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Symposium one: Contributions of nutrition science to human health

Contribution of folic acid to human health and challenges of translating the science into effective policy: a call to action for the implementation of food fortification in Ireland

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Over 30 years ago it was proven beyond doubt that folic acid supplementation of mothers in early pregnancy protects against neural tube defects (NTD) in their babies. Such conclusive scientific evidence led to clear recommendations for women worldwide to take 0·4 mg/d folic acid before conceiving and in early pregnancy, but implementing these into effective policy has been problematic. As a result, there has been no change in the incidence of NTD in Ireland, the UK or any other European country over the 25-year period that the current strategy, recommending periconceptional folic acid supplements to women, has been in place. Thus preventable NTD are not being prevented. Notably, in September 2021, the UK government announced that starch is to be fortified with folic acid on a mandatory basis. A similar decision is now urgently needed in Ireland, where rates of NTD are among the highest in the world. A policy of mandatory folic acid fortification of food would be highly effective in preventing NTD because it reaches all women, including those who have not planned their pregnancy. International evidence shows that wherever such a policy has been introduced, it has proved to be effective in reducing rates of NTD in that country. Apart from preventing NTD, the driver of policy in the area, other potential health benefits across the lifecycle can be anticipated from folic acid fortification. Urgent action is needed on implementation of mandatory food fortification with folic acid in Ireland so that mothers and their babies can benefit.

Folate: Folic acid: Neural tube defects: Food fortification: Policy

Over 30 years ago it was proven beyond doubt that folic acid supplementation of mothers in early pregnancy protects against neural tube defects (NTD) in their babies. After over two decades of deliberation, in September 2021 the UK government announced that starch is to be fortified with folic acid on a mandatory basis. A similar decision is awaited in Ireland where rates of NTD are among the highest in the world. What is the evidence supporting such a policy? What next steps are required to ensure that the benefit of folic acid can be achieved for mothers and their babies in a safe and effective way?

This review will consider the evidence for the contribution of folate to human health and the effects of folic acid

Abbreviations: NTD, neural tube defects; THF, tetrahydrofolate.

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intervention via supplementation and food fortification. With a particular focus on the role of folic acid in preventing NTD, the challenges of translating science into policy and practice will be considered.

Contribution of folate to human health

Structure and function of folate

The terms 'folic acid' and 'folate' are often used interchangeably, but there are important structural differences with implications for folate bioavailability from food sources[1,2]. Folic acid should be used to refer to the synthetic vitamin form (i.e. pteroylmonoglutamic acid) as found only in supplements and fortified food, whereas the natural reduced folate forms are found in human, animal and plant tissues.

All folate forms comprise three moieties: a pteridine; a p-aminobenzoic acid and a glutamate residue. Folic acid is completely oxidised and not found in nature. The natural folate forms are reduced molecules, with the addition of two or four hydrogen atoms to the pteridine, giving rise to dihydrofolate or the various tetrahydrofolate (THF) forms (Fig. 1). THF can carry one-carbon groups attached at the N-5 (methyl, formyl or formimino), the N-10 (formyl) or bridging N-5 and N-10 (methylene or methenyl) positions of the pteridine ring, giving rise to a number of different cofactor forms of folate. Notably, whereas folic acid is a monoglutamate, containing only one glutamic acid residue, most natural food folates exist as polyglutamate derivatives containing additional glutamate residues bound in peptide linkage to the gamma-carboxyl group.

Biologically folates function as cofactors within one-carbon metabolism, involving the transfer and utilisation of one-carbon units (e.g. a methyl, formyl or formimino group) in a network of pathways required for DNA and RNA biosynthesis, serine and glycine metabolism, histidine catabolism, methionine synthesis and methylation processes[3]. To function effectively within the one-carbon network, folates interact closely with other B vitamins, namely, B12, B6 and riboflavin. Reduced folates enter the one-carbon cycle as THF which acquires a carbon unit from serine in a B6-dependent reaction to form 5,10 methyleneTHF. This cofactor form is then either converted to 5 methylTHF or serves as the one-carbon donor in the synthesis of nucleic acids, where it is required by thymidylate synthetase in the conversion of deoxyuridine to deoxythymidine for pyrimidine biosynthesis, or is converted to other folate cofactor forms essential for purine biosynthesis. Methylenetetrahydrofolate reductase is a riboflavin-dependent enzyme that catalyses the reduction of 5,10 methyleneTHF to 5 methylTHF. Once formed, 5 methylTHF, along with vitamin B12, is used in the synthesis of methionine from homocysteine (catalysed by the enzyme methionine synthase), and in turn, the generation of *S*-adenosylmethionine, a methyl group donor used in numerous methylation reactions, including the methylation of a number of sites within DNA, RNA, proteins and phospholipids.

Roles of folate through the lifecycle

Given these essential functions, folate plays a crucial role in human health. The discovery of folate as an essential nutrient dates back to the 1930s when a fatal anaemia of pregnancy was first described in India which was subsequently proven to be responsive to treatment with food sources of the vitamin[4,5]. Severe deficiency of folate (or vitamin B12) leads to megaloblastic anaemia which clinically manifests as fatigue, weakness and shortness of breath owing to a low erythrocyte count. Haematologically, megaloblastic anaemia is characterised by the presence of large, immature, nucleated cells (megaloblasts) in the bone marrow and macrocytes in the peripheral blood, a condition that is reversible with folic acid treatment[6]. Folate deficiency typically arises when folate requirement is increased (e.g. in pregnancy) and/or when folate availability is reduced as a result of low dietary intakes or malabsorption (e.g. in coeliac disease)[7]. Owing to increased folate requirements to sustain the growth of maternal, fetal and placental tissues, maternal folate concentrations typically decrease throughout pregnancy. Supplementation with folic acid prevents this decline[8] and can thus prevent the occurrence of megaloblastic anaemia of pregnancy[9].

The absence of anaemia however does not imply that folate status is sufficient. There is conclusive and emerging scientific evidence showing that folate has a number of roles in maintaining health through the lifecycle (Fig. 2). Thus, even if not severe enough to lead to the clinical folate deficiency manifested as megaloblastic anaemia, suboptimal folate status is associated with adverse outcomes from early life to older age.

Neural tube defects. Maternal folate status has a major impact on early development of the embryo up to the first 4 weeks of pregnancy. Conclusive evidence has existed for over 30 years of the benefits at this time of folic acid in preventing both first occurrence[13] and recurrence[14] of NTD (Table 1). These are major congenital malformations of the central nervous system occurring as a result of failure of the neural tube to close properly in early pregnancy, resulting in death of the fetus or newborn or lifelong disability. Normally, the neural tube closes to form the brain and spinal cord within the first 28 days after conception. The most common forms of NTD are anencephaly (a brain defect) and spina bifida (a spinal cord defect), depending on the portion of the neural tube that fails to close. Failure of the cranial portion to close causes anencephaly, a fatal brain defect, whereas failure of the more caudal neural tube to close causes myelomeningocele or meningocele, two forms of spina bifida. Most children with NTD who survive beyond birth will have serious disabilities.

The finding that folic acid can prevent NTD ranks as one of the most important discoveries both in birth defects research and in human nutrition. This conclusive evidence has led to clear folic acid recommendations for women of reproductive age which are in place worldwide. The biological mechanisms to explain the beneficial effects of periconceptional folic acid against NTD

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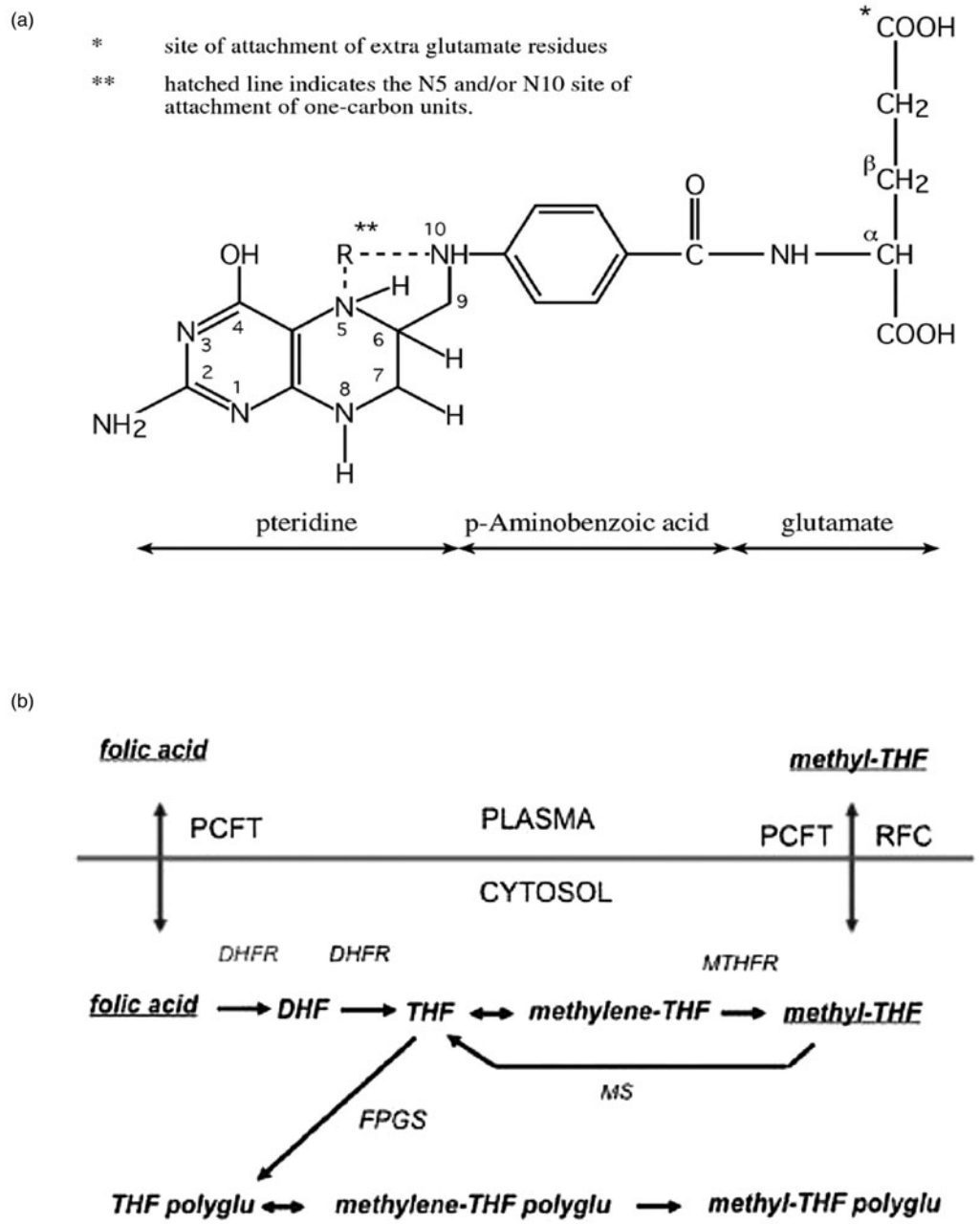

Fig. 1. (a) Structure of tetrahydrofolate and (b) transport of folic acid and 5-methyl-THF into tissues and their metabolism to retainable polyglutamate forms. DHF, dihydrofolate; DHFR, dihydrofolate reductase; FPGS, folylpolyglutamate synthase; MS, methionine synthase; MTHFR, methylenetetrahydrofolate reductase; PCFT, proton coupled folate transporter; polyglu, polyglutamate; RFC, reduced folate carrier; THF, tetrahydrofolate.

remain to be fully elucidated, but research efforts are focused on the factors that could potentially impair normal folate metabolism, including polymorphisms in folate genes. Of these, an increased risk of NTD is most strongly associated with the C677T variant in the gene encoding the folate-metabolising enzyme methylenetetrahydrofolate reductase[18]. Autoantibodies against folate receptors have also been implicated in pregnancies affected by NTD[19].

Other pregnancy outcomes. Apart from preventing NTD, there is good evidence that periconceptional folic acid use may prevent congenital heart defects in infants[20], and possibly orofacial clefts, although the latter evidence is somewhat controversial[21,22].

As pregnancy progresses, folate continues to play an important role in maternal, fetal and neonatal health[7]. Low maternal folate status (and/or elevated homocysteine) is associated with an increased risk of a number

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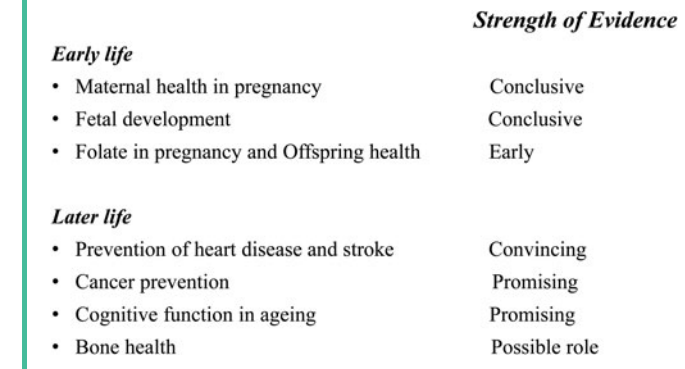

Fig. 2. Known and emerging roles of folate in human health.

of adverse pregnancy outcomes including gestational hypertension, preeclampsia, placental abruption, pregnancy loss, low birth weight and intrauterine growth restriction[23]. There is some, albeit inconsistent, evidence that folic acid supplementation in pregnancy can reduce the risk of gestational hypertension and pre-eclampsia[24,25]. Emerging evidence also links maternal folate during pregnancy with neurodevelopment and cognitive function in the child. Notably, the Folic Acid Supplementation in the Second and Third Trimesters (FASSTT) offspring trial from our centre studied the effect of maternal folic acid supplementation during pregnancy on the subsequent cognitive performance of the child using validated assessment tools. We showed that the children of folic acid-treated mothers compared to placebo not only scored significantly higher in several cognitive domains at 3, 7 and 11 years, but also demonstrated more efficient semantic processing of language as assessed using magnetoencephalographic brain imaging[26,27]. The biological mechanisms linking maternal folate with the offspring brain are unclear, but likely involve folate-mediated epigenetic changes related to brain development and function[28]. DNA methylation, the most widely studied epigenetic mechanism for gene regulation, is dependent upon the supply of methyl donors provided by folate and related B vitamins via *S*-adenosylmethionine[3]. Folate deficiency could thus lead to aberrant gene expression with consequential adverse health outcomes[29].

Middle and older age. There is considerable evidence to link low status of folate and related B vitamins (B12 and B6) with an increased risk of CVD and stroke in particular[30]. Notably, randomised controlled trials show that folic acid intervention may decrease the risk of stroke by as much as 18 % overall, and by over 25 % in trials with a treatment duration of >36 months and in participants with poorer baseline folate status and/or no previous history of stroke[31]. Also, population data from the USA and Canada show an improvement in stroke mortality corresponding to the time that mandatory folic acid food fortification was introduced[32]. Although a number of secondary prevention trials in at-risk patients failed to show a benefit of folic acid (typically in combination with vitamins B12 and B6) for CVD events generally[30], all trials were aimed at preventing further cardiovascular events in patients with well-established pathology. A reasonable conclusion from the evidence therefore is that the administration of high-dose B vitamins to CVD patients is of no benefit in preventing another event. Also, in one such trial testing B vitamin intervention in CVD risk, the heart outcomes prevention evaluation-2 trial, a clear benefit in reducing the risk of stroke was detected but for some reason this result was overlooked in the original report[33], and subsequently reported separately[34]. Also, much of the evidence in this area focuses specifically on plasma homocysteine (a functional indicator that is invariably elevated with folate insufficiency), high concentrations

Table 1. Periconceptional folic acid supplementation and NTD risk

Study	Folic acid (mg/d)	No. of NTD	Relative risk	Comments
Laurence *et al.*[10]	4·0	2/60 supplemented*	0·42	NS
Wales, UK		4/51 not supplemented		Underpowered
Smithells *et al.*[11]	0·36	3/454 supplemented	0·14	Significant†
UK		24/519 not supplemented		
Vergel *et al.*[12]	5·0	0/81 supplemented	0·00	NS
Cuba		4/114 not supplemented		Underpowered
UK Medical Research Council[13]	4·0	6/593 supplemented	0·29	Significant†
International		21/602 not supplemented		
Czeizel and Dudas[14]	0·8	0/2104 supplemented	0·00	Significant†
Hungary		6/2052 not supplemented		NS
Kirke *et al.*[15]	0·36	0/172 supplemented	0·00	Underpowered
Ireland		1/89 not supplemented		
Berry *et al.*[16]	0·4	13/13 012 supplemented	0·21	Significant†
Northern region, China		16/3318 not supplemented		
Berry *et al.*[16]	0·4	34/58 638 supplemented	0·59	Significant†
Southern region, China		28/28 265 not supplemented		
Indian council of medical research[17]	4·0	4/137 supplemented	0·41	NS
India		10/142 not supplemented		Underpowered

* Two NTD pregnancies in sixty women supplemented with folic acid and four NTD pregnancies in fifty-one women not supplemented with folic acid.
† Statistically significant difference in NTD rate between supplemented and non-supplemented groups.
References included chronologically in Table 1 (10–17).

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of which are associated with endothelial dysfunction, atherosclerosis and thrombosis. It is however possible that the link of folate with CVD is via mechanisms that are independent of homocysteine, including a role for one-carbon metabolism and related B vitamins in blood pressure[35,36].

A growing body of evidence shows that folate and related B vitamins are important for maintaining cognitive health in ageing and links lower B vitamin status and/or elevated homocysteine concentrations with cognitive dysfunction and greater risk of dementia[37]. Research in this area has been very substantially underpinned by the B vitamin treatment for cognitive outcomes trial which showed that intervention with B vitamins not only improved cognitive performance in patients with mild cognitive impairment, but also slowed the rate of global and regional brain atrophy as determined using MRI[38]. The totality of trial evidence suggests that any benefit of intervention with folic acid (alone or combined with vitamins B12 and B6) on cognitive function arises through correction of deficient/low status, whereas providing additional folic acid to those with optimal status likely has little effect on cognition. Apart from memory deficits and cognitive dysfunction, depressive symptoms are well described in patients with folate deficiency[39]. Likewise, in observational studies, low folate is associated with a greater risk of depression[40]. One large cohort study from our centre of older Irish adults found an incremental increase in the risk of depression as erythrocyte folate concentrations declined, while regular consumption of fortified foods increased dietary folate and related B vitamins, substantially improved corresponding biomarkers, and was associated with a reduced risk of depression (by 50 %) in those who consumed fortified foods on a daily basis compared to non-consumers[41].

Thus, optimising folate status through population-based folic acid intervention primarily aimed at reducing NTD in early pregnancy would also prevent folate-related megaloblastic anaemia across the lifecycle. It may also have benefits in improving cognitive development in early life and maintaining better cognitive and cardiovascular health in older age, although a conclusive role for folate in the latter health outcomes has yet to be confirmed.

Effects of folate /folic acid intervention: what works?

For the past 30 years there has been conclusive scientific evidence of the benefit of enhanced maternal folate status before and in early pregnancy in preventing NTD. There are theoretically three intervention options to increase folate status in women of reproductive age: (1) increased intake of foods naturally rich in folate; (2) folic acid supplements; (3) folic acid-fortified foods. As described below, however, these intervention options have been shown to differ in their ability to achieve optimal folate status in women of reproductive age (Table 2).

Food folate sources

The richest sources of food folates are green leafy vegetables, asparagus, beans, legumes, liver and yeast.

Table 2. Interventions to achieve optimal folate status in women of reproductive age

Strategy shown to be effective in		
Intervention	Individuals	Populations
Natural food folates	No	No
Folic acid supplementation	Yes	No
Folic acid fortification	Yes	Yes

However, at a population level when the frequency of consumption of food sources is considered, data from the Irish National Adult Nutrition Survey show that the major dietary contributors to total folate intake are bread (14 %), breakfast cereals (12 %), vegetables (10 %), potatoes (10 %)[42].

Notably, the bioavailability of naturally occurring food folates is limited and variable. As a result of the structural differences between natural folates and folic acid, all natural food sources of folate are much less bioavailable than folic acid[1]. Folic acid is fully oxidised and is a monoglutamate, with just one glutamate moiety in its structure, whereas naturally occurring food folates are a mixture of reduced folate forms (predominantly 5 methylTHF) which are typically found as polyglutamates, containing a variable number of glutamate residues[2]. Apart from their limited bioavailability, food folates can be unstable during cooking, and this will substantially reduce the folate content of certain foods (particularly green vegetables) before ingestion[43]. Thus, folic acid is much more stable and more bioavailable compared to an equivalent amount of the vitamin eaten as naturally occurring food folates[1]. The instability and poor bioavailability of food folates means that they have very limited ability to increase blood folate concentrations, as we demonstrated many years ago in a controlled 12-week feeding study in young women comparing the effects of intervention with food folates, folic acid-fortified foods and folic acid supplements[44]. As a result, increasing dietary intakes of food folates is largely ineffective as a means of achieving optimal folate status. To take into account the greater bioavailability of folic acid from fortified foods compared to naturally occurring food folates, folate intakes and recommendations are now typically expressed as dietary folate equivalents[45].

Thus, to optimise folate status in women of reproductive age for preventing NTD, folic acid intervention strategies are needed, for individuals and populations. Folic acid, the vitamin form used in fortified foods and supplements, is very stable and highly bioavailable and is readily converted to the natural cofactor forms of folate after its ingestion.

Folic acid supplements

For the prevention of NTD, women worldwide are recommended to take 0·4 mg/d from preconception until the end of the first trimester of pregnancy. Women with a previous pregnancy affected by NTD are considered to be at a higher risk and thus are recommended to take higher folic acid doses (4–5 mg/d).

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Evidence shows that folic acid supplementation is a highly effective means to optimise folate status in individual women who take their supplements as recommended[44,46]. However, it is not an effective public health strategy for populations because, in practice, very few women take folic acid as recommended before and in early pregnancy. This means that maternal folate status is often found to be suboptimal in terms of reaching biomarker concentrations known to be protective against NTD[47–49].

Folic acid-fortified foods

Food fortification may be undertaken on a voluntary (at the discretion of the food manufacturer) or mandatory (regulated by a government) basis. At a population level, the observed differences in folate biomarkers (erythrocyte and serum folate) between countries are primarily due to differences in exposure to folic acid-fortified foods, in turn reflecting local fortification policy[3]. Because folic acid is so much more stable and bioavailable than naturally occurring food folates, folate status in populations is found to be highest in countries with mandatory folic acid fortification, followed by those with voluntary fortification, and lowest in countries where fortified foods are not consumed.

Voluntary folic acid fortification. In countries, including the UK and Ireland, that permit voluntary fortification with folic acid and other micronutrients, the consumer will have ready access to fortified foods (e.g. breakfast cereals). In such countries, when consumed regularly, fortified foods are associated with significantly higher erythrocyte folate concentrations, as shown in studies in Irish adults[50,51] (Table 3). Thus, fortification of food is highly effective as a means of optimising folate status, albeit when conducted on a voluntary basis, the benefit will be limited to only those individuals who choose to consume fortified products[50,51].

Mandatory folic acid fortification. When folic acid fortification is undertaken on a mandatory (i.e. population-wide) basis, it has proven itself to be highly effective as a means to increase folate status in that population. Data from the US National Health and Nutritional Examination Survey, and from retrospective longitudinal studies in Canada, demonstrate that mandatory folic acid fortification has resulted in marked increases in both short-term (serum folate) and long-term (erythrocyte folate) biomarkers of folate status[52,53]. Correspondingly, the prevalence of low folate status in US women of reproductive age has dropped from 21 and 30 % to 0·8 and 2·8 %, for serum and erythrocyte folate, respectively. Mandatory fortification with folic acid, wherever it has been implemented, has produced similar results worldwide[3].

Global folic acid policy for preventing NTD: lessons learnt

As a result of the conclusive evidence of the benefits of folic acid against NTD, public health authorities globally have in place clear folic acid recommendations for women of reproductive age. The implementation of policy in this area is however problematic because, despite a proven benefit in NTD, there are concerns that folic acid could be harmful at high levels of exposure. The relative success of the contrasting approaches to prevent NTD in North America (mandatory folic acid fortification) and Europe (folic acid supplementation) provides important lessons for countries re-considering policy in this area.

Effect of folic acid policy on NTD prevalence in Europe

In Europe, policy to prevent NTD has proven to be largely ineffective. For over 25 years, policy in European countries has been based on recommending women of reproductive age (and/or those planning a pregnancy) to take a supplement containing folic acid. In the UK and Ireland, as elsewhere in Europe, despite active health promotion campaigns over many years recommending women to take folic acid supplements periconceptionally, this policy has had little or no impact in preventing NTD[54,55]. This is primarily because the neural tube closes by day 28 post-conception and therefore the timing of folic acid usage by women is critical. In many cases, the early period of pregnancy when folic acid is protective against

Table 3. Impact of voluntary fortification on dietary intakes and status of folate in Irish adults (NANS)*

	Non-consumers of folic acid* *n* 200	Consumers fortified food† *n* 767	Supplement users‡ *n* 36	Fortified food and supplements§ *n* 123	*P*
Dietary folate intake (μg/d)					
Total folate	206 (160, 293)[a]	322 (264, 392)[b]	558 (267, 636)[c]	582 (431, 746)[c]	<0·001
Folic acid	–	90 (69, 121)[a]	203 (150, 400)[b]	287 (220, 438)[b]	<0·001
Natural folate	206 (160, 293)	224 (175, 286)	237 (179, 306)	246 (185, 309)	0·983
Folate biomarkers					
Erythrocyte folate (nmol/l)	699 (538, 934)[a]	883 (716, 1163)[b]	1013 (812, 1487)[bc]	1156 (831, 1501)[c]	<0·001

Data are median (IQR).
* Consumed no folic acid from fortified foods or supplements.
† Consumed folic acid-fortified foods at least once weekly, but no supplements.
‡ Consumed folic acid from supplements at least once weekly, but no fortified foods.
§ Consumed folic acid from fortified foods and supplements. Values in a row without a common superscript letter are significantly different, $P < 0·05$ (Bonferroni post hoc test). Data adapted from Hopkins *et al.*[51].

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NTD may have passed before women start taking folic acid supplements.

In the UK, where there is voluntary (but not mandatory) fortification of foods with folic acid, the percentage of women with insufficient erythrocyte concentrations (<906 nmol/l) to prevent folate-responsive NTD was estimated to be 83 % in Northern Ireland, 81 % in Scotland and 79 % in Wales[56]. In Ireland, also with voluntary folic acid fortification only, evidence from the National Adult Nutrition Survey showed that non-consumers of folic acid from fortified food or supplements were at particularly high risk of suboptimal folate status[51] (Table 3), again using the cut-point of 906 nmol/l erythrocyte folate to define optimal status. In contrast, mandatory fortification reaches everyone in a population and is therefore a much more effective strategy for optimising folate status in women of reproductive age, regardless of socioeconomic or other factors that could potentially limit access to fortified foods.

In European countries in the absence of mandatory fortification policy, there has been no significant change in NTD rates over the past 25 years, with NTD rates recently estimated to be 1·6 times higher than in regions of the world with mandatory folic acid fortification programmes in place[57]. The European data show that failure to implement mandatory folic acid fortification has caused, and continues to cause, NTD to occur in almost 1000 pregnancies every year[58]. Notably, one recent study estimated that from 1998 to 2017, a total of 95 213 NTD pregnancies have occurred amongst 104 million births in twenty-eight European countries; a prevalence of 0·92 per 1000 births[58].

Ireland is recognised as having one of the highest rates of NTD-affected pregnancies in the world. Of particular concern are reports that the incidence of NTD in Ireland is increasing in recent years[59]. This is possibly related to a decline in folic acid-fortified products[60]. In 2016, following an extensive scientific review, the Food Safety Authority of Ireland published an updated report recommending mandatory fortification of bread or starch with folic acid[54]. Similarly, in 2017, the UK Scientific Advisory Committee on Nutrition confirmed its long-standing advice that mandatory fortification of cereal flours with folic acid should be introduced for the prevention of NTD[55]. Subsequently, in 2021, the UK Government announced that it will introduce the mandatory fortification of non-wholemeal wheat starch with folic acid, but the legislation to enact the new policy has not yet been implemented.

Effects of folic acid policy on NTD prevalence in North America

A policy of folic acid fortification of food on a mandatory basis (in place in over ninety countries worldwide to date including the USA and Canada) is highly effective in preventing NTD because it reaches all women, including those who have not planned their pregnancy. International evidence shows that wherever such a policy has been introduced, it has proved to be effective in reducing rates of NTD in that country, with reported rates of NTD declining by between 27 and 50 % in the USA, Canada and Chile in response to mandatory folic acid fortification of food[52,61,62]. The effect of mandatory fortification on NTD rates has been striking in Canada, and particularly so in Newfoundland and Nova Scotia where rates were highest before the implementation of folic acid fortification. It is worth noting that NTD data from Canada are generally considered to be more accurate than the USA, where national data on prenatally diagnosed NTD cases tend to be somewhat limited and inconsistently recorded across States. Globally, countries with mandatory policies on folic acid fortification of staple foods in place have a significantly lower prevalence of NTD compared with elsewhere[63].

In the USA, mandatory large-scale fortification of enriched cereal grain products with folic acid has been fully implemented since 1998[64]. Within 5 years, the prevalence of NTD was dramatically reduced to six per 10 000 pregnancies or fewer, indicating powerful programme effectiveness. It was recently estimated that 14 600 NTD pregnancies could have been prevented if European countries had implemented folic acid fortification at the level adopted by the USA in 1998[58]. There are also important economic impacts to consider. Mandatory fortification is estimated to have reduced the annual number of live-born spina bifida cases in the USA by 767. Direct lifetime costs per infant with spina bifida were estimated in 2016 at $791 900, or $577 000 excluding caregiving costs[65].

Fig. 3 shows NTD prevalence rates pre- and post folic acid fortification in 11 areas where mandatory fortification has been implemented; the data are from countries that have implemented fortification and have recorded the change in NTD rates. The greatest drop in prevalence was recorded in countries with the highest indigenous NTD rate (e.g. Nova Scotia and Newfoundland, Canada). The lowest NTD rates achieved in most countries to date is five to six per 10 000 births.

Challenges of translating science into effective policy and practice

Implementing effective policy and practice is challenging. As discussed earlier, as a sole public health measure and despite active health promotion campaigns over many years, folic acid supplementation has had little or no impact in preventing NTD at a population level. The lack of success of this approach is primarily because women typically start taking folic acid after the period of neural tube closure (i.e. the third to fourth week of pregnancy). For many women, the early period when folic acid is protective against NTD may have passed before folic acid supplements are even started. An even greater challenge is that an estimated 50 % of pregnancies are unplanned. Thus, a large number of women are not protected in early pregnancy and this has resulted in unacceptably high rates of NTD in Europeans countries compared to regions of the world with mandatory folic acid fortification policies in place.

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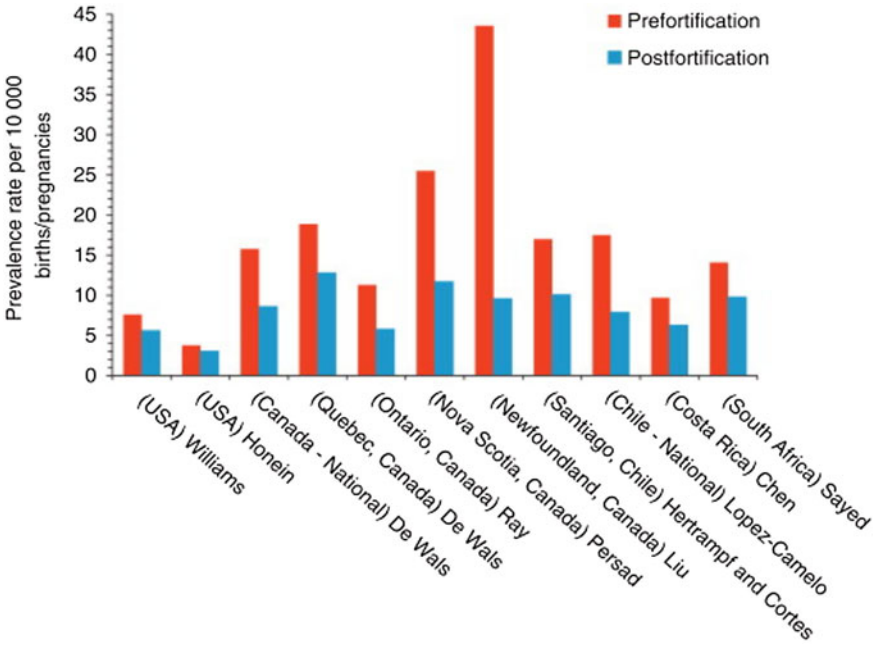

Fig. 3. NTD prevalence rates pre- and post-fortification of foods with folic acid in eleven areas where mandatory fortification has been implemented. The data are from countries that have implemented fortification and have recorded the change in NTD rates. The greatest drop in prevalence was recorded in countries with the highest indigenous NTD rate.

Considerations for emerging folic acid policy

Over 90 countries worldwide to date, including the USA, Canada and Australia, have passed regulations to implement the mandatory fortification of staple foods with folic acid in order to prevent NTD (Fig. 4). Elsewhere, including in the UK and Ireland, mandatory fortification has been delayed over many years owing to concerns relating to potential adverse effects of excess intakes of folic acid, the synthetic vitamin form. Excessive folic acid intake constitutes exposure doses that exceed the tolerable upper intake level of 1000 μg/d (i.e. 1·0 mg/d) for adults, as set by the US Institute of Medicine[66]. At the time of implementing mandatory fortification in North America, the main safety concern with folic acid fortification was that some sectors of the population, particularly older people, might be exposed to very high folic acid intakes because of concomitant fortification and supplement use.

Once ingested, folic acid is reduced by dihydrofolate reductase and, after methylation, is released in the systemic circulation as 5-methylTHF. However, the reduction of folic acid is a slow process that is influenced by individual variations in dihydrofolate reductase activity[67] and thus exposure to high oral doses of folic acid can result in the appearance of unmetabolised folic acid in the circulation. As folic acid is not a normal constituent of plasma or other tissues, concerns have been raised regarding potential (although as yet unconfirmed) adverse health effects of unmetabolised folic acid arising in the circulation through high folic acid exposures from supplements and fortified foods. Unlike the case with 5-methylTHF (the normal folate form entering cells), the uptake of folic acid by cells does not require vitamin B12; therefore, folic acid entering a cell might initiate DNA synthesis in a vitamin B12-deficient person, thereby preventing the development of (or 'masking') anaemia and potentially delaying a diagnosis of B12 deficiency, allowing the irreversible associated neurologic damage to progress and become irreversible. Although evidence drawn from the experience of over 25 years of mandatory folic acid fortification in the USA indicates that this is not a public health issue[3], nonetheless concerns remain about the potential physiological impacts of the nutrient imbalance caused by high folic acid intakes together with low vitamin B12 concentrations. Adding vitamin B12, along with folic acid, to fortified food has been suggested as a solution, but more evidence on efficacy, dosage and feasibility is required before this could be considered.

Other concerns have arisen from reports that the presence of unmetabolised folic acid in plasma in older people with low vitamin B12 status is associated with worse cognitive performance compared to those with low B12 status and no detectable folic acid in the circulation[68]. Some subsequent studies have not been able to confirm such findings and therefore this issue remains controversial[69].

Another concern is the possibility that, because of its role in DNA synthesis, high folic acid intakes could promote malignant transformation of premalignant lesions. One

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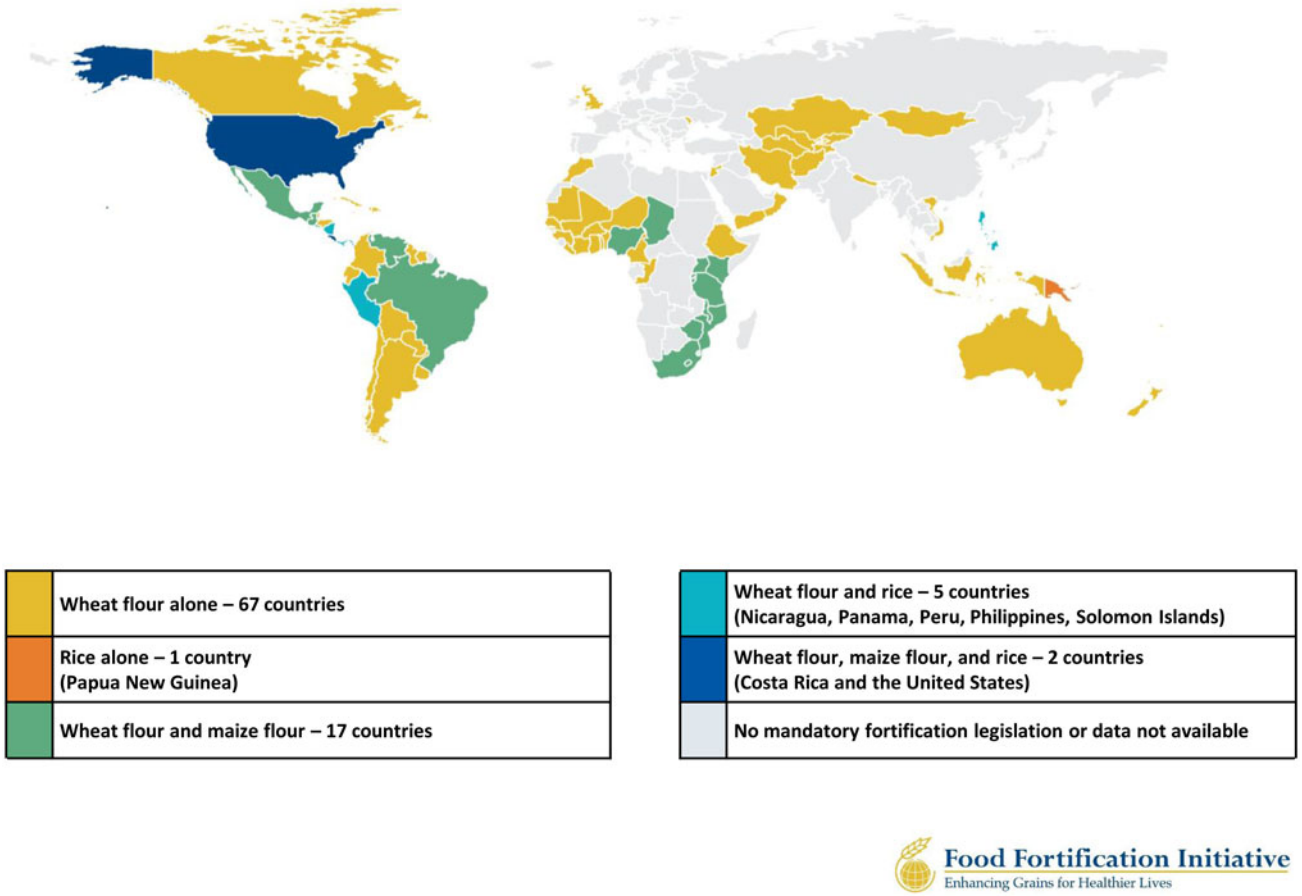

Fig. 4. Map reflecting ninety-two countries with legislation to fortify milled wheat starch, maize starch and/or rice. Legislation has effect of mandating grain fortification with at least iron or folic acid. All countries in colour fortify with iron and folic acid except Australia which does not include iron, and UK, Venezuela, the Philippines, and Trinidad and Tobago which to date fortify with iron only and not folic acid. From the Food Fortification Initiative (www.FFInetwork.org); July 2022.

notable randomised controlled trial suggested that folic acid doses in excess of 1 mg/d could potentially promote the growth of undiagnosed colorectal adenomas in those with pre-existing lesions[70]. However, a meta-analysis using data from 50 000 individuals subsequently concluded that folic acid supplementation neither increased nor decreased site-specific cancer within the first 5 years of treatment[71]. We investigated the effects on circulating unmetabolised folic acid concentrations from supplements at a dose of 400 µg/d folic acid, continued beyond the period currently recommended (i.e. to the end of trimester one of pregnancy). Folic acid intervention at this dose was shown to improve maternal and neonatal folate status[8], but did not lead to higher concentrations of unmetabolised folic acid[72], suggesting that there are no adverse impacts from the exposure of pregnant women to 400 µg/d supplemental folic acid, over and above typical folic acid intakes through fortified foods. Other potential adverse effects of high folic acid intake have been suggested, including decreased natural killer cell cytotoxicity, increased twinning rates and increased childhood asthma and autism rates[73–76]. Although none of these reports have been substantiated, vigilance remains an important public health position in relation to any food fortification strategy[69,77].

A recent report from a 2019 expert workshop tasked with reviewing the evidence in this area, as convened by the US National Institutes of Health, concluded that there is an insufficient body of evidence to support adverse human health outcomes as a result of high intakes of folic acid. Nonetheless, these experts called for further high-quality research to determine the safety of excess folic acid intake[69].

In summary, it is unlikely that there are adverse effects associated with the presence of unmetabolised folic acid in the circulation at the generally low concentrations arising through mandatory food fortification. However, given that the long-term effects of exposure to high-dose folic acid remain uncertain, it is important to avoid population-wide chronic exposures to folic acid at levels higher than are necessary. Notably, there is evidence that beneficial effects are likely to be achievable at low folic acid intakes and exposure to higher doses is unnecessary[78]. Although the risk–benefit debate surrounding food fortification with folic acid continues among policymakers, the totality of the evidence at this time indicates that the proven benefits of folic acid fortification would more than outweigh any potential risks. Nonetheless, effective

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monitoring should remain a key aspect of policy in this area, both to ensure that the target folic acid levels for beneficial effects are reached and to avoid any risk of overexposure at a population level. Also, restricting access to high-dose folic acid supplements only to individuals with a prescription will be essential.

The way forward: a call to action for preventing NTD in Ireland

Population-based strategy

Despite the public health challenges, the case for implementing folic acid fortification of food on a mandatory basis in Ireland is compelling. Inaction for over 25 years has had adverse impacts in terms of failing to prevent preventable NTD. The authors of this paper join recent calls for action globally[79–82] and urge the authorities to implement the necessary legislation in Ireland without delay.

Globally, an estimated 300 000 babies are born each year with NTD, resulting in 88 000 deaths and 8·6 million disability adjusted life years[83] and affecting approximately one in a 1000 pregnancies in Europe[84]. A national audit in Ireland during 2012–2015[85] determined that of 274 732 live and stillbirths, there were a total of 288 NTD cases and an overall rate of 1·05 per 1000 births compared with 1·04 per 1000 in 2009–11. With one of the highest rates in the world, Ireland has a higher rate of NTD-affected pregnancies than the rest of Europe. Ireland also has the highest proportion of children with spina bifida that are live-born, with an average of 86 % live-born from 2007 to 2011.

The implementation of mandatory fortification must be accompanied by rigorous monitoring to ensure that the target folic acid levels for beneficial effects are reached, whilst avoiding any risk of overexposure at a population level.

Recommendations to individual women

As a result of the conclusive evidence of the benefits of folic acid against NTD, public health authorities globally recommend women to take folic acid supplements from before conceiving until the twelfth week of pregnancy. Thus, irrespective of population-based fortification policy, targeted folic acid supplementation should continue and women should be advised to take folic acid supplements, before and in early pregnancy to ensure optimal maternal folate status, especially to cover the time (third to fourth week post conception) when the neural tube is closing. Internationally, the established recommendations distinguish between occurrent (first-time) and recurrent NTD.

- For the prevention of first occurrence of NTD, most public health authorities worldwide recommend that all women capable of becoming pregnant consume 0·4 mg/d folic acid and that total folic acid consumption should not be more than 1·0 mg/d to avoid the possible risks of excessive intakes. The only effective ways of achieving optimal erythrocyte folate concentrations associated with lowest risk of NTD are by consuming folic acid supplements or fortified foods, rather than increasing intakes of foods naturally rich in folate.
- Women with a previous pregnancy affected by NTD are advised to take the much higher dose of 4·0 mg/d folic acid, from at least 4 weeks before conception until the end of the third month of pregnancy. The 4·0 mg dose should be taken under the supervision of a doctor. Women with epilepsy on anticonvulsant therapy require individual counselling before starting folic acid supplementation.
- A recent study addressed the issue of high-dose folic acid usage and concluded that, whereas there was high-quality evidence from a large randomised controlled trial to support using 4 mg/d folic acid for those who had a previous pregnancy affected by NTD, there was a lack evidence to indicate that high doses have additional benefit in preventing NTD in women with diabetes or obesity (as recommended in certain guidelines[86]).

Similarly, in another study just published, folate concentrations were related to folic acid supplement dose and use in pregnant women across Canada, and it was concluded that higher-than-recommended folic acid doses are unwarranted for the prevention of first occurrence of NTD[87].

Conclusions

The achievement of optimal folate status is an urgent public health priority, particularly in women in early pregnancy where it has a proven effect in preventing NTD in their offspring. There is also substantial (although not conclusive) evidence to suggest health benefits of folate at other lifecycle stages. Optimal folate status cannot be achieved through natural food folates alone; the solution requires intervention with folic acid, the synthetic form, via food fortification or supplementation. Supplementation with folic acid is highly effective in optimizing folate status in individuals who take supplements. Food fortification is highly effective in consumers of fortified foods. Mandatory folic acid fortification, in place for over 25 years in the USA and Canada and ninety other countries worldwide, has a proven effect in reducing NTD at a population level. Concerns regarding potential adverse effects of folic acid have delayed the implementation of effective folic acid policy to prevent NTD in Ireland, the UK and other European countries. The balance of available scientific evidence at this time suggests that the proven benefits of mandatory folic acid fortification would more than outweigh any risks. Folic acid is however biologically highly potent, and dose is an important consideration. To maximise the benefits for women and their babies, food fortification with folic acid (for population health), once implemented, should be accompanied by continuing with the advice (for individuals) to take folic acid supplements at recommended levels periconceptionally.

Despite the important public health challenges, the case for implementing folic acid fortification of food on

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a mandatory basis in Ireland is compelling. Inaction for over 25 years has had adverse impacts in terms of failing to prevent preventable NTD. Now is the time for urgent action. The implementation of mandatory fortification must be accompanied by rigorous monitoring to ensure that the target folic acid levels for beneficial effects are reached, whilst avoiding any risk of overexposure at a population level.

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Conflict of Interest

None.

Authorship

H. McN. drafted the manuscript; M. W., A. C. and K. P. critically revised the manuscript for important intellectual content. All the authors have read and approved the final manuscript.

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