

Supplementary Online Content

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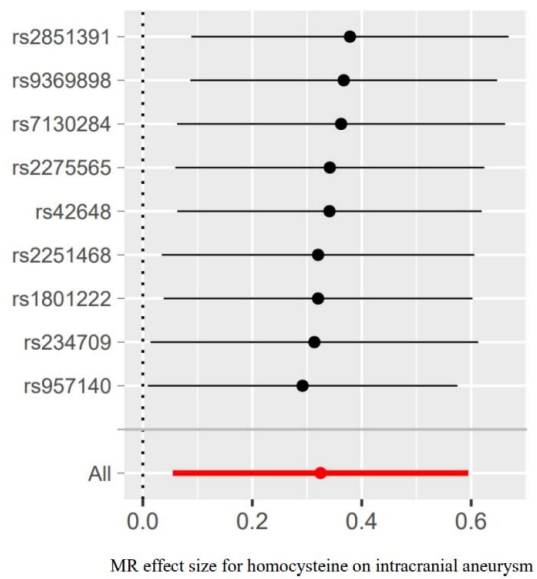
Table S3. Association between tHcy and Intracranial Aneurysm Based on IPTW Analysis

Table S4. Additive Interaction Analysis on tHcy and Hypertension

Table S1. Single Nucleotide Polymorphism Associated with Serum total Homocysteine

SNP	Chr	Position	Nearest gene	EA	EAF	NEA	Beta	SE	P
rs2275565	1	237048676	MTR	G	0.79	T	0.0542	0.009	1.96e-10
rs9369898	6	49382193	MUT	A	0.62	G	0.0449	0.007	2.17e-10
rs7130284	11	89148372	NOX4	C	0.93	T	0.1242	0.013	1.88e-20
rs234709	21	44486964	CBS	C	0.55	T	0.0718	0.007	3.9e-24
rs42648	7	89977760	GTPB10	G	0.6	A	0.0395	0.007	1.97e-08
rs1801222	10	17156151	CUBN	A	0.34	G	0.0453	0.007	8.43e-10
rs2251468	12	121405126	HNF1A	C	0.35	A	0.0512	0.007	1.28e-12
rs957140	11	89201627	NOX4	G	0.55	A	0.045	0.008	2.43e-08
rs2851391	21	43067294	CBS	T	0.47	C	0.056	0.008	1.7e-12

Abbreviation: SNP, single nucleotide polymorphism ; Chr, chromosome; EA, effect allele; EAF, effect allele frequency; NEA non-effective allele; Beta, coefficient presented as the number of SD difference in homocysteine concentrations per allele; SE, standard error.

Figure S1. Leave-one-out analysis on the MR estimates by removing each SNP individually

The leave-one-out analysis confirmed that Mendelian Randomization result for causal association of tHcy with intracranial aneurysm was robust and reliable as it was not driven by any single SNP.

Table S2 Baseline Characteristics Before and After IPTW (Inverse Probability of Treatment Weighting)						
	Before IPTW			IPTW		
	non-IAs	IAs	p	non-IAs	IAs	p
	n = 9831	n = 5496		n = 15464.1	n = 15084.1	
Sex, No.(%)			<0.001			0.447
Male	5693 (57.9)	2254 (41.0)		8021.1 (51.9)	7935.8 (52.6)	
Female	4138 (42.1)	3242 (59.0)		7440.0 (48.1)	7148.3 (47.4)	
Age, mean, (SD), y	63.9 (13.5)	57.8 (12.0)	<0.001	61.3 (13.9)	61.2 (13.2)	0.717
Age class, No.(%)			<0.001			0.654
18-39 y	477 (4.9)	394 (7.2)		934.7 (6.0)	964.7 (6.4)	
40-59 y	2981 (30.3)	2656 (48.3)		5779.9 (37.4)	5679.4 (37.7)	
≥60 y	6373 (64.8)	2446 (44.5)		8749.5 (56.6)	8439.9 (56.0)	
BP class, mmHg,			<0.001			0.746
SBP / DBP, No.(%)						
< 140 / < 90	3449 (35.1)	2434 (44.3)		5947.3 (38.5)	5767.8 (38.2)	
140~159 / 90~99	3404 (34.6)	1111 (20.2)		4484.0 (29.0)	4268.2 (28.3)	
160~179 / 100~109	2065 (21.0)	888 (16.2)		2953.0 (19.1)	2973.3 (19.7)	
≥180 / ≥110	913 (9.3)	1063 (19.3)		2079.8 (13.4)	2074.8 (13.8)	
Hyperlipidemia, No.(%)			<0.001			0.688
No	4726 (48.1)	3060 (55.7)		7900.4 (51.2)	7764.3 (51.5)	
Yes	5105 (51.9)	2436 (44.3)		7563.7 (48.9)	7319.8 (48.5)	
Diabetes, type 1 and 2			<0.001			0.803
No	7098 (72.2)	4319 (78.6)		11559.5 (74.8)	11241.9 (74.5)	
Yes	2733 (27.8)	1177 (21.4)		3904.6 (25.2)	3842.2 (25.5)	
Smoke*, No.(%)			<0.001			0.823
No	7684 (78.2)	4778 (86.9)		12601.2 (81.5)	12318.3 (81.7)	
Yes	2147 (21.8)	718 (13.1)		2862.9 (18.5)	2765.8 (18.3)	
Alcohol use†, No.(%)			<0.001			0.507
No	7892 (90.0)	4775 (92.6)		12711.3 (81.0)	13719.7 (91.2)	
Yes	875 (9.98)	383 (7.43)		2752.8 (9.0)	1364.4 (8.8)	

* †: missing data was imputed for 830 (5.4%) and 1,402 (9.1%) patients about smoking and alcohol using by Multiple Imputation utilizing Mice package (3.14) for R (4.2.2)

Abbreviation: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table S3 Association between tHcy and Intracranial Aneurysm Based on IPTW Analysis						
IPTW						
	non-IAs	IAs	Crude OR		Adjusted OR*	
	n=15464.1	n=15084.1	95% CI	p	95% CI	p
tHcy [†] (SD), umol/L	12.5 (6.2)	14.9 (10.7)	1.51 (1.46;1.56)	< .001	1.56 (1.50;1.61)	< .001
tHcy [‡]			1.28 (1.26;1.31)	< .001	1.31 (1.28;1.34)	< .001
Group tHcy, No.(%)				<.001[§]		<.001[§]
Low	12321.0 (79.7)	10078.4 (66.8)	Reference.		Reference.	
Moderate	2868.3 (18.5)	4423.3 (29.3)	1.89 (1.79;1.99)	< .001	1.97 (1.69;2.30)	< .001
High	274.9 (1.8)	582.4 (3.9)	2.59 (2.23;3.00)	< .001	0.97 (0.87;1.08)	.558
Moderate + High	796 (16.1)	1487 (30.0)	1.95 (1.85;2.05)	< .001	1.71 (1.61;1.81)	< .001

P-value for OR (odd ratios) was based on Wald tests;

*: Odds ratios was adjusted by age, sex, blood pressure level and smoke;

†: OR was estimated by per 1 standard difference increase of tHcy (8.2 μmol/L);

‡: OR was estimated by per 5μmol/L increase of tHcy;

§: P value for trend.

Table S4 Additive Interaction Analysis on tHcy and Hypertension						
	PSM Model			IPTW Model		
	OR*	95% CI†	p	OR*	95% CI†	p
tHcy<15umol/L + no HBP	Reference.			Reference.		
tHcy≥15umol/L + no HBP	1.18	(1.08; 1.30)	<0.001	1.16	(1.11; 1.22)	<0.001
tHcy<15umol/L + HBP	0.68	(0.61; 0.75)	<0.001	0.71	(0.67; 0.75)	<0.001
tHcy≥15umol/L + HBP	2.51	(2.25; 2.81)	<0.001	2.14	(2.01; 2.27)	<0.001
Estimation of Interaction						
Statistic	Value	95% CI		Value	95% CI	
RERI	1.65	(1.29;2.01)		1.27	(1.27;1.44)	
AP	0.66	(0.58;0.74)		0.60	(0.54;0.65)	

*: OR, Odds Ratio

†: CI, Confidence Interval

‡: RERI, Relative excess risk due to interaction (part of the total effect that is due to interaction), defined as $OR_{A+B} - OR_{A+B-} - OR_{A-B+} - 1$; RERI > 1 means positive interaction or more than additivity.^[1] RERI < 1 means negative interaction or less than additivity.

§: AP, Proportion attributable to interaction (proportion of the combined effect that is due to interaction), $AP = RERI / OR_{A+B+}$ ^[1]. AP > 0 means positive interaction or more than additivity.

AP < 0 means negative interaction or less than additivity.

References.

1. Knol MJ, VanderWeele TJ, Groenwold RH, Klungel OH, Rovers MM, Grobbee DE. Estimating measures of interaction on an additive scale for preventive exposures. *EUR J EPIDEMIOL.* 2011;26(6):433-8. doi:10.1007/s10654-011-9554-9