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Appendix S1. Categorisation of the probable folate status of each study by region & year conducted (before or after nationwide folate supplementation)

Legislation in 1996 permitted or mandated folic acid fortification in the United States, Canada, Australia, New Zealand, the United Kingdom and some other European countries. Changes soon followed that appreciably affected population-wide mean folate levels, but elsewhere in Europe (including Russia) the sale of manufactured foods with added folic acid remained forbidden (UK DH Scientific Advisory Committee: Folate and disease prevention. London, HMSO, 2006).

Hence, as a surrogate measurement of folate status, “probable folate status” categories were devised, based only on geographic region and calendar year of blood collection. Studies in Asia were classified as “Asia (no supplementation)”. Studies in Scandinavia, the Netherlands and Russia were classified as “Europe (pre-supplementation)” at all times, whereas studies carried out elsewhere in Europe were classified as “Europe (pre-supplementation)” before 1996 and as “Europe (post-supplementation)” from 1996 onwards. Studies carried out in North America, Australia and New Zealand were classified as “US & ANZ (pre-supplementation)” before 1996 and as “US & ANZ (post-supplementation)” from 1996 onwards.

Population mean folate levels for these 5 categories of study were estimated from a meta-analysis of all general population surveys of folate status involving more than 100 disease-free participants that were published before 2009, including not only population-based surveys of healthy individuals but also control participants in case-control studies or in randomized trials of healthy volunteers (identified using MEDLINE with search criteria folic acid, folate and B-vitamins). From 81 such population surveys, involving a total of 200,103 individuals, mean serum folate concentrations were estimated for these 5 probable folate status categories (Figure 1 and Table S1 in Text S1)

Appendix S2. 19 unpublished *MTHFR* datasets by study panel size, and calculation of the -0.1% OR bias arising from non-publication

Classification of unpublished datasets by genotyping panel size; GW=genome-wide

Dataset, ordered by number of cases	*Genotyping platform*	*Number of SNPs*	*Number of genes*	*Panel size* [a] *(large/small)*
ISIS	Taqman	67	24	small
deCODE	HumanHap300	300K	GW	large
PROCARDIS	HumanHap 610 Quad	50K	GW	large
PROMIS	HumanHap 660 Quad	660K	GW	large
OACIS [b]	Taqman	–	–	Large [b]
INTERHEART	GoldenGate	1536	103	small
LOLIPOP	HumanHap 610 Quad	610K	GW	large
HPS	HumanHap 610 Quad	610K	GW	large
BHF-FHS	HumanCVD	50K	2100	large
Blood-omics (Germany)	HumanCVD	50K	2100	large
Blood-omics (NL)	HumanCVD	50K	2100	large
EPIC-NL	HumanCVD	50K	2100	large
UCP	HumanCVD	50K	2100	large
Ottawa Heart Study	Affymetrix 500K / 6.0	>500K	GW	large
PennCath	HumanCVD	50K	2100	large
Yamada, GAG-u	Luminex	112	71	small
Yamada, Aichi	Luminex	300	Not spec.	small
MONICA-KORA	HumanCVD	50K	2100	large
ADVANCE	Illumina 550k v3	>500K	Not spec.	large

[a] Large panel size: at least 50K SNPs genotyped (so data-dependent publication would have required an extreme p-value, eg 10^{-6} to 10^{-8}; small panel size: <2000 SNPs genotyped (so publication could well have been triggered by a less extreme p-value, eg 10^{-3}).

[b] OACIS: Investigators were approached because they had done a 92K GWAS (on 94 MI cases, 658 controls). *MTHFR* C677T was not in that 92K panel, and was genotyped specifically for this collaboration on the much larger number of participants (3794 cases, 3479 controls) recruited into OACIS by March 2010. Although OACIS and its genotyping methods have been published, it has no *MTHFR*-related publication bias. Hence, it is grouped with the large-panel unpublished datasets that have little such bias (see below).

Size of negative bias arising from non-publication of any *MTHFR* result

If the true log OR for the *MTHFR* polymorphism is no more than about 0.08 (the value suggested by meta-analyses of prospective studies of homocysteine: see main text) then the bias in the observed log OR in a particular dataset arising from the fact that the *MTHFR* result had not been published can be shown to be less than 0.003, which would correspond to a negligibly small change (about 0.3%) in the OR. (The bias would be less than 0.003 even for small-panel studies of a limited number of polymorphisms that would have published their *MTHFR* results only if $2p<10^{-3}$ [for p calculated without allowance for multiple hypothesis testing], and it would be less than 0.0002 for large-panel studies that would have published only if $2p<10^{-6}$, so on average over all studies it would be about 0.1%).

Calculation of bias from non-publication: For a standard normal deviate d with probability P of being less than some fixed value k, it can be shown that if d is less than k then the expectation of d is $-1/(P\sqrt{2\pi})\exp(-0.5k^2)$, and that if P is close to 1 then $1/(P\sqrt{2\pi})$ is 0.4, so the expectation of d is $-0.4\ \exp(-0.5k^2)$.

Let β, with standard error s, denote the observed log OR from one particular study; let $z=\beta/s$; let b denote the true (but unknown) log OR, and consider the case b=0.08. (Smaller values of b would yield even smaller biases from non-publication.) If that study would have published its results on *MTHFR* only if z had been suitably large, ie, if z>X for some cut-off X, then (as long as X>b/s) the expected bias in β that arises because the result remained unpublished is $-0.4\ s\ \exp(-[X - b/s]^2/2)$.

For studies of only a small panel of polymorphisms, X might be 3.3 (corresponding to $2p<0.001$), which even for the biggest of the small-panel datasets (ISIS, with s=0.08) would give a negative bias of less than 0.003. If X was 4.9 (corresponding to $2p<10^{-6}$, as used by PROCARDIS), which could arise in large-panel datasets, then even for the biggest such dataset (deCODE, with s=0.05) the bias would be less than 0.0002.

Study (country or region)	Study folate status[a]	Cases				Controls				Odds ratio, OR (99%CI)[b]	Weight[c]	Weight x log OR
		CC	CT	TT	Odds, TT/CC	CC	CT	TT	Odds, TT/CC			
Large genotyping panels (>50k SNPs)												
OACIS[d] Yokohama (Japan)[1]	1	1359	1785	650	0.478	1272	1648	559	0.439	1.09 (0.91, 1.30)	206.2	17.5
PROMIS (Pakistan)[2]	1	3383	1200	123	0.036	3262	1130	127	0.039	0.96 (0.70, 1.33)	64.0	-2.4
Blood-omics (Netherlands)[3]	2	644	656	162	0.252	567	533	122	0.215	1.17 (0.83, 1.65)	56.5	8.8
EPIC-NL (Netherlands)[4]	2	544	495	130	0.239	806	671	167	0.207	1.15 (0.83, 1.61)	59.7	8.5
MONICA-KORA [e] (Germany)[5]	2	122	119	34	0.279	597	642	174	0.291	0.96 (0.55, 1.65)	22.2	-1.0
UCP, Utrecht (Netherlands)[6]	2	535	474	119	0.222	409	372	117	0.286	0.78 (0.53, 1.13)	47.0	-11.8
PROCARDIS[f] (Sweden)[7]	2	347	251	56	0.161	350	250	69	0.197	0.82 (0.47, 1.43)	21.4	-4.3
LOLIPOP (UK South Asians)[8]	3	1830	810	101	0.055	2555	1045	96	0.038	1.30 (0.88, 1.91)	44.4	11.6
BHF-FHS (UK)[9]	3	916	943	242	0.264	1105	1027	294	0.266	0.99 (0.77, 1.28)	104.9	-0.7
Blood-omics (Germany)[10]	3	806	837	266	0.330	799	903	230	0.288	1.15 (0.88, 1.50)	94.3	12.9
deCODE (Iceland)[11]	3	2682	2886	761	0.284	11790	12145	3245	0.275	1.03 (0.92, 1.16)	480.8	14.6
HPS (UK)[12]	3	1171	1210	320	0.273	1280	1270	335	0.262	1.04 (0.83, 1.31)	129.1	5.6
PROCARDIS (UK)[7]	3	1884	1846	474	0.252	1377	1251	363	0.264			
PROCARDIS (Germany)[7]	3	151	168	41	0.272	131	142	41	0.313			
PROCARDIS (Italy)[7]	3	166	242	90	0.542	120	204	79	0.658			
PROCARDIS[f] (stratified for UK/Germany/Italy)[7]	3	2201	2256	605	0.275	1628	1597	483	0.297	0.93 (0.77, 1.13)	177.8	-12.9
Ottawa Heart Study (Canada)[13]	5	543	482	93	0.171	514	492	65	0.126	1.35 (0.87, 2.12)	33.4	10.1
PennCath (USA)[14]	5	416	465	146	0.351	200	210	79	0.395	0.89 (0.58, 1.36)	37.2	-4.4
ADVANCE (USA)[15]	5	110	127	41	0.373	135	131	46	0.341	1.09 (0.57, 2.09)	16.0	1.4
Small genotyping panels (<2000 SNPs)												
Yamada[g], GAG-U (Japan)[16]	1	293	411	167	0.570	997	1509	677	0.679	0.84 (0.63, 1.11)	84.2	-14.7
Yamada[g], Aichi (Japan)[17]	1	148	208	74	0.500	158	208	64	0.405	1.23 (0.73, 2.10)	23.7	5.0
INTERHEART-Middle East (Arab countries/Iran)[18]	1	486	372	85	0.175	612	438	85	0.139	1.26 (0.82, 1.93)	36.7	8.5
INTERHEART-South Asia (India/PK/BD/Nepal)[18]	1	909	307	32	0.035	1014	295	34	0.034	1.05 (0.55, 2.00)	15.9	0.8
ISIS[h] (UK)[19]	2	2981	2958	731	0.245	1168	1099	291	0.249	0.98 (0.81, 1.20)	166.8	-2.6
INTERHEART-Northern Europe (Scandinavia)[18]	2	77	75	12	0.156	179	134	32	0.179	0.87 (0.34, 2.23)	7.5	-1.0
INTERHEART-Southern Europe (Italy/Spain)[18]	3	501	486	139	0.277	495	483	138	0.279	1.00 (0.70, 1.41)	54.2	-0.3
INTERHEART-US & ANZ (Australia/Canada/USA)[18]	5	110	132	27	0.245	126	143	39	0.310	0.79 (0.38, 1.64)	12.5	-2.9

Table S1: *MTHFR* C677T genotypes in cases and controls and TT/CC CHD odds ratio (OR) in 19 unpublished datasets (with 5 parts of INTERHEART and 4 parts of PROCARDIS given separately) classified by genotyping panel size

[a] 1 = Low folate, Asia, no supplementation; 2 = Low folate, Europe, pre-supplementation; 3 = Mid folate, Europe, post-supplementation; 4 = Mid folate, US & ANZ, pre-supplementation; 5 = High folate, US & ANZ, post-supplementation

[b] OR = odds ratio = (odds of TT/CC in cases) / (odds of TT/CC in controls)

[c] Weight = inverse of (variance of log OR). Note that in PROMIS, PROCARDIS and LOLIPOP population-adjusted odds ratios were provided.

[d] OACIS: Investigator was approached because they had done a 92K GWAS (94 MI cases and 658 controls);[20] *MTHF*R C677T was not available from their panel but in response to our request it was genotyped specifically for this collaboration on the much larger number of participants (3794 cases and 3479 controls) that had been recruited into this ongoing study by March 2010. OACIS and the genotyping methods are described in the cited reference.[1] The OACIS dataset is grouped with large panels because there was no publication bias.

[e] Data from a case-cohort study analysed as case-control. If analysed as case-cohort using logistic regression the odds ratio and 99% CI are 0.94 (0.54, 1.64)

[f] PROCARDIS analyses are stratified by country, and allow for first-degree relatedness of many cases; to 2dp, this allowance does not change the OR.

[g] Yamada, GAG-U: Unpublished data (U) on those recruited 3/2005-2008 in a study in Gifu, Aomori and Gunma (GAG) prefectures. *MTHFR* results from earlier recruitment have been published and the genotyping methods remained the same.[16 21] Yamada, Aichi: Unpublished data from the screening GWA phase of a published study in the Aichi prefecture.[17]

[h] ISIS: Genotyping of *MTHFR* rs1801133 in ISIS was done along with 66 other SNPs in 24 candidate genes (population and genotyping methods described in cited reference).

Study (Country)	Year bled	Study folate status[a]	Cases				Controls				Odds ratio, OR (99%CI)[b]	Weight [c]	Weight[c] x log OR
			CC	CT	TT	Odds, TT/CC	CC	CT	TT	Odds, TT/CC			
Abu-Amero (Saudi Arabia)[1]	2003	1	350	175	20	0.057	451	161	13	0.029	1.98 (0.79, 4.98)	7.8	5.4
Chao (Taiwan)[2]	1997	1	60	47	9	0.150	41	25	10	0.244	0.61 (0.17, 2.25)	3.9	-1.9
Chen (Taiwan)[3]	2003	1	33	23	4	0.121	62	42	5	0.081	1.52 (0.23, 9.87)	1.9	0.8
Gulec (Turkey)[4]	1999	1	42	39	15	0.357	60	35	5	0.083	3.85 (1.09,13.56)	4.2	5.7
Hong (Korea)[5]	1999	1	40	74	26	0.650	37	78	25	0.676	0.96 (0.38, 2.44)	7.7	-0.3
Hsu (China)[6]	1999	1	120	85	13	0.108	125	78	15	0.120	0.90 (0.32, 2.52)	6.3	-0.6
Ilhan (Turkey)[7]	2008	1	52	44	4	0.077	72	26	2	0.028	2.72 (0.31,23.82)	1.4	1.4
Inbal (Israel)[8]	1996	1	29	56	27	0.931	85	82	20	0.235	4.06 (1.59,10.36)	7.6	10.7
Izumi (Japan)[9]	1995	1	90	110	50	0.556	74	102	25	0.338	1.62 (0.78, 3.36)	12.5	6.1
Jang (Korea)[10]	2000	1	49	77	23	0.469	67	115	48	0.716	0.66 (0.30, 1.47)	10.5	-4.3
Kawashiri (Japan)[11]	2000	1	33	51	15	0.455	48	45	7	0.146	2.98 (0.86,10.27)	4.3	4.7
Kihara (Japan)[12]	1997	1	29	57	13	0.448	51	65	16	0.314	1.43 (0.46, 4.49)	5.1	1.8
Kim (Korea)[13]	2000	1	30	41	14	0.467	56	68	28	0.500	0.93 (0.34, 2.59)	6.4	-0.4
Kou (Taiwan)[14]	2000	1	29	19	6	0.207	35	18	2	0.057	3.23 (0.47,22.07)	1.8	2.1
Mager (Israel)[15]	1999	1	16	32	19	1.188	130	139	44	0.338	3.94 (1.39,11.13)	6.2	8.4
Morita (Japan)[16]	1996	1	117	188	57	0.487	338	361	79	0.234	2.18 (1.25, 3.79)	21.8	17.0
Nakai (Japan)[17]	1997	1	93	95	42	0.452	81	96	21	0.259	1.71 (0.80, 3.67)	11.4	6.1
Ou (Japan)[18]	1997	1	69	84	61	0.884	110	158	42	0.382	2.29 (1.21, 4.34)	16.3	13.5
Shioji (Japan)[19]	2003	1	193	250	88	0.456	663	878	305	0.460	0.99 (0.68, 1.44)	47.0	-0.4
Tokgozoglu (Turkey)[20]	1998	1	69	71	11	0.159	47	39	5	0.106	1.47 (0.36, 5.98)	3.4	1.3
Yamada 2006 (Japan) [21]	2004	1	375	570	247	0.659	804	1134	353	0.439	1.51 (1.15, 1.98)	90.5	37.2
Zhang (China)[22]	2000	1	32	33	8	0.250	37	47	16	0.432	0.59 (0.17, 2.02)	4.4	-2.3
Zheng (China)[23]	1999	1	41	29	2	0.049	62	45	15	0.242	0.30 (0.07, 1.21)	3.4	-4.1
Abbate (Italy)[24]	1995	2	19	41	24	1.263	26	48	32	1.231	1.03 (0.36, 2.90)	6.2	0.2
Ardissino (Italy)[25]	1995	2	68	97	35	0.515	60	102	38	0.633	0.81 (0.38, 1.73)	11.7	-2.4
Fowkes (UK)[26]	1989	2	59	66	12	0.203	132	147	21	0.159	1.29 (0.45, 3.65)	6.1	1.5
Frederiksen-CC[d] (Denmark)[27]	2002	2	1048	867	210	0.200	3675	3258	692	0.188	1.06 (0.85, 1.33)	131.5	8.3
Frederiksen-P[d] (Denmark)[27]	2002	2	506	443	94	0.186	3675	3258	692	0.188	0.99 (0.73, 1.34)	70.3	-0.9
Gallagher (Ireland)[28]	1991	2	44	48	19	0.432	53	45	7	0.132	3.01 (0.97, 9.35)	5.2	5.7
Kluijtmans (Netherlands)[29]	1990	2	337	328	70	0.208	617	527	106	0.172	1.21 (0.78, 1.88)	34.3	6.6
Kostulas (Sweden)[30]	1997	2	63	50	13	0.206	63	50	13	0.206	1.00 (0.33, 3.03)	5.4	0.0
Meleady (Ireland)[31]	1991	2	313	307	91	0.291	352	314	81	0.230	1.26 (0.81, 1.96)	34.2	8.0
Roest (Netherlands)[32]	1977	2	109	95	21	0.193	209	248	58	0.278	0.71 (0.35, 1.41)	14.0	-4.9
Spiridonova (Russia)[33]	2002	2	44	41	9	0.205	64	48	10	0.156	1.31 (0.36, 4.79)	4.0	1.1
Tanis (Netherlands)[34]	1999	2	78	81	22	0.282	280	262	59	0.211	1.36 (0.64, 2.89)	11.6	3.5
Thogersen (Sweden)[35]	1988	2	32	32	5	0.156	71	51	7	0.099	1.62 (0.30, 8.66)	2.4	1.1
Verhoef (Netherlands)[36]	1993	2	59	59	13	0.220	45	48	7	0.156	1.40 (0.39, 4.99)	4.1	1.4
Verhoeff (Netherlands)[37]	1997	2	115	83	19	0.165	129	105	38	0.295	0.57 (0.27, 1.23)	11.5	-6.4
Adams (UK)[38]	1996	3	133	145	32	0.241	96	97	29	0.302	0.80 (0.38, 1.68)	11.9	-2.7
Araujo (Portugal)[39]	1999	3	74	103	22	0.297	10	8	2	0.200	1.43 (0.22, 9.48)	1.9	0.7
Benes (Czech Rep.)[40]	1998	3	264	309	68	0.258	234	265	59	0.252	1.02 (0.61, 1.71)	25.2	0.5
Brulhart (France)[41]	1997	3	86	84	23	0.267	188	195	73	0.388	0.70 (0.36, 1.37)	14.8	-5.3
Chambers-Asian (UK)[42]	1999	3	160	61	3	0.019	279	90	12	0.043	0.49 (0.12, 2.01)	3.3	-2.4
Chambers-European (UK)[42]	1999	3	108	91	31	0.287	188	195	41	0.218	1.32 (0.66, 2.66)	13.6	3.8
Fernandez-Arcas (Spain)[43]	1998	3	104	107	61	0.587	82	92	39	0.476	1.23 (0.64, 2.35)	15.9	3.3
Ferrer (Portugal)[44]	1998	3	14	19	7	0.500	26	16	8	0.308	1.62 (0.33, 7.99)	2.6	1.3
Ferrer-Antunes (Portugal)[45]	1998	3	54	59	14	0.259	71	51	5	0.070	3.37 (0.95,11.97)	4.1	5.0
Gardemann (Germany)[46]	1996	3	891	805	197	0.221	88	82	15	0.170	1.27 (0.64, 2.55)	13.8	3.3
Gemmati (Italy)[47]	1999	3	32	81	47	1.469	68	102	30	0.441	3.22 (1.47, 7.05)	10.8	12.6
Girelli (Italy)[48]	1997	3	146	217	70	0.479	75	105	42	0.560	0.86 (0.46, 1.60)	17.0	-2.6
Gorqcy (Poland)[49]	1999	3	46	45	9	0.196	39	50	11	0.282	0.70 (0.19, 2.50)	4.1	-1.5
Kadziela (Poland)[50]	2003	3	58	51	11	0.190	46	49	11	0.239	0.79 (0.24, 2.67)	4.5	-1.0
Kolling (Germany)[51]	2004	3	915	955	251	0.274	266	283	68	0.256	1.07 (0.73, 1.59)	43.5	3.0
Kozich (Czech Rep.)[52]	1999	3	123	117	38	0.309	245	287	59	0.241	1.29 (0.69, 2.39)	17.4	4.4
Malik (UK)[53]	1998	3	107	134	26	0.243	106	110	17	0.160	1.50 (0.64, 3.56)	9.0	3.7
Mannucci (Italy)[25]	2000	3	371	547	292	0.787	356	607	247	0.694	1.13 (0.85, 1.52)	77.3	9.7
Meisel (Germany)[54]	1996	3	458	442	81	0.177	443	442	96	0.217	0.82 (0.53, 1.25)	37.0	-7.5
Pinto (Spain)[55]	2004	3	31	34	11	0.355	39	43	13	0.333	1.06 (0.31, 3.61)	4.5	0.3
Raslova (Slovakia)[56]	1999	3	22	29	7	0.318	59	46	6	0.102	3.45 (0.66,18.13)	2.4	3.0
Reinhardt (Germany)[57]	1996	3	91	66	23	0.253	49	46	9	0.184	1.36 (0.47, 3.94)	5.9	1.8
Rossi (Italy)[58]	2000	3	42	53	29	0.690	23	33	17	0.739	0.93 (0.33, 2.62)	6.3	-0.4
Rothenbacher (Germany)[59]	1996	3	155	126	31	0.200	219	210	50	0.228	0.88 (0.46, 1.67)	16.1	-2.1
Sarecka-Hujar (Poland)[60]	2002	3	75	85	17	0.227	103	89	10	0.097	2.31 (0.79, 6.73)	5.8	4.9
Szczeklik (Poland)[61]	2000	3	105	39	17	0.162	201	94	15	0.075	2.25 (0.83, 6.11)	6.7	5.4
Tobin (UK)[62]	1998	3	236	246	65	0.275	214	230	61	0.285	0.97 (0.57, 1.63)	24.6	-0.8
Todesco (Germany)[63]	1999	3	30	34	11	0.367	103	93	28	0.272	1.36 (0.45, 4.09)	5.5	1.7
Zuntar (Croatia)[64]	2003	3	114	111	22	0.193	134	146	18	0.134	1.43 (0.60, 3.46)	8.6	3.1
Brugada (USA)[65]	1995	4	76	69	10	0.132	70	73	12	0.171	0.77 (0.24, 2.50)	4.8	-1.3
Dilley (USA)[66]	1995	4	91	17	2	0.022	153	28	4	0.026	0.84 (0.09, 7.63)	1.4	-0.2
Folsom (USA)[67]	1988	4	148	109	17	0.115	271	187	47	0.173	0.68 (0.33, 1.41)	12.5	-4.9
Hopkins (USA)[68]	1995	4	124	82	24	0.194	69	62	16	0.232	0.83 (0.33, 2.11)	7.7	-1.4
Ma (USA)[69]	1982	4	136	124	33	0.243	135	116	39	0.289	0.84 (0.42, 1.66)	14.3	-2.5
Schmitz (USA)[70]	1982	4	95	66	29	0.305	71	90	27	0.380	0.80 (0.36, 1.79)	10.4	-2.3
Schwartz (USA)[71]	1993	4	28	34	7	0.250	154	141	43	0.279	0.90 (0.28, 2.83)	5.0	-0.5
Silberberg (Australia)[72]	1993	4	139	101	34	0.245	50	51	11	0.220	1.11 (0.42, 2.93)	7.0	0.7
Verhoef (USA)[73]	1994	4	230	209	61	0.265	228	200	72	0.316	0.84 (0.51, 1.40)	25.8	-4.5
Wilcken (Australia)[74]	1995	4	186	217	53	0.285	88	113	24	0.273	1.04 (0.51, 2.13)	13.1	0.6
Anderson (USA)[75]	1997	5	241	212	57	0.237	73	73	22	0.301	0.78 (0.37, 1.66)	11.6	-2.9
Brilakis (USA)[76]	2002	5	117	123	31	0.265	53	52	17	0.321	0.82 (0.33, 2.03)	8.2	-1.6
Christensen (Canada)[77]	1996	5	62	68	22	0.355	47	61	13	0.277	1.28 (0.46, 3.52)	6.5	1.6
Hanson (USA)[78]	2000	5	324	364	84	0.259	130	158	41	0.315	0.82 (0.46, 1.45)	20.4	-4.1
Malinow (USA)[79]	1996	5	40	83	17	0.425	49	45	8	0.163	2.49 (0.78, 7.98)	4.9	4.5
Payne (USA)[80]	2001	5	20	20	5	0.250	17	6	1	0.059	3.24 (0.33,31.49)	1.3	1.5
Topol (USA)[81]	2000	5	151	115	47	0.311	191	172	46	0.241	1.29 (0.71, 2.37)	18.2	4.7
Tsai (USA)[82]	1998	5	159	177	40	0.252	35	35	12	0.343	0.72 (0.26, 2.01)	6.4	-2.1
van Bockxmeer (Australia)[83]	1996	5	234	226	58	0.248	67	57	16	0.239	1.04 (0.46, 2.32)	10.3	0.4

Table S2: *MTHFR* C677T genotypes in cases and controls and TT/CC CHD odds ratio (OR) in 86 published CHD case-control studies (NB Many studies did not measure homocysteine)

[a] 1 = Low folate, Asia, no supplementation; 2 = Low folate, Europe, pre-supplementation; 3 = Mid folate, Europe, post-supplementation; 4 = Mid folate, US & ANZ, pre-supplementation; 5 = High folate, US & ANZ, post-supplementation

[b] OR = (odds of TT/CC in cases)/(odds of TT/CC in controls)

[c] Weight = inverse of (variance of log OR)

[d] Combined result for Frederiksen (CC&P): 1.04 (0.86,1.26), weight = 175.2, weight x (log OR) = 6.7

Study (Country)	Year bled	Folate status[a]	CHD study (Y=Yes)	No. of disease-free people [b]			Geometric mean homocysteine µmol/L		
				CC	CT	TT	CC	CT	TT
Chao (Taiwan)[1]	1997	1	Y	101	72	19	9.6	10.7	12.4
Nakai (Japan)[2]	1997	1	Y	81	96	21	7.9	8.2	10.6
Ou (Japan)[3]	1997	1	Y	110	158	42	10.2	10.8	14.6
Tokgozoglu (Turkey)[4]	1998	1	Y	24	21	3	12.2	16.2	33.0
Friedman (Israel)[5]	1999	1	N	150	172	55	8.7	8.7	10.4
Ho (China)[6]	2000	1	N	280	186	69	7.5	7.7	8.5
Jang (Korea)[7]	2000	1	Y	67	115	48	8.1	8.2	12.4
Kawashiri (Japan)[8]	2000	1	Y	33	51	15	9.3	10.2	19.5
Kim (Korea)[9]	2000	1	Y	30	40	15	11.7	12.1	12.9
Saw (Singapore)[10]	2000	1	N	273	165	39	9.7	10.0	12.3
Somekawa (Japan)[11]	2001	1	N	96	91	30	9.6	10.3	10.6
Inamoto (Japan)[12]	2002	1	N	1189	1539	520	11.0	11.2	13.3
Jee (South Korea)[13]	2002	1	N	135	184	76	8.5	8.6	11.8
Yingdong (China)[14]	2002	1	N	21	16	5	10.9	13.2	20.5
Ilhan (Turkey)[15]	2008	1	Y	72	26	2	12.4	12.3	11.2
Thogersen (Sweden)[16]	1988	2	Y	67	49	7	11.8	11.1	11.4
Kluijtmans (Netherlands)[17]	1990	2	Y	231	233	51	12.6	13.4	15.4
Meleady (Ireland)[18]	1991	2	Y	340	305	78	9.3	9.6	12.2
Devlin (UK)[19]	1993	2	N	488	432	121	12.3	12.8	14.7
Verhoef (Netherlands)[20]	1993	2	Y	45	48	7	10.9	12.1	17.4
Verhoeff (Netherlands)[21]	1997	2	Y	129	105	38	12.7	13.2	17.6
Tanis (Netherlands)[22]	1999	2	Y	296	272	60	11.3	12.2	14.0
Hustad-1 (Norway)[23]	2000	2	N	204	182	37	8.6	9.1	11.5
Silaste (Finland)[24]	2001	2	N	19	13	5	7.8	7.8	8.8
deBree (Netherlands)[25]	2001	2	N	983	907	206	12.9	13.6	17.1
Bathum (Denmark)[26]	2002	2	N	556	475	102	6.9	7.5	10.5
Frederiksen-P (Denmark)[27]	2002	2	Y	1804	1600	315	10.9	11.0	13.8
Husemoen (Denmark)[28]	2003	2	N	1361	1181	246	7.8	8.2	9.8
Hustad-2 (Norway)[29]	2007	2	N	5452	4299	850	9.9	10.4	11.2
Dekou (UK)[30]	1996	3	N	345	337	82	11.1	11.4	12.3
Meisel (Germany)[31]	1996	3	Y	418	410	93	9.7	9.7	10.0
Rothenbacher (Germany)[32]	1996	3	Y	219	210	50	8.0	8.1	9.8
Chango (France)[33]	1997	3	N	29	25	12	8.5	8.8	10.1
Chango(S) (France)[34]	1997	3	N	117	125	49	9.3	9.0	10.7
Girelli (Italy)[35]	1997	3	Y	40	74	23	12.9	13.5	13.6
Ferrer (Portugal)[36]	1998	3	Y	24	12	6	7.3	9.1	7.9
Thuillier (France) [37]	1998	3	N	27	32	10	7.6	8.2	8.5
Zittoun (France)[38]	1998	3	N	20	20	6	10.9	11.5	19.0
Chambers-Asian (UK)[39]	1999	3	Y	278	89	12	11.0	10.4	10.4
Chambers-European (UK)[39]	1999	3	Y	187	194	41	10.1	10.1	11.6
Gemmati (Italy)[40]	1999	3	Y	70	98	32	6.9	7.5	10.7
Kozich (Czech Rep.)[41]	1999	3	Y	245	287	59	9.2	9.7	11.5
Todesco (Germany)[42]	1999	3	Y	102	92	26	10.1	10.2	10.9
D'Angelo (Italy)[43]	2000	3	N	45	98	39	9.3	10.4	16.6
Passaro (Italy)[44]	2000	3	N	28	72	20	9.1	10.3	12.4
Szczeklik (Poland)[45]	2000	3	Y	199	95	15	10.8	11.1	9.8
Cappuccio (UK)[46]	2001	3	N	916	391	64	10.0	10.4	11.3
Fohr (Germany)[47]	2001	3	N	64	75	21	8.2	8.2	8.1
Madonna (Italy)[48]	2001	3	N	102	105	45	8.8	9.0	13.6
Pullin (UK)[49]	2001	3	N	42	42	42	8.3	8.8	11.8
Castro (Portugal)[50]	2002	3	N	51	54	12	8.3	9.2	9.8
Litynski (Switzerland)[51]	2002	3	N	20	.	20	11.9	.	15.9
Reyes-Engel (Spain)[52]	2002	3	N	249	413	119	9.8	10.1	11.9
Kolling (Germany)[53]	2004	3	Y	266	283	68	11.0	11.2	12.4
Ma (USA)[54]	1982	4	Y	136	116	39	9.8	10.3	11.1
Schmitz (USA)[55]	1982	4	Y	28	25	6	9.0	9.8	8.7
Folsom (USA)[56]	1988	4	Y	266	186	46	8.6	9.0	11.3
Jacques (USA)[57]	1993	4	N	149	152	149	8.9	9.1	9.8
Schwartz (USA)[58]	1993	4	Y	167	159	47	10.5	10.2	12.2
Silberberg (Australia)[59]	1993	4	Y	30	32	5	11.3	12.2	12.7
Zee (USA)[60]	1994	4	N	11229	10966	2773	10.2	10.5	11.5
Hopkins (USA)[61]	1995	4	Y	69	62	16	9.5	10.2	9.9
Christensen (Canada)[62]	1996	5	Y	47	61	13	8.0	8.9	9.2
Malinow (USA)[63]	1996	5	Y	47	47	11	9.2	8.2	9.2
Anderson (USA)[64]	1997	5	Y	63	61	17	14.0	14.7	13.3
Eikelboom (Australia)[65]	1997	5	N	84	98	23	10.2	11.5	11.9
Tsai (USA)[66]	1998	5	Y	29	34	12	8.0	8.7	9.0
Hanson (USA)[67]	2000	5	Y	512	585	141	8.7	8.9	9.6
Caudill (USA)[68]	2001	5	N	75	50	9	5.3	5.4	4.0
Guinotte (USA)[69]	2002	5	N	14	12	17	5.2	5.8	5.3

Table S3: Effects of *MTHFR* C677T genotype on homocysteine in 70 biochemical studies of 68 369 disease-free individuals: 37 CHD case-control studies of *MTHFR* and 33 other studies of *MTHFR* with homocysteine measured in some disease-free people.

[a] 1 = Low folate, Asia, no supplementation; 2 = Low folate, Europe, pre-supplementation; 3 = Mid folate, Europe, post-supplementation; 4 = Mid folate, US & ANZ, pre-supplementation; 5 = High folate, US & ANZ, post-supplementation

[b] Controls only, except for a few case-control studies where biochemical results were available only for cases, or only for cases and controls combined

Study (Country)	Year bled	Folate status [a]	No. of people	Mean serum folate (nmol/L)
Ronnenberg (China)[1]	1997	1	563	9.7
Wang (China)[2]	1998	1	963	10.6
Friedman (Israel)[3]	1999	1	377	8.9
Jang (South Korea)[4]	2000	1	230	11.9
Saw (Singapore)[5]	2000	1	477	13.8
Hao (China)[6]	2001	1	1836	11.1
Jee (South Korea)[7]	2002	1	395	11.2
Hultdin (Sweden)[8]	1985	2	514	8.8
vanGuelpen (Sweden)[9]	1985	2	671	7.2
Hartman (Finland)[10]	1986	2	325	9.7
Meleady (Ireland)[11]	1991	2	723	9.7
Nurk (Norway)[12]	1992	2	7031	7.1
Voutilainen (Finland)[13]	1992	2	749	10.5
Clarke (UK)[14]	1993	2	1500	11.0
Devlin (UK)[15]	1993	2	1042	11.0
deBree (Netherlands)[16]	1994	2	2051	7.4
Dierkes-1 (Germany)[17]	1995	2	198	21.0
Melse-Boonstra (Netherlands)[18]	1995	2	2435	8.3
Naurath (Belgium)[19]	1995	2	285	9.7
Woodside (Ireland)[20]	1995	2	112	9.2
Alfthan (Finland)[21]	1997	2	318	14.6
Wahlin (Sweden)[22]	1997	2	961	17.9
Brouwer (Netherlands)[23]	1998	2	144	11.0
Tanis (Netherlands)[24]	1999	2	617	8.7
Durga (Netherlands)[25]	2000	2	801	12.0
Hustad-1 (Norway)[26]	2000	2	423	15.3
Bjorkegren (Sweden)[27]	2004	2	266	10.0
Hustad-2 (Norway)[28]	2007	2	10601	17.1
Dekou (UK)[29]	1996	3	408	6.0
Trobs (Germany)[30]	1996	3	817	18.0
Brown (Ireland)[31]	1997	3	922	11.6
Chango(S) (France)[32]	1997	3	291	16.4
Girelli (Italy)[33]	1997	3	124	15.5
Dierkes-2 (Germany)[34]	1998	3	150	29.3
Friso (Italy)[35]	1998	3	267	12.9
Chambers-Asian (UK)[36]	1999	3	379	16.6
Chambers-European (UK)[36]	1999	3	418	18.1
Duthie (UK)[37]	1999	3	331	17.2
Gemmati (Italy)[38]	1999	3	200	11.5
Kozich (Czech Rep.)[39]	1999	3	591	16.1
MacMahon (UK)[40]	1999	3	137	16.2
Ravaglia (Italy)[41]	1999	3	599	13.6
Ashfield-Watt (UK)[42]	2000	3	126	17.7
D'Angelo (Italy)[43]	2000	3	182	11.9
Dierkes-3 (Germany)[44]	2000	3	336	16.8
Mayer (Czech Rep.)[45]	2000	3	543	14.0
Rauh (Germany)[46]	2000	3	172	16.5
Szczeklik (Poland)[47]	2000	3	309	13.6
Fohr (Germany)[48]	2001	3	160	15.7
Pullin (UK)[49]	2001	3	126	17.2
Ruston (UK)[50]	2001	3	1314	21.5
Wolters (Germany)[51]	2001	3	178	20.1
Castro (Portugal)[52]	2002	3	117	14.5
Hatzis (Greece)[53]	2002	3	486	17.3
Kadziela (Poland)[54]	2003	3	106	20.2
Kolling (Germany)[55]	2004	3	617	21.8
Nelson (UK)[56]	2004	3	2796	25.0
Obeid (Germany)[57]	2004	3	302	15.3
Ma (USA)[58]	1982	4	290	12.6
Verhoef (USA)[59]	1983	4	118	9.9
Folsom (USA)[60]	1988	4	480	9.8
Pfeiffer-1 (USA)[61]	1990	4	23361	12.4
Zhang (USA)[62]	1990	4	712	16.5
Dalery (Canada)[63]	1991	4	584	9.3
Jacques-1 (USA)[64]	1993	4	756	10.4
Jacques-2 (USA)[65]	1993	4	450	12.7
Schwartz (USA)[66]	1993	4	368	15.7
Hopkins (USA)[67]	1995	4	146	24.7
Jacques-3 (USA)[68]	1995	4	365	15.4
Lawrence-1 (USA)[69]	1995	4	29243	28.7
Robinson (USA)[70]	1995	4	231	17.9
Christensen (Canada)	1996	5	121	9.5
Jacques-4 (USA)[64]	1996	5	350	22.7
Malinow (USA)[71]	1996	5	105	19.5
Aronow (USA)[72]	1997	5	306	21.3
Eikelboom (Australia)[73]	1997	5	205	16.8
Lawrence-2 (USA)[69]	1998	5	67109	35.2
Caudill (USA)[74]	2001	5	134	50.0
Hickling (Australia)[75]	2001	5	936	19.5
McMahon (New Zealand)[76]	2003	5	276	22.2
Pfeiffer-2 (USA)[61]	2004	5	23345	29.4

Table S4: Population-based surveys of serum folate, subdivided by probable folate status category, as defined by country and year of blood collection (NB Many had unknown homocysteine or genotype.)

[a] 1 = Low folate, Asia, no supplementation; 2 = Low folate, Europe, pre-supplementation; 3 = Mid folate, Europe, post-supplementation; 4 = Mid folate, US & ANZ, pre-supplementation; 5 = High folate, US & ANZ, post-supplementation

Trial name	Number of participants	Number of CHD events
SU.FOL.OM3[1]	2501	104
VISP[2]	3680	170
WAFACS[2]	5442	194
VITATOPS[3]	8164	232
WENBIT[2]	3090	248
HOST[2]	2056	325
FAVORIT[a 4]	4110	488
NORVIT[2]	3749	689
HOPE-2[2]	5522	814
SEARCH[2]	12064	1550
ALL	**50378**	**4814**

Table S5: Published randomized controlled trials that assessed the effects of folic acid on major coronary events.

[a] Results for the FAVORIT trial, that assessed the effects of homocysteine reduction in 4110 renal transplant participants have not yet been published for CHD alone, but, preliminary results indicated no significant effect of homocysteine reduction on cardiovascular disease.

	Cases						Controls						Odds ratio, OR[a] (99% or 95% CI[c])	Weight[b]	Weight[b] x log OR
	CC	CT	TT	Odds, T allele TT/CC	freq.	H-W p-value	CC	CT	TT	Odds, T allele TT/CC	freq	H-W p-value			
Japanese unpublished datasets															
OACIS, Yokohama	1359	1785	650	0.478	0.407	0.124	1272	1648	559	0.439	0.398	0.514	1.09 (0.91, 1.30)	206.2	17.5
Yamada, GAG-U	293	411	167	0.570	0.428	0.287	997	1509	677	0.679	0.450	0.017	0.84 (0.63, 1.11)	84.2	-14.7
Yamada, Aichi	148	208	74	0.500	0.414	0.950	158	208	64	0.405	0.391	0.740	1.23 (0.73, 2.10)	23.7	5.0
Subtotal (by addition)	**1800**	**2404**	**891**				**2427**	**3365**	**1300**				**1.02 (0.92, 1.14)**	**314.1**	**7.7**
Japanese large published studies															
Morita, 1996	117	188	57	0.487	0.417	0.196	338	361	79	0.234	0.334	0.223	2.08 (1.23, 3.53)	24.0	17.6
Shioji, 2003	193	250	88	0.456	0.401	0.644	663	878	305	0.460	0.403	0.619	0.99 (0.68, 1.44)	46.9	-0.4
Yamada, 2006	375	570	247	0.659	0.446	0.262	804	1134	353	0.439	0.402	0.153	1.50 (1.15, 1.96)	92.7	37.6
Subtotal (by addition)	**685**	**1008**	**392**				**1805**	**2373**	**737**				**1.40 (1.20, 1.63)**	**163.5**	**54.8**
Japanese comparators, from Table S3[d]							1509	1935	628	0.416					

Table S6: Details of datasets and calculations used to derive the CHD odds ratio (OR, TT vs CC *MTHFR* C677T genotype) in the large Japanese studies; p-values test genotype frequencies for Hardy-Weinberg equilibrium.

[a] In individual studies, CHD odds ratio (OR) = (odds of TT/CC in cases) / (odds of TT/CC in controls)

[b] Weight = inverse of (variance of log OR). Additivity of weights is therefore only approximate.

[c] 95% CIs are given for subtotals and totals, 99% CIs for other results

[d] There is no overlap between the controls in the large published studies in this table and the comparators (ie, the genotyped Japanese participants in Table S3 in Text S1).

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