Overview of Evidence for Impact of Flour Fortification with Folic Acid

Helene McNulty PhD RD
Northern Ireland Centre for Food and Health (NICHE)
University of Ulster

Impact of Flour Fortification with Folic Acid

This talk will cover

- Background on folate
- Fortification with folic acid
- Impact of folic-acid fortification on nutrition and health outcomes

Functional role of folate

One-Carbon Metabolism

Transfer and utilisation of one-carbon units in

- amino acid metabolism
- methylation processes (e.g. when impaired, plasma homocysteine will be elevated)
- synthesis of DNA

The *clinical effects of folate deficiency* are the result of impaired synthesis of DNA

Megaloblastic anaemia

The clinical sign of folate deficiency

- characterised by
  - megaloblasts in the bone marrow
  - macrocytes in the peripheral blood
  - giantism in the morphology of proliferating cells

- 95% of all cases due to deficiency of folate, vitamin B-12 or both

Folate deficiency: causes

- *Increased requirement*
  - increased physiological requirement
  - pathological conditions
  - drugs
- *Decreased availability*
  - reduced dietary intake
  - impaired folate absorption

Folate deficiency in pregnancy

Consequences

- Maternal health:
  - maternal folate deficiency (i.e. megaloblastic anaemia)
  - preeclampsia
- Foetal health/neonatal health:
  - early pregnancy loss (e.g. abruptio placenta)
  - intrauterine growth retardation
  - low-birth weight
  - pre-term delivery
  - neonatal folate deficiency

Optimal folate status

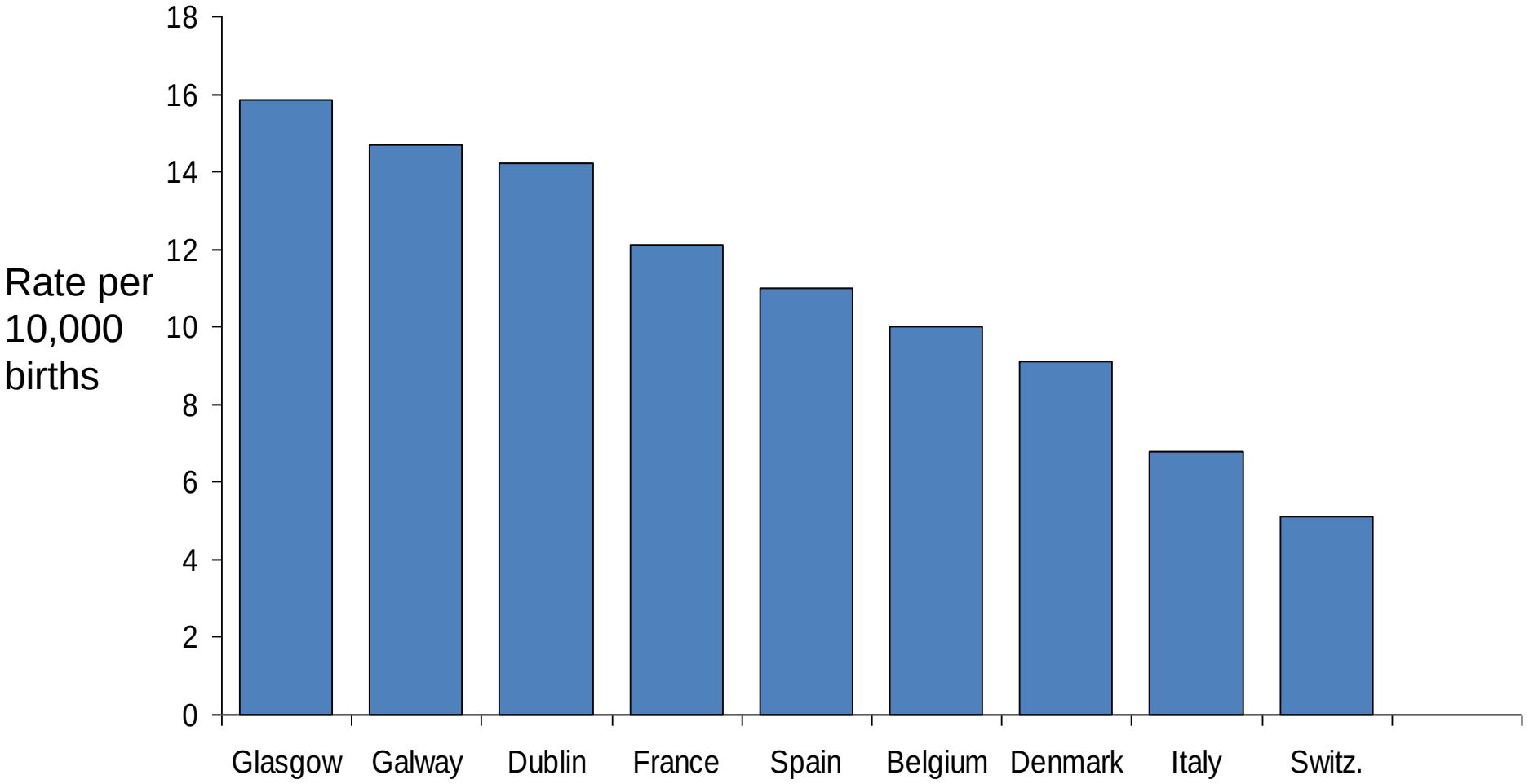
Role in maintaining health throughout the lifecycle

	Evidence
• Maternal health in pregnancy	conclusive
• Foetal development	conclusive
• Cognitive health in childhood	early evidence
• Prevention of heart disease/stroke	convincing
• Cancer prevention	promising
• Bone health	possible role
• Cognitive function in ageing	possible role

Folic acid and congenital defects

- NTDs [spina bifida; anencephaly]
  - ✓Preventive role of peri-conceptional folic acid: known
  - – Mechanism (under investigation)
    - Role of genetic polymorphisms in folate metabolism
    - Role of immunological factors
    - Autoantibodies against folate receptors (Rothenberg et al 2004)
- Orofacial clefts
  - – Conflicting results
- Congenital heart defects
  - – Recent evidence that periconceptional folic acid reduces CHD by 20% (*Beynum et al EHJ 2010*)

Prevalence rates of NTDs in Europe

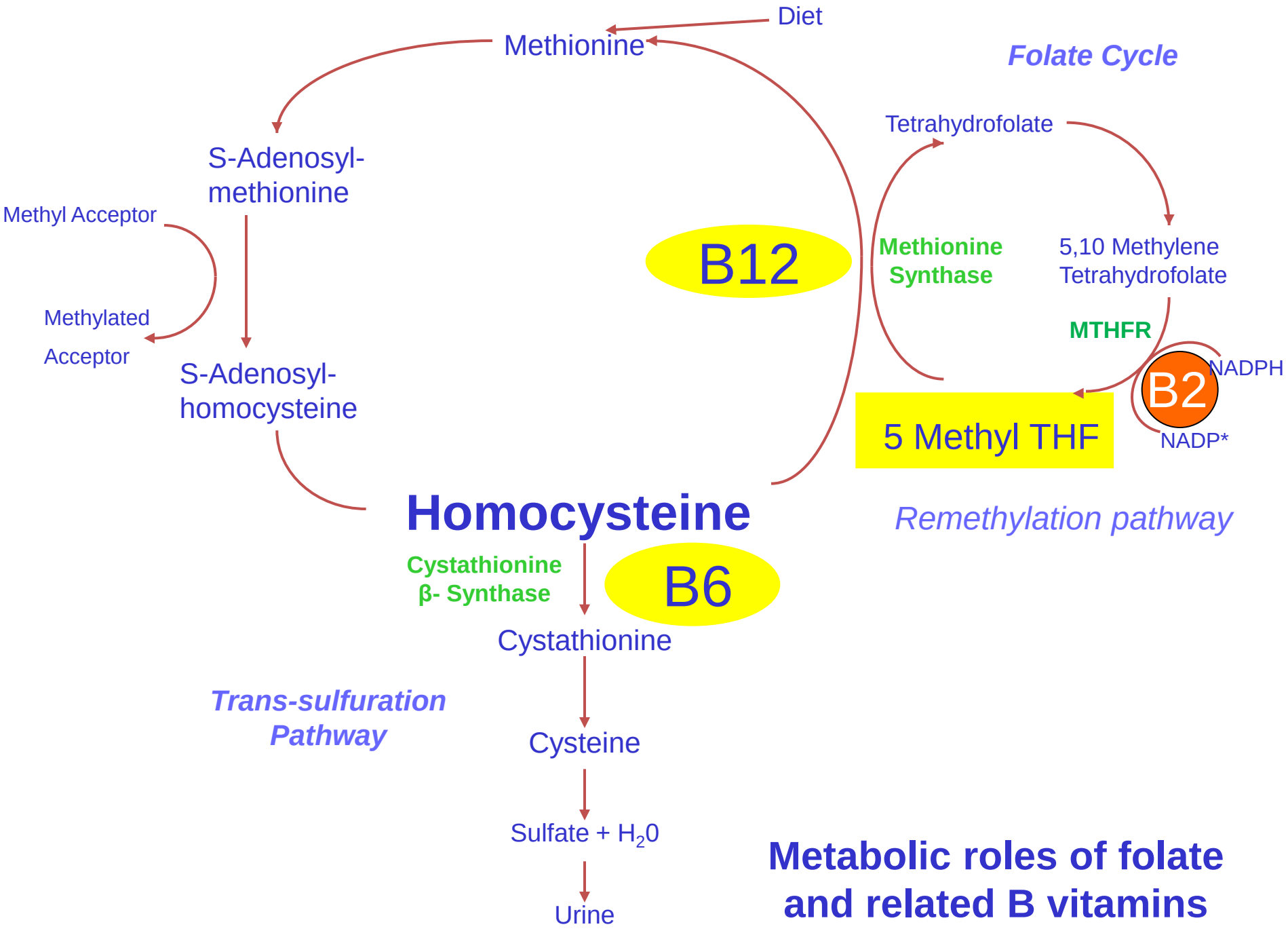


Source: EUROCAT Central Registry, Brussels

Current global recommendations for preventing NTDs

To be commenced prior to conception and during the first 12 weeks of pregnancy:

- Recurrence: 4 mg/d folic acid
- First Occurrence: 0.4 mg/d folic acid


Diet
Methionine
Folate Cycle
S-Adenosyl-
methionine
Tetrahydrofolate
Methyl Acceptor
B12
Methionine
Synthase
5,10 Methylene
Tetrahydrofolate
Methylated
Acceptor
MTHFR
NADPH
B2
S-Adenosyl-
homocysteine
5 Methyl THF
NADP*
Homocysteine
Remethylation pathway
Cystathionine
β- Synthase
B6
Cystathionine
Trans-sulfuration
Pathway
Cysteine
Sulfate + H20
Urine
Metabolic roles of folate
and related B vitamins

Elevated homocysteine as a risk factor for CVD

Evidence until 2004 [1,2]

- a similar magnitude of risk to that of elevated cholesterol
- an independent risk factor, but may enhance the effect of "conventional" risk factors
- estimated that a lowering of homocysteine by 3 µmol/l would reduce the risk of
  - coronary heart disease by 11-16%
  - **stroke by 19-24%**

Evidence 2004 – 2010 [3]

- Publication of several RCTs (secondary prevention trials)

[1]The Homocysteine Studies Collaboration 2002 ***JAMA***; 288:2015-2022
[2] Wald et al. 2002 ***BMJ***; 325:1202-08
[3]Reviewed by McNulty et al. 2012 ***Proc Nutr Soc***; 71:213-221

Randomized controlled trials of folic acid and risk of stroke: a meta-analysis

Wang et al 2007 *Lancet*;369:1876-82

	Relative risk (95% CI)	P value
Overall	0.82 (0.68-1.00)	0.045
Duration of intervention		
≤36 months	1.00 (0.83-1.21)	0.95
>36 months	0.71 (0.57-0.87)	0.001
Homocysteine lowering		
<20%	0.89 (0.55-1.42)	0.62
≥20%	0.77 (0.63-0.94)	0.012
History of stroke		
Yes	1.04 (0.84-1.29)	0.71
No	0.75 (0.62-0.90)	0.002

Genetic Studies
Is *MTHFR* 677C→T Polymorphism a risk factor for CVD?

- Most important genetic determinant of elevated homocysteine
- Meta-analyses[1-4] (> 25,000 CVD cases) estimate a 14-21% excess CVD risk in homozygous individuals (TT genotype), but large geographical variation between countries
- Provides good evidence to support
  - A causal relationship between homocysteine and CVD ***or***
  - A preventative role for folate in CVD

Wald DS et al. *BMJ* 2002; **325**: 1202–1206.
Klerk et al. *JAMA* 2002; **288**: 2023–2031.
Lewis et al. *BMJ* 2005; **331**: 1053–1056.
Holmes et al. *Lancet* 2011; **378**: 584-594.

Folate and cancer

- Strong and consistent epidemiological and animal evidence to link low folate status to increased cancer risk (evidence most compelling for colorectal cancer)
  - Mechanism for this relationship is that low folate leads to:
    - reduced availability of S-adenosylmethionine (SAM) for DNA methylation and/or
    - abnormal DNA synthesis (owing to misincorporation of deoxyuridine into DNA) and repair

However

- "Dual role" of folic acid in cancer now being proposed by some

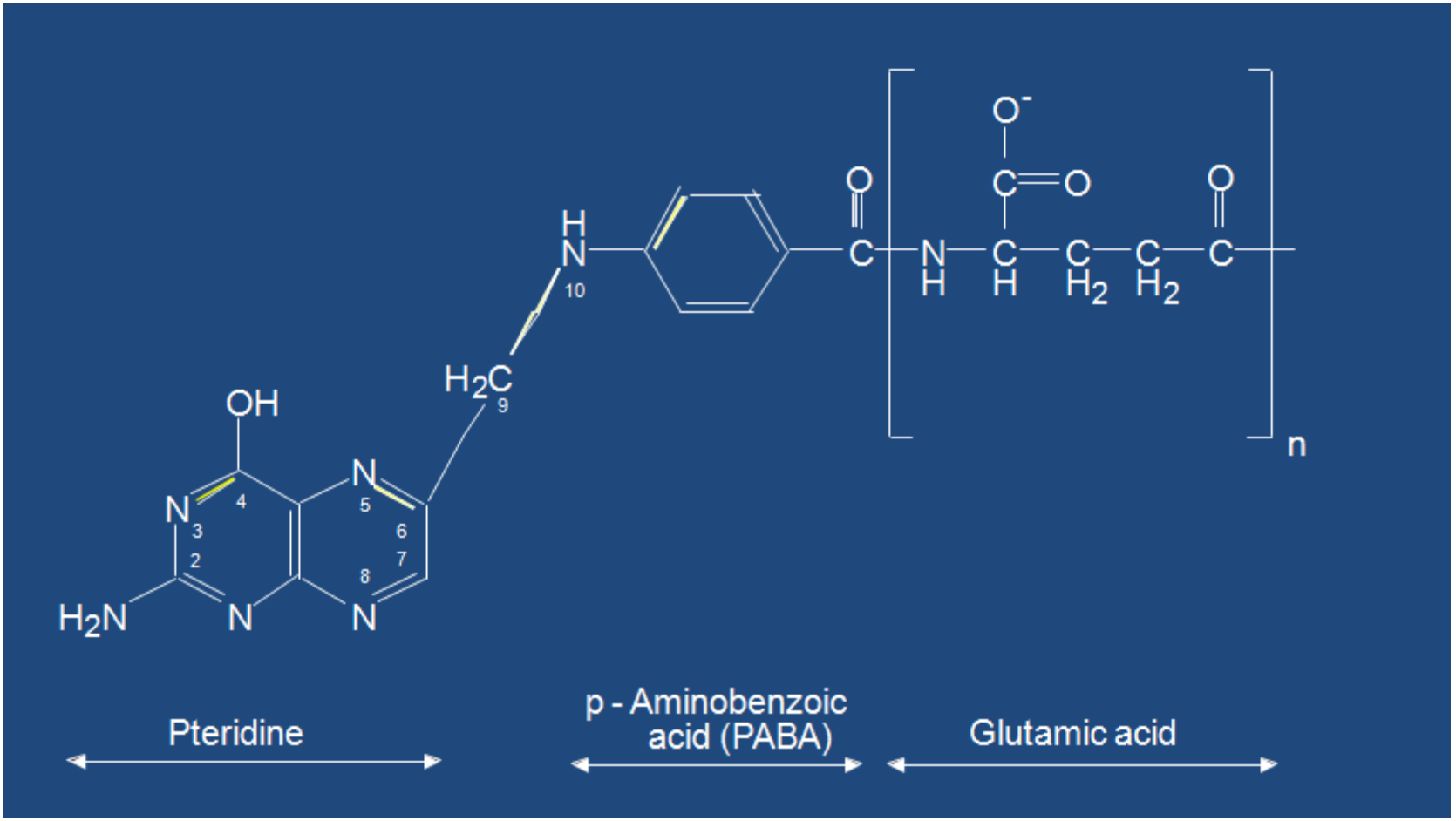
Folic acid

the folate form used in food fortification

- Folates
  -natural forms (plant and animal tissues)
  -polyglutamates
  -usually have a one-carbon attachment

- Folic acid
  -synthetic form (fortified foods and supplements)
  -a monoglutamate
  -no one-carbon attachment

Structure of pteroylglutamic acid (i.e. folic acid)



Food folates compared with folic acid

- **Food folates** are
  - reduced molecules
  - predominantly polyglutamates but
  - converted to monoglutamates for absorption

- Compared with folic acid, **food folates** are
  - much less stable to cooking
  - much less bioavailable once ingested

Dietary Folate Equivalents (DFE)

- Dietary Folate Equivalents (DFE) now used in the United States
  - based on differences in bioavailability between natural folates and added folic acid
  - DFE=μg natural food folate + 1.6 times μg FA

Impact of food fortification with folic acid

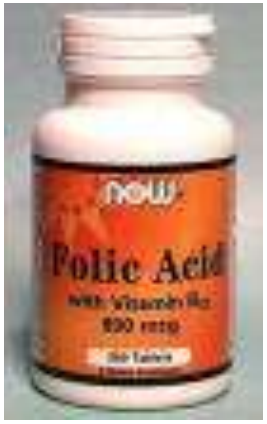
- Can folic-acid fortification improve biomarker status of folate?
- Can folic-acid fortification improve health outcomes
  - NTD risk?
  - Stroke risk?
- How does this route of optimising folate compare with the alternative routes?

3 routes to achieve optimal folate status

Natural food sources

Fortified Foods

Supplements



Option 1: Natural food folates

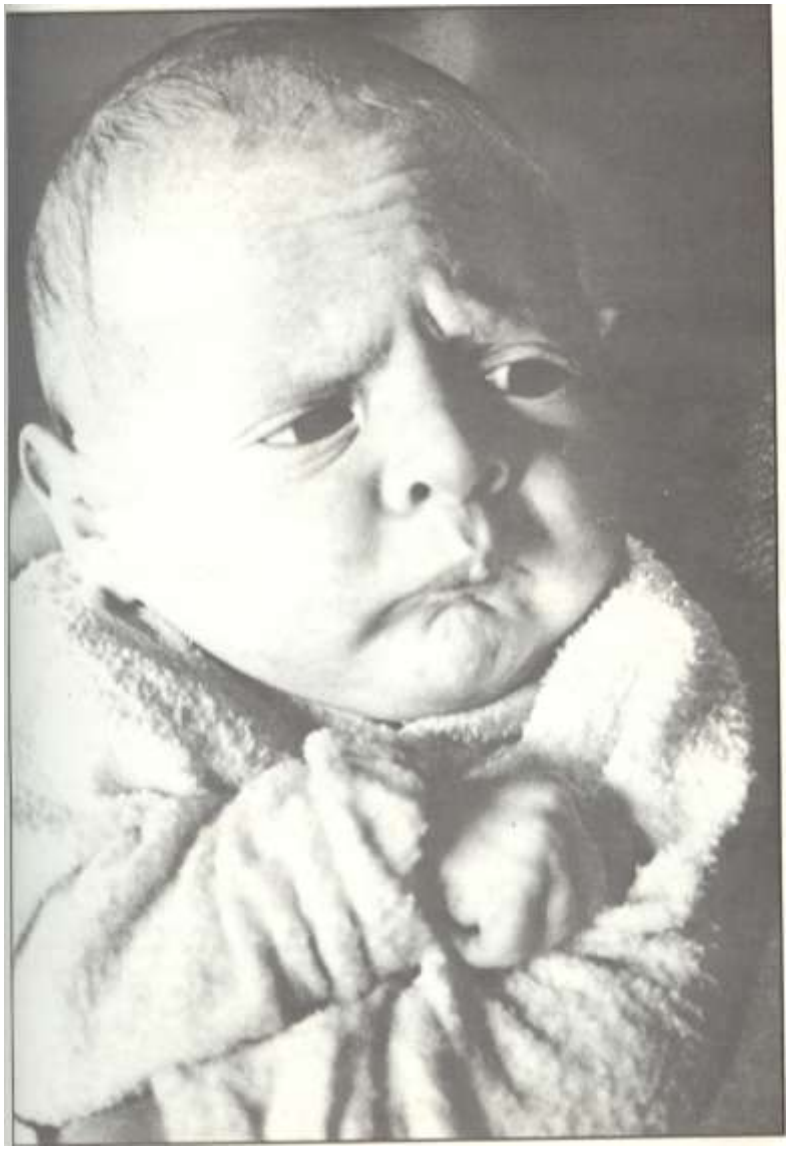
- The potential to optimise folate status by means of natural food folate sources is very limited

- Food folates
  - may be unstable during cooking
  - show incomplete bioavailability once ingested

Option 2

Folic acid supplementation

Timeframe for preventing NTDs



The neural tube closes 21-28 days after conception….

…..just when most women are beginning *to suspect* that they might be pregnant!

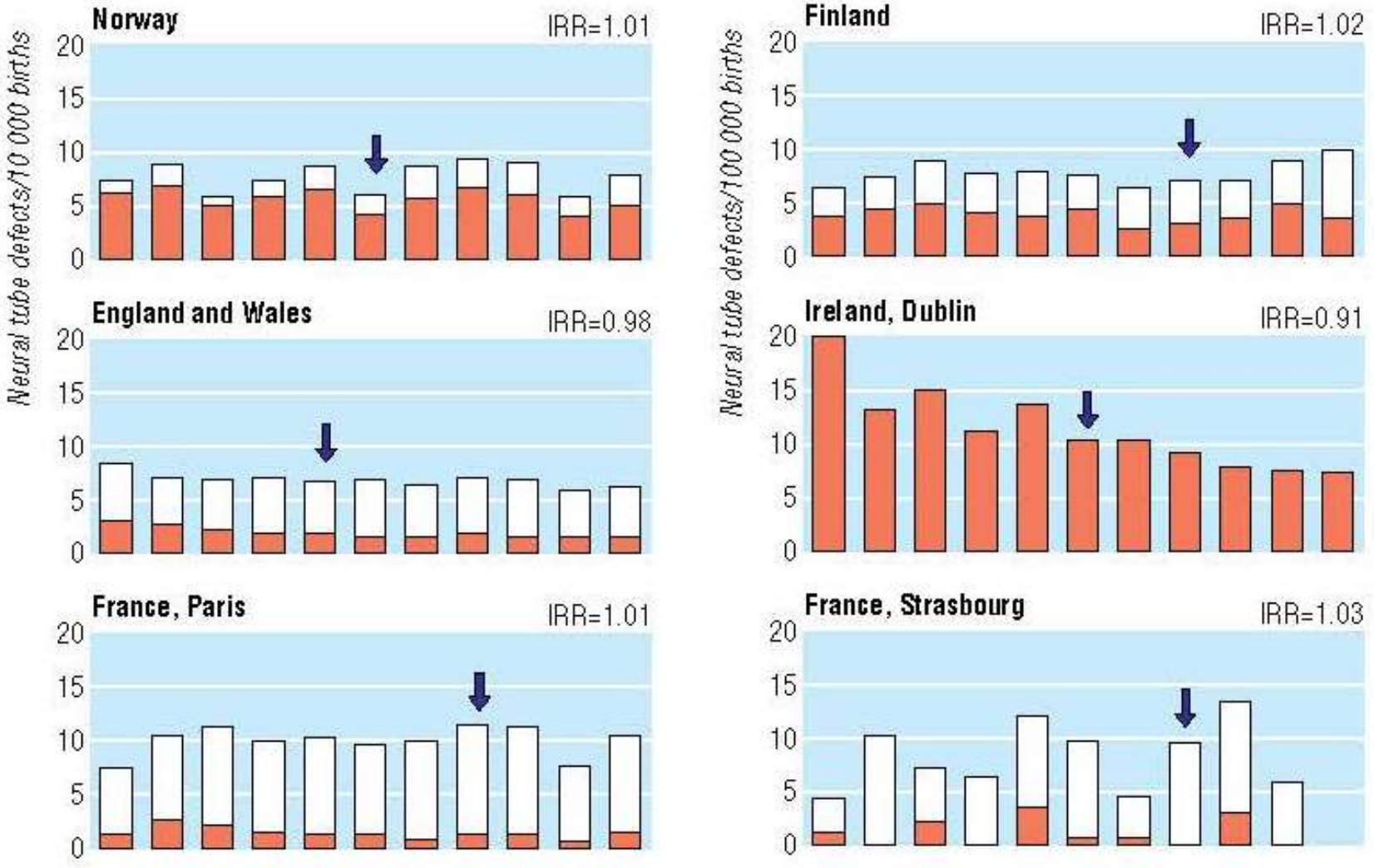
Recent evidence[1] (N Ireland; pregnant women at 14 wks; n=296) showed that

- 84% were taking FA in pregnancy BUT
- Only 1 in 5 had commenced FA before conception *as recommended*

[1]McNulty et al. ***Hum Reprod*** 2011; 26: 1530-1536

Rates of NTDs per 10 000 births: 1988-98

Botto et al *BMJ* 2005;330:571-576



Option 3

Folic acid fortification

Intervention study to increase folate status in women by the 3 routes

Cuskelly *et al.*1996 *Lancet* **347**:657-659:

- Folic acid-fortified foods were as effective as folic acid supplements in optimizing folate status
- Increased consumption of foods naturally rich in folate resulted in no significant response in folate status
- The explanation for these findings probably relates to
  - the poorer stability and poorer bioavailability of natural food folates compared with the synthetic vitamin, folic acid

Impact of folic acid-fortified food on folate intake and status

Hoey et al *AJCN* 2007; 86: 1405-1413

	Non-Consumers *(n=97)* (FA= 0µg/d)	Low Consumers *(n=111)* (FA=1-39µg/d)	Medium Consumers *(n=118)* (FA 40-98µg/d)	High Consumers *(n=115)* (FA ≥ 99µg/d)
Dietary Folate Intake				
Total folate (µg/d)	186 (142, 223) [a]	206 (173, 246) [a]	259 (212, 310) [b]	422 (333, 549) [c]
Added folic acid (µg/d)	0 (0, 0) [a]	25 (17, 33) [b]	60 (50, 75) [c]	208 (125, 291) [d]
Natural folate (µg/d)	186 (142, 223) [a]	179 (151, 215) [a]	196 (150, 248) [a]	197 (157, 238) [a]
Biomarker Status of Folate				
Plasma Hcy (µmol/l)	11.5 (9.4, 13.9) [a]	10.7 (8.9, 13.4) [a]	9.6 (7.8, 11.2) [b]	9.4 (7.7, 12.0) [b]
RCF (nmol/l)	653 (532, 830) [a]	697 (564, 857) [a]	862 (680, 1082) [b]	1040 (798, 1413) [c]
Serum Folate (nmol/l)	15.1 (10.0, 21.1) [a]	16.2 (11.6, 22.1) [a]	22.6 (16.7, 30.5) [b]	30.1 (21.5, 45.5) [c]

Current folic acid fortification worldwide: the evidence

- Mandatory folic acid fortification has been in place for several years in a number of countries worldwide

- This measure has reduced the incidence of NTD in the US[1] and Canada[2] by between 27% and 50%.

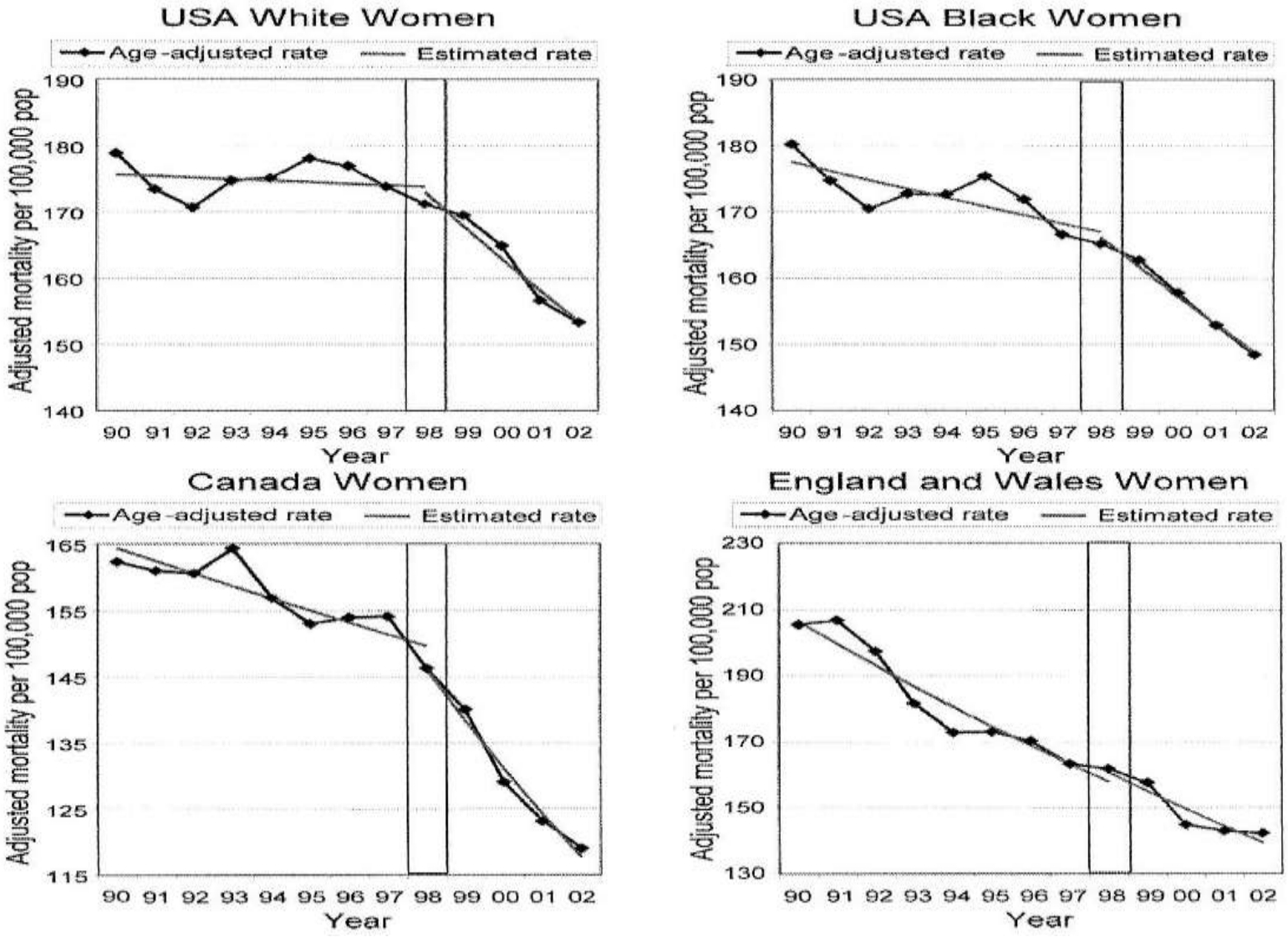
- Some evidence that this measure has also reduced the risk of stroke in North America (next slide)

[1]Honein et al *JAMA* 2001;285:2981-6

[2]De Wals et al *N Engl J Med* 2007; **357**: 135-142.

Decline in stroke related mortality in the US and Canada

Evidence for beneficial effect of folic acid-fortification



Yang et al 2006 *Circulation*;113:1335-43

Options to achieve optimal folate status for nutrition and health benefits

Intervention	Strategy shown to be effective in	
	individual	population
Natural food folates	no	no
Folic acid supplementation	yes	no
Folic acid-fortification	yes	yes

Overview of evidence: Take home messages

- Current folate intakes in many populations are *insufficient* for the achievement of optimal folate status
- Natural food folates show incomplete bioavailability *and* poor stability
  - in comparison, folic acid is very stable and highly bioavailable
- Folic acid supplementation is very effective in individuals, but does not work at a population level
- Folic acid fortification offers
    - an effective means of increasing folate status in populations
    - a proven effect in preventing NTD
    - a probable effect in preventing disease, especially stroke

Folate research at UU

The Current Players

NICHE

Sean Strain
Mary Ward
Kristina Pentieva
Leane Hoey
The TUDA project team
The JINGO project team
The EURRECA team

Our Collaborators in TCD

John Scott
Anne Molloy
Conal Cunningham

Clinical Collaborators

Owen Finnegan
John Purvis
Tom Trouton
Barry Marshall
Mark Rollins
Fergal Tracey

International Collaborators

Per Magne Ueland, Norway
Steve Whitehead, Pennsylvania
Jacob Selhub, Boston

Folate research at UU

PhD Students

Past	*Present*
Geraldine Cuskelly (1997)	Michelle Clarke
Mary Ward (1998)	Rosie Reilly
Michelle McKinley (1999)	Catherine McGarel
Barbara Wilson (2000)	
Derek McKillop (2001)	
Paula Tighe (2004)	
Geraldine Horigan (2006)	
Maeve Kerr (2006)	
Breige McNulty (2007)	
Nadina Askin (2008)	
Claire Whittle (2009)	
Catherine Hughes (2010)	
Carol Wilson (2010)	