Folate and prevention of neural tube defects: Tracking red blood cell concentrations will help guide policy decisions about fortification

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Outline

- Background to folate supplementation
- Optimum red blood cell (RBC) folate concentrations
- Possible benefits of folate supplementation
- Possible hazards of folate supplementation

Background

- Observational studies of pregnant women have shown that intake and plasma concentrations of folate are inversely associated with neural tube defects (NTD).

- Randomised trials have confirmed a protective effect of folate.

- Folate is now routinely recommended as a supplement before and during pregnancy.

Folic acid fortification

- Population-wide folate fortification of flour for prevention of NTD has been mandatory since 1998 in North America.
- It is mandatory in some other countries including:
  - Chile, Argentina, Brazil, South Africa and Australia
  - But not in others (such as New Zealand), because of concerns about adverse effects
  - Asian populations such as China have low plasma folate concentrations

Optimum RBC levels to prevent NTDs

Aim:

- To determine the optimal red blood cell (RBC) folate concentration required to prevent NTD

- Data: Two Chinese studies

  (i) Prospective community intervention study of folic acid to prevent neural tube defects

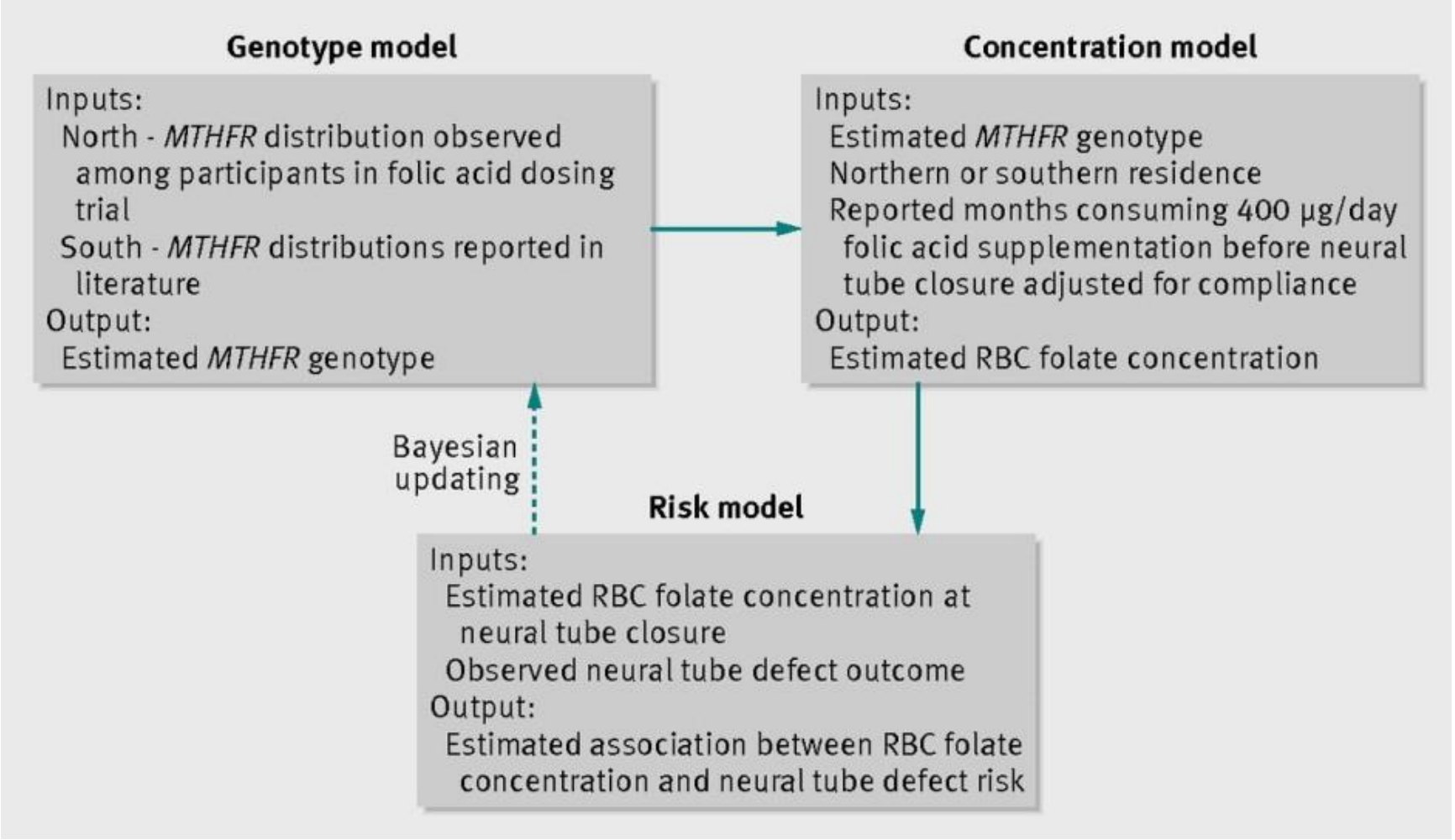
  (ii)Population-based randomized trial to evaluate the effect of folic acid on RBC folate concentrations in women of reproductive age

Crider et al. BMJ, 2014; Commentary Clarke and Bennett, BMJ, 2014

Optimum RBC folate level: Methods

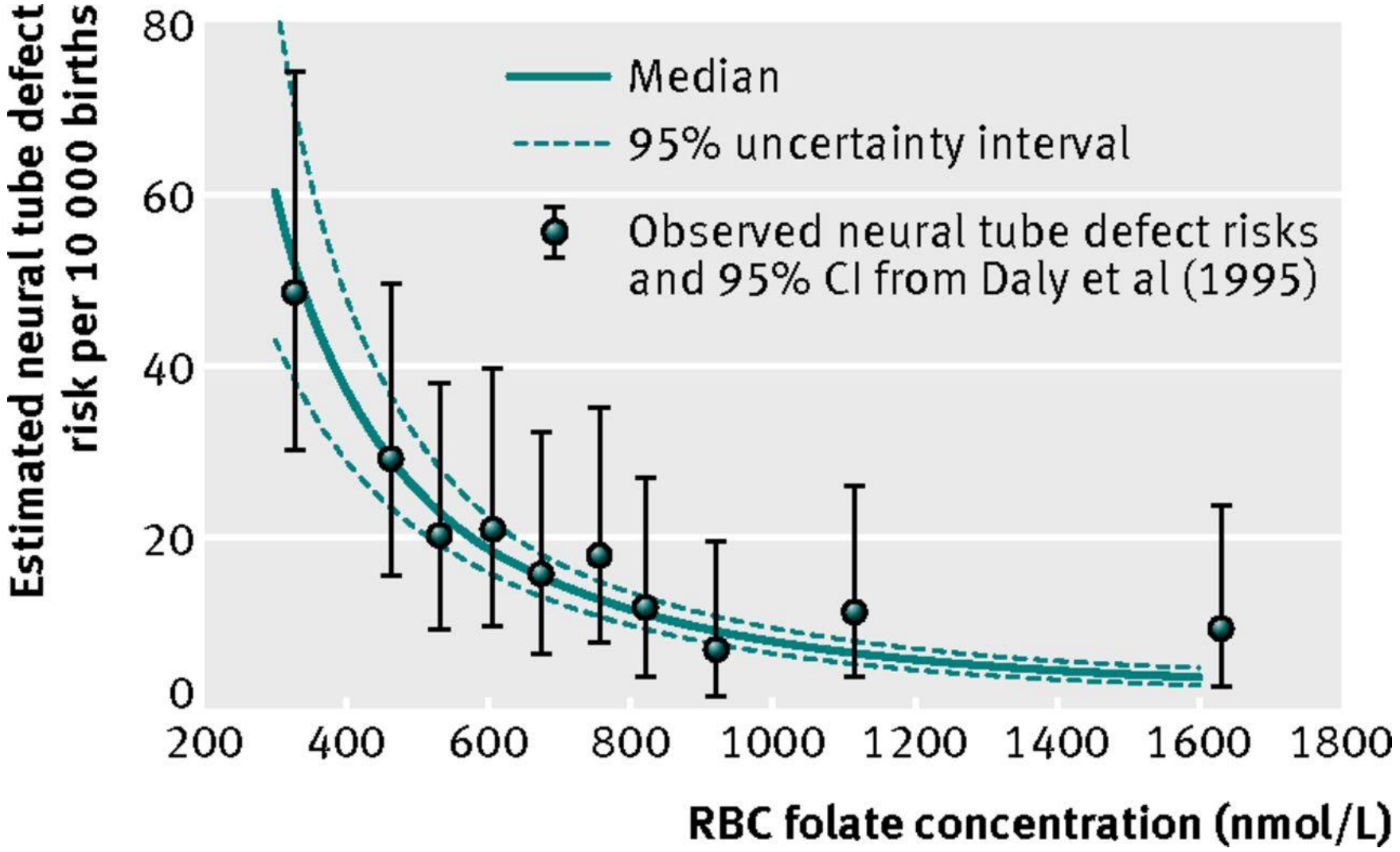
- Genetic variants in the methylene-tetrahydrofolate reductase (*MTHFR)* gene C677T (rs1801133) are associated with low folate and higher risks of NTD.
- The community trial was conducted in northern and southern regions of China, but did not measure rs1801133 polymorphism.
- The randomized controlled trial had serial data on RBC folate levels for subjects consuming 400μg of folic acid or placebo as well as the rs1801133 polymorphism.
- This enabled the joint modelling of RBC folate levels and NTD risk while taking account of rs1801133.

Statistical analyses



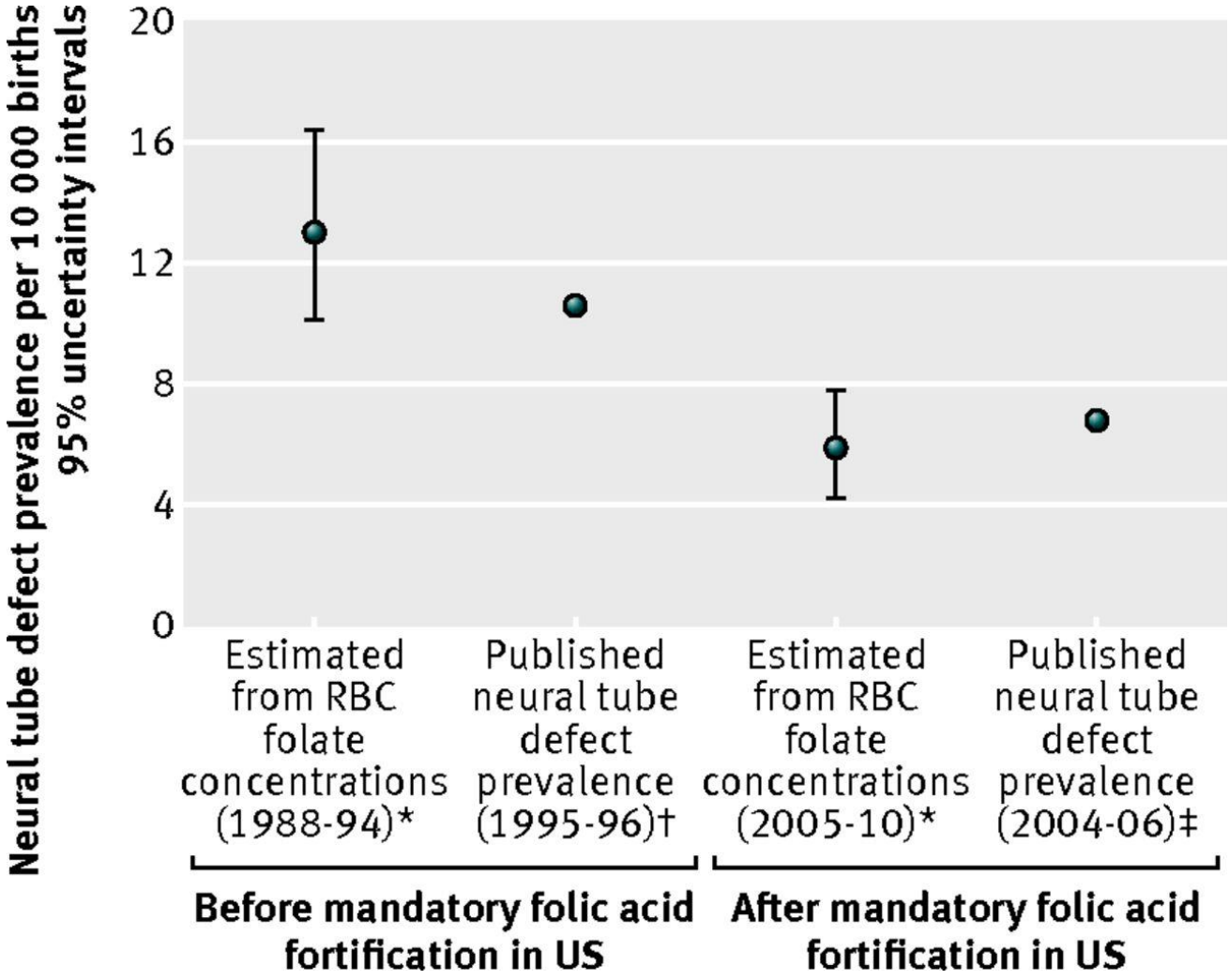
Source: Crider et al. BMJ *2014; 349 doi: http://dx.doi.org/10.1136/bmj.g4554 (Published 29 July 2014)*

NTD risk in China by RBC folate concentration (nmol/L) vs observed NTD risk in Ireland by RBC folate concentrations (Daly et al: 1995).



Crider K S et al. BMJ 2014;349:bmj.g4554

Observed vs predicted NTD risk in USA using RBC folate modelling before and after folic acid fortification



Crider K S et al. BMJ 2014;349:bmj.g4554

Recommendations

- The predicted NTD risk estimates were concordant with the observed risk estimates for NTD in the USA for both pre- and post-supplementation of foods with folic acid.
- Results indicated a threshold of 1000 nmol/L was the optimum RBC concentration that was associated with the lowest risk of NTD.
- RBC folate measurements can be used to identify potential subpopulations at increased risk of NTD.

Other claims of benefits of folate supplementation

Improvement in stroke mortality in Canada and United States, 1990 to 2002 Yang et al (Circulation 2006)

"The improvement in stroke mortality observed after folic acid fortification in the United States and Canada but not in England and Wales is consistent with the hypothesis that folic acid fortification helps to reduce deaths from stroke"

Associated Press: *"Adding the vitamin folate to flour ... appears to have a striking effect against cardiovascular disease, preventing an estimated 48,000 [US] deaths a year from strokes and heart attacks"*

B-Vitamin Treatment Trialists' (BVTT) Collaboration Meta-analysis of folic acid trials

- Data were available for 11 trials involving 52,260 participants with a prior history of vascular disease
  - (6 in non-fortified and 5 in fortified populations)

- All but one trial provided individual data, but published results were only available for the FAVORIT trial (n=4110).

Arch Int Med 2010;170:1622-31

Characteristics of included trials

	Number randomised	Prior disease	Duration of treatment	Daily dose of B-vitamins		
				Folic acid	B12	B6
CHAOS-2	1882	CHD	2.0	5.0		
HOST	2056	Renal	3.2	40.0	2.0	100
SU.FOL.OM3	2501	CVD	4.7	0.6	0.0	3
WENBIT	3090	CHD	3.2	0.8	0.4	40
VISP	3680	Stroke	2.0	2.5	0.4	25
NORVIT	3749	CHD	3.4	0.8	0.4	40
FAVORIT	4110	Renal	4.0	5.0	1.0	50
WAFACS	5442	CVD	7.3	2.5	1.0	50
HOPE-2	5522	CVD	5.0	2.5	1.0	50
VITATOPS	8164	Stroke	3.4	2.0	0.5	25
SEARCH	12064	CHD	7.0	2.0	1.0	
TOTAL	**52260**		**4.9***			

CHD: Coronary heart disease
CVD: Cardiovascular disease
*** - does not include FAVORIT**

Characteristics of participants with prior vascular disease (11 trials; n=52,260)

Prior disease, age and sex

Prior CHD	80%
Prior Stroke	16%
Age (years)	65
Male,%	67%

Folic acid fortification

Non-fortified population	6 trials
Fortified population	5 trials

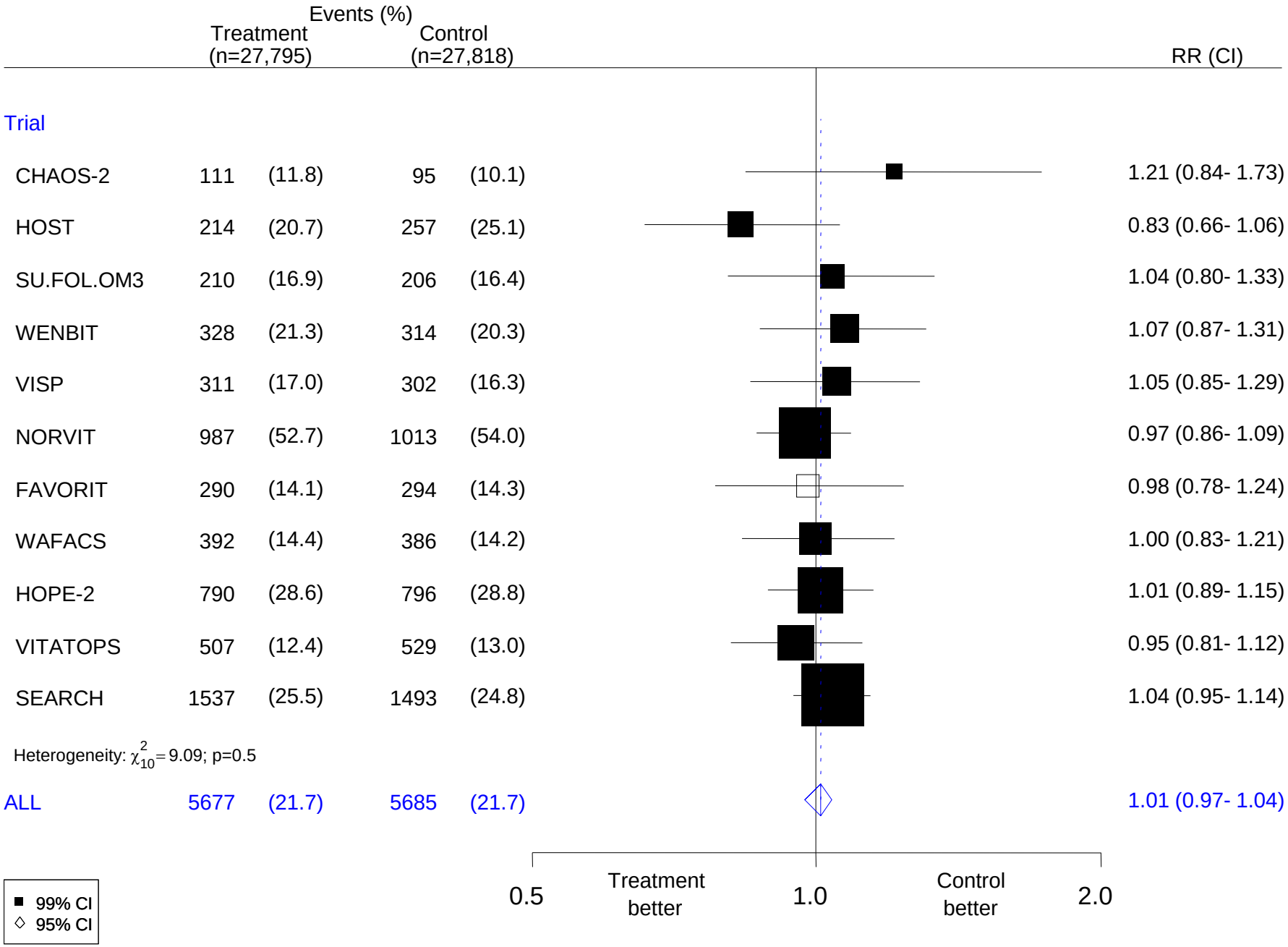
Median folate and homocysteine levels before and after B-vitamin therapy

	Non-fortified (n=22,371)		Fortified (15,114)	
	Treated	Control	Treated	Control
Folate				
Baseline (nmol/L)	12.2	12.1	22.4	22.3
Follow-up	53.5	9.8	69.2	22.3
Homocysteine				
Baseline (µmol/L)	12.2	12.2	13.2	13.2
Follow-up	8.7	11.8	11.0	13.5
		27%		20%

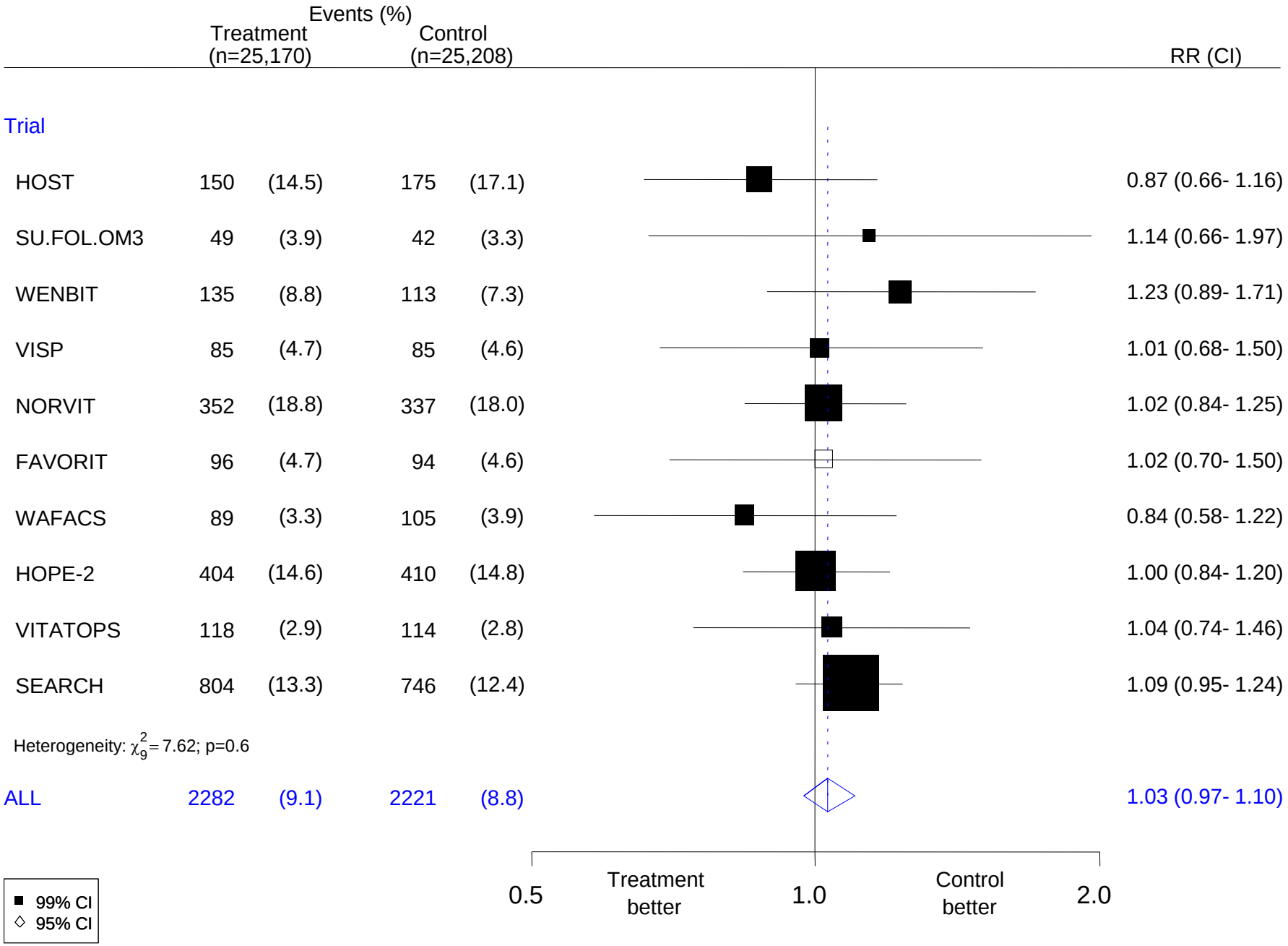
BVTT: Primary outcomes

- Effects of lowering homocysteine on risk of :
  - **Major Vascular Events** (MVE)
    (*MCE, stroke, or coronary or non-coronary revascularisation)*
  - **Major Coronary Events** (MCE)
    (Non-fatal MI or coronary death)
  - **Stroke**
    (Fatal or non-fatal stroke of any type, excl. TIA)
  - **Mortality**
  - *(Vascular and non-vascular mortality)*
- during scheduled treatment period

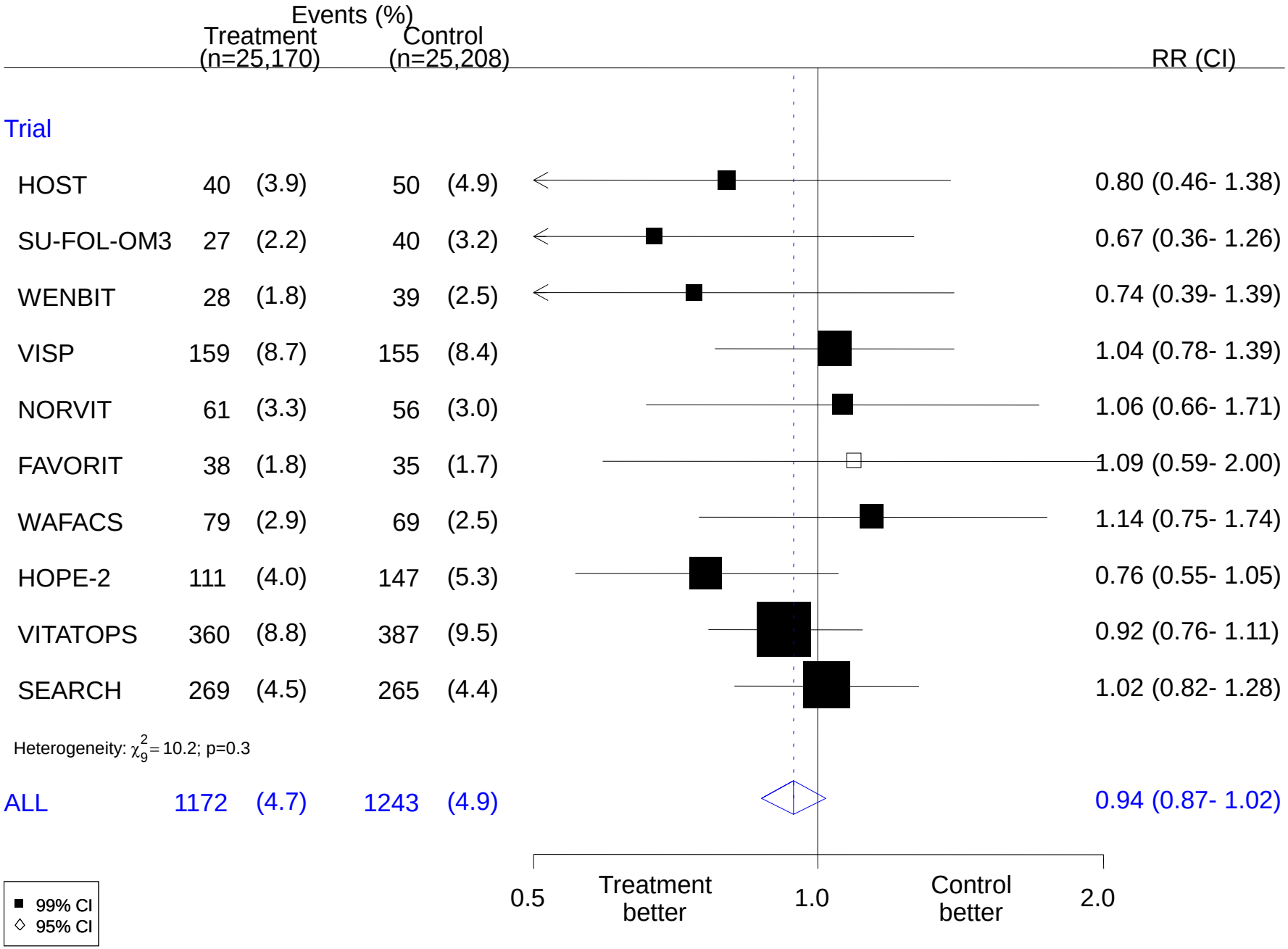
Effects of folic acid on MAJOR VASCULAR EVENTS, by trial



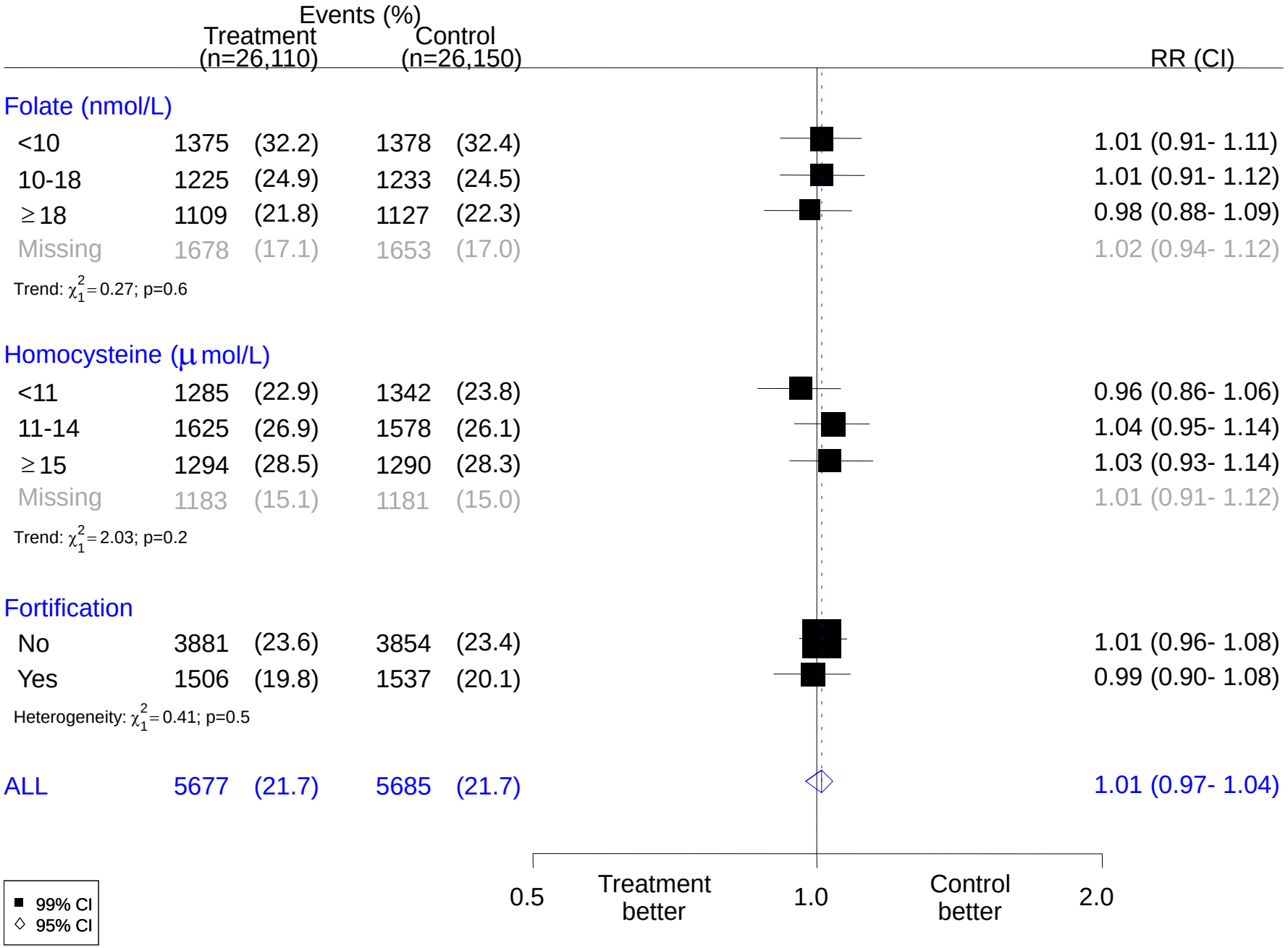
Effects of folic acid on MAJOR CORONARY EVENTS, by trial



Effects of folic acid on STROKE, by trial



Effects of folic acid on MAJOR VASCULAR EVENTS, by vitamin status



Evidence for adverse effects of folate supplementation

Folate and risk of CANCER

- High folate is associated with lower risk of cancer (especially colorectal) in observational studies.

- A small trial of **folic acid** supplements versus control in patients with colorectal adenomas (n=1021) reported:
  - 30 vs 13 recurrent adenomas; and
  - 54 vs 32 non-colorectal cancers

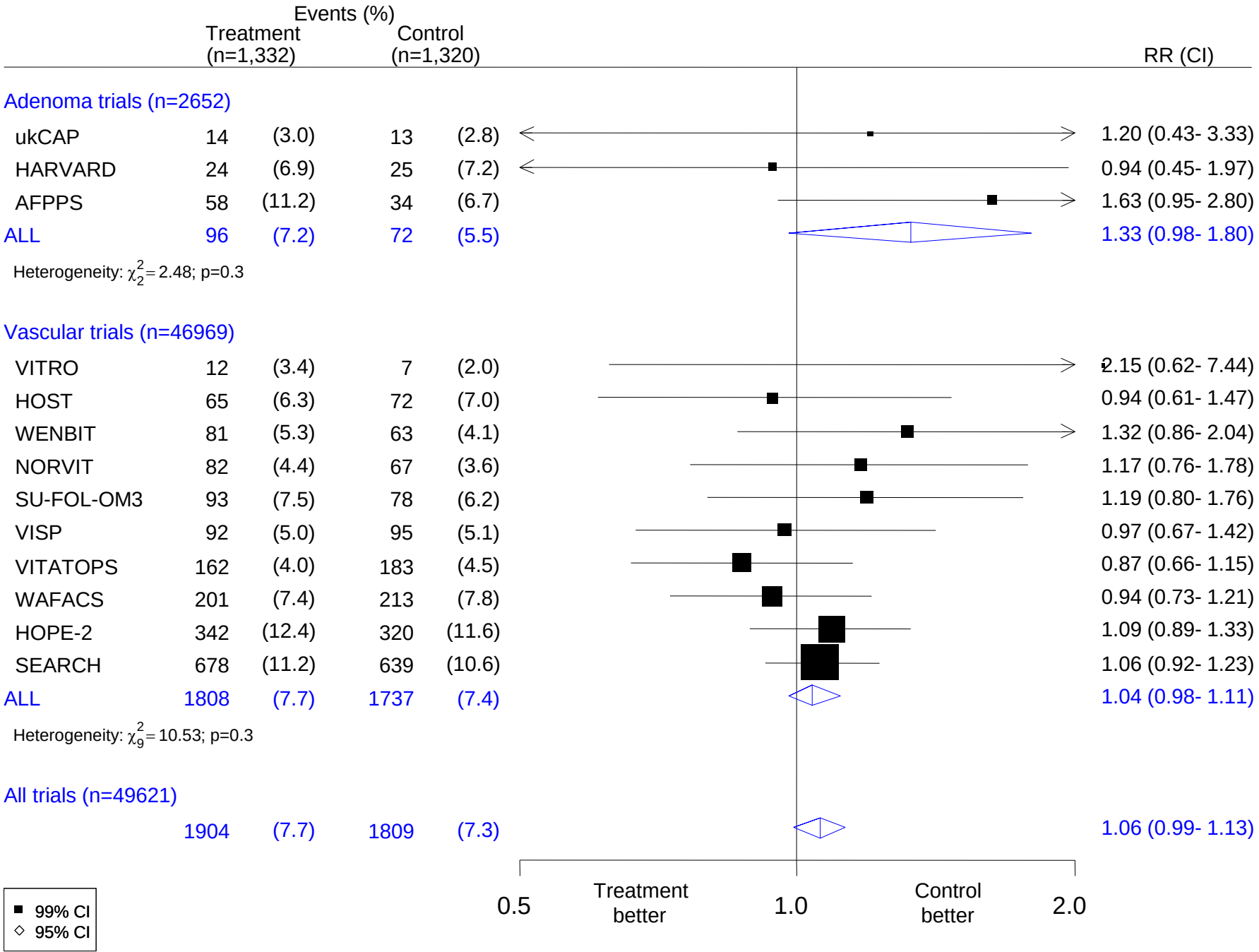
- Cancer trends in USA in the late 1990s indicated a transient increase in colorectal cancer incidence:

"Folic acid supplementation might prevent cancer, but enhance the growth of established cancers"

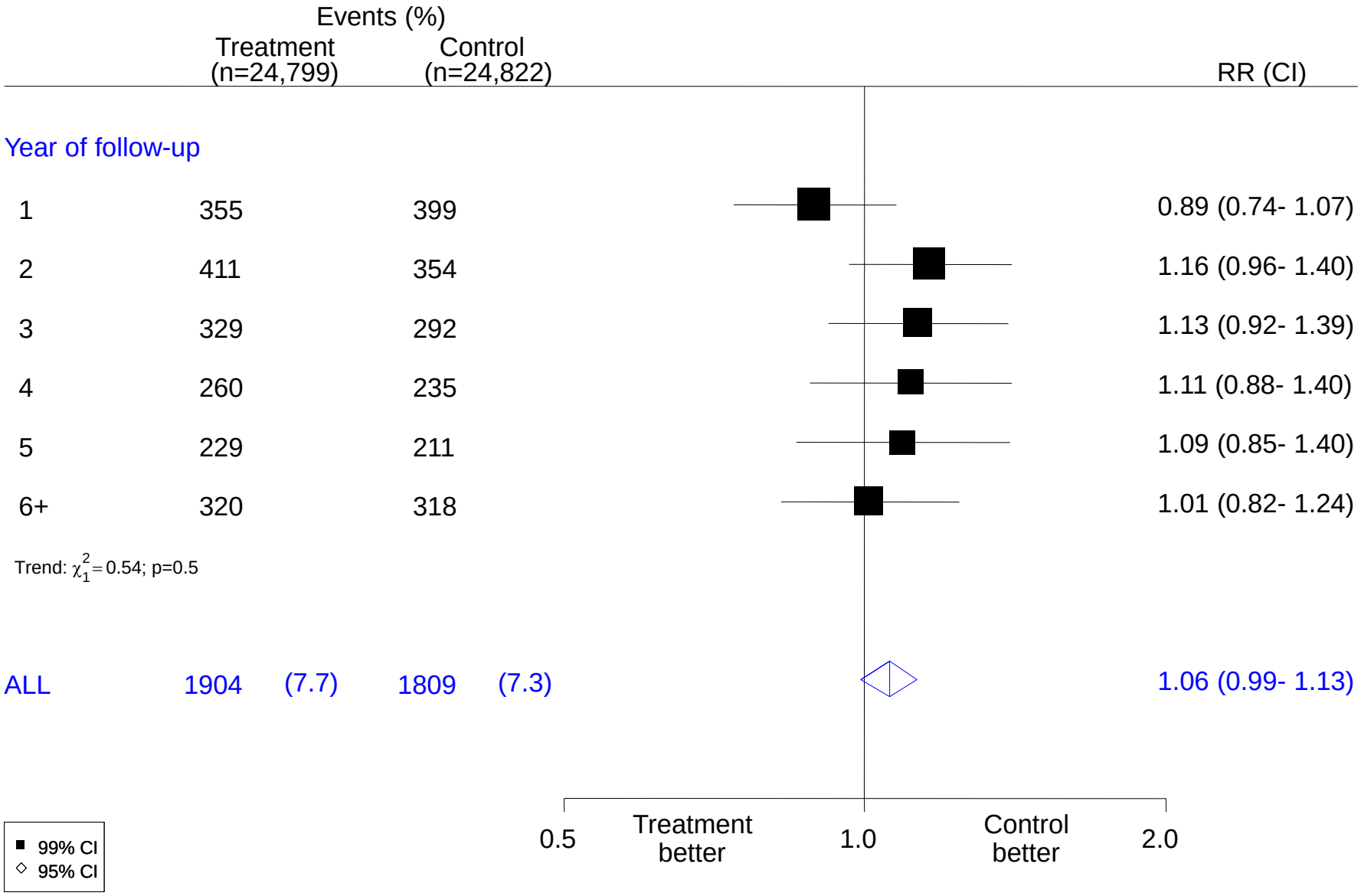
B-Vitamin Treatment Trialists' Collaboration
Effects of folic acid on cancer

- Meta-analysis of 13 trials involving ~50,000 individuals
  - ~ 3 trials of folic acid in people with colorectal adenoma
  - ~ 10 trials of folic acid in people with vascular disease
- Analysis involved comparisons of effect of folic acid on any cancer overall or by duration of treatment.
- Analysis involved comparisons of the effect of folic acid on cancer at specific sites including colon, lung and prostate cancer.

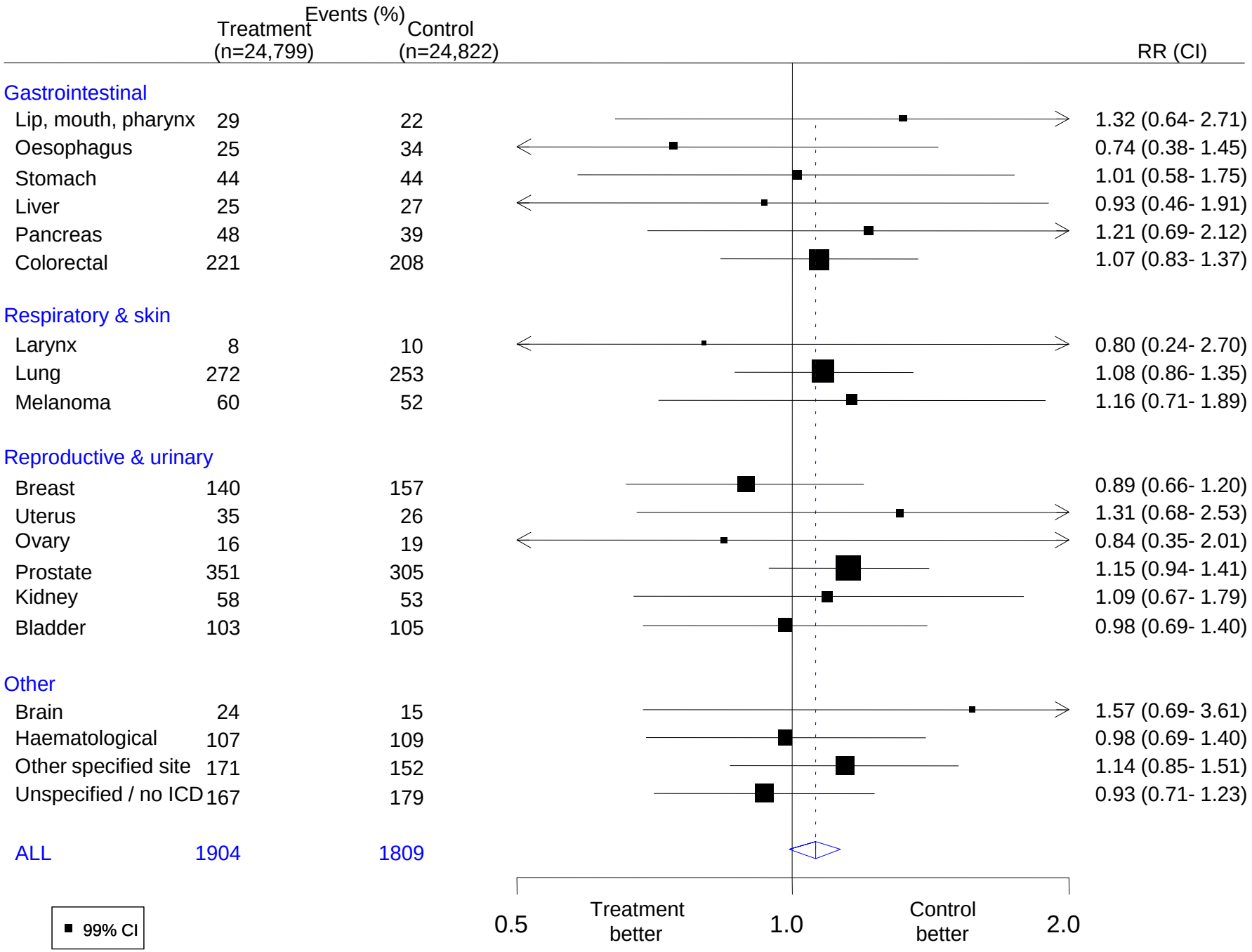
Effects of folic acid on CANCER INCIDENCE, by prior disease



Effects of folic acid on CANCER INCIDENCE, by year of follow-up



Effects of folic acid on CANCER INCIDENCE, by type



Effects of folic acid on cancer

- Folic acid had no material effect on any cancer in people with prior colorectal adenoma or prior CVD.
- There was no heterogeneity in the effect of folic acid on any cancer for up to 7 years or by dose from 0.5 to 40 mg.
- Folic acid had no significant effect on cancer at any site, including colon, prostate or lung cancer.
- Most trials will continue to monitor cancer incidence to exclude any longer term effects on cancer.

Summary

- A threshold of 1000 nmol/L was the optimum RBC concentration that was associated with the lowest risk of NTD.
- Randomized trials of folate show no evidence of benefit for prevention of cardiovascular disease.
- Randomized trials show no evidence of hazard for colorectal or prostate or other cancers for folate supplementation.
- But, dietary fortification involves doses of folic acid that are an order of magnitude lower than the doses used in the RCTs.

Acknowledgements

B-Vitamin Treatment Trialists' (BVTT) Secretariat

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Collaborators in trials assessing effects on vascular events

CHAOS-2: F Mir, M Brown **HOPE-2**: E Lonn, S Yusuf;

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VISP: JD Spence; J Toole, **WAFACS**: JE Manson, R Glynn, F Grodstein, S Zhang, F Grodstein; **WENBIT**: O Nygard, M Ebbing, JE Nordrehaug, DWT Nilsen, PM Ueland, SE Vollset.

Collaborators in additional trials assessing effects on cancer

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