Joint effect of Maternal Pre-pregnancy Body Mass Index and Folic Acid Supplements on Gestational Diabetes Mellitus Risk: A prospective cohort study

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Research Article

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Abstract

Background: The joint effect of folic acid (FA) supplements and maternal pre-pregnancy body mass index (ppBMI) on gestational diabetes mellitus (GDM) has not been fully addressed. We aimed to examine the joint effect of FA supplements and ppBMI on GDM.

Methods: Pregnant women at 4 to 14 weeks of gestation (n=3186) were recruited to this study during their first prenatal visit in Qingdao from May 1, 2019, to June 27, 2021. The main outcome was GDM and GDM screening based on 75g 2-hour OGTT, a fasting glucose ≥5.1 mmol/L, or a 1-hour result ≥10.0 mmol/L, or a 2-hour result ≥8.5 mmol/L at 24-28 weeks' gestation. The interactive effect of FA supplements and ppBMI on GDM was examined by logistic regression models.

Results: A total of 2095 pregnant women were included analysis, and GDM incidence was 17.76%. The joint effect of ppBMI and FA supplements was statistically significant on GDM. The risk effect was most prominent among pregnant women with FA-D and pre-pregnant obese (adjusted OR [aOR]=5.10, 95% CI: 1.83-14.19). This synergistic effect was more obvious when stratified by FA intake time. The aORs of FA-S and FA-D among the obesity women were 2.75 (95% CI: 1.42-5.34) vs. 4.49 (95% CI: 1.22-16.50) in FA intake <3 months. An increased risk of GDM was more apparent for obesity women with FA-D in FA intake ³3 months (aOR=9.83, 95%CI: 1.52-63.47). However, as for pre-pregnant overweight, FA-D appeared to be positively associated with GDM only in the group of FA supplements ³3 months (aOR= 2.13, 95% CI: 1.46-3.11).

Conclusion: Coexistence of pre-pregnancy overweight or obese and deficiency of FA supplements increased risk of GDM compared with each of these risk factors alone. Public awareness about the risk effects of FA deficiency, especially among pregnant women with a higher BMI, are necessary.

Introduction

Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications worldwide [1–3]. Hyperglycemia during pregnancy is linked with adverse pregnancy outcomes, such as neonatal adiposity, macrosomia, large for gestational age, caesarean section and shoulder dystocia[4–6]. It also has long-term negative effects on women and their offspring[7–10]. Despite extensive public health efforts, prevalence of GDM all over the world remains high and continues to rise at an alarming rate, imposes an immense burden on global health[11–13]. Particularly in China, the increase was most noticeable, and our previous preliminary research showed the incidence of GDM was up to17.42% in 2018–2019[14]. In view of the adverse effect of GDM, there is an urgent need to identify modifiable risk factors for GDM.

Folic acid (FA) supplements are recommended before and during pregnancy all over the world. Periconceptional consumption of FA, or multivitamins that contain FA, reduces the risk for neural tube defects (NTDs)[15, 16]. Since the beneficial effect of FA was well established, the link between daily FA supplement and GDM remained controversial at present. Recent reports suggest that the incidence of

GDM may be increased in women who take FA supplements during pregnancy[17, 18]. However, a cohort study showed that a higher intake of habitual FA from supplements before pregnancy was significantly associated with a lower risk of GDM[19]. Moreover, experimental studies have shown that high-dose FA supplement throughout pregnancy may via lowering blood homocysteine (Hcy) levels protect against oxidative stress[20], which is known to contribute to endothelial dysfunction and insulin resistance[21], Hcy concentrations have also been strongly linked with GDM risk among pregnant women[22].

Previous studies have identified pre-pregnancy body mass index(ppBMI) as a potent risk factor for GDM[23]. Furthermore, the effect of FA supplements or dietary folate intake on GDM may differed by maternal ppBMI. Studies have reported that there is an inverse interaction between ppBMI and serum folate levels. Obese individuals may be at risk for folate deficiency even after controlling for dietary and supplemented intake of folic acid[24–27]. Several potential mechanisms have been suggested to identify causal pathways for relative folate deficiency in obese women, such as chronic inflammation and hyperinsulinemia[28].

However, the joint effect of ppBMI and FA supplements on GDM is unclear. To address this gap in knowledge, our cohort study aimed to examine the interaction between FA supplements and ppBMI for the risk of GDM, while considering the time of the supplementation, in order to provide favorable evidence for antenatal nutritional interventions.

Mothods

Data Sources and Cohort

We performed a prospective cohort study of pregnant women at 4 to 14 weeks of gestation from May 1, 2019, to June 30, 2021. We recruited a total of 3186 pregnant women. Details of the study have been described previously[29]. In brief, all the pregnant women in the study were from the Qingdao Women and Children Hospital Health Cohort, which is a prospective cohort aimed at determining the impact of maternal dietary, environmental, and lifestyle exposures on the health of pregnant women and their offspring. At registration, questionnaire-based interviews were used to gather information on social demographic status, reproductive variables, family history of diseases, the use of supplementation, lifestyle factors, and illnesses. Throughout the follow-up visits during midpregnancy and late pregnancy, information on lifestyle, dietary intake, and the use of supplements was acquired.

Population Research

We included pregnant women with detailed information on FA supplements doses and duration, as well as height and weight prior to pregnancy. Exclusion criteria are: (1) multiple pregnancy (n = 52); (2) termination or abortion (n = 126) and loss to follow-up before 24–28 gestational weeks (n = 229), no 75g oral glucose tolerance test (OGTT) screening (n = 409); (3) height and weight of pregnant women before pregnancy is incomplete or missing (n = 14); (4) FA supplements information is incomplete, with unclear doses, unclear duration, or varying doses (n = 215); (5) History of diabetes(n = 26) and with diabetes

mellitus before pregnancy or within 20 weeks of gestation(n = 30) **(Fig. 1)**. A total of 2,095 single-ton births were considered for the final analysis. Participation in the study was entirely voluntary, and each study subject provided written informed consent.

Assessment of FA Supplements and pre-pregnancy BMI

FA supplements' information was inquired and assessed at enrollment, supplements use details including brand, daily doses, and the time of supplements were collected. In this study, FA supplements sufficient was defined as taking either FA specific supplement or FA-containing supplements ≥ 400μg/d (FA-S), deficiency of FA supplements was defined as taking either FA specific supplement or FA-containing supplements < 400μg/d (FA-D)[30]. Pregnant women are divided into underweight/normal people (ppBMI < 24kg/m^2), overweight people (24kg/m^2≤ppBMI < 28kg/m^2) and obese people (ppBMI ≥ 28kg/m^2) according to their ppBMI.

Diagnosis of GDM

According to the Ministry of Health of China's (MOH) Diagnostic Criteria for Gestational Diabetes Mellitus (WS311-2011), all participants were screened for GDM using a 75g oral glucose tolerance test (OGTT) at 24 to 28 weeks gestation[31]. The MOH criterion cut-off values were consistent with the International Association of Diabetes and Pregnancy Study Groups Consensus Panel recommendations[32]. In summary, a diagnosis of GDM could be made if any of the following values in the 75g OGTT were met or exceeded: 0-hour (fasting plasma glucose [FPG]) ≥ 5.1mmol/L, 1-hour ≥ 10.0 mmol/L, or 2-hour ≥ 8.5 mmol/L.

Assessment of Covariates

When collecting questionnaire information, we collected social demographic characteristics, living environment, personal and family disease history, dietary content, and anthropometric information. When enrolled in the group, we measured weight, height, waist circumference, hip circumference, and blood pressure. The ppBMI was calculated by dividing self-reported weight before pregnancy in kilograms by the square of height in meters measured at enrollment. Smoking activities are divided into active smoking and passive smoking (second-hand smoke exposure). Passive smoking is divided into pre-pregnancy contact, pregnancy contact, and pre-pregnancy to pregnancy exposure. Drinking was defined as those consuming alcohol > 3×/wk. vitamin B_{12} supplements were grouped according to whether they were taken from supplements. The calculation formula for weight gain during pregnancy is weight measured at inclusion minus pre-pregnancy weight.

Statistical Analysis

Numerical variables were expressed as mean ± SD. Categorical variables were expressed as n (%). Maternal characteristics were compared according to FA supplements use status using ANOVA for continuous variables and Chi-square test for categorical data. Logistic regression models were performed and odds ratios (OR, with 95% confidence intervals [CI]) were calculated to evaluate the risk associated with GDM. We examined interaction effects on the multiplicative scale. For multiplicative interaction, we

calculated two-sided *P* values to assess the significance of each product term in the logistic regression models and compared the odds ratios (ORs) for ppBMI across FA supplement doses. And in order to clarify the relationship even further, the stratified analysis by FA supplements intake time was performed to determine the joint effect of ppBMI and FA supplements level on GDM in different groups. All the data were analyzed with SAS and SPSS 22.0 software.

Results

Among the 2095 women in the Qingdao Women and Children's Hospital Cohort, the overall incidence of GDM was 17.76% (n = 372). 186 (8.88%) of the participants had not taking any FA supplements or daily supplement consumption was less than 400μg before pregnancy and in the first trimester. The proportion of women with FA supplements consumption less than 400μg/d was higher among those with ppBMI higher than 28 kg/m², whereas the difference was no significant ($P > 0.05$). Supplementation intake of vitamin B_{12} was higher among pregnant women with FA ≥ 400μg/d ($P < 0.05$) (Table 1). Table 2 shows the effects of ppBMI and daily FA supplement on GDM. Compared with ppBMI < 24kg/m^2, pregnant women who were overweight (OR = 2.06, 95% CI: 1.58–2.69) or obese (OR = 2.83, 95% CI: 1.93–4.25) had increased risk of GDM. Table 2 also shows the adjusted OR, and similar results were observed in the association between ppBMI and GDM in adjusted model. Our results did not indicate a significant association between FA supplements and GDM, regardless of adjustment (all $P > 0.05$).

Table 1
Characteristics of Participants According to FA Supplement use Status (n = 2095)

	Total (n = 2095)	**FA-D (n = 186,8.88%)**	**FA-S (n = 1909,91.12%)**	***p-value***
Age (years)				0.374
< 35	1802	176(9.8%)	1626(90.2%)	
≥ 35	291	26(8.9%)	265(91.1%)	
Pre-pregnancy BMI (kg/m^2)				0.520
< 24	1569	137(8.7%)	1432(91.3%)	
24≤ppBMI < 28	387	33(8.5%)	354(91.5%)	
≥ 28	139	16(11.5%)	123(88.5%)	
Education(years)				0.748
Under the high school	314	26(26%)	288(91.7%)	
High school and above	1781	160(9%)	1621(91.0%)	
Monthly income (¥)				0.320
< 5000	584	39(6.7%)	545(93.3%)	
≥ 5000	1355	146(9.7%)	1355(90.3%)	
parity				0.060
0	1510	123(8.1%)	1387(91.9%)	
≥ 1	585	63(10.8%)	522(89.2%)	
Smoking				
Active smoking				0.606
No	1994	191	1803	
Yes	101	11	90	
Passive smoking				0.850
No	1807	159(8.8%)	1648(91.2%)	
pre-pregnancy	120	12(10.0%)	108(90.0%)	
after pregnancy	7	0(0.0%)	7(90%)	
Pre-pregnancy to pregnancy	161	15(9.3%)	146(90.7%)	

	Total (n = 2095)	FA-D (n = 186,8.88%)	FA-S (n = 1909,91.12%)	*p-value*
Drinking				0.653
No	2031	182(9.0%)	1849(91.0%)	
Yes	59	4(6.8%)	55(93.2%)	
Family history of diabetes mellitus				0.310
No	1565	132(8.4%)	1433(91.6%)	
Yes	507	53(10.5%)	454(89.5%)	
Unclear	18	1(5.6%)	17(94.4%)	
Family history of hypertension				0.531
No	1113	106(9.5%)	1007(90.5%)	
Yes	927	75(8.1%)	853(91.9%)	
Unclear	50	5(8.9%)	45(90.9%)	
Fertilization way				0.618
Natural conception	1880	169(9.0%)	1711(91.0%)	
Non-natural conception	215	17(7.9%)	198(92.1%)	
History of GDM				0.677
No	2022	181(9.0%)	1841(91.0%)	
Yes	73	5(6.8%)	68(93.2%)	
Gestational weight gain (kg)		1.18(±2.70)	1.21(± 2.78)	0.811
vitamin B_{12} supplements				**0.000**
No	1050	179(17.0%)	871(83.0%)	
Yes	1045	23(2.2%)	1022(97.8%)	

Table 2
Odds ratio (ORs, 95% confidence interval (CIs)) of GDM according to pre-pregnancy BMI and FA supplement use doses as categorical using a logistic regression model (N = 2095)

	N(%)	Crude OR	*P-value*	Adjusted OR	*P-value*
ppBMI(kg/m^2)					
< 24	1569(74.9%)	Ref	-	Ref	-
24≤ppBMI < 28	38(18.5%)	**2.06(1.58–2.69)**	**0.000**	**1.91(1.45–2.52)**	**0.000**
≥ 28	139(6.6%)	**2.83(1.93–4.25)**	**0.000**	**2.89(1.94–4.30)**	**0.000**
FA intake					
< 400μg /d	186 (8.9%)	1.12(0.77–1.65)	0.550	1.49(0.53–4.23)	0.453
≥ 400μg /d	1909(91.1%)	Ref	-	Ref	-
Adjusted OR: adjusted for age, education level, monthly income, passive smoking, drinking, family history of diabetes mellitus, fertilization way, history of GDM, the use of vitamin B12 supplement.					
Variables with statistical significance were shown in boldface. n (%): numbers and prevalence rates of GDM of each layer.					

To further determine the joint effect of FA supplements and ppBMI on GDM risk (Table 3), we divided pregnant women into 6 groups according to ppBMI and FA supplement levels [group1: FA-S and ppBMI < 24 kg/m^2; group2: FA-D and ppBMI < 24kg/m^2; group3: FA-S and ppBMI (24kg/m^2≤ppBMI < 28kg/m^2); group4: FA-D and ppBMI (24kg/m^2≤ppBMI < 28kg/m^2); group5: FA-S and ppBMI≥28 kg/m^2; group 6: FA-D and ppBMI≥28 kg/m^2]. Compared with FA-S and ppBMI < 24 kg/m^2, the risk effect was most prominent among pregnant women with FA-D and pre-pregnant obese [crude and adjusted ORs of 4.55(95% CI: 1.68–12.35) and 5.10 (95% CI: 1.83–14.19)].

Table 3
Interaction analysis of pre-pregnancy BMI and FA supplement intake dose on the risk of GDM

Interaction	n (%)	Crude OR	P-value	Adjusted OR	P-value
FA-S*ppBMI (< 24 kg/m^2)	1432(66.7%)	Rf		Rf	
FA-D*ppBMI (< 24 kg/m^2)	137(6.4%)	0.89(0.53–1.48)	0.644	0.92(0.54–1.57)	0.754
FA-S*ppBMI(24kg/m^2≤ppBMI < 28kg/m^2)	354(16.5%)	**1.97(1.48–2.60)**	**0.000**	**1.84(1.38–2.47)**	**0.000**
FA-D*ppBMI(24kg/m^2≤ppBMI < 28kg/m^2)	33(1.5%)	**2.93(1.40–6.12)**	**0.004**	**2.60(1.21–5.57)**	**0.014**
FA-S*ppBMI (≥ 28 kg/m^2)	123(5.7%)	**2.62(1.74–3.94)**	**0.000**	**2.63(1.72–4.03)**	**0.000**
FA-D*ppBMI (≥ 28 kg/m^2)	16(0.7%)	**4.55(1.68–12.35)**	**0.003**	**5.10(1.83–14.19)**	**0.002**
Adjusted OR: adjusted for age, education level, monthly income, passive smoking, drinking, family history of diabetes mellitus, fertilization way, history of GDM, he use of vitamin B12 supplement.					
Variables with statistical significance were shown in boldface. n (%): numbers and prevalence rates of GDM of each layer.					

To clarify the effect of FA supplements and ppBMI on GDM, stratified analyses were performed based on the time of FA intake (Fig. 2-Fig. 3). Pregnant women with pre-pregnant obese was inversely associated with GDM irrespective of FA supplements consumption and time of FA intake [for FA supplements ≥ 3 months and FA-D: aOR = 9.83, 95%CI: 1.52–63.47; for FA supplements ≥ 3 months and FA-S: aOR = 2.54, 95%CI: 1.44–4.46; for FA supplements < 3 months and FA-D: aOR = 4.49, 95%CI: 1.22–16.50; for FA supplements < 3 months and FA-S: aOR = 2.75, 95%CI: 1.42–5.34]. Among pre-pregnancy obesity women, FA-D had the highest risk of GDM in FA intake ≥ 3 months. However, as for pre-pregnant overweight, FA-D appear to be positively associated with GDM only in the group of FA supplements ≥ 3 months (OR = 2.13, 95% CI: 1.46–3.11).

Discussion

In this prospective cohort, we discovered significant interactions between FA supplements and ppBMI in the risk of GDM. More specifically, we discovered that the risk effect was most pronounced in pregnant women with insufficient FA intake and obese women. Our findings further support the hypothesis that FA levels during pregnancy may play an important role in maternal metabolic disease, particularly in women with higher ppBMI.

FA is an important pregnancy nutrient for its protective effects against birth defects. Previous studies evaluating the association of FA supplementation before or during pregnancy with GDM risk have conflicting results[18]. A large prospective cohort (n = 20,199) showed that preconception habitual intake of FA supplements was inversely associated with GDM risk in the United States[19]. Conversely, a prospective Chinese study of 326 pregnant women showed that high-dose FA supplementation in early pregnancy was associated with an increased risk of GDM[33]. The discrepancy of findings might be due to a smaller sample size in the latter study. Consistent with this, a prospective cohort showed that daily FA supplementation in the first trimester was positively associated with GDM risk[17]. However, it is difficult to interpret this finding as details of the research methods and results are not reported. Heidi T Cueto and colleagues[35] reported that there was no clear association between preconception FA use and diabetes diagnosis, and our result are consistent with them. Considering the inconsistent results mentioned above, the relationship between maternal FA status and GDM need further larger cohort studies to examine.

Previous studies have suggested that different BMI levels may influence the effect of FA supplementation on disease. According to a case–control study, the association between FA supplements and the NTDs risk was weaker in overweight/obese mothers than in underweight/normal weight mothers, indicating that maternal BMI could affect the association between FA supplement and the NTDs risk in offspring[34]. Meanwhile, a retrospective cohort study[35] report that the protective effect of FA supplements for PTD is reduced in women whose BMI was equal or greater than 24 kg/m^2. We are not aware of direct evidence regarding biological mechanisms for the effect of FA supplement on the association between ppBMI and GDM. However, an intervention study comparing the relationship between BMI and the short-term pharmacokinetic response to oral doses of FA showed that distribution of folate in the body is significantly affected by BMI[28]. A retrospective case-control study found that higher BMI recorded in the first trimester was negatively correlated with serum folate levels measured in the third trimester[36]. Another possible explanation is that obesity can increase estrogen, which has been reported to be associated with decreased serum folate availability[37]. Thus, it is plausible that pathways related to metabolic regulation may underlie associations between BMI and serum folate.

One of the most interesting observations of this study is that the risk for GDM is increased in obese women regardless of adequate folate intake, but the risk of GDM is higher when folate intake is deficiency. Two prospective cohort studies in China have assessed the association of the impact of FA supplement use on GDM with consideration of both doses and durations. One of them shows a U-shape relation between duration of FA supplements and risk of GDM[33], and another suggested that long-term use of high-dose FA increases GDM risk[38]. Thus, we also compared the interaction between the FA supplements and ppBMI, in the case of FA $\geq$ 3 months and FA < 3 months. Risk of GDM in obese women with FA-D and FA-S were still higher than women with BMI < $24kg/m^2$ and FA-S. Although the biological mechanisms that underlie the modified association were complicated and remained unclear, our findings could be partly explained by the theory that FA could inhibit Hcy production[39, 40]. And Hcy concentrations declined as FA concentrations increased, as did the prevalence of

hyperhomocysteinemia[41], while high concentrations of Hcy are associated with insulin resistance[42, 43]. These findings suggest that FA might have a protective effect GDM by reducing Hcy concentration and improving insulin resistance. However, the higher ppBMI decreased the levels of serum folic acid or dietary folate intake[44–46]. The combinative effect of high ppBMI and low dose FA intake leads to the accumulation of Hcy concentrations and reduce insulin resistance, ending up with GDM. Therefore, we suggest that a diverse plan of FA supplementation should be carried out according to women's BMI category.

Our study has several advantages. Firstly, this study is a prospective cohort, which reduces the effects of selection or recall bias. We excluded women with hypertension or established diabetes to avoid information bias. Furthermore, some studies have shown that vitamin B_{12} in multivitamin supplements has an impact on the risk of GDM[47, 48]. We collected sufficient data to include various confounders in adjusted analyses and matched for vitamin B_{12} as a confounder. The effects of the interaction of FA supplements alone with ppBMI on GDM were obtained. Several limitations are present in this study. First, dietary FA was also not estimated, and we were unable to calculate exact FA levels, and the results of this study need further research to verify. Second, we mainly analyzed daily intake of FA by pregnant women during pre-pregnancy to first trimester. Although the FA intake during the whole pregnancy was not analyzed, our study is consistent with the recommended folic acid intake time in the Nationwide Folic Acid Supplementation Program of China[3]. Third, the relatively small sample size in our study also limited our ability to investigate the relationship between FA supplements and ppBMI at different levels. Our findings provide a new perspective on the development of prevention strategies, and further studies should consider larger sample sizes, total time from pre-conception to post-conception, and sophisticated statistical methods to examine the relationship between FA supplements, ppBMI, and pregnancy disorders.

Conclusion

Coexistence of pre-pregnancy overweight or obese and deficiency of FA supplement increased risk of GDM compared with each of these risk factors alone. The risk effect was most prominent among pregnant women with FA-D and pre-pregnant obese. Public awareness about the risk effects of FA deficiency, especially among pregnant women with a higher BMI, are necessary.

Declarations

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Ethics approval and consent to participate:

Ethical approval for this study has been obtained from the Ethics Committee of Qingdao Women's and Children's Hospital (Number: 019–2019-FEKY). All participants sign a consent form prior to participating in the study.

Consent for publication

Not applicable.

Availability of data and materials

Data are available from the corresponding author on reasonable request.

Competing interests

The authors declared that they have no competing interests.

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Authors' contributions

M.Y. Li and Z.H. Du conceived the study and organized data, carried out the statistical analysis, and drafted the manuscript. L.J. Wang and Q.Q. Shen participated in the study design, in the coordination and the execution of data collection and statistical analysis. Others contributed to the data management and gave critical appraisal of the manuscript. G.J. Li coordinated the study design and gave critical appraisal of the manuscript. All authors read and approved the final manuscript.

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Figures

Fingure1. Flow chart of the screening process for the selection of eligible participants

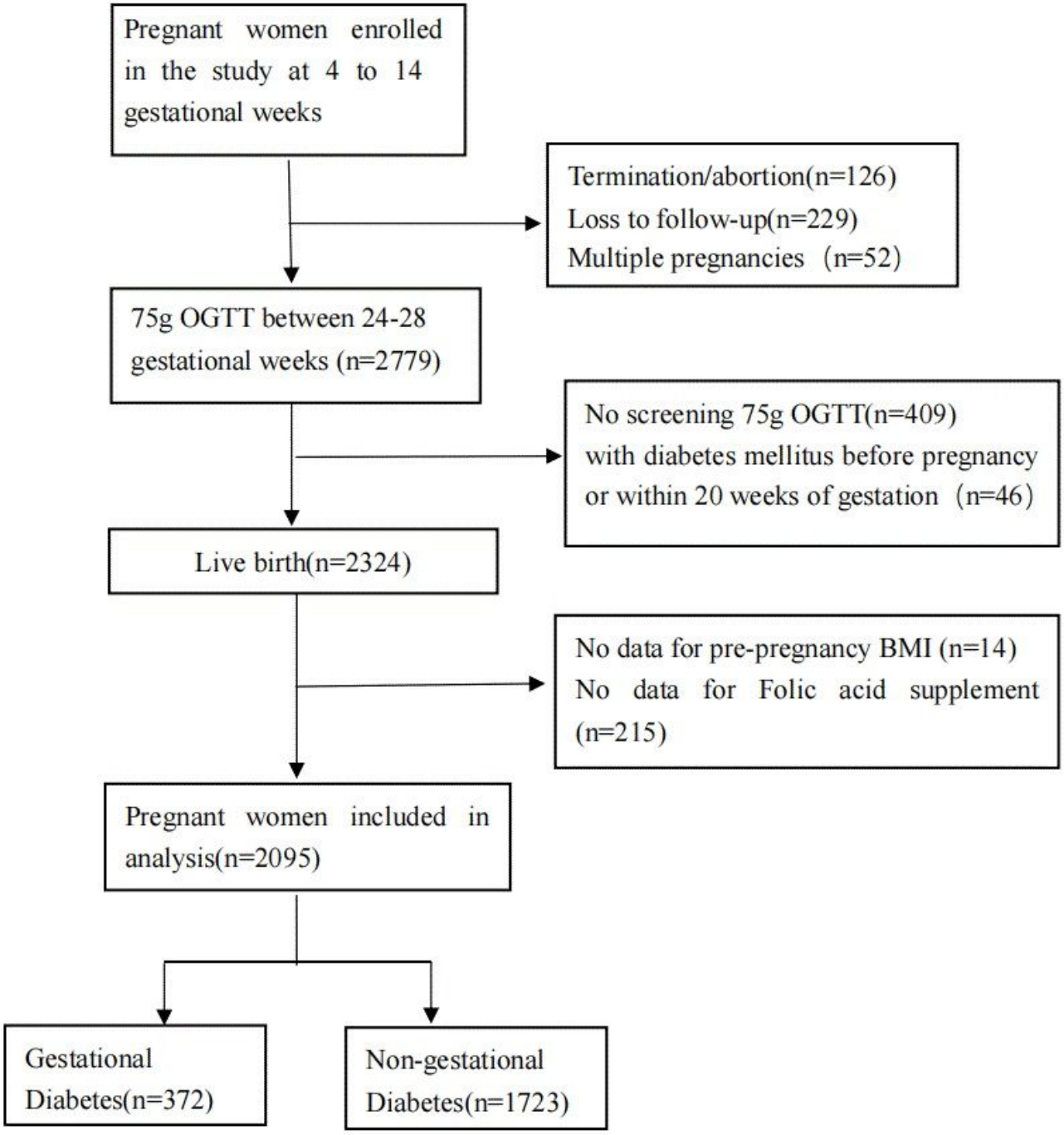
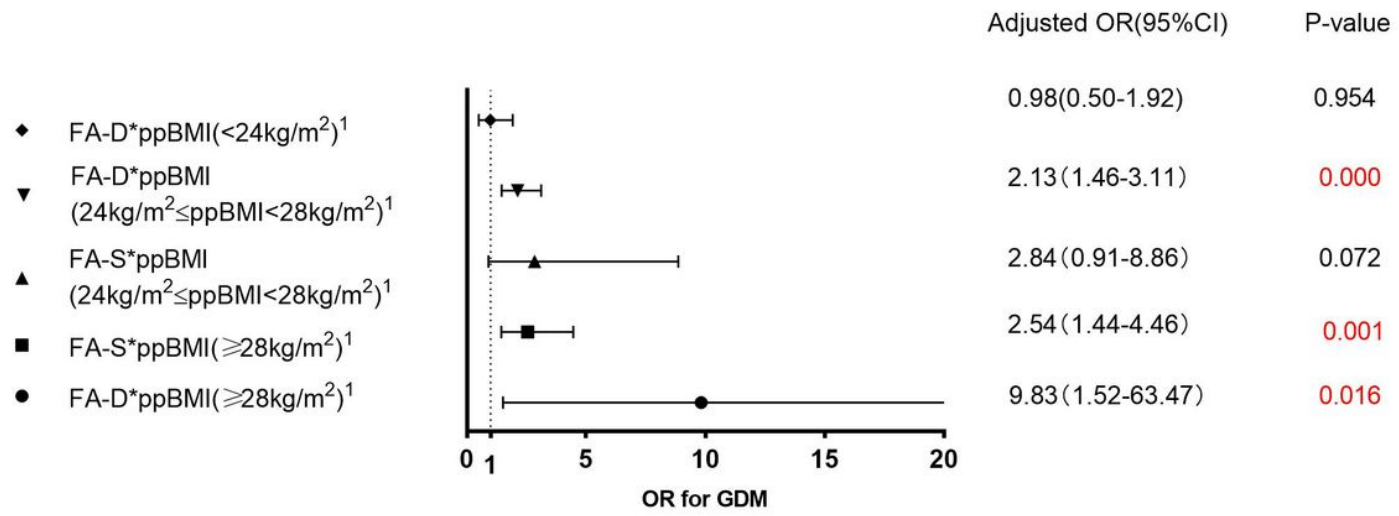


Figure 1

See image above for figure legend



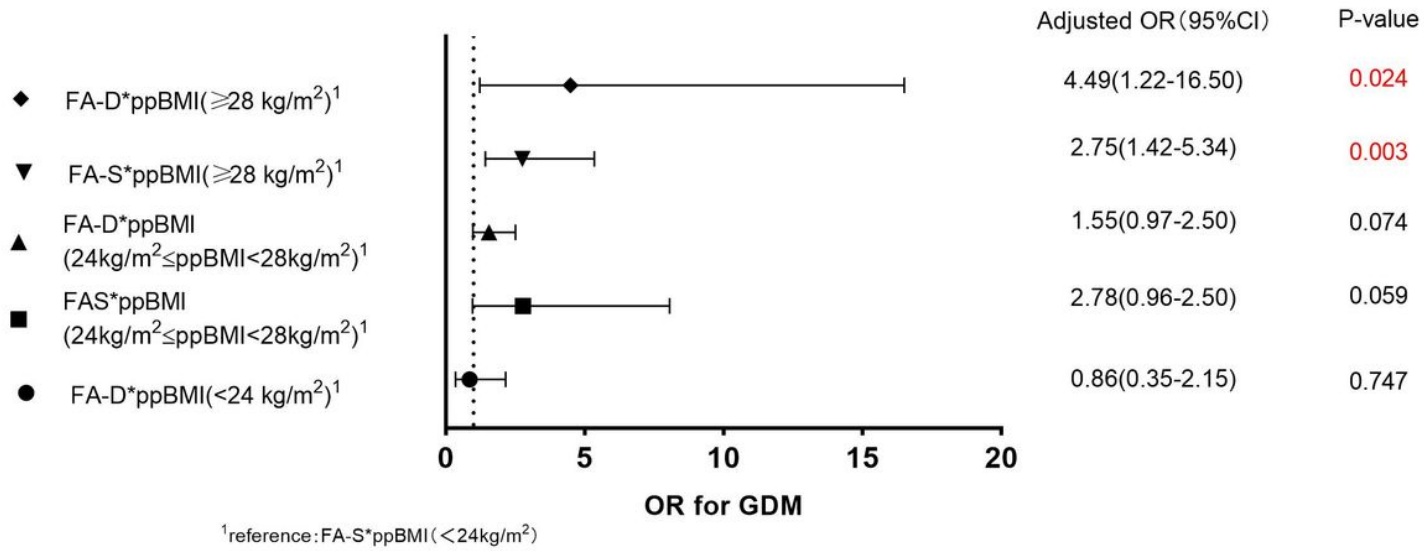
[1]reference:FA-S*ppBMI(<24kg/m^2)

Model adjusted for age, education level, monthly income, passive smoking, drinking, family history of diabetes mellitus, fertilization way, history of GDM, the use of vitamin B12 Supplement.

Fingure2: Interaction analysis of pre-pregnancy BMI and folic ac

Figure 2

Caption not included with this version.



[1]reference:FA-S*ppBMI(<24kg/m^2)

Model adjusted for age, education level, monthly income, passive smoking, drinking, family history of diabetes mellitus, fertilization way, history of GDM, the use of vitamin B12 Supplement.

Fingure3:Interaction analysis of pre-preganancy BMI and folic acid supplement intake dose on the risk of GDM(FA supplement intake time <3months)

Figure 3

Caption not included with this version.