



Institute of Food Research

THE IMPORTANCE OF SUFFICIENT FOLATE

**Paul Finglas, Senior Research Scientist
Nutrition Division**

Outline

- Folates and disease risk
- NTDs - current dietary recommendations and fortification strategies
- Folate bioavailability – recent results from EU folate project (FolateuncHealth)
- Homocysteine and vascular disease
- Results from homocysteine-lowering study from EU folate project (FolateFuncHealth)
- Further research questions

Folates and Disease Risk

- Protects against birth defects (NTDs)
- Lowers plasma Hcy – risk factor for vascular disease & stroke, cognitive function (?) & dementia (?)
- Low body stores - ?risk of some cancers
- Adequate status + MTHFR TT:
?colorectal/breast cancers – mechanisms?
- Current requirements based on absence of deficiency not optimal health to reduce disease risk?

Neural Tube Defects (NTDs)

- NTDs (Spina bifida, anencephaly)
- Clearly-established reduction in risk with 0.4-4mg/d PGA
 - $<150\text{mg/L}$ RCF = x7 risk compared to $>400\text{ mg/L}$ RCF (Daly et al, 1995, JAMA 274, 1698-1702)
- Periconceptual ($<28\text{d}$)
- Causes:
 - genetic (MTHFR: C677T & A1298C variants)
 - environmental

Current Recommendations - NTDs

- DoH (1992): +400mg/d (occurrence) or 4-5mg/d (recurrence) – similar levels in other countries
- DoH/HEA (1995):
 - folate rich foods (50% - bioavailability?)
 - fortified foods (folic acid or 6S-5MTHF)
 - taking supplements (folic acid or 6S-5MTHF)
- USA (1999) - mandatory fortification (140ug/100g grain products) - Chile

Folic Acid Fortification

- Rate of NTDs is 6-10/10,000 births
- Proposed fortification in UK (240 $\mu\text{g}/100\text{g}$) prevent 41%
- Masking of B-12 deficiency in elderly leading irreversible neural damage
- 200,000 elderly (60y+) exposed to $>1\text{mg}/\text{d}$ (240 $\mu\text{g}/100\text{g}$ + 17% overage)

=> INCREASE IN NATURAL FOLATES FROM FOODS

Recent results from FolateFuncHealth on folate bioavailability

- Three human models used:

- Ileostomy
- Plasma/RCF responses
- Stable isotope/kinetic modelling

- Absorption of natural food folates higher (70-90%) compared to previous estimates (ca 50%)

- +400mg/d PGA = 444-571mg/d natural folate (rather than >800 mg/d)

- Also investigating MTHFR TT on folate absorption & metabolism - increased requirements?

HEALTH COSTS - CVD

- CVDs in EU >250,000 deaths (CHD & stroke)
- >28,000 coronary artery bypasses & >25,000 angioplasties (UK)
- CHD health costs >30beuros (1% spent on prevention)
- Total costs (days lost to illness & care) >100beuros
- ?25% Hcy (ca 3 μ mol/l) = ?11% risk of ischaemic heart disease & ?19% stroke (JAMA 2002, 288, 2015-22)

Homocysteine & Vascular Disease

- Risk marker or factor?

- Proposed mechanisms include:

- Impairment of functions of endothelial & vascular smooth muscle cells
- Increased coagulation
- Impaired fibrinogen synthesis

- Inhibits methyl fluxes during transmethylation of methionine

- ?SAH – inhibitor

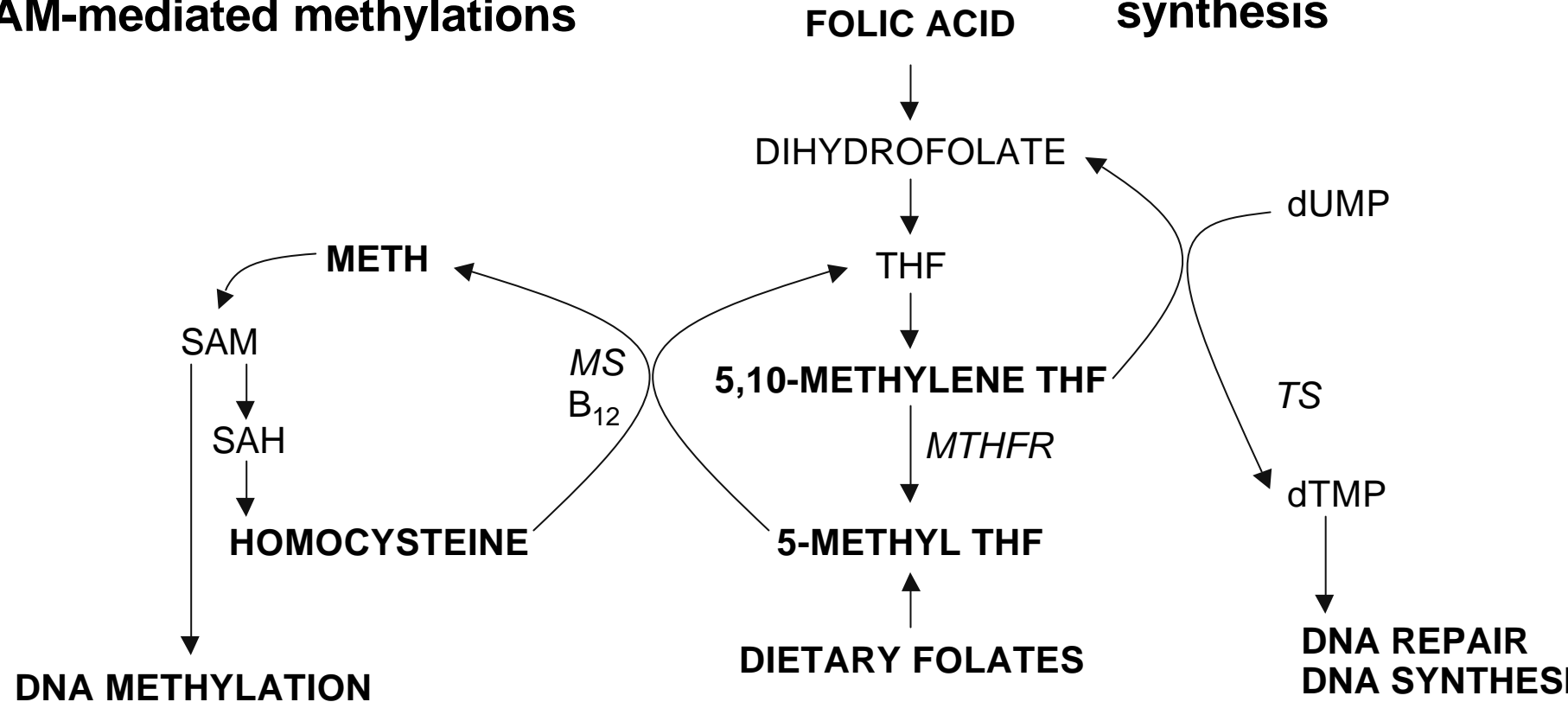
- Folate therapy reduces hyperhomocysteinaemia, restored DNA methylation & corrected gene expression (Lancet, 361, May 2003)

- Toxic action of Hcy mediated by DNA hypomethylation?

Folate Metabolism

**methionine synthesis and
SAM-mediated methylations**

**Thymidilate
synthesis**



Performed

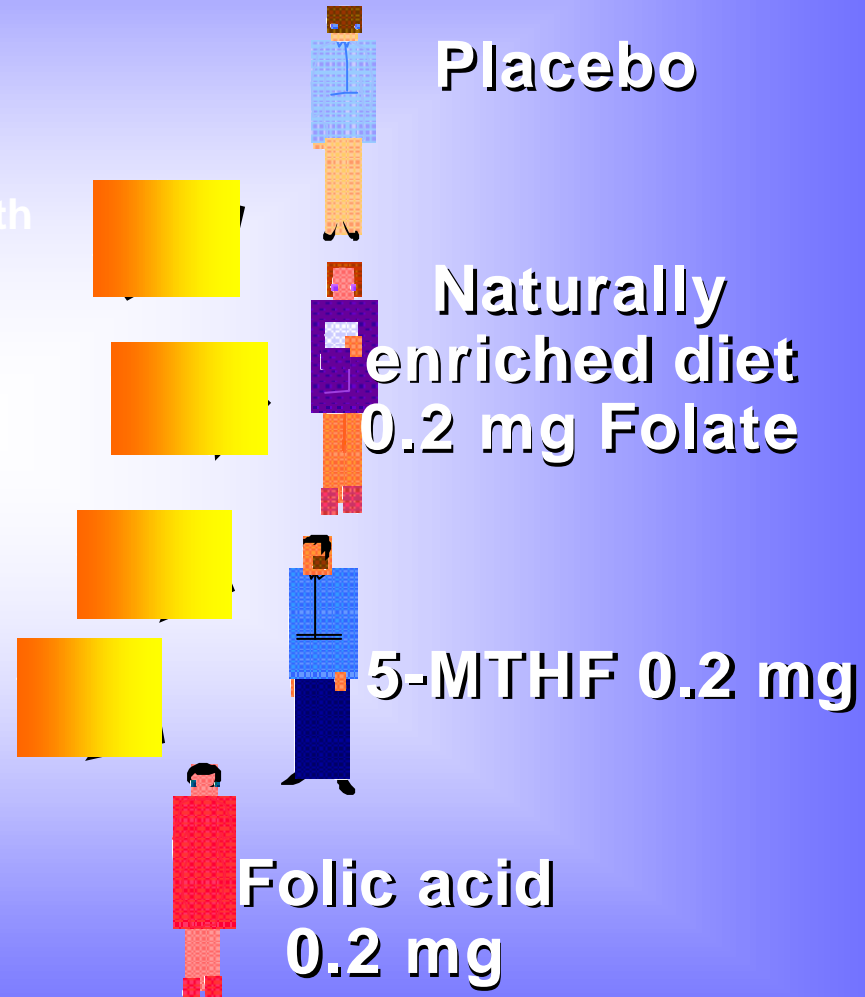


Upper 25th



241 subjects enrolled

Upper 25th percentile
selected = 310 subjects



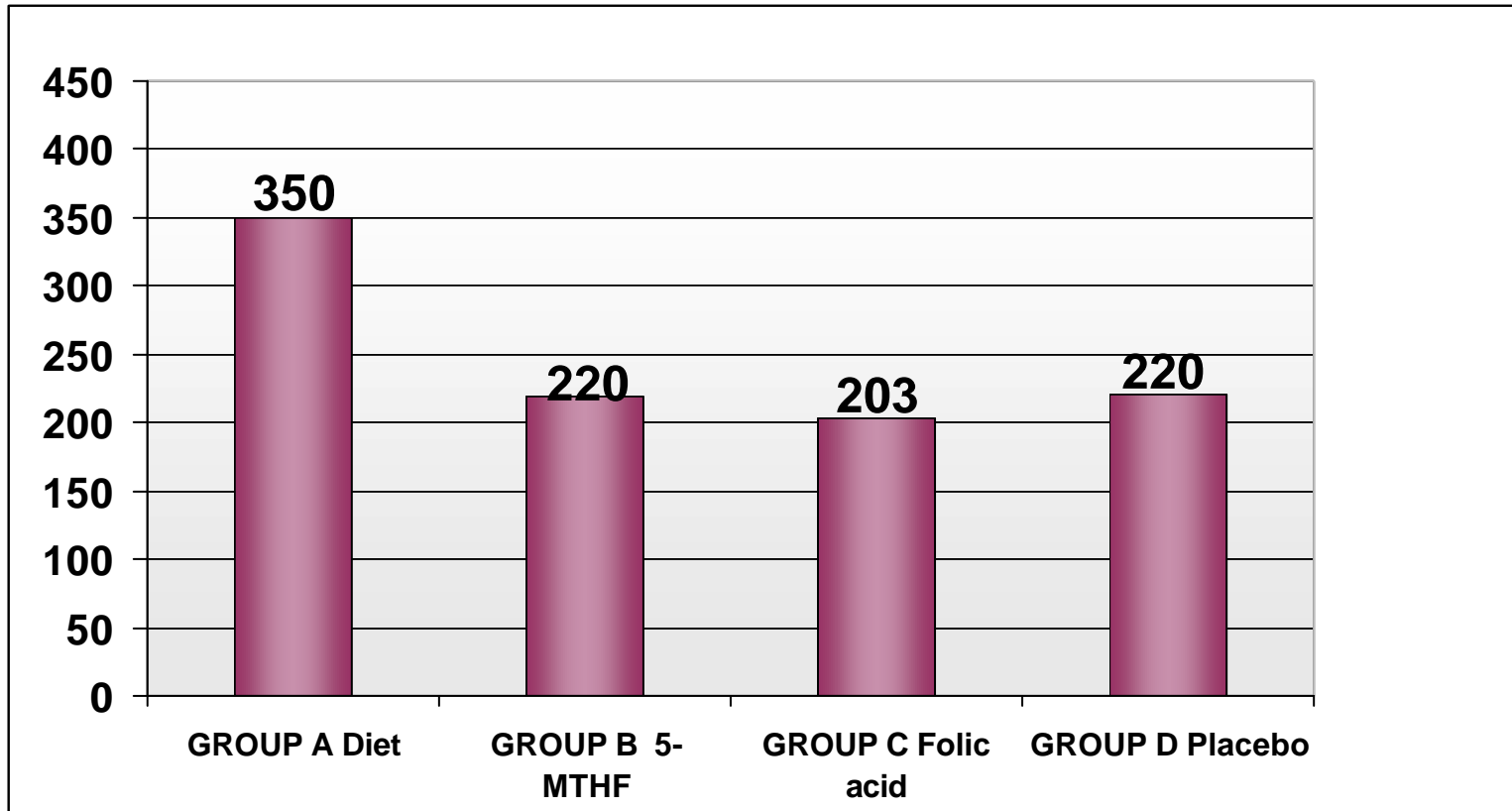
Status of Study 1 (April 2002)

MTHFR C677T
Genotype
Stratification

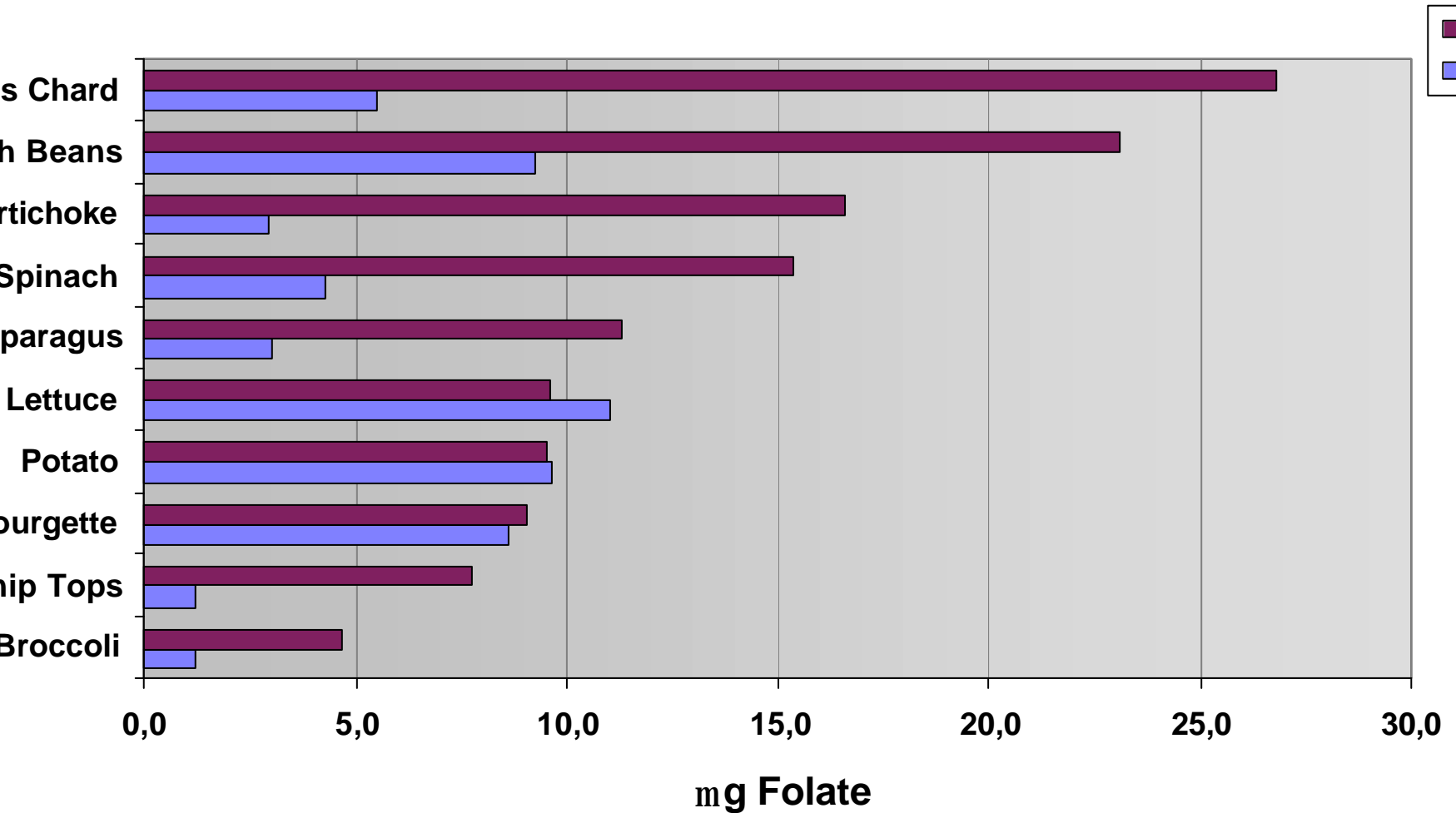


Genotype	Total	Randomized	Completed
TT	82	A = 21	8
		B = 21	10
		C = 20	10
		D = 20	10
TC	99	A = 24	12
		B = 25	14
		C = 26	15
		D = 24	15
CC	90	A = 23	14
		B = 23	13
		C = 21	12
		D = 23	12
		Totale	145

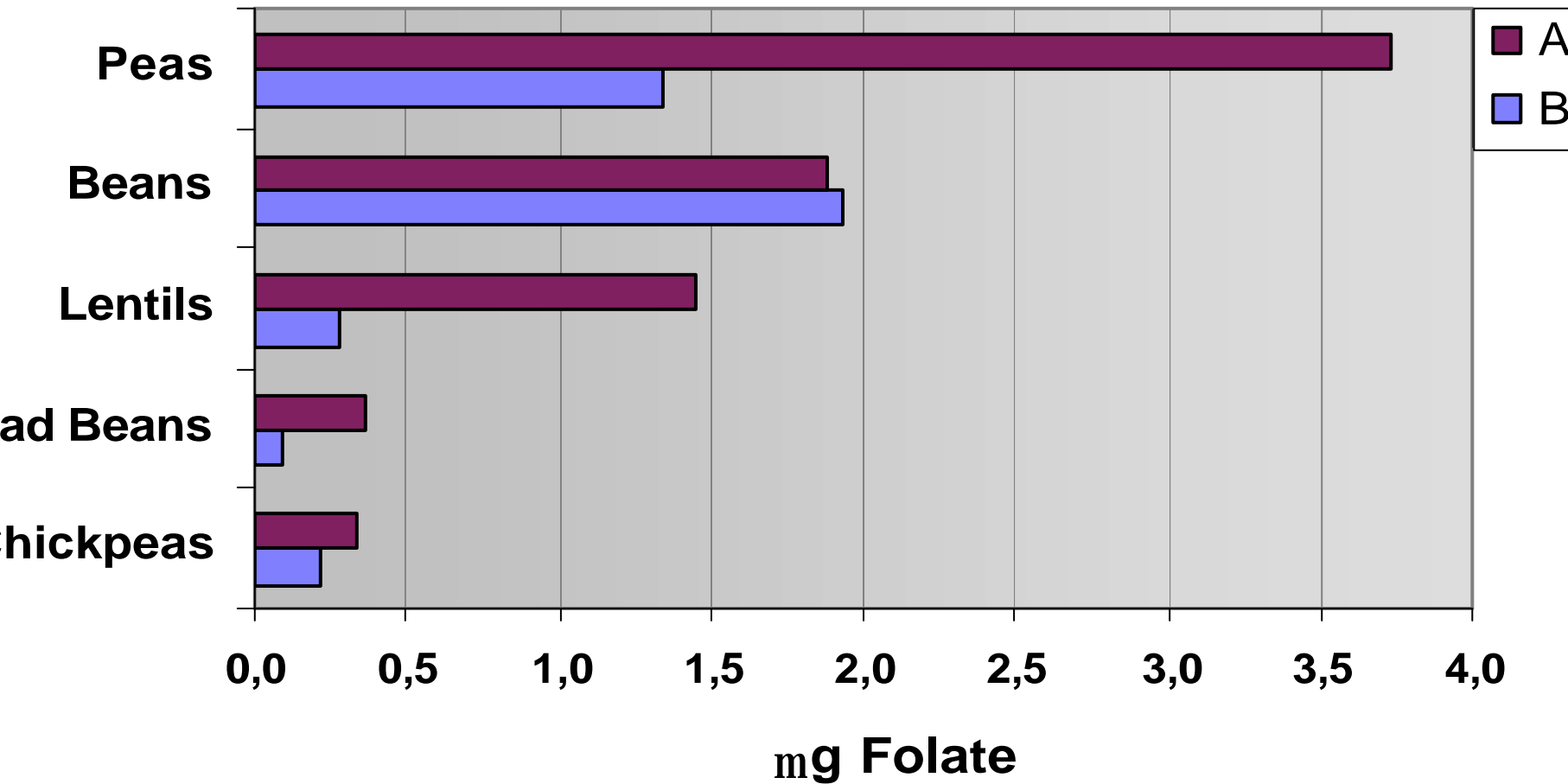
FOLATE INTAKE FROM FOOD IN THE FOUR INTERVENTION STUDIES (mg/day)



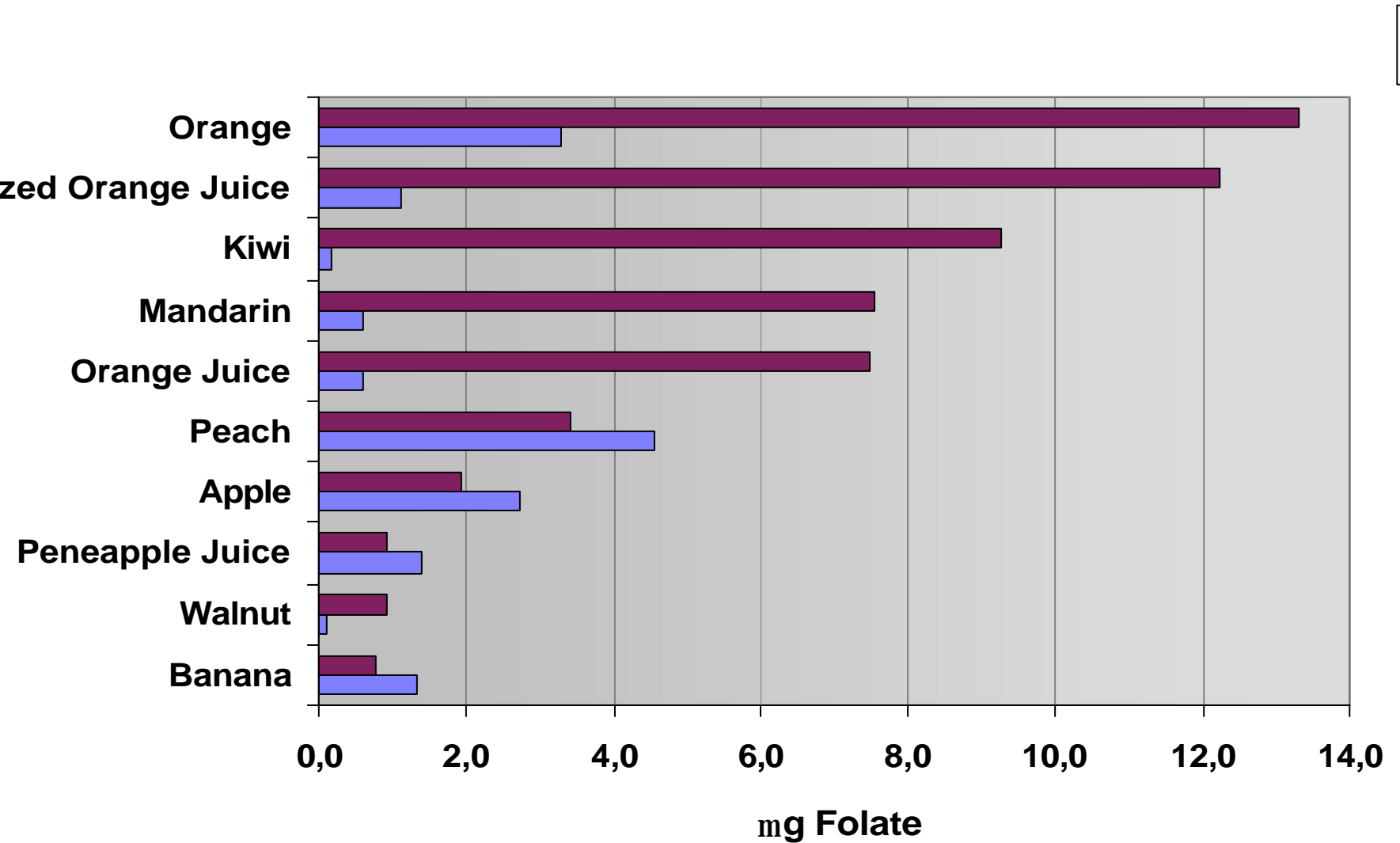
Daily folate intake from vegetables per person



Daily folate intake from legumes per person

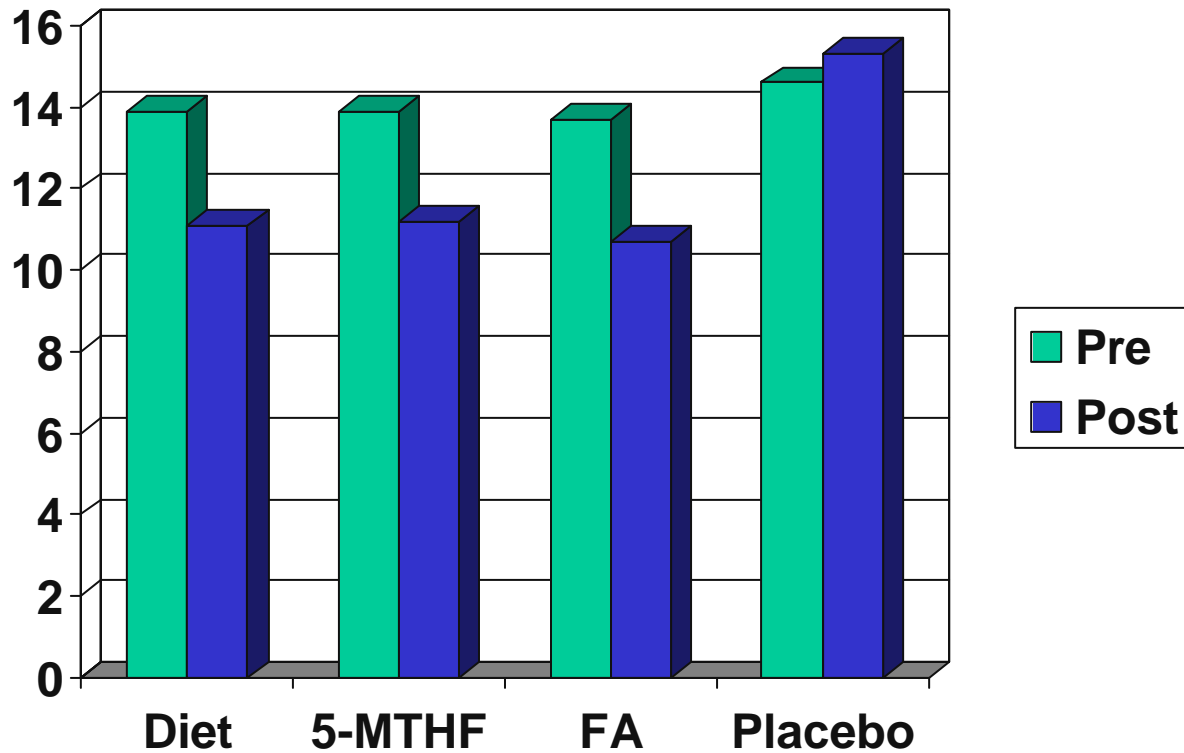


Daily folate intake from fruits per person



tHcy values pre & post intervention (by treatment group)

Geometric
Means



Changes in tHcy, geometric means (95% CI) by treatment group

Treatment	Pre	Post	Change %	P (t test)
A = Enriched Diet	13.9 (12.2 – 15.9)	11.1 (9.5 – 12.9)	- 20.1 % §	.0004
B = 5-MTHF	13.9 (12.1 – 15.9)	11.2 (9.8 – 12.8)	-19.4 % §	.0018
C = Folic Acid	13.7 (12.5 – 15.1)	10.7 (9.6 – 11.9)	-21.9 % §	.00001
D = Placebo	14.6 (12.7 – 16.8)	15.3 (13.2 – 17.7)	+ 4.8 %	_____

Conclusion on the primary outcome (tHcy)

- Treatment for 13 weeks of healthy free-living subjects with: 5-MTHF, folci acid or an enriched folate diet (all ca 0.2 mg/d)
- Have similar efficacy since we find:
 - a statistically significant decrease of the tHcy
 - a 20% decrease of the mean pre-treatment tHcy
 - an absolute benefit of 35% (NNT=3) to decrease of 25% the individual tHcy

Further Research Questions

- Absorption of natural folates may be higher – can we absorb sufficient to protect against chronic disease?
- Clinically significant reductions in plasma tHcy using folate rich diets but will dietary approach work?
- Optimal folate intakes may be higher than current recommendations - not achievable with diet alone?
- Should recommendations be raised for genetic differences in individuals (e.g. MTHFR TT in 10-20% populations)?

EUROFOODFOLATE 2004

- **Final Folate Conference (11-14 February 2004, Warsaw)**
- **Supported under EU Accompanying Measures (Food, Nutrition & Health; QLK1-CT-2002-30475)**
- **See www.ifr.bbsrc.ac.uk/folate for details**
- **Bursaries for students, researchers & SMEs**

ACKNOWLEDGEMENTS

- **Funding from EU under QLRT-1999-00576 & QLRT-2002-2740**