SUPPLEMENTARY MATERIALS

Blood lead levels, iron metabolism gene polymorphisms, and homocysteine: A gene-environment interaction study

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Table S1. Genotyped and imputed single-nucleotide polymorphisms analysed in the study

SNP rs no.	Gene	Chromosome	Position
Genotyped SNPs			
rs8177277	*TF*	3	134967520
rs8177201	*TF*	3	134952545
rs4241357	*TF*	3	134958253
rs8177235	*TF*	3	134958773
rs1799852	*TF*	3	134958412
rs7638018	*TF*	3	134978151
rs1049296	*TF*	3	134977044
rs8177272	*TF*	3	134965560
rs8177203	*TF*	3	134952715
rs8177220	*TF*	3	134956315
rs2715632	*TF*	3	134968520
rs1358022	*TF*	3	134970311
rs2715631	*TF*	3	134965579
rs2715627	*TF*	3	134977539
rs1800277	*TF*	3	134948845
rs2071303	*HFE*	6	26199315
rs707889	*HFE*	6	26203910
rs2124459	*CBS*	21	43348783
rs4920037	*CBS*	21	43354960
rs234711	*CBS*	21	43360180
rs6860725	*BHMT*	5	78455565
rs558133	*BHMT*	5	78460944
rs10733117	*MTR*	1	235030490
rs2185208	*MTR*	1	235034979
rs7526063	*MTR*	1	235038621
rs3820573	*MTR*	1	235046034
rs2385504	*MTR*	1	235066279
rs2385509	*MTR*	1	235073596
rs2385500	*MTR*	1	235083531
rs17599657	*MTR*	1	235083699
rs10495386	*MTR*	1	235099431
rs4659738	*MTR*	1	235107481
rs4659739	*MTR*	1	235107536
rs1805087	*MTR*	1	235115123

rs2275565	*MTR*	1	235115299
rs10158822	*MTR*	1	235116799
rs10158222	*MTR*	1	235117305
rs1266164	*MTR*	1	235117574
rs10925261	*MTR*	1	235119809
rs3768152	*MTR*	1	235120153
rs3768156	*MTR*	1	235122548
rs1252252	*MTR*	1	235122625
Imputed SNPs			
rs8177177	*TF*	3	133463195
rs8177178	*TF*	3	133463272
rs8177179	*TF*	3	133463457
rs8177181	*TF*	3	133463798
rs8177313	*TF*	3	133464102
rs8177185	*TF*	3	133464618
rs4481157	*TF*	3	133464684
rs8177186	*TF*	3	133465201
rs1130459	*TF*	3	133465283
rs4459901	*TF*	3	133465699
rs6796795	*TF*	3	133466222
rs6785596	*TF*	3	133466457
rs4532136	*TF*	3	133466885
rs8177190	*TF*	3	133467696
rs8177191	*TF*	3	133468139
rs9880615	*TF*	3	133470909
rs8177213	*TF*	3	133472227
rs3811658	*TF*	3	133476852
rs8177252	*TF*	3	133480174
rs1880669	*TF*	3	133483696
rs3811647	*TF*	3	133484029
rs1525892	*TF*	3	133484712
rs2692695	*TF*	3	133485454
rs2718806	*TF*	3	133486093
rs8649	*TF*	3	133486958
rs1525890	*TF*	3	133489583
rs1525889	*TF*	3	133490033
rs9824452	*TF*	3	133492471

rs1115219	*TF*	3	133495017
rs12595	*TF*	3	133496553
rs4846048	*MTHFR*	1	11846252
rs3737967	*MTHFR*	1	11847449
rs1537516	*MTHFR*	1	11847861
rs1537514	*MTHFR*	1	11847861
rs4846049	*MTHFR*	1	11850365
rs2274976	*MTHFR*	1	11850927
rs13306556	*MTHFR*	1	11852110
rs1476413	*MTHFR*	1	11852300
rs1801131	*MTHFR*	1	11854476
rs12121543	*MTHFR*	1	11854671
rs1994798	*MTHFR*	1	11854755
rs2066462	*MTHFR*	1	11854896
rs6541003	*MTHFR*	1	11855867
rs17421511	*MTHFR*	1	11857788
rs4846052	*MTHFR*	1	11857951
rs17421560	*MTHFR*	1	11858324
rs11121832	*MTHFR*	1	11860120
rs2066471	*MTHFR*	1	11860458
rs7533315	*MTHFR*	1	11860683
rs17037390	*MTHFR*	1	11860843
rs17037396	*MTHFR*	1	11862047
rs17037397	*MTHFR*	1	11862163
rs2066470	*MTHFR*	1	11863057
rs7553194	*MTHFR*	1	11864149
rs3753582	*MTHFR*	1	11865542
rs13306561	*MTHFR*	1	11865804
rs3737965	*MTHFR*	1	11866451
rs3737964	*MTHFR*	1	11867044

Abbreviations: *BHMT*, betaine-homocysteine S-methyltransferase; *CBS*, cystathionine beta-synthase; *HFE*, hemochromatosis protein; *MTHFR*, Methylenetetrahydrofolate reductase; *MTR*, methionine synthase; SNP, single-nucleotide polymorphism; *TF*, transferrin.

Table S2. Associations between blood lead concentrations and plasma homocysteine levels (μmol/L)[a], further adjusted for the dietary levels of vitamin B6, folate, and both

	Q1	**Q2**	**Q3**	**Q4**	***p*-value**[b]
Further adjusted for vitamin B6	10.72 (1.04)	11.11 (1.05)	11.55 (1.05)	11.57 (1.05)	0.0630
Further adjusted for folate	10.73 (1.04)	11.14 (1.05)	11.58 (1.05)	11.60 (1.05)	0.0574
Further adjusted for both	10.70 (1.04)	11.10 (1.05)	11.54 (1.05)	11.57 (1.05)	0.0576

Abbreviations: Q1, first quartile of blood lead concentrations; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

[a]Results are shown as geometric means (geometric standard deviations) of homocysteine concentrations by each quartile of blood lead level.

[b]Basic models were adjusted for age at the time of lead measurement, sex, alcohol drinking, tobacco smoking, education level, body mass index, time between lead and homocysteine measurements, and creatinine clearance.

Table S3. Interactions between blood lead concentrations and *TF* polymorphisms with respect to plasma homocysteine levels[a]

Lead levels	**Q1**		**Q2**		**Q3**		**Q4**		
	n	**β (95% CI)**	***n***	**β (95% CI)**	***n***	**β (95% CI)**	***n***	**β (95% CI)**	***p*-value[b]**
rs2715632 variant allele (T)									
0	82	Reference	75	0.05 (-0.04, 0.15)	77	0.09 (-0.01, 0.18)	73	0.03 (-0.07, 0.13)	0.3186
1–2	19	-0.02 (-0.17, 0.13)	15	-0.08 (-0.24, 0.08)	11	0.05 (-0.15, 0.24)	24	0.21 (0.07, 0.34)	0.0291
p-value[c]		0.7169		0.0822		0.9976		0.0146	
rs2715631 variant allele (G)									
0	84	Reference	75	0.05 (-0.05, 0.15)	78	0.09 (-0.005, 0.18)	73	0.03 (-0.07, 0.13)	0.2650
1–2	20	-0.04 (-0.19, 0.11)	17	-0.05 (-0.20, 0.11)	12	-0.01 (-0.19, 0.18)	25	0.23 (0.09, 0.36)	0.0149
p-value[c]		0.5486		0.1743		0.6951		0.0052	
rs2715627 variant allele (C)									
0	84	Reference	76	0.05 (-0.04, 0.15)	78	0.09 (-0.004, 0.18)	73	0.03 (-0.06, 0.13)	0.2807
1–2	20	-0.04 (-0.19, 0.11)	16	-0.06 (-0.22, 0.09)	12	-0.005 (-0.19, 0.18)	25	0.23 (0.09, 0.36)	0.0126
p-value[c]		0.5486		0.1042		0.6951		0.0052	

Abbreviations: *TF*, transferrin; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

[a]Linear regression models adjusted for age at the time of lead measurement, sex, alcohol drinking, tobacco smoking, education level, body mass index, time from lead measurement to homocysteine measurement, and creatinine clearance were used to assess the associations.

[b]*p*-values were estimated within strata of genotype.

[c]*p*-values were estimated within strata of lead quartile group.

Table S4. Associations between blood lead concentrations and plasma homocysteine levels[a], stratified by the presence or absence of selected single-nucleotide polymorphism variant alleles

	Q1	Q2	Q3	Q4	*p*-value[b]
rs2715632 variant allele (T)					
0	11.15 (1.05)	11.80 (1.05)	12.15 (1.05)	11.60 (1.06)	0.3186
1–2	9.70 (1.15)	9.06 (1.14)	10.15 (1.16)	12.24 (1.14)	0.0291
rs2715631 variant allele (G)					
0	11.05 (1.05)	11.64 (1.05)	12.09 (1.05)	11.52 (1.06)	0.2650
1–2	8.70 (1.14)	8.46 (1.13)	8.83 (1.14)	11.29 (1.13)	0.0149
rs2715627 variant allele (C)					
0	11.03 (1.05)	11.65 (1.05)	12.06 (1.05)	11.49 (1.06)	0.2807
1–2	8.70 (1.14)	8.43 (1.13)	8.99 (1.14)	11.42 (1.13)	0.0126

Abbreviations: Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

[a]Results are shown as geometric means (geometric standard deviations).

[b]Linear regression models adjusted for age at the time of lead measurement, sex, alcohol drinking, tobacco smoking, education level, body mass index, time from lead measurement to homocysteine measurement, and creatinine clearance were used to assess the associations.

Table S5. Imputed single-nucleotide polymorphisms in *TF* and *MTHFR* found to interact with lead levels versus homocysteine levels with the 2 df joint test[a]

SNP rs no.	Gene	Chr	Position	MAF	β (main)	SE (main)	β (int)	SE (int)	1 df *p*-value	2 df *p*-value
rs2718806	*TF*	3	134968791	0.10	0.01	0.04	0.04	0.02	0.0084	0.0265
rs8649	*TF*	3	134969648	0.10	0.01	0.04	0.04	0.02	0.0084	0.0265
rs1525890	*TF*	3	134972281	0.10	0.01	0.04	0.04	0.02	0.0084	0.0265
rs1115219	*TF*	3	134977715	0.10	0.01	0.04	0.04	0.02	0.0084	0.0265
rs4846049	*MTHFR*	1	11784631	0.16	0.07	0.03	0.01	0.02	0.6934	0.0450
rs1801131	*MTHFR*	1	11788742	0.16	0.07	0.03	0.01	0.02	0.6727	0.0482
rs12121543	*MTHFR*	1	11788937	0.15	0.07	0.03	0.01	0.02	0.4773	0.0385
rs1994798	*MTHFR*	1	11789021	0.17	0.07	0.03	0.01	0.02	0.6513	0.0423
rs6541003	*MTHFR*	1	11790133	0.16	0.07	0.03	0.01	0.02	0.6727	0.0483
rs4846052	*MTHFR*	1	11792217	0.16	0.07	0.03	0.01	0.02	0.6727	0.0483
rs3737964	*MTHFR*	1	11801310	0.11	0.09	0.04	0.02	0.02	0.2949	0.0361

Abbreviations: Chr, chromosome; df, degree-of-freedom; int, interaction; MAF, minor allele frequency; *MTHFR*, Methylenetetrahydrofolate reductase; SE, standard error; SNP, single-nucleotide polymorphism; *TF*, transferrin.

Figure Legend

Figure S1. Linkage disequilibrium in the selected *TF* region