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Recent Developments in Folate Nutrition

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Conclusive evidence has been available for over a decade showing that folic acid* given to mothers before conception and in early pregnancy prevents neural tube defects (NTDs) in the growing baby. Thus, for the prevention of NTDs, health bodies around the world recommend an additional 400µg/day of folate* for women, to be started prior to conception and continued until the twelfth week of pregnancy. However, in recent years, new potential roles for folate have been emerging, to the extent that folate can no longer be seen only as "a woman's nutrient". Folate is now attracting major interest as having possible preventive roles against heart disease and stroke[1], certain cancers[2] and neuro-psychiatric conditions[3].

The most convincing of these emerging roles is the potential for optimal folate status to protect against heart disease and stroke, by preventing the build up of homocysteine in the blood. A number of large clinical trials aimed at proving a cause-and-effect relationship between raised homocysteine levels and vascular disease are underway, with the first results expected in the next couple of years. In the meantime, there is considerable evidence from a range of studies suggesting that high plasma homocysteine is an independent risk factor for both heart disease and stroke. To put this risk factor into context, the evidence suggests that a high homocysteine level as a risk factor for cardiovascular disease is similar to the risk of having an elevated cholesterol level.

Homocysteine metabolism is carefully controlled by two metabolic pathways, which are dependent on an adequate supply of folate and vitamins B_{12} and B_6. Homocysteine levels are therefore very responsive to changes which increase the levels of these vitamins. For example supplementation with folate can lower homocysteine levels by about 25%, which is equivalent to an absolute reduction of about 3 mmol/l (based on typical homocysteine levels (12 mmol/l) of Western populations). One recent meta-analysis predicts that lowering homocysteine levels by this amount would reduce the risk of coronary heart disease by 16% and stroke by 24%.[1]

Homocysteine levels are also influenced by genetic factors. In particular, about 12% of healthy people are homozygous (i.e. carry two copies of a genetic factor, one from their mother, one from their father) for one particular genetic variant, and have what is known as the C677T or TT genotype. This genotype results in a much reduced activity of a key enzyme (MTHFR) involved in folate re-cycling, which in turn causes homocysteine levels to be raised. It has been known for some time that individuals who carry this genetic variant have a higher requirement for folate.

However, intriguing new evidence has highlighted the role of a fourth, previously overlooked B-vitamin - riboflavin (vitamin B_2) - in preventing the build up of homocysteine specifically in those people with the TT genotype. This makes sense because the activity of the enzyme affected (MTHFR) is dependant on riboflavin. Recent human evidence shows that the high homocysteine levels associated with the TT genotype occur only when riboflavin status is poor.[4] In fact increasing riboflavin in those with low status lowers homocysteine levels by as much as 28%.[5] In contrast, people without this genetic variant show no such sensitivity to riboflavin[4], and therefore no lowering of homocysteine

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levels in response to riboflavin supplementation.[5]

This effect of riboflavin on homocysteine levels specifically in people with the TT genotype may help to address one previously unexplained inconsistency in the homocysteine theory of vascular disease - that although some studies have shown this common mutation to be associated with increased risk of CVD, others have failed to show this expected relationship. Such studies have not considered riboflavin status, which may vary considerably depending on the population under investigation. For example, in the USA flour has been fortified with riboflavin for many years ensuring high intakes in the whole population (irrespective of individual dietary choices). This could reduce the extent to which the TT genotype is found to carry an increased risk of vascular disease, compared to European populations where the risk of low riboflavin status is much more likely and thus risk of vascular disease linked to the TT genotype much higher.

Most healthy people are unaware of their riboflavin status or their MTHFR genotype (because neither measurement is routinely performed), making riboflavin an important, but previously un-recognised consideration in achieving optimum nutritional status among the general population to lower homocysteine levels.

Therefore, in order to provide maximum protection against raised homocysteine levels in all individuals, including those with the TT genotype, the optimal status of all four relevant B-vitamins needs to be ensured. The interplay between folate, and vitamins B_2, B_6 and B_{12}, and the genetic factors involved, are now a major focus of research worldwide. The results of this research will have important implications for the prevention of a number of diseases. Current scientific investigation is focused on understanding the protective effects of these nutrients, not only against birth defects and heart disease, but also against various forms of cancer, and possibly against dementia and depression.

However, major public-health challenges are involved since the diets of most Europeans contain levels of these key nutrients that are too low for optimal health. Achieving an ideal folate status is a particular challenge. Not only is folate vulnerable to major losses during food preparation, cooking and storage, but it may also be poorly absorbed by the body. Folic acid is less vulnerable to these losses and is more easily absorbed by the body. Fortified foods which provide folate in the form of folic acid can therefore make an important contribution to folate status. This is especially so in most European countries where, unlike the USA and Canada, there are no policies requiring the fortification of flour with folic acid to ensure an optimal folate status in the general population.

** Folate is part of the B group of vitamins. Folate is the natural form of this vitamin, which occurs in foods such as green leafy vegetables, pulses and red meats. Folic acid is the form of the vitamin that is added to foods during fortification, for example breakfast cereals and some breads. Both folate and folic acid both increase the body's folate levels, helping to protect against deficiency and promote good health.*

Reference:

1. *Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. British Medical Journal 2002; 325:1202-1208.*
2. *Rampersaud GC, Bailey LB, Kauwell GPA. Relationship of folate to colorectal and cervical cancer: review and recommendations for practitioners. Journal of the American Dietetic Association 2002; 102:1273-1282.*
3. *Reynolds EH. Folic acid, ageing, depression, and dementia. British Medical Journal 2002; 324:1512-1515.*
4. *McNulty H , McKinley MC, Wilson B, McPartlin J, Strain JJ, Weir DG, Scott JM. The impaired functioning of thermolabile methylenetetrahydrofolate reductase is dependent upon riboflavin status: implications for riboflavin requirements. American Journal of Clinical Nutrition 2002; 76:436-441.*
5. *McNulty H, Dowey LC, Scott JM, Molloy AM, McAnena LB, Hughes JP, Ward W, Strain JJ. Riboflavin supplementation lowers plasma homocysteine in individuals homozygous for the MTHFR C677T polymorphism. Journal of Inherited Metabolic Disease 2003; 26 (suppl 1): 12.*

Public support for Folic Acid Fortification in the UK

Reference: The use of "willingness to pay" to assess public preferences towards the fortification of foodstuffs with folic acid. Dixon S, Shackley P. Health Expect. 2003 6: 140-148

The Committee on Medical Aspects of Food and Nutrition Policy (COMA) in the UK have reviewed the feasibility of fortifying flour with folic acid in order to reduce the incidence of neural tube defects (NTD). The conclusion of the review was that the universal fortification of wheat flour at 240µg per 100g in food products as consumed would reduce the incidence of NTD affected pregnancies by 41%, without resulting in an unacceptably high intake in any group of the population. Following this a public consultation was undertaken which invoked 167 responses

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from academics, consumer groups, trade organisations, companies, health authorities and individuals. However only 29 (17%) of these were from individual members of the

public. In brief the results of the consultation were that; 59% (99) agreed with the proposal, 30% (50) disagreed and 11% (18) were unsure.

This study builds on the consultation exercise by directly assessing public preferences regarding the proposed fortification of wheat flour with folic acid in the UK. Short interviews were conducted on the doorstep of households in Sheffield, an industrial UK town. The interviews used a "willingness to pay" technique, which is commonly used in health economics, in order to measure both preference and value of health information to individuals. Participants read a written scenario which presented a simple overview of the reasons for folic acid fortification. They were then asked whether they supported or opposed the fortification of flour with folic acid. Participants were also asked to indicate whether they would be willing to pay extra taxes in order to fund the fortification. If opposed to fortification they were asked if they were willing to pay additional food prices for non-fortified foods to be available.

Key Findings:

- 67% (51) were in favour of fortification, 20% (15) were against and 13% (10) did not know.
- Those in favour of fortification tended to be younger and poorer than those opposed to it.
- Of those in favour of fortification, 51% (26) were willing to pay to ensure the programme went ahead, 16% (8) wanted no cost to themselves, 16% (8) protested at paying and the remaining 17% (9) were unsure about paying.
- Among those opposed to fortification, 40% (6) were willing to pay extra for non-fortified foods, 13% (2) wanted no extra cost, while the remaining 47% (7) were unsure.

These results suggest a strong level of public support for fortification of flour with folic acid and demonstrate a willingness in principle to pay for this public health intervention. However study numbers were small and more robust estimates of public preferences for fortification need to be made in order to inform public policy decision making.

Comment: The evidence supporting the need for additional folic acid, and other B vitamins in the diet is growing. The debate continues as to whether compulsory fortification of flour with folic acid should be undertaken in the UK, or indeed across Europe. However what we do know is that the individual foods currently fortified with folic acid, and other B vitamins, such as breakfast cereals, play an important role in boosting the intakes of these vitamins in several populations of Europe.

Vegetable Folates halved during cooking

Reference: The effect of different cooking methods on folate retention in various foods that are amongst the major contributors to folate intake in the UK diet. McKillop DJ, Pentieva K, Daly D, McPartlin JM, Hughes J, Strain JJ, Scott JM, McNulty H. 2002 BJN 88; 681-688.

The amount of folate in a food which is available to the body is strongly affected by storage and cooking, both of which can reduce the levels of this vitamin. Folate is affected by both heat and water, and thus substantial losses can occur when foods are cooked, particularly if boiled in water. This study looked at the effects of different cooking methods on the folate levels in those foods that are major contributors to folate intakes in the UK diet.

Initially a survey was conducted outside a local supermarket in order to assess the form in which folate rich foods were purchased (e.g. fresh or frozen) and typical cooking practices of the four foods which are the major contributors to folate intakes. Breakfast cereals and breads, the largest contributors of folate in the UK diet (21% of total folate) were not included as they do not usually require cooking at home.

The study concentrated on green vegetables which provide 16% of intake, of which spinach and broccoli were selected for testing. Potatoes were also included as despite their not being a rich source of folates, they are eaten frequently in large amounts, and provide some 14% of total folate intake. Meat folates account for 9% of total folate, and beef was selected as the largest contributor from this food group. The effects of boiling and steaming for various lengths of time on folate content were investigated for spinach, broccoli and potatoes (boiled both with and without peeling). Beef was cooked by grilling.

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Key Findings:

- Significant reductions of 51% in spinach and 56% in broccoli, occurred as a result of boiling, compared with the folate contained in the raw vegetable.
- In contrast, steaming of broccoli and spinach resulted in no significant losses of folate, even after long cooking periods.
- Compared with raw values, boiling potatoes did not result in significant losses of folate, whether or not they were peeled prior to boiling.
- No effect was found from grilling on the folate content of beef.

Preservation of folate in these various foods was highly dependent both on the food in question and the method of cooking. Folates of animal origin and in potatoes appeared to be unaffected by typical ways of cooking, even for prolonged periods. However the way in which green vegetables were cooked and length of time for which they were cooked, were found to have major effects on the amount of folate remaining in the food when eaten. It is therefore essential for any public-health effort aimed at increasing folate intakes to include practical advice on cooking methods for vegetables.

Comment: It is difficult advising individuals to increase their folate intake by eating more vegetables, if in cooking about half of the folate is destroyed. This study highlights how vulnerable water-soluble vitamins such as folate are to cooking methods and the need for communicating changes to cooking practices in order to ensure that benefits can be gained from improved dietary habits.

Reducing Homocysteine levels cuts heart disease

Reference: Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. Wald DS, Law M, Morris JK 2002 BMJ 325:1202-1207.

We have known for some time that elevated serum homocysteine is linked to cardiovascular disease, but it has not been clear whether it is a cause of cardiovascular disease or an effect of the condition. The TT genotype is a gene variant that reduces the activity of an enzyme involved in homocysteine metabolism. It affects around 10-12% of the population and causes a moderate (20%) increase in serum homocysteine levels. However studies looking at the impact of increased homocysteine levels on the risk of cardiovascular disease, need to include large numbers of individuals to be able to detect statistically significant differences. These are not yet available.

A recent meta-analysis assessed raised serum homocysteine level as possible cause for ischaemic heart disease, deep vein thrombosis, pulmonary embolism and stroke. It also looked at whether reducing homocysteine levels can play a role in preventing these conditions. A total of 72 studies where individuals with the TT genotype were and 20 prospective studies of serum homocysteine and disease risk were included in this analysis. The chance of developing the three diseases was calculated following a 5µmol/l increase in serum homocysteine level.

Key Findings:

- There were significant associations between homocysteine levels and the three diseases.
- A 5µmol/l increase in serum homocysteine level resulted in a
- 42% increase in risk of ischaemic heart disease in those with the TT genotype and a 32% increase in risk in the prospective studies
- 60% increase in risk for deep vein thrombosis with or without pulmonary embolism among those with the TT genotype (there were no prospective studies on this condition).
- 65% increase in risk for stoke among those with the TT genotype and a 59% increase in risk in the prospective studies.

This analysis found a highly significant link between homocysteine levels and cardiovascular disease and provides strong evidence that the association between homocysteine and cardiovascular disease is causal. Based on these findings, lowering homocysteine levels in the general population by 3µmol/l from current levels (achievable by increasing folate intake to 800µg per day) would reduce the risk of ischaemic heart disease by 16%, deep vein thrombosis by 25% and stroke by 24%.

Comment: This is an important study for two reasons: firstly it strengthens the association between high homocysteine levels and vascular diseases and secondly it has estimated the benefit that can be achieved from increasing folate intakes in order to lower homocysteine levels. A folate intake of 800µg is extremely difficult to achieve from natural folates alone, once again highlighting the important role of foods fortified with this vitamin in our daily diet.

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Increasing iron intake improves unexplained fatigue

Reference: Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. Verdon F, Burnand B, Fallab Stubi CL, Bonad C et al 2003 BMJ 325:1124-1127.

Feeling tired is common. Fatigue is thought to affect some 14-27% of the general population. Women are three times more likely to mention fatigue than men during consultations with their doctor. Symptoms of fatigue are related to iron deficiency anaemia, and possibly low serum ferritin levels, a measure of poor iron stores. Low serum ferritin levels in the absence of overt anaemia can indicate borderline deficiency of iron. This is thought to affect around 20% of women of childbearing age in Europe.

A randomised, double-blind placebo controlled trial among women with unexplained fatigue, looked at the rate of low serum ferritin levels and the effect of increasing iron intakes on the symptoms reported by these women.

A total of 144 women, aged between 18 and 55, with unexplained fatigue either took an iron supplement (80mg/day) or a placebo for four weeks. Low levels of serum ferritin were common, with 51% having levels below 20µg/l and more than 85% with levels below 50µg/l. The level of fatigue was measured on a 10-point visual analogue scale ranging from 1 (no fatigue at all) to 10 (very severe fatigue). A questionnaire was also used to measure fatigue, anxiety and depression.

Key Findings:

- Taking an iron supplement resulted in a significant reduction in fatigue of 29% after one month compared to a reduction of 13% in the placebo group.
- Results from the questionnaire also found significant reductions in fatigue.
- Analysis of subgroups found that only women with ferritin concentrations below 50µg/l showed significant improvements in response to iron supplementation.

This study suggests that iron deficiency may be an under-recognised cause of fatigue in women of child-bearing age, and thus identifying iron deficiency without anaemia as a potential cause of fatigue is important. The authors conclude that iron supplementation may benefit women aged between 18-55 years who are suffering from unexplained fatigue. However the improvements are likely to be greatest among women with low or borderline serum ferritin levels.

Comment: A recent Australian study (Patterson et al 2001) found that both iron supplementation and increasing dietary intakes of iron resulted in improved mental well being and lower levels of fatigue among women of childbearing age who again reported unexplained fatigue. The recent National Dietary Survey of adults in the UK reported that one quarter of women aged between 18-64 years were consuming levels of iron below the Lower Reference Nutrient Intake for iron (< 4.7mg/day) and that average intakes were just 82% of recommended intakes (14.8mg/day). Similar low levels of intake have been reported in populations across Europe. Raising awareness of the importance of iron rich foods (red meat, pulses, eggs, fortified breakfast cereals and breads etc.), among women should be an important public health strategy for Europe.

Risk Factors for Iron deficiency among children

Reference: Risk factors for low iron intake and poor iron status in a national sample of British young people aged 4-18 years. Thane CW, Bates CJ and Prentice A. Pub Health Nutr 2003 6:485-496.

Young people are more likely to be iron deficient than adults, due to their high requirement for this mineral. Iron deficiency affects up to 40% of children and adolescents throughout Europe and is associated with anaemia, tiredness, loss of appetite, impaired physical activity, poor learning capacity and lowered resistance to infection, which together result in poor educational achievement. The onset of menstruation and adoption of poor eating habits and slimming diets accentuates the problem among girls.

This paper is a further analysis of the UK National Diet and Nutrition Survey of Young People aged 4-18 years, published in 2000, examining the relationship between iron status and intake in relation to consumption of the main food groups.

Key Findings:

- 54% of 4-18 years olds had intakes below the recommended nutrient intake and 12% had intakes below the lower recommended nutrient intake.
- Iron intakes were lowest in the 11-18 year age group, especially among girls who were almost five times more likely to report low dietary iron intakes compared to boys.
- Breakfast cereal consumption (expressed as g per MJ energy intake) was significantly related with iron intake.
- Overall, haem iron (from animal sources such as meat) provided just 4% of total iron intake.
- Consumption of the other main food groups, with the possible exception of fruits, nuts and dairy foods among 11-18 year old girls, were not associated with higher dietary iron intake.
- Among girls, low intakes of both iron and vitamin C resulted in a significantly higher incidence of low haemoglobin levels, with and without low serum ferritin levels.
- Vegetarian girls were more likely to have poor iron status compared to their counterparts.

Advice to reduce the risk of low iron intake and/or poor iron status in young people is important, particularly for adolescent girls. In addition attention should be given to highlighting not only sources of iron in the diet (e.g. meat and iron-fortified breakfast cereals), but also dietary components that may improve iron status such as vitamin C rich foods and drinks.

Comment: Iron deficiency is the most common nutritional disorder, affecting in particular children and women. The potential lasting impact in terms of poor educational achievement is particularly concerning. Sources of iron in the modern diet reflect the considerable changes in dietary habits that have occurred over recent decades. For example fortified breakfast cereals have become an important source of iron in the diets of children. Following the publication of this paper the author called for at minimum maintenance of current levels of fortification with iron and preferably an extension of the range of foods fortified with iron in order to help combat this major public health issue across Europe (FENS 2003).

The addition of Vitamins and Minerals to food

Reference: Vitamins and Minerals: a model for safe addition to foods. Flynn A, Moreiras O, Stehle P, Fletcher RJ, Muller DJG, Rolland V. Eur J Nutr 2003 42:118-130.

Dietary surveys have established that a significant proportion of the population in many European countries have intakes below nationally recommended levels for several vitamins and minerals. Such individuals have an increased risk of sub-optimal nutritional status for important nutrients, including iron, calcium, zinc, vitamins B_1, B_2, B_6, D and folate. There is clear evidence that the voluntary addition of vitamins and minerals to foods (fortification) which is undertaken by some food manufacturers provides an important contribution to total dietary intakes. However, legislation controlling fortification varies considerably across Europe, which has led to a proposal for harmonised regulation in the EU.

This paper sets put to address concerns in some quarters that more wide-spread fortification may result in unacceptably high intakes of some micronutrients.

It describes a theoretical model to calculate the amount of each nutrient which can be safely added to foods based on actual food intakes from European national dietary surveys. The model takes into account individuals consuming the largest amounts of foods (i.e. with the top 5% of energy intakes) and thus having the greatest intakes of vitamins and minerals. The benchmark for safety used in the model is the current European Upper Safe Levels of each micronutrient, i.e. the amount of each which can be safely consumed over a long period of time.

Also included into the model are estimates of the proportion of foods in the diets of the highest consumers, which are fortified based on available data from the French, Irish and British dietary surveys, as these are countries where fortification is practiced. Also estimated was the proportion of foods to which micronutrients might realistically be added, taking into account the commercial, practical and technical limitations.

The paper concluded that foods which might be fortified in principle could account for up to 50% of energy intakes. In practice however, only 3-9 percent of food energy comes from foods fortified with one or more nutrients, in those countries where voluntary fortification has occurred for many years (e.g. Germany, France and the UK).

The model identified three main categories of vitamins and minerals:

Group 1 – those which can be safely added to foods generally at levels greater than the EC RDA per 100g portion of food. This includes vitamins B_{12}, C, E, riboflavin, pantothenic acid, niacin and thiamine.

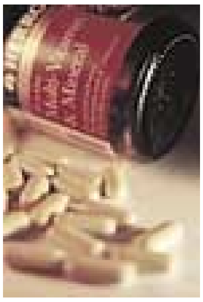
Group 2 - those that can be added safely between 50-100% of the EC RDA per 100g portion of food. This includes vitamins B_6, D, folic acid, biotin and the minerals copper, iodine and selenium.

Group 3 - those that can be safely added at levels between 10-40% of EC RDA per 100g portion of food. This includes iron, zinc, calcium, phosphorous and magnesium.

A fourth category consisting solely of retinol (vitamin A) for which present levels of fortification of foods, such as margarine appear to pose no problems in the diets of Europeans. However consideration may be needed regarding further general fortification for this nutrient.

In its present form, the model was developed for adults, but may be also valid for children since their intakes of both foods and nutrients are lower than those of adults. Some nutrients such as calcium present a lower hazard to children. This is because although children have a lower food intake, the upper tolerable intake level is the same for children as for adults.

The model, which was designed to protect high consumers of fortified foods, suggests that 15% or more of the EU RDA per 100g portion of most nutrients can be safely added to foods in Europe. This is consistent with a similar assessment carried out by AFSSA (the French food standards agency) in the context of the French diet.



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