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Supplementary webappendix

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Supplement to: Holmes MV, Newcombe P, Hubacek JA, et al. Effect modification by population dietary folate on the association between MTHFR genotype, homocysteine, and stroke risk: a meta-analysis of genetic studies and randomised trials. *Lancet* 2011; published online Aug 1. DOI:10.1016/S0140-6736(11)60872-6.

Effect modification by population dietary folate on the association between *MTHFR* genotype, homocysteine, and stroke risk: a meta-analysis of genetic studies and randomised trials

Supplementary materials

Methods

Search Strategy

Randomised clinical trials

For MEDLINE, the MesH terms “cardiovascular disease”, “coronary heart disease”, “coronary stenosis”, “myocardial infarction”, “cerebrovascular accident”, “stroke”, and “randomised controlled trial”, “clinical trial”, and “folic acid” were utilised. We also searched for trials published only as an abstract in conferences or meetings[1] as well as in previously published meta-analyses addressing this question[2,3].

For inclusion in the analysis, studies had to: (i) be randomised and parallel in design; (ii) be conducted in adults; (iii) examine the effects of folic acid supplementation (with or without additional vitamin B supplementation); (iv) record stroke as an outcome, and; (v) have 12 months minimum follow-up. Studies using folic acid combined with a multivitamin/mineral tablet versus placebo/standard care were excluded[4].

Genetic studies

We used the text words, which were also MeSH terms, “polymorphism”, “mutation”, “genotype”, “genetic”, “gene(s)”, “allele(s)” in combination with “stroke”, “cerebrovascular disorder/disease”, “cerebral ischemia”, “hemorrhagic stroke”, “(silent) brain infarction”. Literature searches were limited to “human”. All languages were included. Additional studies in the references of all identified publications, including previous relevant meta-analyses were identified.

In the analysis of the *MTHFR*/C677T variant on Hcy levels, studies were included if the design was case-control, cohort or cross-sectional. For inclusion in the analysis of *MTHFR*/C677T variant and stroke, case-control, cohort, or cross-sectional studies evaluating ischaemic, haemorrhagic or undifferentiated stroke were included. In all searches, when relevant information was not reported or there was doubt about duplicate publications, we contacted authors for clarification.

We supplemented information from published studies with unpublished genetic data obtained through direct contact with investigators of any study that had previously reported at least one genetic finding in stroke (for case-control studies) or in cardiovascular disease (for cohorts) in a peer reviewed journal. This allowed us to minimise the scope for reporting and publication bias. A total of 52 investigators of newly identified studies were asked to provided the most up-to-date information on the *MTHFR*/C677T variant and stroke risk in the form of genotype counts by disease status (cases [ischaemic, hemorrhagic or undifferentiated stroke] and controls) and the average values of Hcy and

folic acid by *MTHFR*/C677T genotypes in subjects without cardiovascular disease. Authors of 44 studies replied and provided information.

Data extraction

Randomised trials

For randomised trials, the following variables were extracted (by MVH and JPC, **see eTable 5**): study design, patient characteristics, calendar years in which trial conducted; geographical region; type of stroke outcome(s) recorded; mean follow-up period, and; type of intervention(s) used as comparator (usual care, placebo, lower-dose folic acid, B vitamin alone). In addition, in each arm we recorded: (a) number of participants; (b) number of stroke events; (c) baseline and post-intervention levels of Hcy (where applicable), and; (d) doses of intervention(s) used. To determine the risk of bias, we evaluated: (i) sequence generation; (ii) allocation concealment; (iii) incomplete outcome data, and; (iv) selective outcome reporting, as suggested by the Cochrane Handbook for Systematic Reviews of Interventions[5]. Disagreements were resolved by consensus.

For each trial, point estimates of relative risk with 95% confidence intervals were derived using values of outcome events in each study arm. For all studies, we used intention to treat analysis. In cases of discrepancy or doubt about the number of events (stroke/TIA), we contacted authors to clarify details. Outcomes were recorded separately for (i) stroke, excluding TIA, and, (ii) stroke including TIA with comparator arms classified as (i) placebo, B-vitamins and/or folic acid [where folic acid in the comparator arm was low-dose compared to the intervention arm], and (ii) placebo only, excluding studies in which no placebo or usual care was used (i.e. Wrone[6] and Toole[7]), or events in participants randomised to vitamin B6 as one of three arms (i.e. Ebbing[8] and Bonaa[9]). To increase comparability of RCTs with genetic studies, we selected only stroke events excluding TIA as the main outcome and compared intervention with any of placebo, vitamin B and/or (low-dose) folic acid.

Genetic studies

For genetic studies the following variables were extracted (by PN and MVH, see **eTable 1 and 2**): study design, participant characteristics, country and calendar year in which the study was conducted, study design, proportion of males, mean age of participants, frequency of genotypes and alleles by case control status, average value (mean, median) and measure of dispersion (standard deviation, standard error, confidence interval, inter-quartile range or range) of Hcy and folic acid concentrations, stroke sub-type(s), language of publication, and ethnic background. We also calculated Hardy-Weinberg equilibriums (HWE) and disequilibrium coefficients for all genetic studies: in studies of *MTHFR*-stroke, only allele frequencies in controls were used; in *MTHFR*-homocysteine studies, allele frequencies of all participants were used. Where the number of subjects per genotype was selected/restricted *a priori* by the study investigators, HWE values were not estimated. For plots of allele frequency, we categorized studies into (i) probable folate status category, and (ii) ethnicity.

Ethnicity was classified according to the subjects investigated: studies or study subsets were categorized as follows: (i) Caucasian: including Israel and Turkey; (ii) African; (iii) East Asia including individuals from Japan, China, Korea, Hong Kong and Mongolia; (iv) South Asia including India, Pakistan and Bangladesh; (v) Latin America, and; (vii) mixed ethnicity. Plots were restricted to those studies that had values for all 3 genotypes and/or had not selected the number of subjects per genotype status.

Categorization of genetic studies by probable folate status

These categories (developed and validated by Dr Robert Clarke, Clinical Trial Service Unit (CTSU) and Epidemiological Studies Unit, University of Oxford, UK) used information on geographical location and dates during which the genetic study was conducted. and considered: (i) whether policies for folic acid fortification had been initiated and the date of implementation, and; (ii) whether there had been a change in folic acid levels at population levels though time. This information was derived from population based studies with information on folic acid. Geographical regions served as proxies of folate supplementation status. Categories were sorted according to the level of folic supplementation from the lowest to the highest as follows. (1) **Asia**: in addition to Asian countries (e.g. China, India, Hong Kong, Korea, Thailand, Mongolia) this category also included countries from North and sub-Saharan Africa conducted at any time. (2) **Europe-low** (pre-fortification): including studies from Ireland, Scandinavia (Denmark, Norway, Sweden, Finland), Netherlands, Russia and Turkey conducted at any time, and European countries conducted prior to folic acid fortification of cereal and flour, initiated in 1996. (3) **Europe mid** (post-fortification): including all European countries in 1996 or thereafter (except Ireland, Scandinavia, Netherlands, Russia or Turkey). (4) **America & Australia & New Zealand mid** (pre-fortification): which included studies from North-America, Australia and New Zealand prior to 1996, and studies from Central and South America conducted at any time, except for Chile, in which only studies conducted prior to 2000 were classified in this category. (5) **America & Australia & New Zealand high** (post-fortification): which included studies from North-America, Australia and New Zealand conducted in 1996 and thereafter, and studies conducted in Chile in 2000 and thereafter. For 67 studies (of 137) on which information was unavailable (from the publication, or previous publications from the same study, or after contacting study authors) on the timing of the study, 2-years prior to the publication date was used as the year the study was conducted. This value (median) was derived from the 70 studies that provided information on time of study conducted and year of publication Information on the categories allocated to each genetic dataset included in the analysis is described in **eTables 1 and 2**.

Data Analysis

All meta analyses were performed using the 'metan' command[10] in Stata (StataCorp, Texas, USA) version 11.1. For meta-analysis of genetic association studies, we followed guidance from the Human Genome Epidemiology Network (HuGENet) HuGE Review Handbook[11].

MTHFR and homocysteine level

The estimate of the mean difference was restricted to individuals without clinical evidence of cardiovascular disease (ischaemic heart disease, stroke, or venous thrombosis). In order to explore the modifying effect of folic acid levels on the *MTHFR*/C677T-Hcy association, two strategies were utilized. First, we conducted a stratified meta analysis of the effect of the *MTHFR*/C677T variant on Hcy levels according to the 'probable folate categories'. Second, we performed a meta-regression analysis of the difference in Hcy levels by genotype against the average concentration of folic acid in each study. Analyses were then repeated only in studies with sample size ≥500 individuals in order to explore the influence of small-study bias in addition to funnel plot and Egger regression tests[12].

MTHFR and Stroke

The outcome 'main stroke comparison' was used to make comparisons with results from RCTs of Hcy lowering therapies. The 'main stroke comparison' included studies reporting: (i) only-ischaemic stroke, (ii) only-haemorrhagic stroke, (iii) both (ischaemic and haemorrhagic separately) stroke, or (iv) only unclassified stroke (studies in which neuroimaging tools were not available to classify the event as haemorrhagic or ischaemic). For studies reporting ischaemic and/or haemorrhagic stroke, diagnosis was by neuroimaging (MRI or CT). For this meta-analysis, we assumed equivalence between risk ratio and OR. We used the probable folate status categories to explore whether the *MTHFR*/C677T effect on stroke was modified by folic acid levels in a meta-regression. For studies with information on Hcy levels and stroke, the effect of the *MTHR*/C677T variant on stroke was stratified according to the difference in Hcy levels (in tertiles) determined by the genetic variant.

Evaluation of small study bias

To evaluate the potential influence of small-study bias on risk of stroke (*MTHFR* TT vs CC) in Asia, we first restricted the analysis to large studies with ≥400 stroke events. Second, we performed Egger regression tests[12], which tests the null hypothesis that the funnel plot is symmetrical. Third, we implemented Duval and Tweedie's 'trim and fill' method[13] using the 'metatrim' command in Stata[14]. This method uses the observed asymmetry in the funnel plot to estimate the number and outcomes of missing studies, and adjusts the meta-analysis to incorporate missing data. Fourth, we generated a hypothetical study with 400 cases distributed evenly to CC and TT genotype groups according to a TT frequency of 15% (derived from HapMap values obtained at dbSNP; www.ncbi.nlm.nih.gov/projects/SNP) for genotype frequencies in Asian populations). We sequentially added the hypothetical studies and the used cumulative meta-analysis to estimate the number of such studies that would have to exist to:

(a) reduce the point estimate to 1.15; the threshold at which evidence for a genetic association is downgraded based on the Venice criteria[15];

(b) reduce the point estimate to 1.10 (comparable to an expected relative risk reduction of 10% in an RCT of a Hcy lowering intervention), a threshold below which the sample size of a trial of a Hcy-lowering intervention on stroke risk might become too large to be considered practical;

(c) reduce the lower bound of the 95%CI to 1.00.

Finally, we compared the number of large studies (≥400 stroke cases) from Asia (low-folate region) category with other geographical regions.

Although Mendelian randomisation studies minimise confounding by environmental factors that may confound the blood marker-disease association, they can still suffer from confounding by linkage disequilibrium (LD). This is particularly relevant since in recent years, genome wide association studies have identified hits for established cardiovascular risk factors such as blood pressure, among those a variant (rs17367504) within the *MTHFR* gene[16]. In addition, since we included studies from different genetic ancestries, it might be possible that a different set of correlations (LD) of the rs1801133 variant occurs amongst different ethnic groups (e.g. Asians vs. Europeans), which therefore could confound our analyses. To explore this, we used the GLIDERS software[17] to evaluate long range LD for the rs1801133 variant among the main ethnic groups and cross-checked this information with genome wide association studies repositories (see Bioinformatics Tools below).

Randomised clinical trials

The trial arm containing Hcy-lowering treatment was assigned as the experimental group and compared against placebo, usual care, vitamin-B6 and/or low-dose folic acid. For the stroke outcome, we estimated log relative risk and log upper and log lower 95%CI and pooled estimates across studies using random (DerSimonian & Laird) and fixed (Mantel and Haenszel) effects modelling. The mean difference in change of Hcy between randomised groups (Δ-experimental arm minus Δ-comparator) was calculated. In a similar fashion to the genetic studies, we evaluated the potential effect of folate status intake on the results of the randomised trials. We conducted meta-regression analysis of the log of the relative risk of the trials against: (i) the probable folate status categories (using the same criteria as for genetic studies) and separately (ii) the mean difference in Hcy achieved by the intervention. Sensitivity analyses were conducted according to: (i) sample size (using 1000 randomised participants as a cut-point to dichotomise studies); (ii) risk of bias (low vs. any/high, according to Cochrane guidance[5]; see **eTable 5**); (iii) the outcome recorded (stroke only vs. stroke plus transient ischaemic attack - we re-estimated the relative risk of stroke for stroke plus TIA in studies where TIA was reported separately as a clinical event (HOPE-2[18], Righetti[19] and Wrone[6] and; (iv) according to the reference arm used (placebo only vs. [placebo or vitamin-B6 alone]). In addition, the meta-analysis estimate computed by omitting one study at a time was conducted to check that no individual trial had a major influence on the summary estimate (**eFigure 7**). We used the DerSimonian and Laird *Q* test in all meta-analyses to evaluate the degree of heterogeneity between studies, and the I^2 measure[20] to describe the proportion of total variation in study estimates due to heterogeneity. Funnel plot and Egger regression tests were conducted to evaluate the presence of small-study bias.

Bioinformatics tools

We used GLIDERS[17] (http://mather.well.ox.ac.uk/GLIDERS) to check for potential confounding by long-range linkage disequilibrium (LD). GLIDERS is a web-based tool that allows users to check long-range LD (>200kb) between SNPs. Using HapMap phase 3, the following criteria were used: Build 36,

MAF≥0.05, cis- and trans-chromosome, r^2≥0.3, no lower/upper range (i.e. associations between any pair-wise HapMap SNPs over any distance would be retrieved), and searching all ancestries (Asian, European, African) separately. We searched for SNPs in long-range LD with rs1801133 retrieved from GLIDERS using 2 genome wide association studies repositories for associations with CVD traits and/or outcomes: (1) NHGRI GWAS Catalog[21] and (2) SNPnexus http://www.snp-nexus.org. Both were accessed on 30th April 2009.

References to Supplementary Materials

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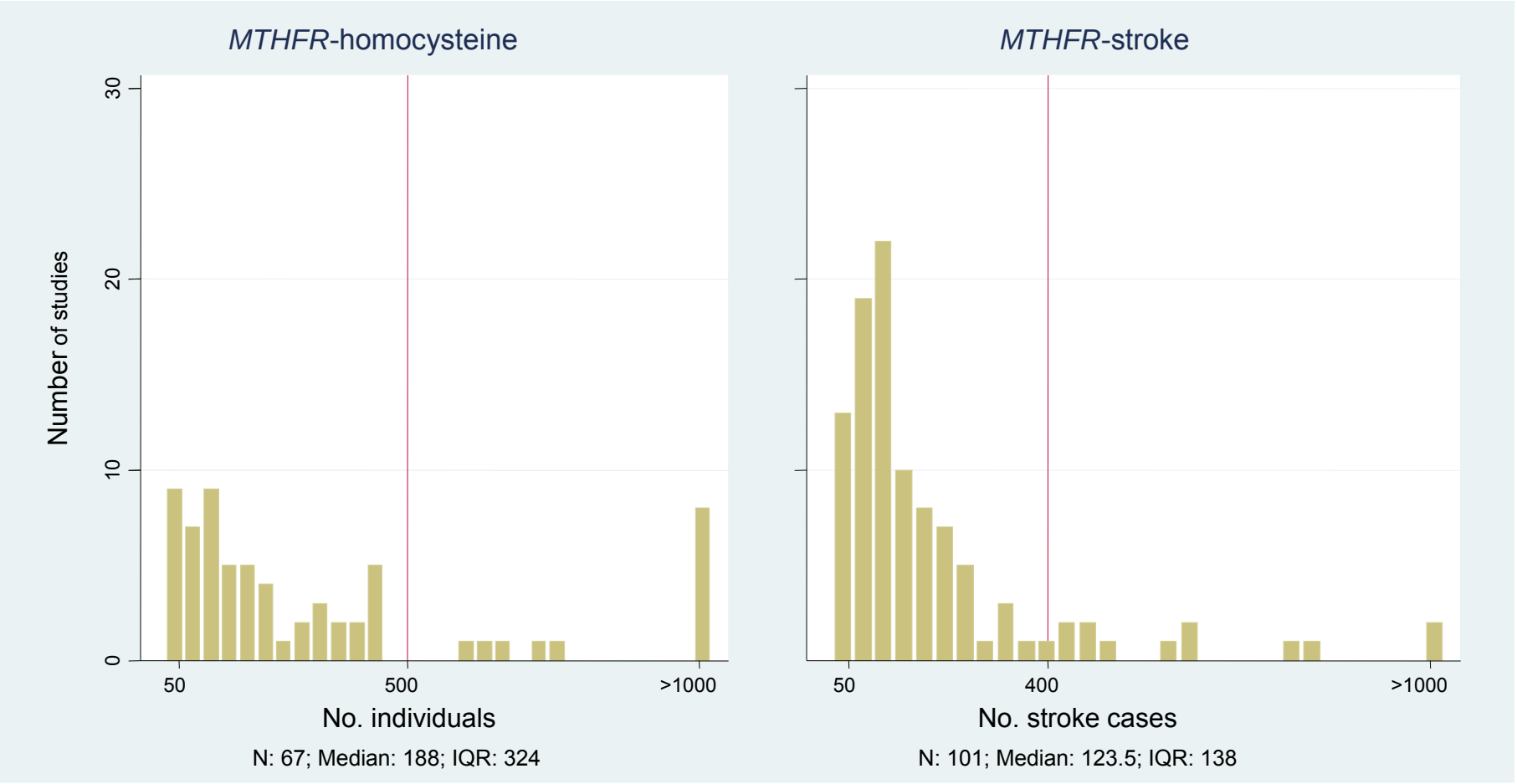
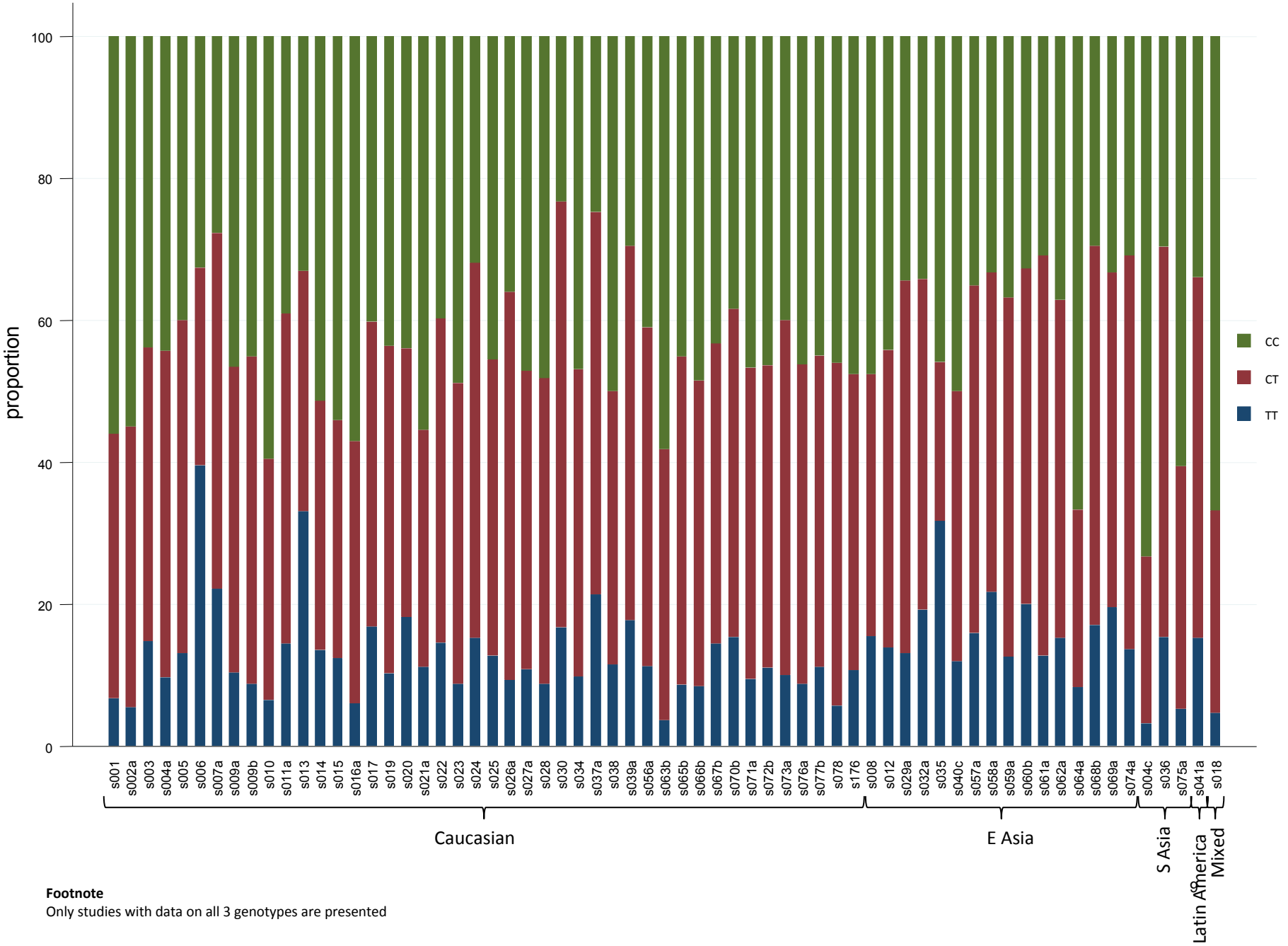
eFigure 1. Frequency histogram of sample size and number of stroke cases for *MTHFR*-homocysteine (left panel) and *MTHFR*-stroke (right panel) datasets.

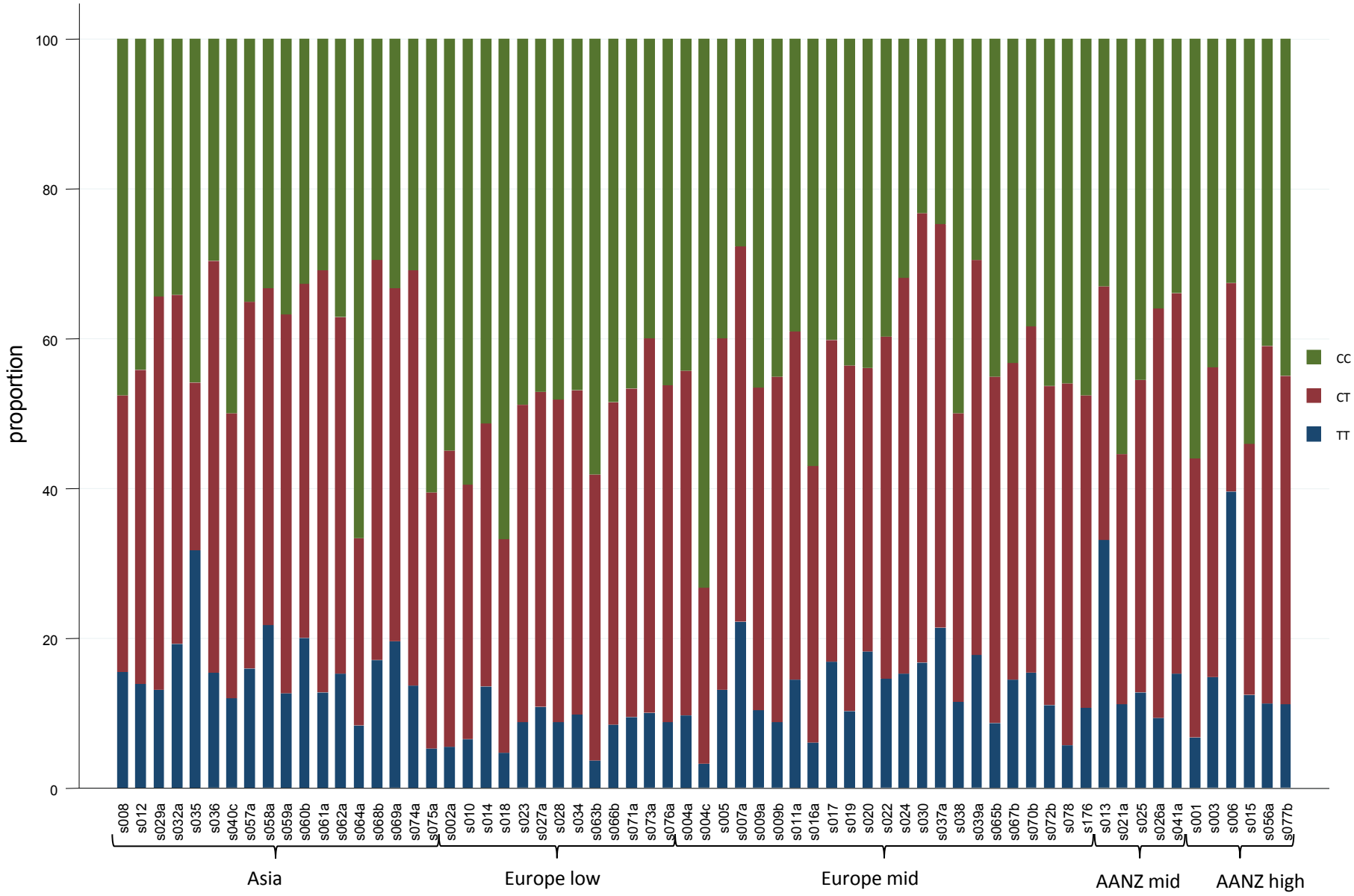


eFigure 2(a) and (b) Genotype frequency of *MTHFR*/C677T variant in studies used to determine the effect on homocysteine levels, classified by (a) ethnicity, and (b) probable folate status categories.



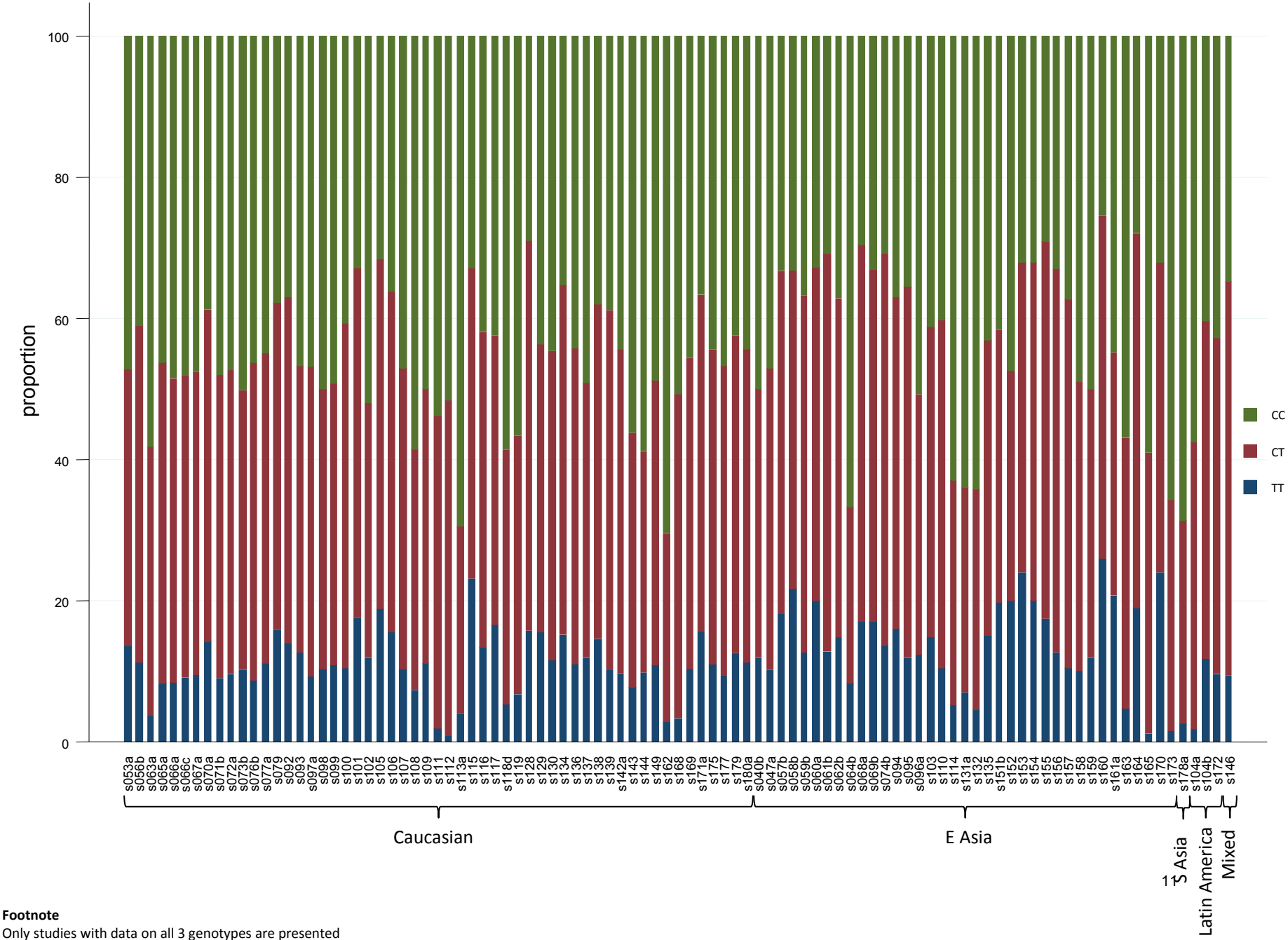
Footnote
Only studies with data on all 3 genotypes are presented

eFigure 2(b)



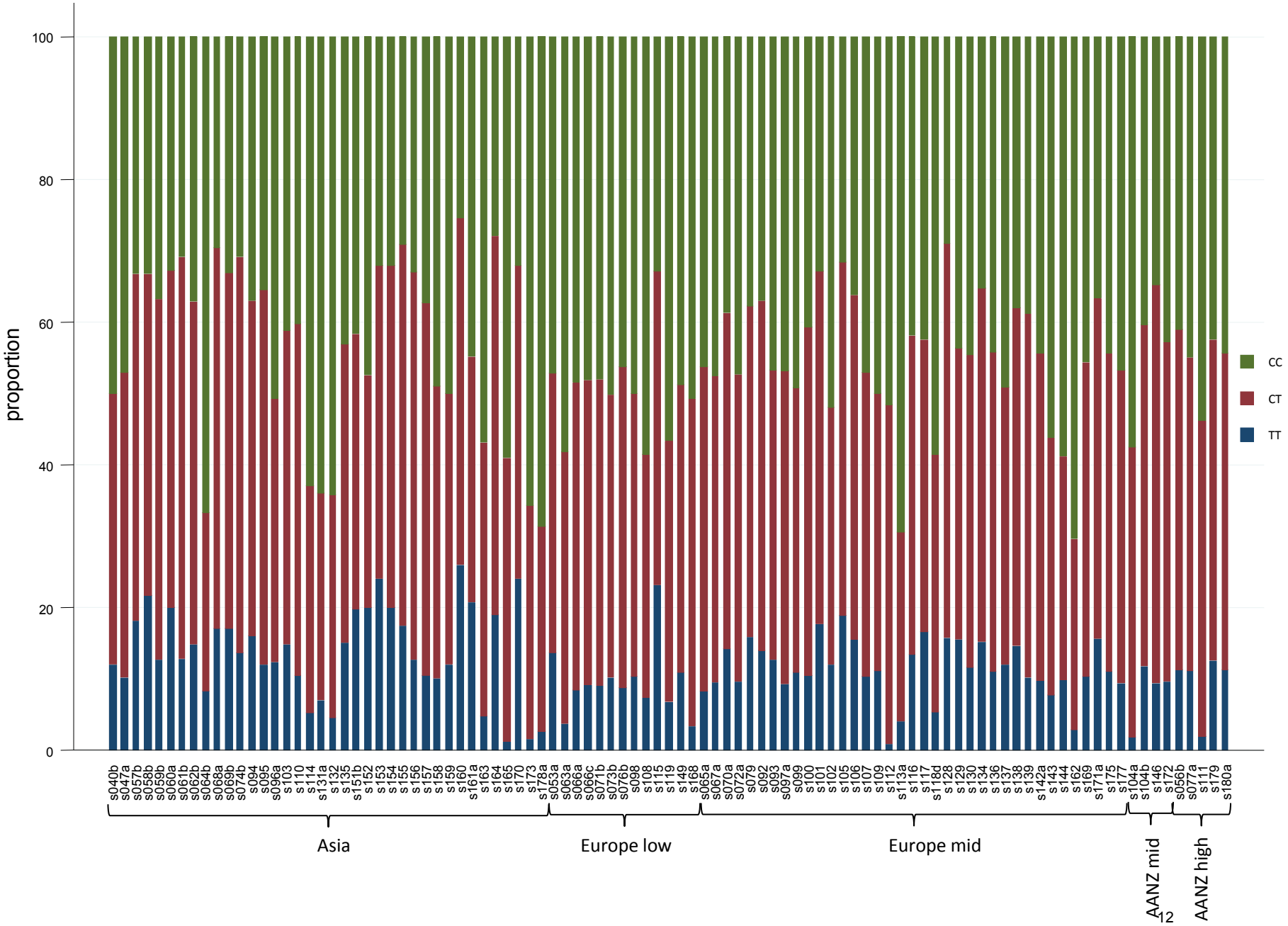
Footnote
Only studies with data on all 3 genotypes are presented

eFigure 3(a) and (b) Genotype frequency of *MTHFR*/C677T variant in studies utilised to estimate the effect on stroke, according to frequency in control samples, classified by (a) ethnicity, and (b) probable folate status category.



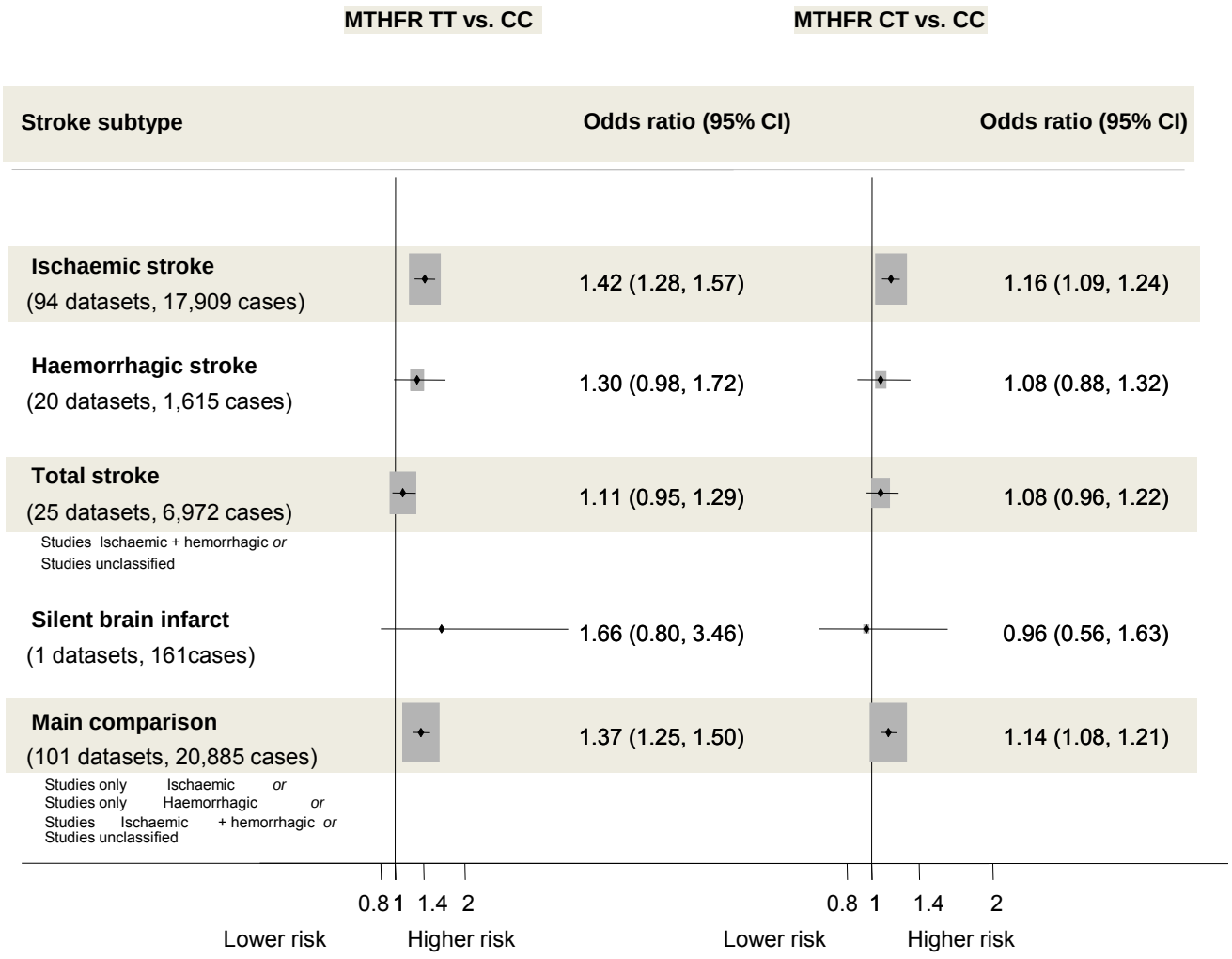
Footnote
Only studies with data on all 3 genotypes are presented

eFigure 3(b)

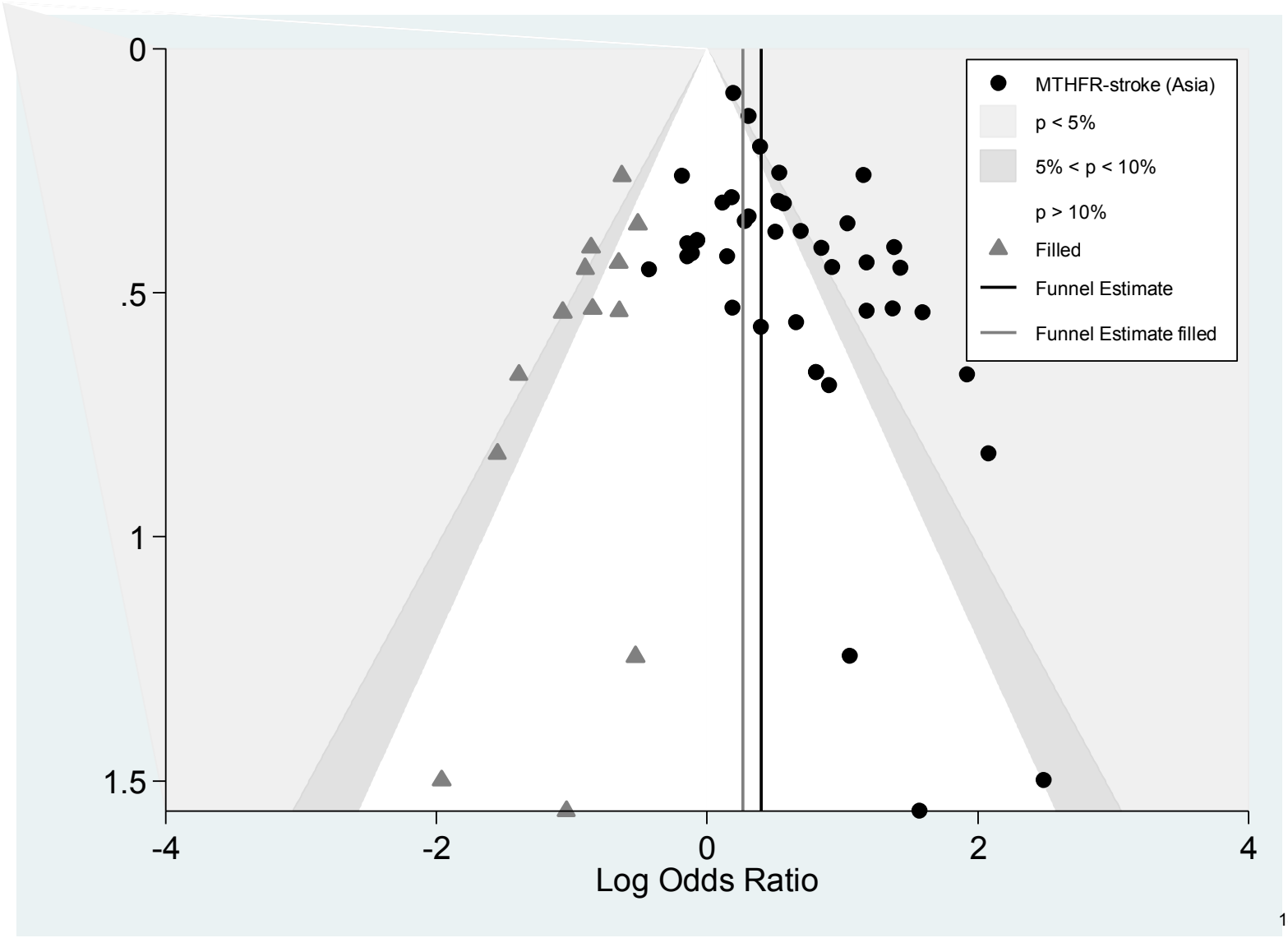


Footnote
Only studies with data on all 3 genotypes are presented

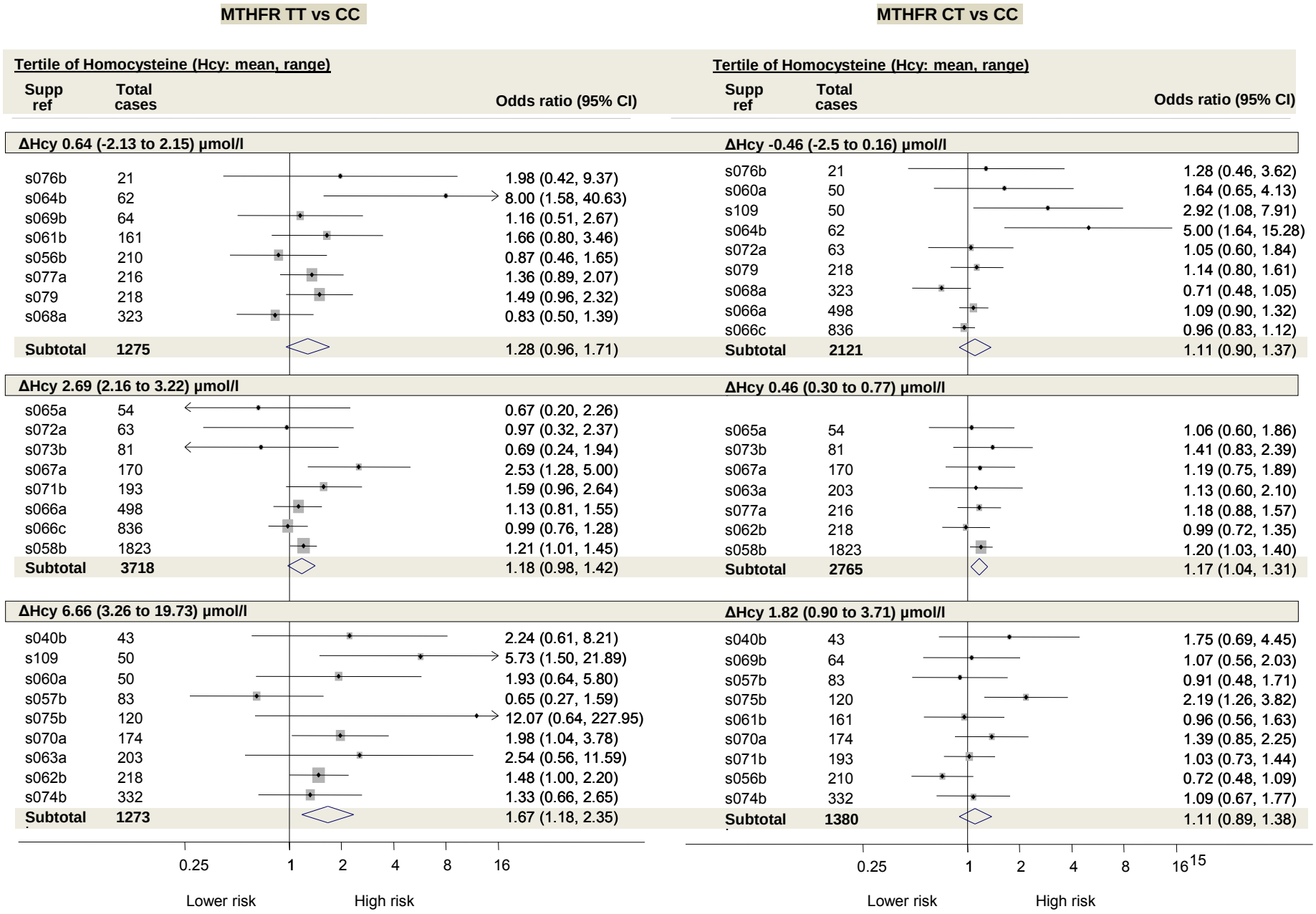
eFigure 4 Odds ratio of the *MTHFR*/C677T variant on different stroke sub-types. Left panel compares individuals homozygous for T allele with CC subjects. Right panel compares heterozygous with CC subjects.



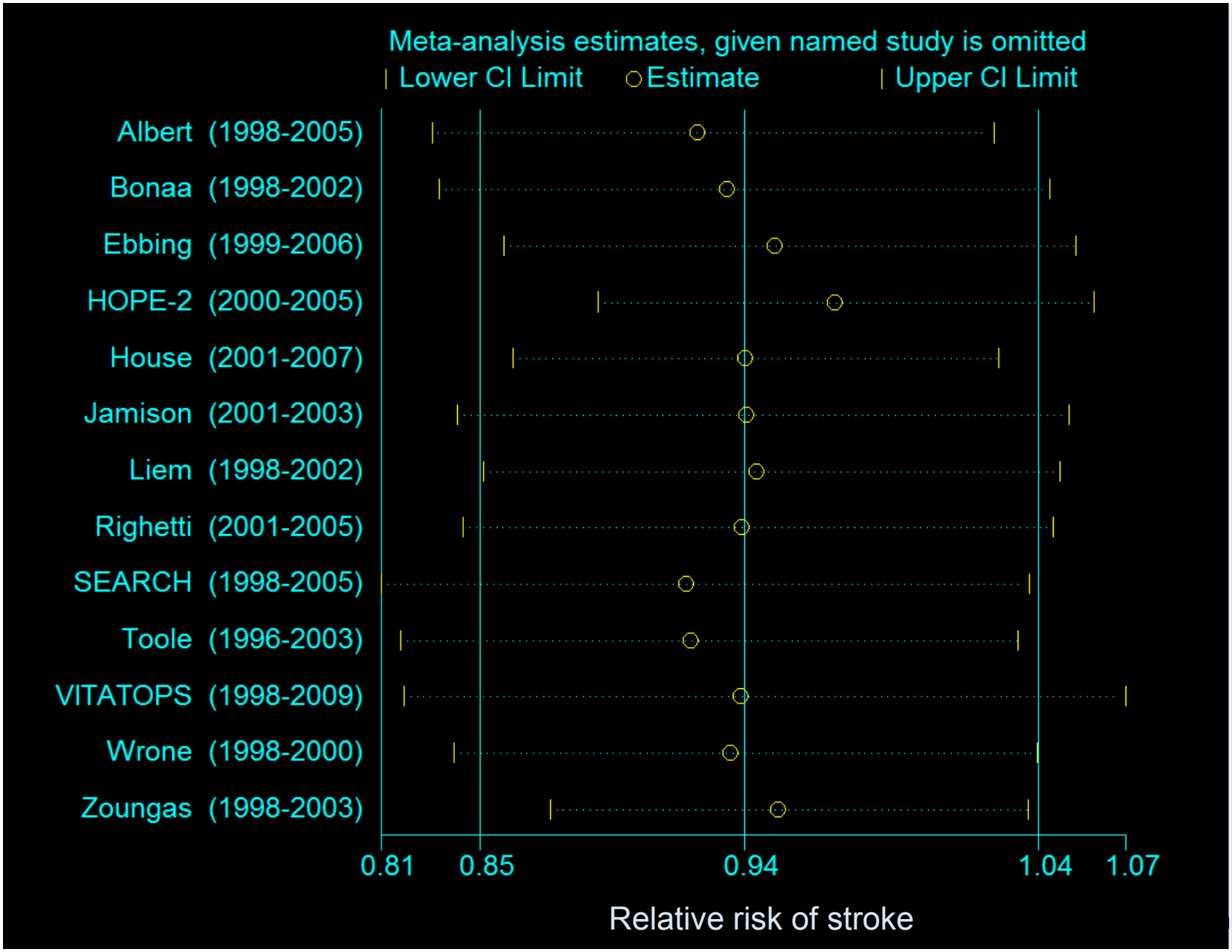
eFigure 5 Contour-enhanced funnel plot of *MTHFR*-stroke studies in Asia using the trim and fill analysis. The black dots represent the observed studies and the grey triangles represent hypothetical missing studies.



eFigure 6. Odds ratio of the *MTHFR*/C677T variant on stroke stratified according to the tertile of difference in homocysteine determined by the genetic variant. Left panel compares individuals homozygous for T-allele with CC subjects. Right panel compares heterozygous with CC subjects.



eFigure 7 Influence analysis to evaluate the effect of individual trials, omitted one at a time, on the summary estimate of randomised clinical trials of homocysteine-lowering interventions in stroke risk.



Supplementary Tables

eTable 1. Characteristics of genetic studies included in the analysis of *MTHFR*/C677T and homocysteine levels.

eTable 2. Characteristics of genetic studies included in the analysis of *MTHFR*/C677T and stroke risk.

eTable 3. Sensitivity analysis to illustrate the number of hypothetical large null studies that are needed to shift the point estimate observed in the *MTHFR*/C677T-stroke meta-analysis to several thresholds.

eTable 4. Linkage disequilibrium of the *MTHFR*/C677T variant by ethnic group.

eTable 5. Characteristics of randomised clinical trials of homocysteine-lowering interventions in stroke.

eTable 1. Characteristics of genetic studies included in the analysis of *MTHFR* C677T and homocysteine levels.

Study	Reference	Years conducted	Proxy year of study conduct †	Country where study performed	Folate regional supplementation	Ethnicity	Male (%)	Mean age (years)	No TT-genotype (all)	No CT-genotype (all)	No CC-genotype (all)	TT expected	CT expected	CC expected	HWE (p-value)	Disequilibrium coefficient
Nakata Y	s057a	1992-1995	NA	Japan	Asia	East Asian	NR	NR	30	92	66	30.72	90.55	66.72	0.8800	-0.0038
Yoo JH-2000	s029a	1996-1997	NA	Korea	Asia	East Asian	53	52	16	64	42	18.89	58.23	44.89	0.3440	-0.0236
Kohara K	s062a	1997-1999	NA	Japan	Asia	East Asian	50	NR	305	956	744	305.78	954.44	744.78	0.9626	-0.0004
Li Z	s058a	2000-2001	NA	China	Asia	East Asian	57	NR	398	824	610	358.13	903.73	570.13	0.0002	0.0218
Choi BO	s059a	2000-2002	NA	Korea	Asia	East Asian	56	NR	25	100	73	28.41	93.18	76.41	0.3654	-0.0172
Kim OJ2	s068b	2000-2002	NA	Korea	Asia	East Asian	53	NR	38	119	66	42.63	109.74	70.63	0.2243	-0.0208
Kim NK	s061a	2000-2003	NA	South Korea	Asia	East Asian	45	NR	16	71	39	21.05	60.90	44.05	0.0960	-0.0401
Biswas A	s075a	2003-2004	NA	India	Asia	South Asian	NR	NR	4	26	46	3.80	26.39	45.80	1.0000	0.0026
Ou T	s035	NR	1996	Japan	Asia	East Asian	86	55	27	19	39	15.67	41.65	27.67	0.0000	0.1333
Ho CH	s008	NR	1998	China	Asia	East Asian	68	64	69	164	212	51.24	199.52	194.24	0.0002	0.0399
Vizcaino G	s036	NR	1999	India	Asia	South Asian	NR	30	14	50	27	16.71	44.57	29.71	0.2907	-0.0298
Somekawa Y	s012	NR	2000	Japan	Asia	East Asian	0	55	30	91	96	26.27	98.46	92.27	0.2945	0.0172
Jee SH	s032a	NR	2000	Korea	Asia	East Asian	44	37	76	184	135	71.45	193.09	130.45	0.3550	0.0115
Yingdong Z	s040a	NR	2000	China	Asia	East Asian	48	59	5	16	21	4.02	17.95	20.02	0.4809	0.0232
Huang Y	s060b	NR	2000	China	Asia	East Asian	NR	NR	11	26	18	10.47	27.05	17.47	0.7870	0.0096
Miyaki K	s069a	NR	2002	Japan	Asia	East Asian	77	NR	10	24	17	9.49	25.02	16.49	0.7791	0.0100
Fang X	s064a	NR	2003	Mongolia	Asia	East Asian	54	NR	2	6	16	1.04	7.92	15.04	0.2324	0.0399
Kim IG	s074a	NR	2005	Korea	Asia	East Asian	45	NR	15	61	34	18.82	53.36	37.82	0.1705	-0.0347
Voutilainen S	s010	1984-1996	NA	Finland	Europe-low	Caucasian	100	54	11	57	100	9.29	60.43	98.29	0.5185	0.0102
Thogersen AM	s002a	1986-1994	NA	Sweden	Europe-low	Caucasian	79	55	7	51	71	8.19	48.62	72.19	0.8147	-0.0092
Meleady R	s027a	1990-1992	NA	9 European Countries	Europe-low	Caucasian	72	44	81	314	352	75.83	324.34	346.83	0.3994	0.0069
Slooter AJ	s071a	1990-2001	NA	Netherlands	Europe-low	Caucasian	0	NR	59	274	292	61.47	269.07	294.47	0.7102	-0.0039
Frederiksen J	s066b	1991-2002	NA	Denmark	Europe-low	Caucasian	42	NR	315	1600	1804	334.29	1561.42	1823.29	0.1378	-0.0052
de Bree A.	s034	1993-1996	NA	Netherlands	Europe-low	Caucasian	53	41	206	907	983	207.51	903.98	984.51	0.9193	-0.0007
Cappuccio FP	s018	1994-1996	NA	UK	Europe-low	Mixed ethnicity	45	50	64	391	916	49.12	420.76	901.12	0.0105	0.0109
Husemoen LLN	s023	1999-2001	NA	Finland	Europe-low	Caucasian	48	46	246	1181	1361	250.98	1171.04	1365.98	0.6849	-0.0018
Hustad S	s028	NR	1998	Norway	Europe-low	Caucasian	62	41	37	182	204	38.73	178.53	205.73	0.7308	-0.0041
Silaste ML	s014	NR	1999	Finland	Europe-low	Caucasian	0	NR	5	13	19	3.57	15.85	17.57	0.2679	0.0385
Shmeleva V	s073a	NR	2003	Russia	Europe-low	Caucasian	NR	NR	6	30	24	7.35	27.30	25.35	0.5746	-0.0225
Karakus Z	s076a	NR	2003	Turkey	Europe-low	Caucasian	52	NR	7	36	37	7.81	34.38	37.81	0.7977	-0.0102
Dikmen M	s063b	NR	2004	Turkey	Europe-low	Caucasian	29	NR	2	21	32	2.84	19.32	32.84	0.7110	-0.0153
D'Angelo A.	s037a	1996	NA	Italy	Europe-mid	Caucasian	52	41	39	98	45	42.55	90.90	48.55	0.3727	-0.0195
Dekou V.	s009a	1996	NA	England	Europe-mid	Caucasian	0	66	36	149	161	35.29	150.42	160.29	0.9016	0.0021
Dekou V.	s009b	1996	NA	England	Europe-mid	Caucasian	100	66	36	188	184	41.42	177.16	189.42	0.2543	-0.0133
Chango A	s017	1997	NA	France	Europe-mid	Caucasian	45	NR	49	125	117	42.72	137.55	110.72	0.1362	0.0216
Reyes-Engel A	s024	1998	NA	Spain	Europe-mid	Caucasian	49	45	119	413	249	135.66	379.68	265.66	0.0153	-0.0213
NPHS_II	s072b	1989- 2005	NA	United Kingdom	Europe-mid	Caucasian	100	NR	150	579	631	142.03	594.94	623.03	0.3217	0.0059
Fowkes G	s065b	1992-2002	NA	United Kingdom	Europe-mid	Caucasian	NR	NR	60	323	315	70.29	302.42	325.29	0.0807	-0.0147
Meisel C	s007a	1995-1997	NA	Germany	Europe-mid	Caucasian	76	61	96	217	120	96.58	215.83	120.58	1.0000	-0.0013
Chambers JC	s004c	1995-1998	NA	UK	Europe-mid	Caucasian	100	50	41	195	188	45.24	186.52	192.24	0.3787	-0.0100
Chambers JC	s004a	1995-1998	NA	UK	Europe-mid	South Asian	100	49	12	90	279	8.53	96.94	275.53	0.1596	0.0091
Gemmati D	s039a	1996-1997	NA	Italy	Europe-mid	Caucasian	61	47	39	116	65	42.77	108.46	68.77	0.3402	-0.0171
Pezzini A	s070b	1997-2000	NA	Italy	Europe-mid	Caucasian	54	NR	20	60	50	19.23	61.54	49.23	0.8529	0.0059
Domagala TB	s016a	1998-2000	NA	Poland	Europe-mid	Caucasian	72	45	6	37	57	6.00	36.99	57.00	1.0000	0.0000
HAPIEE study	S176	2002-2005	NA	zech Republic, Poland, Russ	Europe-mid	Caucasian	47	NR	70	273	312	65.10	282.79	307.10	0.3667	0.0075
Thuillier L	s011a	NR	1996	France	Europe-mid	Caucasian	34	43	10	32	27	9.80	32.41	26.80	1.0000	0.0029
Zittoun J	s038	NR	1996	France	Europe-mid	Caucasian	46	33	6	20	26	4.92	22.15	24.92	0.5179	0.0207
Friedman G	s022	NR	1997	Israel	Europe-mid	Caucasian	50	57	55	172	150	52.73	176.53	147.73	0.6598	0.0060
Chango A	s020	NR	1998	France	Europe-mid	Caucasian	45	NR	12	25	29	9.09	30.81	26.09	0.1220	0.0440
Passaro A	s030	NR	1999	Italy	Europe-mid	Caucasian	0	62	20	72	28	26.13	59.73	34.13	0.0295	-0.0511
Pullin C	s031	NR	1999	UK	Europe-mid	Caucasian	42	39	42	42	42	31.50	63.00	31.50	0.0002	0.0833
Litynski P	s033	NR	2000	Switzerland	Europe-mid	Caucasian	80	NR	20	NR	20	NA	NA	NA	NA	NA
Fohr IP	s005	NR	2000	Germany	Europe-mid	Caucasian	0	24	21	75	64	21.39	74.22	64.39	1.0000	-0.0024
Castro R	s019	NR	2001	Portugal	Europe-mid	Caucasian	39	41	12	54	51	13.00	52.00	52.00	0.8353	-0.0085
Hassan A	s067b	NR	2002	United Kingdom	Europe-mid	Caucasian	58	NR	49	144	147	43.06	155.88	141.06	0.1573	0.0175
Linnebank M	s078	NR	2004	Germany	Europe-mid	Caucasian	NR	NR	8	67	64	12.39	58.22	68.39	0.1045	-0.0316
Ma J	s021a	1982	NA	USA	America-ANZ mid	Caucasian	100	60	39	116	193	27.04	139.93	181.04	0.0020	0.0344
Christensen B.	s026a	1986-1987	NA	Canada	America-ANZ mid	Caucasian	100	42	8	47	31	11.54	39.92	34.54	0.1615	-0.0411
Jacques PF	s013	1991-1994	NA	USA	America-ANZ mid	Caucasian	50	57	149	152	149	112.50	225.00	112.50	0.0000	0.0811
Schwartz SM	s025	1991-1995	NA	USA	America-ANZ mid	Caucasian	0	NR	43	141	154	38.11	150.77	149.11	0.2251	0.0145
Varela MI	s041a	1997-2000	NA	Argentina	America-ANZ mid	Latin American	56	40	22	73	49	23.77	69.47	50.77	0.6068	-0.0123
Schmitz C	s003	1996	NA	USA	America-ANZ high	Caucasian	NR	59	56	156	166	47.50	172.99	157.50	0.0566	0.0225
Guinotte ChL	s006	1998	NA	USA	America-ANZ high	Caucasian	100	25	17	12	14	12.30	21.40	9.30	0.0052	0.1092
Caudill MA	s001	1999	NA	USA	America-ANZ high	Caucasian	0	26	9	50	75	8.63	50.73	74.63	0.8221	0.0028

Zee RY_WHS	s077b	1992-2000	NA	USA	America-ANZ high	Caucasian	0	NR	2773	10966	11229	2729.96	11052.09	11185.96	0.2189	0.0017
Eikelboom JW	s056a	1996-1998	NA	Australia	America-ANZ high	Caucasian	60	NR	23	98	84	25.29	93.42	86.29	0.5419	-0.0112
Bailey LB	s015	NR	2000	USA	America-ANZ high	Caucasian	0	NR	23	62	100	15.76	76.48	92.76	0.0123	0.0391

Footnotes

Arranged by folate regional supplementation.

† year of conduct calculated for unknown studies by subtracting the median time between study conclusion and publication date (2 years)

For HWE calculations, allele frequencies from all individuals included

References with suffix a,b,c denotes different datasets used from same study

ANZ: Australia & New Zealand; NR: Not reported; NA: Not applicable

eTable 2. Characteristics of genetic studies included in the analysis of *MTHFR/C677T* and stroke risk

Study	Reference	Stroke outcome	Years conducted	Proxy year of study conduct †	Place where study performed	Folate regional supplementation	Ethnicity	Male (%)	No TT-genotype (control)	No CT-genotype (control)	No CC-genotype (control)	TT expected	CT expected	CC expected	HWE (p-value)	Disequilibrium coefficient
Morita H	s047a	Ischaemic	1996-1997	NA	Japan	Asia	East Asian	54	33	139	153	32.33	140.35	152.33	0.8978	0.0021
Nakata Y	s057d	Ischaemic	1992-1995	NA	Japan	Asia	East Asian	NR	19	51	35	18.86	51.28	34.86	1.0000	0.0013
Notsu Y	s103	Ischaemic	1995-1997	NA	Japan	Asia	East Asian	58	31	92	86	28.37	97.26	83.37	0.4578	0.0126
Teng L	s156	Ischaemic	NR	1997	China	Asia	East Asian	NR	10	43	26	12.56	37.88	28.56	0.3466	-0.0324
Yoo JH	s095	Ischaemic	1998	NA	Korea	Asia	East Asian	40	26	114	77	31.75	102.51	82.75	0.1152	-0.0265
Zheng YZ	s096c	Ischaemic	NR	1998	China	Asia	East Asian	52	15	45	62	11.53	51.95	58.53	0.1400	0.0285
Wu Y	s110	Ischaemic	NR	1999	Japan	Asia	East Asian	52	24	113	92	28.30	104.40	96.30	0.2477	-0.0188
Kawamoto R	s135	Ischaemic	1999-2000	NA	Japan	Asia	East Asian	NR	28	78	80	24.13	85.73	76.13	0.2645	0.0208
Zhang YD	s159	Ischaemic	NR	1999	China	Asia	East Asian	NR	5	16	21	4.02	17.95	20.02	0.4809	0.0232
Zhang G	s094	Ischaemic	1999-2000	NA	China	Asia	East Asian	70	16	47	37	15.60	47.80	36.60	0.8370	0.0040
Li C	s114	Ischaemic	NR	2000	China	Asia	East Asian	NR	8	49	97	6.86	51.28	95.86	0.6273	0.0074
Tu	s157	Ischaemic	NR	2000	China	Asia	East Asian	NR	7	35	25	8.96	31.08	26.96	0.4299	-0.0292
Yingdong Z	s040b	Ischaemic	NR	2000	China	Asia	East Asian	48	5	16	21	4.02	17.95	20.02	0.4809	0.0232
Huang Y	s060a	Ischaemic	NR	2000	China	Asia	East Asian	NR	11	26	18	10.47	27.05	17.47	0.7870	0.0096
Gao HF	s152	Ischaemic	NR	2001	China	Asia	East Asian	NR	8	13	19	5.26	18.49	16.26	0.0837	0.0686
Sun WP	s155	Ischaemic	NR	2001	China	Asia	East Asian	NR	15	46	25	16.79	42.42	26.79	0.5155	-0.0208
Zhang Y	s160	Ischaemic	NR	2001	China	Asia	East Asian	NR	67	126	66	65.25	129.50	64.25	0.7092	0.0068
Li Z	s058d	Ischaemic	2000-2001	NA	China	Asia	East Asian	57	398	824	610	358.13	903.73	570.13	0.0002	0.0218
Choi BO	s059b	Ischaemic	2000-2002	NA	Korea	Asia	East Asian	56	25	100	73	28.41	93.18	76.41	0.3654	-0.0172
Kohara K	s062b	Ischaemic	1997-1999	NA	Japan	Asia	East Asian	50	290	940	727	295.15	929.71	732.15	0.6345	-0.0026
Ye H	s131c	Ischaemic	NR	2002	China	Asia	East Asian	NR	21	87	192	13.87	101.27	184.87	0.0167	0.0238
Baum L	s132	Ischaemic	2002-2003	NA	Hong Kong	Asia	East Asian	71	14	95	195	12.44	98.12	193.44	0.5938	0.0051
Fang L	s151b	Ischaemic	NR	2002	China	Asia	East Asian	NR	19	37	40	14.65	45.70	35.65	0.0846	0.0453
NG KM	s165	Ischaemic	NR	2002	China	Asia	East Asian	NR	1	33	49	3.69	27.62	51.69	0.1041	-0.0324
Miyaki K	s069b	Ischaemic	NR	2002	Japan	Asia	East Asian	77	32	93	62	32.95	91.09	62.95	0.8807	-0.0051
Alluri RV	s127c	Ischaemic	2002-2003	NA	India	Asia	South Asian	NR	0	1	48	0.01	0.99	48.01	1.0000	-0.0001
Li YJ	s153	Ischaemic	NR	2003	China	Asia	East Asian	NR	24	44	32	21.16	49.68	29.16	0.3130	0.0284
Qin	s154	Ischaemic	NR	2003	China	Asia	East Asian	NR	5	12	8	4.84	12.32	7.84	1.0000	0.0064
Fang X	s064d	Ischaemic	NR	2003	Mongolia	Asia	East Asian	54	2	6	16	1.04	7.92	15.04	0.2324	0.0399
Yamada Y	s148a	Ischaemic	2002-2005	NA	Japan	Asia	East Asian	42	NR§	NR§	NR§	NA	NA	NA	NA	NA
Xiao YQ	s158	Ischaemic	NR	2004	China	Asia	East Asian	NR	10	41	49	9.30	42.39	48.30	0.8133	0.0070
Li CM	s163	Ischaemic	NR	2004	China	Asia	East Asian	NR	16	128	190	19.16	121.68	193.16	0.4518	-0.0095
Nan GX	s164	Ischaemic	2003-2004	NA	China	Asia	East Asian	70	19	53	28	20.70	49.60	29.70	0.5503	-0.0170
XuGuang G	s170	Ischaemic	2004	NA	China	Asia	East Asian	71	24	44	32	21.16	49.68	29.16	0.3130	0.0284
Fang L	s161a	Ischaemic	NR	2005	China	Asia	East Asian	NR	24	40	52	16.69	54.62	44.69	0.0053	0.0630
Kim OJ	s068d	Ischaemic	2000-2002	NA	Korea	Asia	East Asian	53	38	119	66	42.63	109.74	70.63	0.2243	-0.0208
Kim IG	s074b	Ischaemic	NR	2005	Korea	Asia	East Asian	45	15	61	34	18.82	53.36	37.82	0.1705	-0.0347
Moe KT	s173	Ischaemic	NR	2006	Singapore	Asia	East Asian	76	3	68	136	6.61	60.77	139.61	0.1016	-0.0175
Biswas A	s075	Ischaemic	2003-2004	NA	India	Asia	South Asian	NR	0	30	90	1.88	26.25	91.88	0.2108	-0.0156
Kim NK	s061b	Silent brain infarction	2000-2003	NA	South Korea	Asia	East Asian	45	16	71	39	21.05	60.90	44.05	0.0960	-0.0401
Nakata Y	s057b	Total stroke (isch+haem)	1992-1995	NA	Japan	Asia	East Asian	NR	19	51	35	18.86	51.28	34.86	1.0000	0.0013
Zheng YZ	s096a	Total stroke (isch+haem)	NR	1998	China	Asia	East Asian	52	15	45	62	11.53	51.95	58.53	0.1400	0.0285
Li Z	s058b	Total stroke (isch+haem)	2000-2001	NA	China	Asia	East Asian	57	398	824	610	358.13	903.73	570.13	0.0002	0.0218
Ye H	s131a	Total stroke (isch+haem)	NR	2002	China	Asia	East Asian	NR	21	87	192	13.87	101.27	184.87	0.0167	0.0238
Alluri RV	s127a	Total stroke (isch+haem)	2002-2003	NA	India	Asia	South Asian	NR	0	1	48	0.01	0.99	48.01	1.0000	-0.0001
Fang X	s064b	Total stroke (isch+haem)	NR	2003	Mongolia	Asia	East Asian	54	2	6	16	1.04	7.92	15.04	0.2324	0.0399
Kim OJ2	s068a	Total stroke (isch+haem)	2000-2002	NA	Korea	Asia	East Asian	53	38	119	66	42.63	109.74	70.63	0.2243	-0.0208
Nakata Y	s057c	Haemorrhagic	1992-1995	NA	Japan	Asia	East Asian	NR	19	51	35	18.86	51.28	34.86	1.0000	0.0013
Zheng YZ	s096b	Haemorrhagic	NR	1998	China	Asia	East Asian	52	15	45	62	11.53	51.95	58.53	0.1400	0.0285
Li Z	s058c	Haemorrhagic	2000-2001	NA	China	Asia	East Asian	57	398	824	610	358.13	903.73	570.13	0.0002	0.0218
Ye H	s131b	Haemorrhagic	NR	2002	China	Asia	East Asian	NR	21	87	192	13.87	101.27	184.87	0.0167	0.0238
Alluri RV	s127b	Haemorrhagic	2002-2003	NA	India	Asia	South Asian	NR	0	1	48	0.01	0.99	48.01	1.0000	-0.0001
Fang X	s064c	Haemorrhagic	NR	2003	Mongolia	Asia	East Asian	54	2	6	16	1.04	7.92	15.04	0.2324	0.0399
Kim OJ2	s068c	Haemorrhagic	2000-2002	NA	Korea	Asia	East Asian	53	38	119	66	42.63	109.74	70.63	0.2243	-0.0208
Somarajan	s178a	Total stroke (isch+haem)	2005-2009	NA	India	Asia	South Asian	72	5	54	129	5.45	53.11	129.45	1.0000	-0.0024
Somarajan	s178b	Ischaemic	2005-2009	NA	India	Asia	South Asian	73	5	54	129	5.45	53.11	129.45	1.0000	-0.0024
Somarajan	s178c	Haemorrhagic	2005-2009	NA	India	Asia	South Asian	70	5	54	129	5.45	53.11	129.45	1.0000	-0.0024
Duca F	s115	Ischaemic	NR	1995	Italy	Europe-low	Caucasian	NR	52	99	74	45.79	111.42	67.79	0.1059	0.0276
Markus HS	s053a	Ischaemic	NR	1995	United Kingdom	Europe-low	Caucasian	48	22	63	76	17.78	71.44	71.78	0.1545	0.0262
Kostulas K	s098	Ischaemic	NR	1996	Sweden	Europe-low	Caucasian	NR	13	50	63	11.46	53.08	61.46	0.5276	0.0122
Kristensen B	s108	Ischaemic	1991-1996	NA	Sweden	Europe-low	Caucasian	49	3	14	24	2.44	15.12	23.44	0.6736	0.0137
Roest M	s140c	Ischaemic	1976-1995	NA	Netherlands	Europe-low	Caucasian	0	NR§	NR§	NR§	NA	NA	NA	NA	NA
Kalashnikova L	s119	Ischaemic	NR	2001	Russia	Europe-low	Caucasian	NR	2	11	17	1.88	11.25	16.88	1.0000	0.0042
Ucar F	s168	Ischaemic	NR	2002	Turkey	Europe-low	Caucasian	87	8	111	123	16.66	93.68	131.66	0.0044	-0.0358
Frederiksen J	s066c	Ischaemic	1991-2002	NA	Denmark	Europe-low	Caucasian	42	315	1600	1804	334.29	1561.42	1823.29	0.1378	-0.0052
Frederiksen J	s066e	Ischaemic	1994-2002	NA	Denmark	Europe-low	Caucasian	42	680	3213	3614	696.43	3180.14	3630.43	0.3833	-0.0022
Slooter AJ	s071b	Ischaemic	1990-2001	NA	Netherlands	Europe-low	Caucasian	0	69	328	367	71.06	323.88	369.06	0.7979	-0.0027
Shmeleva V	s073b	Ischaemic	NR	2003	Russia	Europe-low	Caucasian	NR	23	90	114	20.37	95.26	111.37	0.4291	0.0116
Karakus Z	s076b	Ischaemic	NR	2003	Turkey	Europe-low	Caucasian	52	7	36	37	7.81	34.38	37.81	0.7977	-0.0102
Dikmen M	s063d	Ischaemic	NR	2004	Turkey	Europe-low	Caucasian	29	2	21	32	2.84	19.32	32.84	0.7110	-0.0153
Kostulas K	s149	Ischaemic	NR	2006	Sweden	Europe-low	Caucasian	NR	56	206	249	49.47	219.05	242.47	0.1803	0.0128
Rotterdam Study	s174c	Ischaemic	1990+	NA	Netherlands	Europe-low	Caucasian	NR	631	2774	2807	655.56	2724.88	2831.56	0.1650	-0.0040
Roest M	s140a	Total stroke (isch+haem)	1976-1995	NA	Netherlands	Europe-low	Caucasian	0	NR§	NR§	NR§	NA	NA	NA	NA	NA
Frederiksen J	s066a	Total stroke (isch+haem)	1991-2002	NA	Denmark	Europe-low	Caucasian	42	315	1600	1804	334.29	1561.42	1823.29	0.1378	-0.0052
Dikmen M	s063a	Total stroke (isch+haem)	NR	2004	Turkey	Europe-low	Caucasian	29	2	21	32	2.84	19.32	32.84	0.7110	-0.0153
Rotterdam Study	s174a	Total stroke (isch+haem)	1990+	NA	Netherlands	Europe-low	Caucasian	NR	631	2774	2807	655.56	2724.88	2831.56	0.1650	-0.0040
Roest M	s140b	Haemorrhagic	1976-1995	NA	Netherlands	Europe-low	Caucasian	0	NR§	NR§	NR§	NA	NA	NA	NA	NA
Frederiksen J	s066d	Haemorrhagic	1991-2002	NA	Denmark	Europe-low	Caucasian	42	315	1600	1804	334.29	1561.42	1823.29	0.1378	-0.0052
Dikmen M	s063c	Haemorrhagic	NR	2004	Turkey	Europe-low	Caucasian	29	2	21	32	2.84	19.32	32.84	0.7110	-0.0153

Rotterdam Study	s174b	Haemorrhagic	1990+	NA	Netherlands	Europe-low	Caucasian	NR	631	2774	2807	655.56	2724.88	2831.56	0.1650	-0.0040
De Stefano V	s101	Ischaemic	1994-1997	NA	Italy	Europe-mid	Caucasian	39	35	98	65	35.64	96.73	65.64	0.8854	-0.0032
Reuner KH	s093	Ischaemic	NR	1996	Germany	Europe-mid	Caucasian	NR	23	74	85	19.78	80.44	81.78	0.3137	0.0177
Salooja N	s097	Ischaemic	NR	1996	United Kingdom	Europe-mid	Caucasian	53	16	76	81	16.86	74.29	81.86	0.8602	-0.0049
Lalouschek W	s100	Ischaemic	NR	1997	Austria	Europe-mid	Caucasian	60	10	47	39	11.69	43.62	40.69	0.5084	-0.0176
Margaglione M	s105	Ischaemic	1996-1998	NA	Italy	Europe-mid	Caucasian	43	196	513	327	197.64	509.72	328.64	0.8500	-0.0016
Harmon DL	s107	Ischaemic	1996-1997	NA	Ireland	Europe-mid	Caucasian	25	19	78	86	18.38	79.23	85.38	0.8646	0.0034
Gross B	s116	Ischaemic	NR	1998	Israel	Europe-mid	Caucasian	NR	15	50	47	14.29	51.43	46.29	0.8369	0.0064
Topic E	s112	Ischaemic	NR	1999	Croatia	Europe-mid	Caucasian	NR	1	59	64	7.50	46.00	70.50	0.0012	-0.0524
De Stefano V	s117	Ischaemic	NR	1999	Italy	Europe-mid	Caucasian	53	80	197	205	66.10	224.79	191.10	0.0082	0.0288
Lopaciuk S	s099	Ischaemic	1996-1999	NA	Poland	Europe-mid	Caucasian	66	26	95	117	22.70	101.60	113.70	0.3614	0.0139
Pezzini A	s109	Ischaemic	1997-2000	NA	Italy	Europe-mid	Caucasian	64	4	14	18	3.36	15.28	17.36	0.6952	0.0177
Pongracz E	s113c	Ischaemic	NR	2000	Hungary	Europe-mid	Caucasian	NR	7	46	120	5.20	49.60	118.20	0.2998	0.0104
McIlroy SP	s162	Ischaemic	NR	2000	Ireland	Europe-mid	Caucasian	20	2	19	50	1.86	19.27	49.86	1.0000	0.0019
Grossmann R	s092	Ischaemic	1997-2000	NA	Germany	Europe-mid	Caucasian	49	26	91	69	27.49	88.03	70.49	0.7567	-0.0080
Szolnoki Z	s102	Ischaemic	1998-2002	NA	Hungary	Europe-mid	Caucasian	53	89	268	386	66.93	312.14	363.93	0.0002	0.0297
Pezzini A	s106	Ischaemic	1997-2000	NA	Italy	Europe-mid	Caucasian	54	23	72	54	23.36	71.28	54.36	1.0000	-0.0024
Pratnicka M	s118d	Ischaemic	NR	2001	Poland	Europe-mid	Caucasian	NR	8	54	88	8.17	53.67	88.17	1.0000	-0.0011
Hassan A	s067a	Ischaemic	NR	2002	United Kingdom	Europe-mid	Caucasian	58	16	73	81	16.21	72.57	81.21	1.0000	-0.0013
Linnebank M	s137	Ischaemic	1999-2001	NA	Germany	Europe-mid	Caucasian	50	19	62	78	15.72	68.55	74.72	0.2685	0.0206
Pezzini A	s138	Ischaemic	1997-2002	NA	Italy	Europe-mid	Caucasian	54	23	75	60	23.17	74.67	60.17	1.0000	-0.0005
Szolnoki Z	s143	Ischaemic	1998-2003	NA	Hungary	Europe-mid	Caucasian	53	23	106	166	19.58	112.84	162.58	0.2892	0.0116
ye H	s079	Ischaemic	1999-2003	NA	Italy	Europe-mid	Caucasian	67	97	286	232	93.66	292.68	228.66	0.6111	0.0054
Bosco P	s128	Ischaemic	NR	2004	Italy	Europe-mid	Caucasian	60	19	67	35	22.78	59.44	38.78	0.1977	-0.0312
Sazci A	s142c	Ischaemic	2001-2003	NA	Turkey	Europe-mid	Caucasian	56	25	119	115	27.57	113.86	117.57	0.5715	-0.0099
Szolnoki Z	s144	Ischaemic	1998-2003	NA	Hungary	Europe-mid	Caucasian	NR	10	32	60	6.63	38.75	56.63	0.1135	0.0331
Sanchez Marin J	s171c	Ischaemic	1998-2001	NA	Spain	Europe-mid	Caucasian	57	14	43	33	14.00	42.99	33.00	1.0000	0.0000
Pezzini A	s070a	Ischaemic	1997-2000	NA	Italy	Europe-mid	Caucasian	54	22	73	60	22.08	72.84	60.08	1.0000	-0.0005
Lalouschek W	s136	Ischaemic	1998-2001	NA	Austria	Europe-mid	Caucasian	52	90	366	361	91.22	363.55	362.22	0.8753	-0.0015
Pezzini A	s139	Ischaemic	1997-2000	NA	Italy	Europe-mid	Caucasian	0	22	110	84	27.45	99.10	89.45	0.1377	-0.0252
NPHS_II	s072d	Ischaemic	1989- 2003	NA	United Kingdom	Europe-mid	Caucasian	100	251	1128	1241	253.52	1122.96	1243.52	0.8553	-0.0010
Salooja N	s097a	Total stroke (isch+haem)	NR	1996	United Kingdom	Europe-mid	Caucasian	53	16	76	81	16.86	74.29	81.86	0.8602	-0.0049
Fowkes G	s065a	Total stroke (isch+haem)	1992-2002	NA	United Kingdom	Europe-mid	Caucasian	48	73	398	405	84.46	375.09	416.46	0.0824	-0.0131
Pongracz E	s113a	Total stroke (isch+haem)	NR	2000	Hungary	Europe-mid	Caucasian	NR	7	46	120	5.20	49.60	118.20	0.2998	0.0104
Hermans MP	s129	Total stroke (isch+haem)	NR	2003	Belgium	Europe-mid	Caucasian	58	22	58	62	18.32	65.37	58.32	0.2015	0.0259
Guiterrez JI	s134	Total stroke (isch+haem)	NR	2003	Spain	Europe-mid	Caucasian	49	24	79	56	25.36	76.28	57.36	0.7417	-0.0086
Sazci A	s142a	Total stroke (isch+haem)	2001-2003	NA	Turkey	Europe-mid	Caucasian	56	25	119	115	27.57	113.86	117.57	0.5715	-0.0099
Sanchez Marin J	s171a	Total stroke (isch+haem)	1998-2001	NA	Spain	Europe-mid	Caucasian	57	14	43	33	14.00	42.99	33.00	1.0000	0.0000
British Women Heart & Health	s130	Total stroke (isch+haem)	1999-2007	NA	United Kingdom	Europe-mid	Caucasian	0	400	1515	1553	386.33	1542.33	1539.33	0.3026	0.0039
NPHS II	s072a	Total stroke (isch+haem)	1989- 2003	NA	United Kingdom	Europe-mid	Caucasian	100	251	1128	1241	253.52	1122.96	1243.52	0.8553	-0.0010
EPIC Norfolk	s175	Total stroke (isch+haem)	1997+	NA	United Kingdom	Europe-mid	Caucasian	NR	1982	7964	7956	1986.89	7954.22	7960.89	0.8797	-0.0003
Weikert C	s177	Total stroke (isch+haem)	1994-2004	NA	Germany	Europe-mid	Caucasian	45	92	421	455	94.53	415.94	457.53	0.7648	-0.0026
Salooja N	s097b	Haemorrhagic	NR	1996	United Kingdom	Europe-mid	Caucasian	53	16	76	81	16.86	74.29	81.86	0.8602	-0.0049
Pongracz E	s113b	Haemorrhagic	NR	2000	Hungary	Europe-mid	Caucasian	NR	7	46	120	5.20	49.60	118.20	0.2998	0.0104
Sanchez Marin J	s142b	Haemorrhagic	1998-2001	NA	Spain	Europe-mid	Caucasian	57	14	43	33	14.00	42.99	33.00	1.0000	0.0000
Sazci A	s171b	Haemorrhagic	2001-2003	NA	Turkey	Europe-mid	Caucasian	56	25	119	115	27.57	113.86	117.57	0.5715	-0.0099
NPHS II	s072c	Haemorrhagic	1989- 2003	NA	United Kingdom	Europe-mid	Caucasian	100	251	1128	1241	253.52	1122.96	1243.52	0.8553	-0.0010
Linnebank M	s169	Haemorrhagic	1999-2001	NA	Germany	Europe-mid	Caucasian	NR	36	152	158	36.25	151.49	158.25	1.0000	-0.0007
Voetsch B	s104a	Ischaemic	1996-1998	NA	Brazil	America-ANZ mid	Latin American	44	2	43	61	5.21	36.58	64.21	0.0936	-0.0303
Voetsch B	s104b	Ischaemic	1996-1998	NA	Brazil	America-ANZ mid	Latin American	44	14	57	48	15.18	54.64	49.18	0.6944	-0.0099
Voetsch B	s146	Ischaemic	1996-2000	NA	Brazil	America-ANZ mid	Mixed	46	11	66	41	16.41	55.19	46.41	0.0484	-0.0458
Shinjo SK	s172	Ischaemic	1994-2004	NA	Brazil	America-ANZ mid	Latin American	57	12	60	54	14.00	56.00	56.00	0.5476	-0.0159
Press RD	s111	Ischaemic	NR	1997	USA	America-ANZ high	Caucasian	58	1	23	28	3.00	18.99	30.00	0.2505	-0.0386
Eikelboom JW	s056d	Ischaemic	1996-1998	NA	Australia	America-ANZ high	Caucasian	60	23	98	84	25.29	93.42	86.29	0.5419	-0.0112
Zee RL	s077a	Ischaemic	1992-2000	NA	USA	America-ANZ high	Caucasian	0	2773	10966	11229	2729.96	11052.09	11185.96	0.2189	0.0017
Eikelboom JW	s056b	Total stroke (isch+haem)	1996-1998	NA	Australia	America-ANZ high	Caucasian	60	23	98	84	25.29	93.42	86.29	0.5419	-0.0112
Eikelboom JW	s056c	Haemorrhagic	1996-1998	NA	Australia	America-ANZ high	Caucasian	60	23	98	84	25.29	93.42	86.29	0.5419	-0.0112
ISGS-SWISS	s179	Ischaemic	200-2009	NA	USA	America-ANZ high	Caucasian	48	186	670	632	182.42	677.16	628.42	0.6902	0.0024

Footnotes

Arranged by folate regional supplementation.

† year of conduct calculated for unknown studies by subtracting the median time between study conclusion and publication date (2 years)

§ we used the measure of effect for the genotype comparisons reported in the manuscript

For HWE calculations, allele frequencies from controls were used only in case control studies; in cohort studies we used values for the entire study population.

References with suffix a,b,c denotes different datasets used from same study. Studies that reported separate stroke subtypes appear more than once.

ANZ: Australia & New Zealand; NR: Not reported; NA: Not applicable

eTable 3. Sensitivity analysis to illustrate the number of hypothetical large null studies that are needed to shift the point estimate observed in the *MTHFR* /C677T-stroke meta-analysis to several thresholds.

Analysis	***MTHFR* TT vs. CC – Asia (low folate region)**			
	All studies		**Large-studies (≥400 cases)**	
	No. of hypothetical studies	OR (95%CI)	No. of hypothetical studies	OR (95%CI)
Observed result meta-analysis	0	1.68 (1.44, 1.97)	0	1.28 (1.11, 1.48)
Reduce point estimate to 1.15	41	1.15 (1.07, 1.23)	6	1.14 (1.03, 1.27)
Reduce point estimate to 1.10	60	1.10 (1.04, 1.16)	12	1.10 (1.00, 1.20)
Lower 95%CI to cross line of 1.00	260	1.02 (1.00, 1.05)	14	1.09 (1.00, 1.18)

Footnotes

The sample size of the hypothetical studies was 400 cases and 400 controls with equal distribution to TT and CC alleles – i.e. generating an OR of 1.0 (95%CI: 0.76, 1.32).

Each hypothetical study was added to the dataset of studies on *MTHFR* -stroke using cumulative meta-analysis techniques.

eTable 4. Linkage disequilibrium of the *MTHFR* /C677T variant by ethnic group.

Ancestry	SNP	Chromosome	Position	r2 with	Complex disease association	
	rs number	number	(base pair)	rs1801133	SNPnexus†	GWAS catalog‡
Asian	9651118	1	11784801	0.38	none	none
	7554327	1	11784801	0.31	none	none
	2336377	1	11872557	0.3	none	none
	2639453	1	11905131	0.33	none	none
European	6540999	1	11755953	0.32	none	none
	11121828	1	11757041	0.32	none	none
	7538516	1	11759269	0.32	none	none
	6697244	1	11761435	0.32	none	none
	4845882	1	11765754	0.34	none	none
	1994798	1	11777342	0.35	none	none
	6541003	1	11778454	0.36	none	none
	4846052	1	11780538	0.37	none	none
	4846054	1	11791817	0.34	none	none
	12404124	1	11796456	0.37	none	none
	198391	1	11799004	0.37	none	none
	198393	1	11802272	0.37	none	none
	198401	1	11810971	0.38	none	none
	535107	1	11812055	0.37	none	none
	198406	1	11820179	0.37	none	none
Africa	4846052	1	11780538	0.56	none	none
	198401	1	11810971	0.62	none	none
	2639453	1	11905131	0.35	none	none

Footnotes

SNPs in long-range LD with rs1801133 identified through Genome-wide Linkage Disequilibrium Repository and Search (GLIDERS) from HapMap phase 3 Build 36, MAF≥0.05, cis- and trans-chromosome, r2≥0.3, no lower/upper range - i.e. associations between any pair-wise HapMap SNPs over any distance would be retrieved (http://mather.well.ox.ac.uk/GLIDERS). Accessed 30th April 2010

† SNPnexus (http://www.snp-nexus.org); all SNPs uploaded using population data from HapMap (not limited to any ancestry) and outcome listed for Complex Diseases and Disorders. Accessed 30th April 2010

‡ from Hindorff LA, Junkins HA, Mehta JP, and Manolio TA. A Catalog of Published Genome-Wide Association Studies. Available at: www.genome.gov/gwastudies. Accessed 30th April 2010. SNP-trait associated traits are limited to those with P<1.0 x 10-5; studies reported in the catalog have genotyped at least 100,000 SNPs in the initial stage.

eTable 5. Characteristics of randomised clinical trials of homocysteine-lowering interventions in stroke

Trial (reference)	Years conducted	Characteristics of participants at study entry	Outcome reported	Geographical Location	Folic acid			Comparator arm (B vitamins and/or placebo or usual care)			Follow-up (months)	Mean Age (years)	Participants with homocysteine measured (%)	Folic acid dose (mg/day)	Vit-B12 dose (mg/day)	Vit-B6 dose (mg/day)	Reference arm	Risk of Bias evaluation (using Cochrane collaboration nomenclature)				
					Number randomised	Stroke only (fatal and non-fatal)	TIA only	Number randomised	Stroke only (fatal and non-fatal)	TIA only								Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting
Righetti (45)	2001-2005	Chronic kidney disease	Fatal and nonfatal stroke and TIA	Italy	37	1	3	51	2	8	29	64	‡	5	0.25	125	Placebo	low-risk	low-risk	unclear	low-risk	low-risk
House (49)	2001-2007	Type 1 or 2 diabetes and diabetic nephropathy	Stroke (fatal and non-fatal) β	Canada	128	6	NA	124	1	NA	32	60.4		2.5	1	25	Placebo	low-risk	low-risk	low-risk	low-risk	low-risk
Liem (42)	1998-2002	Stable CHD	Fatal stroke, non-fatal stroke and TIA	Netherlands	300	8*	NA	293	12*	NA	42	65	‡Ω	0.5	0	0	Usual care	low-risk	unclear	high-risk	low-risk	low-risk
Zoungas (50)	1998-2003	Chronic kidney disease	Fatal and nonfatal stroke	Australia, New Zealand	156	8	NA	159	18	NA	43	56	‡	15	0	0	Placebo	unclear	unclear	low-risk	low-risk	low-risk
Wrone (51)	1998-2000	Chronic kidney disease	Stroke (unspecified) and TIA	USA	351 ⁋	19	6	177	8	1	24	60	‡	5 or 15	0.006	12.5	1 mg/d folic acid	low-risk	low-risk	low-risk	low-risk	low-risk
Jamison (52)	2001-2003	Chronic kidney disease	Fatal and nonfatal thromboembolic stroke	USA	1032	37	NA	1024	41	NA	38	66	113 (5.5)	40	2	100	Placebo	low-risk	unclear	low-risk	low-risk	low-risk
Ebbing (43)	1999-2006	Stable angina, ACS or aortic valve stenosis	Nonfatal thromboembolic stroke and fatal stroke	Norway	1544	28	NA	1552	39	NA	38	61	2557 (82.6)	0.8	0.4	40	Placebo / B6	low-risk	low-risk	low-risk	low-risk	high-risk
Bonaa (44)	1998-2002	Myocardial infarction	Any fatal and nonfatal stroke (including SAH)	Norway	1872	49	NA	1877	49	NA	36	63	3027 (80.7)	0.8	0.4	40	Placebo / B6	low-risk	low-risk	low-risk	low-risk	low-risk
Albert (53)	1998-2005	CVD or 3 risk factors for CVD	Fatal and nonfatal stroke (ischaemic, haemorrhagic)	USA	2721	79	NA	2721	69	NA	87	64	600 (11)	2.5	1	50	Placebo	unclear	unclear	low-risk	low-risk	low-risk
HOPE-2 (48)	2000-2005	CVD or diabetes	Fatal and nonfatal stroke (ischaemic, haemorrhagic) and TIA	Canada, USA (72.1 %); Brazil, Western Europe, Slovakia (27.9 %)	2758	111	131	2764	147	120	60	69	1064 (19.3)	2.5	1	50	Placebo	low-risk	low-risk	low-risk	low-risk	low-risk
Toole (54)	1996-2003	Ischaemic Stroke	Recurrent ischaemic stroke (fatal & non-fatal)	USA, Canada, Scotland	1827	152	NA	1853	148	NA	24	66	‡	2.5	0.4	25	20 *micro* g/d folic acid †	low-risk	low-risk	low-risk	low-risk	low-risk
SEARCH (46)	1998-2005	Myocardial infarction	Any fatal and nonfatal stroke (including SAH)	United Kingdom	6033	269	NA	6031	265	NA	80	64	§ (10)	2	1	0	Placebo	low-risk	low-risk	low-risk	low-risk	low-risk
VITATOPS (47)	1998-2009	Stroke or TIA	Fatal and nonfatal stroke	20 Countries Σ	4089	360	NA	4075	388	NA	41	62.6	1164 (14.3)	2	0.5	25	Placebo	low-risk	low-risk	low-risk	low-risk	low-risk

Footnotes

Studies were independently reviewed for risk of bias (MVH and JPC)

ACS: acute coronary syndrome; CHD: coronary heart disease; CVD: cardiovascular disease; SAH: subarachnoid haemorrhage; TIA: transient ischaemic attack

* TIA reported together with stroke values

‡ No specific value reported in manuscript for the number of participants tested for Hcy

Ω only the group randomised to intervention was tested for Hcy at follow-up

§ No absolute value of the number of participants tested for Hcy recorded in manuscript (percentage reported)

† reference arm also contained 200 µg B6 and 6µg of B12

⁋ For Wrone (51), we combined doses of 15mg/day and 5mg/day folic acid together as the intervention arm against the comparator comparator group of 1mg/day folic acid

β House (49) used the same diagnostic criteria as Toole (54)

Σ 20 countries: Australia, Austria, Belgium, Brazil, Hong Kong, India, Italy, Malaysia, Moldova, Netherlands, New Zealand, Pakistan, Philippines, Portugal, Republic of Georgia, Serbia & Monte Negro, Singapore, Sri Lanka, United Kingdom and United States of America

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