

Abstract

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Meta-Analysis of Folic Acid Supplementation Trials on Risk of Cardiovascular Disease and Risk Interaction With Baseline Homocysteine Levels.

Miller ER 3rd, Juraschek S, Pastor-Barriuso R, Bazzano LA, Appel LJ, Guallar E.

The Johns Hopkins School of Medicine, Baltimore, Maryland; The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; The Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, Maryland.

BACKGROUND: Experimental models and observational studies suggest that homocysteine-lowering therapy with folic acid (FA) may prevent cardiovascular disease (CVD). However, FA also stimulates cell proliferation and might promote progression of atherosclerosis.

OBJECTIVE: Our objectives were to perform a meta-analysis of FA supplementation trials on CVD events and to explore a potential interaction between FA supplementation and baseline homocysteine levels on CVD events.

METHODS: We searched MEDLINE for randomized controlled trials of FA supplementation to prevent CVD events (January 1966 to July 2009) and performed meta-analyses using random effects models. For trials that reported responses to FA supplementation stratified by baseline levels of homocysteine, we pooled within-trial estimates of differences in log-relative risks by baseline homocysteine levels using a random effects model.

RESULTS: Overall, FA supplementation did not affect primary cardiovascular clinical end points (relative risk 1.02, 95% confidence interval [CI] 0.93 to 1.13, $p = 0.66$) or stroke (relative risk 0.95, 95% CI 0.84 to 1.08, $p = 0.43$). However, in trials that reported analyses stratified by baseline homocysteine, effect of FA supplementation differed by strata of baseline homocysteine (p for interaction = 0.030). Specifically, risks of primary clinical CVD events comparing FA supplementation to control were 1.06 (95% CI 1.00 to 1.13) in strata with mean baseline homocysteine levels >12 $\mu\text{mol/L}$ and 0.94 (95% CI 0.86 to 1.03) in strata with baseline homocysteine levels <12 $\mu\text{mol/L}$.

CONCLUSION: In conclusion, FA had no effect on CVD or stroke. However, analysis of within-trial results stratified by baseline homocysteine suggests potential harm in those with high homocysteine at baseline. This interaction may have important implications for recommendations of FA supplement use. In the meantime, FA supplementation should not be recommended as a means to prevent or treat CVD or stroke.

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