



Riboflavin, other dairy B vitamins and cardiovascular health

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Scope of the talk

- Importance of dairy products to B vitamin intakes
- Epidemiological evidence linking B vitamins with cardiovascular disease
- The mechanistic basis for such links



Epidemiology of milk consumption and CVD

- Ischaemic heart disease or stroke
 - 10 cohort studies
 - High degree of consistency
 - Pooled OR for highest v lowest consumers
 - IHD 0.87 (0.74-1.03)
 - Stroke 0.83 (0.77-0.90)

Elwood et al (2004)



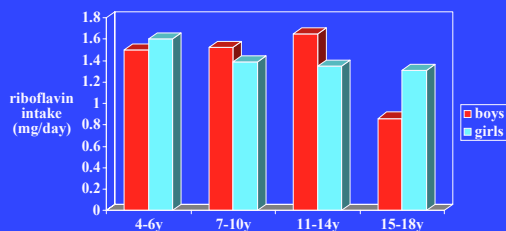
Contribution of milk and milk products to B vitamin intake

Vitamin	Preschool children (1-4y)	Children and young people (4-18y)	Adults (16-64y)	Older adults (65+y)
Thiamin (B ₁)		6	9	8
Riboflavin (B ₂)	51	35	27	34
Pyridoxine (B ₆)	25	12	12	15
Cobalamin (B ₁₂)	47	46	18	22
Folate	17	12	8	8

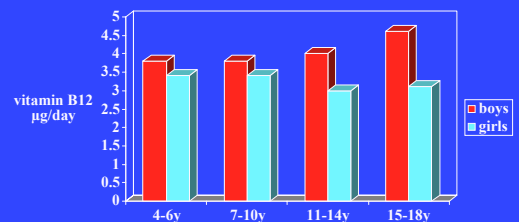
Barker (2002)



Riboflavin intakes according to age

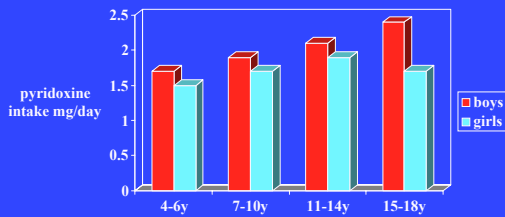


Vitamin B₁₂ intakes according to age

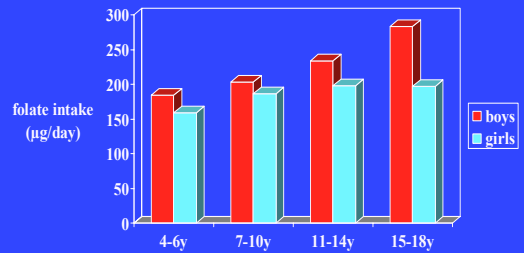




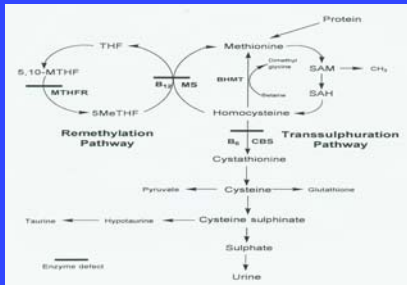
Pyridoxine intake according to age



Folate intake according to age



A metabolic basis for a link between B vitamin and cardiovascular disease



Elevated Plasma Total Homocysteine is a Risk Factor for CVD

Meta-analysis of 27 studies:

(Boushey et al (1995) JAMA 274: 1049-1057)

- ➡ OR for CAD for 5µmol/l tHcy was M 1.6; F 1.8
- ➡ Estimated 10% of CAD risk attributed to Hcy
- ➡ 5µmol/l increment in tHcy increased CAD risk by as much as 0.5 mmol/l cholesterol



Elevated Plasma Total Homocysteine is a Risk Factor for Cardiovascular Disease

Prospective Studies:

The Physician's Health Study
Stampfer et al (1992) JAMA &: 877



Top 5% for tHcy had a RR for MI of 3.4

Tromso Study

(Ameson et al (1995) Int J Epidemiol 24: 704)



RR of 1.4 for 4µmol/l tHcy

BUPA Study

(Perry et al (1995) Irish J Med Sci 164:16)



RR of stroke =2.5 for top quartile v bottom quartile of tHcy



Dietary determinants of plasma homocysteine

Variable	Range (per day)	P* (trend for regression coefficient)
Folate	<191->387 µg	<0.001*
Vitamin B12	<3.05->7.57µg	0.06*
Vitamin B6	<1.25->2.40 mg	<0.001*
Riboflavin	<1.11->2.21mg	0.003*
B Vitamin supplements	Yes or No	<0.001

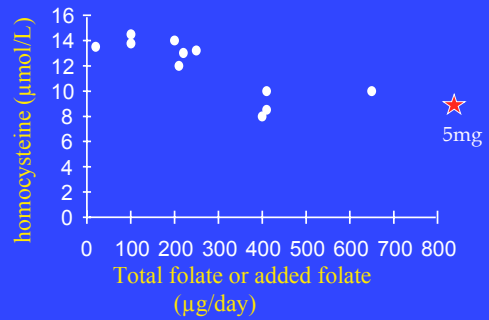
Jacques et al. 2001



Does increasing B vitamin intake lower homocysteine?



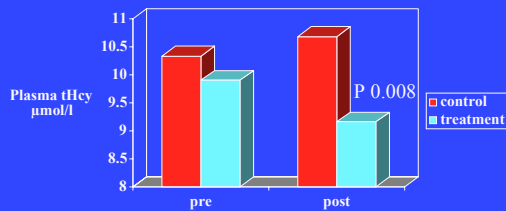
Folate intake and plasma total homocysteine



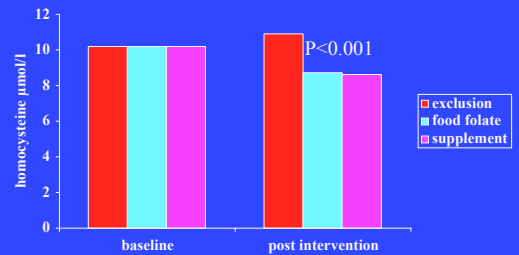
Boushey et al (1995) JAMA 274:1049-1057



Vitamin B₆ lowers plasma tHcy



Food folate lowers plasma tHcy



Ashfield-Watt et al 2001

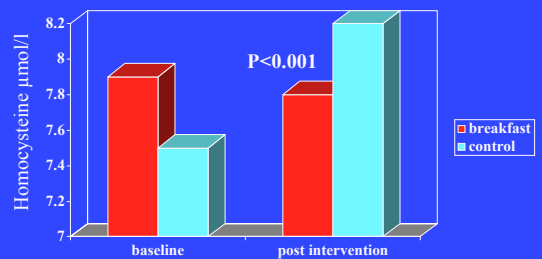


Breakfast cereal increases B vitamin status

Variable	Treatment group	Control group
Folate nmol/l	24.7 (0.7) 32.2* (0.7)	24.7 (0.7) 22.4 (0.7)
Vitamin B ₁₂ pmol/l	296 (10) 354* (13)	293 (10) 290 (10)
Vitamin B ₆ nmol/l	51.8 (4.9) 82.3* (5.5)	45.9 (2.6) 42.1 (2.4)



.....and lowers plasma homocysteine



Tucker et al 2003



Riboflavin is an independent predictor of homocysteine



Epidemiological evidence for a link between B vitamin intake and CVD

- Case control studies
 - Friso et al 2004
OR 1.89 for B₆
 - Cattaneo et al 2001
OR 1.80 for B₆
 - Robinson et al 1998
OR for folate 1.50, 1.81 for B₆
- Prospective cohort
 - Rimm et al 1998
RR for highest quintiles, 0.69 for folate, 0.67 for B₆.
 - Merchant et al 2003
RR for highest quintile for folate 0.67



Low plasma vitamin B₆ associated with increased CAD risk

	Unadjusted	Model 1	Model 2	Model 3
OR (95% CI)	1.71 (1.26-2.32)	1.61 (1.05-2.45)	1.73 (1.11-2.72)	1.89 (1.18-3.03)

Model 1: adjusted for major risk factors

Model 2: plus inflammatory markers

Model 3: plus tHcy, vitamin B₁₂, folate

Friso et al 2004



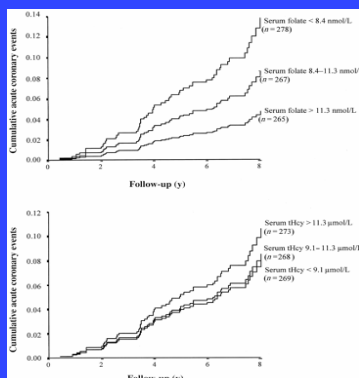
Intakes of folate and B₆ associated with CHD risk

Quartiles of intake	1	2	3	4	5	P for trend
Folate RR	1.0	0.86	0.86	0.78	0.69	0.003
Vitamin B ₆ RR	1.0	0.92	0.86	0.88	0.67	0.002

Rimm et al 1998



Acute coronary events according to homocysteine and folate status



Voutilainen et al 2004



B vitamin interventions and clinical outcomes

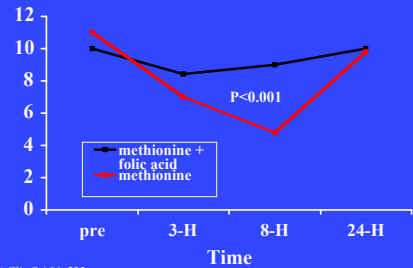
- Very few trials
- Usually patient groups and moderate to high B vitamin intakes (usually folate and B₆)
 - Vermeulen et al 2000; 2004 showed folate plus B₆ lowered markers of atherosclerosis
 - Doshi et al 2001 showed improved endothelial function in CAD patients, with high dose folate



Do B vitamins have homocysteine-independent effects on CVD?



Flow-Mediated Dilatation Following Methionine Loading



Usui et al (1999) Clin Sci 96: 235



High dose folate and endothelial function

- Participants 52 CAD patients
- Design double-blind placebo-controlled crossover
- Protocol 6 weeks of 5mg folic acid or placebo with 16weeks washout
- Endpoint endothelial function (FMD)
- Result impaired FMD improved, and increased plasma folate but also reduction in tHcy

Doshi et al 2001



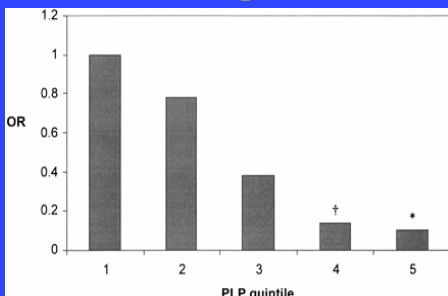
tHcy independent effects of folate on endothelial function

- 10 CAD patients
- 5-MeTHF infused at 50µg/min for 30 mins
- Endothelial function measured as FMD
- FMD improved over 30 mins, no reduction in plasma tHcy
- Folate acts directly on endothelial function, independent of homocysteine lowering effect

Doshi et al 2002



Low vitamin B6 is associated with stroke independent of tHcy



Kelly et al 2003



Conclusions

- Milk makes a useful contribution to the dietary intake of B vitamins
- Milk intake declines with increasing age in young people
- Folate, pyridoxine, riboflavin, and vitamin B₁₂ all contribute to homocysteine metabolism
- Homocysteine-lowering may have vascular protective effects
- There may be homocysteine-independent protective effects of some B vitamins