The impact of mandatory fortification of flour with folic acid on the blood folate levels of an Australian population

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ABSTRACT

Objective: To determine the impact that mandatory fortification with folic acid of wheat flour used in breadmaking has had on the blood folate levels of an Australian population since it was introduced in September 2009.

Design, setting and patients: A retrospective analysis of serum and red blood cell (RBC) folate levels of 20 592 blood samples collected between April 2007 and April 2010 from a wide variety of inpatients and outpatients and analysed in a large public hospital diagnostic pathology laboratory.

Main outcome measures: Prevalences of low levels of serum and RBC folate and monthly mean levels before and after introduction of mandatory fortification.

Results: Between April 2009 and April 2010, there was a 77% reduction in the prevalence of low serum folate levels (from 9.3% to 2.1%) in all samples tested and an 85% reduction in the prevalence of low RBC folate levels (from 3.4% to 0.5%). In April 2010, the prevalence of low RBC folate levels for females of childbearing age was 0.16% for all samples. There was a 31% increase in mean serum folate level (from 17.7 nmol/L to 23.1 nmol/L; $t = 9.3$, $P < 0.01$), and a 22% increase in mean RBC folate level (from 881 nmol/L to 1071 nmol/L). The greatest increment in mean serum folate levels occurred in September 2009, the month that mandatory fortification was introduced, although there was evidence of a gradual change during the preceding months.

Conclusion: The introduction of mandatory fortification with folic acid has significantly reduced the prevalence of folate deficiency in Australia, including in women of childbearing age.

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There is convincing evidence that an increased periconceptional intake of folate can reduce the incidence of neural tube defects in newborn infants.[1,2] This has led to the introduction of a range of government-sponsored health promotion campaigns encouraging women of childbearing age to supplement their daily intake of folate, and in many countries has also led to new food standards which provide for fortification of some food products with folic acid.

After the introduction of voluntary fortification of selected foods with folic acid in Australia in 1995, there was a significant rise in the population's blood folate levels and a reduction in the incidence of neural tube defects between 1996 and 2006.[2,3] However, by 1999 there were still only 104 folic acid-fortified products available in Australia,[4] and the impact of the voluntary fortification program fell short of what could be achieved with a universal fortification program. It was considered that mandatory fortification of flour would have a wider impact on blood folate levels and result in a further reduction in the incidence of neural tube defects.[4]

Since September 2009, Australian millers have been required to add folic acid to wheat flour used for breadmaking. Under Clause 4 (2) of Standard 2.1.1 of the Australian New Zealand Food Standards Code, this flour must now contain 2–3 mg of folic acid per kilogram.[5] This should result in 0.135 mg of folic acid per 100 g of bread, which is the equivalent of about three slices and approximately half of the recommended daily intake of folate (0.2 mg).[4]

A large number of blood samples are regularly tested for serum and red blood cell (RBC) folate levels in diagnostic pathology laboratories. To determine the impact that the introduction of mandatory fortification has had on folate levels in an Australian population, we retrospectively reviewed serum and RBC folate levels for samples collected during the period 2007–2010 and analysed in a large public hospital laboratory.

METHODS

De-identified results of all 20 592 serum and RBC folate assays performed in our diagnostic pathology laboratory between April 2009 and April 2010, as well as the months of April 2007 and April 2008, were retrieved from our database. The samples were from a wide variety of inpatients and outpatients. The demographic profile of the patients did not change significantly during the study period. All tests were performed on a Unicel DxI 800 random access immunoassay analyser (Beckman Coulter, Calif, USA); reference ranges for this assay had been established previously (serum folate, 7–25 nmol/L; RBC folate, 310–1000 nmol/L). The statistical analysis was performed using GraphPad Prism, version 5.01 (GraphPad Software, San Diego, Calif, USA).

The Sydney South West Area Health Service (SSWAHS) Royal Prince Alfred Hospital Ethics Review Committee (RPAH Zone) gave permission for our study.

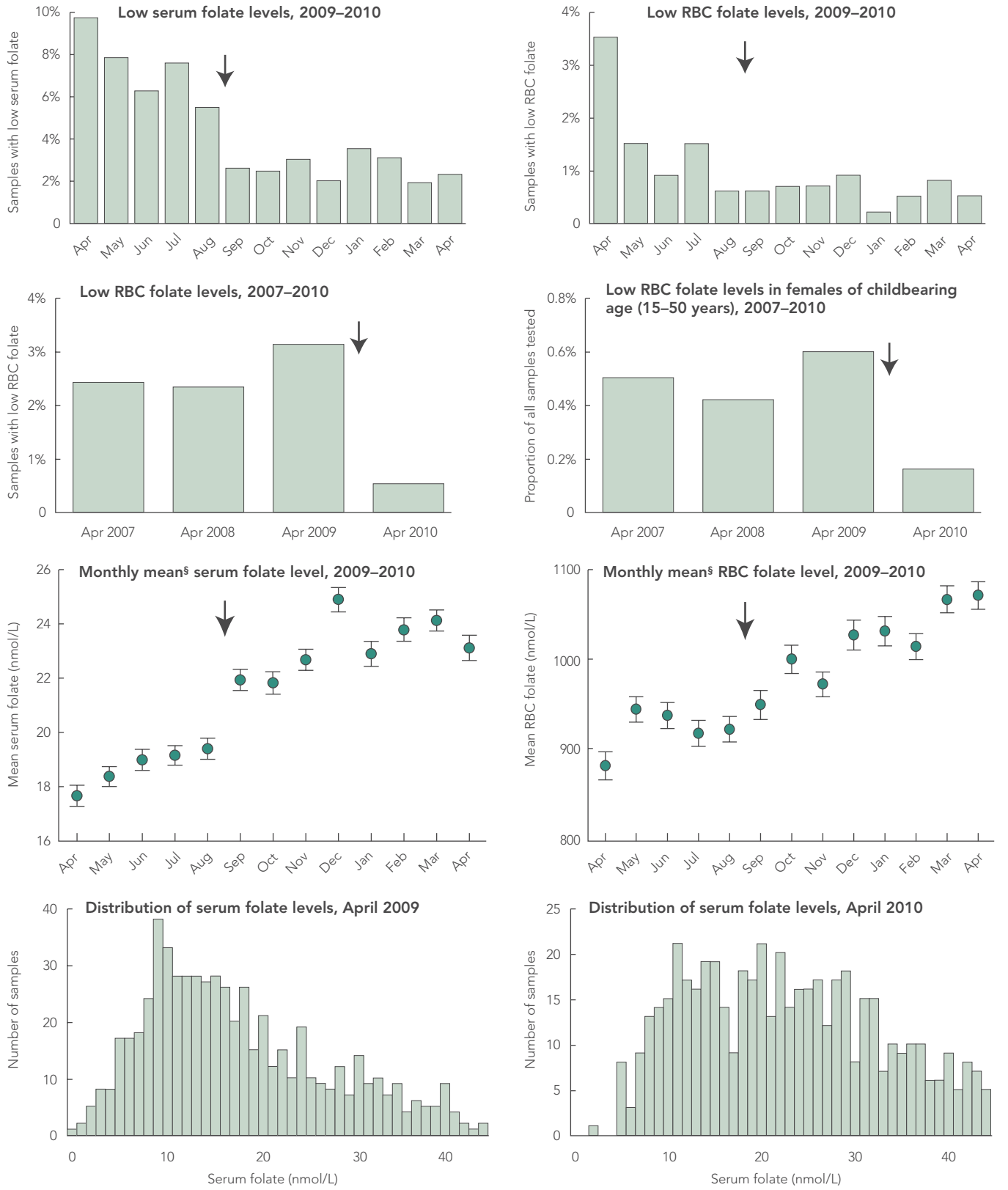
RESULTS

Between April 2009 and April 2010, the prevalence of low serum folate levels decreased by 77% (from 9.3% to 2.1%) and the prevalence of low RBC folate levels decreased by 85% (from 3.4% to 0.5%) (Box). Our analysis of results for each April from 2007 to 2010 showed a marked decrease in low RBC folate levels after April 2009 (Box). The prevalence of low RBC folate levels among females of childbearing age (15–50 years) also decreased after April 2009 (Box), and in April 2010, there was only one sample from a female of childbearing age out of a total of 609 samples tested (0.16%) which had a low RBC folate level.

Between April 2009 and April 2010, there was a 31% increase in the mean serum folate level (from 17.7 nmol/L to 23.1 nmol/L; $t = 9.3$; $P < 0.001$) and a 22% increase in the mean RBC folate level (from 881 nmol/L to 1071 nmol/L; $t = 8.7$; $P < 0.001$) (Box). In the same period, the prevalence of serum folate levels > 45 nmol/L (the upper limit of assay detection in serum) increased from 6.6% to 12.8% ($\chi^2 = 29.7$; $P < 0.001$) and the prevalence of RBC folate levels > 2000 nmol/L (the upper limit of assay detection in RBCs) increased from 6.9% to 7.9% ($\chi^2 = 12.0$; $P < 0.001$).

An overall shift towards increased folate levels in the population was evident from analysing the distribution of serum folate

Trends in serum folate* and red blood cell (RBC) folate† levels for 20 592 samples analysed in one Australian diagnostic pathology laboratory, 2007–2010‡



* Reference range (RR), 7–25 nmol/L. † RR, 310–1000 nmol/L. ‡ Arrows indicate the introduction of mandatory fortification of flour used in breadmaking. § Bars indicate 95% confidence intervals. ◆

levels between April 2009 and April 2010 (Box). Monthly mean serum and RBC folate levels increased gradually between April 2009 and April 2010. The greatest increase in mean serum folate levels was during September 2009 — the month that mandatory fortification was introduced (Box).

DISCUSSION

We have determined that mandatory fortification with folic acid of wheat flour used in breadmaking has had an impact on the blood folate levels of an Australian population since it was introduced in September 2009. To our knowledge, this study provides the first clear evidence that the prevalence of folate deficiency in Australia has significantly decreased since the implementation of mandatory fortification.

An evaluation of the effect of mandatory fortification of cereal-grain products with folic acid in the United States was reported in the National Health and Nutrition Examination Survey (NHANES) studies and showed a doubling of the mean serum folate level from 11.4 nmol/L to 26.9 nmol/L.[6] Our study showed a 31% increase in the mean serum folate level by April 2010, even when the 77 patients with levels above 45 nmol/L were excluded. In 2008, the NHANES report showed that after mandatory fortification was introduced in the US, the prevalence in women of childbearing age of low RBC folate levels was 4.5%, and of low serum folate levels was 0.5%.[7] In our study, by April 2010 the prevalences of low RBC and serum folate levels in all samples were 0.5% and 2.1%, respectively, and only one low RBC folate level (0.16%) was from a woman of childbearing age.

The population studied was not necessarily representative of the whole Australian population. The blood samples were obtained serendipitously from a population for whom a blood folate test was requested for the investigation of possible folate deficiency, and thus are likely to be biased towards low folate levels. In addition, different patients were studied before and after the introduction of mandatory fortification, and the samples would have included blood samples from patients with coeliac disease and patients on wheat-free diets. However, in view of the large number of samples studied, it is reasonable to assume that samples from similar groups of patients were collected at each interval. We do not know how many samples were from patients already taking a folate supplement, but previous studies suggest that excluding these patients would make little difference to our results.[3] The low prevalence of folate deficiency in populations who consume fortified flour may lead to a future consideration of reducing the frequency of folate testing.[8]

While increased folic acid intake can reduce the incidence of neural tube defects, it cannot prevent all cases.[9] Neural tube defects occur at a low incidence even in the babies of women with normal or high blood folate levels. Genetic and environmental factors can cause a "floor effect" for folate-preventable neural tube defects.[9]

In the US, mandatory fortification of cereal-grain products with folic acid was expected to increase the folate intake by 100 μg/day in women (and more in men), whereas in Australia it was expected that there would be a 250 μg/day increase in women's intake after voluntary fortification was introduced.[1,4] An RBC folate level of 906 nmol/L is considered to significantly reduce the risk of neural tube defects.[10] It has been suggested that supplementing a usual diet with 400 μg of folic acid daily would result in RBC folate levels over 906 nmol/L in a majority of women.[10] In the US, even after mandatory fortification was introduced, fewer than 10% of women reached this level, and the mean RBC folate level among women was 590 nmol/L.[6] In our group of Australian patients, a much higher proportion of women (64%) had an RBC folate level of greater than 906 nmol/L in April 2010. The impact of mandatory fortification on the incidence of neural tube defects has still not been evaluated.

There is ongoing controversy regarding possible harmful effects of folic acid intake from fortified products, driven by conflicting reports regarding whether risk of cancer, heart disease and masking of vitamin B_{12} deficiency increase after folic acid supplementation.[1,11] It is reassuring that the mean rise in RBC folate levels shown in the large group of patients we studied was only 22% and the prevalence of RBC folate levels over 2000 nmol/L only increased from 6.9% to 7.9%. These relatively minor overall increases in blood folate levels have led to an impressive reduction in the prevalence of folate deficiency in this Australian population.

COMPETING INTERESTS

None identified.

AUTHOR DETAILS

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REFERENCES

1 National Health and Medical Research Council. Folate fortification. Report of the expert panel on folate fortification. Endorsed at the 117th session of the NHMRC; 1994 1–2 Jun; Sydney. Canberra: Australian Government Publishing Service, 1995.
2 Bower C, D'Antoine H, Stanley FJ. Neural tube defects in Australia: trends in encephaloceles and other neural tube defects before and after promotion of folic acid supplementation and voluntary food fortification. *Birth Defects Res A Clin Mol Teratol* 2009; 85: 269-273.
3 Hickling S, Hung J, Knuiman M, et al. Impact of voluntary folate fortification on plasma homocysteine and serum folate in Australia from 1995 to 2001: a population based cohort study. *J Epidemiol Community Health* 2005; 59: 371-376.
4 Abraham B, Webb K. Interim evaluation of the voluntary folate fortification policy. Canberra: Australian Food and Nutrition Monitoring Unit, 2001. http://www.health.gov.au/internet/main/publishing.nsf/Content/84026385A0EC6DC9CA256F190004C8E1/$File/folate.pdf (accessed Jul 2010).
5 Australian New Zealand Food Standards. Standard 2.1.1 Clause 4 (2). 2009. http://www.foodstandards.gov.au/_srcfiles/Standard_2_1_1_Cereals_v114.pdf (accessed Jul 2010).
6 Deitrich M, Brown CJ, Block G. The effect of folate fortification of cereal-grain products on blood folate status, dietary folate intake, and dietary folate sources among adult non-supplement users in the United States. *J Am Coll Nutr* 2005; 24: 266-274.
7 McDowell MA, Lacher DA, Pfeiffer CM, et al. Blood folate levels: the latest NHANES results. *NCHS Data Brief* 2008; (6): 1-8.
8 Shojania AM, Kuster K. Ordering folate assays is no longer justified for investigation of anaemias, in folic acid fortified countries. *BMC Res Notes* 2010; 3: 22.
9 Heseker HB, Mason JB, Selhub J, et al. Not all cases of neural-tube defect can be prevented by increasing the intake of folic acid. *Br J Nutr* 2009; 102: 173-180.
10 Daly LE, Kirke PN, Molloy A, et al. Folate levels and neural tube defects. Implications for prevention. *JAMA* 1995; 274: 1698-1702.
11 Mathers JC. Folate intake and bowel cancer risk. *Genes Nutr* 2009; 4: 173-178.

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