

Supplementary Materials

Plasma One-Carbon Metabolism-Related Micronutrients and the Risk of Breast Cancer: Involvement of DNA Methylation

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Supplementary Materials

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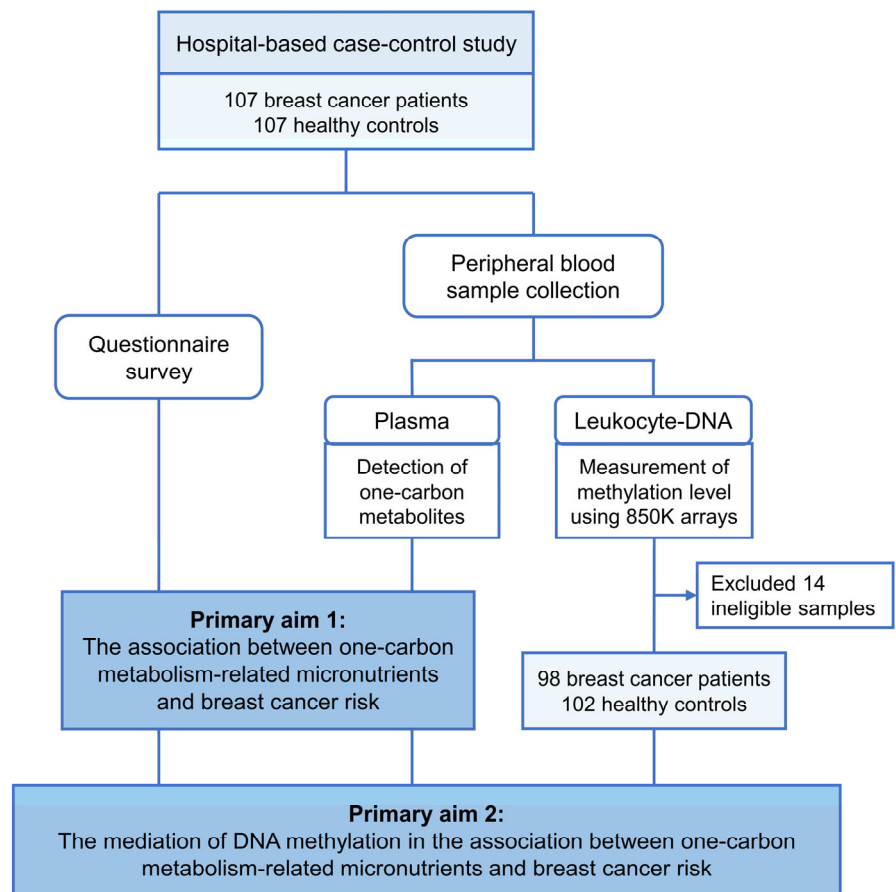


Figure S1. Flow chart of the study.

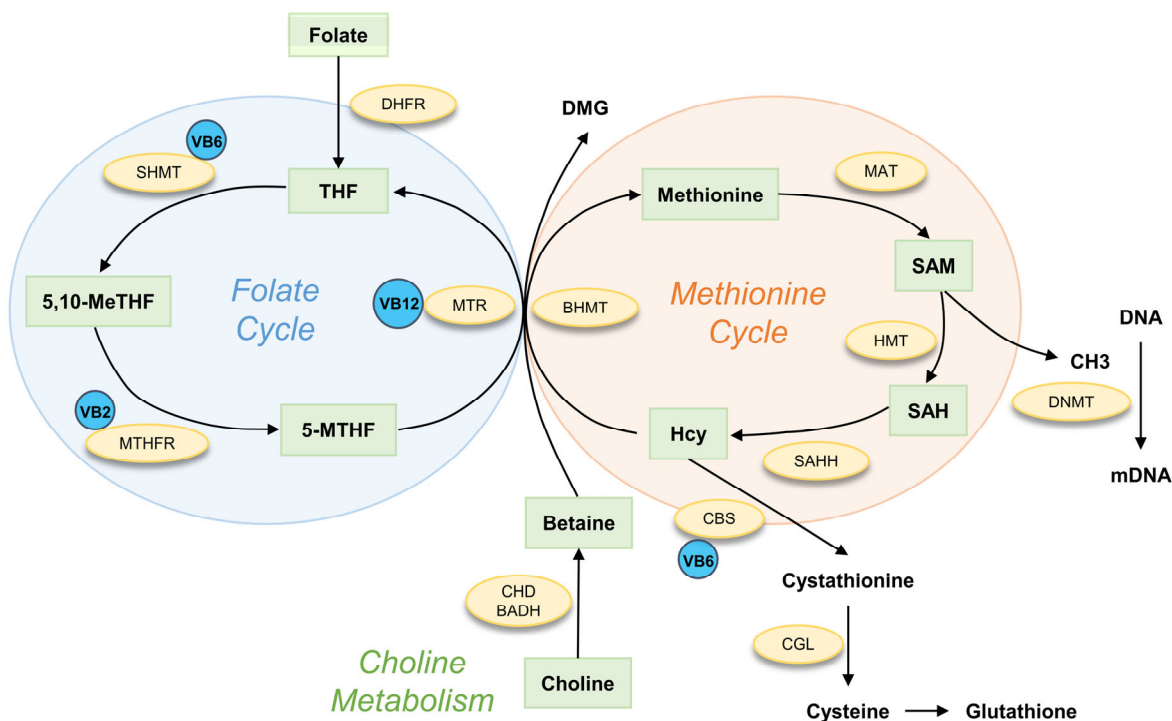


Figure S2. Overview of one-carbon metabolism and its related micronutrients. Two major components of one-carbon metabolism comprise the folate cycle and methionine cycle. The choline metabolism is mainly involved in the re-methylation of Hcy, parallel to the widespread folate-dependent homocysteine re-methylation pathway. The Vitamins B2, B6 and B12 participate in one-carbon metabolism as enzymatic factors. The SAM acts as a methyl-donor to provide methyl for DNA methylation process under the action of DNMT. Abbreviations: 5,10-MeTHF, 5,10-methylenetetrahydrofolate; 5-MTHF, 5-methyltetrahydrofolate; BADH, betaine aldehyde dehydrogenase; BHMT, betaine homocysteine methyltransferase; CBS, cystathionine β -synthase; CGL, Cystathionine γ -lyase; CHD, choline dehydrogenase; DHFR, dihydrofolate reductase; DMG, dimethylglycine; DNMT, DNA methyltransferase; Hcy, homocysteine; HMT, histone methyl transferase; MAT, methionine adenosyltransferase; MTHFR, methyltetrahydrofolate reductase; MTR, methionine synthase; SAH, S-adenosylhomocysteine; SAHH, S-adenosylhomocysteine hydrolase; SAM, S-adenosylmethionine; SHMT, serine hydroxymethyltransferase; THF, tetrahydrofolate; VB12, vitamin B12; VB2, vitamin B2; VB6, vitamin B6.

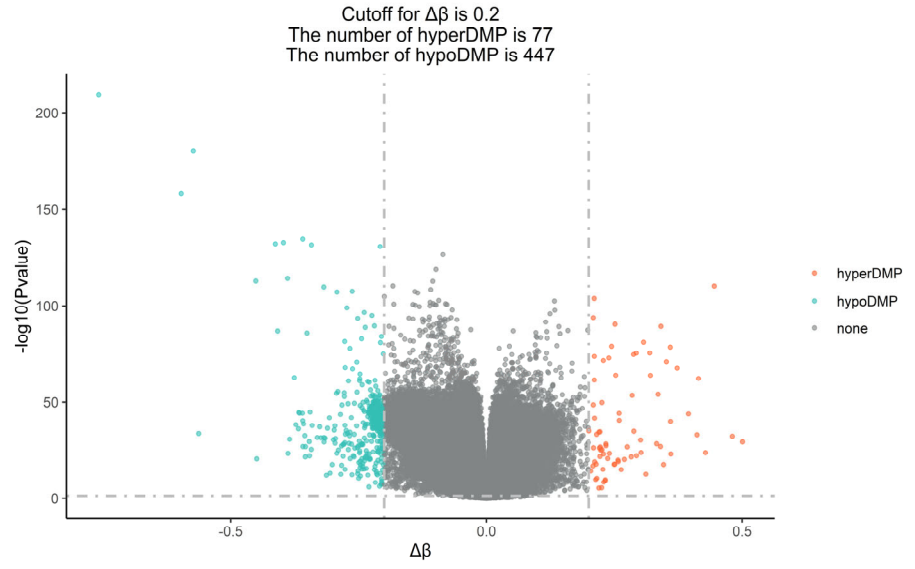


Figure S3. Volcano plot of analysis of differential methylation probes (DMPs). The 524 DMPs contained 77 hypermethylated and 447 hypomethylated DMPs using the cut-off value of adjusted P -value = 0.05 and $|\Delta\beta| \geq 0.2$.

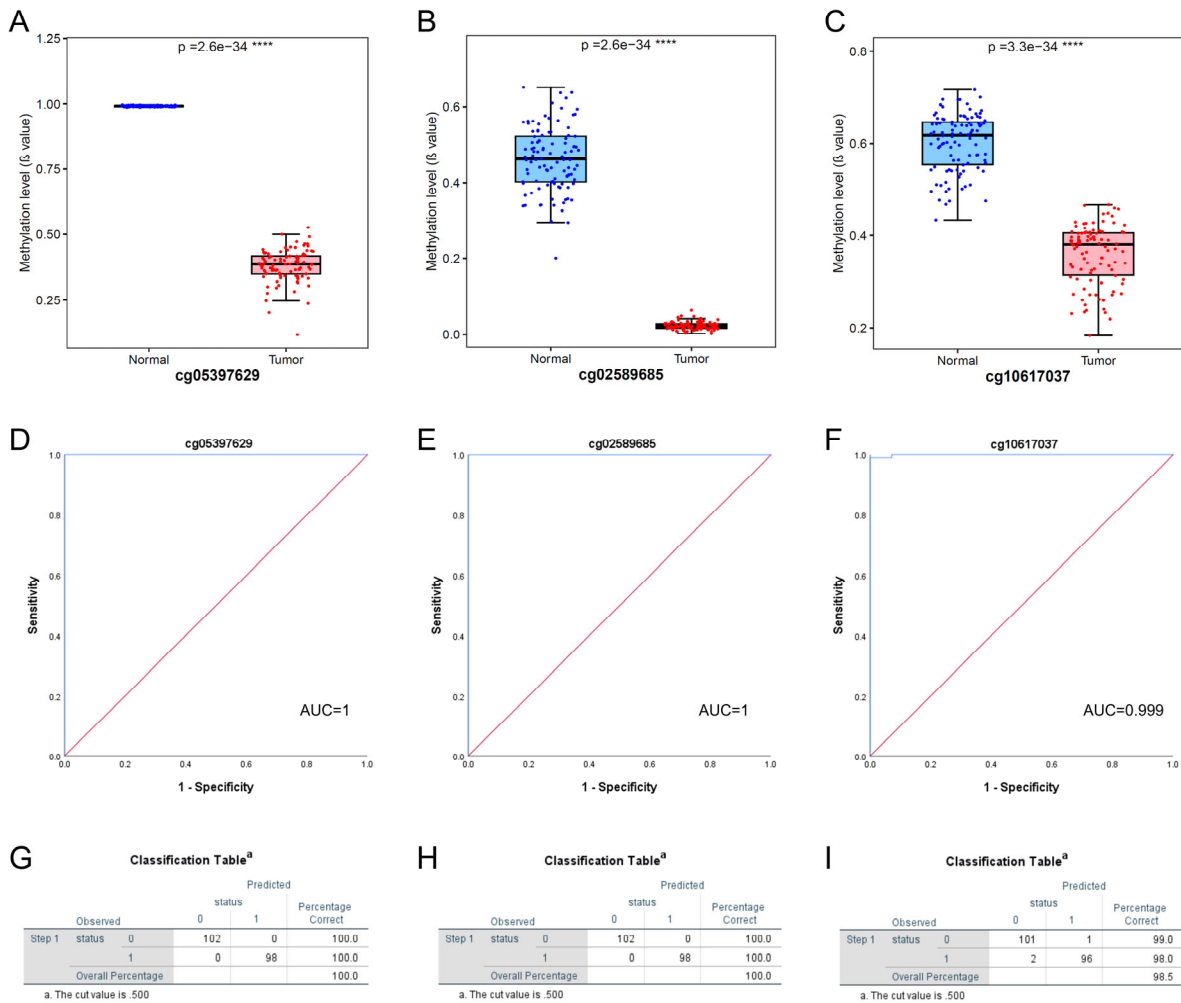


Figure S4. Details about distinguishing capacity of three differential methylation probes (DMPs). The P -value represents the significance of rank-sum test. ****, <0.0001 . The AUC is calculated from the area under the ROC curve. The classification tables were generated from logistic models for CpG and breast cancer. Abbreviations: AUC, area under curve.

Table S1. Information of 524 differentially methylation probes (DMPs).

The tables S1 and S2 are uploaded as an additional file (Excel).

Table S2. Information of 524 differentially methylation probes (DMPs).

The tables S1 and S2 are uploaded as an additional file (Excel).

Table S3. Gene ontology terms that were significantly enriched in an analysis of differentially methylation probes (DMPs).

ONTOLOGY	ID	Description	GeneRatio	BgRatio	pvalue	p.adjust	qvalue	geneID	Count
GO:0030667	CC	GO:0030667 secretory granule membrane	14/267	312/19594	0.000104	0.041983	0.038845	391/9342/7879/8904/ 161/5795/9725/3708/ 1729/51143/11031/ 8895/338339/5023	14

Table S4. Gene ontology terms that were significantly enriched in an analysis of differentially methylation regions (DMRs).

ONT OLO GY	ID	Description	Gen eRat io	BgR atio	pv e	p.a dju st	qva lue	geneID	C ou nt
GO:0 0485 68	GO:0 BP 0485 68	embryonic organ development	43/6 56	449/ 2.2 1.0 8.9 3205/ 6299/ 60529/ 5080/ 7545/ 2201/ 3207/ 3481/ 3784/ 7042/ 3204/ 8092/ 11078/ 3249/ 23414/ 5914/ 8854/ 121227/ 2668/ 188 5E- 4E- 3E- 8323/ 7472/ 4762/ 2290/ 430/ 57545/ 7291/ 1909/ 10653/ 3199/ 56034/ 3217/ 4487/ 4254/ 3236/ 79977/ 639/ 2202/ 220/ 668/ 43 00 09 05 06				9096/ 6491/ 585/ 7020	
GO:0 0974 85	GO:0 BP 0974 85	neuron projection guidance	28/6 56	235/ 1.5 6.9 2.8 188 0E- 6E- 7E- 00 08 05 05				2044/ 389549/ 5080/ 137970/ 5364/ 53942/ 10570/ 9369/ 54538/ 627/ 6091/ 91624/ 2668/ 10752/ 23768/ 115557/ 4009/ 2290/ 6586/ 1909/ 214/ 3199/ 9378/ 9353/ 399/ 80031/ 9048/ 1630	28
GO:0 0303 26	GO:0 BP 0303 26	embryonic limb morphogenesis	19/6 56	119/ 2.9 0.0 2.8 188 8E- 001 7E- 00 08 38 05				6423/ 6299/ 60529/ 2201/ 3207/ 340419/ 4488/ 7042/ 8854/ 22943/ 27152/ 8323/ 7291/ 4487/ 3236/ 3238/ 79977/ 6910/ 7020	19
GO:0 0351 13	GO:0 BP 0351 13	embryonic appendage morphogenesis	19/6 56	119/ 2.9 0.0 2.8 188 8E- 001 7E- 00 08 38 05				6423/ 6299/ 60529/ 2201/ 3207/ 340419/ 4488/ 7042/ 8854/ 22943/ 27152/ 8323/ 7291/ 4487/ 3236/ 3238/ 79977/ 6910/ 7020	19
GO:0 0987 42	GO:0 BP 0987 42	cell-cell adhesion via plasma-membrane adhesion molecules	30/6 56	279/ 4.9 0.0 2.8 188 0E- 002 7E- 00 08 27 05				56114/ 1825/ 5010/ 1006/ 137970/ 7042/ 56132/ 869/ 56147/ 54538/ 1003/ 1005/ 2895/ 83872/ 6091/ 24146/ 56126/ 91624/ 26011/ 28316/ 22865/ 214/ 57689/ 22871/ 1824/ 140628/ 5100/ 1365/ 56121/ 2195	30
GO:0 0074 11	GO:0 BP 0074 11	axon guidance	27/6 56	234/ 5.3 0.0 2.8 188 5E- 002 7E- 00 08 48 05				2044/ 389549/ 5080/ 137970/ 5364/ 53942/ 9369/ 54538/ 627/ 6091/ 91624/ 2668/ 10752/ 23768/ 115557/ 4009/ 2290/ 6586/ 1909/ 214/ 3199/ 9378/ 9353/ 399/ 80031/ 9048/ 1630	27
GO:0 0487 36	GO:0 BP 0487 36	appendage development	23/6 56	177/ 5.8 0.0 2.8 188 6E- 002 7E- 00 08 71 05				6423/ 6299/ 60529/ 2201/ 3207/ 340419/ 3664/ 4488/ 5066/ 7042/ 5914/ 8854/ 22943/ 27152/ 8323/ 3229/ 7291/ 4487/ 3236/ 3238/ 79977/ 6910/ 7020	23
GO:0 0601 73	GO:0 BP 0601 73	limb development	23/6 56	177/ 5.8 0.0 2.8 188 6E- 002 7E- 00 08 71 05				6423/ 6299/ 60529/ 2201/ 3207/ 340419/ 3664/ 4488/ 5066/ 7042/ 5914/ 8854/ 22943/ 27152/ 8323/ 3229/ 7291/ 4487/ 3236/ 3238/ 79977/ 6910/ 7020	23
GO:0 0603 24	GO:0 BP 0603 24	face development	12/6 56	48/1 6.4 0.0 2.8 880 9E- 003 7E- 0 08 05				84159/ 83690/ 5914/ 8854/ 22943/ 5083/ 1909/ 4487/ 4313/ 79977/ 220/ 585	12
GO:0 0905 96	GO:0 BP 0905 96	sensory organ morphogenesis	28/6 56	266/ 2.1 0.0 8.5 188 4E- 009 0E- 00 07 89 05				7068/ 5080/ 7545/ 2201/ 3784/ 11078/ 3249/ 4211/ 121227/ 27152/ 8323/ 7472/ 4762/ 2290/ 3229/ 6015/ 7291/ 1909/ 3199/ 4487/ 639/ 2202/ 220/ 668/ 9096/ 2195/ 585/ 7020	28
GO:0 0163 31	GO:0 BP 0163 31	morphogenesis of embryonic epithelium	20/6 56	150/ 2.7 0.0 0.0 188 9E- 012 001 00 07 92 01				6423/ 6046/ 7042/ 5914/ 8854/ 2668/ 8323/ 7472/ 57545/ 7291/ 10653/ 79977/ 5100/ 10395/ 220/ 9096/ 6491/ 585/ 7041/ 7020	20
GO:0 0487 05	GO:0 BP 0487 05	skeletal system morphogenesis	25/6 56	228/ 4.4 0.0 0.0 188 2E- 020 001 00 07 46 3				6423/ 3205/ 60529/ 2201/ 3207/ 4488/ 84159/ 2268/ 2690/ 3204/ 8092/ 79925/ 5914/ 4762/ 4057/ 7291/ 3199/ 55790/ 3217/ 4487/ 3236/ 4313/ 79977/ 134701/ 7020	25

GO:0	GO:0			38/1 4.8 0.0 0.0						
0351	BP	0351	forelimb morphogenesis	10/6	880 8E-022 001	60529/ 3207/ 340419/ 4488/ 8854/ 7291/ 4487/ 3236/ 6910/ 7020				10
36		36		56	0 07 58 3					
GO:0	GO:0				294/ 5.1 0.0 0.0					
0485	BP	0485	embryonic organ morphogenesis	29/6	188 5E-023 001	3205/ 60529/ 5080/ 7545/ 2201/ 3207/ 3784/ 3204/ 8092/ 11078/ 3249/ 121227/ 8323/ 4762/ 2290/ 7291/ 1909/ 3199/ 3217/ 4487/ 3236/ 79977/ 2202/ 220/ 668/ 9096/ 6491/ 585/ 7020				29
62		62		56	00 07 82 3					
GO:0	GO:0				142/ 5.2 0.0 0.0					
0351	BP	0351	appendage morphogenesis	19/6	188 3E-024 001	6423/ 6299/ 60529/ 2201/ 3207/ 340419/ 4488/ 7042/ 8854/ 22943/ 27152/ 8323/ 7291/ 4487/ 3236/ 3238/ 79977/ 6910/ 7020				19
07		07		56	00 07 19 3					
GO:0	GO:0				142/ 5.2 0.0 0.0					
0351	BP	0351	limb morphogenesis	19/6	188 3E-024 001	6423/ 6299/ 60529/ 2201/ 3207/ 340419/ 4488/ 7042/ 8854/ 22943/ 27152/ 8323/ 7291/ 4487/ 3236/ 3238/ 79977/ 6910/ 7020				19
08		08		56	00 07 19 3					
GO:0	GO:0				131/ 6.9 0.0 0.0					
0600	BP	0600	regulation of postsynaptic membrane potential	18/6	188 8E-032 001	6622/ 2567/ 56853/ 2898/ 1140/ 869/ 23316/ 2895/ 2555/ 2897/ 401190/ 18/ 2559/ 2911/ 22871/ 9378/ 2557/ 2030				18
78		78		56	00 07 28 62					
GO:0	GO:0				31/1 7.3 0.0 0.0					
0351	BP	0351	embryonic forelimb morphogenesis	9/65	880 5E-034 001	60529/ 3207/ 340419/ 4488/ 8854/ 7291/ 4487/ 6910/ 7020				9
15		15		6	0 07 01 62					
GO:0	GO:0				463/ 1.0 0.0 0.0	6423/ 3205/ 389549/ 7092/ 60529/ 5080/ 7545/ 3207/ 4488/ 2066/ 3204/ 6091/ 4211/ 8854/ 22943/ 27152/ 2668/ 7472/ 4762/ 2290/ 3229/ 57545/ 6015/ 1745/ 3199/ 3217/ 10655/ 4487/ 3236/ 92749/ 3238/ 134701/ 140628/ 5100/ 6910/ 9096/ 6491/ 585				38
0073	BP	0073	pattern specification process	38/6	188 2E-047 002					
89		89		56	00 06 43 04					
GO:0	GO:0				192/ 1.0 0.0 0.0	6423/ 1910/ 389549/ 5080/ 57795/ 627/ 4211/ 5914/ 22943/ 4762/ 4009/ 2290/ 7101/ 4803/ 238/ 1745/ 3199/ 22871/ 30012/ 4058/ 4825/ 79727				22
0456	BP	0456	regulation of neuron differentiation	22/6	188 3E-047 002					
64		64		56	00 06 47 04					
GO:0	GO:0				51/1 1.1 0.0 0.0					
0519	BP	0519	synaptic transmission, GABAergic	11/6	880 5E-053 002	2567/ 2555/ 6869/ 8224/ 6529/ 2559/ 22865/ 22871/ 2557/ 766/ 148				11
32		32		56	0 06 06 17					
GO:0	GO:0				479/ 2.3 0.0 0.0	2044/ 389549/ 5080/ 2917/ 1496/ 137970/ 8578/ 5364/ 53942/ 9369/ 54538/ 627/ 6091/ 4929/ 91624/ 2668/ 10752/ 23768/ 115557/ 4009/ 2290/ 7101/ 4803/ 6586/ 22865/ 1909/ 214/ 3199/ 57689/ 9378/ 4313/ 9353/ 399/ 80031/ 9048/ 1630/ 4825/ 706				38
0615	BP	0615	axon development	38/6	188 2E-107 004					
64		64		56	00 06 54 2					
GO:0	GO:0				425/ 2.5 0.0 0.0	6622/ 2567/ 56853/ 3781/ 2898/ 1140/ 3784/ 783/ 869/ 23316/ 2895/ 63895/ 2555/ 40/ 2897/ 401190/ 10008/ 3775/ 6869/ 18/ 2559/ 2911/ 22871/ 3728/ 9378/ 1824/ 2557/ 6910/ 54207/ 2030/ 706/ 64208/ 50801/ 9096/ 148				35
0423	BP	0423	regulation of membrane potential	35/6	188 4E-117 004					
91		91		56	00 06 41 39					
GO:0	GO:0				58/1 4.3 0.0 0.0					
0427	BP	0427	embryonic digit morphogenesis	11/6	880 9E-203 007	6423/ 6299/ 60529/ 3207/ 4488/ 27152/ 8323/ 7291/ 4487/ 3238/ 79977				11
33		33		56	0 06 21 25					
GO:0	GO:0				226/ 4.5 0.0 0.0	6423/ 6299/ 3207/ 2674/ 2099/ 84159/ 9985/ 7042/ 5872/ 1299/ 5806/ 23414/ 5914/ 5798/ 11086/ 6586/ 4254/ 132625/ 4313/ 9353/ 23626/ 675/ 668				23
0084	BP	0084	gonad development	23/6	188 6E-211 007					
06		06		56	00 06 05 25					
GO:1	GO:1				260/ 4.9 0.0 0.0	7068/ 1910/ 3781/ 10060/ 3784/ 7042/ 1129/ 783/ 5142/ 40/ 10008/ 5020/ 5144/ 6869/ 2166/ 1909/ 3728/ 4313/ 1824/ 5743/ 6910/ 6870/ 3350/ 9096/ 148				25
9035	BP	9035	regulation of blood circulation	25/6	188 2E-227 007					
22		22		56	00 06 69 52					

GO:0 0343 29	BP	GO:0 0343 29	cell junction assembly	34/6 56	420/ 5.1 0.0 0.0 188 2E- 236 007 00 06 97 52	6622/ 2066/ 5010/ 1006/ 153562/ 5364/ 5872/ 53942/ 56132/ 869/ 627/ 1003/ 23316/ 1005/ 2895/ 2555/ 24146/ 91862/ 56126/ 40/ 22943/ 28316/ 23768/ 5020/ 79953/ 22865/ 22871/ 3728/ 9378/ 79977/ 6910/ 10395/ 23136/ 1365	34
GO:0 0305 34	BP	GO:0 0305 34	adult behavior	17/6 56	136/ 5.3 0.0 0.0 188 0E- 245 007 00 06 24 52	4852/ 6622/ 7545/ 1140/ 9369/ 80243/ 4929/ 2668/ 10752/ 285671/ 18/ 7200/ 238/ 9378/ 3236/ 8772/ 585	17
GO:0 0519 60	BP	GO:0 0519 60	regulation of nervous system development	35/6 56	440/ 5.4 0.0 0.0 188 9E- 253 007 00 06 95 52	389549/ 4311/ 4049/ 5080/ 5364/ 869/ 627/ 23316/ 2895/ 6091/ 400746/ 5914/ 40/ 22943/ 26011/ 84504/ 6258/ 23768/ 5020/ 7472/ 79953/ 2290/ 7101/ 430/ 4803/ 1745/ 22865/ 22871/ 9378/ 9353/ 80031/ 1630/ 4825/ 706/ 79727	35
GO:0 0099 52	BP	GO:0 0099 52	anterior/posterior pattern specification	22/6 56	214/ 6.2 0.0 0.0 188 2E- 287 008 00 06 73 24	6423/ 3205/ 389549/ 60529/ 5080/ 3207/ 4488/ 3204/ 8854/ 22943/ 7472/ 4762/ 3229/ 6015/ 3199/ 3217/ 10655/ 4487/ 3236/ 134701/ 5100/ 9096	22
GO:0 0451 37	BP	GO:0 0451 37	development of primary sexual characteristics	23/6 56	231/ 6.5 0.0 0.0 188 8E- 304 008 00 06 32 44	6423/ 6299/ 3207/ 2674/ 2099/ 84159/ 9985/ 7042/ 5872/ 1299/ 5806/ 23414/ 5914/ 5798/ 11086/ 6586/ 4254/ 132625/ 4313/ 9353/ 23626/ 675/ 668	23
GO:0 0219 53	BP	GO:0 0219 53	central nervous system neuron differentiation	19/6 56	169/ 7.3 0.0 0.0 188 2E- 338 009 00 06 61 09	26468/ 4852/ 5080/ 84871/ 161357/ 869/ 219409/ 2895/ 4929/ 401/ 1996/ 4009/ 2290/ 7101/ 1745/ 3236/ 9353/ 1630/ 4825	19
GO:0 0074 09	BP	GO:0 0074 09	axonogenesis	34/6 56	430/ 8.4 0.0 0.0 188 8E- 392 010 00 06 39 22	2044/ 389549/ 5080/ 1496/ 137970/ 5364/ 53942/ 9369/ 54538/ 627/ 6091/ 4929/ 91624/ 2668/ 10752/ 23768/ 115557/ 4009/ 2290/ 7101/ 4803/ 6586/ 22865/ 1909/ 214/ 3199/ 57689/ 9378/ 9353/ 399/ 80031/ 9048/ 1630/ 4825	34
GO:0 0487 06	BP	GO:0 0487 06	embryonic skeletal system development	16/6 56	127/ 9.0 0.0 0.0 188 1E- 416 010 00 06 95 54	3205/ 60529/ 3207/ 3204/ 8092/ 3231/ 56243/ 1745/ 7291/ 1909/ 3199/ 3217/ 10655/ 3236/ 79977/ 7020	16
GO:0 0486 08	BP	GO:0 0486 08	reproductive structure development	34/6 56	433/ 9.8 0.0 0.0 188 3E- 454 011 00 06 71 16	6423/ 4311/ 6299/ 3207/ 2674/ 2099/ 84159/ 9985/ 3481/ 7042/ 5872/ 1299/ 5806/ 23414/ 5914/ 9420/ 7472/ 5798/ 4762/ 430/ 11086/ 6586/ 10653/ 4254/ 132625/ 4313/ 9353/ 23626/ 5743/ 79977/ 639/ 675/ 668/ 51673	34
GO:0 0519 65	BP	GO:0 0519 65	positive regulation of synapse assembly	11/6 56	63/ 1.0 0.0 0.0 880 1E- 469 011 0 05 13 2	869/ 627/ 23316/ 2895/ 40/ 23768/ 5020/ 79953/ 22865/ 22871/ 9378	11
GO:0 0987 93	CC	GO:0 0987 93	presynapse	42/6 94	492/ 1.4 6.9 6.2 195 4E- 5E- 8E- 94 07 05 05	4852/ 5179/ 4311/ 6622/ 2917/ 93664/ 2898/ 2066/ 9892/ 6456/ 143425/ 1006/ 114569/ 9829/ 5872/ 6530/ 53942/ 91752/ 783/ 6857/ 6854/ 627/ 5142/ 8618/ 2555/ 6539/ 401190/ 5020/ 5798/ 79953/ 8224/ 6529/ 80863/ 4803/ 284612/ 148281/ 22871/ 9378/ 22895/ 5100/ 2030/ 148	42
GO:0 0970 60	CC	GO:0 0970 60	synaptic membrane	34/6 94	373/ 5.0 0.0 0.0 195 7E- 002 001 94 07 44 1	2567/ 2917/ 2898/ 2066/ 1140/ 9892/ 2893/ 1006/ 9123/ 1129/ 6530/ 53942/ 6857/ 869/ 2895/ 2555/ 2897/ 401190/ 79953/ 3775/ 6529/ 80863/ 2559/ 22865/ 57689/ 2911/ 22871/ 9378/ 22895/ 5100/ 2557/ 399694/ 1630/ 148	34
GO:0 0452 11	CC	GO:0 0452 11	postsynaptic membrane	27/6 94	271/ 1.4 0.0 0.0 195 0E- 006 002 94 06 74 03	2567/ 2917/ 2898/ 2066/ 1140/ 2893/ 9123/ 1129/ 869/ 2895/ 2555/ 2897/ 401190/ 79953/ 6529/ 80863/ 2559/ 22865/ 57689/ 2911/ 22871/ 22895/ 5100/ 2557/ 399694/ 1630/ 148	27
GO:0 0703 82	CC	GO:0 0703 82	exocytic vesicle	21/6 94	214/ 2.5 0.0 0.0 195 6E- 123 027 94 05 29 86	5179/ 4311/ 6622/ 9892/ 143425/ 114569/ 5872/ 6857/ 6854/ 627/ 5142/ 2555/ 79953/ 8224/ 80863/ 4803/ 284612/ 148281/ 22895/ 1809/ 84258	21

[illegible]

Table S5. Correlation analysis between plasma one-carbon metabolism-related micronutrients and 14 differential methylation probes (DMPs).

Micronutrients	Probes	r	Crude <i>P</i> -value	FDR <i>P</i> -value	Bonferroni <i>P</i> -value
Methionine	cg15740243	0.186342	0.008243	0.017517	0.140138
	cg21042336	0.106159	0.134618	0.134618	1
	cg04622888	0.136532	0.053881	0.064311	0.915985
	cg00901687	0.132963	0.060528	0.064311	1
	cg13824270	-0.23717	0.000721	0.003494	0.01226
	cg03363289	0.165831	0.018937	0.029266	0.321923
	cg04794268	0.226955	0.00123	0.004183	0.020913
	cg24312537	0.133792	0.058926	0.064311	1
	cg21697381	0.234701	0.000822	0.003494	0.013977
	cg01701207	0.150085	0.033901	0.044332	0.576314
	cg09491380	0.167952	0.017443	0.029266	0.296535
	cg04657470	0.193628	0.006011	0.014597	0.102182
	cg25755428	-0.18302	0.009486	0.017917	0.161254
	cg06536614	0.158763	0.02474	0.035048	0.420581
Cysteine	cg15740243	-0.19126	0.006667	0.014168	0.113344
	cg21042336	-0.22144	0.001626	0.007503	0.027638
	cg04622888	-0.05351	0.451699	0.47993	1
	cg00901687	-0.10239	0.149094	0.194969	1
	cg13824270	0.14778	0.03677	0.052091	0.625097
	cg03363289	-0.0871	0.22007	0.249413	1
	cg04794268	-0.181	0.010322	0.019497	0.175471
	cg24312537	-0.22182	0.001595	0.007503	0.027122
	cg21697381	-0.09719	0.170962	0.207597	1
	cg01701207	-0.21979	0.001765	0.007503	0.030013
	cg09491380	-0.20395	0.00377	0.011367	0.064092
	cg04657470	-0.17722	0.012059	0.0205	0.204997
	cg25755428	0.014576	0.837691	0.837691	1
	cg06536614	-0.15123	0.032548	0.050302	0.553318
Homocysteine	cg15740243	0.008995	0.8994	0.955613	1
	cg21042336	0.048811	0.492475	0.909338	1
	cg04622888	0.014693	0.836405	0.947926	1
	cg00901687	0.095656	0.177854	0.909338	1
	cg13824270	-0.05724	0.42075	0.909338	1
	cg03363289	0.002599	0.970862	0.970862	1
	cg04794268	0.047965	0.500014	0.909338	1
	cg24312537	0.026797	0.70643	0.909338	1
	cg21697381	0.103145	0.146107	0.909338	1
	cg01701207	0.043544	0.54038	0.909338	1
	cg09491380	0.04369	0.539021	0.909338	1
	cg04657470	0.025005	0.725243	0.909338	1

	cg25755428	0.038743	0.585971	0.909338	1
	cg06536614	-0.04232	0.551816	0.909338	1
SAM	cg15740243	0.274309	8.47E-05	0.00018	0.00144
	cg21042336	0.256091	0.000252	0.000473	0.004284
	cg04622888	0.252623	0.000307	0.000475	0.005226
	cg00901687	0.224367	0.001403	0.001491	0.023857
	cg13824270	-0.23941	0.000639	0.000903	0.010867
	cg03363289	0.33137	1.64E-06	5.59E-06	2.79E-05
	cg04794268	0.383957	1.99E-08	1.13E-07	3.39E-07
	cg24312537	0.254382	0.000278	0.000473	0.004727
	cg21697381	0.23797	0.000691	0.000903	0.011744
	cg01701207	0.22536	0.001334	0.001491	0.022686
	cg09491380	0.291122	2.89E-05	7.01E-05	0.000491
	cg04657470	0.322525	3.20E-06	9.06E-06	5.44E-05
	cg25755428	-0.19338	0.006077	0.006077	0.103312
	cg06536614	0.229493	0.00108	0.001311	0.018353
SAH	cg15740243	0.071905	0.311624	0.4532	1
	cg21042336	0.152975	0.030574	0.176197	0.51976
	cg04622888	0.022217	0.754842	0.754842	1
	cg00901687	0.100723	0.155863	0.4532	1
	cg13824270	-0.04275	0.547776	0.582012	1
	cg03363289	0.069886	0.325436	0.4532	1
	cg04794268	0.081579	0.25081	0.4532	1
	cg24312537	0.062192	0.381646	0.4532	1
	cg21697381	0.086587	0.222793	0.4532	1
	cg01701207	0.059848	0.399882	0.4532	1
	cg09491380	0.085573	0.228278	0.4532	1
	cg04657470	0.078502	0.269188	0.4532	1
	cg25755428	-0.15251	0.031094	0.176197	0.528592
	cg06536614	0.167721	0.017601	0.176197	0.299213
Folate	cg15740243	0.335299	1.21E-06	3.39E-06	2.06E-05
	cg21042336	0.274624	8.31E-05	0.000128	0.001412
	cg04622888	0.165134	0.019451	0.022045	0.330671
	cg00901687	0.144839	0.040728	0.043273	0.692371
	cg13824270	-0.16847	0.017096	0.02076	0.290638
	cg03363289	0.238393	0.000675	0.000957	0.011481
	cg04794268	0.333493	1.40E-06	3.39E-06	2.37E-05
	cg24312537	0.329249	1.93E-06	4.10E-06	3.28E-05
	cg21697381	0.323377	3.00E-06	5.67E-06	5.10E-05
	cg01701207	0.33619	1.13E-06	3.39E-06	1.93E-05
	cg09491380	0.360896	1.52E-07	8.63E-07	2.59E-06
	cg04657470	0.289215	3.27E-05	5.56E-05	0.000556
	cg25755428	-0.12583	0.075822	0.075822	1
	cg06536614	0.231087	0.000994	0.0013	0.016896
5-MTHF	cg15740243	-0.00653	0.926867	0.967454	1

	cg21042336	0.025796	0.716917	0.967454	1
	cg04622888	0.01993	0.77939	0.967454	1
	cg00901687	-0.1941	0.005886	0.100069	0.100069
	cg13824270	0.07655	0.28131	0.613435	1
	cg03363289	-0.0029	0.967454	0.967454	1
	cg04794268	-0.10069	0.156006	0.587114	1
	cg24312537	-0.05773	0.416803	0.708566	1
	cg21697381	-0.00802	0.910254	0.967454	1
	cg01701207	-0.07539	0.288675	0.613435	1
	cg09491380	-0.05863	0.409544	0.708566	1
	cg04657470	-0.01496	0.833467	0.967454	1
	cg25755428	0.117377	0.097867	0.554578	1
	cg06536614	-0.08957	0.207217	0.587114	1
Choline	cg15740243	0.179564	0.010953	0.046548	0.186193
	cg21042336	0.030174	0.671457	0.671457	1
	cg04622888	0.122217	0.0847	0.110761	1
	cg00901687	0.04983	0.483475	0.513693	1
	cg13824270	-0.13399	0.058556	0.082955	0.995459
	cg03363289	0.166356	0.018557	0.047884	0.315472
	cg04794268	0.149952	0.034061	0.057904	0.579038
	cg24312537	0.13618	0.054509	0.082955	0.926648
	cg21697381	0.24512	0.000468	0.007959	0.007959
	cg01701207	0.107643	0.129223	0.146453	1
	cg09491380	0.161262	0.022534	0.047884	0.383073
	cg04657470	0.163487	0.020715	0.047884	0.352152
	cg25755428	-0.16462	0.019836	0.047884	0.33721
	cg06536614	0.110165	0.12044	0.146249	1
Betaine	cg15740243	0.230258	0.001038	0.001877	0.01764
	cg21042336	0.142234	0.044526	0.047309	0.756939
	cg04622888	0.242997	0.000526	0.001118	0.008945
	cg00901687	0.14704	0.037734	0.042765	0.64147
	cg13824270	-0.21147	0.002648	0.003751	0.045011
	cg03363289	0.293931	2.40E-05	9.78E-05	0.000407
	cg04794268	0.297566	1.88E-05	9.78E-05	0.000319
	cg24312537	0.211699	0.002619	0.003751	0.044515
	cg21697381	0.229057	0.001104	0.001877	0.018772
	cg01701207	0.198812	0.004769	0.006237	0.081076
	cg09491380	0.248464	0.000389	0.000944	0.006609
	cg04657470	0.254304	0.000279	0.000791	0.004748
	cg25755428	-0.10754	0.129589	0.129589	1
	cg06536614	0.162061	0.021866	0.026551	0.371714
P5P	cg15740243	0.420745	5.53E-10	1.57E-09	9.40E-09
	cg21042336	0.328727	2.01E-06	2.44E-06	3.42E-05
	cg04622888	0.2959	2.10E-05	2.38E-05	0.000357
	cg00901687	0.375972	4.10E-08	7.75E-08	6.98E-07

	cg13824270	-0.36748	8.66E-08	1.47E-07	1.47E-06
	cg03363289	0.355233	2.45E-07	3.78E-07	4.16E-06
	cg04794268	0.434266	1.32E-10	5.62E-10	2.25E-09
	cg24312537	0.404591	2.82E-09	6.61E-09	4.79E-08
	cg21697381	0.350242	3.69E-07	5.23E-07	6.28E-06
	cg01701207	0.403582	3.11E-09	6.61E-09	5.29E-08
	cg09491380	0.424814	3.62E-10	1.23E-09	6.15E-09
	cg04657470	0.33324	1.42E-06	1.86E-06	2.42E-05
	cg25755428	-0.20277	0.003982	0.004231	0.067689
	cg06536614	0.126829	0.073514	0.073514	1
Vitamin B2	cg15740243	0.389228	1.22E-08	4.16E-08	2.08E-07
	cg21042336	0.293039	2.54E-05	3.60E-05	0.000432
	cg04622888	0.291379	2.84E-05	3.71E-05	0.000482
	cg00901687	0.26825	0.000123	0.000138	0.002087
	cg13824270	-0.33273	1.48E-06	2.80E-06	2.52E-05
	cg03363289	0.363037	1.27E-07	3.55E-07	2.16E-06
	cg04794268	0.40846	1.92E-09	1.09E-08	3.27E-08
	cg24312537	0.31714	4.75E-06	8.07E-06	8.07E-05
	cg21697381	0.348994	4.09E-07	8.69E-07	6.95E-06
	cg01701207	0.300679	1.52E-05	2.35E-05	0.000258
	cg09491380	0.361362	1.46E-07	3.55E-07	2.49E-06
	cg04657470	0.283423	4.77E-05	5.79E-05	0.00081
	cg25755428	-0.26734	0.00013	0.000138	0.002206
	cg06536614	0.214254	0.002315	0.002315	0.039362
Vitamin B12	cg15740243	0.337764	1.00E-06	2.13E-06	1.70E-05
	cg21042336	0.307775	9.28E-06	1.75E-05	0.000158
	cg04622888	0.304148	1.19E-05	2.03E-05	0.000203
	cg00901687	0.284372	4.48E-05	5.86E-05	0.000762
	cg13824270	-0.26706	0.000132	0.00015	0.002243
	cg03363289	0.381196	2.56E-08	8.72E-08	4.36E-07
	cg04794268	0.402901	3.32E-09	1.41E-08	5.65E-08
	cg24312537	0.294662	2.28E-05	3.23E-05	0.000388
	cg21697381	0.366565	9.37E-08	2.66E-07	1.59E-06
	cg01701207	0.300808	1.50E-05	2.32E-05	0.000256
	cg09491380	0.349637	3.88E-07	9.43E-07	6.60E-06
	cg04657470	0.276029	7.61E-05	9.24E-05	0.001294
	cg25755428	-0.1095	0.122725	0.122725	1
	cg06536614	0.127003	0.073118	0.077688	1

Abbreviations: FDR, false discovery rate; P5P, pyridoxal 5-phosphate; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine.

Table S6. Mediation analysis of differential methylation probes (DMPs) in the association between plasma one-carbon metabolism-related nutrients and risk of breast cancer.

Micronutrients	CpG	R	Total effect β	Direct effect β	Indirect effect β	Proportion
Methionine	cg13824270	-0.237*	-0.0862***	-0.0353	-0.0510***	60.35%***
	cg04794268	0.236*	-0.1265***	-0.0366	-0.0899***	72.88%***
	cg21697381	0.221*	-0.0796	-0.0324	-0.0472	62.31%
Cysteine	cg21042336	-0.221*	0.0493	0.0165	0.0327*	50.17%
	cg24312537	-0.222*	0.0716*	0.0375	0.0341	47.99%
	cg01701207	-0.220*	0.0621	0.0264	0.0356	55.64%
SAM	cg15740243	0.274**	-0.2694***	-0.1843***	-0.0851***	32.06%***
	cg21042336	0.256**	-0.2369***	-0.2121***	-0.0248	10.81%
	cg04622888	0.253**	-0.2111***	-0.1680***	-0.0431*	21.20%*
	cg00901687	0.224*	-0.2392***	-0.2185	-0.0207	9.01%
	cg13824270	-0.239*	-0.2307***	-0.2004***	-0.0303***	13.13%***
	cg03363289	0.331***	-0.2043***	-0.1516***	-0.0527***	26.43%***
	cg04794268	0.384***	-0.2610***	-0.129	-0.1320***	51.20%***
	cg24312537	0.254***	-0.3046***	-0.2295***	-0.0751***	24.61%***
	cg21697381	0.238*	-0.2162***	-0.1442***	-0.0720***	33.35%***
	cg01701207	0.225*	-0.3221***	-0.2602***	-0.0619***	18.99%***
	cg09491380	0.291***	-0.2925***	-0.2035***	-0.0889***	29.93%***
	cg04657470	0.323***	-0.2214***	-0.1722*	-0.0493***	22.22%***
	cg06536614	0.229*	-0.2551***	-0.2376***	-0.0175*	6.86%*
Folate	cg15740243	0.335***	-0.1184*	-0.0468	-0.0716***	63.41%*
	cg21042336	0.275**	-0.1083***	-0.0534	-0.0549***	51.77%***
	cg03363289	0.238*	-0.1670***	-0.1240***	-0.0430	26.90%
	cg04794268	0.333***	-0.1690***	-0.0361	-0.1328***	79.43%***
	cg24312537	0.329***	-0.1288*	-0.0697*	-0.0591***	44.26%*
	cg21697381	0.323***	-0.0908*	-0.0249	-0.0659*	75.80%***
	cg01701207	0.336***	-0.1343***	-0.0725*	-0.0619***	47.34%***
	cg09491380	0.361***	-0.1230*	-0.0495	-0.0734***	62.48%*
	cg04657470	0.289***	-0.1312***	-0.0890***	-0.0423	33.75%
	cg06536614	0.231*	-0.1512***	-0.1236***	-0.0275*	18.95%*
Choline	cg21697381	0.245**	-0.1014*	-0.0309	-0.0705*	71.49%***
Betaine	cg15740243	0.230*	-0.1442*	-0.0904	-0.0538***	33.22%*
	cg04622888	0.243**	-0.1389***	-0.0716	-0.0673***	48.48%***
	cg03363289	-0.211*	-0.1501***	-0.0740	-0.0761***	50.09%***
	cg04794268	0.294***	-0.1737***	-0.0547***	-0.1190***	69.01%***
	cg24312537	0.298***	-0.1362***	-0.0969	-0.0393*	27.96%*
	cg21697381	0.293***	-0.1080***	-0.0453	-0.0627*	59.50%*
	cg01701207	0.229*	-0.1275***	-0.0921*	-0.0354	27.29%
	cg09491380	0.248**	-0.1321	-0.0764	-0.0557***	38.72%
	cg04657470	0.254**	-0.1544***	-0.1069*	-0.0475***	30.10%***
P5P	cg15740243	0.421***	-0.1968***	-0.0846	-0.1122***	57.71%***

	cg21042336	0.329***	-0.2218***	-0.1773***	-0.0445*	19.30%*
	cg04622888	0.296***	-0.2234***	-0.1668***	-0.0565*	24.66%*
	cg00901687	0.376***	-0.2476***	-0.1968***	-0.0508***	20.34%***
	cg13824270	-0.367***	-0.2229***	-0.1606***	-0.0623***	27.71%***
	cg03363289	0.355***	-0.2131***	-0.1579*	-0.0552*	25.54%*
	cg04794268	0.434***	-0.2452***	-0.0840	-0.1612***	67.69%***
	cg24312537	0.405***	-0.2330***	-0.1503*	-0.0826***	35.35%***
	cg21697381	0.351***	-0.2610***	-0.1580***	-0.1040***	40.40%***
	cg01701207	0.404***	-0.2239***	-0.1382*	-0.0857***	38.64%***
	cg09491380	0.425***	-0.1971*	-0.0985	-0.0986***	49.40%*
	cg04657470	0.333***	-0.2043***	-0.1547***	-0.0496*	24.59%*
Vitamin B2	cg15740243	0.389***	-0.1157	-0.0772	-0.0385	38.39%
	cg21042336	0.293***	-0.2546***	-0.2119***	-0.0427***	16.29%***
	cg04622888	0.291***	-0.2440***	-0.1754***	-0.0686***	26.06%***
	cg00901687	0.268***	-0.2461***	-0.2174***	-0.0287*	11.41%*
	cg13824270	-0.333***	-0.2292***	-0.1980***	-0.0311	12.16%
	cg03363289	0.363***	-0.2291***	-0.1518***	-0.0773***	32.40%***
	cg04794268	0.408***	-0.1476*	-0.0365*	-0.1111*	76.79%***
	cg24312537	0.317***	-0.2367*	-0.1967*	-0.0400	17.05%
	cg21697381	0.349***	-0.0156	-0.0081	-0.0074	27.99%
	cg01701207	0.301***	-0.2276	-0.1923	-0.0353*	13.41%
	cg09491380	0.361***	-0.1952***	-0.1310	-0.0642*	31.89%*
	cg04657470	0.283***	-0.2111***	-0.1617***	-0.0494*	23.89%*
	cg25755428	-0.267*	-0.2469***	-0.2323***	-0.0145	4.76%
	cg06536614	0.214*	-0.2476***	-0.2324***	-0.0152	6.58%
Vitamin B12	cg15740243	0.338***	-0.0784	-0.0503	-0.0281	11.23%
	cg21042336	0.308***	-0.2902***	-0.2635***	-0.0266*	8.47%*
	cg04622888	0.304***	-0.2591***	-0.2210*	-0.0381***	13.08%***
	cg00901687	0.284***	-0.2710***	-0.2517***	-0.0192***	7.04%***
	cg13824270	-0.267**	-0.2581*	-0.2346*	-0.0234***	8.35%*
	cg03363289	0.381***	-0.2428*	-0.2035*	-0.0393***	13.46%*
	cg04794268	0.403***	-0.2850***	-0.1550***	-0.1300***	46.10%***
	cg24312537	0.295***	-0.2883*	-0.2622*	-0.0261*	7.93%
	cg21697381	0.367***	-0.1839	-0.1448	-0.0391***	15.61%
	cg01701207	0.301***	-0.2783*	-0.2488*	-0.0295*	9.77%
	cg09491380	0.350***	-0.1718	-0.1306	-0.0413	13.26%
	cg04657470	0.276**	-0.2470***	-0.2264***	-0.0206	8.06%

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Abbreviations: P5P, pyridoxal 5-phosphate; SAM, S-adenosylmethionine.