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Mini review

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Folate status and health: challenges and opportunities

Abstract: Each year approximately 2400 pregnancies develop folic acid-preventable spina bifida and anencephaly in Europe. Currently, 70% of all affected pregnancies are terminated after prenatal diagnosis. The prevalence of neural tube defects (NTDs) has been significantly lowered in more than 70 countries worldwide by applying fortification with folic acid. Periconceptional supplementation of folic acid also reduces the risk of congenital heart diseases, preterm birth, low birth weight, and health problems associated with child mortality and morbidity. All European governments failed to issue folic acid fortification of centrally processed and widely eaten foods in order to prevent NTDs and other unwanted birth outcomes. The estimated average dietary intake of folate in Germany is 200 μg dietary folate equivalents (DFE)/day. More than half of German women of reproductive age do not consume sufficient dietary folate to achieve optimal serum or red blood cell folate concentrations (>18 or 1000 nmol/L, respectively) necessary to prevent spina bifida and anencephaly. To date, targeted supplementation is recommended in Europe, but this approach failed to reduce the rate of NTDs during the last 10 years. Public health centers for prenatal care and fortification with folic acid in Europe are urgently needed. Only such an action will sufficiently improve folate status, prevent at least 50% of the NTD cases, reduce child mortality and morbidity, and alleviate other health problems associated with low folate such as anemia.

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Background

Folates have a central role in prevention of birth defects and other diseases. Folate deficiency without anemia occurs in a large number of individuals [1]. An estimated 4800 pregnancies are affected by neural tube defects (NTDs) each year in Europe [2]. Between 700 and 1000 of these cases are yearly diagnosed in Germany and at least 50% of these birth defects could be prevented by sufficient periconceptional supplementation of folic acid (FA) [3]. This article aims at reviewing recent evidence on the role of folate mainly during pregnancy and discussing strategies for improving folate intake and status. Efforts to increase folate intake through natural folate-rich foods are unlikely to be effective for health prevention on a population basis and would leave a large portion of the population, particularly women of reproductive age, at increased risk for diseases related to folate insufficiency.

The term dietary folate equivalent (DFE) has been introduced which refers to 1 μg natural folate or 0.5 μg of FA. The recommended dietary allowance (RDA) for folate in German population is 300 μg DFE/day [4] (Table 1), whereas the Institute of Medicine (IOM) of the US National Academy of Sciences set the RDA for folate to 400 μg DFE [5]. Different intake data from the national survey on German population (NVSII 2012) showed a mean folate intake of 200 μg DFE/day [6]. The median intake of dietary folate in young women (19–35 years) is from 170 to 181 μg DFE/day, thus clearly showing that the majority of them are at risk for insufficient intake of folate [6]. To recommend doubling the folate intake from dietary sources [4] (increase by ~200 μg DFE/day) in the population appears unrealistic. In fact, the German nutrition survey NVSII

Table 1: Folate intake recommendations (μg/day) and suppplementation recommendations.

Organization	EFSA	D-A-CH	NNR	WHO	IOM
Year	2014	2013	2012	2004	1998
For adults	330	300	300	400	400
Women of reproductive age	As for adults	As for adults	400	As for adults	As for adults
Pregnant women	600 μg DFE/day	550 μg DFE/day	500 μg DFE/day	600 μg DFE/day	600 μg DFE/day
Women planning pregnancy	No recommendations to supplement FA	Additional FA: 400 μg/day	No recommendations to supplement	Additional FA: 400 μg/day	Additional FA: 400 μg/day

NNR=Nordic Nutrition Recommendations, EFSA=European Food Safety Authority, D-A-CH=Deutschland-Austria-Confoederatio Helvetica, WHO=World Health Organization, IOM=US Institute of Medicine of the National Academy of Sciences.

showed that healthy lifestyle patterns did not predict a difference in dietary folate intake of more than 30 μg DFE/day [6]. In contrast, only people using vitamin supplements with FA were able to obtain a median total folate intake of 500 μg DFE/day [6].

Pteroylglutamic acid [folic acid (FA)] is the synthetic form of folate that is used in supplements and fortification of foods. FA is not biologically active unless reduced to tetrahydrofolate and then converted to methylfolate. FA from supplements or fortified foods is easily absorbed and converted to the active forms that increase serum folate and prevent anemia, hyperhomocysteinemia, and birth defects. FA increases serum and red blood cell (RBC)-folate in a dose-, time-, and baseline-dependent manner [1]. The serum concentration of folate mirrors recent folate status, RBC-folate concentration is a long-term marker that reflects folate storage, and total homocysteine (tHcy) represents a surrogate functional markers for folate status [7]. Serum folate is preferred over RBC-folate because it can be reliably measured using immunological or chromatography methods, shows faster response after supplementation, and reflects the amount available for transfer via the placenta. Polymorphisms in the folate cycle [i.e., methylenetetrahydrofolate reductase (MTHFR)] interfere with folate status, requirements, and diseases susceptibility. Because screening for the polymorphism on a population level is not recommended, the RDA for folate should be adequate to cover the requirements of the most liable genotype (i.e. MTHFR677 TT). A significant association between NTDs and the MTHFR677 TT genotype has been reported [8]. Irrespective of the genotype, a serum folate concentration of at least 18 nmol/L (or RBC-folate > 1000 nmol/L) is necessary to prevent most cases of folate-responsive birth defects. This level must be reached before conception. However, unless women use supplementary FA doses ranging from 400 to 800 μg/day, sufficient folate levels cannot be achieved within 1 month in the majority of women who start from low or intermediate baseline folate (discussed in [9]).

Timely supplementation of folate prevents birth defects

NTDs such as spina bifida and anencephaly are structural malformations of the central nervous system caused by delayed closure of the neural tube in the first few weeks after conception [10]. NTD births constitute considerable social and economic burden for the affected families and the health system [11]. The lifetime hospital admissions because of secondary conditions is markedly higher in patients with spina bifida compared to healthy individuals [12]. The relative risk (RR) of death among children with spina bifida is higher compared to children without birth defects [13]. The higher rate of premature death in adults [14] causes loss of working years and healthy life years. The disease is associated not only with early mortality [14], but also with greater need for health care services, in particular during the first years of life. In general, children aged from 1 to 17 years had 13 times higher medical expenditures than non-spina bifida children [15].

At least 50% of these birth defects can be prevented by improving maternal folate status before conception [3, 16–19]. The prevention potential of NTDs by providing FA depends on the women's baseline folate status markers. A dose-response relationship is observed between the risk and maternal serum or RBC-folate even within the reference range [20]. Protective levels of serum and RBC-folate are estimated to be >18 nmol/L and >1000 nmol/L respectively [9, 20, 21]. After introducing a population-wide fortification of staple foods with FA, the prevalence of NTDs in the US, Costa Rica [22], and many other countries declined to <5–6 cases per 10,000 births and thus, it is now only about half as high as the average rate of 9.3 cases per 10,000 births in Europe in 2012 (source EUROCAT, University of Ulster). The pathogenesis of NTDs and the protective mechanisms of FA are still not well understood [23], but it appears that FA cannot prevent all NTD cases.

Lower risks for congenital heart defects (CHDs) [24, 25] were also related to improving maternal folate status starting from the periconceptional period, although the evidence is not as strong as for the NTDs. However, because CHDs are more prevalent [26], the significance of preventing CHD is expected to be even higher than that for NTDs. Approximately, one in four major cardiac defects are predicted to be prevented by timely multivitamin use [24]. For example, a Dutch EUROCAT register-based study has shown that periconceptional use of FA is associated with approximately 20% reduced CHD risk in the infants [27]. The results were confirmed by a recent Chinese study that showed that the use of FA-containing supplements for ≥3 months before pregnancy is associated with approximately 70% reduction in CHD risk (OR=0.31, 95% CI 0.18–0.54) [28]. Ionescu-Ittu et al. showed that the risk of severe CHD (tetralogy of Fallot, endocardial cushion defects, univentricular hearts, truncus arteriosus, or transposition complexes) in Quebec administrative databases declined by approximately 6% in the years following FA fortification in 1998 in Canada (i.e., analyzing birth data between 1990 and 2005) [29]. In contrast, a recent study in Alberta showed that only the prevalence of cases with left ventricular outflow tract obstruction declined after fortification when comparing birth data between 1995 and 1997 and between 1999 and 2002 [30]. A further case-control study on fetuses and infants with conotruncal or limb defects in a Californian birth cohort from 1987 to 1988 showed that consuming FA-containing supplements reduces the risk for conotruncal heart defects [odds ratio 0.53 (0.34–0.85)] [31]. However, when looking at soluble folate markers in maternal blood, no association was observed between one carbon metabolites or B-vitamins in mid-pregnancy and the risk of having a child with conotruncal heart defects in a population sample from California (2002–2007) [32]. The lack of association may be due to the fact that the study was conducted after the start of FA fortification in the US in 1998. In general, the extent of the CHD risk reduction varied, was related to the lesion, and was absent in some studies [32].

Birth weight shows a positive association with FA intake or folate status [33–35] which is explained by extension of the gestational age or prevention of preterm birth. Newborns of Dutch women with serum folate >25.8 nmol/L were on average 167 g heavier than those of women with serum folate <9.3 nmol/L [36]. Considering FA supplementation, birth outcomes were studied in newborns of Hungarian women. Mean gestational age was 0.3 week longer and mean birth weight was by 37 g higher in women taking FA alone (relatively high dose 5.6 mg/day) than in the group without any supplementation [33]. The rate of preterm births was significantly lower in the FA group compared with the reference sample (without vitamin supplement) [7.6% vs. 11.8%: OR (95% CI)=0.68 (0.63–0.73)], but the rate of low-birth-weight newborns was not different [OR (95% CI)=0.88 (0.62–1.14)] [33]. The longest gestational age and lowest rate of preterm birth was found after FA supplementation during 2nd to 3rd trimesters (39.9 weeks and 3.8%) and during the entire pregnancy, that is, 1st to 3rd trimesters (39.8 weeks and 4.9%), followed by the 3rd trimester alone (39.5 weeks and 7.6%) [33]. Likewise, the risk for spontaneous preterm birth was lowered by approximately 50% in one large Chinese study using lower doses of FA (that is, 400 μg/day) starting periconceptionally [37]. An elevated plasma tHcy, a folate status marker, has been related to a 25% higher risk in the offspring to be small for gestational age [38]. Hogeveen et al. estimated that a 1.9-μmol/L increase in maternal tHcy would result in a decrease in birth weight of 31 g (95% CI: –13, –51 g) [38]. A significant public health benefit would be expected from reducing the rate of preterm births and births with low birth weight.

In addition to poor birth outcome, folate deficiency and hyperhomocysteinemia have been related to maternal health, particularly the risk for preeclampsia. FA supplementation showed no consistent protective effect against preeclampsia [39, 40]. Adequate folate supply is also important during lactation. The concentrations of folate (the main form is 5-methyltetrahydrofolate) in human milk are maintained at levels between 100 and 193 nmol/L even at low maternal serum folate concentrations [41, 42]. Maternal FA supplementation (400 μg/day) after birth increased maternal serum folate (10.9–39.0 nmol/L) and milk folate levels (from a median of 103 nmol/L to 155 nmol/L) postpartum [41]. Maternal serum concentrations of folate was not a determinant of milk folate [41], suggesting that folate is actively transported into the milk. Nonetheless, FA supplementation during lactation is important for preserving maternal folate stores, in particular with regard to subsequent conceptions.

Folate and postnatal health

Adequate maternal folate status before and during pregnancy has been related to better child development [43]. Some studies reported a positive effect of maternal folate on social competence [44], reduced likelihood to develop behavioral problems at 18 month [45], better cognitive ability [43], and less risk of hyperactivity and peer problems in childhood [46]. An association between low

maternal serum folate at early pregnancy (≤11 nmol/L) and emotional problems of the child at 3 years [OR 95%CI=1.70 (1.28–2.25)] was observed in a study on Dutch women [47].

Cerebral folate deficiency was observed in a significant number of patients with autistic spectrum disorders [48]. A recent case-control study on 429 children with autism and 278 controls reported that maternal prenatal intake of FA ≥600 μg/day (vs. <600 μg/day) was associated with a lower probability of autism in the offspring [49]. The association was more impressive in mothers with the MTHFR677 TT genotype [49], in accordance with an earlier study showing an increased risk for autism in the offspring of MTHFR677 TT mothers who were not supplemented with FA prenatally [50]. The Norwegian Mother and Child Cohort (MoBa) study, a prospective study on 85,176 children born between 2002 and 2008 in Norway [51], showed that autistic disorders were found in 0.10% of children whose mothers took FA (starting before conception and lasting at least up to the 8th gestational week) but in 0.21% of those unexposed [adjusted OR 0.61 (95%CI 0.41–0.90] [51]. Potential negative impact of low maternal whole blood folate on behavioral disorders in the children has been reported [46]. Emotional problems in the child at the age of 3 years were related to maternal folate deficiency during early pregnancy [OR 1.57 (95% CI 1.03–2.38, P=0.03] in the Generation R study [47]. Thus, several lines of evidence suggest that improving maternal folate before and early in pregnancy is protective against disorders of psychological development.

Studies showing high asthma risk in children born to mothers supplemented with FA had severe limitations in design because they were either not based on accurate measurements of folate intake or serum folate, lacked a validated definition of asthma, and did not consider child age or relevant environmental factors [52]. Hungarian children born to women supplemented with multivitamin-containing FA or trace elements without FA were examined between postnatal months 8 and 12 [53]. There was no difference in the occurrence of serious or chronic diseases except for atopic dermatitis, asthma, and wheezy bronchitis which were more frequent in the infants of multivitamin-supplemented mothers [53]. In a long-term follow-up study on 6-year-old children of the same Hungarian trial, 147 children born to mothers with FA-containing multivitamin supplementation and 142 children who had mothers with trace element supplementation only were re-examined [54]. There were no differences in the rate and distribution of disorders including allergies or any other adverse effect [54]. Therefore, the previously found association of atopic dermatitis, asthma, or wheezy bronchitis with maternal multivitamin supplementation during gestation was not confirmed [54].

Folate, aging, and population-attributable risk of diseases

An intriguing issue is whether tHcy is a marker for B-vitamin deficiency or a causal risk factor for age-related disorders. Hyperhomocysteinemia is associated with coronary heart disease (CVD) and stroke in case-control studies. A meta-analysis estimated that lowering tHcy by 25% may reduce the risk of coronary heart disease by 11% and that of stroke by 19% [55]. However, analyzing data on the association of tHcy with the MTHFR C677T polymorphism from published and unpublished datasets did not confirm a significant effect of tHcy on CVD [56]. Lowering tHcy failed to reduce cardiovascular events or mortality, but lowered stroke risk [57] which is in line with a moderate reduction of stroke incidence after FA fortification in North America in 1998 [58].

Elevated concentrations of plasma tHcy predicted the risk of future dementia in longitudinal studies [59]. Brain neuroimaging revealed an association between elevated tHcy and lower subcortical brain volumes and cortical thickness, volume, and surface area in elderly people [60]. Vitamin B treatment has been shown to slow brain volume shrinkage [61], prevent atrophy of gray matter [62], and slow cognitive decline in people with mild cognitive impairment [63], an effect that was not confirmed by all studies [64]. The effect of Hcy-lowering was confined to participants with baseline tHcy >11.0 μmol/L.

The risk of osteoporosis, hip fractures, bone mineral density [65, 66], or age-related macular degeneration has been also related to hyperhomocysteinemia, but the response to tHcy was not conclusive. Therefore, considering the current evidence, we conclude that tHcy lowering will not reduce secondary CVD or already manifested cognitive dysfunction but is likely to reduce the risk of stroke.

Folic acid fortification has been shown to be safe for the entire population. Large trials of FA supplementation with doses up to 10 times higher than the average intake confirms that such a policy is safe [18, 56, 67, 68]. Reports on increased colon cancer risk that appeared in 1996 almost simultaneously with the approval of food fortification by the FDA [69] were not confirmed later [70] or even by controlled trials using FA supplementation [68, 71–73]. Considering results from controlled trials and data from countries applying fortification programs since 1998, there is no evidence that cancer risk can be attributed to or

altered by (i.e., increased or decreased) low or moderate intake of FA.

Improving population folate status

Currently, there is no consensus on folate intake recommendations for the population in several parts of the world. Although, there is a firm evidence that periconceptional supplementation is crucial, the recommendations vary even for women of reproductive age or those planning for pregnancy (Table 1). Fortification strategies provide approximately 150 μg/day FA, an amount which is lower than all current RDAs. This amount is thought to achieve optimal folate markers for preventing NTDs. The traditional "reference range" for serum folate was based on experiments conducted by Victor Herbert who induced experimental folate depletion and defined the cut-off for serum folate where anemia becomes expressed [74]. However, recent evidence suggests that anemia may be a late manifestation of severe folate deficiency [75] and NTD prevention by FA occur in women without frank anemia or folate deficiency [21].

One strategy to improve maternal folate status is targeted supplementation of young women. In spite of strategies targeting the public as well as health care professionals, the recommendation to supplement FA periconceptionally was not successful in 60–70% of the women [76] because of the short-time interval available for NTD prevention. The importance of periconceptional services as an obligatory medical infrastructure of effective FA/multivitamin supplementation is supported by the Hungarian experience [77]. Periconceptional services are not offered by the current European health care structure. In Germany and in other parts of Europe, supplementation recommendations failed to enhance vitamin use and to reduce the incidence of NTDs during the last 10 years [78]. Therefore, integrating antenatal centers within the health care system, which can provide personalized care for all young women, is urgently needed in countries not applying mandatory fortification.

The most important factors associated with maternal folate deficiency or lack of supplementation before pregnancy were young age, low education, low income, smoking before pregnancy, obesity, and immigration background. Educational programs showed a significant increase in the awareness of women; however, the effect on supplement usage was insufficient [79]. The use of FA supplements is highly dependent on the educational and economic status of the individuals. For prepregnancy supplementation of FA to be effective, long-term and repeated educational and monitoring programs must be implemented. Obviously, engagement of health care providers and policy makers is required to reach adequate preventive measures on a population level.

The mandatory fortification of staple foods with FA is an alternative strategy that has been practiced in the US and Canada since 1998 and meanwhile has been implemented in over 70 countries with the aim of increasing the daily folate intake by approximately 200 μg DFE. The fortification has shown to be effective in terms of lowering tHcy, increasing serum, and RBC-folate [80, 81], eliminating anemia [82], and reducing NTD [22]. Fortification of staple foods requires supportive legislations or regulations, and its implementation and effects should be monitored. Compared to targeted supplementation, fortification is far more efficient and cost-effective [83].

Conclusions

The low dietary folate intake in European women explains endemic spina bifida and anencephaly. Mandatory fortification of staple foods with FA has proven to be efficient and cost-effective in more than 70 countries worldwide, but it requires legislation and continuous monitoring. Optimal folate status should be defined based on serum or RBC folate concentrations. An optimal status cannot be achieved on a population level by only recommending increased intake of natural folates. Targeted supplementation currently recommended in Europe can improve folate status. However, this theoretical option has been ineffective and failed to reduce NTDs in Europe in the last 10 years. Although voluntary fortification can offer an option, consumer's health awareness, education, and economic status determine its efficacy. There are currently no nutritional policies in Europe to monitor the results. Population folate status as a public health issue requires more awareness from health care providers and authorities.

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References

[1] Hao L, Yang QH, Li Z, Bailey LB, Zhu JH, Hu DJ, et al. Folate status and homocysteine response to folic acid doses and withdrawal among young Chinese women in a large-scale randomized double-blind trial. Am J Clin Nutr. 2008;88:448–57.

[2] European surveillance of congenital anomalies. EUROCAT special report: prevalence of neural tube defects in younger mothers in Europe 2000–2008: analysis of EUROCAT database. 2010.

[3] De-Regil LM, Fernandez-Gaxiola AC, Dowswell T, Pena-Rosas JP. Effects and safety of periconceptional folate supplementation for preventing birth defects. Cochrane Database Syst Rev 2010;CD007950.

[4] Krawinkel MB, Strohm D, Weissenborn A, Watzl B, Eichholzer M, Bärlocher K, et al. Revised D-A-CH intake recommendations for folate: how much is needed? Eur J Clin Nutr 2014;68:719–23.

[5] Institute of Medicine. In: Dietary reference intakes for thiamin, riboflavin, niacin, vitamin b6, folate, vitamin b12, pantothenic acid, biotin, and choline. Washington DC, USA: National Academy Press; 1998. p. 390–422.

[6] Deutsche Gesellschaft für Ernährung e.V. 12. Ernährungsbericht. 2012:40–85.

[7] Berti C, Fekete K, Dullemeijer C, Trovato M, Souverein OW, Cavelaars A, et al. Folate intake and markers of folate status in women of reproductive age, pregnant and lactating women: a meta-analysis. J Nutr Metab. 2012;2012:470656.

[8] Zhang T, Lou J, Zhong R, Wu J, Zou L, Sun Y, et al. Genetic variants in the folate pathway and the risk of neural tube defects: a meta-analysis of the published literature. PLoS One 2013;8:e59570.

[9] Obeid R, Koletzko B, Pietrzik K. Critical evaluation of lowering the recommended dietary intake of folate. Clin Nutr. 2014;33:252–9.

[10] Wallingford JB, Niswander LA, Shaw GM, Finnell RH. The continuing challenge of understanding, preventing, and treating neural tube defects. Science 2013;339:1222002.

[11] Bowles D, Wasiak R, Kissner M, van Nooten F, Engel S, Linder R, et al. Economic burden of neural tube defects in Germany. Public Health 2014;128:274–81.

[12] Kinsman SL, Doehring MC. The cost of preventable conditions in adults with spina bifida. Eur J Pediatr Surg. 1996;6(suppl 1):17–20.

[13] Wang Y, Hu J, Druschel CM. A retrospective cohort study of mortality among children with birth defects in New York State, 1983–2006. Birth Defects Res A Clin Mol Teratol. 2010;88:1023–31.

[14] Kancherla V, Druschel CM, Oakley GP, Jr. Population-based study to determine mortality in spina bifida: New York State Congenital Malformations Registry, 1983 to 2006. Birth Defects Res A Clin Mol Teratol. 2014;100:563–75.

[15] Ouyang L, Grosse SD, Armour BS, Waitzman NJ. Health care expenditures of children and adults with spina bifida in a privately insured U.S. population. Birth Defects Res A Clin Mol Teratol. 2007;79:552–8.

[16] Blencowe H, Cousens S, Modell B, Lawn J. Folic acid to reduce neonatal mortality from neural tube disorders. Int J Epidemiol 2010;39(suppl 1):i110–21.

[17] Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 1992;327:1832–5.

[18] Clarke R, Bennett D. Folate and prevention of neural tube defects. Br Med J 2014;349:g4810.

[19] Czeizel AE. Periconceptional folic acid-containing multivitamin supplementation for the prevention of neural tube defects and cardiovascular malformations. Ann Nutr Metab. 2011;59:38–40.

[20] Daly LE, Kirke PN, Molloy A, Weir DG, Scott JM. Folate levels and neural tube defects. Implications for prevention. J Am Med Assoc 1995;274:1698–702.
[21] Crider KS, Devine O, Hao L, Dowling NF, Li S, Molloy AM, et al. Population red blood cell folate concentrations for prevention of neural tube defects: bayesian model. Br Med J 2014;349:g4554.
[22] Barboza-Arguello MD, Umana-Solis LM, Azofeifa A, Valencia D, Flores AL, Rodríguez-Aguilar S, et al. Neural tube defects in Costa Rica, 1987–2012: origins and development of birth defect surveillance and folic acid fortification. Matern Child Health J. 2015;19:583–90.
[23] Greene ND, Copp AJ. Neural tube defects. Annu Rev Neurosci. 2014;37:221–42.
[24] Botto LD, Mulinare J, Erickson JD. Occurrence of congenital heart defects in relation to maternal mulitivitamin use. Am J Epidemiol. 2000;151:878–84.
[25] Czeizel AE. Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation. Am J Med Genet. 1996;62:179–83.
[26] Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. Am Heart J. 2004;147:425–39.
[27] van Beynum I, Kapusta L, Bakker MK, den Heijer M, Blom HJ, de Walle HE. Protective effect of periconceptional folic acid supplements on the risk of congenital heart defects: a registry-based case-control study in the northern Netherlands. Eur Heart J. 2010;31:464–71.
[28] Li X, Li S, Mu D, Liu Z, Li Y, Lin Y, et al. The association between periconceptional folic acid supplementation and congenital heart defects: a case-control study in China. Prev Med. 2013;56:385–9.
[29] Ionescu-Ittu R, Marelli AJ, Mackie AS, Pilote L. Prevalence of severe congenital heart disease after folic acid fortification of grain products: time trend analysis in Quebec, Canada. BMJ. 2009;338:b1673.
[30] Bedard T, Lowry RB, Sibbald B, Harder JR, Trevenen C, Horobec V, et al. Folic acid fortification and the birth prevalence of congenital heart defect cases in Alberta, Canada. Birth Defects Res A Clin Mol Teratol. 2013;97:564–70.
[31] Shaw GM, O'Malley CD, Wasserman CR, Tolarova MM, Lammer EJ. Maternal periconceptional use of multivitamins and reduced risk for conotruncal heart defects and limb deficiencies among offspring. Am J Med Genet. 1995;59:536–45.
[32] Shaw GM, Yang W, Carmichael SL, Vollset SE, Hobbs CA, Lammer EJ, et al. One-carbon metabolite levels in mid-pregnancy and risks of conotruncal heart defects. Birth Defects Res A Clin Mol Teratol. 2014;100:107–15.
[33] Czeizel AE, Puho EH, Langmar Z, Acs N, Banhidy F. Possible association of folic acid supplementation during pregnancy with reduction of preterm birth: a population-based study. Eur J Obstet Gynecol Reprod Biol. 2010;148:135–40.
[34] Timmermans S, Jaddoe VW, Hofman A, Steegers-Theunissen RP, Steegers EA. Periconception folic acid supplementation, fetal growth and the risks of low birth weight and preterm birth: the Generation R Study. Br J Nutr. 2009;21:1–9.
[35] Papadopoulou E, Stratakis N, Roumeliotaki T, Sarri K, Merlo DF, Kogevinas M, et al. The effect of high doses of folic acid and iron supplementation in early-to-mid pregnancy on prematurity and fetal growth retardation: the mother-child cohort study in Crete, Greece (Rhea study). Eur J Nutr 2013;52:327–36.
[36] Bergen NE, Jaddoe VW, Timmermans S, Hofman A, Lindemans J, Russcher H, et al. Homocysteine and folate concentrations in early pregnancy and the risk of adverse pregnancy outcomes: the Generation R Study. Br J Obstet Gynecol. 2012;119:739–51.
[37] Li Z, Ye R, Zhang L, Li H, Liu J, Ren A. Periconceptional folic acid supplementation and the risk of preterm births in China: a large prospective cohort study. Int J Epidemiol. 2014;43:1132–9.
[38] Hogeveen M, Blom HJ, den HM. Maternal homocysteine and small-for-gestational-age offspring: systematic review and meta-analysis. Am J Clin Nutr. 2012;95:130–6.
[39] Wen SW, Chen XK, Rodger M, White RR, Yang Q, Smith GN, et al. Folic acid supplementation in early second trimester and the risk of preeclampsia. Am J Obstet Gynecol. 2008;198:45–7.
[40] Li Z, Ye R, Zhang L, Li H, Liu J, Ren A. Folic acid supplementation during early pregnancy and the risk of gestational hypertension and preeclampsia. Hypertension 2013;61:873–9.
[41] Khambalia A, Latulippe ME, Campos C, Merlos C, Villalpando S, Picciano MF, et al. Milk folate secretion is not impaired during iron deficiency in humans. J Nutr. 2006;136:2617–24.
[42] West AA, Yan J, Perry CA, Jiang X, Malysheva OV, Caudill MA. Folate-status response to a controlled folate intake in non-pregnant, pregnant, and lactating women. Am J Clin Nutr. 2012;96:789–800.
[43] Veena SR, Krishnaveni GV, Srinivasan K, Wills AK, Muthayya S, Kurpad AV, et al. Higher maternal plasma folate but not vitamin B-12 concentrations during pregnancy are associated with better cognitive function scores in 9- to 10-year-old children in South India. J Nutr. 2010;140:1014–22.
[44] Julvez J, Fortuny J, Mendez M, Torrent M, Ribas-Fito N, Sunyer J. Maternal use of folic acid supplements during pregnancy and four-year-old neurodevelopment in a population-based birth cohort. Paediatr Perinat Epidemiol. 2009;23:199–206.
[45] Roza SJ, van Batenburg-Eddes T, Steegers EA, Jaddoe VW, Mackenbach JP, Hofman A, et al. Maternal folic acid supplement use in early pregnancy and child behavioural problems: the Generation R Study. Br J Nutr. 2010;103:445–52.
[46] Schlotz W, Jones A, Phillips DI, Gale CR, Robinson SM, Godfrey KM. Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring. J Child Psychol Psychiatry. 2010;51:594–602.
[47] Steenweg-de Graaff J, Roza SJ, Steegers EA, Hofman A, Verhulst FC, Jaddoe VW, et al. Maternal folate status in early pregnancy and child emotional and behavioral problems: the Generation R Study. Am J Clin Nutr. 2012;95:1413–21.
[48] Ramaekers VT, Blau N, Sequeira JM, Nassogne MC, Quadros EV. Folate receptor autoimmunity and cerebral folate deficiency in low-functioning autism with neurological deficits. Neuropediatrics 2007;38:276–81.
[49] Schmidt RJ, Tancredi DJ, Ozonoff S, Hansen RL, Hartiala J, Allayee H, et al. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. Am J Clin Nutr. 2012;96:80–9.
[50] Schmidt RJ, Hansen RL, Hartiala J, Allayee H, Schmidt LC, Tancredi DJ, et al. Prenatal vitamins, one-carbon metabolism gene variants, and risk for autism. Epidemiology 2011;22:476–85.
[51] Suren P, Roth C, Bresnahan M, Haugen M, Hornig M, Hirtz D, et al. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. J Am Med Assoc 2013;309:570–7.

[52] Yang L, Jiang L, Bi M, Jia X, Wang Y, He C, et al. High dose of maternal folic acid supplementation is associated to infant asthma. Food Chem Toxicol. 2015;75:88–93.
[53] Czeizel AE, Dobo M. Postnatal somatic and mental development after periconceptional multivitamin supplementation. Arch Dis Child. 1994;70:229–33.
[54] Dobo M, Czeizel AE. Long-term somatic and mental development of children after periconceptional multivitamin supplementation. Eur J Pediatr. 1998;157:719–23.
[55] Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. J Am Med Assoc 2002;288:2015–22.
[56] Clarke R, Bennett DA, Parish S, Verhoef P, Dötsch-Klerk M, Lathrop M, et al. Homocysteine and coronary heart disease: meta-analysis of MTHFR case-control studies, avoiding publication bias. PLoS Med. 2012;9:e1001177.
[57] Huo Y, Li J, Qin X, Huang Y, Wang X, Gottesman RF, et al. CSPPT Investigators. Efficacy of Folic Acid Therapy in Primary Prevention of Stroke Among Adults With Hypertension in China: The CSPPT Randomized Clinical Trial. J Am Med Assoc. In press. doi: 10.1001/jama.2015.2274.
[58] Yang Q, Botto LD, Erickson JD, Berry RJ, Sambell C, Johansen H, et al. Improvement in stroke mortality in Canada and the United States, 1990 to 2002. Circulation 2006;113:1335–43.
[59] Hooshmand B, Solomon A, Kareholt I, Rusanen M, Hänninen T, Leiviskä J, et al. Associations between serum homocysteine, holotranscobalamin, folate and cognition in the elderly: a longitudinal study. J Intern Med. 2012;271:204–12.
[60] Madsen SK, Rajagopalan P, Joshi SH, Toga AW, Thompson PM. Higher homocysteine associated with thinner cortical gray matter in 803 participants from the Alzheimer's Disease Neuroimaging Initiative. Neurobiol Aging 2015;36(suppl 1):S203–10.
[61] Smith AD, Smith SM, de Jager CA, Whitbread P, Johnston C, Agacinski G, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. PLoS ONE 2010;5:e12244.
[62] Douaud G, Refsum H, de Jager CA, Jacoby R, Nichols TE, Smith SM, et al. Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. Proc Natl Acad Sci USA 2013;110:9523–8.
[63] de Jager CA, Oulhaj A, Jacoby R, Refsum H, Smith AD. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. Int J Geriatr Psychiatry. 2012;27:592–600.
[64] Ford AH, Almeida OP. Effect of homocysteine lowering treatment on cognitive function: a systematic review and meta-analysis of randomized controlled trials. J Alzheimers Dis. 2012;29:133–49.
[65] Enneman AW, Swart KM, Zillikens MC, van Dijk SC, van Wijngaarden JP, Brouwer-Brolsma EM, et al. The association between plasma homocysteine levels and bone quality and bone mineral density parameters in older persons. Bone 2014;63:141–6.
[66] Clarke M, Ward M, Strain JJ, Hoey L, Dickey W, McNulty H. B-vitamins and bone in health and disease: the current evidence. Proc Nutr Soc. 2014;73:330–9.
[67] Clarke R, Bennett D, Parish S, Lewington S, Skeaff M, Eussen SJ, et al. Effects of homocysteine lowering with B vitamins on cognitive aging: meta-analysis of 11 trials with cognitive data on 22,000 individuals. Am J Clin Nutr. 2014;100:657–66.
[68] Vollset SE, Clarke R, Lewington S, Ebbing M, Halsey J, Lonn E, et al. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50,000 individuals. Lancet 2013;381:1029–36.
[69] Berry RJ, Bailey L, Mulinare J, Bower C. Fortification of flour with folic acid. Food Nutr Bull. 2010;31:S22–35.
[70] Gibson TM, Weinstein SJ, Pfeiffer RM, Hollenbeck AR, Subar AF, Schatzkin A, et al. Pre- and postfortification intake of folate and risk of colorectal cancer in a large prospective cohort study in the United States. Am J Clin Nutr. 2011;94:1053–62.
[71] Oaks BM, Dodd KW, Meinhold CL, Jiao L, Church TR, Stolzenberg-Solomon RZ. Folate intake, post-folic acid grain fortification, and pancreatic cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Am J Clin Nutr. 2010;91:449–55.
[72] Stevens VL, McCullough ML, Sun J, Gapstur SM. Folate and other one-carbon metabolism-related nutrients and risk of postmenopausal breast cancer in the Cancer Prevention Study II Nutrition Cohort. Am J Clin Nutr. 2010;91:1708–15.
[73] Maruti SS, Ulrich CM, White E. Folate and one-carbon metabolism nutrients from supplements and diet in relation to breast cancer risk. Am J Clin Nutr. 2009;89:624–33.
[74] Herbert V. Minimal daily adult folate requirement. Arch Intern Med. 1962;110:649–52.
[75] Golding PH. Severe experimental folate deficiency in a human subject – a longitudinal study of biochemical and haematological responses as megaloblastic anaemia develops. Springerplus 2014;3:442.
[76] Barbour RS, Macleod M, Mires G, Anderson AS. Uptake of folic acid supplements before and during pregnancy: focus group analysis of women's views and experiences. J Hum Nutr Diet. 2012;25:140–7.
[77] Czeizel AE. Experience of the Hungarian Preconception Service between 1984 and 2010. Eur J Obstet Gynecol Reprod Biol. 2012;161:18–25.
[78] Bundesrat. Entschließung des Bundesrates zur Verbesserung der Folsäureversorgung der Bevölkerung. Beschluss des Bundesrates. Bundesrat, 2006.
[79] Rofail D, Colligs A, Abetz L, Lindemann M, Maguire L. Factors contributing to the success of folic acid public health campaigns. J Public Health (Oxf). 2012;34:90–9.
[80] Pfeiffer CM, Hughes JP, Lacher DA, Bailey RL, Berry RJ, Zhang M, et al. Estimation of trends in serum and RBC folate in the U.S. population from pre- to postfortification using assay-adjusted data from the NHANES 1988–2010. J Nutr. 2012;142:886–93.
[81] Pfeiffer CM, Osterloh JD, Kennedy-Stephenson J, Picciano MF, Yetley EA, Rader JI, et al. Trends in circulating concentrations of total homocysteine among US adolescents and adults: findings from the 1991–1994 and 1999–2004 National Health and Nutrition Examination Surveys. Clin Chem. 2008;54:801–13.
[82] Odewole OA, Williamson RS, Zakai NA, Berry RJ, Judd SE, Qi YP, et al. Near-elimination of folate-deficiency anemia by mandatory folic acid fortification in older US adults: reasons for geographic and racial differences in stroke study 2003–2007. Am J Clin Nutr. 2013;98:1042–7.
[83] Jentink J, van de Vrie-Hoekstra NW, de Jong-van den Berg LT, Postma MJ. Economic evaluation of folic acid food fortification in The Netherlands. Eur J Public Health. 2008;18:270–4.

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