BMC Pregnancy and Childbirth

RESEARCH

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Fasting or 2-hour postprandial plasma glycemic criteria for gestational diabetes mellitus are aassociated with distinct adverse outcomes

Qifa Song[1†], Xuejing Song[2†], Li Li[3] and Huiqing Ding[2*]

Abstract

Objective We aimed to evaluate the heterogeneity of gestational diabetes mellitus (GDM) patients diagnosed with various screening criteria.

Methods We stratified pregnant women using consecutive fasting plasma glucose (FPG) and 2-hour postprandial plasma glucose (2hPPG) intervals of 0.2 mmol/L. The incidence of abnormal neonatal birthweight and birth-related adverse outcomes was compared with that of pregnant women without GDM.

Results The study included 39,988 pregnant women (18–45 years, mean [SD], 31.5 [4.7] years) in Ningbo, China. The means (SDs) of FPG and 2hPPG within 24–28 weeks of gestation were 4.5 (0.5) and 6.8 (1.3) mmol/L, respectively. A total of 3025 (7.6%) women had 5.1–6.9 mmol/L FPG and 4560 (11.4%) had 8.5–11.0 mmol/L 2hPPG. The incidence of GDM according to the two combination criteria was 17.3% (6908 cases). The relative risk (RR) for < 10th percentile birthweight (< 10th WT) was 0.82 (95% CI, 0.74–0.91, $p < 0.001$) by 5.1 mmol/L FPG criterion and 1.14 (95% CI, 1.06–1.23, $p < 0.001$) by 8.5 mmol/L 2hPPG criterion, while the RRs for > 90th percentile birthweight (> 90th WT) were 1.48 (95% CI, 1.35–1.63, $p < 0.001$) and 0.95 (95% CI, 0.86–1.04, $p = 0.29$) according to the corresponding criteria. The FPG criterion was more strongly associated with maternal hypertension than the 2hPPG criterion. Both criteria did not show a distinct association with other composite adverse outcomes.

Conclusion High FPG is significantly associated with high birth weight, whereas high 2hPPG is slightly associated with low birth weight. Our findings highlight the heterogeneity of patients with GDM diagnosed by different criteria.

Keywords Gestational diabetes mellitus (GDM), Birth weight percentile, Fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2hPPG), Oral glucose tolerance test (OGTT)

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Introduction

Gestational diabetes mellitus (GDM) refers to glucose intolerance with onset or first recognition during pregnancy [1]. GDM is considered a risk factor for multiple short- and long-term adverse outcomes that affect both mothers and newborns, including increased birthweight, gestational hypertension, stillbirth and neonatal death, and future cardiometabolic disease in mothers and offspring [2, 3]. GDM is typically diagnosed at 24–28 weeks of gestation and affects 6–25% of pregnant women according to differential diagnostic criteria [4]. However, there is no scientific consensus for the preferred screening strategy or diagnostic glycemic thresholds for early GDM, as illustrated by several versions of diagnostic criteria that depend on fasting glucose (FPG), 1-hour, 2-hour, and 3-hour glucose levels from the oral glucose tolerance test (OGTT). [5] The decision to adopt the lower or higher glycemic criterion is also controversial [6]. The lower criterion adopts FPG of ≥5.1 mmol/L or 2-hour glucose of ≥8.5 mmol/L, [7, 8] whereas the higher criterion adopts an FPG of ≥5.8 mmol/L or 2-hour glucose of ≥9.2 mmol/L [9]. Consequently, inconsistent diagnostic criteria for GDM lead to a varied incidence of GDM as reported and make international comparisons difficult [10].

Given that various incidences of women with GDM were found using different GDM criteria, we hypothesized that the inconsistent incidence implied heterogeneity in GDM. Our study aimed to investigate the incremental impact of increasingly abnormal glucose levels on maternal and neonatal adverse outcomes via FPG and 2-hour postprandial plasma glucose (2hPPG) criteria, which would address the changing impact of various glucose levels on adverse gestational outcomes, as well as the most clinically relevant cut-off points for plasma glucose levels for the screening of GDM.

Materials and methods

Study design and participants

This was a population-based retrospective study involving pregnant women aged 18–45 years with at least one hospital birth in Ningbo, China, from 1 January 2016 to 31 December 2022. This study included patients from Level 2 and Level 3 hospitals that participated in the inter-laboratory quality parity to ensure the accuracy and consistency of blood glucose measurements. The study used 100% of pregnant women who underwent GDM screening using 75-g OGTT or FPG measurements within 24–28-week gestation in general hospitals, women's hospitals, and community health service centers. The exclusion criteria were a history of T1DM or T2DM, an FPG of >6.9, and a 2hPPG of >11 mmol/L. The data sets of mothers and their newborns were linked through unique identifiers that were deidentified to protect privacy. The data included OGTT or FPG measurements and clinical features. All the data were archived at the Ningbo Municipal Health Information Centre, Zhejiang Province, China. The statistician had access to anonymized data, whereas the coauthors had access to summarized data. The study complied with the Declaration of Helsinki.

Handling of plasma glucose levels

All measurements of glucose were obtained from venous plasma samples. We used FPG and 2hPPG from the OGTT as GDM screening criteria. The FPG screening criterion of 5.1–6.9 mmol/L was divided into 11 intervals of <5.1, 5.1–5.29, and up to ≥6.9 mmol/L with an interval of 0.2 mmol/L. The 2hPPG screening criterion of 8.5–10.9 mmol/L was divided into 14 intervals of <8.5, 8.5–8.69, and up to ≥10.9 mmol/L at an interval of 0.2 mmol/L. Consecutive intervals of two criteria were applied to stratify pregnant women. One measurement at the middle of the study period was chosen if there was more than one measurement of FPG and 2hPPG for each delivery of pregnant women. If the number of events in a subgroup was under three, we combined the two neighboring subgroups to ensure reliable statistical results.

GDM diagnosis, adverse outcomes, and insulin treatment

We diagnosed GDM according to the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria in 2013 on the basis of an FPG of 5.1–6.9 mmol/L and 2hPPG of 8.5–11.0 mmol/L [11]. We used the following adverse outcomes to evaluate the impact of different glucose levels: overweight status of newborns defined as >90th percentile birthweight (>90th WT); underweight status of newborns defined as <10th percentile birthweight (<10th WT); gestational preeclampsia and hypertension diagnosed during pregnancy; and a composite of multiple adverse outcomes of 1-min and 5-min Apgar scores below 8, neonatal death, intrauterine distress, labor dystocia, and birth trauma. The percentage of insulin treatment and the mean age of pregnant women were computed for each subgroup.

Statistical analysis

Categorical variables including the incidence of adverse outcomes and insulin use were expressed as percentages and 95% confidence interval (95% CI). Continuous variables including glucose level and age were expressed as mean and standard deviation (SD). We first examined the outliers for continuous variables by graphing and sorting the data. The erroneous and illogical values were removed. As a selection bias might exist among pregnant women who underwent OGTT, we created a reference population from the whole population without GDM according to both the FPG and 2hPPG criteria during

24–28 weeks of gestation. This reference population was used for all subgroups that were classified by both the FPG and 2hPPG criteria. The incidence of adverse outcomes among subgroups classified by consecutive glucose levels was compared with that of the reference population to obtain the relative risk (RR). Since older age was an important confounding factor in the incidence of GDM, we performed multiple logistical regression using binary abnormal neonatal weights as outcomes, glucose levels as factors, and age as a covariate to assess the confounding effect of age. Statistical analysis was performed using R (version 4.3) with a two-tailed type 1 error rate of $p<0.05$ indicating statistical significance.

Results

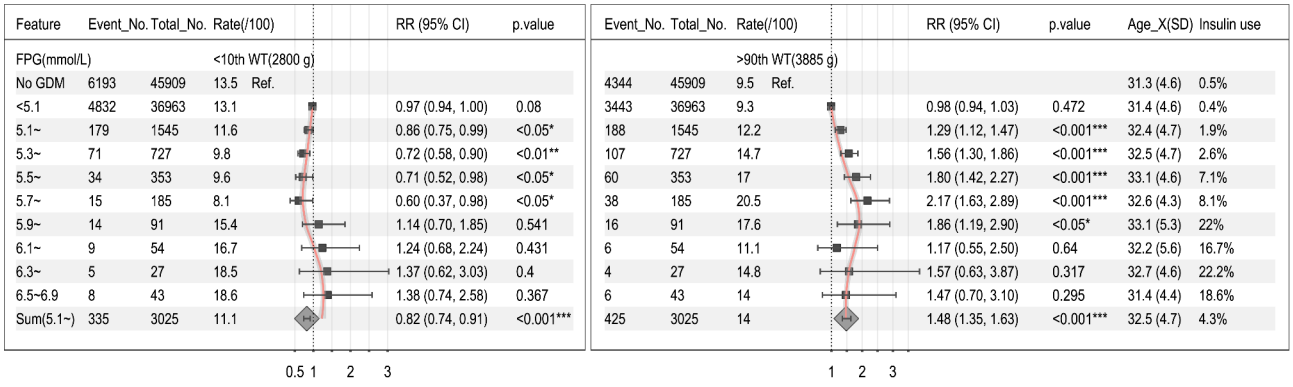
The present study included 67,369 pregnant women (aged 18–45 years; mean [SD], 31.6 [4.7] years) who had at least one measurement of FPG or 2hPPG during 24–28 weeks of gestation through a search of the local medical electronic record data. The mean (SD) birth weight was 3322 (447) g. The cut-off values for the <10th WT and >90th WT were 2800 g and 3885 g, respectively. We used these cut-off values as the threshold values to identify abnormal birth weights. Among the 67,369 women, 45,909 had<5.1 mmol/L FPG and/or <8.5 mmol/L 2hPPG and were designated the reference population without GDM (Fig. 1).

Moreover, 39,988 (age: mean [SD], 31.5 [4.7] years) women had both FPG (mean (SD), 4.5 [0.5] mmol/L) and 2hPPG (mean (SD), 6.8 [1.3] mmol/L) measurements, which were designated the study population and classified by two glucose levels to investigate the incidence of adverse gestational outcomes. Among these 39,988 women, 3025 (7.6%) had 5.1–6.9 mmol/L FPG (Fig. 1A) and 4560 (11.4%) had 8.5–11.0 mmol/L 2hPPG (Fig. 1B). The incidence of GDM according to the two combination criteria was 17.3% (6908 cases).

The notable finding was the distinct effects on <10th WT and >90th WT between higher FPG and higher 2hPPG identified by two GDM criteria. Overall, women

A.

Feature	Event_No.	Total_No.	Rate(/100)	<10th WT(2800 g)	RR (95% CI)	p.value	Event_No.	Total_No.	Rate(/100)	>90th WT(3885 g)	RR (95% CI)	p.value	Age_X(SD)	Insulin use
FPG(mmol/L)														
No GDM	6193	45909	13.5	Ref.			4344	45909	9.5	Ref.			31.3 (4.6)	0.5%
<5.1	4832	36963	13.1		0.97 (0.94, 1.00)	0.08	3443	36963	9.3		0.98 (0.94, 1.03)	0.472	31.4 (4.6)	0.4%
5.1~	179	1545	11.6		0.86 (0.75, 0.99)	<0.05*	188	1545	12.2		1.29 (1.12, 1.47)	<0.001***	32.4 (4.7)	1.9%
5.3~	71	727	9.8		0.72 (0.58, 0.90)	<0.01**	107	727	14.7		1.56 (1.30, 1.86)	<0.001***	32.5 (4.7)	2.6%
5.5~	34	353	9.6		0.71 (0.52, 0.98)	<0.05*	60	353	17		1.80 (1.42, 2.27)	<0.001***	33.1 (4.6)	7.1%
5.7~	15	185	8.1		0.60 (0.37, 0.98)	<0.05*	38	185	20.5		2.17 (1.63, 2.89)	<0.001***	32.6 (4.3)	8.1%
5.9~	14	91	15.4		1.14 (0.70, 1.85)	0.541	16	91	17.6		1.86 (1.19, 2.90)	<0.05*	33.1 (5.3)	22%
6.1~	9	54	16.7		1.24 (0.68, 2.24)	0.431	6	54	11.1		1.17 (0.55, 2.50)	0.64	32.2 (5.6)	16.7%
6.3~	5	27	18.5		1.37 (0.62, 3.03)	0.4	4	27	14.8		1.57 (0.63, 3.87)	0.317	32.7 (4.6)	22.2%
6.5~6.9	8	43	18.6		1.38 (0.74, 2.58)	0.367	6	43	14		1.47 (0.70, 3.10)	0.295	31.4 (4.4)	18.6%
Sum(5.1~)	335	3025	11.1		0.82 (0.74, 0.91)	<0.001***	425	3025	14		1.48 (1.35, 1.63)	<0.001***	32.5 (4.7)	4.3%



B.

Feature	Event_No.	Total_No.	Rate(/100)	<10th WT(2800 g)	RR (95% CI)	p.value	Event_No.	Total_No.	Rate(/100)	>90th WT(3885 g)	RR (95% CI)	p.value	Age_X(SD)	Insulin use
2hPPG(mmol/L)														
No GDM	6193	45909	13.5	Ref.			4344	45909	9.5	Ref.			31.3 (4.6)	0.5%
<8.5	4464	35428	12.6		0.93 (0.90, 0.97)	<0.001***	3459	35428	9.8		1.03 (0.99, 1.08)	0.15	31.3 (4.6)	0.5%
8.5~	137	860	15.9		1.18 (1.01, 1.38)	<0.05*	62	860	7.2		0.76 (0.60, 0.97)	<0.05*	33.3 (4.5)	1.6%
8.7~	99	761	13		0.96 (0.80, 1.16)	0.748	65	761	8.5		0.90 (0.71, 1.14)	0.417	32.9 (4.5)	1.3%
8.9~	103	611	16.9		1.25 (1.05, 1.49)	<0.05*	59	611	9.7		1.02 (0.80, 1.30)	0.835	33.1 (4.4)	1%
9.1~	71	479	14.8		1.10 (0.89, 1.36)	0.383	62	479	12.9		1.37 (1.08, 1.73)	<0.05*	33.3 (4.4)	2.3%
9.3~	63	434	14.5		1.08 (0.86, 1.35)	0.525	46	434	10.6		1.12 (0.85, 1.47)	0.41	33.3 (4.5)	1.4%
9.5~	48	334	14.4		1.07 (0.82, 1.39)	0.63	17	334	5.1		0.54 (0.34, 0.86)	<0.01**	33.4 (4.6)	2.1%
9.7~	50	302	16.6		1.23 (0.95, 1.58)	0.128	25	302	8.3		0.87 (0.60, 1.27)	0.554	33.5 (4.4)	3%
9.9~	45	217	20.7		1.54 (1.18, 2.00)	<0.01**	15	217	6.9		0.73 (0.45, 1.19)	0.244	33.6 (4.4)	1.8%
10.1~	30	176	17		1.26 (0.91, 1.75)	0.184	19	176	10.8		1.14 (0.75, 1.75)	0.519	33.7 (4.8)	2.8%
10.3~	18	125	14.4		1.07 (0.70, 1.64)	0.793	12	125	9.6		1.01 (0.59, 1.74)	0.879	33.2 (4.5)	4%
10.5~	20	109	18.3		1.36 (0.91, 2.02)	0.158	13	109	11.9		1.26 (0.76, 2.10)	0.41	33.5 (4.9)	5.5%
10.7~11	19	152	12.5		0.93 (0.61, 1.41)	0.812	14	152	9.2		0.97 (0.59, 1.60)	1	33.9 (4.7)	4.6%
Sum(8.5~)	703	4560	15.4		1.14 (1.06, 1.23)	<0.001***	409	4560	9		0.95 (0.86, 1.04)	0.288	33.3 (4.5)	2%

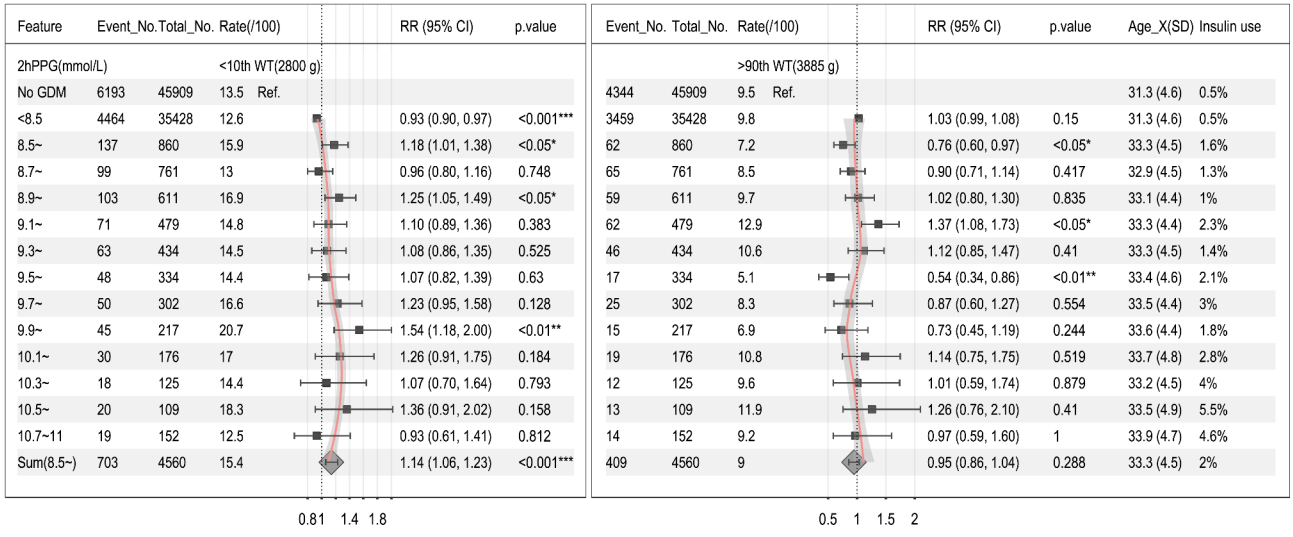


Fig. 1 Associations of consecutive intervals of FPG (**A**) and 2hPPG (**B**) with < 10th WT and > 90th WT. Note: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$. 5.1~: indicates FPG from 5.1 mmol/L to the beginning level (not included) of the next subgroup

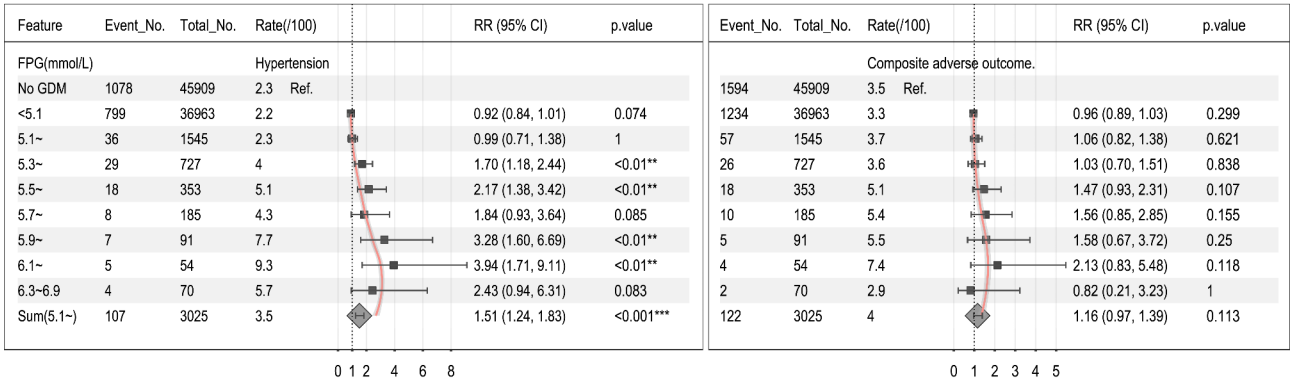
with 5.1–6.9 mmol/L FPG were associated with a lower risk of <10th WT (RR, 0.82; 95% CI, 0.74–0.91; $p<0.001$) and with an increased risk of >90th WT (RR, 1.48; 95% CI, 1.35–1.63; $p<0.001$) (Fig. 1A). In contrast, women with 8.5–11.0 mmol/L 2hPPG were associated with an increased risk of <10th WT (RR, 1.14; 95% CI, 1.06–1.23; $p<0.001$) and with no increased risk of >90th WT (RR, 0.95; 95% CI, 0.86–1.04; $p=0.29$) (Fig. 1B). On the basis of the RRs obtained by the consecutive intervals of glucose measurements, we found several remarkable findings. There was a rapid increase in the RRs (from 1.29 to 2.17) of the >90th WT from 5.1 to 5.9 mmol/L FPG intervals, and the RRs remained high (Fig. 1A). Our study clearly revealed an increasing trend in insulin use by the categorization of FPG levels, increasing from the lowest 0.4% below 5.1 mmol/L FPG to the highest 22.2% at 6.3 ~ mmol/L FPG (Fig. 1A). In contrast, the trend in insulin use among subgroups by 2hPPG was not as significant (Fig. 1B).

Figures 2 and 3 show the differential associations of the two GDM criteria with maternal hypertension and several other adverse outcomes. Among the study population of 39,988 women, 906 (2.3%) cases had hypertension and 1356 (3.4%) cases of composite adverse outcomes (Fig. 2A). Compared with the non-GDM reference population, 5.1–6.9 mmol/L FPG was much more strongly associated with an increased risk of hypertension (RR, 1.51; 95% CI, 1.24–1.83; $p<0.001$) (Fig. 2A) than was 8.5–11.0 mmol/L 2hPPG (RR, 1.04; 95% CI, 0.85–1.26; $p=0.72$) (Fig. 2B). Further analysis revealed that most FPG levels (6 levels >5.2 mmol/L) were strongly associated with hypertension (RR, 1.7 to 3.94) (Fig. 2A), whereas only two levels of 2hPPG (>10.5 mmol/L) had an evident association (RR, 1.56 and 1.68) with hypertension (Fig. 2B). With respect to the composite adverse outcomes, 5.1–6.9 mmol/L FPG slightly increased this risk (RR, 1.16; 95% CI, 0.97–1.39; $p=0.11$) (Fig. 2A), and the same was true for the 8.5–11.0 mmol/L 2hPPG (RR, 1.04; 95% CI, 0.89–1.22; $p=0.61$) (Fig. 2B).

Among the 1356 patient with composite adverse outcomes, 605 (1.5%) had 1-min and 5-min Apgar below 8 scores, 425 (1.1%) had breech presentations, 85 (0.2%)

A.

Feature	Event_No.	Total_No.	Rate(/100)	RR (95% CI)	p.value	Event_No.	Total_No.	Rate(/100)	RR (95% CI)	p.value
FPG(mmol/L)			Hypertension					Composite adverse outcome.		
No GDM	1078	45909	2.3 Ref.			1594	45909	3.5 Ref.		
<5.1	799	36963	2.2	0.92 (0.84, 1.01)	0.074	1234	36963	3.3	0.96 (0.89, 1.03)	0.299
5.1~	36	1545	2.3	0.99 (0.71, 1.38)	1	57	1545	3.7	1.06 (0.82, 1.38)	0.621
5.3~	29	727	4	1.70 (1.18, 2.44)	<0.01**	26	727	3.6	1.03 (0.70, 1.51)	0.838
5.5~	18	353	5.1	2.17 (1.38, 3.42)	<0.01**	18	353	5.1	1.47 (0.93, 2.31)	0.107
5.7~	8	185	4.3	1.84 (0.93, 3.64)	0.085	10	185	5.4	1.56 (0.85, 2.85)	0.155
5.9~	7	91	7.7	3.28 (1.60, 6.69)	<0.01**	5	91	5.5	1.58 (0.67, 3.72)	0.25
6.1~	5	54	9.3	3.94 (1.71, 9.11)	<0.01**	4	54	7.4	2.13 (0.83, 5.48)	0.118
6.3~6.9	4	70	5.7	2.43 (0.94, 6.31)	0.083	2	70	2.9	0.82 (0.21, 3.23)	1
Sum(5.1~)	107	3025	3.5	1.51 (1.24, 1.83)	<0.001***	122	3025	4	1.16 (0.97, 1.39)	0.113



B.

Feature	Event_No.	Total_No.	Rate(/100)	RR (95% CI)	p.value	Event_No.	Total_No.	Rate(/100)	RR (95% CI)	p.value
2hPPG(mmol/L)			Hypertension					Composite adverse outcome.		
No GDM	1078	45909	2.3 Ref.			1594	45909	3.5 Ref.		
<8.5	795	35428	2.2	0.96 (0.87, 1.05)	0.334	1191	35428	3.4	0.97 (0.90, 1.04)	0.392
8.5~	20	860	2.3	0.99 (0.64, 1.53)	1	33	860	3.8	1.11 (0.79, 1.55)	0.572
8.7~	18	761	2.4	1.01 (0.64, 1.60)	0.904	22	761	2.9	0.83 (0.55, 1.26)	0.483
8.9~	15	611	2.5	1.05 (0.63, 1.73)	0.788	20	611	3.3	0.94 (0.61, 1.45)	0.911
9.1~	10	479	2.1	0.89 (0.48, 1.65)	0.879	21	479	4.4	1.26 (0.83, 1.92)	0.26
9.3~	8	434	1.8	0.79 (0.39, 1.56)	0.631	10	434	2.3	0.66 (0.36, 1.23)	0.233
9.5~	10	334	3	1.28 (0.69, 2.35)	0.464	10	334	3	0.86 (0.47, 1.59)	0.764
9.7~	7	302	2.3	0.99 (0.47, 2.06)	1	13	302	4.3	1.24 (0.73, 2.11)	0.428
9.9~	5	217	2.3	0.98 (0.41, 2.34)	1	8	217	3.7	1.06 (0.54, 2.10)	0.851
10.1~	8	301	2.7	1.13 (0.57, 2.25)	0.7	14	301	4.7	1.34 (0.80, 2.24)	0.266
10.5~	4	109	3.7	1.56 (0.60, 4.10)	0.329	4	109	3.7	1.06 (0.40, 2.77)	0.792
10.7~11	6	152	3.9	1.68 (0.77, 3.69)	0.177	10	152	6.6	1.89 (1.04, 3.46)	<0.05*
Sum(8.5~)	111	4560	2.4	1.04 (0.85, 1.26)	0.72	165	4560	3.6	1.04 (0.89, 1.22)	0.611

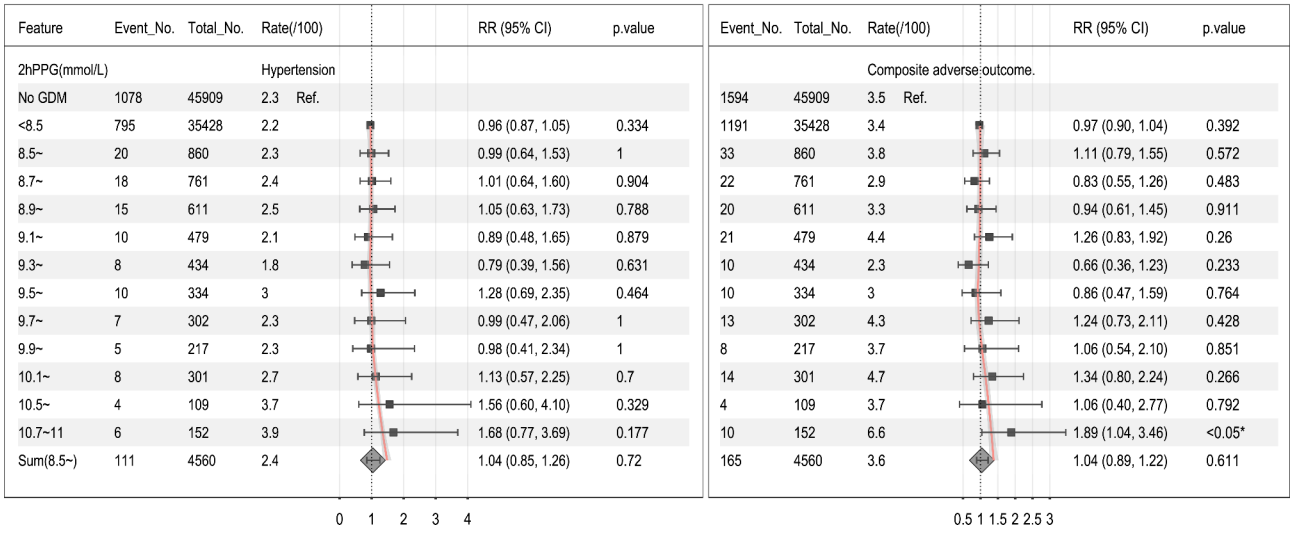
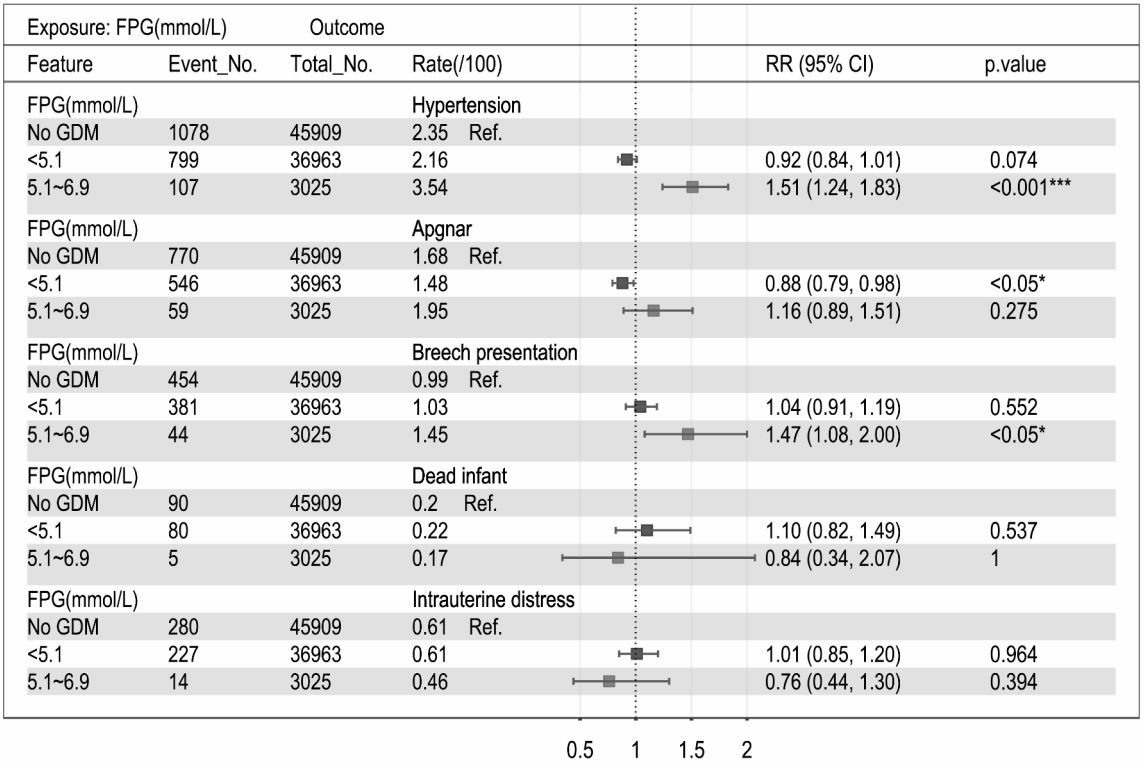


Fig. 2 Associations of consecutive intervals of FPG (**A**) and 2hPPG (**B**) with maternal hypertension and composite adverse outcomes

A.

Exposure: FPG(mmol/L)	Outcome				
Feature	Event_No.	Total_No.	Rate(/100)	RR (95% CI)	p.value
FPG(mmol/L)			Hypertension		
No GDM	1078	45909	2.35 Ref.		
<5.1	799	36963	2.16	0.92 (0.84, 1.01)	0.074
5.1~6.9	107	3025	3.54	1.51 (1.24, 1.83)	<0.001***
FPG(mmol/L)			Apgnar		
No GDM	770	45909	1.68 Ref.		
<5.1	546	36963	1.48	0.88 (0.79, 0.98)	<0.05*
5.1~6.9	59	3025	1.95	1.16 (0.89, 1.51)	0.275
FPG(mmol/L)			Breech presentation		
No GDM	454	45909	0.99 Ref.		
<5.1	381	36963	1.03	1.04 (0.91, 1.19)	0.552
5.1~6.9	44	3025	1.45	1.47 (1.08, 2.00)	<0.05*
FPG(mmol/L)			Dead infant		
No GDM	90	45909	0.2 Ref.		
<5.1	80	36963	0.22	1.10 (0.82, 1.49)	0.537
5.1~6.9	5	3025	0.17	0.84 (0.34, 2.07)	1
FPG(mmol/L)			Intrauterine distress		
No GDM	280	45909	0.61 Ref.		
<5.1	227	36963	0.61	1.01 (0.85, 1.20)	0.964
5.1~6.9	14	3025	0.46	0.76 (0.44, 1.30)	0.394



B.

Exposure: 2hPPG(mmol/L)	Outcome				
Feature	Event_No.	Total_No.	Rate(/100)	RR (95% CI)	p.value
2hPPG(mmol/L)			Hypertension		
No GDM	1078	45909	2.35 Ref.		
<8.5	795	35428	2.24	0.96 (0.87, 1.05)	0.334
8.5~11	111	4560	2.43	1.04 (0.85, 1.26)	0.72
2hPPG(mmol/L)			Apgnar		
No GDM	770	45909	1.68 Ref.		
<8.5	526	35428	1.48	0.89 (0.79, 0.99)	<0.05*
8.5~11	79	4560	1.73	1.03 (0.82, 1.30)	0.763
2hPPG(mmol/L)			Breech presentation		
No GDM	454	45909	0.99 Ref.		
<8.5	368	35428	1.04	1.05 (0.92, 1.20)	0.48
8.5~11	57	4560	1.25	1.26 (0.96, 1.66)	0.103
2hPPG(mmol/L)			Dead infant		
No GDM	90	45909	0.2 Ref.		
<8.5	74	35428	0.21	1.07 (0.78, 1.45)	0.694
8.5~11	11	4560	0.24	1.23 (0.66, 2.30)	0.486
2hPPG(mmol/L)			Intrauterine distress		
No GDM	280	45909	0.61 Ref.		
<8.5	223	35428	0.63	1.03 (0.87, 1.23)	0.752
8.5~11	18	4560	0.39	0.65 (0.40, 1.04)	0.084

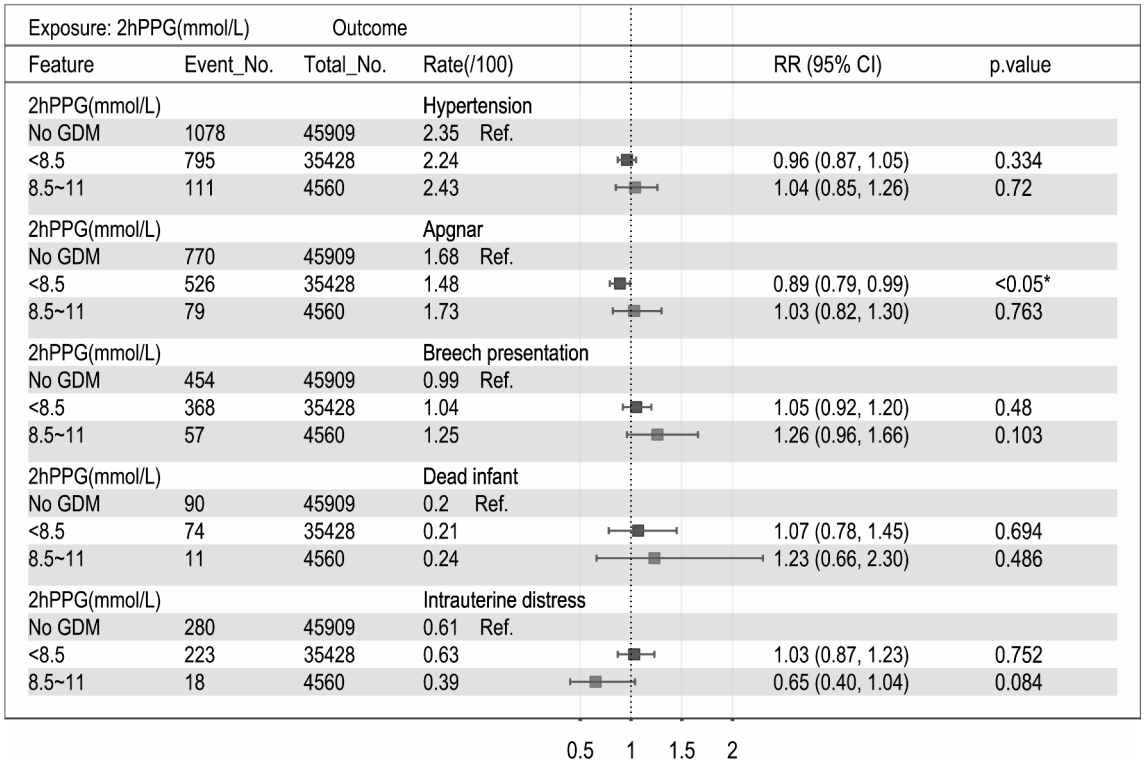


Fig. 3 Associations of 5.1–6.9 mmol/L FPG and 8.5–11.0 mmol/L 2hPPG with maternal hypertension and single adverse outcomes

had neonatal deaths, and 241 (0.6%) had intrauterine distress (Fig. 3). Further investigation of associations with different types of adverse outcomes revealed that 5.1–6.9 mmol/FPG increased maternal hypertension (RR, 1.51; 95% CI, 1.24–1.83; $p<0.001$) and breech presentation (RR, 1.47; 95% CI, 1.08–2.0; $p<0.05$). Moreover, 8.5–11.0 mmol/L 2hPPG slightly increased the risk of breech presentation (RR, 1.26; 95% CI, 0.96–1.66; $p=0.10$) and death (RR, 1.23; 95% CI, 0.66–2.3; $p=0.48$), which were not statistically significant due to low occurrence. Both elevated FPG and 2hPPG were associated with a reduced risk of intrauterine distress.

As older age was an important confounding factor for the incidence of GDM, Next, we compared the mean age between the reference population and study population. The mean age of the reference population was 31.3 (SD, 4.6) years. Among the study population, the mean ages of the patients in the <5.1 mmol/L and 5.1–6.9 mmol/L FPG subgroups were 31.4 (SD, 4.6) years and 32.5 (SD, 4.7) years, respectively (Fig. 1A). The mean age of the <8.5 mmol/L and 8.5–11.0 mmol/L 2hPPG subgroups was 31.4 (SD, 4.6) years and 33.3 (SD, 4.5) years, respectively (Fig. 1B). These findings indicated that women with GDM diagnosed with 8.5–11.0 mmol/L 2hPPG were 0.8 years older than those diagnosed with 5.1–6.9 mmol/L FPG ($p<0.001$). We performed multiple logistic regression using binary abnormal weights as outcomes, glucose levels as risk factors, and age as covariate (Table 1). The regression analysis revealed that after adjustment for age, 5.1–6.9 mmol/L FPG was more likely to lower the incidence of <10th WT (RR, 0.94; 95% CI, 0.89–0.99; $p<0.001$) and to increase the incidence of >90th WT (RR, 1.36; 95% CI, 1.26–1.46; $p<0.001$), whereas 8.5–11.0 mmol/L 2hPPG only increased the incidence of <10th WT (RR, 1.14; 95% CI, 1.09–1.2; $p<0.001$) with a noteworthy effect size. With respect to age, all the association sizes with <10th WT and >90th WT were small, ranging from 0.995 to 1.01, although the RR of 1.01 was statistically significant ($p<0.01$) because of the large sample size. This finding implied that compared with the much larger effect sizes of increased FPG, the confounding effect of age was minor. These consistent findings after adjustment further supported our findings.

Discussion

Our main findings revealed that higher FPG was significantly associated with higher birthweight, whereas higher 2hPPG was more strongly associated with lower birthweight. This difference in the impact of the two GDM diagnosis criteria on neonatal birthweight was independent of the age of the women. GDM patients screened by the FPG criterion had a more significantly increased incidence of maternal hypertension than those diagnosed by the 2hPPG criterion.

Among the study population of our study, 7.6% of women were diagnosed with GDM according to the 5.1–6.9 mmol/L FPG criterion and 11.4% according to the 8.5–11.0 mmol/L 2hPPG via the OGTT during 24–28 weeks of gestation. The incidence of GDM according to the two combination criteria was 17.3% (6908 cases), which was close to that reported in a previous meta-analysis in which the incidence of GDM was 14.8% among 79,064 Chinese participants [12]. As different populations may have inconsistent plasma glucose levels, previous studies used 1 SD of glucose measurements to evaluate the impact size of elevated glucose. The seminal Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study included 25,505 women who underwent a 75 g OGTT at 24–32 weeks of gestation, and reported that 1 SD of elevated FPG (0.4 mmol/L) and 2hPPG (1.3 mmol/L) had a similar RR of 1.38 for birthweight>90th WT. However, this strategy failed to detect an accurate trend in the impact of different glucose levels on gestation.

Our strategy was the application of finer consecutive 0.2 mmol/L intervals of FPG and 2hPPG to investigate the incremental impact of elevated glucose, which provided information about both the overall impact and its trend on adverse outcomes during gestation from elevated glucose. Our important finding was that 5.1–6.9 mmol/L FPG had a significantly positive association with >90th WT (RR, 1.48; 95% CI, 1.35–1.63; $p<0.001$) and with a lower risk of <10th WT (RR, 0.82; 95% CI, 0.74–0.91; $p<0.001$) (Fig. 1A), whereas 8.5–11.0 mmol/L 2hPPG had the opposite effect, i.e., it was associated with an increased risk of <10th WT (RR, 1.14; 95% CI, 1.06–1.23; $p<0.001$) and with no increased risk of >90th WT (RR, 0.95; 95% CI, 0.86–1.04; $p=0.29$) (Fig. 1B). This

Table 1 Multiple logistic regression for associations of outcomes of birth weights with FPG, 2hPPG, and age

Multiple independent factors		Outcome: <10th WT		Outcome: >90th WT	
	Level	RR (95%CI)	p-value	RR (95%CI)	p-value
FPG + Age	5.1–6.9 mmol/L FPG	0.94 (0.89–0.99)	< 0.001	1.36 (1.26–1.46)	< 0.001
	Age (/year)	0.995 (0.99–1)	0.03	1.01 (1.01–1.02)	< 0.001
2hPPG + Age	8.5–11 mmol/L 2hPPG	1.14 (1.09–1.2)	< 0.001	0.94 (0.89–0.99)	< 0.001
	Age (/year)	0.99 (0.99–1.0)	0.06	1.01 (1.01–1.02)	< 0.001

Note: The whole population with FPG<5.1 mmol/L and 2hPPG<8.5 mmol/L is used as the reference population. Compared with the reference population, the association sizes (RR, 95% confidence interval [95% CI]) for FPG and 2hPPG represent the incidence change with their corresponding GDM diagnosis. The RR values for age represent the incidence change in a one-year increase

discrepancy was independent of age since the RR values adjusted for age led to identical conclusions (Table 1). We further investigated these characteristic associations by stratifying the population using a series of consecutive glucose levels of FPG and 2hPPG. The results revealed that the associations with >90th WT according to the FPG criterion sharply increased from 5.1 to 5.9 with the strongest association (RR, 2.17) occurring at 5.7–5.9 mmol/L (Fig. 1A).

To our knowledge, no previous studies have reported an association between 2hPPG and low birthweight. In our study, the opposite action on <10th WT between higher FPG and higher 2hPPG might have important clinical implications for the intervention of GDM regarding abnormally high and low birthweight. Currently, low birth weight has been increasingly found to be associated with elevated maternal glucose levels and is a risk factor for childhood and adult metabolic syndrome [13]. Previous research revealed that high birthweight predicted metabolic health in obese subjects with a higher whole-body insulin sensitivity index and lower trunk fat percentage than did low birthweight ($P<0.05$) [14], whereas the recent study by Colaus reported that middle-aged adults born with low birthweight presented a greater incidence of diabetes and obesity than did those with a normal weight [15].

GDM is essentially characterized by a glucose tolerance disorder that may first appear during pregnancy or preexist before conception as a form of prediabetes. Research has shown that women with prior GDM have a 13.0-fold multivariable-adjusted risk (95% CI: 5.54–30.6) for diabetes and a 2.15-fold risk (95% CI: 1.76–2.62) for prediabetes compared with women without GDM [16]. According to statements by the American Diabetes Association (ADA), prediabetes includes impaired fasting tolerance (IFT) and impaired glucose tolerance (IGT) [17]. IFT is determined by elevated FPG and responds to hepatic glycogen metabolism. The IGT is determined by 2hPPG and responds to pancreatic problems [18]. Despite these disparate mechanisms for the two types of prediabetes, GDM is clinically diagnosed on the basis of a combination of FPG and 2hPPG criteria. Comparisons between cases that are diagnosed separately by two different criteria are rarely reported. This clinical context may partly explain our findings that GDM cases diagnosed by FPG and the 2hPPG criteria had distinct impacts on neonatal birth weight.

In addition to the different impacts on neonatal weight among women with GDM diagnosed by FPG and 2hPPG criteria, our study also revealed that women with GDM diagnosed by FPG were more likely to use insulin. There was an increasing trend in insulin use according to the categorization of FPG levels, increasing from the lowest 0.4% below 5.1 mmol/L FPG to the highest 22.2% at 6.3 ~ mmol/L FPG (Fig. 1A). In contrast, the trend in insulin use among subgroups by 2hPPG was not significant (Fig. 1B). The clinical meaning of these findings remains to be further clarified.

Another remarkable finding concerning the differences between the FPG and 2hPPG diagnostic criteria was the great disparity in the associations with maternal hypertension (Fig. 2). The findings indicated that elevated FPG was strongly associated with maternal hypertension (RR, 1.51; 95% CI, 1.24–1.83; $p<0.001$) compared with elevated 2hPPG (RR, 1.04; 95% CI, 0.85–1.26; $p=0.72$), only two levels (>10.5 mmol/L) had an evident association (RR, 1.56 and 1.68) with hypertension (Fig. 2B). Concerning other adverse outcomes, only the incidence of breech presentation was increased among patients diagnosed by FPG and 2hPPG.

Finally, since high and low birth weights have differential clinical meanings, the distinctive associations of FPG and 2hPPG with birth weight deserve attention in future studies. Metabolically, an increase in 2hPPG is an indicator of abnormal insulin secretion in which the pancreas becomes insensitive to an increase in blood glucose and does not adequately secrete insulin, predicting declining beta cell function and worsening glucose tolerance over time [19]. Declining beta cell function also affects protein synthesis and leads to low birthweight, which explains our findings about the association between increased 2hPPG and low birth weight. This cause supports the evidence that low birth weight is a risk factor for future metabolic syndrome [20]. Therefore, based on our findings, future studies should include data on beta cell function to clarify the distinct associations with adverse outcomes among patients with GDM diagnosed by FPG or 2hPPG criteria.

The strengths of our study were the large sample size and the entire population of pregnant women. The application of consecutive intervals ensured a reliable description of the changing impacts of different maternal glucose levels on birth weight and adverse outcomes within each subgroup, which provided insight into the turning point and the trend of the effects. The limitation was that selection bias was likely among women who underwent or did not undergo the OGTT test, which was addressed using a common reference population and adjustment for age.

Conclusions

We obtained an incremental effect of increased FPG and 2hPPG from the OGTT on abnormal newborn birth weight, maternal hypertension, and a composite of adverse outcomes by stratifying large population-based pregnant women with consecutive intervals of glucose levels. Our study revealed that the FPG criterion was significantly associated with high birth weight, whereas 2hPPG was significantly associated with low birth weight.

Our findings highlight the heterogeneity of patients with GDM diagnosed by different criteria.

Author contributions
QS and XS contributed to the design, analysis and interpretation of the data, and wrote the manuscript. LL and HD contributed to the acquisition of data and revised the manuscript. QS and HD are the guarantors of this work, have full access to all study data, and assume responsibility for data integrity and analytical accuracy. All authors read and approved the final manuscript.

Funding
This study was funded by the Natural Science Foundation of Ningbo (No. 2019F1003) and the Zhejiang Provincial Medical and Health Science and Technology Plan Project (2021KY996).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This retrospective observational study was approved by the Ethics Committee of the First Affiliated Hospital of Ningbo University (2023No.192RS-01). The need for informed consent to participate was waived by the Ethics Committee of the First Affiliated Hospital of Ningbo University.

Competing interests
The authors declare no competing interests.

Received: 29 April 2024 / Accepted: 20 August 2024
Published online: 30 August 2024

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