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Association of free fatty acid in first trimester with the risk of gestational diabetes mellitus: a nested case-control study

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Abstract

Background Accumulating evidence shows that free fatty acids (FFA) are associated with gestational diabetes mellitus (GDM). However, most of the studies focus on a few specific types of FFA, such as α-linolenic acid (C18:3n3) and Arachidonic acid (C20:4n6) or a total level of FFA.

Objective This study aimed to test the association between a variety of FFAs during the first trimester and the risk of GDM.

Methods The participants came from the Zhoushan Pregnant Women Cohort (ZWPC). A 1:2 nested case-control study was conducted: fifty mothers with GDM were matched with 100 mothers without GDM by age, pre-pregnancy body mass index (BMI), month of oral glucose tolerance test (OGTT) and parity. Thirty-seven FFAs (including 17 saturated fatty acids (SFA), 8 monounsaturated fatty acids (MUFA), 10 polyunsaturated fatty acids (PUFA) and 2 trans fatty acids (TFA)) in maternal plasma during the first trimester were tested by Gas Chromatography–Mass Spectrometry (GC-MS). Conditional logistic regression models were performed to assess the associations of FFA with the risk of GDM.

Results Nine FFAs were respectively associated with an increased risk of GDM ($P<0.05$), and four FFAs were respectively associated with a decreased risk of GDM ($P<0.05$). SFA risk score was associated with a greater risk of GDM (OR = 1.34, 95% CI: 1.12–1.60), as well as UFA risk score (OR = 1.26, 95% CI: 1.11–1.44), MUFA risk score (OR = 1.70, 95%CI: 1.27–2.26), PUFA risk score (OR = 1.32, 95%CI: 1.09–1.59) and TFA risk score (OR = 2.51, 95%CI: 1.23–5.13). Moreover, joint effects between different types of FFA risk scores on GDM were detected. For instance, compared with those with low risk scores of SFA and UFA, women with high risk scores of SFA and UFA had the highest risk of GDM (OR = 8.53, 95%CI: 2.41–30.24), while the Odds ratio in those with a low risk score of SFA and high risk score of UFA and those with a high risk score of SFA and low risk score of UFA was 6.37 (95%CI:1.33– 30.53) and 4.25 (95%CI: 0.97–18.70), respectively.

Conclusion Maternal FFAs during the first trimester were positively associated with the risk of GDM. Additionally, there were joint effects between FFAs on GDM risk.

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Condensation Elevated FFA levels in the first trimester increased the risk of GDM.

Keywords Gestational diabetes mellitus, Free fatty acids, Risk score, Joint effect

Introduction

It is estimated that 1-30% of pregnant women would suffer from gestational diabetes mellitus (GDM) [1]. As is reported in previous studies, GDM is often associated with adverse outcomes for both the mother and the baby, such as macrosomia, preterm, cesarean section, preeclampsia, hypertension, and type-2 diabetes mellitus (T2DM) [2]. However, the risk factors of GDM are not clarified completely. Research has shown that the maternal dietary pattern is associated with the risk of gestational diabetes mellitus (GDM) [3, 4]. What's more, one study [5] pointed out that dietary intake might influence the FFAs. Therefore, FFA may be involved in the development of GDM.

Fatty acid (FA) is a hydrocarbon chain carboxylic acid and can be divided into SFAs and UFAs. Synthesis of FAs occurs in the endoplasmic reticulum and cytoplasm. SFAs can be synthesized by all mammals, and the final products are usually stearic acid (C18:0) and palmitic acid (C16:0). Long-chain FAs are transformed by fatty acid synthase (FAS) from Malonyl-CoA. Palmitic acid is the primary fatty acid that is synthesized by FAS and then palmitic acid will go through elongation to synthesize longer chain SFAs by elongases (ELOVL). MUFAs and PUFAs are then transformed by fatty acid desaturates (FADS). The $-CH_3$ is called omega (ω) carbon. Depending on the first double bond from the methyl end of molecule backbone, UFAs can be divided into omega-3 (n3), omega-6 (n6), and omega-9 (n9) UFAs. As mentioned above, SFAs can be synthesized to generate omega-9 MUFAs, but SFAs can not be used to generate the precursors of omega-6 and omega-3 series of PUFAs [6]. Thus, two parent fatty acids of omega-3 and omega-6 fatty acids are known to be essential fatty acids: alpha-linoleic acid (C18:3n3) and linoleic acid (C18:2 *cis*-n6) [7]. When the FAs are circulating in the plasma rather than in easter form, fatty acids are also known as non-esterified fatty acids (NEFAs) or free fatty acids (FFAs).

During pregnancy, maternal lipid metabolism will change to adapt to fetal growth and development, including the accumulation of adipose tissue in the first trimester, accompanied by insulin resistance, enhanced lipolysis in the third trimester, and elevated FFA levels [8]. Increased blood FFA levels are associated with insulin resistance and impaired glucose tolerance [9]. However, some studies show that FFAs such as Palmitoleic acid, Oleic acid, Linoleic acid and alpha-Linolenic acid are negatively connected with homeostatic model assessment of insulin resistance [5]. These studies indicate a controversial role that FFAs might play in the process of GDM. An elevated level of FFAs was discovered in individuals diagnosed with normal glucose tolerance, impaired glucose tolerance and type 2 diabetes [10].However, these studies measured either an overall level of FFAs or only a few types of FFAs. A detailed relationship between different FFAs and GDM needs to be discovered.

This study aimed to explore the associations of both the concentration of various FFAs in the first trimester and their risk scores with the risk of GDM by a nested case-control study. In addition, the joint effects and interactions analysis of different types of FFAs on the risk of GDM were also evaluated.

Materials and methods

Participants

Zhoushan Pregnant Cohort (ZWPC) is a prospective cohort that was initiated in 2011 at Zhoushan Maternal and Child Care Hospital in Zhoushan (N30°). Under the ZWPC study, women who met the following conditions were included: (1) enrollment at the gestational age of 8-12th week; (2) accomplishment of perinatal examination and delivery of infants in Zhoushan Maternal and Child Care Hospital; (3) Women who were between 18 and 45 years old; (4) No family history of mental disorder (5) Agreement on participation in the study. Exclusion criteria included (1) a history of serious chronic or acute disease; (2) a psychic disorder before pregnancy; (3) threatened abortion; (4) fetal malformations or fetal development abnormalities; (5) incapability of completing the questionnaire due to intellectual problems. The detailed information about this cohort has been previously described [11, 12]. Briefly, up to May 2018, the cohort recruited 3431 women who had taken the OGTT test. The study protocol was approved by the Medical Ethical Committee of the School of Medicine, Zhejiang University. A nested case-control study was conducted to detect the effect of FFA on the risk of GDM. In the current study, 50 pregnant women diagnosed with GDM were randomly selected, and 100 healthy pregnant women were matched with GDM cases by maternal age (±3 years), pre-pregnancy BMI (±1 kg/m^2), OGTT month (±1 month) and parity.

Information and blood sample collection

After pregnant women provided the informed consent form, a face-to-face interview would be conducted by a well-trained nurse to collect socio-demographic, lifestyle and health behavior information using a structured questionnaire in 8th -14th gestational week, and a 5 ml fasting venous blood sample would be drawn, and centrifuged

under 4 °C, then the plasma and white blood cell were stored under −80 °C until use. Each pregnant woman would be followed up in the 24th -28th gestational week, 32th -36th gestational week and 42nd day postpartum, respectively. The corresponding questionnaire was investigated, and a 5 ml fasting venous blood sample would also be drawn at each visit.

Diagnosis of GDM

Diagnosis of GDM was determined with criteria proposed by the International Association of Diabetes and Pregnancy Study Groups [13]. A 75 g oral glucose tolerance test (OGTT) was performed during gestational age of 24–28 weeks. Pregnant women who had not been previously diagnosed with diabetes, and then GDM was diagnosed if one of the following conditions was met: fasting plasma glucose ≥ 5.1 mmol/L, 1 h glucose ≥ 10.0 mmol/L or 2 h plasma glucose ≥ 8.5 mmol/L.

Measurement of FFA and data management

A total of 37 FFAs were selected including SFAs (C4:0, C6:0, C8:0, C10:0, C11:0, C12:0, C13:0, C14:0, C15:0, C16:0, C17:0, C18:0, C20:0, C21:0, C22:0, C23:0, C24:0), MUFAs (C14:1, C15:1, C16:1, C17:1, C18:1 *cis*-n9, C20:1, C22:1n9, C24:1), PUFAs (C18:2 *cis*-n6, C18:3n6, C18:3n3, C20:2, C20:3n6, C20:3n3, C20:4n6, C22:2, C20:5n3, C22:6n3), TFAs(C18:1 *trans*-n9, C18:2 *trans*-n6).

Concentrations of 37 types of FFAs during the first trimester were measured using Gas chromatography–mass spectrometry (SHIMADZU, GC-MS), which allows analysis and detection of a small amount of substance [14], ranging from nanogram (10^{-9} g) to femtogram (10^{-15} g). In order to control the quality of measurement, ten of the blood samples were tested twice to test the stability of the result. The inter assay coefficient of variation (CV) for FFA is 6.42%.

Outliers were defined as values that deviated by three times the standard deviation and marked as missing values; then (x-min)/(max-min) was used for the standardization of each FFA. This allows for the integration of variables on different scales into a single risk assessment model. Similarly, by standardizing FFA concentrations, we aimed to facilitate the combined analysis of FFAs with varying concentrations, ensuring that each contributes proportionately to the risk assessment. Out of 37 FFAs, 27 have missing values; the highest missing rate was less than 5%. A detailed description of the missing rate of each fatty acid was summarized in Supplement Table 1. Missing values of FFA were filled using multiple imputation with R software package mice (3.9.0).

Statistical analysis

Shapiro-Wilk test of normality was performed to determine whether the variables met a normal distribution. Mean ± SD or median (Q1, Q3) were used to present variables of normal and abnormal distribution, respectively; and comparison of corresponding variables between GDM and no-GDM group were conducted with student's t-test and Kruskal-Wallis Rank Sum Test, respectively. Comparison of categorical variables between two groups was conducted using the chi-square test or Fisher exact test.

Firstly, multivariable conditional logistic regression was performed to detect the association of the original value of each FFA concentration with a risk of GDM. Secondly, due to very different concentrations between FFAs, ranging from less than 1 nmol/mL to almost 4000 nmol/mL (Supplement Table 2), in order to detect the comprehensive effect of each specific category of FFAs and all FFAs, the standardized concentration of each FFA was generated by formula: (x-min)/(max-min), then standardized regression coefficient (β) of each FFA with GDM was evaluated. If their association (β) was negative, the standardized concentration was furtherly transferred by 1- standardized concentration to ensure each standardized FFA positively correlates with GDM risk. Then, the standardized regression coefficient (β) of each FFA with GDM was used to generate the weighted risk scores. The conditional logistic regression model was used to evaluate the association of the weighted risk score with GDM risk.

In addition, all the FFA risk scores were divided into high and low by median; crossover analysis was used to detect the joint effect of risk scores among different types of FFAs. All the models were adjusted for weight gain from pregnancy to 24th gestational weeks and exercise during pregnancy.

Besides, one previous study [4] with a case-control study design indicated that dietary factors and GDM history may influence GDM. Therefore, the frequency of dietary intake of protein, fiber, and carbohydrates and the history of diabetes diagnosis were also included as covariates. Our questionnaire collected the intake frequency of sugar drinks, sweets, meat, seafood, milk, eggs, vegetables, and fruit. They were divided into three categories (< 1 time a week, 1–4 times a week, ≥ 5 times a week). Main food intake frequency was divided into three categories (< 200 g a day, 200–400 a day, and > 400 g a day). Supplement intake frequency was divided into 3 categories (Never, 1–3 times a week, ≥ times a week). Finally, carbohydrate intake frequency score was calculated as the sum of the main food, sugar drink and sweets intake. Protein intake frequency score was calculated as the sum of meat, milk, bean products, and egg intake. Fiber intake frequency score was calculated as the sum of vegetable and fruit intake. All the intake frequencies were used to represent the intake level of the nutrients.

Table 1 Baseline of the population characteristics

Variables	GDM (*N* = 50)	Control (*N* = 100)	*P*
	Median(Q1, Q3) / Mean ± SD		
Age (y)	28.00 (26.00, 29.00)	28.00 (26.00, 29.00)	0.596
Prepregnancy BMI (kg/m2) [a]	20.12 (18.97, 21.70)	20.08 (18.75, 21.43)	0.842
Weight gain (kg) [b]	7.86 (2.71)	7.64 (2.94)	0.651
Carbohydrate intake frequency score [a]	4.00 (4.00, 4.75)	4.00 (3.00, 4.00)	0.369
Protein intake frequency score[a]	9.00 (8.00, 11.00)	9.00 (7.00, 10.00)	0.126
Fiber intake frequency score[a]	5.00 (5.00, 6.00)	5.00 (4.00, 6.00)	0.048
	N(%)		
Supplement intake			0.57
Never	14 (28.0)	35 (35.0)	
1–3 times a week	16 (32.0)	33 (33.0)	
≥ 4 times a week	20 (40.0)	32 (32.0)	
Diabetes History			0.338
No	46 (92.0)	97 (97)	
Yes	4 (8.0)	3 (3.0)	
Season of OGTT			0.949
Winter/Spring	36 (72.00)	70 (70.00)	
Summer/Autumn	14 (28.00)	30 (30.00)	
First parity			1.000
No	5 (10.0)	10 (10.0)	
Yes	45 (90.0)	90 (90.0)	
Planned birth			0.207
No	14 (28.0)	40 (40.0)	
Yes	36 (72.0)	60 (60.0)	
Education			0.92
Middle school or less	3 (6.0)	5 (5.0)	
High school	6 (12.0)	14 (14.0)	
College or more	41 (82.0)	81 (81.0)	
Annual Income [c]			0.162
< 30,000 yuan	8 (16.0)	13 (13.0)	
≥ 30,000 yuan	42 (84.0)	80 (80.0)	
Not sure	0 (0.0)	7 (7.0)	
Exercise after pregnancy [d]			0.379
0 day/week	41 (82.0)	87 (87.0)	
1–3 days/week	8 (16.0)	9 (9.0)	
≥3 day/week	1 (2.0)	4 (4.0)	

[a] the variable didn't follow a normal distribution, and the corresponding *P* was obtained through the Kruskal-Wallis Rank Sum Test

[b] the variable followed a normal distribution, and the corresponding P was obtained through t-test, and weight gain calculation is based on pre-pregnancy weight and weight at a gestational age of 24 weeks

[c] the *P* value was obtained through the Fisher exact test

[d] the *P* value was obtained through continuity correction c^2method

Detailed distribution of all the nutrient intake was in Supplement Table 3.

All the analysis was based on R version 3.6.3. *P* value less than 0.05 was regarded as statistically significant.

Results

Population characteristics

Table 1 summarizes the baseline traits of participants by GDM status. GDM-Control pairs were perfectly matched in maternal age, pre-pregnancy BMI, parity, OGTT month, and exercise during pregnancy. There is also no difference in carbohydrate intake, protein intake, and supplement intake. A slight difference occurred in fiber intake between the GDM and the control group.

Plasma fatty acids and GDM

Women with GDM were more likely to have higher levels of FFAs except for C18:1 *trans*-n9 (Supplement Table 2). Even-chain SFAs especially increased the risk of GDM (C8:0, OR = 1.42, 95%CI: 1.14–1.76, *P* = 0.0028, Table 2). C10:0 is also associated with an elevated risk of GDM. Other even-chain SFAs did not show a significant

Table 2 Associations between FFAs concentration and GDM[b]

FFA	GDM (*N* = 50)	Control (*N* = 100)	OR(95%CI)	*P*[c]
SFA[a]				
C4:0	0.13 (0.10, 0.28)	0.14 (0.06, 0.24)	4.19 (0.24, 72.21)	0.315
C6:0	1.45 (1.13, 1.84)	0.93 (0.55, 1.63)	1.25 (0.85, 1.82)	0.244
C8:0	4.74 (4.04, 5.16)	2.46 (0.44, 4.87)	1.42 (1.14, 1.76)	**0.003**
C10:0	1.96 (1.54, 2.24)	1.46 (0.72, 2.13)	2.02 (1.10, 3.72)	**0.024**
C11:0	0.21 (0.14, 0.30)	0.27 (0.13, 0.57)	0.08 (0.01, 0.50)	**0.009**
C12:0	9.60 (7.28, 13.18)	8.33 (6.59, 10.36)	1.05 (0.97, 1.15)	0.224
C13:0	0.46 (0.27, 0.51)	0.51 (0.25, 0.92)	0.26 (0.07, 0.92)	**0.037**
C14:0	107.94 (86.66, 136.23)	98.30 (77.40, 131.82)	1.00 (0.99, 1.01)	0.615
C15:0	21.46 ± 5.09	20.49 ± 5.44	1.02 (0.95, 1.10)	0.588
C16:0	3648.64 (3289.18, 4093.15)	3741.44 (3270.67, 4588.65)	1.00 (1.00, 1.00)	0.256
C17:0	27.99 ± 5.60	27.33 ± 6.07	1.01 (0.94, 1.08)	0.763
C18:0	1023.17 (946.67, 1158.01)	1075.37 (941.64, 1690.35)	1.00 (1.00, 1.00)	0.073
C20:0	21.13 (19.21, 22.43)	20.85 (18.33, 24.28)	0.99 (0.91, 1.08)	0.819
C21:0	1.77 ± 0.43	1.73 ± 0.36	1.33 (0.49, 3.65)	0.569
C22:0	33.50 (29.41, 38.48)	35.41 (29.96, 40.30)	0.99 (0.95, 1.04)	0.784
C23:0	12.81 (10.75, 13.97)	13.41 (11.66, 15.42)	0.87 (0.77, 1.00)	**0.048**
C24:0	25.81 (23.78, 29.95)	25.89 (22.24, 31.18)	0.98 (0.93, 1.04)	0.475
MUFA[a]				
C14:1	3.58 (2.43, 5.22)	2.54 (1.72, 3.65)	1.23 (1.04, 1.46)	**0.015**
C15:1	2.08 (1.47, 3.03)	1.41 (0.71, 2.91)	1.16 (0.83, 1.62)	0.378
C16:1	163.31 (132.29, 201.84)	134.67 (106.67, 163.86)	1.01 (1.00, 1.02)	**0.023**
C17:1	9.12 (7.04, 11.09)	7.86 (6.62, 9.78)	1.07 (0.94, 1.23)	0.290
C18:1 *cis*-n9	1321.75 ± 221.88	1237.22 ± 222.55	1.00 (1.00, 1.00)	0.067
C20:1	26.11 (21.59, 30.47)	20.06 (11.91, 28.20)	1.06 (1.01, 1.12)	**0.019**
C22:1n9	19.89 (18.52, 20.92)	19.37 (18.20, 20.55)	0.96 (0.79, 1.16)	0.647
C24:1	47.44 ± 10.44	51.19 ± 13.31	0.96 (0.92, 0.99)	**0.021**
PUFA[a]				
C18:2 *cis*-n6	2905.56 ± 459.26	2710.16 ± 438.90	1.00 (1.00, 1.00)	0.065
C18:3n6	26.46 (13.03, 39.86)	19.78 (12.20, 32.46)	1.03 (1.00, 1.06)	**0.025**
C18:3n3	91.65 (75.75, 110.36)	78.76 (63.04, 101.80)	1.01 (1.00, 1.02)	0.169
C20:2	29.93 ± 8.21	27.59 ± 7.68	1.03 (0.98, 1.08)	0.226
C20:3n6	132.49 (101.08, 157.34)	108.27 (81.82, 144.06)	1.01 (1.00, 1.02)	**0.044**
C20:3n3	2.93 (2.37, 3.93)	2.60 (1.95, 3.45)	1.21 (0.88, 1.67)	0.230
C20:4n6	544.71 ± 142.42	505.48 ± 139.99	1.00 (1.00, 1.01)	0.149
C22:2	3.12 (2.56, 4.29)	2.85 (2.50, 3.84)	1.20 (0.86, 1.68)	0.279
C20:5n3	75.74 (56.48, 115.34)	57.12 (34.58, 92.37)	1.01 (1.00, 1.02)	**0.028**
C22:6n3	439.67 (388.11, 517.04)	372.30 (278.76, 481.00)	1.00 (1.00, 1.01)	**0.015**
TFA[a]				
C18:1 *trans*-n9	6.98 (4.37, 11.27)	9.61 (6.51, 18.97)	0.91 (0.85, 0.98)	**0.015**
C18:2 *trans*-n6	1.01 (0.68, 1.81)	0.99 (0.55, 1.40)	1.17 (0.67, 2.04)	0.578

[a] Multiple imputation was performed on the concentration of FFAs; [b] adjusted for exercise after pregnancy, weight gain from pregnancy to gestational age of week 24, diabetes history, carbohydrate intake frequency score, protein intake frequency score, fiber intake frequency score, and supplement intake ; [c] *P* was obtained through conditional logistic regression

connection with GDM. On the other hand, odd-chain SFAs reduced the risk for GDM (C11:0, OR = 0.08, 95%CI: 0.01–0.50, *P* = 0.0089 Table 2). Other SFAs with an odd number of carbon atoms (C13:0, C23:0) also served as protecting factors against GDM.

Besides, almost all of the MUFAs, including C14:1, C16:1, and C20:1, showed an adverse effect on GDM (C14:1, OR = 1.23, 95%CI: 1.04–1.46, *P* = 0.0153, Table 2). Nevertheless, C24:1 showed a protective effect on GDM (OR = 0.96, 95%CI: 0.92–0.99, *P* = 0.0214).

Similar to the result of MUFA, a higher level of PUFA was linked to a higher risk of GDM (C18:3 n6, OR = 1.03, 95%CI: 1.00-1.06, *P* = 0.0248). Other PUFAs, such as C20:3n6, C20:5n3 and C22:6n3, were all associated with a higher risk of GDM.

Specially, one trans fatty acid C18:1 *trans*-n9 (OR = 0.91, 95%CI: 0.85–0.98, *P* = 0.0145) protected women from

Table 3 Joint effect of weighted FFA risk scores and GDM[a]

FFA Risk Score	FFA Risk Score	GDM	Control	OR(95%CI)	*P*
SFA Risk Score[b]	MUFA Risk Score				
-	-	7	47	Ref-	-
-	+	9	12	6.21(1.46–26.49)	**0.0136**
+	-	5	16	2.03(0.46–8.90)	0.3499
+	+	29	25	9.55(2.84–32.05)	**0.0003**
SFA Risk Score	PUFA Risk Score				
-	-	6	37	Ref-	-
-	+	10	22	3.26(0.77–13.83)	0.1084
+	-	12	20	4.09(0.94–17.79)	0.0608
+	+	22	21	6.45(1.81–23.00)	**0.0041**
SFA Risk Score	TFA Risk Score				
-	-	10	43	Ref-	-
-	+	6	16	1.78(0.44–7.10)	0.4171
+	-	10	12	3.77(0.97–14.62)	0.0553
+	+	24	29	3.46(1.19–10.08)	**0.0227**
MUFA Risk Score	PUFA Risk Score				
-	-	8	45	Ref-	-
-	+	4	18	0.76(0.15–3.86)	0.7412
+	-	10	12	4.44(1.05–18.74)	**0.0426**
+	+	28	25	6.46(2.02–20.61)	**0.0016**
MUFA Risk Score	TFA Risk Score				
-	-	7	44	Ref-	-
-	+	5	19	1.59(0.34–7.31)	0.5531
+	-	13	11	16.62(3.28–84.09)	**0.0007**
+	+	25	26	6.81(1.96–23.69)	**0.0025**
PUFA Risk Score	TFA Risk Score				
-	-	7	36	Ref-	-
-	+	11	21	1.94(0.53–7.08)	0.3144
+	-	13	19	2.77(0.85–9.06)	0.0916
+	+	19	24	3.68(1.13–11.95)	**0.0303**
SFA Risk Score	UFA Risk Score				
-	-	6	42	Ref-	-
-	+	10	17	6.37(1.33–30.53)	**0.0206**
+	-	9	18	4.25(0.97–18.70)	0.0555
+	+	25	23	8.53(2.41–30.24)	**0.0009**

[a] FFA risk score was calculated in the way described in the method part and median and joint effect analysis was performed; results were adjusted for exercise after pregnancy and weight gain from pregnancy to gestational age of week 24, fiber intake frequency score, carbohydrate intake frequency score, protein intake frequency score, supplement intake and history of diabetes

[b] "+" means FFA risk score was higher than the median of the corresponding FFA risk score, and "-" means the FFA risk score was lower than the median of the corresponding FFA risk score

[c] TFAs were excluded when calculating the risk score

GDM, and the other TFA showed no statistical significance (C18:2 *trans*-n6, OR=1.17, 95%CI: 0.67–2.04, *P*=0.5775).

FFAs weighted risk score and GDM

The associations of FFAs weight risk score with GDM risk were presented in Table 4. Weighted risk score of SFA (OR=1.34, 95% CI: 1.12–1.60), UFA (OR=1.26, 95%CI: 1.11–1.44), MUFA (OR=1.70, 95%CI: 1.27–2.26), PUFA (OR=1.32, 95%CI: 1.09–1.59), TFA (OR=2.51, 95%CI: 1.23–5.13) and overall (OR=1.19, 95%CI: 1.09–1.31) was significantly associated with GDM, respectively.

Joint effect of FFA and GDM

Since most FFAs' concentrations were highly correlated with each other (Supplement Fig. 1), a crossover analysis was implemented to explore the joint effect of different types of FFAs (Table 3). Compared with women with both lower MUFA Risk score and PUFA risk score, women with higher MUFA risk score (OR=4.44, 95%CI=1.05–18.74, *P*=0.0426) had a higher risk of GDM. Furthermore, a joint effect of FFA risk scores emerged in women with both higher risk scores (OR=6.46, 95%CI=2.02–20.61, *P*=0.0016). Joint effects of other risk scores are

Table 4 Association of weighted risk score of fatty acids with GDMRiska[a]

Risk Score	GDM (*N* = 50)	Control (*N* = 100)	OR (95%CI)	*P*
Overall Risk Score	29.71 (27.92, 32.55)	24.90 (19.41, 29.41)	1.19(1.09–1.31)	**0.0002**
SFA Risk Score	12.53 (11.89, 12.89)	11.53 (7.07, 12.85)	1.34(1.12–1.60)	**0.0014**
UFA Risk Score[b]	15.23 ± 3.33	12.70 ± 3.51	1.26(1.11–1.44)	**0.0006**
MUFA Risk Score[b]	6.76 ± 1.36	5.63 ± 1.52	1.70(1.27–2.26)	**0.0003**
PUFA Risk Score[b]	8.47 ± 2.41	7.07 ± 2.42	1.32(1.09–1.59)	**0.0045**
TFA Risk Score	2.14 (1.89, 2.37)	2.00 (1.02, 2.30)	2.51(1.23–5.13)	**0.0118**

[a] the calculation was based on the normalization of FFAs with coefficients of conditional logistic regression as weigh; results were adjusted for exercise after pregnancy and weight gain from pregnancy to gestational age of week 24, fiber intake frequency score, carbohydrate intake frequency score, protein intake frequency score, supplement intake and history of diabetes

similar, including PUFA and TFA, SFA and PUFA, SFA and UFA.

Comment

Principal findings

FFAs in the first trimester changed the risk of GDM. There was synergistic effect on the risk of GDM between different FFAs.

Strengths and weaknesses of the study

A major strength of this study was using data collected from a longitudinal cohort, thus reducing the risk of recall bias. Besides, this is a study integrating thirty-seven FFAs tested with GC-MS, which is an accurate technique for FFA detection. Employment of this technology, together with the amount of FFAs, is an assurance of depicting the relationship of FFA and GDM.

However, our study has several limitations. Variables such as annual income and education should be considered as adjustments in the regression models. Allowing for the power of the regression, we only adjusted the exercise after pregnancy and weight gain from pre-pregnancy to 24 weeks of gestational age. This could lead to an underfit problem, reducing the accuracy of the study. Besides, the sample size was not big enough to explore the associations of FFAs with the risk of GDM subgroup. Thus, Multi-center research is needed to increase sample size and avoid selection bias. Finally, we controlled the general dietary intake frequency, including carbohydrates, fiber, protein, and supplements, rather than a detailed intake of dietary ingredients.

Results in the context of what is known

There were very few studies investigating plasma levels of FFA and GDM. FFAs were often taken as an insulin resistance marker in nonpregnant individuals. FFAs were thought to support 30–50% of basic insulin secretion, which allowed obese people to compensate for peripheral insulin resistance [15]. In women diagnosed with GDM, the plasma FFA level is usually higher in the first trimester [16], which is in line with our study.

One hypothesis is that FFAs serve as energy producers since Oxidation of 1 g FA generates 37 kJ energy. FAs are considered to provide energy for the fetus after crossing the placenta [17]. However, an Acute exposure of FFAs leads to insulin secretion and a chronic exposure suppresses insulin secretion [18]. Thus, during the period of pregnancy, as FFA concentration grows higher, insulin resistance comes along.

A study conducted by Zhu et al. [19]. revealed a positive relationship between plasma phospholipid SFA at the gestational age of 10 to 14 weeks and GDM and a negative relationship between odd-chain SFA. A similar trend of odd-chain and even-chain SFA also appeared in our study. However, in Zhu et al.'s research, C16:0 was related to a higher risk for GDM, and C17:0 protected women from GDM, while in our study, C16:0 and C17:0 did not reduce or increase the risk for GDM. Given the literature mentioned above, a deduction was made that the number of carbons of SFA might influence its biological function.

Gouaref et al. [19] suggested that total MUFA concentration was higher in the T2DM group compared with healthy individuals. Our study revealed a similar pattern of MUFA in GDM women. Furthermore, a higher level of C18:1n9 and C14:1n9 was detected in GDM women. Consistent with the finding found by Amélie et al. [20]. , a higher level of FFA was observed in T2DM patients compared with healthy people.

In addition to MUFA, serum PUFAs were also higher in the GDM group [21], and the same increase in PUFA levels in the GDM group in the first trimester was also detected. Interestingly, essential FFAs did not show a clear tendency of protection from GDM. To be specific, the concentration of essential FFA C20:4n6 did not differ between the GDM group and the control group. Literature also showed that C20:4n6 was either the same in healthy people and T2DM patients or a little bit higher in the T2DM group [20]. This is also close to one study that suggests no correlation between serum FFA and T2DM [21]. An elevation in C22:6n3 (Docosahexaenoic Acid, DHA) and C20:5n3 (Eicosapentaenoic Acid, EPA) was also observed. Previous study suggest that a higher level of DHA and EPA in serum was associated with markers of insulin sensitivity [22]. Another meta-analysis indicated that omega-3 supplementation was not associated with GDM but was slightly relevant to insulin resistance

[23]. This could be due to the anti-inflammatory properties of DHA and EPA, which might help reduce systemic inflammation and, consequently, insulin resistance [24]. DHA and EPA can also alter cell membrane fluidity [25], enhancing insulin receptor function and promoting better insulin sensitivity.

In particular, one of the trans-FFA (C18:1 *trans*-n9) was higher in healthy control, meaning that it could be linked with lower GDM risk. On the other hand, it may also be for the small sample size, since the result was different from most of the studies' opinion on trans FFAs. When converted into risk scores, TFA risk score has a positive relationship with GDM. To our knowledge, there were few studies demonstrating the beneficial effect of specific TFAs [23], and the function of TFAs still needs to be studied.

Except for seeking links between one specific FFA risk score and GDM, we investigated that the total risk score of the FFAs had a robust positive relationship with GDM. However, in the crossover analysis, it seems the TFA risk score had a suppressive effect with other risk scores of FFAs on the risk of GDM. This conclusion differed from most studies that investigate the dietary intake of TFAs, but it may be out of the small sample size. In addition, a joint adverse effect of the FFA risk score was detected, indicating that the risk may increase with the FFA risk score growing higher.

Previous studies indicated that dietary products might influence the risk of GDM [26]. Therefore, we additionally controlled the effect of dietary factors, including protein, carbohydrate, fiber and supplements intake. The results remained similar, suggesting that FFA may have an independent effect on GDM during pregnancy.

Clinical implications

The progress of GDM involves multiple factors; this paper put a spotlight on FFA in the first trimester, which has been studied by few investigations previously. Our study highlights the importance of FFA in the first trimester in order to identify potential risk factors of GDM. The intervention of FFA in early pregnancy would protect the mothers from GDM.

Research implications

There was a high correlation between FFAs in early pregnant women. Hence, which FFA was really associated with GDM must be further explored, and the detailed molecular mechanism is still unclear.

Conclusion

Our study found that most FFAs increased the risk of GDM, and there were joint effects on GDM risk between different FFAs.

Abbreviations

BMI	Body Mass Index
DHA	Docosahexaenoic Acid
Elongases	ELOVL
EPA	Eicosapentaenoic Acid
FA	Fatty Acid
FADS	Fatty Acid Desaturases
FAS	Fatty Acid Synthase
FFA	Free Fatty Acids
GDM	Gestational Diabetes Mellitus
GC-MS	Gas Chromatography–Mass Spectrometry
MUFA	Monounsaturated fatty acids
NEFAs	Non-esterified fatty acids
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
PUFA	Polyunsaturated Fatty Acid
SFA	Saturated Fatty Acid
T2DM	Type-2 Diabetes Mellitus
TFA	Trans Fatty Acids
UFA	Unsaturated Fatty Acid
ZWPC	Zhoushan Pregnant Women Cohort

Supplementary Information

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Supplementary Material 1

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Author contributions

Haibo Zhou and Liuyan Pu analyzed the data. Hui Liu, Wen Jiang, Jinhua Wu, Yunxian Yu reviewed the manuscript. Haoyue Cheng, Wenliang Luo, Zhicheng Peng prepared the manuscript. Xing Xin, Danqing Chen, and Shuting Si prepared all the tables in the paper.

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Data availability

The data presented in this study are available on request from the corresponding author. The data are not publicly available because they contain information that could compromise the privacy of research participants.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the institutional review board of Zhejiang University School of Medicine on 2 March 2016 ((2016) Lun Shen Yan (Shen 017)). Informed consent was obtained from all the participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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