CASA DI CURA SAN FRANCESCO
ISTITUTO MADRE RUBATTO

SCREENING DELL'OMOCISTEINA: PRO E CONTRO

Dr.ssa Elena Lucca

Clinica San Francesco, Bergamo

LA STORIA:

CASA DI CURA SAN FRANCESCO
ISTITUTO MADRE RUBATTO

METABOLIC ABNORMALITIES DETECTED IN A SURVEY OF MENTALLY BACKWARD INDIVIDUALS IN NORTHERN IRELAND

BY

NINA A. J. CARSON and D. W. NEILL
From the Royal Belfast Hospital for Sick Children and the Royal Victoria Hospital, Belfast

(RECEIVED FOR PUBLICATION JUNE 8, 1962)

Homocystinuria—a rare inherited disorder characterized by extremely elevated homocysteine levels and premature vascular complications, including arterial thrombosis in children

LA STORIA:

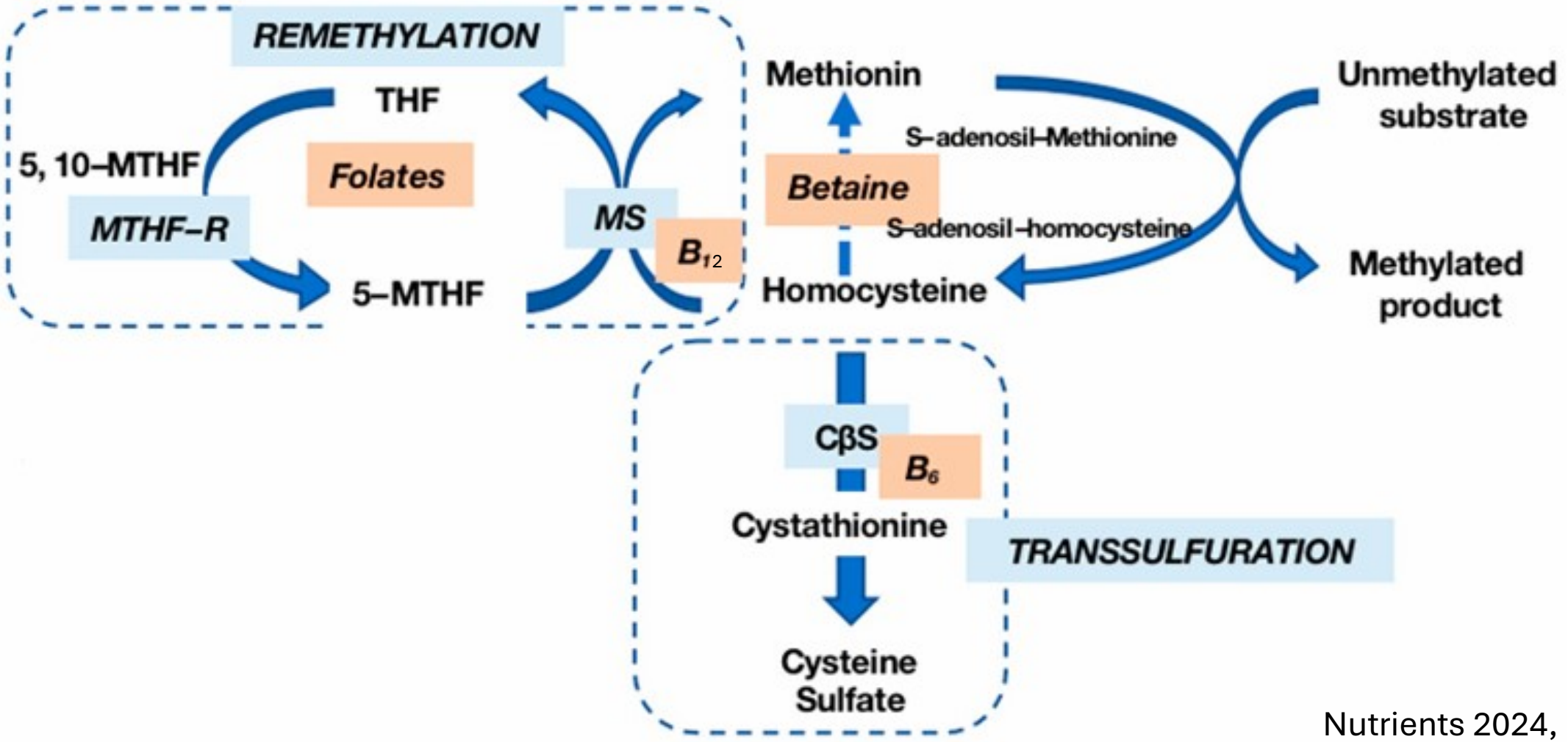
Vascular Pathology of Homocysteinemia: Implications for the Pathogenesis of Arteriosclerosis

Kilmer S. McCully, MD

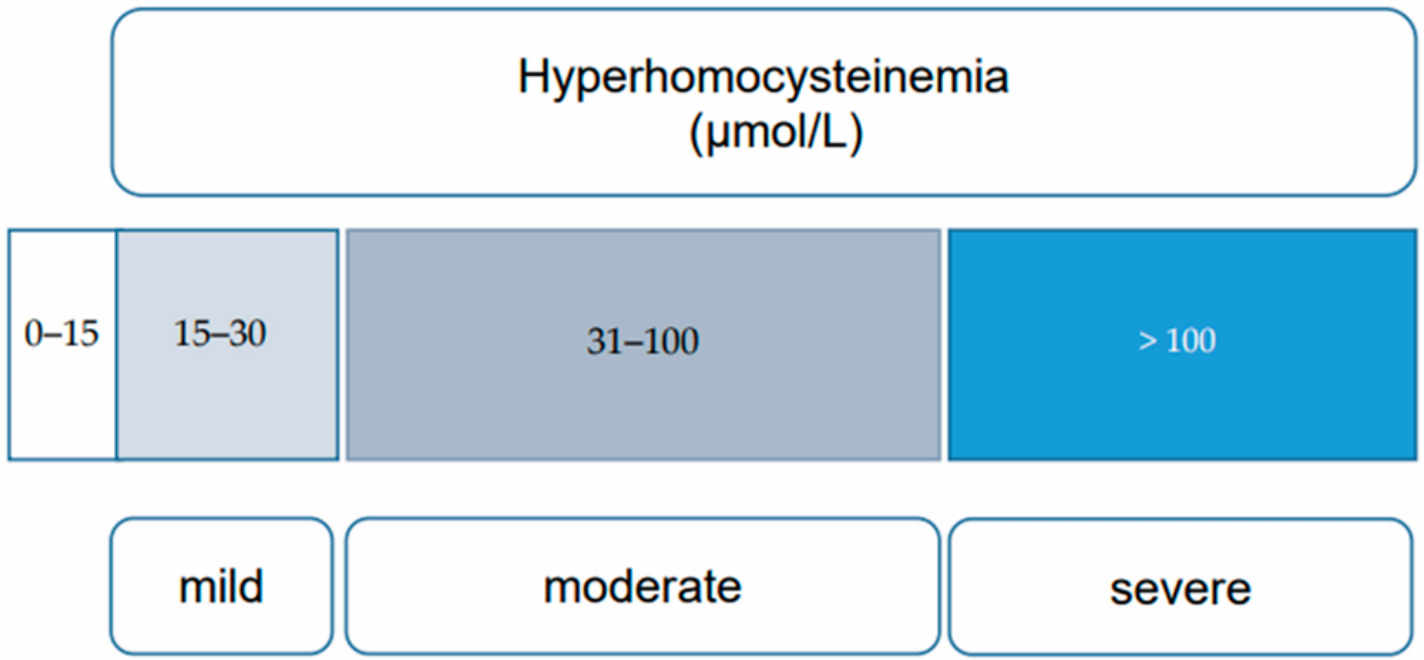
Summary

The arterial lesions discovered in a child who has an abnormality of cobalamin metabolism resulting in homocystinemia, cystathioninemia, and methylmalonic acidemia, resemble in a striking way many of those lesions found in patients with cystathionine synthetase deficiency with homocystinemia. Since the two disorders of sulfur amino-acid metabolism both result in elevation of homocysteine concentration, the arterial damage found in association with both diseases is attributed to the metabolic effects of increased concentrations of homocysteine, homocystine, or a derivative of homocysteine. The implications of this finding for the pathogenesis of arteriosclerosis in individuals free of known enzyme deficiencies are discussed and interpreted with particular reference to the findings in experimentally induced arteriosclerosis.

Metabolismo dell'omocisteina



Nutrients 2024, 16, 13



Classificazioni leggermente variabili:
- fino a 15 µmol/L la concentrazione è normale.
- 15 e 30 µmol/L è considerato lievemente elevato,
- 30 e 60 µmol/L è moderatamente elevato e
- > 60 µmol/L è gravemente elevato (2).
- omocistinuria è una condizione molto rara, solitamente valori di omocisteina > 100 µmol/L.

Nutrients 2024, 16, 13

L'omocistinuria è una malattia metabolica ereditaria con trasmissione autosomica recessiva con incidenza di circa 1/300000 (in Irlanda del nord l'incidenza è 1/65000) .

Il gene responsabile è la cistationina-beta-sintetasi di cui sono state identificate più di 150 mutazioni.

- Manifestazioni sistemiche (oculari, scheletriche, vascolari, cutanee)
- Manifestazioni neurologiche (Ritardo psicomotorio , Disturbi psichiatrici , Epilessia , Infarti cerebrali , Disturbi extrapiramidali)

.

Possibili fattori associati all'aumento di omocisteinemia:

Carenza diatetica di: acido folico, vitamina B12, vitamina B6
Anomalie genetiche (CBS*; MTHFR**)
Insufficienza renale
Obesità
Ipotiroidismo
Diabete mellito
Ipertensione arteriosa
Fumo di sigaretta
Ipercolesterolemia
Inattività fisica
Farmaci: metotrexate, atorvastatina, fenofibrato, …

Inquinamento

*CBS: cistationina-beta-sintetasi
**MTHFR: metilentetraidrofolato reduttasi

A Quantitative Assessment of Plasma Homocysteine as a Risk Factor for Vascular Disease

Probable Benefits of Increasing Folic Acid Intakes

Carol J. Boushey, PhD, MPH, RD; Shirley A. A. Beresford, PhD; Gilbert S. Omenn, MD, PhD; et al

Objective. —To determine the risk of elevated total homocysteine (tHcy) levels for arteriosclerotic vascular disease, estimate the reduction of tHcy by folic acid, and calculate the potential reduction of coronary artery disease (CAD) mortality by increasing folic acid intake.

Meta-analysis of 27 studies relating homocysteine to arteriosclerotic vascular disease and 11 studies of folic acid effects on tHcy levels

Data Synthesis. —Elevations in tHcy were considered an independent graded risk factor for arteriosclerotic vascular diseases. The odds ratio (OR) for CAD of a 5-μmol/L tHcy increment is 1.6(95% confidence interval [Cl], 1.4 to 1.7) for men and 1.8 (95% Cl, 1.3 to 1.9) for women. A total of 10% of the population's CAD risk appears attributable to tHcy. The OR for cerebrovascular disease (5-μmol/L tHcy increment) is 1.5 (95% Cl, 1.3 to 1.9). Peripheral arterial disease also showed a strong association. Increased folic acid intake (approximately 200 μg/d) reduces tHcy levels by approximately 4 μmol/L. Assuming that lower tHcy levels decrease CAD mortality, we calculated the effect of (1) increased dietary folate, (2) supplementation by tablets, and (3) grain fortification. Under different assumptions, 13 500 to 50 000 CAD deaths annually could be avoided; fortification of food had the largest impact.

JAMA. 1995;274:1049-1057

A Quantitative Assessment of Plasma Homocysteine as a Risk Factor for Vascular Disease

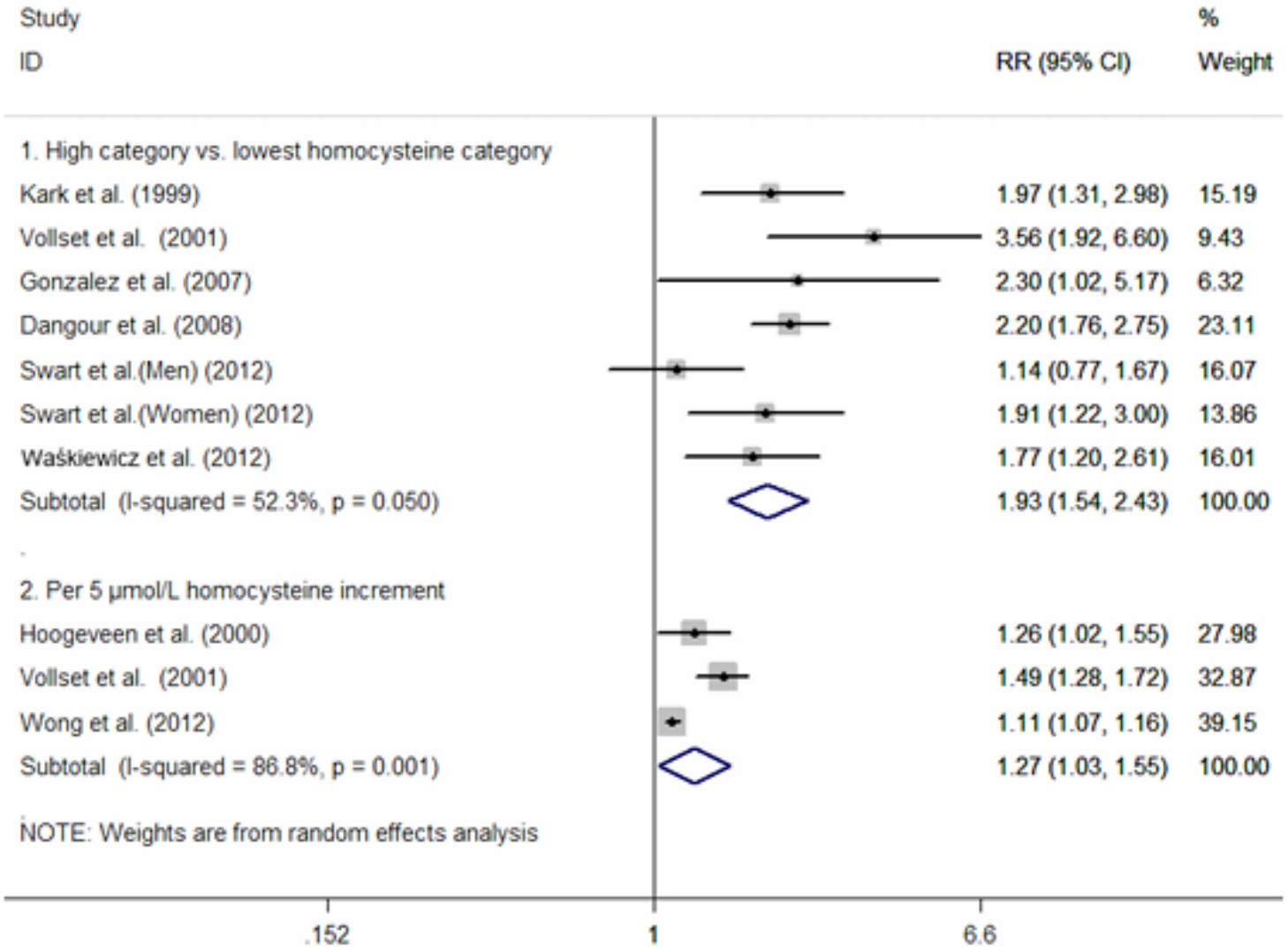
Probable Benefits of Increasing Folic Acid Intakes

Carol J. Boushey, PhD, MPH, RD; Shirley A. A. Beresford, PhD; Gilbert S. Omenn, MD, PhD; et al

Conclusions. —A 5-μmol/L tHcy increment elevates CAD risk by as much as cholesterol increases of 0.5 mmol/L (20 mg/dL). Higher folic acid intake by reducing tHcy levels promises to prevent arteriosclerotic vascular disease. Clinical trials are urgently needed. Concerns about masking cobalamin deficiency by folic acid could be lessened by adding 1 mg of cobalamin to folic acid supplements.(*JAMA*. 1995;274:1049-1057)

JAMA. 1995;274:1049-1057

MORTALITA' DA OGNI CAUSA

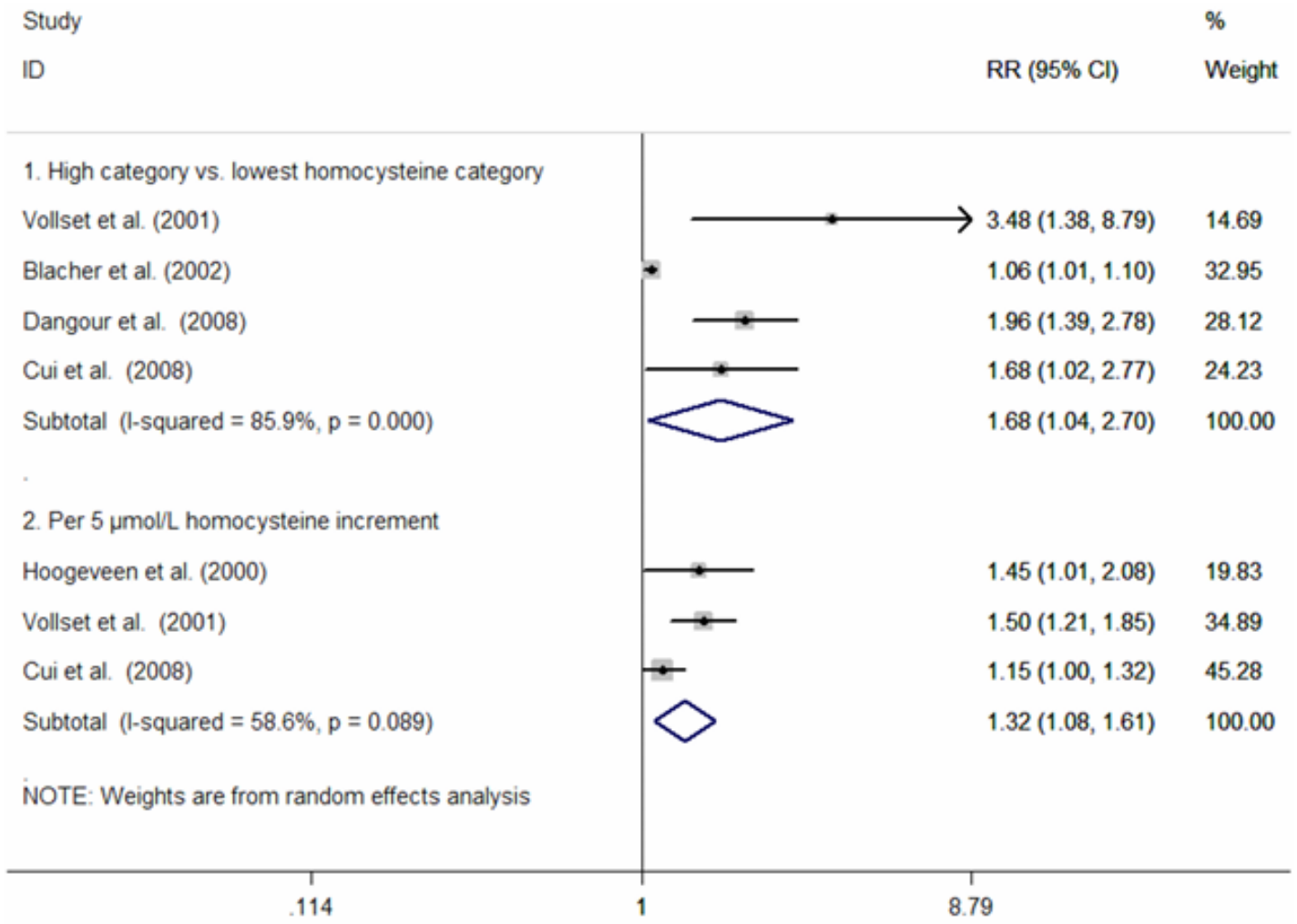


7 studi
15904 pz
Follow-up 4.1 - 14 anni

3 studi
9825 pz

Peng et al. / J Zhejiang Univ-Sci B (Biomed & Biotechnol) 2015 16(1):78-86

MORTALITA' DA CAUSE CARDIOVASCOLARI

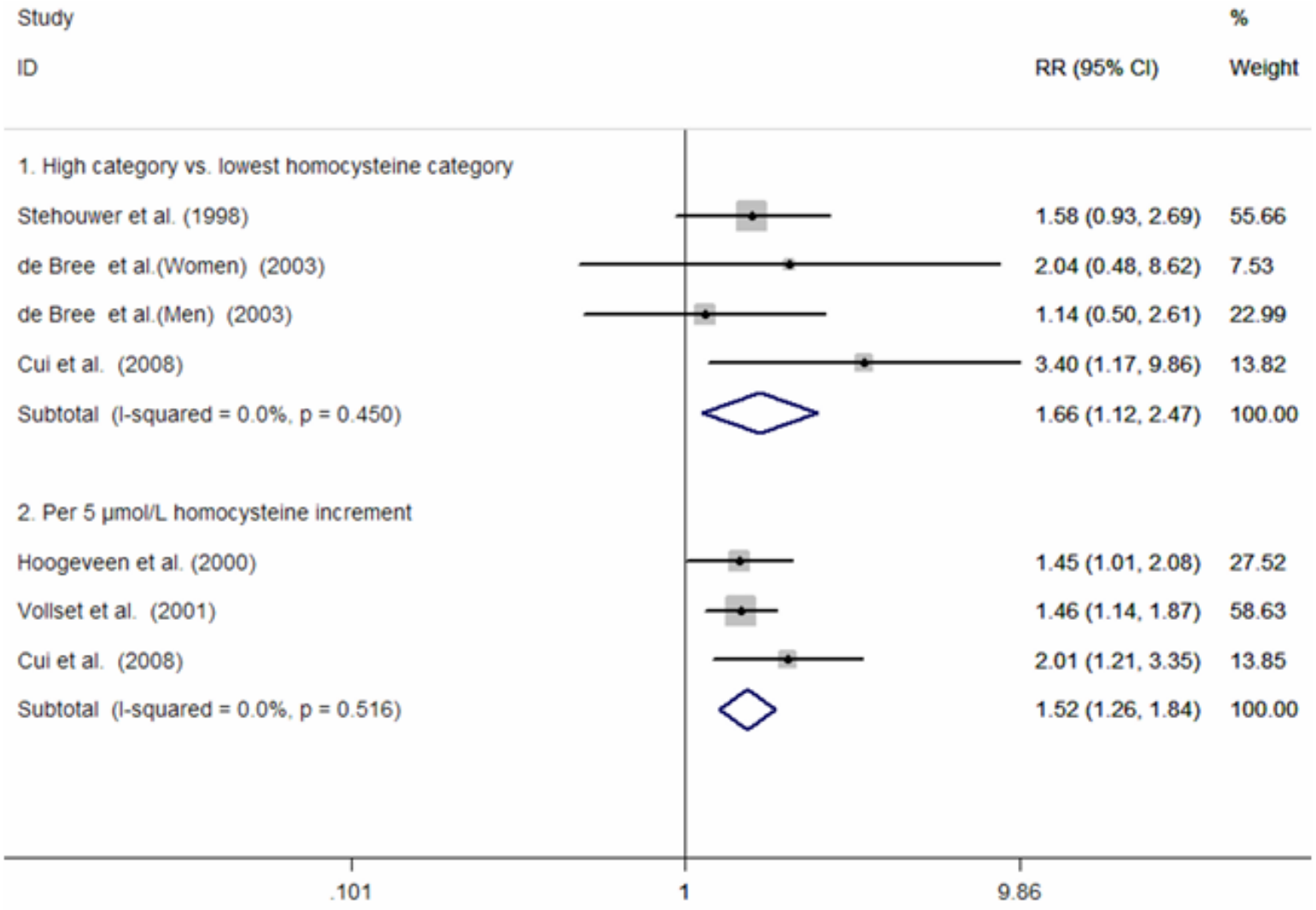


4 studi
6771 pazienti

3 studi
6465 pazienti

Peng et al. / J Zhejiang Univ-Sci B (Biomed & Biotechnol) 2015 16(1):78-86

MORTALITA' DA PATOLOGIA CORONARICA



4 studi
2396 pazienti

3 studi
6208 pazienti

Peng et al. / J Zhejiang Univ-Sci B (Biomed & Biotechnol) 2015 16(1):78-86

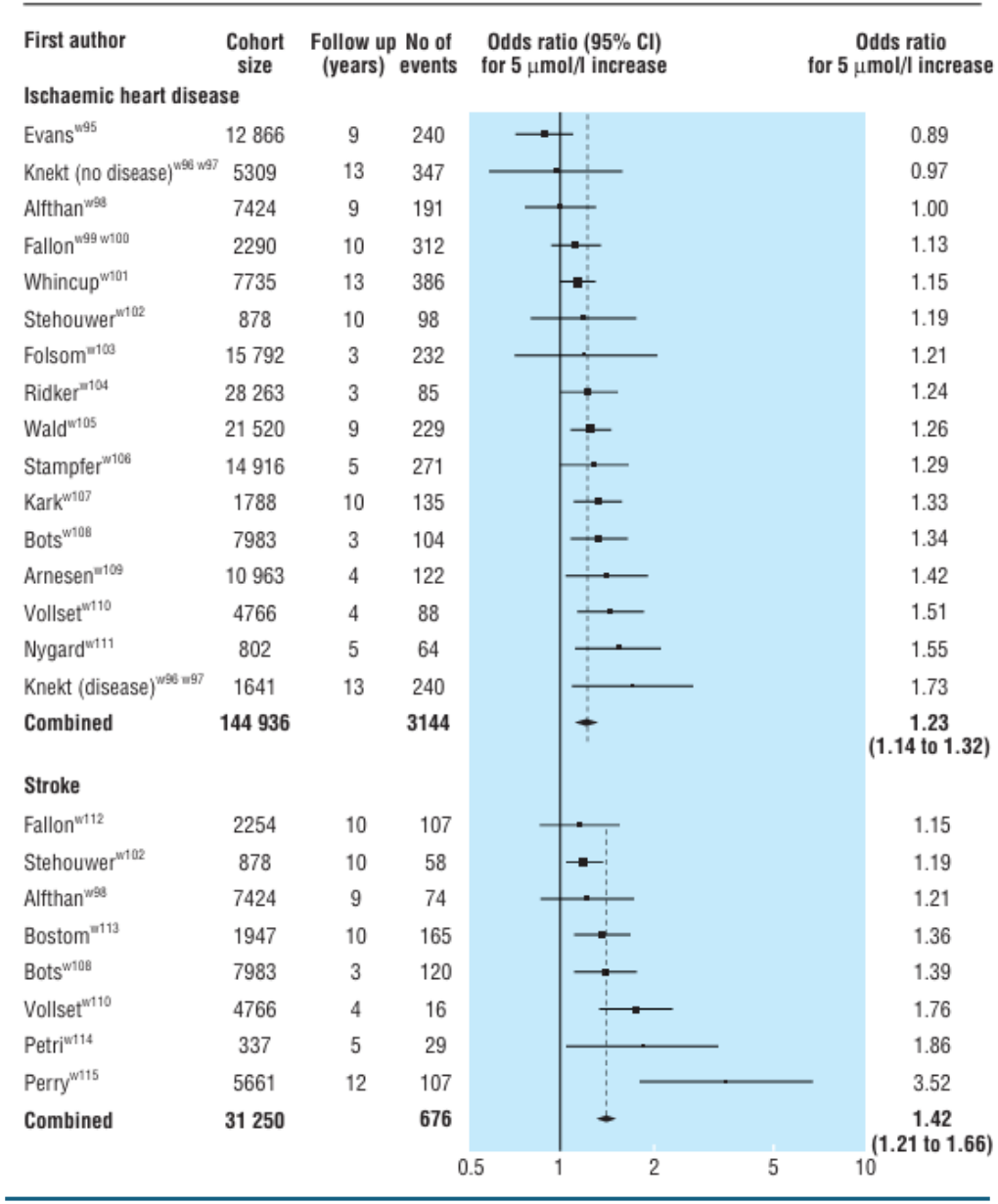
Comparing the highest to lowest homocysteine level categories:

- CHD mortality increased by 66% (RR 1.66; 95% CI 1.12–2.47; P=0.012),
- cardiovascular mortality increased by 68% (RR 1.68; 95% CI 1.04–2.70; P=0.033),
- all-cause mortality increased by 93% (RR 1.93; 95% CI 1.54–2.43; P < 0.001

For each 5 μmol/L homocysteine increment, the pooled RR was

- 1.52 (95% CI 1.26–1.84; P<0.001) for CHD mortality,
- 1.32 (95% CI 1.08-1.61; P=0.006) for cardiovascular mortality
- 1.27 (95% CI 1.03-1.55; P=0.023) for all cause mortality.

Peng et al. / J Zhejiang Univ-Sci B (Biomed & Biotechnol) 2015 16(1):78-86



First author	Cohort size	Follow up (years)	No of events	Odds ratio (95% CI) for 5 μmol/l increase	Odds ratio for 5 μmol/l increase
Ischaemic heart disease					
Evans[w95]	12 866	9	240		0.89
Knekt (no disease)[w96 w97]	5309	13	347		0.97
Alfthan[w98]	7424	9	191		1.00
Fallon[w99 w100]	2290	10	312		1.13
Whincup[w101]	7735	13	386		1.15
Stehouwer[w102]	878	10	98		1.19
Folsom[w103]	15 792	3	232		1.21
Ridker[w104]	28 263	3	85		1.24
Wald[w105]	21 520	9	229		1.26
Stampfer[w106]	14 916	5	271		1.29
Kark[w107]	1788	10	135		1.33
Bots[w108]	7983	3	104		1.34
Arnesen[w109]	10 963	4	122		1.42
Vollset[w110]	4766	4	88		1.51
Nygard[w111]	802	5	64		1.55
Knekt (disease)[w96 w97]	1641	13	240		1.73
Combined	**144 936**		**3144**		**1.23 (1.14 to 1.32)**
Stroke					
Fallon[w112]	2254	10	107		1.15
Stehouwer[w102]	878	10	58		1.19
Alfthan[w98]	7424	9	74		1.21
Bostom[w113]	1947	10	165		1.36
Bots[w108]	7983	3	120		1.39
Vollset[w110]	4766	4	16		1.76
Petri[w114]	337	5	29		1.86
Perry[w115]	5661	12	107		3.52
Combined	**31 250**		**676**		**1.42 (1.21 to 1.66)**

Studi di varianti genetiche di MTHFR (omozigoti vs eterozigoti) + concentrazione di omocisteina
Studi prospettici di concentrazione dell'omocisteina

EP:
CAD
TVP
Stroke

Fig 2 Results of prospective studies of serum homocysteine concentration and ischaemic heart disease and stroke: values are odds ratios (95% confidence intervals) for a 5 μmol/l increase in serum homocysteine, adjusted for age, sex, smoking, cholesterol concentration, and blood pressure (except in one study, adjusted for age and sex alone[w106]) but not for regression dilution bias

Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis, BMJ 2002;325:1202

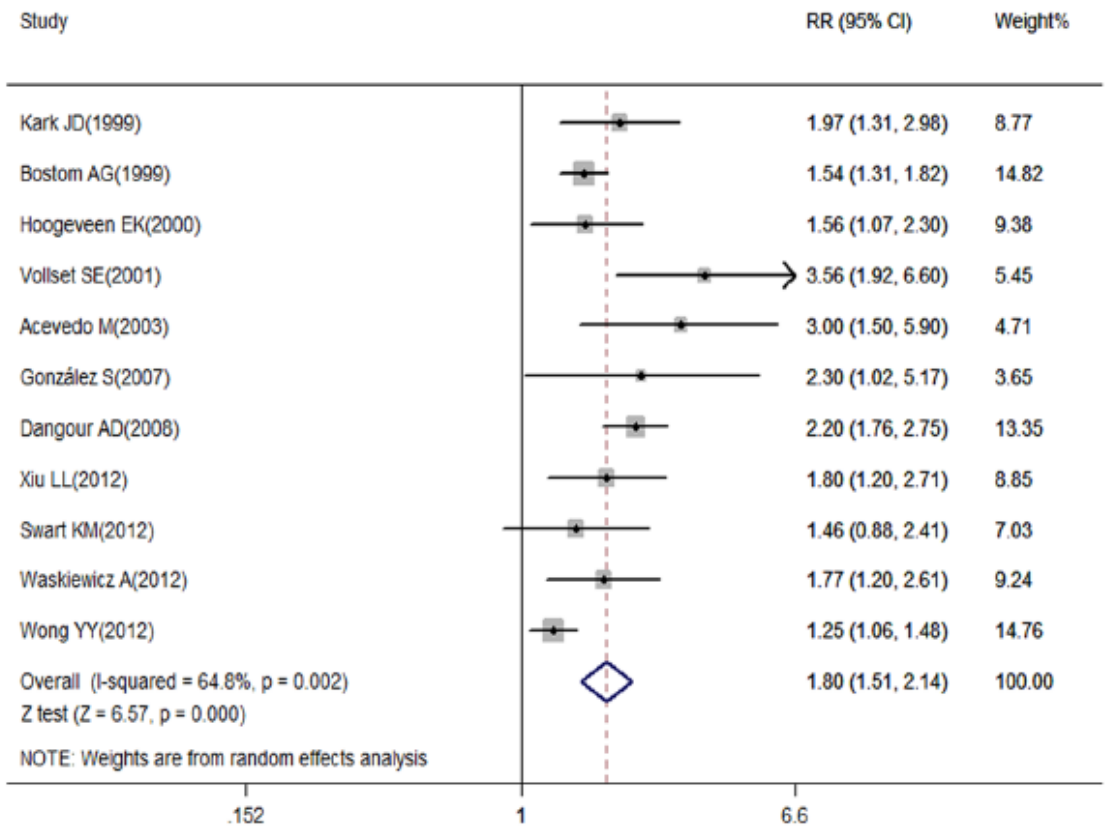


Figure 2. Association between Hcy levels and all-cause mortality risk analyzed by forest plot.

Rischio mortalità ogni causa + 33% per ogni 5 umol/L

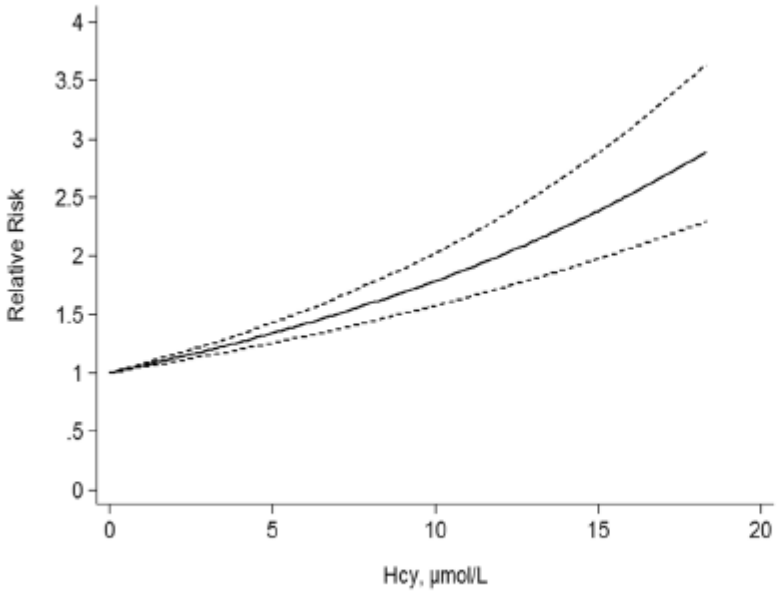


Figure 4. Dose-response relationships between Hcy levels and all-cause mortality risk.

11 studi
27.737 pazienti

Rui Fan, Association between Homocysteine Levels and All-cause Mortality: A Dose-Response Meta-Analysis of Prospective Studies Scientific Reports 2017 | 7: *4769*

Original Article

Systematic review and meta-analysis of the correlation between plasma homocysteine levels and coronary heart disease

Bo Wang[1#], Xiaoyun Mo[2#], Ze Wu[3], Xiaorong Guan[3]

Results: A total of 10 studies with a total of 10,103 subjects were included. All studies were of case-control studies or cohort studies with good quality. Meta-analysis showed that for every 5 μmol/L increase in Hcy level, the pooled risk ratio of coronary events was 1.22, 95% CI: 1.11, 1.34. These results demonstrate that when plasma Hcy level increased, the risk of CHD also increased.

Conclusions: Compared with traditional risk factors, the incidence of CHD increases by 22% for every 5 μmol/L increase in plasma Hcy levels. This mean that clinicians can timely take preventive measures for coronary heart disease when the patients' elevated plasma Hcy.

Journal of Thoracic Disease, Vol 14, No 3 March 2022

Table 1 *Plasma total homocysteine as a disease biomarker*

Disease/outcome
Insufficient B vitamin status
Folate, B12, B6, B2
Inborn errors of homocysteine and vitamin metabolism and transport
Cardiovascular diseases
Myocardial infarction
Severity of coronary artery disease
Restenosis of coronary arteries and adverse outcomes after angioplasty
Vascular calcification
Heart failure
Cardiac hypertrophy
Hypertension
Stroke
Stroke mortality
Silent brain infarct
Carotid plaque area, stenosis, intima–media thickness
Intracerebral arterial stenosis
Peripheral vascular disease
Venous thrombosis
Arterial aneurysm
Arterial stiffness
Atrial fibrillation
Cerebral small vessel disease
Cerebral microbleeds
Disruption of blood–brain barrier
Endothelial mediated dilatation – impaired
Vascular complications of diabetes
Raynaud's syndrome
Takayasu arteritis
Thromboangiitis obliterans (Buerger's disease)
Moyamoya disease
Behçet disease
Erectile dysfunction
Other outcomes
Mortality
Frailty in elderly
Muscle strength, impaired
Sarcopenia
Physical function, gait speed – impaired
Intrinsic capacity (WHO), impaired
Cancer
Metabolic syndrome
Obesity
Bone disease, osteoporosis
Inflammatory bowel disease, Crohn's disease
Gluten-sensitive enteropathy (celiac disease)
Nonalcoholic fatty liver disease
Renal insufficiency, chronic kidney disease
Chronic obstructive pulmonary disease
Alcohol abuse
Alcohol-withdrawal seizures
Psoriasis
Vitiligo
Sclerosis
Sickle cell disease
Burning mouth syndrome
Atrophic glossitis
Quality of life in centenarians
Obstructive sleep apnoea
Hypothyroidism
Polycystic ovarian syndrome
Telomere shortening
Systemic lupus erythematosus (SLE)
Dermatomyositis
Inflammatory response
Periodontal disease
Hearing loss
Gout
Blood lead concentration
Diabetic neuropathy
Cellular senescence; impairment of autophagy
Maternal tHcy
Pregnancy complications
Outcomes in child
Small for gestational age, foetal growth
Neural tube defects
Congenital heart disease
Orofacial clefts
Renal function
Child cognition, impaired
Child behaviour, impaired
Schizophrenia
Autism spectrum disorder
Central nervous system diseases
Incident Alzheimer's disease/dementia
Vascular dementia, vascular cognitive impairment
Poststroke cognitive impairment
Cognitive decline after concussion
Cognition in infants and children, impaired
Cognition in elderly, impaired
Initiation of cognitive decline in ageing
Conversion from cognitive impairment to dementia
Cognitive decline in dementia
Atrophy of brain tissue/grey matter
Atrophy of brain white matter
White matter damage
Alzheimer brain pathology (P-tau)
Multiple sclerosis
Cognitive decline in Parkinson's disease
Depression
Bipolar disorder
Anxiety
Obsessive–compulsive disorder (OCD)
Post-traumatic stress disorder (PTSD)
Schizophrenia
Amyotrophic lateral sclerosis/ motor neuron disease
Multiple system atrophy
Motor development in infant, impaired
Disruption of blood–brain barrier
Early neurological deterioration after stroke
Glasgow coma scale
Migraine
Autism spectrum disorder
Ocular diseases
Macular degeneration
Ectopia lentis
Retinal vascular occlusion
Retinal arteriosclerosis
Diabetic retinopathy
Exfoliation syndrome and glaucoma
Nutritional blindness

The table lists diseases and syndromes for which there are reports of association with raised total homocysteine. Most of the reports are of prospective studies. Table S1 in the Supplementary files gives references to key original papers and reviews.

Journal of Internal Medicine, 2021, 290; 826–854

Meccanismi patogenetici

- Aumento attività dell'HMG-CoA Reduttasi, aumento colesterolemia, ossidazione delle LDL
- Proliferazione muscolatura liscia vascolare, aumento sintesi collagene
- Danno endoteliale (cellule endoteliali vena ombelicale umana)
- N-Hcy proteins hanno proprietà proamiloidogeniche, proaterogeniche, protrombogene
- Stress ossidativo cellule endoteliali e ridotta produzione NO
- Infiammazione (mediata da attivazione della via NF-kB nella muscolatura liscia) ed aumento sintesi PCR
- Effetto Protrombotico (attivazione dei fattori della coagulazione, Inibizione della fibrinolisi, attivazione piastrinica)
- Effetto sulla metilazione del DNA

Studi di intervento

- Supplementazione con folati/B12/B6
- Riduzione dei livelli di omocisteina

- Effetto sugli endpoints?

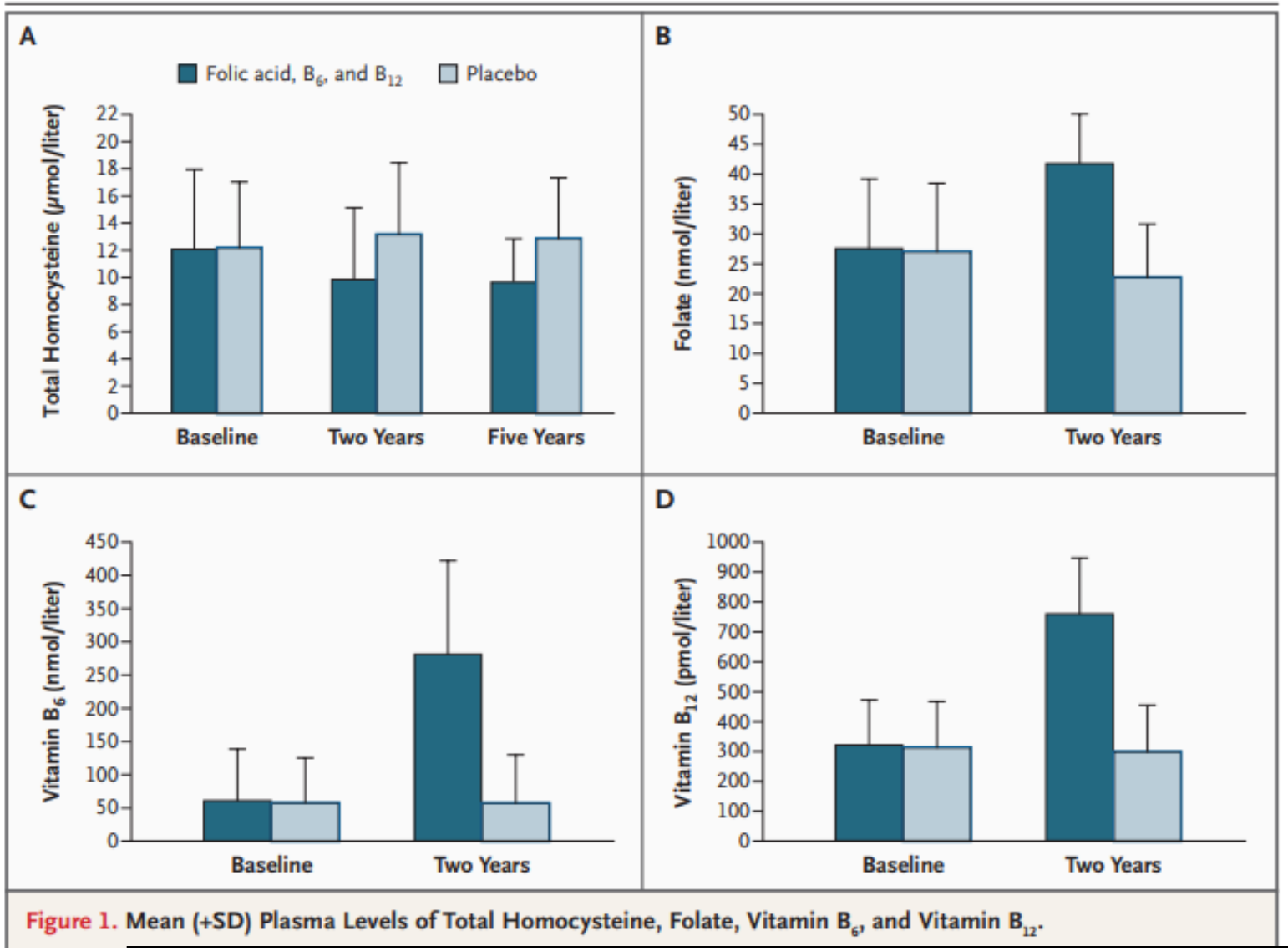


Figure 1. Mean (+SD) Plasma Levels of Total Homocysteine, Folate, Vitamin B_6, and Vitamin B_{12}.

5522 pz
55 aa
Malattia vascolare o DM

HOPE 2 trial; N Engl J Med 2006;354:1567-77

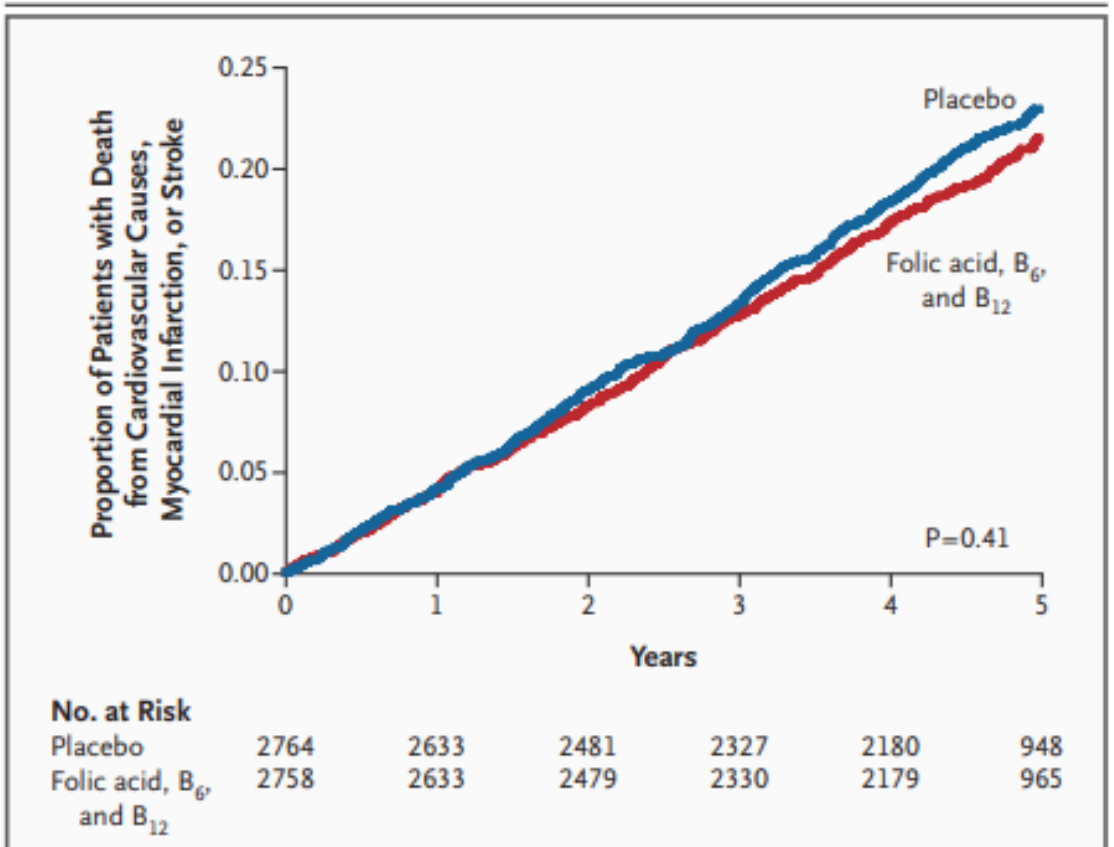


Figure 2. Kaplan–Meier Estimates of the Proportion of Patients with the Composite Primary Outcome of Death from Cardiovascular Causes, Myocardial Infarction, or Stroke.

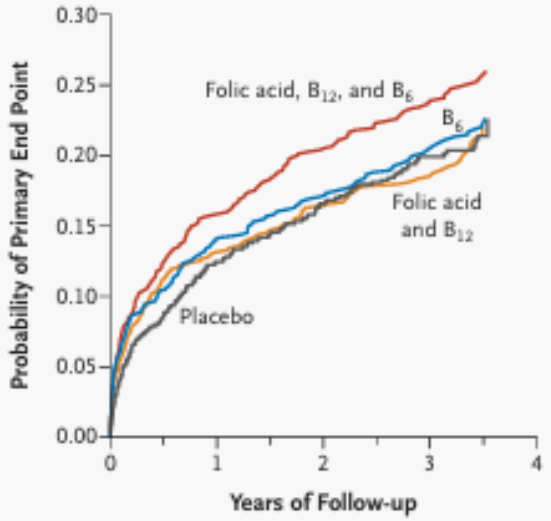
The relative risk of the composite primary outcome in the active-treatment group, as compared with the placebo group, was 0.95 (95 percent confidence interval, 0.84 to 1.07; P=0.41 by the log-rank test).

HOPE 2 trial; N Engl J Med 2006;354:1567-77

Table 2. Plasma Levels of Total Homocysteine and B Vitamins at Baseline, after Two Months, and at the End of the Intervention.*

Variable	Folic Acid, B_{12}, and B_6 (N=937)†	Folic Acid and B_{12} (N=935)‡	B_6 (N=934)§	Placebo (N=943)¶
Total homocysteine (μmol/liter)				
Baseline	13.1±5.0	12.9±4.3	13.3±6.1	13.2±5.2
2 Mo	9.4±3.0	9.5±2.8	13.7±5.7	13.7±5.6
End of intervention	9.5±3.6	9.8±4.0	13.3±5.4	13.6±6.2
Folate (nmol/liter)				
Baseline	13.1±27.5	11.7±28.4	9.4±6.6	9.6±6.0
2 Mo	59.9±29.5	68.2±30.0	7.9±7.1	9.9±6.3
End of intervention	61.8±31.7	70.4±36.4	10.4±9.6	13.1±14.5
Vitamin B_{12} (pmol/liter)				
Baseline	388±161	400±311	388±167	383±182
2 Mo	571±212	578±372	398±158	393±143
End of intervention	638±370	648±414	398±320	390±171

* Values are means ±SD. To convert values for homocysteine to millligrams per liter, divide by 7.396. To convert values for folate to nanograms per milliliter, divide by 2.266. To convert values for vitamin B_{12} to picograms per milliliter, divide by 0.7378.
† Blood samples were available from 935 patients at baseline, 855 at two months, and 750 at the end of the intervention.
‡ Blood samples were available from 933 patients at baseline, 849 at two months, and 770 at the end of the intervention.
§ Blood samples were available from 930 patients at baseline, 819 at two months, and 747 at the end of the intervention.
¶ Blood samples were available from 935 patients at baseline, 851 at two months, and 760 at the end of the intervention.



No. at Risk

Folic acid, B_{12}, and B_6	937	795	745	517
Folic acid and B_{12}	935	812	764	518
B_6	934	805	766	511
Placebo	943	823	771	523

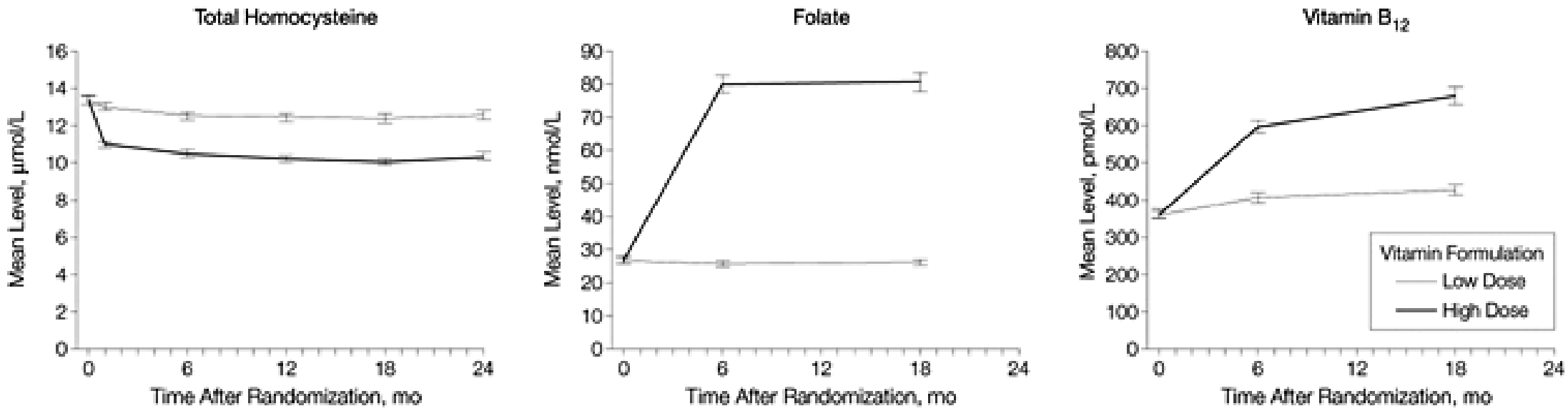
Figure 1. Kaplan–Meier Estimates of the Probability of Reaching the Primary End Point during Follow-up.
The primary end point was a composite of fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, and sudden death attributed to coronary heart disease.

3749 pz
IMA < 7 giorni

NORVIT trial; N Engl J Med 2006;354:1578-88

JAMA Network™

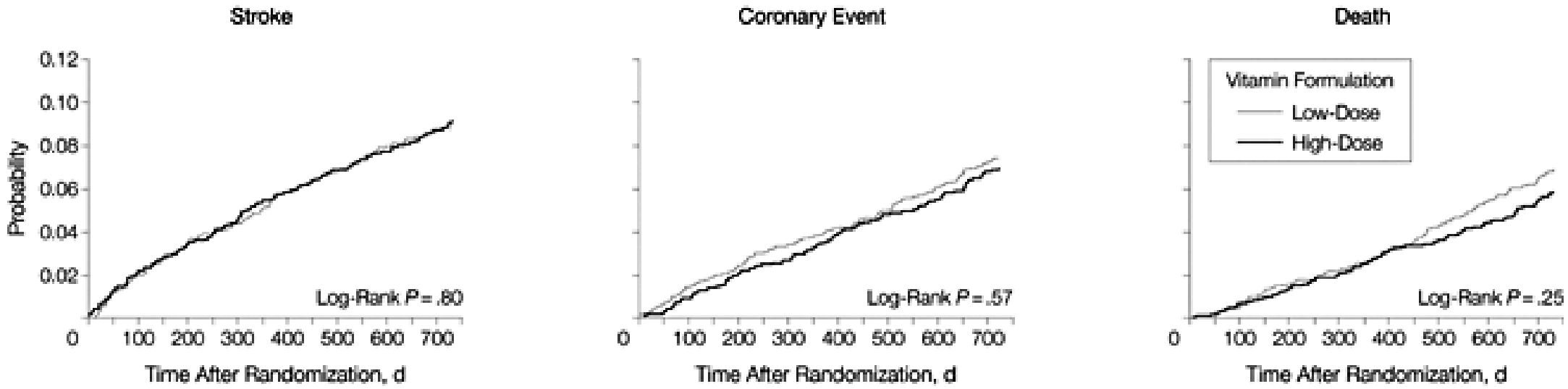
From: **Lowering Homocysteine in Patients With Ischemic Stroke to Prevent Recurrent Stroke, Myocardial Infarction, and Death: The Vitamin Intervention for Stroke Prevention (VISP) Randomized Controlled Trial**



3680 pz
Infarto cerebrale

JAMA. 2004;291(5):565-575. doi:10.1001/jama.291.5.565

From: **Lowering Homocysteine in Patients With Ischemic Stroke to Prevent Recurrent Stroke, Myocardial Infarction, and Death: The Vitamin Intervention for Stroke Prevention (VISP) Randomized Controlled Trial**



JAMA. 2004;291(5):565-575. doi:10.1001/jama.291.5.565

The Vitamins and Thrombosis (VITRO) study investigated the effect of homocysteine lowering by daily supplementation of B vitamins on the risk reduction of deep vein thrombosis (DVT) and pulmonary embolism (PE).

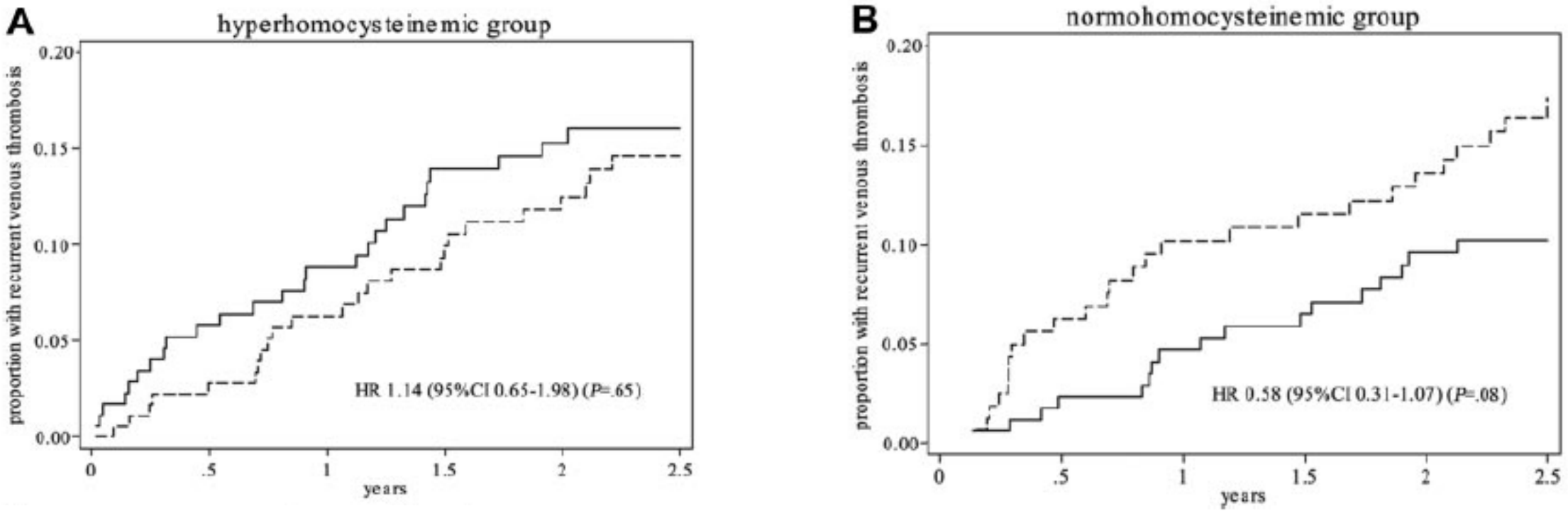


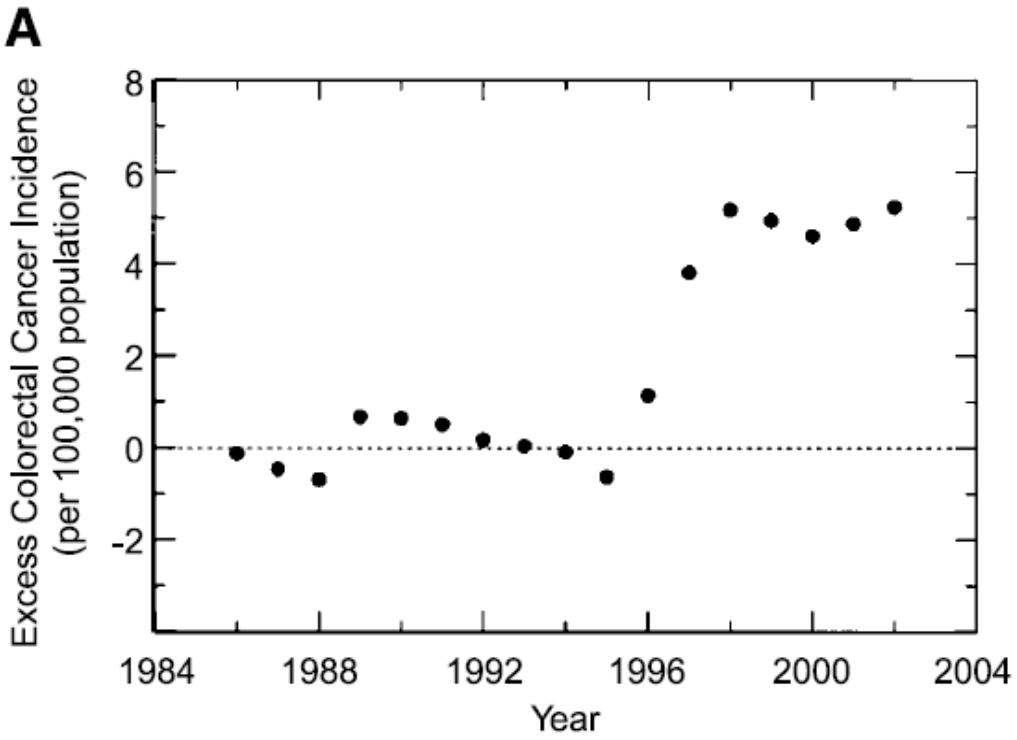
Figure 2. Recurrent thrombosis cumulative incidence. Recurrent thrombosis cumulative incidence in patients treated with multivitamin (solid line) or placebo (dashed line) in a hyperhomocysteinemic and a normohomocysteinemic group.

Blood. 2007;109:139-144

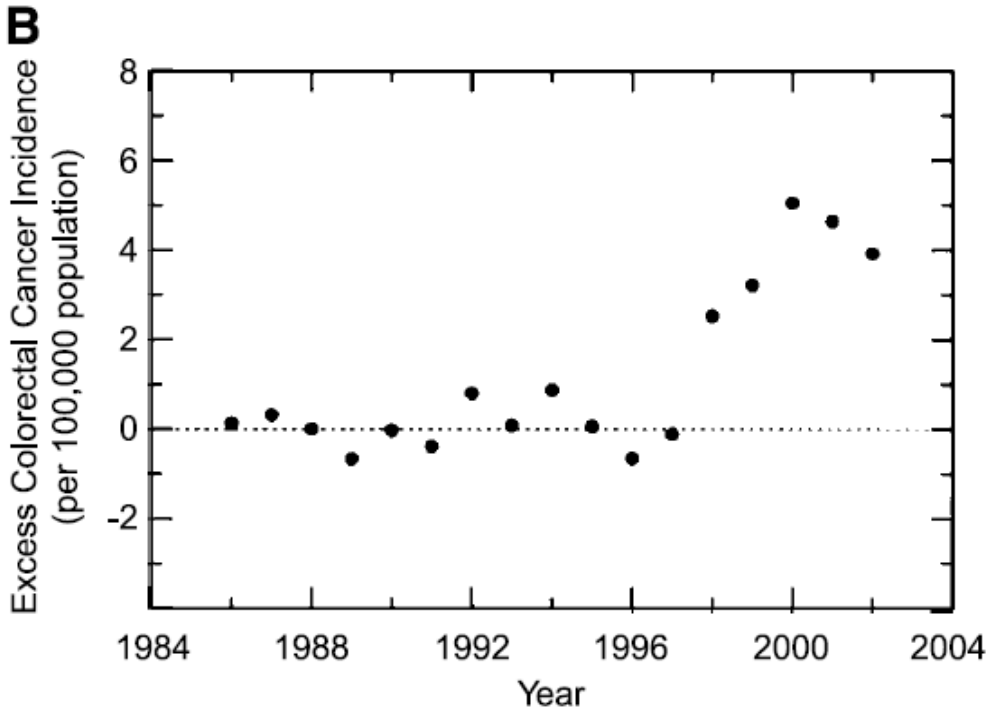
‘The homocysteine hypothesis is dead. Homocysteine in not a causal risk factor. It is an innocent bystander’.

From the principal investigator of NORVIT, at the press conference at the European Society for Cardiology in Stockholm in 2005.

USA



CANADA



Cancer Epidemiol Biomarkers Prev 2007;16(7):1325–9

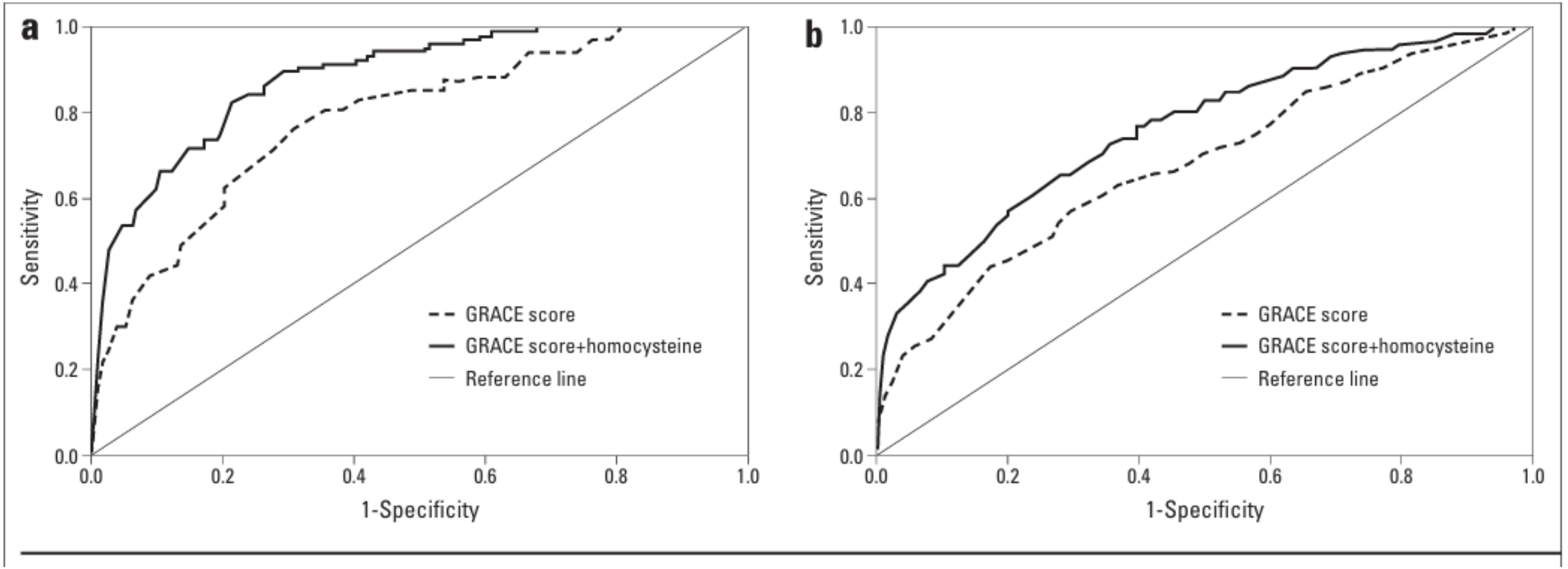


Figure 5. ROC curve analysis. The addition of homocysteine improved the predictive power of the GRACE risk scoring system for all-cause death (a) and major adverse cardiovascular events (b)

Fan et al. Homocysteine and value of the GRACE risk score Anatol J Cardiol 2017; 18: 182-93

Table 5 6-Year Risk of Hard CHD Event in the MESA Population in Models With and Without Homocysteine

	Model With Homocysteine					Risk Reclassification	
Model Without Homocysteine	0% to <3%	3% to <6%	6% to <12%	≥12%	Total	Higher	Lower
0% to <3%							
Persons included	5,476	264	20	5	5,765		
No. of events	69	16	2	0	87	18	NA
No. of nonevents	5,407	248	18	5	5,678	271	NA
3% to <6%							
Persons included	150	296	62	6	516		
No. of events	3	18	3	1	25	4	3
No. of nonevents	147	280	59	5	491	64	147
6% to 12%							
Persons included	1	36	80	8	125		
No. of events	0	2	6	2	10	2	2
No. of nonevents	1	34	74	6	115	6	35
>12%							
Persons included	0	0	7	37	44		
No. of events	0	0	0	2	2	NA	0
No. of nonevents	0	0	7	35	42	NA	7
Total							
Persons included	5,627	598	169	56	6,450		
No. of events	72	36	11	5	124	24	5
No. of nonevents	5,555	562	158	51	6,326	341	189
Net reclassification improvement							
Overall						12.9% ($p < 0.001$)	
Intermediate risk						21.2% ($p < 0.001$)	

Veeranna et al. JACC Vol. 58, No. 10, 2011:1025–33

Table 6 Ten-Year Risk of CHD Death in the NHANES III Population in Models With and Without Homocysteine

	Model With Homocysteine					Risk Reclassification	
Model without Homocysteine	0% to <5%	5% to <10%	10% to <20%	>20%	Total	Higher	Lower
0% to <5%							
Persons included	5,273	229	32	5	5,529		
No. of events	53	31	4	1	89	36	NA
No. of nonevents	5,220	188	28	4	5,440	220	NA
5% to <10%							
Persons included	264	460	114	6	826		
No. of events	9	41	18	1	69	19	9
No. of nonevents	237	419	96	5	757	101	237
10% to <20%							
Persons included	7	108	217	64	396		
No. of events	0	14	22	7	43	7	14
No. of nonevents	7	419	96	57	353	57	426
>20%							
Persons included	0	1	19	26	46		
No. of events	0	0	1	2	3	NA	1
No. of nonevents	0	1	18	24	43	NA	19
Total							
Persons included	5,526	788	382	101	6,797		
No. of events	62	86	45	11	204	62	24
No. of nonevents	5,464	702	337	90	6,593	378	357
Net reclassification improvement							
Overall						18.3% ($p < 0.001$)	
Intermediate						19.1% ($p < 0.001$)	

Veeranna et al. JACC Vol. 58, No. 10, 2011:1025–33

LE LINEE GUIDA

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Personal details

Birth date *

/
(month / year)

Sex *

○ male ○ female

Systolic blood pressure: *
mmHg

Total Cholesterol: *

◉ mmol/L ○ mg/dl

HDL-Cholesterol *
mmol/L

LDL-Cholesterol
mmol/L

Current Smoker: *

○ Yes ○ No

Calculate Risk

* denotes a mandatory field

HeartScore

EAPC
European Society of Cardiology

Calculate the 10-year risk of fatal and non-fatal cardiovascular disease events of your patients

The SCORE2 and SCORE2-OP charts apply to apparently healthy people only. SCORE2 and SCORE2-OP do not apply to persons with documented atherosclerotic cardiovascular disease or other high-risk conditions such as diabetes mellitus, familial hypercholesterolaemia, or other genetic or rare lipid or blood pressure disorders, chronic kidney disease and in pregnant women.

Box 1 Risk modifiers for consideration beyond the risk estimation based on the SCORE2 and SCORE2-OP algorithms

Demographic/clinical conditions

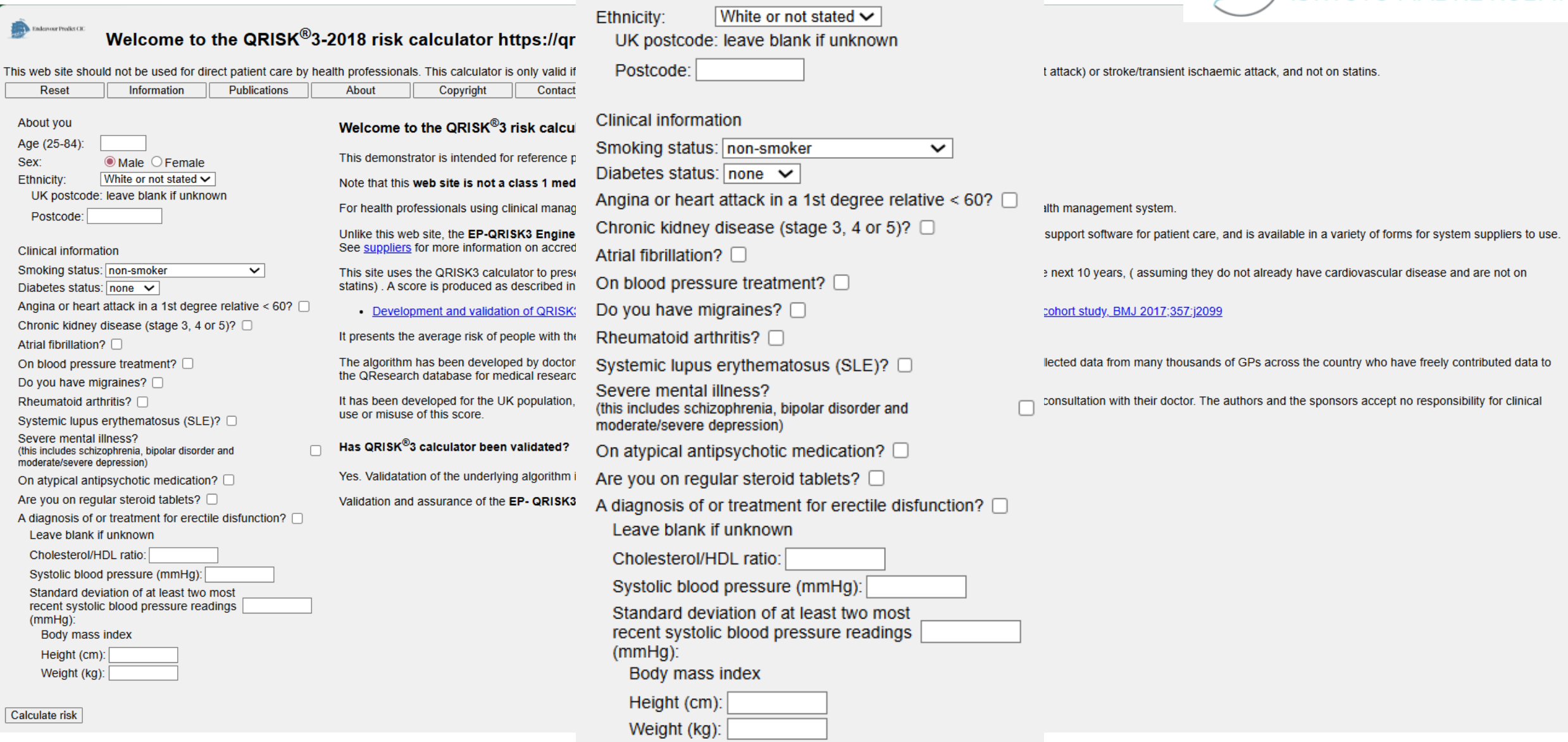
- Family history of premature CVD (men: <55 years; women: <60 years)
- High-risk ethnicity (e.g. Southern Asian)
- Stress symptoms and psychosocial stressors
- Social deprivation
- Obesity
- Physical inactivity
- Chronic immune-mediated/inflammatory disorders
- Major psychiatric disorders
- History of premature menopause
- Pre-eclampsia or other hypertensive disorders of pregnancy
- Human immunodeficiency virus infection
- Obstructive sleep apnoea syndrome

Biomarkers

- Persistently elevated hs-CRP (>2 mg/L)
- Elevated Lp(a) [>50 mg/dL (>105 nmol/L)].

CVD, cardiovascular disease; hs-CRP, high sensitivity C-reactive protein; Lp(a), lipoprotein(a).

European Heart Journal (2025) **46**, 4359–4378



Endeavour Predict CIC

Welcome to the QRISK®3-2018 risk calculator https://qr

This web site should not be used for direct patient care by health professionals. This calculator is only valid if

Reset | Information | Publications | About | Copyright | Contact

About you

Age (25-84):

Sex: Male Female

Ethnicity: White or not stated

UK postcode: leave blank if unknown

Postcode:

Clinical information

Smoking status: non-smoker

Diabetes status: none

Angina or heart attack in a 1st degree relative < 60?

Chronic kidney disease (stage 3, 4 or 5)?

Atrial fibrillation?

On blood pressure treatment?

Do you have migraines?

Rheumatoid arthritis?

Systemic lupus erythematosus (SLE)?

Severe mental illness?
(this includes schizophrenia, bipolar disorder and moderate/severe depression)

On atypical antipsychotic medication?

Are you on regular steroid tablets?

A diagnosis of or treatment for erectile disfunction?

Leave blank if unknown

Cholesterol/HDL ratio:

Systolic blood pressure (mmHg):

Standard deviation of at least two most recent systolic blood pressure readings (mmHg):

Body mass index

Height (cm):

Weight (kg):

Calculate risk

Welcome to the QRISK®3 risk calcu

This demonstrator is intended for reference p

Note that this **web site is not a class 1 med**

For health professionals using clinical manag

Unlike this web site, the **EP-QRISK3 Engine**
See suppliers for more information on accred

This site uses the QRISK3 calculator to prese
statins) . A score is produced as described in

- Development and validation of QRISK3

It presents the average risk of people with the

The algorithm has been developed by doctor
the QResearch database for medical researc

It has been developed for the UK population,
use or misuse of this score.

Has QRISK®3 calculator been validated?

Yes. Validatation of the underlying algorithm i

Validation and assurance of the **EP- QRISK3**

About you

Age (25-84):

Sex: Male Female

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(this includes schizophrenia, bipolar disorder and moderate/severe depression)

On atypical antipsychotic medication?

Are you on regular steroid tablets?

A diagnosis of or treatment for erectile disfunction?

Leave blank if unknown

Cholesterol/HDL ratio:

Systolic blood pressure (mmHg):

Standard deviation of at least two most recent systolic blood pressure readings (mmHg):

Body mass index

Height (cm):

Weight (kg):

Calculate risk

t attack) or stroke/transient ischaemic attack, and not on statins.

lth management system.

support software for patient care, and is available in a variety of forms for system suppliers to use.

e next 10 years, (assuming they do not already have cardiovascular disease and are not on

cohort study. BMJ 2017;357:j2099

llected data from many thousands of GPs across the country who have freely contributed data to

consultation with their doctor. The authors and the sponsors accept no responsibility for clinical

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NICE National Institute for Health and Care Excellence

Dec 2023

CONCLUSIONI:

L’omocisteina è associata al rischio cardiovascolare (studi osservazionali)

Molteplici effetti dell’omocisteina sul sistema cardiovascolare (danno endoteliale, effetto protrombotico, proliferazione muscolatura liscia, effetto epigenetico)

MA studi di intervento mostrano che ridurre i valori di omocisteina NON comporta una riduzione del rischio cardiovascolare

Ridurre il marker non significa necessariamente ridurre il rischio.

CONCLUSIONI:

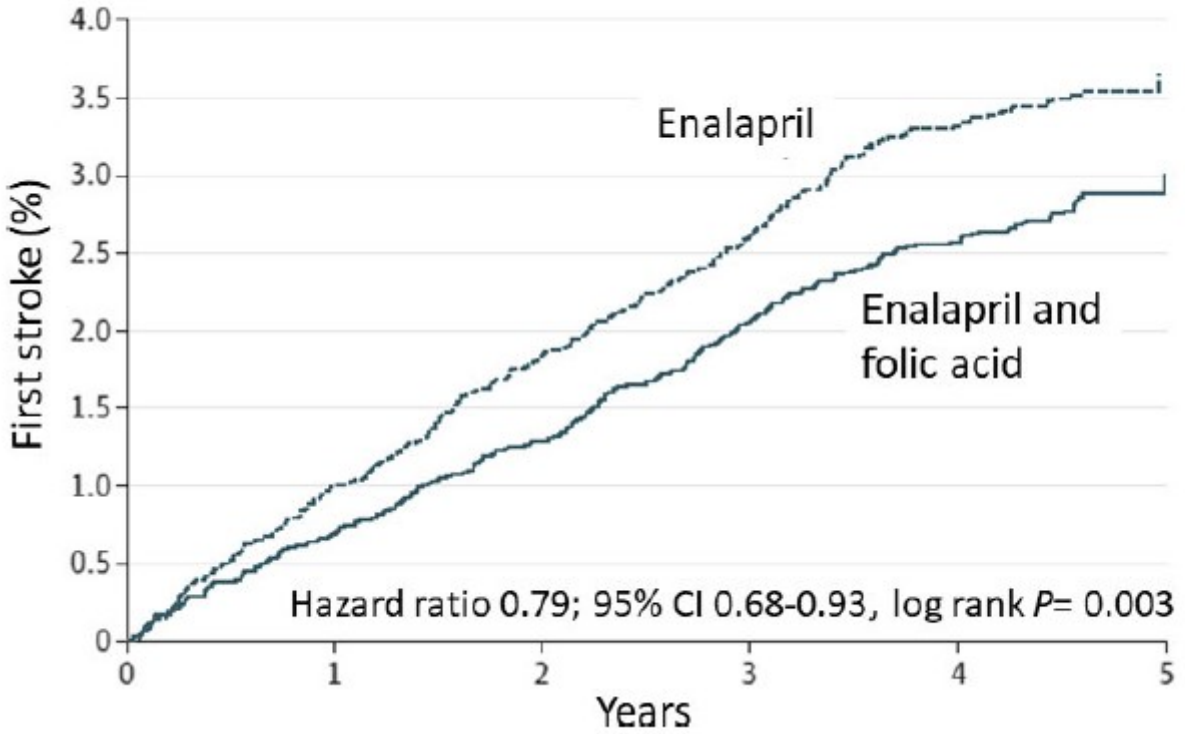
Le linee guida NON includono il dosaggio dell'omocisteina nei test di screnning per stratificazione del rischio cardiovascolare.

Quando può essere utile:

- sospetta omocistinuria
- ictus in età molto giovane senza causa evidente
- infarto miocardico o trombosi in altra sede in età giovane senza fattori di rischio
- sospetto deficit di vitamina B12 o folati

Riduzione significativa per alcuni sottogruppi:

- Concentrazioni più basse di PLT
- Colesterolemia > 200



CSPPT. From Huo et al. 2015

2) Se si riscontra un'iperomocisteinemia occorre trattarla?

Sebbene l'utilizzo di una supplementazione di acido folico, vitamina B6 o B12 riduca efficacemente i livelli circolanti di omocisteina, questa riduzione non comporta una riduzione del rischio cardiovascolare o di tromboembolismo venoso. Per questo motivo la supplementazione vitaminica sia in prevenzione primaria che secondaria non è attualmente raccomandata (2).

Rimangono dei dubbi nella popolazione con valori di omocisteina superiori a 45 µmol/L per la mancanza di dati solidi su cui basare le scelte.

La supplementazione deve invece essere eseguita in caso di deficit vitaminici significativi che principalmente sono da imputare a ridotto introito alimentare o ad alterato assorbimento intestinale.

Common Causes of B Vitamins Deficiency	Atrophic gastritis (achlorhydria), alcohol use, medications (metformin, methotrexate, niacin), chronic conditions (T2DM, CKD, hypothyroidism).
Mechanism of Action	B vitamins (folic acid, B12, B6) lower plasma homocysteine (Hcy), a known marker of cardiovascular risk.
Framingham Study	Linked low B vitamin levels to hyperhomocysteinemia (HHcy), which correlates with increased CVD risk.
Positive Findings	↓ Stroke risk in meta-analysis ↓ Carotid intima–media thickness (one trial) Association between HHcy and subclinical atherosclerosis [92]
Negative Findings (RCTs)	VITATOPS: No benefit in stroke/TIA prevention CHAOS-2: No effect on CAD events NORVIT: No MI/stroke reduction HOPE-2: No effect on CVD death; ↑ unstable angina hospitalizations
Potential Explanations	Inadequate dosing or trial duration Confounding from standard secondary prevention therapy (aspirin, statins, etc.) [92]
Current Guidelines (AHA)	Do not recommend routine homocysteine screening or B-vitamin supplementation for cardiovascular prevention [53].
Alternative Hypothesis	Homocysteine may be an "innocent bystander" rather than a causative agent in CVD [90].
Independent Risk Factors	AdoHcy and Hcy-thiolactone not affected by B-vitamin supplementation; may contribute to CVD independently [22].

J. Cardiovasc. Dev. Dis. **2025**, 12, 383

Homocysteine is a sulfur-containing intermediate product in the normal metabolism of methionine, an essential amino acid. Folic acid, vitamin B12, and vitamin B6 deficiencies and reduced enzyme activities inhibit the breakdown of homocysteine, thus increasing the intracellular homocysteine concentration. Numerous retrospective and prospective studies have consistently found an independent relationship between mild hyperhomocysteinemia and cardiovascular disease or all-cause mortality. Starting at a plasma homocysteine concentration of approximately 10 micromol/l, the risk increase follows a linear dose-response relationship with no specific threshold level. Hyperhomocysteinemia as an independent risk factor for cardiovascular disease is thought to be responsible for about 10% of total risk. Elevated plasma homocysteine levels (>12 micromol/l; moderate hyperhomocysteinemia) are considered cytotoxic and are found in 5 to 10% of the general population and in up to 40% of patients with vascular disease. Additional risk factors (smoking, arterial hypertension, diabetes, and hyperlipidemia) may additively or, by interacting with homocysteine, synergistically (and hence over-proportionally) increase overall risk. Hyperhomocysteinemia is associated with alterations in vascular morphology, loss of endothelial anti-thrombotic function, and induction of a procoagulant environment. Most known forms of damage or injury are due to homocysteine-mediated oxidative stress.

An adequate intake of at least 400 microg of folate per day

Meccanismi patogenetici

- HHcy determined the increased activity of HMG-COA reductase, resulting in increased cholesterol levels
- HHcy was positively related to increased systolic and diastolic blood pressure, mainly in women. Furthermore, induced HHcy in rats resulted in increased secretion of catecholamines that produced brain and cardiovascular systems damages
- increased vascular smooth muscle cell proliferation, increased collagen synthesis, and arterial wall elastic deterioration.
- Inflammation is mediated by NF-kB pathway activation in smooth muscle cells, resulting in increased CRP synthesis

- I metaboliti: N-Hcy-proteins are responsible for pro-immunogenic, pro-amyloidogenic, pro-atherogenic, and pro-thrombogenic properties.
- Hcy metabolites are involved in endothelium damage, as studied in human umbilical vein endothelial cells (HUVECs). In these cell cultures, a dysregulation of the mTOR pathway (which plays an important role in vascular physiology) and autophagy was observed, resulting in endothelial dysfunction
- urinary homocysteine (uHcy)-thiolactone correlated with fibrin clot lysis time (CLT) and elevated CLT was associated with worse prognosis. Furthermore, these metabolites cause a dysregulation of proteins involved in the coagulation pathway with the formation of N-Hcy-fibrinogen which has prothrombotic properties. Indeed, N-Hcy-fibrin clots, derived from N-Hcy-fibrinogen, are lysed slower by plasminogen because of its dysfunctional activation [22]. Thrombosis is also favored by higher levels of B-thromboglobulin and factor VIIc
- HHcy also results in arterial stiffness, as a consequence of oxidative endothelial cell stress and reduced nitric oxide synthesis, associated with increased blood pressure in vitro and in animal studies

Treatment for Stroke Patients with other Specific Conditions

Aortic Arch Atheroma

Patent Foramen Ovale

Hyperhomocysteinemia

Hypercoagulable States

Antiphospholipid Antibodies

Sickle Cell Disease

Pregnancy and Breast Feeding

Homocysteinemia Recommendations

2014 Recommendation	Revisions (2011)
Routine screening for hyperhomocysteinemia among patients with a recent ischemic stroke or TIA is not indicated. (Class III, LOE C)	New Recommendation

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AGENDA

- Perché si parla di omocisteina
- Metabolismo dell'omocisteina

- Marker di rischio cardiovascolare e trombotico
- Controversie sul ruolo causale

- Evidenze da studi di supplementazione
- Raccomandazioni dalle linee guida sulle indicazioni al dosaggio dell'omocisteinemia come metodica di screening: quando e' indicato?

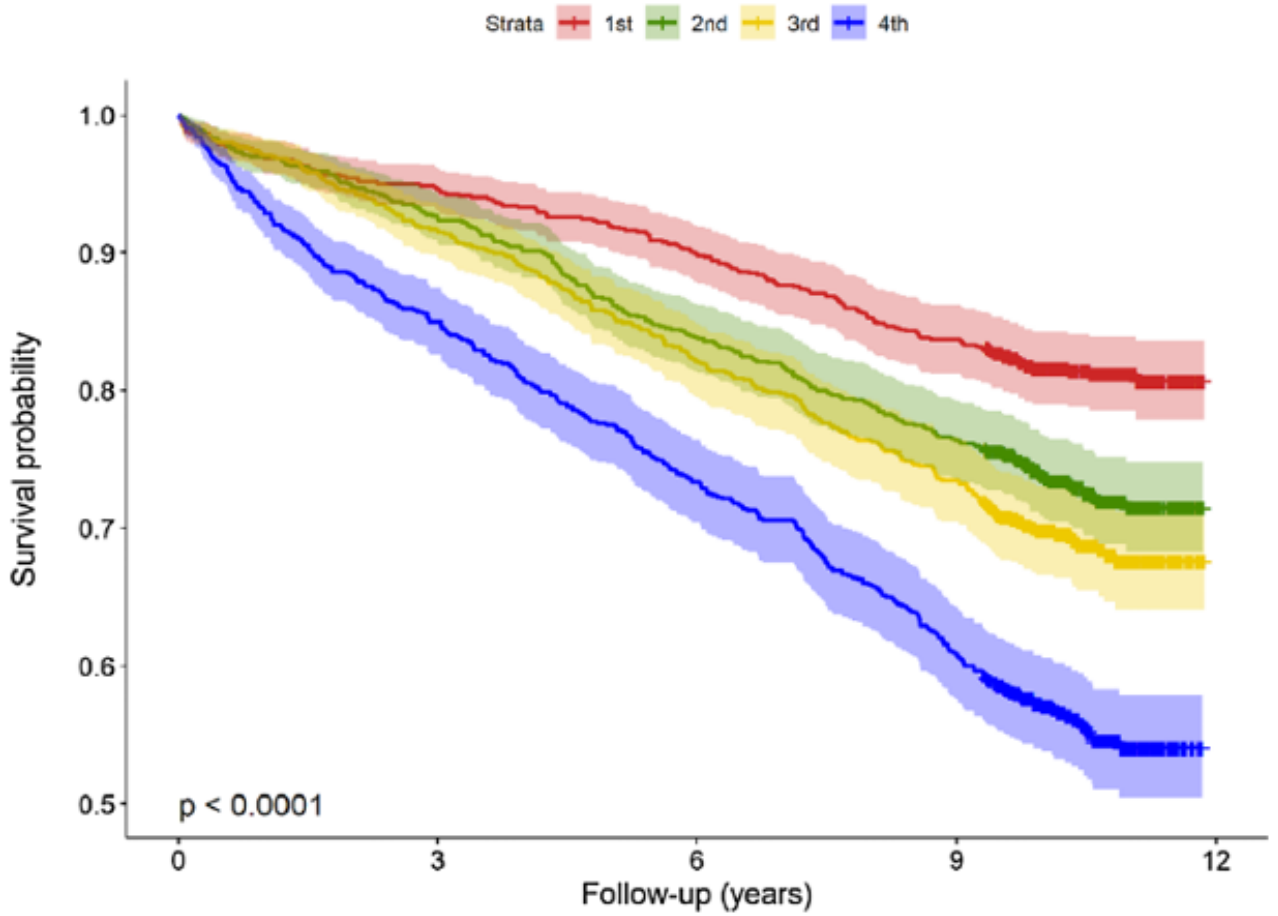


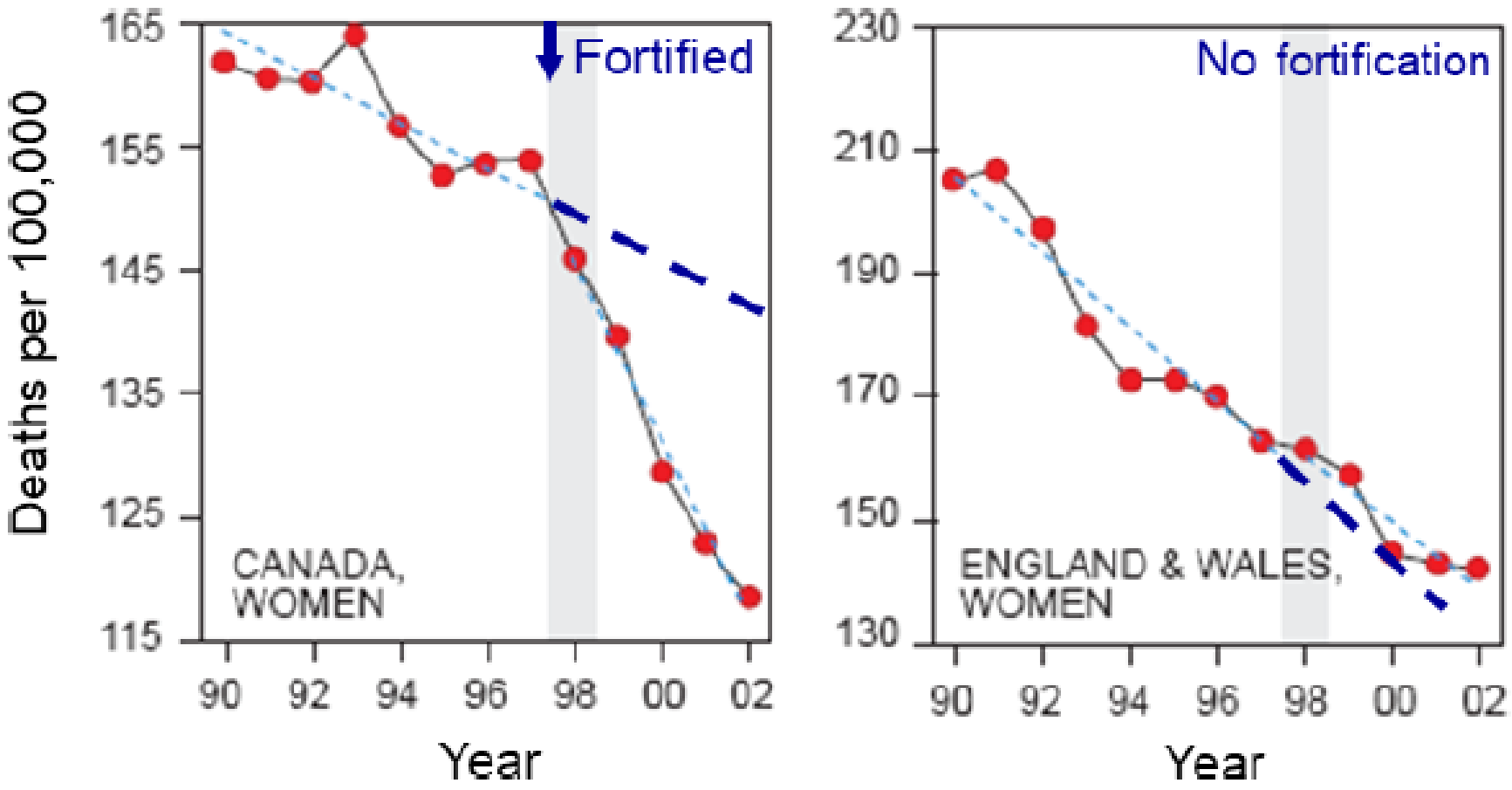
Fig. 1 *Kaplan–Meier plots showing survival probability according to quartiles of tHcy in a cohort of 2,968 CVD patients. Quartiles shown are as follows: 1st, red; 2nd, green; 3rd, yellow; and 4th, blue. The 4th quartile was tHcy > 15.6 μmol/L. From Pusceddu et al. (fig. 1)[16].*

Pusceddu et al. Eur J Nutr2020; 59:1399-411

DACH-LIGA Homocystein (German, Austrian and Swiss Homocysteine Society): Consensus Paper on the Rational Clinical Use of Homocysteine, Folic Acid and B-Vitamins in Cardiovascular and Thrombotic Diseases: Guidelines and Recommendations

O. Stanger, W. Herrmann, K. Pietrzik, B. Fowler, J. Geisel, J. Dierkes and M. Weger

homocysteine assay. Except where manifestations are already present, intervention, if any, should be guided by the severity of hyperhomocysteinemia. Consistent with other working parties and consensus groups, we recommend a target plasma homocysteine level of <10 μmol/l. Based on various calculation models, reduction of elevated plasma homocysteine concentrations may theoretically prevent up to 25% of cardiovascular events. Supplementation is inexpensive, potentially effective, and devoid of adverse effects and, therefore, has an exceptionally favorable benefit/risk ratio. The results of ongoing randomized controlled intervention trials must be available before screening for, and treatment of, hyperhomocysteinemia can be recommended for the apparently healthy general population.



J Int Med. 2021; 290: 826-854