

### Supplementary Online Content

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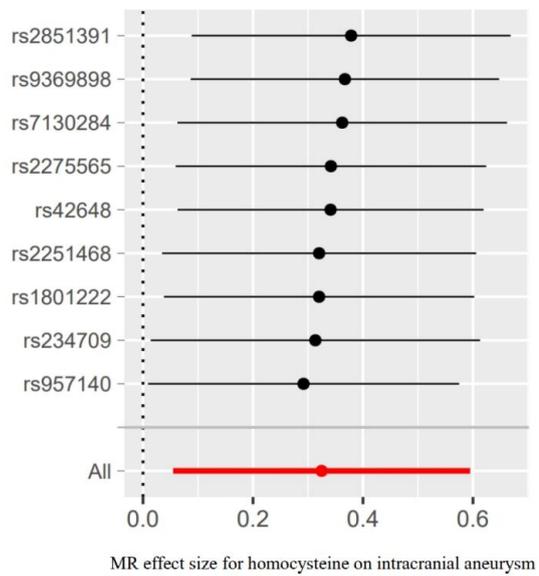
**Table S3.** Association between tHcy and Intracranial Aneurysm Based on IPTW Analysis

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**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.

<b>Table S2</b> Baseline Characteristics Before and After IPTW (Inverse Probability of Treatment Weighting)						
	<b>Before IPTW</b>			<b>IPTW</b>		
	<b>non-IAs</b>	<b>IAs</b>	<b>p</b>	<b>non-IAs</b>	<b>IAs</b>	<b>p</b>
	<b>n = 9831</b>	<b>n = 5496</b>		<b>n = 15464.1</b>	<b>n = 15084.1</b>	
<b>Sex, No.(%)</b>			<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)	
<b>Age, mean, (SD), y</b>	63.9 (13.5)	57.8 (12.0)	<0.001	61.3 (13.9)	61.2 (13.2)	0.717
<b>Age class, No.(%)</b>			<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)	
<b>BP class, mmHg,</b>			<0.001			0.746
<b>SBP / DBP, No.(%)</b>						
< 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)	
<b>Hyperlipidemia, No.(%)</b>			<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)	
<b>Diabetes, type 1 and 2</b>			<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)	
<b>Smoke*, No.(%)</b>			<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)	
<b>Alcohol use†, No.(%)</b>			<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.

<b>Table S3</b> Association between tHcy and Intracranial Aneurysm Based on IPTW Analysis						
<b>IPTW</b>						
	<b>non-IAs</b>	<b>IAs</b>	<b>Crude OR</b>		<b>Adjusted OR*</b>	
	n=15464.1	n=15084.1	<b>95% CI</b>	<b>p</b>	<b>95% CI</b>	<b>p</b>
tHcy <sup>†</sup> (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 <sup>‡</sup>			1.28 (1.26;1.31)	< .001	1.31 (1.28;1.34)	< .001
Group tHcy, No.(%)				<b>&lt;.001<sup>§</sup></b>		<b>&lt;.001<sup>§</sup></b>
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.<sup>[1]</sup> RERI < 1 means negative interaction or less than additivity.

§: AP, Proportion attributable to interaction (proportion of the combined effect that is due to interaction),  $AP = RERI / OR_{A+B+}$ <sup>[1]</sup>. 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