

L-5-methyltetrahydrofolate supplementation increases blood folate concentrations to a greater extent than folic acid supplementation in Malaysian women

ABSTRACT

Background: Folic acid fortification of grains is mandated in many countries to prevent neural tube defects. Concerns regarding excessive intakes of folic acid have been raised. A synthetic analog of the circulating form of folate, l-5-methyltetrahydrofolate (l-5-MTHF), may be a potential alternative. **Objective:** The objective of this study was to determine the effects of folic acid or l-5-MTHF supplementation on blood folate concentrations, methyl nutrient metabolites, and DNA methylation in women living in Malaysia, where there is no mandatory fortification policy. **Methods:** In a 12-wk, randomized, placebo-controlled intervention trial, healthy Malaysian women (n = 142, aged 20–45 y) were randomly assigned to receive 1 of the following supplements daily: 1 mg (2.27 μ mol) folic acid, 1.13 mg (2.27 μ mol) l-5-MTHF, or a placebo. The primary outcomes were plasma and RBC folate and vitamin B-12 concentrations. Secondary outcomes included plasma total homocysteine, total cysteine, methionine, betaine, and choline concentrations and monocyte long interspersed nuclear element-1 (LINE-1) methylation. **Results:** The folic acid and l-5-MTHF groups had higher (P < 0.001) RBC folate (mean \pm SD: 1498 \pm 580 and 1951 \pm 496 nmol/L, respectively) and plasma folate [median (25th, 75th percentiles): 40.1 nmol/L (24.9, 52.7 nmol/L) and 52.0 nmol/L (42.7, 73.1 nmol/L), respectively] concentrations compared with RBC folate (958 \pm 345 nmol/L) and plasma folate [12.6 nmol/L (8.80, 17.0 nmol/L)] concentrations in the placebo group at 12 wk. The l-5-MTHF group had higher RBC folate (1951 \pm 496 nmol/L; P = 0.003) and plasma folate [52.0 nmol/L (42.7, 73.1 nmol/L); P = 0.023] at 12 wk than did the folic acid group [RBC folate, 1498 \pm 580 nmol/L; plasma folate, 40.1 nmol/L (24.9, 52.7 nmol/L)]. The folic acid and l-5-MTHF groups had 17% and 15%, respectively, lower (P < 0.001) plasma total homocysteine concentrations than did the placebo group at 12 wk; there were no differences between the folic acid and l-5-MTHF groups. No differences in plasma vitamin B-12, total cysteine, methionine, betaine, and choline and monocyte LINE-1 methylation were observed. **Conclusion:** These findings suggest differential effects of l-5-MTHF compared with folic acid supplementation on blood folate concentrations but no differences on plasma total homocysteine lowering in Malaysian women. This trial was registered at clinicaltrials.gov as NCT01584050.

Keyword: DNA methylation; Folic acid; l-5-methyltetrahydrofolate (l-5-MTHF); Folate, Supplement; Vitamin B-12