Plasma Phospholipid Monounsaturated Fatty Acids and Gestational Diabetes Mellitus: A Longitudinal Study in the NICHD Fetal Growth Studies–Singletons Cohort

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Fatty acids (FAs) have been implicated in the development of gestational diabetes mellitus (GDM), but the role of monounsaturated FAs (MUFAs) remains understudied. We investigated the associations of plasma phospholipid MUFAs in early to mid-pregnancy with cardiometabolic biomarkers and GDM risk. From the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies-Singletons cohort (2009–2013), we identified 107 women with GDM according to Carpenter and Coustan criteria and 214 control participants without GDM matched (2:1) on age, race/ethnicity, and gestational week (GW) of blood collection. MUFAs were measured at 10–14, 15–26, 23–31, and 33–39 GWs by gas chromatography mass spectrometry. We found that the concentration of total 18:1 MUFAs was significantly lower among women with GDM than those without GDM at 15–26 GWs. Each SD increment in the level of total 18:1 MUFAs was associated with a 40% lower risk of GDM at 15–26 GWs. Moreover, each SD increment in vaccenic acid (18:1n-7) levels at 10–14 and 15–26 GWs were associated with a 36% and 45% lower risk of GDM, respectively. Our extensive assessments of MUFAs advance our understanding of the unique associations of FA composition with GDM risk, suggesting the potentially beneficial role of MUFAs in GDM pathophysiology.

Circulating monounsaturated fatty acids (MUFAs) reflect both short-term dietary consumption and endogenous metabolism, which have been shown to increase insulin sensitivity (1), improve metabolic health, and even reduce the risk of diabetes (2). It has been suggested that supplementation with MUFAs potentially improves glucose tolerance by promoting glucagon-like peptide 1 secretion (3) and modulating the inhibitory insulin effect of inflammatory cytokines (4). In previous studies, we observed a unique metabolic pattern of fatty acids (FAs) in the development of gestational diabetes mellitus (GDM). Specifically, even-chain saturated FAs (SFAs) and n-6 polyunsaturated FAs were associated with a higher risk of GDM, but odd-chain SFAs were associated with a lower risk of GDM (5,6). Such findings suggest that FAs, even in the same category, may be associated

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with the risk and pathophysiology of GDM differentially. In this case-control study, we investigated the prospective associations of individual and subclasses of plasma phospholipid MUFAs in early to mid-pregnancy with levels of cardiometabolic biomarkers and the risk of GDM in later pregnancy.

RESEARCH DESIGN AND METHODS

Study Population and Design

From the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies–Singletons cohort, a multiracial prospective study of women with singleton pregnancies (2009–2013) (7), 107 cases of GDM were identified through medical record review according to Carpenter and Coustan criteria, as recommended by the American College of Obstetricians and Gynecologists and American Diabetes Association (8). The 3-h oral glucose tolerance test for participants with GDM was conducted at mean ± SD of 27 ± 4 gestational weeks (GWs). GDM case participants were individually matched at a ratio of 1:2 to 214 control participants without GDM on age (±2 years), race/ethnicity, and GW of blood sample collection (±2 weeks) (Supplementary Fig. 1). This study was approved by the institutional review boards of all participating institutions. Written informed consent was obtained from all participants.

Biomarker Assessment

Maternal blood specimens were longitudinally collected at four visits: 8–13, 16–22, 24–29, and 34–37 GWs (actual range 10–14, 15–26, 23–31, and 33–39 weeks); the second visit specimen was a fasting sample (overnight fast ≥8 h). All biospecimens were stored at −80°C until being thawed immediately before assay. Plasma phospholipid FAs were measured using a Hewlett Packard 5890 gas chromatography system with flame ionization detection. Six individual MUFAs, including palmitoleic acid (POA) (16:1n-7), petroselinic acid (18:1n-12), vaccenic acid (VA) (18:1n-7), oleic acid (OA) (18:1n-9), gondoic acid (20:1n-9), and nervonic acid (24:1n-9), and three MUFA subclasses, including total 18:1, total 18:1 *cis*, and total 18:1n-6–9 *trans* were identified. The content of plasma phospholipid MUFAs was expressed as weight percentage of the total phospholipid FAs. We also estimated the desaturase and elongase enzyme activities using the ratio of products to precursors, including desaturase Δ9-16 (16:1n-7/16:0), desaturase Δ9-18 (18:1n-9/18:0), and elongase (18:1n-7/16:1n-7) (9) (Supplementary Fig. 2). A panel of glucose metabolism and cardiometabolic biomarkers, including glucose, insulin, C-peptide, hs-CRP, high-molecular-weight adiponectin, leptin, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides, were measured at 15–26 weeks. All assays were performed blinded to the case-control status.

Data on maternal demographic, lifestyle, and clinical factors were obtained from a structured questionnaire and medical records review. Covariates, namely parity (nulliparous/multiparous), family history of diabetes (yes, no), prepregnancy BMI categories (<25.0, 25.0–29.9, 30.0–34.9, 35.0–44.9 kg/m^2), maternal age (years), and gestational age of blood collection, were all included in the full adjustment.

Statistical Methods

Differences in participant characteristics between GDM case and non-GDM control participants, among plasma phospholipid MUFA concentrations (%), and among desaturase Δ9-16, desaturase Δ9-18, and elongase activities at the two visits before GDM diagnosis were assessed by linear mixed models with associated likelihood ratio tests for continuous variables and by logistic regression with generalized estimating equations for categorical variables, accounting for matched case-control pairs. We calculated Spearman correlation coefficients to compare individual and subclasses of circulating MUFAs and desaturase Δ9-16, desaturase Δ9-18, and elongase activities at 10–14 GWs with glucose metabolism and cardiometabolic biomarkers at 15–26 GWs, including fasting plasma glucose, insulin, C-peptide, HOMA of insulin resistance (HOMA-IR), and hs-CRP (10).

Multivariable conditional logistic regression models adjusting for covariates were fitted to assess the associations of circulating MUFAs and desaturase Δ9-16, desaturase Δ9-18, and elongase activities at the first two visits (10–14 and 15–26 GWs) with subsequent risk of GDM. We analyzed MUFA and desaturase and elongase activities as continuous variables per SD and as categorical variables in quartiles on the basis of the distribution among non-GDM control participants to allow examination of potentially nonlinear associations.

Tests of linear trend were conducted by using the median value for each quartile and fitted as a continuous variable in the conditional logistic regression models. We also assessed the risk estimates associated with the joint effect of combining low 16:1 and high 18:1 MUFA levels, defined as below and above the respective median at each of the first two visits (10–14 and 15–26 GWs). In a sensitivity analysis, we additionally adjusted for plasma phospholipid SFAs to explore the potential impact of interplay with SFAs on MUFA-GDM associations. Heat maps were created to visualize and evaluate the correlations between individual MUFA, desaturase Δ9-16, and desaturase Δ9-18 activities and cardiometabolic biomarkers at 10–14 and 15–26 GWs among non-GDM control participants. All analyses were conducted using SAS 9.4 statistical software (SAS Institute, Cary, NC), and significance was defined as a two-tailed $P < 0.05$. The detailed methodology is provided in Supplementary Material 1.

Data and Resource Availability

The data sets analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

RESULTS

Plasma Phospholipid MUFA Profiles Before GDM Diagnosis

Compared with non-GDM control participants, GDM case participants had a higher likelihood of a family history of diabetes and high prepregnancy BMI (Table 1). The 18:1 MUFAs were the most abundant FAs, accounting for 9.5–10.3% of the total plasma phospholipid MUFAs (Supplementary Table 1). The concentration of plasma phospholipid VA (18:1 MUFA) was significantly lower among GDM case participants at both 10–14 and 15–26 GWs (Fig. 1). The changes of plasma phospholipid MUFAs between non-GDM control and GDM case participants at 10–14 and 15–26 GWs were not significant (Supplementary Fig. 3).

Plasma Phospholipid MUFAs in Early Pregnancy in Relation to Fasting Glucose Metabolism and Cardiometabolic Biomarkers in Later Pregnancy at 15–26 GWs

The concentration of total 18:1 MUFAs at 10–14 GWs had a significant and inverse association with subsequent glucose intolerance biomarkers (e.g., fasting insulin, C-peptide, HOMA-IR) at 15–26 GWs (Table 2). Supplementary Fig. 4 shows heat maps illustrating other associations between individual and subclasses of MUFAs at 10–14 GWs and these biomarkers at 15–26 GWs.

Plasma Phospholipid MUFAs in First and Second Trimester in Relation to Subsequent GDM Risk

Adjusting for covariates, per-SD increases in plasma phospholipid VA at both 10–14 and 15–26 GWs were associated with a 36% (adjusted odds ratio [aOR] 0.64; 95% CI 0.47, 0.88) and 45% (aOR 0.55; 95% CI 0.38, 0.79) lower risk of GDM, respectively (Table 3). In contrast, POA was

Table 1—Participant characteristics among GDM case participants and matched non-GDM control participants: the NICHD Fetal Growth Studies-Singletons cohort

	GDM (*n* = 107)	Non-GDM (*n* = 214)	*P**
Age (years)	30.5 ± 5.7	30.4 ± 5.4	—†
Race/ethnicity			—†
Non-Hispanic White	25 (23.4)	50 (23.4)	
Non-Hispanic Black	15 (14.0)	30 (14.0)	
Hispanic	41 (38.3)	82 (38.3)	
Asian/Pacific Islander	26 (24.3)	52 (24.3)	
Education			0.18
Less than high school	17 (15.9)	26 (12.1)	
High school graduate or equivalent	15 (14.0)	23 (10.7)	
More than high school	75 (70.1)	165 (77.1)	
Insurance type			0.43
Private or managed care	68 (63.5)	143 (66.8)	
Medicaid, self-pay, or other	39 (36.5)	71 (33.1)	
Marital status			0.12
Never married	11 (10.3)	35 (16.4)	
Married/living with a partner	92 (86.0)	167 (78.0)	
Divorced/separated	4 (3.7)	12 (5.6)	
Nulliparity	48 (44.9)	96 (44.9)	1
Parity			
0	48 (44.9)	96 (44.9)	0.912
1	28 (26.1)	59 (27.6)	
2	20 (18.7)	42 (19.6)	
≥3	11 (10.3)	17 (7.9)	
Family history of diabetes	40 (37.4)	48 (22.4)	0.003
Prepregnancy BMI (kg/m^2)			<0.001
<25.0	37 ± 34.6	123 ± 58.0	
25.0–29.9	35 ± 32.7	56 ± 26.4	
30.0–34.9	20 ± 18.7	17 ± 8.0	
35.0–44.9	15 ± 14.0	16 ± 7.6	
Smoking 6 months preconception	4 (3.7)	1 (0.5)	0.06
Alcoholic beverage consumption 3 months preconception	61 (57.0)	137 (64.0)	0.22

Data are mean ± SD for continuous variables or *n* (%) for categorical variables. *Obtained by linear mixed models with associated likelihood ratio tests for continuous variables and binomial/multinomial logistic regression with generalized estimating equation for binary/multilevel categorical variables (Wald tests), accounting for matched case-control pairs. †*P* values are not shown for the matching variables age and race/ethnicity.

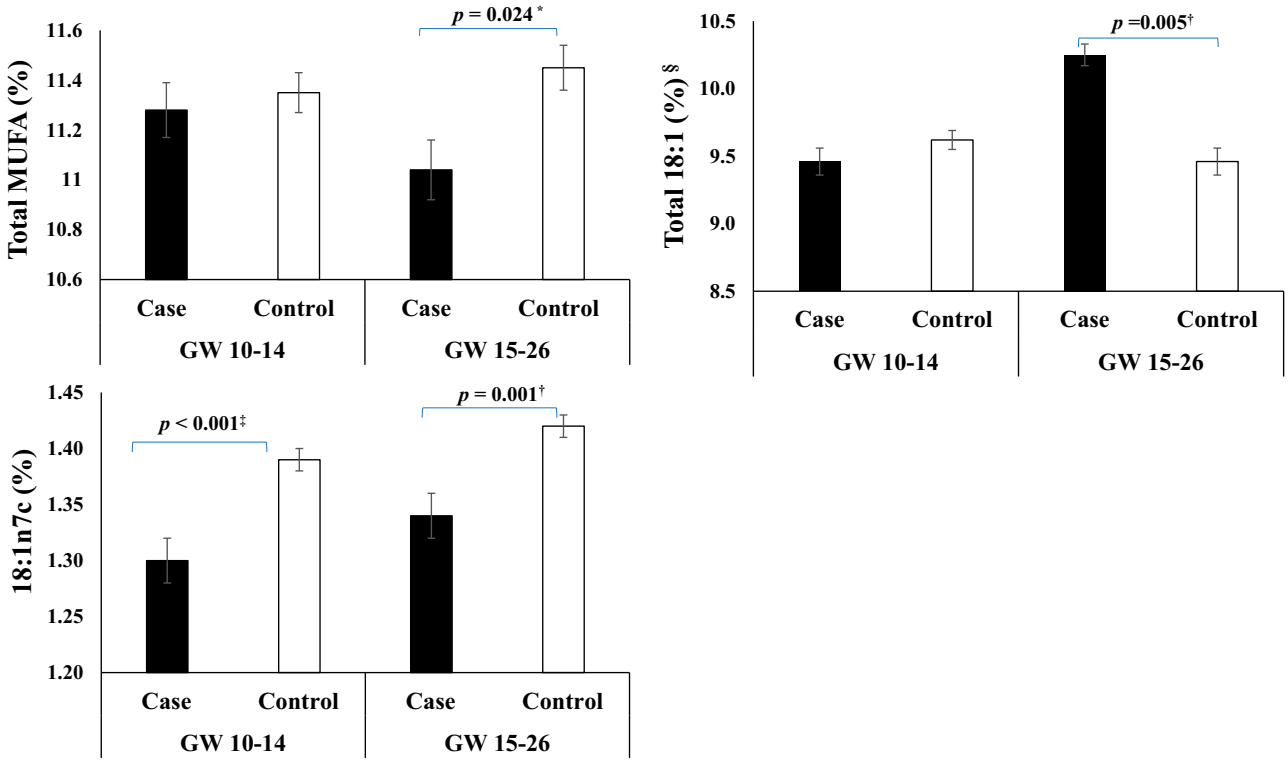

Figure 1—The concentration of total plasma phospholipid MUFAs, total 18:1 MUFAs, and VA (18:1n-7) (median, area %) at 10–14 and 15–26 GWs among GDM case and non-GDM control participants. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$; §Total 18:1 MUFAs: sum of total 18:1 *cis* and total 18:1n-6–9 *trans*.

associated with a 1.40-fold increased risk of GDM (aOR 1.40; 95% CI 1.04, 1.89) at 10–14 GWs. Moreover, per-SD increases in elongase 18:1n-7/16:1n-7 activity were significantly associated with a 38% (aOR 0.62; 95% CI 0.44, 0.86) and 76% (aOR 0.24; 95% CI 0.08, 0.67) lower risk of GDM at 10–14 and 15–26 GWs, respectively. Consistently, compared with the lowest quartile, the highest quartiles of plasma phospholipid VA and elongase 18:1n-7/16:1n-7 activity were associated with a reduced risk of GDM (Table 3). In the sensitivity analysis, adjusted for plasma phospholipid SFAs, only the inverse associations of VA at both 10–14 and 15–26 GWs remained significant.

Given the opposite directions in relation to the risk of GDM found in 18:1 and 16:1 MUFAs, the joint associations of centiles of both 18:1 MUFA (total 18:1 *cis* greater than or equal to the median percent) and 16:1 MUFA (16:1n-7 *cis* less than the median percent) with the risk of GDM were examined. Women with high 16:1 MUFAs and low 18:1 MUFAs had a fourfold increased risk of GDM. After adjustment for SFAs in the sensitivity analysis, the risk of GDM remained significant at 15–26 GWs (Supplementary Table 2).

DISCUSSION

In this study, we found that greater total plasma phospholipid 18:1 MUFAs, particularly VA, was associated with a lower risk of GDM. The plasma phospholipid 18:1 MUFAs in early pregnancy were inversely associated with levels of biomarkers of glucose intolerance (e.g., fasting insulin, C-peptide, HOMA-IR) (Table 2). Our extensive assessment of MUFAs may potentially advance our understanding of the metabolic role of MUFAs associated with the pathophysiology of GDM.

Previous studies investigating the associations between plasma phospholipid MUFA profiles and the risk of GDM are limited. We were aware of only four prospective studies (11–14) that measured selected individual MUFAs (e.g., OA, POA, VA) before GDM screening. Our findings of an inverse association of VA with the risk of GDM are in line with findings from other research on GDM and hyperglycemia (13,15). Animal models have shown that VA not only has a lipid-lowering effect through suppressing hepatic de novo lipogenesis and chylomicron secretion (16) but also demonstrates an anti-inflammatory tendency by normalizing the production of cytokines (17), where the increase in circulating cytokines has been linked to hyperglycemia (18).

MUFAs are involved in mediating cellular differentiation and metabolic homeostasis (19). Hence, the regulation of MUFA synthesis, through the coordination between elongation and desaturation, may influence insulin sensitivity and glucose and lipid metabolism. Increases in Δ9 desaturase have been adversely linked to the insulin resistant state (15,20) and increased risk for metabolic abnormalities (20) and diabetes (15). However, we found opposing associations, where desaturase Δ9-16 was positively and desaturase

Table 2—Crude Spearman correlation coefficients of plasma phospholipid MUFAs and desaturase Δ9-16, desaturase Δ9-18, and elongase activities at 10–14 GWs with subsequent fasting plasma cardiometabolic biomarkers at 15–26 GWs among non-GDM control participants

	Glucose	Insulin	C-peptide	HOMA-IR	hs-CRP	HbA_{1c}	HMW adiponectin	Leptin	Total cholesterol	HDL-C	LDL-C	TG	TFFA
Total MUFAs	−0.037	**−0.230**‡	**−0.167***	**−0.218**†	−0.087	**−0.249**‡	**0.177**†	**0.206**†	**−0.159***	−0.023	0.043	0.006	−0.131
Total 18:1 MUFAs§	−0.028	**−0.284**‡	**−0.222**†	**−0.265**‡	**−0.135***	**−0.307**‡	**0.212**†	**0.213**†	**−0.209**†	0.005	0.121	−0.019	−0.111
Total 18:1 *cis*‖	−0.016	**−0.259**‡	**−0.198**†	**−0.239**‡	**−0.196**†	**−0.311**‡	**0.188**†	**−0.223**‡	0.019	0.12	−0.023	−0.063	−0.191†
Total 18:1n-6–9 *trans*¶	−0.093	−0.103	−0.064	−0.108	**0.216**†	0.027	0.105	0.121	0.071	−0.064	−0.061	0.019	−0.144*
POA (16:1n-7 *cis*)	0.106	0.052	0.077	0.058	0.097	0.008	−0.005	0.016	0.063	0.094	0.0157	0.065	0.160*
PSA (18:1n-12 *cis*)	−0.028	−0.136*	−0.095	−0.128	**0.196**†	0.017	**0.156***	**0.208**†	−0.002	−0.059	−0.0139	0.026	−0.221†
VA (18:1n-7 *cis*)	0.034	−0.123	−0.066	−0.098	**−0.192**†	**−0.217**†	0.102	0.101	−0.107	−0.011	0.058	−0.04	−0.029
OA (18:1n-9 *cis*)	−0.029	**−0.224**‡	**−0.180**†	**−0.210**†	**−0.186**†	**−0.281**‡	**0.164***	**0.155***	**−0.211**†	0.016	0.101	−0.029	−0.04
Godonic acid (20:1n-9)	**−0.159***	**−0.155***	−0.124	**−0.181**†	0.107	−0.11	0.045	0.093	−0.057	−0.105	−0.076	−0.059	−0.116
NA (24:1n-9)	−0.084	−0.001	0.038	−0.014	0.071	0.039	−0.005	0.027	0.049	−0.094	**−0.158***	0.028	**−0.137***
Desaturase Δ9-16 (16:n-7/16:0)	0.118	0.03	0.058	0.04	0.075	0.009	0.043	0.05	0.059	0.084	0.039	0.059	0.123
Desaturase Δ9-18 (18:1n-9/18:0)	0.05	**−0.140***	−0.084	−0.123	**−0.202**†	**−0.231**‡	0.08	0.061	**−0.191**†	0.078	**0.140***	−0.009	0.067
Elongase (18:1n-7/16:1n-7)	−0.107	−0.119	−0.117	−0.111	−0.160*	−0.092	0.064	0.05	−0.118	−0.084	0.009	−0.072	−0.154

HDL-C, HDL cholesterol; HMW, high molecular weight; LDL-C, LDL cholesterol; NA, nervonic acid; PSA, petroselinic acid; TG, triglyceride; TFFA, total free fatty acid. *$P < 0.05$. †$P < 0.01$. ‡$P < 0.001$. §Total 18:1 MUFAs: sum of total 18:1 *cis* and total 18:1n-6–9 *trans*. ‖Total 18:1 *cis*: sum of 18:1n-12 *cis*, 18:1n-7 *cis*, and 18:1n-9 *cis*. ¶Total 18:1n-6–9 *trans*: sum of n-6 (unsaturated n-6), 18:1n-7 *trans*, 18:1n-8 *trans*, and 18:1n-9 *trans* and mix of n-7–9 (unsaturated n-7–n-9).

Table 3—Subsequent risk of GDM according to quartiles of plasma phospholipid MUFAs and desaturase and elongase activities at 10–14 and 15–26 GWs

	OR (95% CI)			
	10–14 GWs		15–26 GWs	
	Crude	Multivariable#	Crude	Multivariable#
Total MUFA				
Q1	Reference	Reference	Reference	Reference
Q2	0.78 (0.41, 1.49)	0.87 (0.42, 1.80)	0.54 (0.27, 1.07)	0.39 (0.17, 0.87)
Q3	0.78 (0.39, 1.54)	0.81 (0.38, 1.76)	**0.49 (0.25, 0.99)**	**0.37 (0.16, 0.86)**
Q4	0.72 (0.35, 1.48)	0.78 (0.35, 1.71)	**0.27 (0.11, 0.65)**	**0.21 (0.07, 0.58)**
Per-SD increment	0.84 (0.64, 1.10)	0.86 (0.63, 1.16)	**0.68 (0.51, 0.91)**	**0.63 (0.44, 0.89)**
P for trend**	0.383	0.524	**0.003**†	**0.003**†
Total 18:1 MUFAs§				
Q1	Reference	Reference	Reference	Reference
Q2	1.07 (0.57, 2.00)	1.12 (0.55, 2.29)	0.88 (0.47, 1.64)	0.73 (0.36, 1.48)
Q3	0.71 (0.35, 1.41)	0.75 (0.35, 1.58)	0.49 (0.23, 1.04)	**0.34 (0.14, 0.85)**
Q4	0.80 (0.39, 1.64)	0.95 (0.42, 2.17)	**0.28 (0.11, 0.69)**	**0.21 (0.07, 0.62)**
Per-SD increment	0.83 (0.64, 1.07)	0.87 (0.65, 1.17)	**0.66 (0.49, 0.89)**	**0.60 (0.41, 0.86)**
P for trend**	0.381	0.687	**0.003**†	**0.003**†
Total 18:1 cis‖				
Q1	Reference	Reference	Reference	Reference
Q2	1.08 (0.56, 2.08)	1.18 (0.56, 2.49)	0.90 (0.47, 1.72)	0.65 (0.31, 1.37)
Q3	0.61 (0.30, 1.26)	0.72 (0.32, 1.61)	0.68 (0.33, 1.40)	0.63 (0.28, 1.43)
Q4	0.92 (0.46, 1.84)	1.23 (0.55, 2.73)	**0.36 (0.15, 0.86)**	**0.30 (0.11, 0.83)**
Per-SD increment	0.88 (0.68, 1.13)	0.95 (0.71, 1.27)	**0.67 (0.50, 0.91)**	**0.63 (0.44, 0.90)**
P for trend**	0.566	0.82	**0.022***	**0.031***
Total 18:1n-6–9 *trans*¶				
Q1	Reference	Reference	Reference	Reference
Q2	1.03 (0.55, 1.94)	0.77 (0.38, 1.55)	0.60 (0.29, 1.22)	0.63 (0.28, 1.44)
Q3	0.72 (0.36, 1.46)	0.69 (0.31, 1.53)	0.71 (0.34, 1.48)	0.70 (0.30, 1.61)
Q4	**0.44 (0.20, 0.97)**	**0.38 (0.16, 0.92)**	0.58 (0.27, 1.26)	0.62 (0.26, 1.50)
Per-SD increment	**0.69 (0.50, 0.95)**	**0.60 (0.42, 0.88)**	0.80 (0.59, 1.10)	0.72 (0.50, 1.03)
P for trend**	**0.043***	**0.041***	0.211	0.313
PSA (18:1n-12 *cis*)				
Q1	Reference	Reference	Reference	Reference
Q2	1.06 (0.53, 2.11)	0.74 (0.34, 1.62)	0.97 (0.48, 1.97)	1.02 (0.44, 2.32)
Q3	0.90 (0.42, 1.91)	0.79 (0.34, 1.82)	0.86 (0.41, 1.83)	0.81 (0.35, 1.87)
Q4	0.69 (0.30, 1.59)	0.59 (0.23, 1.51)	0.58 (0.25, 1.35)	0.63 (0.24, 1.63)
Per-SD increment	0.79 (0.57, 1.09)	0.77 (0.54, 1.12)	0.76 (0.55, 1.06)	0.76 (0.52, 1.11)
P for trend**	0.377	0.313	0.201	0.284
POA (16:1n-7 *cis*)				
Q1	Reference	Reference	Reference	Reference
Q2	0.96 (0.44, 2.10)	0.66 (0.27, 1.61)	0.92 (0.38, 2.20)	0.87 (0.32, 2.34)
Q3	1.94 (0.92, 4.10)	1.66 (0.73, 3.78)	1.64 (0.76, 3.52)	1.59 (0.65, 3.84)
Q4	2.13 (0.93, 4.87)	1.50 (0.60, 3.77)	1.56 (0.68, 3.55)	1.58 (0.63, 3.99)
Per-SD increment	**1.52 (1.15, 2.02)**	**1.40 (1.04, 1.89)**	1.20 (0.91, 1.57)	1.22 (0.90, 1.65)
P for trend**	**0.022***	0.089	0.142	0.169
VA (18:1n-7)				
Q1	Reference	Reference	Reference	Reference
Q2	0.66 (0.37, 1.19)	0.77 (0.40, 1.49)	**0.47 (0.23, 0.98)**	**0.39 (0.17, 0.90)**
Q3	**0.42 (0.21, 0.84)**	**0.35 (0.16, 0.79)**	0.59 (0.30, 1.16)	0.45 (0.19, 1.02)
Q4	**0.32 (0.15, 0.67)**	**0.40 (0.18, 0.89)**	**0.24 (0.10, 0.57)**	**0.23 (0.09, 0.62)**
Per-SD increment	**0.61 (0.45, 0.81)**	**0.64 (0.47, 0.88)**	**0.57 (0.42, 0.78)**	**0.55 (0.38, 0.79)**
P for trend**	**0.001**†	**0.005**†	**0.003**†	**0.004**†
OA (18:1n-9 *cis*)				
Q1	Reference	Reference	Reference	Reference
Q2	0.89 (0.48, 1.64)	0.84 (0.42, 1.71)	0.93 (0.49, 1.75)	0.62 (0.29, 1.33)
Q3	0.60 (0.30, 1.23)	0.64 (0.30, 1.39)	0.66 (0.33, 1.32)	0.61 (0.28, 1.34)
Q4	1.16 (0.59, 2.28)	1.45 (0.67, 3.15)	0.46 (0.21, 1.04)	0.41 (0.16, 1.04)
Per-SD increment	0.99 (0.77, 1.27)	1.06 (0.80, 1.41)	0.74 (0.56, 1.00)	0.70 (0.49, 1.00)
P for trend**	0.802	0.405	0.056	0.064

Continued on p. 2713

Table 3—Continued

	OR (95% CI)			
	10–14 GWs		15–26 GWs	
	Crude	Multivariable#	Crude	Multivariable#
Gondoic acid (20:1n-9)				
Q1	*Reference*	*Reference*	*Reference*	*Reference*
Q2	0.97 (0.47, 1.99)	0.68 (0.30, 1.53)	1.02 (0.49, 2.11)	0.79 (0.33, 1.88)
Q3	0.68 (0.26, 1.73)	0.59 (0.20, 1.71)	0.97 (0.38, 2.50)	0.82 (0.29, 2.34)
Q4	0.38 (0.14, 1.08)	0.35 (0.11, 1.12)	0.53 (0.19, 1.52)	0.50 (0.16, 1.64)
Per-SD increment	**0.61 (0.40, 0.94)**	**0.56 (0.34, 0.92)**	**0.59 (0.38, 0.92)**	**0.57 (0.35, 0.94)**
P for trend**	0.088	0.086	0.211	0.264
NA (24:1n-9)				
Q1	Reference	Reference	Reference	Reference
Q2	0.53 (0.24, 1.18)	0.60 (0.25, 1.41)	1.24 (0.58, 2.66)	1.12 (0.46, 2.73)
Q3	0.48 (0.20, 1.18)	0.49 (0.18, 1.36)	0.88 (0.40, 1.94)	0.48 (0.18, 1.26)
Q4	0.47 (0.18, 1.26)	0.42 (0.14, 1.27)	0.84 (0.36, 1.94)	0.71 (0.28, 1.83)
Per-SD increment	0.82 (0.58, 1.16)	0.75 (0.51, 1.12)	0.81 (0.57, 1.16)	0.75 (0.50, 1.11)
P for trend**	0.143	0.124	0.498	0.262
Desaturase Δ9-16 (16:1n-7/16:0)				
Q1	Reference	Reference	Reference	Reference
Q2	0.53 (0.23, 1.21)	0.45 (0.18, 1.12)	0.95 (0.41, 2.22)	1.08 (0.42, 2.78)
Q3	1.59 (0.75, 3.39)	1.39 (0.59, 3.25)	1.51 (0.66, 3.47)	1.49 (0.58, 3.85)
Q4	1.74 (0.79, 3.83)	1.39 (0.59, 3.29)	1.81 (0.80, 4.11)	2.10 (0.83, 5.35)
Per-SD increment	**1.44 (1.08, 1.92)**	1.33 (0.98, 1.81)	1.15 (0.88, 1.50)	1.17 (0.87, 1.58)
P for trend**	**0.025***	0.079	0.079	0.063
Desaturase Δ9-18 (18:1n-9/18:0)				
Q1	Reference	Reference	Reference	Reference
Q2	1.26 (0.67, 2.36)	1.32 (0.65, 2.67)	0.93 (0.49, 1.74)	0.78 (0.39, 1.58)
Q3	0.73 (0.36, 1.46)	0.79 (0.37, 1.69)	0.63 (0.30, 1.30)	0.51 (0.22, 1.21)
Q4	0.85 (0.41, 1.76)	1.04 (0.46, 2.38)	**0.31 (0.13, 0.77)**	**0.26 (0.09, 0.73)**
Per-SD increment	1.02 (0.79, 1.33)	1.06 (0.79, 1.43)	0.80 (0.58, 1.09)	0.76 (0.52, 1.10)
P for trend**	0.412	0.77	**0.010***	**0.012***
Elongase (18:1n-7/16:1n-7)				
Q1	Reference	Reference	Reference	Reference
Q2	0.61 (0.32, 1.15)	0.65 (0.32, 1.32)	0.79 (0.43, 1.46)	0.76 (0.38, 1.53)
Q3	**0.25 (0.12, 0.54)**	**0.32 (0.14, 0.73)**	**0.42 (0.20, 0.87)**	**0.42 (0.19, 0.94)**
Q4	**0.30 (0.13, 0.68)**	**0.37 (0.15, 0.89)**	**0.26 (0.10, 0.67)**	**0.30 (0.11, 0.86)**
Per-SD increment	**0.57 (0.41, 0.78)**	**0.62 (0.44, 0.86)**	**0.62 (0.45, 0.85)**	**0.24 (0.08, 0.67)**
P for trend**	**0.0003‡**	**0.0053†**	**0.0015†**	**0.0079†**

NA, nervonic acid; PSA, petroselinic acid; Q, quartile; VA, vaccenic acid. *$P < 0.05$. †$P < 0.01$. ‡$P < 0.001$. §Total 18:1 MUFAs: sum of total 18:1 *cis* and total 18:1n-6–9 *trans*. ||Total 18:1 *cis*: sum of 18:1n-12 *cis*, 18:1n-7 *cis*, and 18:1n-9 *cis*. ¶Total 18:1n-6–9 *trans*: sum of n-6 (unsaturated n-6), 18:1n-7 *trans*, 18:1n-8 *trans*, and 18:1n-9 *trans* and mix of n-7–9 (unsaturated n-7–n-9). #Adjusted for age (years), gestational age at blood collection (weeks), parity (nulliparous, multiparous), family history of diabetes (yes, no), and prepregnancy BMI (<25.0, 25.0–29.9, 30.0–34.9, 35.0–44.9 kg/m^2). **P for trend was corrected using the false discovery rate method.

Δ9-18 inversely associated with the risk of GDM. A previous lifestyle intervention study (improved diet and physical activity) demonstrated changes in Δ9 desaturase and insulin resistance, suggesting that desaturase activities may link to lifestyle modification (21). While pregnancy is a unique physiological state characterized by insulin resistance, whether a insulin resistant state affects desaturation or whether lifestyle factors modify desaturation with consequences for insulin resistance are not yet determined.

While insulin resistance increases desaturase activity (22), in turn it may also affect elongation, which has been linked to the risk of diabetes in a previous study (23). Of note, there are very limited dietary sources of VA. Although the association with VA was independent of SFAs (16:0 and 18:0), elongase could be playing an important metabolic role, contributing to the conversion of POA to VA. Although the exact metabolic pathways whereby plasma phospholipid MUFAs and desaturase and elongase activities are involved in glucose homeostasis and the pathogenesis of GDM remain to be elucidated, our findings have biological plausibility and warrant further investigation.

Strengths and Limitations

A strength of our study includes the objective measurement of a range of plasma phospholipid FAs during early to mid-pregnancy, which allows adjustment for the influence of

SFAs to examine the association of MUFAs with GDM risk. Another strength is that the longitudinal measurements of FAs early in pregnancy provided an opportunity to evaluate the potential implication of metabolic changes in pregnancy. Our study is limited by the inclusion of plasma phospholipid MUFAs as the relative (weighted percentage of total) rather than absolute concentration of individual phospholipid FAs. Nonetheless, this approach has been validated and is widely used and accepted in epidemiological studies (24). In addition, our observational findings cannot infer a causal relationship between MUFAs and the risk of GDM; therefore, whether the changes in circulating MUFAs are the precursor or the consequence of adaptation to the metabolic condition requires future investigation.

In summary, in this prospective study, we investigated individual plasma phospholipid MUFAs and desaturation and elongation activities associated with cardiometabolic biomarkers in pregnancy and GDM risk. Our findings suggest that 18:1 MUFAs, particularly VA, have potential beneficial roles in GDM pathophysiology. The overall findings might advance our understanding of the unique associations of various types of MUFAs with GDM risk. Further clinical studies are needed to explore the interventional value of specific modifiable MUFAs in terms of GDM prevention.

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