up for these unfavorable changes.<sup>12</sup>

Numerous studies have suggested that women who develop GDM have evidence of metabolic dysfunction before conception, including pancreatic β-cell defects and increased insulin resistance.<sup>13</sup> Most women who develop GDM are overweight/obese or older, which are related to

**Table 5** GDM by group

Age ≤24	BMI <18.5	BMI ≤18.5–≤23.9	BMI ≥24	Sum
GDM	6	28	18	52
Non-GDM	150	377	62	589
Sum	156	405	80	641
GDM incidence	3.85%	6.91%	22.50%	8.11%
Age ≤25–≤29	BMI <18.5	BMI ≤18.5–≤23.9	BMI ≥24	Sum
GDM	44	228	95	367
Non-GDM	579	2,091	319	2,989
Sum	623	2,319	414	3,356
GDM incidence	7.06%	9.83%	22.95%	10.94%
Age ≤30–≤34	BMI <18.5	BMI ≤18.5–≤23.9	BMI ≥24	Sum
GDM	21	299	107	427
Non-GDM	268	1571	276	2115
Sum	289	1870	383	2542
GDM incidence	7.27%	15.99%	27.94%	16.80%
Age ≥35	BMI <18.5	BMI ≤18.5–≤23.9	BMI ≥24	Sum
GDM	8	172	85	265
Non-GDM	52	508	121	681
Sum	60	680	206	946
GDM incidence	13.33%	25.29%	41.26%	28.01%
GDM	79	727	305	1,111
Non-GDM	1,049	4,547	778	6,374
Sum	1,128	5,274	1,083	7,485
GDM incidence	7.00%	13.78%	28.16%	14.84%

**Notes:** Units of age and BMI are years old and kg/m<sup>2</sup>, respectively. GDM incidence is equal to GDM/sum.

**Abbreviations:** GDM, gestational diabetes mellitus, BMI, body-mass index.

inflammatory status.<sup>14</sup> The progress of pregnancy and associated metabolic changes (increased insulin resistance and demand for increased  $\beta$ -cell response) causes insulin to be less effective in suppressing endogenous glucose production and glucose uptake, and thus can lead to clinical hyperglycemia.<sup>13</sup>

Obesity is a proinflammatory state in which both hypertrophic adipocytes and immune cells (mainly lymphocytes and macrophages) in adipose tissue introduce increased circulating levels of proinflammatory cytokines.

Obesity-related chronic low-grade systemic inflammation, known as “metabolic inflammation”, is considered the focus of insulin resistance and the pathogenesis of DM in humans and rodent models.<sup>15,16</sup>

Laine et al<sup>17</sup> assessed the effects of age and obesity on GDM in primiparous pregnant women, and found that the risk of GDM increased with maternal age after adjusting for pre-BMI and number of previous pregnancies. An almost universal finding of the risk of GDM increasing linearly with age has been reported in the literature, although the degree of GDM risk varies from study to study. The exact mechanism of the association between maternal age and GDM has not been clearly proven, and high levels of insulin resistance, circulating adipokines, and inflammatory markers and oxidative stress may partially explain this phenomenon.<sup>18,19</sup>

## Conclusion

This study is the first in China to compare the incidence of GDM in older underweight pregnant women vs young overweight/obese ones, and was inspired by the doubt of pregnant women at clinic. These ladies are just curious about the incidence of GDM they will be diagnosed and they compared with the others'. Our data indicated that the influence of obesity/overweight was higher than advanced maternal age, resulting in the rate of GDM in older underweight pregnant women being lower than young overweight/obese ones, which is logical yet new information, as no such research has been conducted before. The final results warn us there should be limitations to the upper BMI range in young expectant mothers for the purpose of avoiding GDM, and also shed light on lowering the chance of GDM in advanced pregnancies.

Limitations of this study include prepregnancy weight being self-reported and all the data coming from five hospitals; therefore, there may exist information bias regarding the original data. It is well known that GDM is influenced by multitudinous factors. Our research focused on the main two factors, but other characteristics were excluded, which is a little one-sided. The data were divided only into GDM and non-GDM, and GDM severity and treatment was not stratified further. The number of women whose BMI indicated obesity or overweight was limited and those of advanced age were rare, so the layers of age and BMI were a little bit rough. We expect to enroll more patients in the near future to perform further deeper research.



## Data Sharing Statement

The data sets used and/or analyzed in this current study are available from the corresponding authors on reasonable request.

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, agreed to submit to the current journal, gave final approval to the version to be published, and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest.

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