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Benefits and concerns regarding folic-acid fortification

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Folate, or its pharmaceutical form folic acid, is essential in amino acid metabolism and for the synthesis of DNA and RNA. Many fruits and vegetables, but also milk, bread and meat, are rich sources of dietary folates. The beneficial effect of folic-acid supplements on the prevalence of neural tube defects is well known. It is presumed that folic acid supplements also exert beneficial effects on the prevalence of other birth defects, cardiovascular disease, neuropsychiatric disease and cancer. A concern regarding folic acid supplementation is the masking of vitamin B_{12} deficiency, although this occurs only at high dosages. Other concerns might be an increased risk of progression of already existing, but still undiagnosed, cancer and, very unlikely, an increased risk of spontaneous abortions. There is, however, no evidence for these effects. Although consumption of folate-rich food increases blood folate levels, this increase remains insufficient, particularly for the prevention of neural tube defects. Much effort is made to stimulate women planning a pregnancy to take folic acid supplements, but most women still refrain from following this advice. By fortification of staple food with folic acid, analogous to the USA, Canada and some other countries, many birth defects can be prevented, while also the risk of cardiovascular disease may be favorably affected.

Keywords: folic acid; fortification; prevention; neural tube defects; cardiovascular disease.

Folate is one of the B-vitamins (vitamin B_{11}). It is essential for C1-unit transfer in amino acid metabolism and for synthesis of DNA and RNA. Folate designates the natural dietary form. It consists of various reduced forms of N-pteroylglutamic acid (PGA) and is mainly polyglutamated. (Citrus) fruits and some vegetables, including asparagus, beets, broccoli, cauliflower, corn, green beans, peas and potatoes, are particularly rich dietary sources of folates. Folic acid or PGA is the common pharmaceutical form (figure 1). The main circulating form of folate is 5-methyltetrahydrofolate. It is converted to tetrahydrofolate and subsequently to other active forms of folate. Tetrahydrofolate is formed from 5-methyltetrahydrofolate by donating the 5-methyl-group to homocysteine to form methionine via a vitamin B_{12}-dependent step (figure 2). The ability to recycle methionine is important for adequate cellular functioning, since it provides us with S-adenosylmethionine, which is the essential methyl-donor in numerous processes, including the methylation of DNA, RNA, histones and phospholipids.

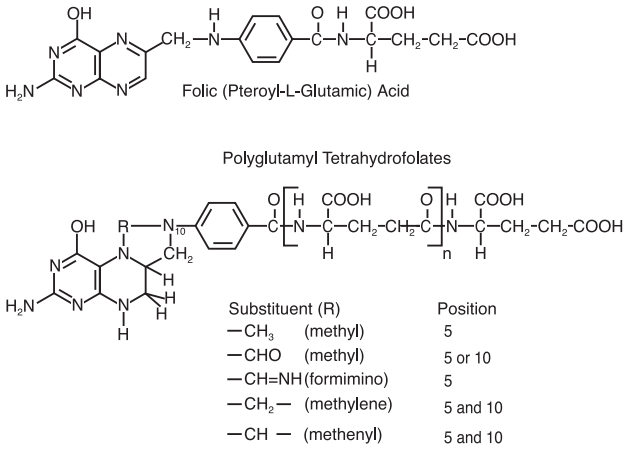

Figure 1. Molecular structures of folic acid (top) and folate (bottom).

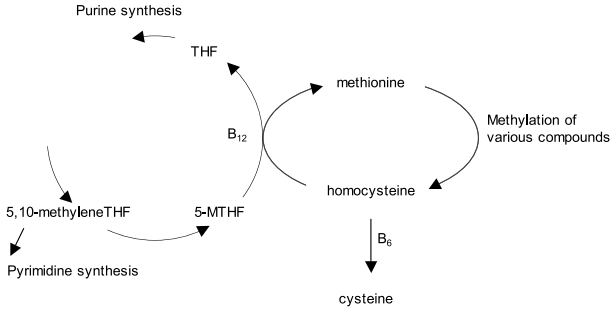

Figure 2. Simplified scheme of folate and homocysteine metabolism. THF = tetrahydrofolate, 5-MTHF = 5-methylTHF.

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Clinical folate deficiency is associated with megaloblastic anemia and some mental disorders including irritability, forgetfulness and hostile and paranoid behavior. This condition is highly uncommon in Western populations. The importance of a so-called subclinical folate deficiency is however increasingly recognized. This stage is characterized by the absence of folate deficiency symptoms, but the presence of an increased risk of certain diseases, mainly in the long term. In this overview, we review currently know relations between folate status and disease. We summarize both the benefits and possible concerns regarding folic acid fortification, and discuss the possibilities to augment the folate status of the general population.

Benefits of increased folate or folic acid intakes

Folate and birth defects

In the early nineties two randomized controlled trials showed that the use of folic acid before and during the first weeks of pregnancy could reduce the risk to give birth to a child with a neural tube defect with 50-70% (1, 2). These findings were confirmed by many observational studies. Other observational studies showed that folic acid might also be protective against other congenital anomalies like heart anomalies, orofacial clefts, limb reduction defects, urinary tract anomalies, omphalocele, and anal atresia. In most studies, folic acid was supplemented through a multivitamin preparation containing ″1 mg folic acid. These studies are summarized in a review by Botto et al. (3). They showed that folic acid supplementation was associated with a general reduction of birth defects, with odds ratios ranging from 0.53 (95% confidence interval (CI) 0.35-0.70) to 0.80 (95%CI 0.69-0.93). Botto et al. also presented an overview of studies that focused on specific groups of anomalies. For clefts, some studies showed a significantly decreased risk after multivitamin use, whereas others failed to do so. For both omphalocele and anal atresia, only one study was performed to show a decreased risk of these defects after periconceptional use of multivitamins. Baseline risks and estimated risk reductions upon folic acid supplementation for heart anomalies, urinary tract anomalies and limb reduction defects, and all defects together are shown in table 1. For all birth defects taken together the estimated number of avoidable defects amounted to 6-14 per 1,000 births (20-47% of 30/1,000).

Folate and cardiovascular disease

Several authors have reported an inverse relation between folate intake, or blood folate levels, and risk of coronary heart disease (4, 5). Three studies were unable to find a significant effect, although two of these suggested that low folate status might increase coronary heart disease risk. The folate-heart disease relation is likely to be mediated by high plasma total homocysteine concentrations. Folate is a co-substrate in the conversion of homocysteine to methionine (figure 2) and conditions of inadequate availability of folate and/or other micronutrients (e.g. vitamin B_{12} and vitamin B_6) involved in methionine metabolism may cause high plasma homocysteine. Plasma homocysteine is considered to be an independent risk factor of coronary heart disease, but also of cerebral and peripheral vascular disease. In a meta-analysis of prospective and genetic studies it was estimated that a 25% reduction of plasma homocysteine, corresponding with about 3 µmol/l, is associated with 16% lower ischaemic heart disease risk, 25% lower risk of deep venous thrombosis and 24% lower risk of stroke (6). The risk reduction may be even higher in subjects with multiple risk factors. Many randomized controlled trials have shown positive effects of folic acid supplementation (with or without vitamins B_{12} and B_6) on intermediate endpoints, particularly in high-risk patients. So far, the results of randomized controlled trials that reported clinical endpoints are contradictory (7). It should however be noted that the expected small relative risk reductions would be hard to prove in these relatively small patient groups, with many of these having advanced cardiovascular disease. Awaiting stronger evidence of a causal relation, many heart foundations, including the Netherlands Heart Foundation (8), already recommend plasma homocysteine testing of all subjects with high coronary heart disease risk and to supplement those with hyperhomocysteinemia with folic acid alone or its combination with the vitamins B_{12} and B_6.

Folate, pregnancy complications, neurological disease and cancer

Improving folate status of the general population may provide other health benefits in addition to the reduction of neural tube defect rates and cardiovascular disease. Folate or folic acid may also reduce the risk of adverse pregnancy outcomes, including recurrent early pregnancy loss, pre-eclampsia and ‘abruptio placentae’

Table 1. Estimated effects of folic acid supplementation on risk reduction of birth defects (3)

Defect	Number of studies	Rate of defect/ 1000 births	Highest OR	Lowest OR	Number of defects avoidable per day worldwide (range)
Heart	5	8	0.76	0.42	700-1,700
Limb reduction	4	0.5	0.64	0.19	50-150
Urinary tract	3	4	0.60	0.17	600-1,200
All birth defects		30	0.80	0.53	2,100-5,200

The number of avoidable birth defects/1,000 can be calculated from the baseline defect rates and the odds ratio’s (OR) by (1-OR)*defect rate.

(9, 10), and of neuropsychiatric disorders, e.g. schizophrenia, Parkinson's disease and dementia (11). Folate intake and status is also associated with a reduced risk of several types of cancers, including colorectal, breast and cervical cancer, cancer of the ovaries, pancreas, brain and lung, and of neuroblastoma and leukemia (12).

Concerns regarding folic acid supplementation

Masking of vitamin B_{12} deficiency

Some concerns exist regarding the possible side-effects of folic acid supplementation. Although folic acid is safe and almost free of adverse side-effects, concerns that folic acid fortification may mask symptoms of vitamin B_{12} deficiency, primarily in the elderly population, have been raised. Vitamin B_{12} deficiency has been estimated to affect up to 10-15% of the population over 60 years of age (13). The amount of fortification chosen in the USA was set at 140 µg per 100 g flour (14), because with this amount only a very small proportion of the population would become exposed to over 1 mg/day. The upper limit of 1 mg was chosen by the Institute of Medicine on the basis of the improbability to cause masking, taking a safety factor of 5 into account. The masking effect has been shown to occur only at folic acid dosages of >5 mg/day (13). Because of the potential of masking the diagnosis of vitamin B_{12} deficiency, several European countries decided not to adopt mandatory food fortification.

Cancer

Although folate seems preventive in the development of new cancers in persons without pre-existing premalignant lesions or neoplastic foci, there are also indications that folate may enhance the development and progression of already existing, undiagnosed, premalignant and malignant lesions (12). In these patients, low folate status is considered to disrupt DNA synthesis, through the reduction of purine and thymidine synthesis, and thereby to inhibit tumor growth. This feature has indeed been the basis of the use of folate antagonists in cancer treatments. According to Kim (12), it is possible that, in addition to folate deficiency, also a high folate status may have detrimental effects on DNA integrity and cancer risk. There are indications that folate may be involved in cancer etiology via the epigenetic machinery that regulates DNA methylation (12). Whether folic acid promotes the progression of cancer should be investigated in long-term follow-up studies that determine the effect of folic acid on the incidence of cancer, especially in countries that adopted mandatory generalized folic acid fortification. A recent study in Canada, showing that folic acid fortification was associated with a significant reduction in the incidence of neuroblastoma among children aged <18 y, is an important piece of information in this discussion (15).

Adverse pregnancy outcomes

The available evidence to show an increased risk of multiple births and spontaneous abortions in relation to folic acid use is inconclusive. Four studies have suggested a possible increase in the occurrence of multiple births (16-19), of which two did not reach significance (16, 17). The two studies with Swedish data described an increased occurrence of dizygotic twins (18, 19), but the intake of folic acid supplements in the Swedish population was very low. In a large population-based prospective cohort study among young women in China, no increase of multiple births (or of dizygotic twins) was found in women who had taken 400 µg folic acid supplements compared with those who did not (20). This study from China seems to be unaffected by important confounding factors, such as increased maternal age and the use of ovulation stimulating drugs.

An increased risk of spontaneous abortion has been reported in relation to folic acid deficiency, use of folic acid antagonists and to genetic polymorphisms in genes involved with folate metabolism (21). By contrast, analyses of data of two randomized trials (1, 2) found (i) a significant 16% increase in miscarriages among women in the Hungarian trial who consumed a multivitamin with 800 µg folic acid, and (ii) an insignificant 15% increase among women in the medical research council vitamin study who received 4,000 µg folic acid (1). The explanation was that folic acid might extend the viability of fetuses that might otherwise be lost much earlier. A large population-based cohort study with 23,806 births and 2,155 miscarriages of first pregnancies in China found no evidence that daily intake of folic acid influenced the risk of miscarriages (22). Neither did a case-control study investigating the relation between plasma folate levels and the risk of spontaneous abortion (23). On the contrary, 'low' plasma folate levels were related to a higher risk of miscarriages in this study.

Augmentation of folate status

Intake of food folate

Folate status in The Netherlands is mainly determined by intakes of vegetables, fruit and potatoes (>33% of total folate intake) and by (unfortified) bread, milk and meat products (another 33%) (24). There is evidence that common folate intakes are insufficient for optimal protection against neural tube defects (1-3). The same may also hold true for cardiovascular disease prevention. Higher food folate intakes are associated with lower cardiovascular disease risk (4, 5, 25). A large protective effect was demonstrated in the prospective Kuopio Ischemic Heart Disease Risk Factor Study. Food folate intakes above 297 µg/day reduced risk of acute coronary events with 55% (95% CI: 19-75%) when compared with folate intakes below 211 µg/d (25). An augmented consumption of food folates is also expected to have a sizeable impact on cardiovascular disease risk and neural tube defect rates in the Dutch population. Mean folate intake in this population is estimated to be about 182 µg/day (24). Interventions to increase folate status and to lower plasma homocysteine through augmented dietary folate intake do not seem feasible in the general population, since strate-

gies to increase fruit and vegetable intakes resulted in a maximal increase of merely 0.9 total daily servings (i.e. about 110 g/day) (26, 27). A 70 g/day fruit and vegetable intake increase did not affect plasma homocysteine in a recent study with free-living subjects (submitted), and is therefore unlikely to augment folate status in the general population.

Intake of folic acid supplements: the high risk strategy
Folic acid, i.e. the pharmaceutical form of folate, is more stable and has higher bioavailability compared with natural folates; 1 µg of food folate is equally available as 0.6 µg of folic acid when consumed with food or taken as a supplement, and as 0.5 µg of folic acid when taken on an empty stomach. Folic acid therefore increases folate status and lowers plasma homocysteine more effectively when compared with similar intakes of food folate. Folic acid supplements (>400 µg/day) are able to lower plasma homocysteine with approximately 25% (28), whereas an ~400 µg increase in the daily food folate consumption lowered homocysteine with merely 10% in randomized controlled trials (29, 30). Intake of folic acid from fortified foods also reduces plasma homocysteine more effectively (i.e. 24 vs. 11%) than equal amounts of natural folates (30). There is ongoing discussion on the dose and frequency of folic acid supplements for the prevention of neural tube defects and cardiovascular disease. Randomized studies addressing the relation between the supplemental folic acid dose and the reduction of disease risk are not yet available, and recommendations should therefore rely on the effects of folic acid on red blood cell folate and plasma homocysteine. The effects of supplements on these markers of folate status are distinct. Lowering of plasma homocysteine with a 0.5 mg/day folic acid dose is as effective (~25%) as larger doses (28). In addition, less frequent, but higher, dosages seem equally effective as daily supplements with lower dosages (31, 32). On the other hand, red blood cell folate gradually increases with increasing folic acid dosage (33, 34). Cardiovascular disease prevention by folic acid is ascribed to the effect on homocysteine. Lowest homocysteine (<10 µmol/l) is associated with lowest risk, and for this reason, folic acid dosages of ≥0.5 mg/day are recommended for cardiovascular disease prevention. The mechanism by which folic acid reduces neural tube defects risk is still unknown. Daly et al. (35) showed a gradual dose response relation between red blood cell folate levels and risk of neural tube defects. Women with red blood cell folate levels >906 nmol/l have a more that eightfold lower risk to give birth to an affected child compared to women with folate levels <340 nmol/l ($p<0.001$). Red cell folate levels above 906 nmol/l may be achieved with 3-6 months intake of 400 µg/day (33, 34) in populations without folic acid food fortification programs. Less frequent higher dosages seem less effective (33). Based on a mathematical model with data from several trials that addressed the relation between folic acid intake and risk of neural tube defects, Wald et al. (36) calculated that women planning a pregnancy should consume folic acid in dosages as high as 5 mg/day. In The Netherlands, women who wish to conceive are advised to take a supplemental folic acid dosage of 0.5 mg/day, starting at least 4 weeks before conception and to continue until 8 weeks of pregnancy. Women who gave birth to a child with a neural tube defect in a previous pregnancy are advised to take 5 mg daily.

Intake of folic acid fortified foods: the population strategy
Soon after the publication of the medical research council vitamin study (1), the US government decided to move forward to fortification of staple foods. Canada, Mexico, Chile, Hungary and several developing countries followed and are now fortifying staple foods or have decided to do so in the near future (37, 38). Currently, most Western European countries have decided not to adopt this strategy, with Hungary and Ireland being the exceptions (39). In many of these Western European countries specific products enriched with folic acid (breakfast cereals) are available. Other European countries initiated official health education programs to promote the use of folic acid supplements. These strategies may have been responsible for the clear decline in the prevalence of neural tube defects across Europe (39). Despite the fact that over 80% of the pregnancies in The Netherlands are planned, and that most women are aware of the protective effect of folic acid, only 36% of them use folic acid in the advised period (40). A review of 52 studies describing the use of folic acid around conception showed that the prevalence of periconceptional use varies between 0.5 and 52%, with lower use among women who have a low educational level, are of young maternal age, have unplanned pregnancies, do not have a stable relationship and belong to the immigrant population (41). Although four studies showed that the use of periconceptional folic acid increased after a campaign, it should be noted that still half of the pregnancies or more were unexposed. The effectiveness of folic acid fortification in improving folate status has already been demonstrated by the increase of the blood folate levels and also by the reduction of the prevalence of neural tube defects with approximately 15-50% in the USA, Canada and Western Australia (42-44).

Conclusion
The mean folate intake of 180 µg/day in the Dutch population is low, and causes exposure of a large proportion of the population to an increased and avoidable risk of neural tube defects, and possibly of other birth defects, cardiovascular disease, neuropsychiatric disorders and certain cancers. Increased consumption of folate-rich food may contribute to the augmentation of folate status, but this option is considered to be insufficient to provide optimal protection against these disorders and especially neural tube defects. Supplemental folic acid intake is effective in reducing the risk of neural tube defects, but many women proved incompliant to the current recommendations to use folic acid in the periconceptional period. What remains is the strategy to augment folic

acid intake by food fortification. More proactive intervention strategies seem necessary for women to obtain the folic acid dosage that is associated with the maximal protective effect. In The Netherlands pharmacists actively place stickers on packages of oral contraceptives that provide information on the benefits of folic acid supplements in the periconceptional period (45). Weighing the possible benefits and concerns, and taking into account the experiences in for example the USA and Canada, we recommend fortification of staple food, and, in addition, the intake of folic acid supplements by women who wish to become pregnant, in order to increase blood folate levels and thereby decrease the risk of several diseases in the general population.

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Samenvatting

Voordelen en bedenkingen betreffende foliumzuursupplementatie. Fokkema MR, Meijer WM en de Jong-van den Berg LTW. Ned Tijdschr Klin Chem Labgeneesk 2005; 30: 218-223

Folaat, of de farmaceutische vorm foliumzuur, is essentieel voor het metabolisme van aminozuren en voor de synthese van DNA en RNA. Veel groente- en fruitsoorten, maar ook melk, brood en vlees, zijn rijke folaatbronnen. Het is bekend dat inname van foliumzuursupplementen de prevalentie van neuralebuisdefecten doet dalen. Er wordt ook verondersteld dat foliumzuursuppletie gunstige effecten heeft op de kans op andere aangeboren afwijkingen: hart- en vaatziekten, neuropsychiatrische ziekten en kanker. Een potentieel nadelig effect van foliumzuursuppletie is het maskeren van een vitamine-B_{12}-deficiëntie. Dit effect treedt echter alleen op bij hoge doseringen. Er is ook gesuggereerd dat foliumzuur de kans verhoogt op de progressie van maligniteiten die wel reeds aanwezig, maar nog niet gediagnosticeerd zijn, en, zeer onwaarschijnlijk, op een miskraam. Voor deze effecten is echter geen bewijs. Hoewel het eten van folaatrijke voeding de folaatspiegels in het bloed kan verhogen, is deze stijging onvoldoende voor met name de preventie van neuralebuisdefecten. Momenteel worden veel inspanningen verricht om vrouwen met een zwangerschapswens foliumzuursupplementen te laten gebruiken, maar nog steeds volgen de meeste vrouwen dit advies niet op. Door voeding te verrijken met foliumzuur, naar het voorbeeld van de USA, Canada en enkele andere landen, kunnen veel aangeboren afwijkingen worden voorkomen. Mogelijk verlaagt deze interventie ook de kans op hart- en vaatziekten.

Trefwoorden: foliumzuur; verrijking; preventie; neuralebuisdefecten; hart- en vaatziekten