thebmj

BMJ 2016;352:i734 doi: 10.1136/bmj.i734 (Published 16 February 2016)

LETTERS

FOLIC ACID FORTIFICATION FOR EUROPE?

Decision on folic acid fortification in Europe must consider both risks and benefits

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We are worried by the following statement in a recent editorial on the safety of folic acid fortification: "No important adverse effects have been identified to date, probably because a modest level of fortification has proved very effective in preventing these devastating birth defects."[1] It is unusual in medicine to claim that a treatment is safe just because it is effective in treating or preventing one condition—objective evidence is needed on overall safety and the side effect profile in all people exposed to the "treatment," not only those who benefit. It seems that WHO also has not fully assessed the possible harmful effects of folic acid because its guideline on folate and neural tube defects (NTDs) states: "high folic acid intake has not reliably been shown to be associated with negative health effects."[2]

The editorial's claim that half of all NTDs could be prevented by mandatory fortification in Europe is misleading, because the effectiveness of fortification depends on the baseline prevalence of NTDs, with a smaller reduction in countries with low prevalence.[3] The accompanying report found a prevalence of NTDs in Europe of 9.1 per 10 000 births.[4] In eight US states the prevalence was 10.7 before fortification but fell to 7.0 after fortification.[5] It is not likely that, if fortification is introduced, the prevalence in Europe will drop to much below 7.0 per 10 000 because only a certain proportion of NTDs are caused by low folate status and a floor effect has been noticed.[3]

Regarding possible adverse effects, for each NTD prevented, mandatory fortification of flour products with folic acid will expose several hundred thousand Europeans to folic acid, a synthetic form of folate not widely found in nature.[6] Increasing evidence suggests that certain subgroups of the population may be harmed by exposure to high levels of folic acid.[6] Some of the most consistent evidence relates to older people. In Chicago, older people who consumed >349 µg total folate per day (half of which came from supplements) had a faster rate of cognitive decline over six years than those who consumed <221 µg folate per day.[7] Furthermore, those who took daily supplements containing >400 µg folic acid showed significant cognitive decline compared with non-supplement users.[7] Another study found that after mandatory fortification in the US, those with poor vitamin B_{12} status but high serum folate (>59 nmol/L) had an increased risk of anaemia or cognitive impairment (or both),[8] which seemed to be related to the presence of unmetabolised folic acid in the circulation.[9] A similar cognitive effect was found in Australia: older people with high red blood cell folate (1594 nmol/L) and low vitamin B_{12} status (<250 pmol/L) showed an increased risk of cognitive impairment.[10] In this study, even those with low-normal B_{12} (median 383 pmol/L) but high red blood cell folate had an increased risk of impairment. In surveys across Europe, typically 6-10% of those aged ≥60 years are vitamin B_{12} deficient (plasma vitamin B_{12} <150 pmol/L) and the prevalence of deficiency increases with age. Furthermore, another 20-30% have marginal status (vitamin B_{12} 148-221 pmol/L).[11-14] Thus a considerable proportion of older people in Europe would be at risk of cognitive impairment if exposed to high folate levels.

The editorial says that the literature on folic acid and cancer is inconsistent.[1] However, a meta-analysis of almost 50 000 people in folic acid trials found a 6% increased risk of cancer in those taking folic acid, although this risk was not quite significant (relative risk 1.06, 95% confidence interval 0.99 to 1.13).[15] We do not know whether this meta-analysis was sufficiently powered to show a significant association of 6%, which is a relevant increase in cancer risk given its high prevalence. A second problem is that several relevant subgroups were not examined. In the Norwegian trials, patients who took folic acid who also had the 677TT genotype of the *MTHFR* gene had a greater risk of dying from cancer than those with the CC genotype.[16] An observational study also reported that women with the 677TT genotype and high serum folate had a higher risk of breast cancer than those with lower folate.[17] Another

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example of the importance of subgroups is that people with different genotypes of the 19bpdel polymorphism in the *DHFR* gene show different associations between folate and cancer and also between folate and cognition.[18]

Although high blood levels of folate may partly be caused by the consumption of fortified breakfast cereals or folate supplements, mandatory fortification in the US undoubtedly increased the prevalence of high serum levels.[19] A similar effect is likely in Europe if fortification is introduced. In view of the evidence that high folate levels may not be harmless, European authorities should carefully consider all the evidence on risks and benefits before recommending mandatory folic acid fortification.

Competing interests: None declared.

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Cite this as: *BMJ* 2016;352:i734