

Folic Acid Food Fortification in Canada

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By January 1998, most Canadian cereal grains (e.g., white flour) were being fortified with folic acid, with a large percentage being fortified by mid-1997. This was in compliance with both American and Canadian mandatory fortification deadlines of January and November 1998, respectively. It was estimated that between 0.1 to 0.2 mg of additional synthetic folic acid per day would be provided through this initiative, the goal of which was to lower the rate of neural tube defects (NTD). The current report outlines some of the changes to the health status of Canadians in relation to its folic acid food fortification initiative.

Key words: folic acid, fortification, Canada

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Findings

Vitamin Blood Levels

Women of reproductive age. In a retrospective longitudinal study design, we considered all concomitantly processed red cell (RBC) folate and serum (Se) vitamin B₁₂ samples analyzed by a community laboratory, which provides diagnostic services to approximately one third of community-based patients in the province of Ontario.¹ These tests were ordered by physicians on clinical grounds. Among more than 38,000 Ontarian women aged 18 to 42 years, the geometric mean RBC folate concentration rose from 527 nmol/L pre-fortification to 741 nmol/L after January 1, 1998 (mean difference 214 nmol/L; unpaired t-test: $P < 0.001$) (Table 1).¹

Elderly women. Using a similar study design as above, we gathered data from two large laboratory databases in the provinces of Ontario and British Columbia, and studied women aged 65 years and over who underwent concomitant clinical testing of Se folate and B₁₂.² Among more than 15,000 women, the mean Se folate

concentration increased by 64% after fortification, from 14.8 to 24.2 nmol/L ($P < 0.001$). This occurred around the time that folic acid food fortification was initiated (Figure 1). On the other hand, the change in the mean Se B₁₂ concentration was less pronounced, rising from 280 to 300 pmol/L (Figure 2). The rate of folate deficiency dropped from 6.3% pre-fortification to 0.88% after fortification, while the rate of B₁₂ deficiency declined only slightly (Table 2).² Similar changes were also seen among Ontarian men.³

Neural Tube Defects

A retrospective population-based study was conducted of 337,000 Ontarian women who underwent antenatal maternal serum screening (MSS) for open NTD between January 1994 and August 2000.⁴ The rate of open NTD pre-fortification was 1.13 per 1000 pregnancies, declining to 0.58 per 1000 pregnancies thereafter (crude rate ratio [RR] 0.52, 95% CI 0.40–0.67). The monthly decline in NTD was also significant ($P < 0.001$) using time series analysis (Figure 2).⁴ These findings are supported by a similar estimate in the decline in open NTD during similar time periods in Nova Scotia, before and after folic acid food fortification (RR 0.46, 95% CI 0.32–0.66).⁵

Other Congenital and Chromosomal Anomalies

Orofacial clefts. An associated decline in the risk of cleft lip and cleft palate (orofacial clefts, [OFC]) has been observed in some case-control studies of periconceptional folic acid and multivitamin exposure.^{6–8} Using a similar study design as for open NTD,⁴ we conducted a retrospective population-based study of all Ontarian women who underwent maternal serum screening (MSS) at 15 to 20 week's gestation, with the option of amniocentesis, level II fetal ultrasonography and genetic counselling as needed.⁹ We found no evidence of a decline in OFC after folic acid fortification (crude RR 1.06, 95% CI 0.86–1.30), which was unchanged after adjusting for maternal age (PR 1.06, 95% CI 0.85–1.32). In the time series analysis, no significant association ($P = 0.30$) was seen between food fortification and the monthly prevalence of OFC.⁹

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Table 1. Red Cell Folate and Serum B₁₂ Concentrations before and after Folic Acid Food Fortification

Measure (mean, 95% CI)	Pre-fortification Period (n = 8408)	Post-fortification Period (n = 30,061)	Mean Absolute Difference between Periods (paired t-test P-value)
Age (years)	31.8 (31.6–31.9)	31.8 (31.7–31.8)	0.0 (NS)
Red cell folate (nmol/L)	527 (522–532)	741 (737–744)	214 (P < 0.001)
Serum B ₁₂ (pmol/L)	276 (273–279)	270 (269–272)	–6 (P < 0.001)

*Before December 31, 1997.

†After January 1, 1998.

Trisomy 21. Genetic polymorphisms for enzymes that remethylate homocysteine to methionine, a pathway dependent on normal folate metabolism, have been associated with trisomy 21,¹⁰ and a familial clustering of NTD and trisomy 21 has also been seen.¹¹ In a similar study design as that for open NTD⁴ and OFC,⁹ we failed to observe a decline in the prevalence of trisomy 21 before (1.71 per 1000) and after (1.70 per 1000) food fortification (maternal age-adjusted RR 0.99, 95% CI 0.82–1.19).¹² No significant decline in the monthly prevalence of trisomy 21 was observed using time series analysis (P = 0.24). Although 0.2 mg daily of extra synthetic folic acid may not be enough to prevent most cases of trisomy 21 cases, we would have expected some reduction in the number of cases, which was not so.¹²

Hypertensive Disorders of Pregnancy

Both folate deficiency and elevated plasma homocysteine are associated with an increased risk of the placenta-mediated diseases of pregnancy, including pre-

eclampsia-eclampsia (PET).¹³ In a recently published study, use of folic acid-containing multivitamins during pregnancy was associated with a reduced risk of developing gestational hypertension (adjusted RR 0.55, 95% CI 0.39–0.79).¹⁴

We conducted a retrospective population-based longitudinal study to assess whether the introduction of the Canadian folic acid fortification program was associated with a decline in the rate of PET and all hypertensive disorders of pregnancy.¹⁵ We studied 1,001,441 consecutive obstetrical deliveries of all liveborn or stillborn infants between April 1990 through March 2000, and found no significant decline in the monthly rate of either PET (time series model, P = 0.9) or all hypertensive disorders of pregnancy (P = 0.6) after fortification. We failed to observe any significant decline in the risk of PET after adjusting for maternal age, but did see a slight increase in the risk of all hypertensive disorders of pregnancy (Table 3).¹⁵

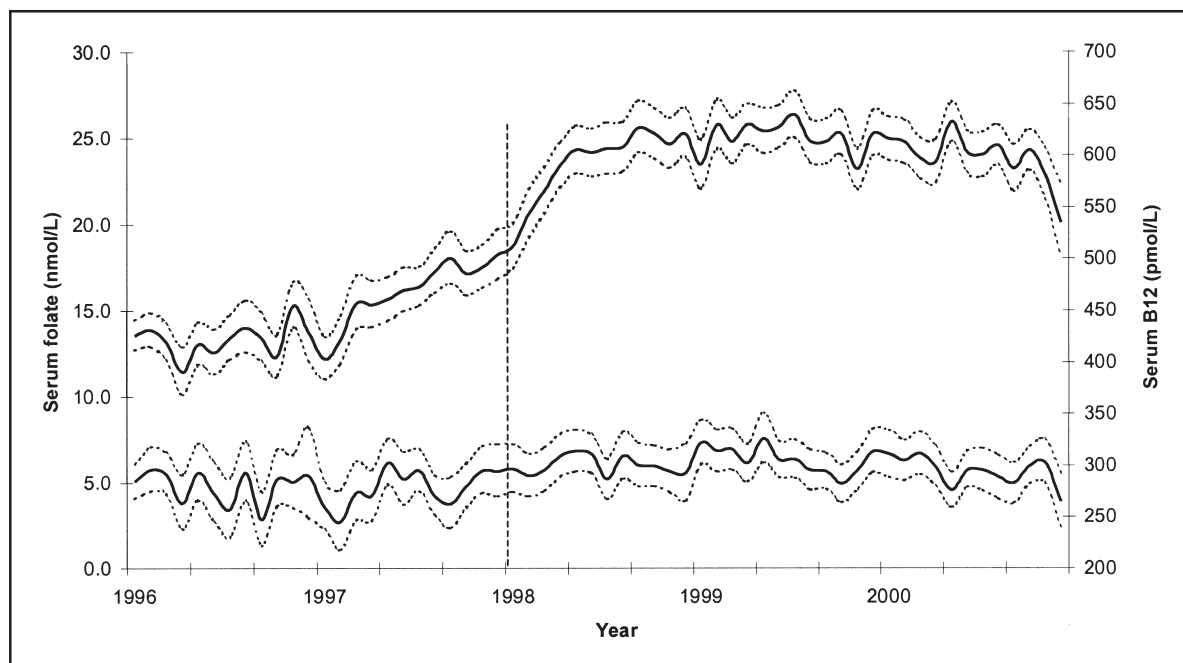


Figure 1. Change in serum folate (top) and vitamin B₁₂ (bottom) concentrations among Canadian women aged 65 years and older, before and after folic acid food fortification (vertical dashed line). Data are presented as means and 95% confidence intervals.

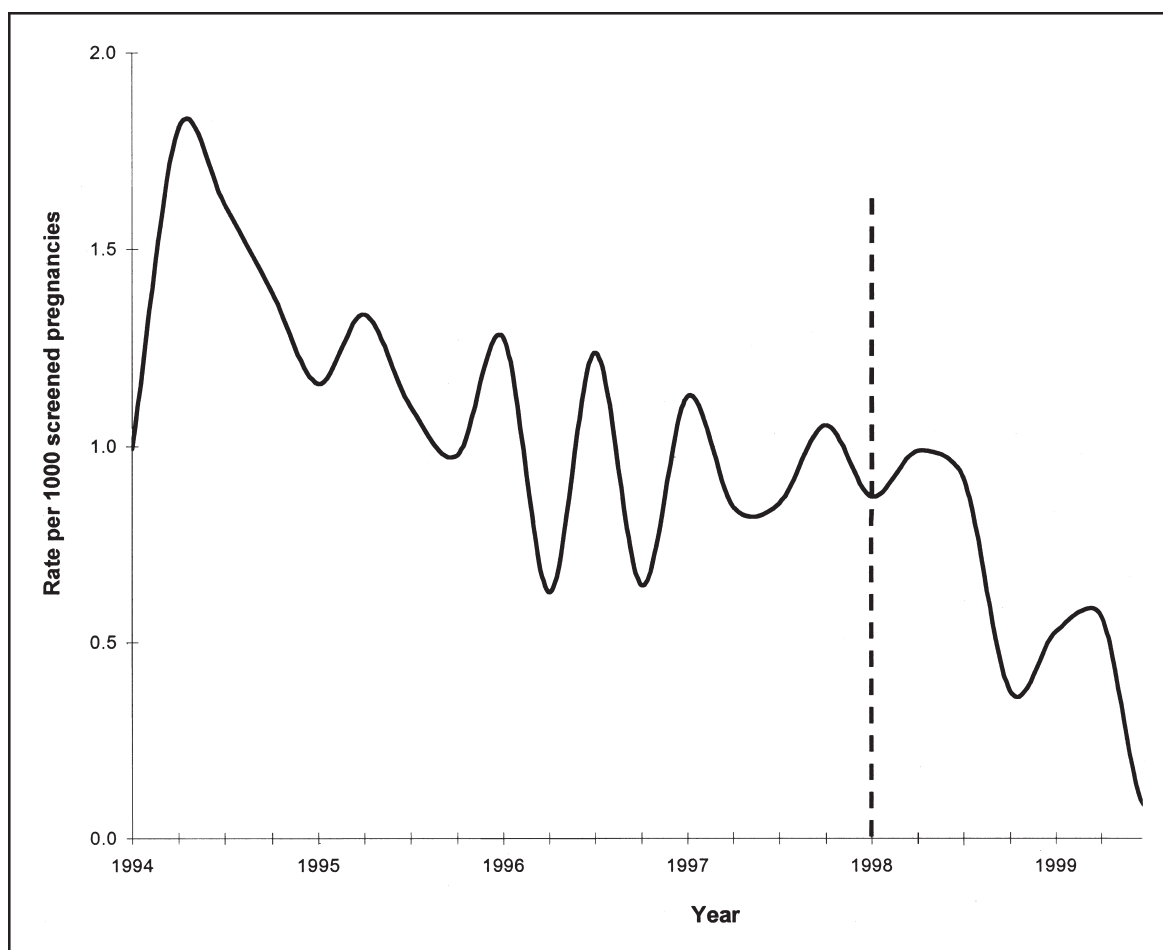


Figure 2. Decline in the prevalence of open neural tube defects after folic acid food fortification (vertical dashed line).

Is There Potential for Harm from Universal Folic Acid Food Fortification?

With universal folic acid food fortification most individuals will be exposed to higher-than-ever daily quantities of synthetic folic acid. Although there exists level 1

evidence in support of a reduction in the risk of NTD,¹⁶ concern has been raised that some groups may not only fail to benefit from higher amounts of folic acid exposure, but may be inadvertently harmed from it. Specifically, there are individual case reports to suggest that, in

Table 2. Risk of Folate and/or Vitamin B₁₂ deficiency, as well as Vitamin B₁₂ Deficiency in the Presence of Supraphysiologic Concentrations of Serum Folate among Canadian Women Aged 65 Years and Older

Outcome	Pre-fortification: (n = 4572)	Post-fortification: (n = 11092) [¶]	Rate Ratio (95% CI), Post- vs. Pre-fortification
No. (%) women with Se folate deficiency*	288 (6.3)	98 (0.88)	0.14 (0.11–0.18)
No. (%) women with Se B ₁₂ deficiency [†]	566 (12.4)	1077 (9.7)	0.78 (0.71–0.86)
No. (%) women with both folate* and Se B ₁₂ [‡] deficiency	62 (1.4)	16 (0.14)	0.11 (0.06–0.18)
No. (%) women with both Se B ₁₂ deficiency [‡] and a supraphysiologic Se folate concentration [§]	4 (0.09)	68 (0.61)	7.0 (2.6–19.2)

*Se folate concentration <6 nmol/L.

[†]Se B₁₂ concentration <150 pmol/L.

[‡]Se B₁₂ concentration ≥150 pmol/L.

[§]Se folate concentration >45 nmol/L.

^{||}January 1996 to December 1997.

[¶]January 1998 to December 2000.

Table 3. Risk of Preeclampsia-eclampsia and All Hypertensive Disorders of Pregnancy before and after Folic Acid Food Fortification

Outcome	Incidence Pre-fortification (%) [*]	Incidence Post-fortification (%) [†]	Rate Ratio (95% CI), Post- vs. Pre-fortification
Preeclampsia-eclampsia	3.8	3.7	0.96 (0.94–0.98) [‡] 0.97 (0.95–1.00) [§]
Any hypertensive disorder of pregnancy	5.8	6.2	1.07 (1.05–1.09) [‡] 1.09 (1.07–1.11) [§]

*1990–1997.

†1998—March 2000.

‡Unadjusted.

§Adjusted for maternal age.

the presence of poor oral intake or gastrointestinal absorption of vitamin B₁₂, excess folic acid consumption may “mask” the hematological (i.e., megaloblastic) manifestations of B₁₂ impairment, especially in the elderly. If unrecognized, B₁₂ deficiency may have neuropsychiatric sequelae, such as progressive subacute combined degeneration of the spinal cord.^{17–19}

No study has systematically addressed the issue of so-called “B₁₂ masking” in the presence of excess folic acid intake. We gathered data on more than 15,000 elderly Canadian women who underwent Se folate and B₁₂ laboratory testing, as described above.² We assumed that B₁₂ masking would be most likely to occur in the combined state of complete folate repletion (i.e., a Se folate concentration above 45 nmol/L) and a sub-normal Se B₁₂ concentration (i.e., below 150 pmol/L). We found that the prevalence of the latter combination increased from 0.09% pre-fortification to 0.61% post (RR 7.0, 95% CI 2.6–19.2) (Table 2).² Thus, it seems that a small number of elderly persons might be at higher risk of masked B₁₂ insufficiency—a statement that is based on a most tenuous data set. Hence, beyond the usual call for better research, adding small amounts of vitamin B₁₂ to folic acid-fortified foods might reduce the likelihood of masking B₁₂ insufficiency by the presence of high folate intake,^{19,20} but this notion is not based on quality evidence.

Conclusion

Since the implementation of folic acid food fortification, both young and older women’s folate stores have increased dramatically, with little change in vitamin B₁₂ concentrations. The only demonstrated benefit to date is that of a 50% relative reduction in the risk of open NTD—the goal of the national fortification program. To minimize inadvertent harm to the elderly, the addition of small quantities of vitamin B₁₂ to a folic acid fortification program might be considered.

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1. Ray JG, Vermeulen MJ, Boss SC, Cole DE. Increased red cell folate concentrations in women of reproductive age after Canadian folic acid food fortification. *Epidemiology*. 2002;13:238–240.
2. Ray JG, Vermeulen MJ, Langman LJ, Boss SC, Cole DEC. Persistence of vitamin B₁₂ insufficiency among elderly women after folic acid food fortification. *Clin Biochem*. 2004. [in press]
3. Ray JG, Vermeulen MJ, Boss SC, Cole DE. Declining rate of folate insufficiency among adults following increased folic acid food fortification in Canada. *Can J Public Health*. 2002;93:249–253.
4. Ray JG, Meier C, Vermeulen MJ, Boss S, Wyatt PR, Cole DEC. Association of neural tube defects and folic acid food fortification in Canada. *Lancet*. 2002;360:2047–2048.
5. Persad VL, Van den Hof MC, Dube JM, Zimmer P. Incidence of open neural tube defects in Nova Scotia after folic acid fortification. *CMAJ*. 2002;167:241–245.

6. Shaw GM, Lammer EJ, Wasserman CR, O'Malley CD, Tolarova MM. Risks of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. [Lancet](#). 1995;346:393-396.
7. Itikala PR, Watkins ML, Mulinare J, Moore CA, Liu Y. Maternal multivitamin use and orofacial clefts in offspring. [Teratology](#). 2001;63:79-86.
8. Loffredo LC, Souza JM, Freitas JA, Mossey PA. Oral clefts and vitamin supplementation. [Cleft Palate Craniofac J](#). 2001;38:76-83.
9. Ray JG, Meier C, Vermeulen MJ, Wyatt PR, Cole DE. Association between folic acid food fortification and congenital orofacial clefts. [J Pediatr](#). 2003;143:805-807.
10. Hobbs CA, Sherman SL, Yi P, et al. Polymorphisms in genes involved in folate metabolism as maternal risk factors for Down syndrome. [Am J Hum Genet](#). 2000;67:623-630.
11. Barkai G, Arbuzova S, Berkenstadt M, Heifetz S, Cuckle H. Frequency of Down's syndrome and neural-tube defects in the same family. [Lancet](#). 2003;361:1331-1335.
12. Ray JG, Meier C, Vermeulen MJ, Cole DE, Wyatt PR. Prevalence of trisomy 21 following folic acid food fortification. [Am J Med Genet](#). 2003;120A:309-313.
13. Ray JG, Laskin CA. Folic acid and homocyst(e)ine metabolic defects and the risk of placental abruption, pre-eclampsia and spontaneous pregnancy loss: a systematic review. [Placenta](#). 1999;20:519-529.
14. Hernandez-Diaz S, Werler MM, Louik C, Mitchell AA. Risk of gestational hypertension in relation to folic acid supplementation during pregnancy. [Am J Epidemiol](#). 2002;156:806-812.
15. Ray JG, Mamdani MM. Association between folic acid food fortification and hypertension or pre-eclampsia in pregnancy. [Arch Intern Med](#). 2002;162:1776-1777.
16. Lumley J, Watson L, Watson M, Bower C. Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects. [Cochrane Database Syst Rev](#). 2001;CD001056.
17. Dickinson CJ. Does folic acid harm people with vitamin B12 deficiency? [QJM](#). 1995;88:357-364.
18. Dhar M, Bellevue R, Carmel R. Pernicious anemia with neuropsychiatric dysfunction in a patient with sickle cell anemia treated with folate supplementation. [N Engl J Med](#). 2003;348:2204-2207.
19. Carmel R. Subtle and atypical cobalamin deficiency states. [Am J Hematol](#). 1990;34:108-114.
20. Oakley GP Jr. Let's increase folic acid fortification and include vitamin B-12. [Am J Clin Nutr](#). 1997;65:1889-1890.