

Article

Associations of Maternal rs1801131 Genotype in *MTHFR* and Serum Folate and Vitamin B₁₂ with Gestational Diabetes Mellitus in Chinese Pregnant Women

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Citation: Li, S.; Tian, X.; Wang, Y.; Zhang, X.; Zhang, L.; Li, C.; Li, J.; Wang, C.; Liu, H.; Liu, J.; et al. Associations of Maternal rs1801131 Genotype in *MTHFR* and Serum Folate and Vitamin B₁₂ with Gestational Diabetes Mellitus in Chinese Pregnant Women. *Nutrients* **2022**, *14*, 1169.

<https://doi.org/10.3390/nu14061169>

Academic Editor: A. Catharine Ross

Received: 20 January 2022

Accepted: 8 March 2022

Published: 10 March 2022

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Abstract: Circumstantial evidence links one-carbon metabolism (OCM) related nutrients, such as folate and vitamin B₁₂, with gestational diabetes mellitus (GDM). However, few studies have evaluated the combined effects of these nutrients with OCM related gene polymorphisms on GDM. This study investigated whether OCM related genetic variants modified the associations of folate and B₁₂ with GDM. Logistic regression was used to estimate odds ratios (ORs) for OCM related nutrients and single nucleotide polymorphisms (SNPs) in genes encoding main OCM related enzymes (*MTHFR*, *MTR*, and *MTRR*) on GDM. Higher folate concentrations were associated with increased GDM risk (OR: 1.59; 95% CI: 1.22, 2.13). However, higher B₁₂ concentrations were associated with reduced GDM risk (OR: 0.76; 95% CI: 0.65, 0.92). Pregnancies with *MTHFR* rs1801131 G alleles had a significantly lower risk of GDM than pregnancies with T alleles (OR: 0.65; 95% CI: 0.47, 0.91) under the dominant model. The genotype-stratified analysis revealed the association between folate and GDM (OR: 1.66, 95% CI: 1.20, 2.30) or B₁₂ and GDM (OR: 0.80, 95% CI: 0.65, 0.98) was more evident in pregnancies with TT genotype. Higher folate and lower B₁₂ are associated with GDM. Pregnancies with *MTHFR* rs1801131 TT genotype are more susceptible to OCM nutrient-related GDM.

Keywords: *MTHFR*; folate; vitamin B₁₂; one-carbon metabolism; gestational diabetes mellitus

Supplementary Materials:

Table S1. OCM related single nucleotide polymorphisms.

SNP	Gene	Genotype	n (%)	HWE <i>P</i> -value ^a	No-GDM	GDM	<i>P</i> -value ^b
rs1532268	MTRR	CC	1035 (74.6)	0.157	824 (79.6)	211 (20.4)	0.311
		CT	302 (21.7)		247 (81.8)	55 (18.2)	
		TT	29 (2.1)		26 (89.7)	3 (10.3)	
		Missing	22 (1.6)				
rs162036	MTRR	AA	935 (67.4)	0.842	738 (78.9)	197 (21.1)	0.147
		AG	399 (28.7)		332 (83.2)	67 (16.8)	
		GG	46 (3.3)		39 (84.8)	7 (15.2)	
		Missing	8 (0.6)				
rs162048	MTRR	AA	474 (34.2)	0.079	376 (79.3)	98 (20.7)	0.834
		AG	686 (49.4)		554 (80.8)	132 (19.2)	
		GG	203 (14.6)		163 (80.3)	40 (19.7)	
		Missing	25 (1.8)				
rs16879334	MTRR	CC	984 (70.9)	0.905	796 (80.9)	188 (19.1)	0.417
		CG	349 (25.1)		278 (79.7)	71 (20.3)	
		GG	32 (2.3)		23 (71.9)	9 (28.1)	
		Missing	23 (1.7)				
rs1801131	MTHFR	TT	987 (71.1)	0.166	774 (78.4)	213 (21.6)	0.021
		TG	355 (25.6)		300 (84.5)	55 (15.5)	
		GG	22 (1.6)		20 (90.9)	2 (9.1)	
		Missing	24 (1.7)				
rs1801133	MTHFR	AA	428 (30.8)	0.222	342 (79.9)	86 (20.1)	0.140
		AG	663 (47.8)		522 (78.7)	141 (21.3)	
		GG	275 (19.8)		232 (84.4)	43 (15.6)	
		Missing	22 (1.6)				
rs1801394	MTRR	AA	778 (56.1)	0.618	633 (81.4)	145 (18.6)	0.510
		AG	494 (35.6)		391 (79.1)	103 (20.9)	
		GG	85 (6.1)		66 (77.6)	19 (22.4)	
		Missing	31 (2.2)				
rs1805087	MTR	AA	1106 (79.7)	0.186	888 (80.3)	218 (19.7)	0.958
		AG	263 (18.9)		211 (80.2)	52 (19.8)	
		GG	9 (0.7)		7 (77.8)	2 (22.2)	
		Missing	10 (0.7)				
rs2229276	MTR	AA	407 (29.3)	0.147	332 (81.6)	75 (18.4)	0.187
		AG	671 (48.4)		526 (78.4)	145 (21.6)	
		GG	300 (21.6)		249 (83.0)	51 (17.0)	
		Missing	10 (0.7)				
rs28372871	MTR	TT	349 (25.1)	0.248	290 (83.1)	59 (16.9)	0.112
		TG	669 (48.2)		522 (78.0)	147 (22.0)	

		GG	330 (23.8)		270 (81.8)	60 (18.2)	
		Missing	40 (2.9)				
rs326119	MTRR	AA	438 (31.6)	0.157	343 (78.3)	95 (21.7)	0.294
		AC	685 (49.3)		561 (81.9)	124 (18.1)	
		CC	243 (17.5)		192 (79.0)	51 (21.0)	
		Missing	22 (1.6)				
rs3776455	MTRR	CC	674 (48.6)	0.313	548 (81.3)	126 (18.7)	0.673
		CT	562 (40.5)		446 (79.4)	116 (20.6)	
		TT	132 (9.5)		105 (79.5)	27 (20.5)	
		Missing	20 (1.4)				

Values are *n* (%).

^a Hardy-Weinberg equilibrium checked in No-GDM subjects.

^b P-values were obtained by Chi-square test or Fisher's exact test.

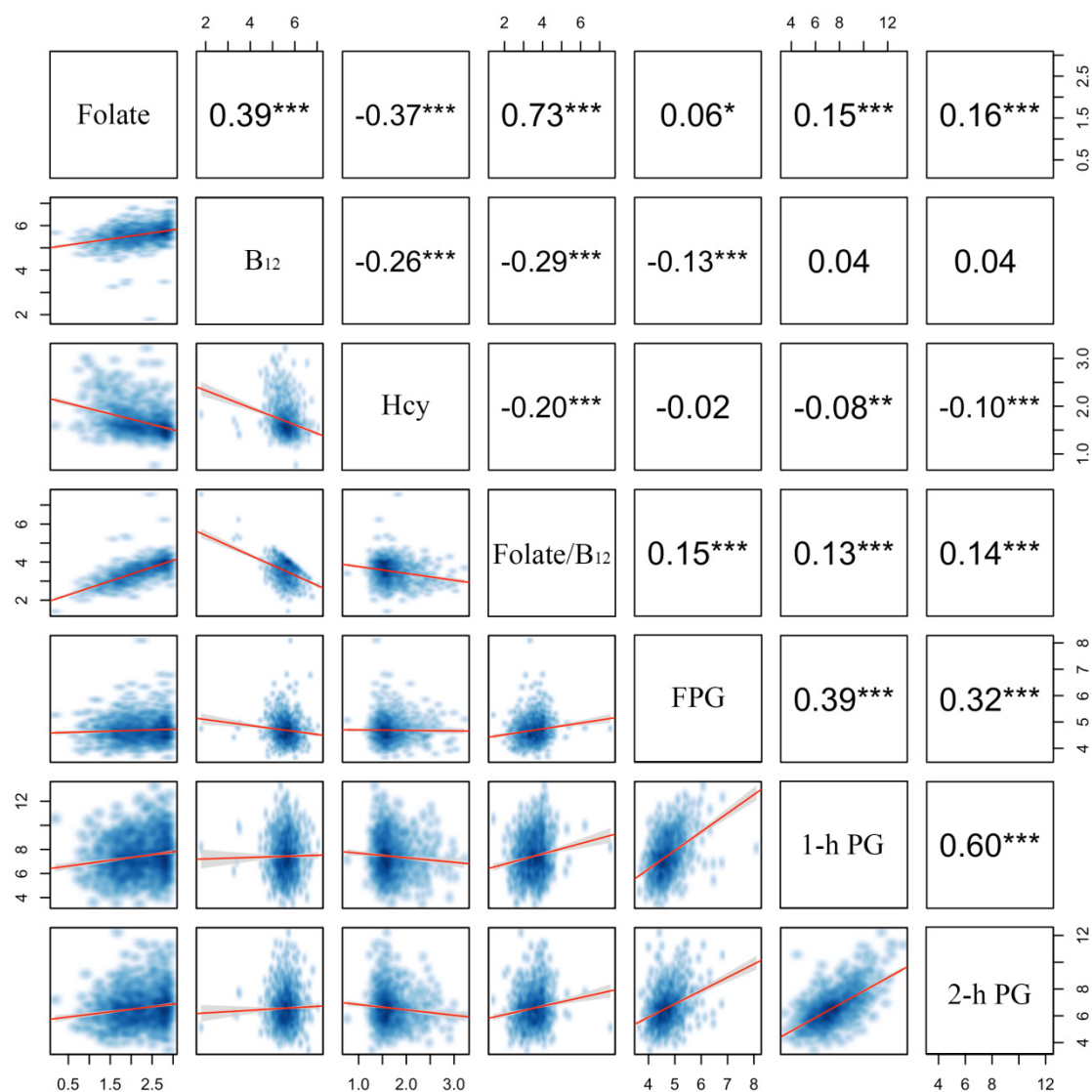


Figure S1. Spearman's correlation matrix of serum OCM indicators, and fasting, 1-h, and 2-h plasma glucose. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. FPG, fasting plasma glucose; B₁₂, vitamin B₁₂; Hcy, homocysteine; 1-h PG, 1-hour plasma glucose; 2-h PG, 2-hour plasma glucose.

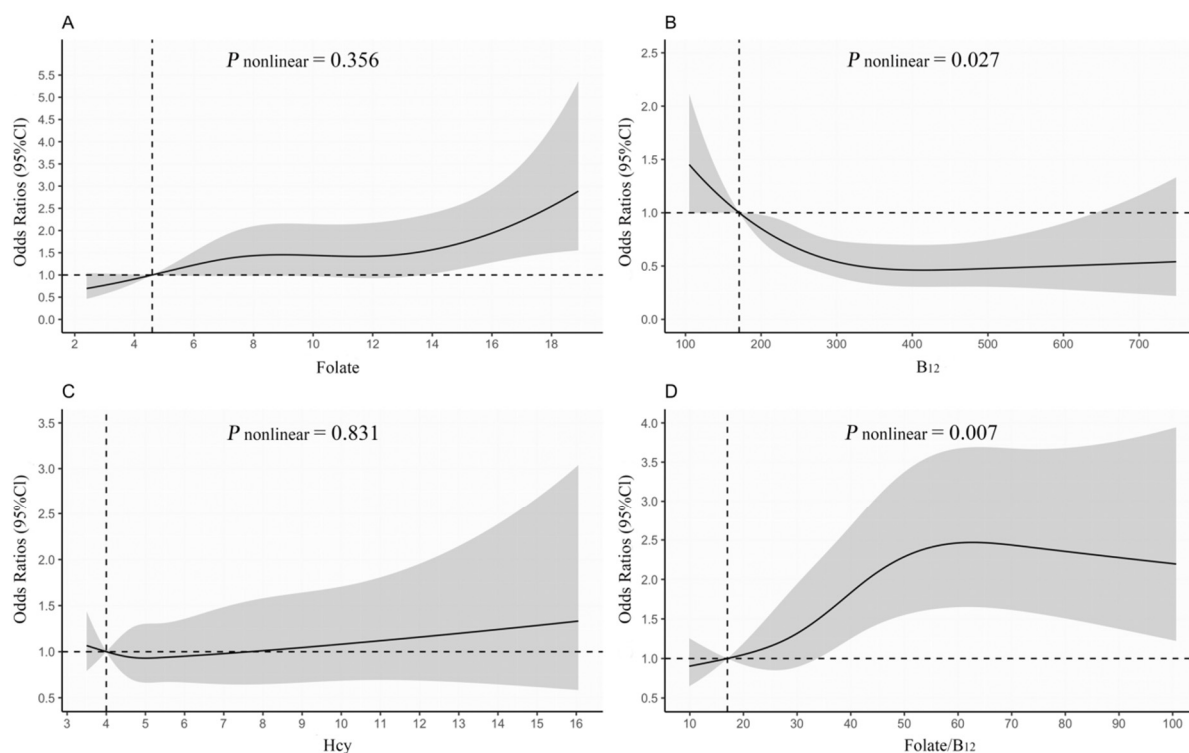


Figure S2. Restricted cubic spline (RCS) regression analysis of OCM indicators with GDM risk. Model adjusted for age, ethnicity, education, drinking, smoking, parity, family history of diabetes, and prepregnancy BMI. In addition, folate, B₁₂, and Hcy were mutually adjusted in estimating the association of another OCM indicator with GDM. 10% percentile value was selected as the reference level for each OCM indicator. (A) 4.6 ng/mL for serum folate; (B) 171 pg/mL for serum B₁₂; (C) 4.0 μmol/L for serum Hcy; (D) 17 for serum folate/B₁₂. The solid lines indicate estimated ORs, and the gray areas represent 95% CI.

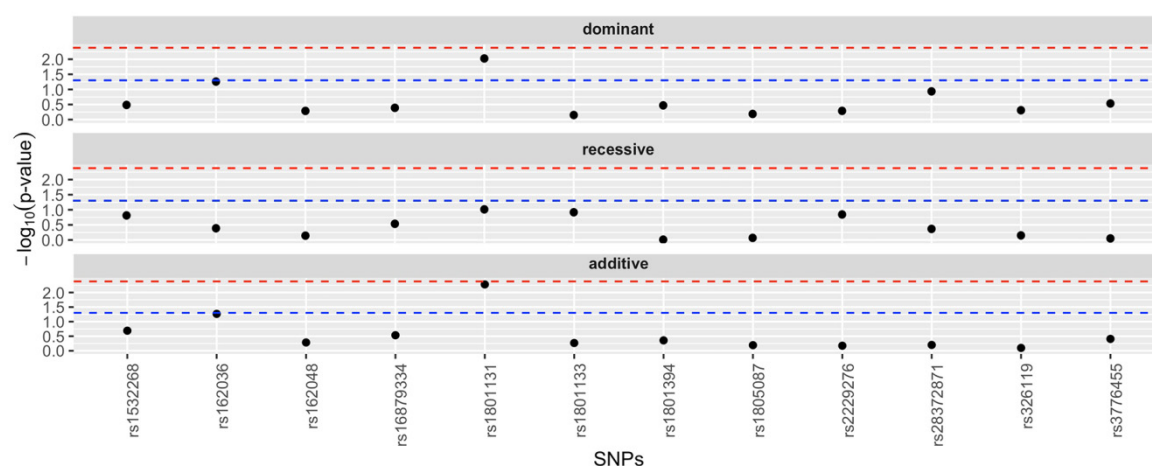


Figure S3. The associations between OCM related SNPs and GDM under three different genetic models: dominant, recessive, and additive. The $-\log p$ values from likelihood ratio test for each SNPs are showed for each genetic model. All models adjusted for age, ethnicity, education, drinking, smoking, parity, family history of diabetes, prepregnancy BMI, and serum folate, B₁₂ and Hcy concentrations. The horizontal dotted lines indicate two different thresholds. One of them based on Bonferroni correction (red line), and another one in the nominal P -value which is set equal to 0.05 (blue line).