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

- 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
Homocysteine

Methionine

S-Adenosyl-homocysteine

S-Adenosyl-methionine

Methyl Acceptor

Methylated Acceptor

Cystathionine $\beta$-Synthase

Cysteine

Sulfate + $H_2O$

Urine

Trans-sulfuration Pathway

Remethylation pathway

Metabolic roles of folate and related B vitamins

Folate Cycle

Diet

Tetrahydrofolate

Methionine Synthase

5,10 Methylene Tetrahydrofolate

MTHFR

NADPH

NADP$^*$

B12

5 Methyl THF

B6

Methyl Acceptor

Methylated Acceptor

Urine
Elevated homocysteine as a risk factor for CVD

 Evidence until 2004\textsuperscript{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 \( \mu \text{mol/l} \) would reduce the risk of
  - coronary heart disease by 11-16%
  - stroke by 19-24%

 Evidence 2004 – 2010\textsuperscript{3}

- Publication of several RCTs (secondary prevention trials)

\textsuperscript{1}The Homocysteine Studies Collaboration 2002 \textit{JAMA}; 288:2015-2022
\textsuperscript{2}Wald et al. 2002 \textit{BMJ}; 325:1202-08
Randomized controlled trials of folic acid and risk of stroke: a meta-analysis
Wang et al 2007 *Lancet*;369:1876-82

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

Klerk et al. *JAMA* 2002; **288**: 2023–2031.
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
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
Option 3

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

Cuskelley 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

<table>
<thead>
<tr>
<th></th>
<th>Non-Consumers (n=97)</th>
<th>Low Consumers (n=111)</th>
<th>Medium Consumers (n=118)</th>
<th>High Consumers (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(FA= 0µg/d)</td>
<td>(FA=1-39µg/d)</td>
<td>(FA 40-98µg/d)</td>
<td>(FA ≥ 99µg/d)</td>
</tr>
<tr>
<td><strong>Dietary Folate Intake</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total folate (µg/d)</td>
<td>186 (142, 223) &lt;sup&gt;a&lt;/sup&gt;</td>
<td>206 (173, 246) &lt;sup&gt;a&lt;/sup&gt;</td>
<td>259 (212, 310) &lt;sup&gt;b&lt;/sup&gt;</td>
<td>422 (333, 549) &lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Added folic acid (µg/d)</td>
<td>0 (0, 0) &lt;sup&gt;a&lt;/sup&gt;</td>
<td>25 (17, 33) &lt;sup&gt;b&lt;/sup&gt;</td>
<td>60 (50, 75) &lt;sup&gt;c&lt;/sup&gt;</td>
<td>208 (125, 291) &lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Natural folate (µg/d)</td>
<td>186 (142, 223) &lt;sup&gt;a&lt;/sup&gt;</td>
<td>179 (151, 215) &lt;sup&gt;a&lt;/sup&gt;</td>
<td>196 (150, 248) &lt;sup&gt;a&lt;/sup&gt;</td>
<td>197 (157, 238) &lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

| **Biomarker Status of Folate** |                      |                       |                          |                        |
| Plasma Hcy (µmol/l) | 11.5 (9.4, 13.9) <sup>a</sup> | 10.7 (8.9, 13.4) <sup>a</sup> | 9.6 (7.8, 11.2) <sup>b</sup> | 9.4 (7.7, 12.0) <sup>b</sup> |
| RCF (nmol/l)       | 653 (532, 830) <sup>a</sup> | 697 (564, 857) <sup>a</sup> | 862 (680, 1082) <sup>b</sup> | 1040 (798, 1413) <sup>c</sup> |
| Serum Folate (nmol/l) | 15.1 (10.0, 21.1) <sup>a</sup> | 16.2 (11.6, 22.1) <sup>a</sup> | 22.6 (16.7, 30.5) <sup>b</sup> | 30.1 (21.5, 45.5) <sup>c</sup> |
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
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

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Strategy shown to be effective in</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>individual</td>
</tr>
<tr>
<td>Natural food folates</td>
<td>no</td>
</tr>
<tr>
<td>Folic acid supplementation</td>
<td>yes</td>
</tr>
<tr>
<td>Folic acid-fortification</td>
<td>yes</td>
</tr>
</tbody>
</table>
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**

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