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Cost-effectiveness of Vitamin Therapy to Lower Plasma Homocysteine Levels for the Prevention of Coronary Heart Disease: Effect of Grain Fortification and Beyond

[Original Contribution]

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Outline

- [Abstract](#)
- [METHODS](#)
 - [CHD Policy Model](#)
 - [Homocysteine Specific Assumptions](#)
 - [Effect of Treatment With Vitamin Therapy on Homocysteine Level](#)
 - [Effect of Change in Homocysteine Level on CHD Event Rates](#)
 - [Fortification of Cereal Grain With Folic Acid](#)
 - [Secondary Prevention](#)
 - [Primary Prevention](#)
 - [Time Frame](#)
 - [Cost Considerations](#)
- [RESULTS](#)
 - [Cereal Grain Fortification With Folic Acid](#)
 - [Secondary Prevention: Folic Acid and Cyanocobalamin Supplementation Plus Grain Fortification](#)
 - [Primary Prevention: Folic Acid and Cyanocobalamin Supplementation Plus Grain Fortification](#)
 - [Primary Prevention With Folic Acid and Cyanocobalamin Supplementation: Sensitivity Analyses](#)
- [COMMENT](#)
- [References](#)

Graphics

- [Table 1](#)
- [Table 2](#)
- [Table 3](#)
- [Table 4](#)
- [Figure. Incremental ...](#)

Abstract

Context: A high homocysteine level has been identified as an independent modifiable risk factor for coronary heart disease (CHD) events and death. Since January 1998, the US Food and Drug Administration has required that all enriched grain products contain 140 µg of folic acid per 100 g, a level considered to decrease homocysteine levels.

Objectives: To examine the potential effect of grain fortification with folic acid on CHD events and to estimate the cost-effectiveness of additional vitamin supplementation (folic acid and cyanocobalamin) for CHD prevention.

Design and Setting: Cost-effectiveness analysis using the Coronary Heart Disease Policy Model, a validated, state-transition model of CHD events in adults aged 35 through 84 years. Data from the third National Health and Nutrition Examination Survey (NHANES III) were used to estimate age- and sex-specific differences in homocysteine levels.

Intervention: Hypothetical comparison between a diet that includes enriched grain products projected to increase folic acid intake by 100 µg/d with the same diet without folic acid fortification; and a comparison between vitamin therapy that consists of 1 mg of folic acid and 0.5 mg of cyanocobalamin and the diet that includes grains fortified with folic acid.

Main Outcome Measures: Incidence of myocardial infarction and death from CHD, quality-adjusted life-years (QALYs) saved, and medical costs.

Results: Grain fortification with folic acid was predicted to decrease CHD events by 8% in women and 13% in men, with comparable reductions in CHD mortality. The model projected that, compared with grain fortification alone, treating all patients with known CHD with folic acid and cyanocobalamin over a 10-year period would result in 310 000 fewer deaths and lower costs. Over the same 10-year period, providing vitamin supplementation in addition to grain fortification to all men aged 45 years or older without known CHD was projected to save more than 300 000 QALYs, to save more than US \$2 billion, and to be the preferred strategy. For women without CHD, the preferred vitamin supplementation strategy would be to treat all women older than 55 years, a strategy projected to save more than 140 000 QALYs over 10 years.

Conclusions: Folic acid and cyanocobalamin supplementation may be cost-effective among many population subgroups and could have a major epidemiologic benefit for primary and secondary prevention of CHD if ongoing clinical trials confirm that homocysteine-lowering therapy decreases CHD event rates.

In 1969, McCully [1](#) proposed homocysteine as an etiologic agent in the pathogenesis of vascular disease. Over the past decade, at least 10 large prospective cohort studies have published data demonstrating a statistically significant association of basal homocysteine levels with coronary heart disease (CHD) events and death. [2-11](#) Nygard et al [11](#) reported that patients with known CHD had a 1.6- to 2.5-fold increase in mortality per each 5- μ mol/L (0.68-mg/L) increase in fasting total homocysteine.

Randomized clinical trials have demonstrated that low-dose B vitamins, particularly folic acid and cyanocobalamin, significantly lower homocysteine levels. [12-39](#) A recent meta-analysis by the Homocysteine Lowering Trialists' Collaboration [40](#) found that folic acid therapy lowered homocysteine levels (standardized at 12 μ mol/L [1.62 mg/L]) by 25% and that the addition of cyanocobalamin therapy lowered levels an additional 7%.

Since January 1998, the US Food and Drug Administration (FDA) has required that all enriched grain products produced in the United States contain 140 μ g of folic acid per 100 g. [41](#) Since that mandate, Framingham cohort data document that homocysteine levels in the general population have decreased. [42](#) In this study, we first estimated the epidemiologic impact of grain fortification on CHD events and then calculated the additional costs and benefits of further homocysteine lowering using vitamin supplementation. These projections, despite their logic, should be interpreted in the context of the absence of clinical trial data that proves the efficacy of reducing homocysteine levels to prevent myocardial infarction or CHD death.

METHODS

CHD Policy Model

The Coronary Heart Disease Policy Model is a validated, state-transition model of CHD events and costs among US residents aged 35 through 84 years. [43](#) The model was recently updated and calibrated using 1980 and 1986 US Vital Statistics to predict CHD mortality within 2% of the reported age- and sex-specific rates in the 1990 US Vital Statistics. [44](#) We refined the model using data from the third National Health and Nutrition Examination Survey (NHANES III) to estimate the age- and sex-specific distribution of homocysteine levels in the US population ([Table 1](#)). [45](#) Validation analyses confirmed that the model incorporating the homocysteine-level distribution predicts CHD mortality within 2% of the 1990 US Vital Statistics. The overall model consists of 3 integrated submodels: the demographic epidemiologic submodel, the bridge submodel, and the disease history submodel.

Group, Age, y	Homocysteine Level, $\mu\text{mol/L}$, at NHANES III Survey [*]	Homocysteine Level, $\mu\text{mol/L}$ (% Reduction)	
		After Grain Fortification [†]	After Grain Fortification Plus Daily Supplement [‡]
Men			
35-44	10.3	9.52 (7.6)	7.47 (21.5)
45-54	11.0	9.98 (9.3)	7.67 (23.1)
55-64	11.8	10.6 (10.2)	7.92 (25.3)
65-74	12.6	11.1 (11.9)	8.15 (26.6)
75-84	12.7	11.2 (11.8)	8.18 (27.0)
Women			
35-44	8.60	8.31 (3.4)	6.96 (16.2)
45-54	8.88	8.51 (4.2)	7.05 (17.2)
55-64	9.83	9.18 (6.6)	7.33 (20.2)
65-74	10.6	9.73 (8.2)	7.56 (22.3)
75-84	11.2	10.1 (9.8)	7.74 (23.4)

*Age- and sex-specific mean homocysteine values from the third National Health and Nutrition Examination Survey (NHANES III) were smoothed by linear averaging. To convert homocysteine from $\mu\text{mol/L}$ to mg/L divide by 7.397.

[†]Estimates of the effect of grain fortification on age- and sex-specific homocysteine levels. These measures assume an average increase in folic acid intake of 100 mg per person-day following the US Food and Drug Administration mandate to fortify every 100 g of grain with 140 μg of folic acid. Estimates of the homocysteine levels after grain fortification were derived from an analysis of covariance model limited to clinical trials of vitamin therapy to lower homocysteine using folic acid doses of 200 $\mu\text{g/d}$ or less (% reduction in homocysteine levels from NHANES III levels).

[‡]Estimates of the homocysteine levels after vitamin supplementation with 1 mg of folic acid and 0.5 mg of cyanocobalamin were derived from a separate analysis of covariance model based on clinical trials of vitamin therapy to lower homocysteine using folic acid doses greater than 200 $\mu\text{g/d}$ (% reduction in homocysteine levels from levels after grain fortification).

Table 1. Age- and Sex-Specific Homocysteine Levels in the US Population: Estimates of the Effects of Homocysteine-Lowering Therapy

The disease epidemiologic submodel uses population risk factor distributions to predict new CHD events in people with no known CHD. The distributions of smoking status, diastolic blood pressure, high-density lipoprotein levels, and total serum cholesterol levels were derived from the NHANES II. [46](#) The 4 risk factor distributions were assumed to be independent, conditional on age range and sex. The number of US residents who enter the model each subsequent year was estimated from projections of the US Bureau of the Census. [47](#)

Age- and sex-specific relative risk coefficients for CHD incidence and all-cause mortality were based on the Framingham Heart Study's 30-year follow-up results for all risk factors other than homocysteine levels. [48](#) Noncardiac disease mortality was based on US Vital Statistics. [49](#) Coronary heart disease incidence rates for persons aged 35 through 74 years were based on the Framingham Heart Study, with adjustment for the secular decline in CHD incidence [44](#) since the beginning of the study. These rates were extrapolated to persons aged 75 through 84 years, and linear interpolation was used to smooth the age-

specific annual rates. [48](#)

The bridge submodel characterizes events occurring during the first 30 days following a primary CHD event, and the disease history submodel predicts subsequent events in those who survived the initial CHD event. The bridge and disease history submodels were based on literature describing the presentation of CHD as angina, myocardial infarction, or cardiac arrest, [50](#) the incidence and case-fatality rates of recurrent coronary events, [43](#) and the age- and sex-specific risk of noncoronary death. [51](#) The disease history submodel estimates the subsequent annual risk of recurrent coronary events and coronary revascularization procedures based on a patient's prior history of angina, myocardial infarction, coronary revascularization, or cardiac arrest.

Health related quality-of-life estimates were calculated for people with angina, congestive heart failure, or both. The health-related quality-of-life weights were derived by pooling the time-trade-off method based responses from patients in the Acute Myocardial Infarct Patient Oriented Research Team and the Beaver Dam Health Outcomes Study. [52](#) Short-term quality of life adjustments were made to account for the dysutility of cardiac events by assuming a utility of 0 during the average hospital length of stay for those events. No other effects of vitamin supplementation on quality of life were modeled.

The age-specific costs of treating CHD including hospital costs, procedure costs, and annual cost of outpatient care were derived from the Medicare Provider Analysis and Review files and the Acute Myocardial Infarction (AMI) Patient Outcome Research Team. [52](#) All costs were inflated to 1997 dollars using the Medical Care Component of the Consumer Price Index.

Homocysteine Specific Assumptions

We searched MEDLINE from 1966 through February 1999 using the keywords *homocysteine*, *folic acid*, *vitamin B₁₂*, and *cardiovascular disease*. The reference lists of all review articles and epidemiologic studies were hand searched for further references. We contacted experts asking for unpublished trials and abstracts presented at research conferences.

Effect of Treatment With Vitamin Therapy on Homocysteine Level

Articles containing data on pretreatment and posttreatment homocysteine levels [12-39](#) were pooled using analysis of covariance to estimate the posttreatment homocysteine levels adjusting for baseline values of homocysteine ([Table 1](#) and [Table 2](#)). [56](#) We estimated that vitamin therapy consisting of 1 mg of folic acid and 0.5 mg of cyanocobalamin would lower the serum homocysteine levels of people with pretreatment levels of 12 $\mu\text{mol/L}$ (1.62 mg/L) by 33%. A recent meta-analysis reported no evidence that age or sex affected the homocysteine-lowering effect of vitamin therapy but that higher pretreatment levels were associated with greater absolute and relative declines. [40](#) The estimated proportional reduction of a blood homocysteine level of 12 $\mu\text{mol/L}$ (1.62 mg/L) of folic acid supplementation was 25%, with the addition of a mean of 0.5-mg cyanocobalamin providing an additional 7% reduction for a 32% total decrease. [40](#) Populations with higher pretreatment homocysteine levels had a greater percentage and absolute reduction in homocysteine levels; those with low pretreatment homocysteine levels had almost no change

in homocysteine level with vitamin supplementation ([Table 1](#)).

Parameter	Baseline Estimate (Range for Sensitivity Analyses)	Reference, y
Decline in homocysteine levels with vitamin therapy (1 mg folic acid, 0.5 mg cyanocobalamin), %*	33 (26-38)	Homocysteine Lowering Trialists' Collaboration, ⁴⁰ 1998
Relative risk reduction per 5- μ mol/L decrease of homocysteine levels, μ mol/L, %	29 (9-45)	Wald et al, ¹⁰ 1998, Boushey et al, ⁵³ 1995
Annual cost per 1 mg of folic acid plus 0.5 mg of cyanocobalamin, US \$	20.29 (10-30)	<i>Drug Topics Red Book</i> , ⁵⁴ 1997
Cost of homocysteine assay, US \$	26.32 (15-40)	<i>Federal Register</i> , ⁵⁵ 1996

*The percentage decrease reported is for a person with a pregrain fortification homocysteine level of 12 μ mol/L (1.62 mg/L). The percentage reduction is a function of the preintervention level as well as the intervention. The baseline estimate for percentage reduction in homocysteine level with vitamin supplementation is less than 33% for people with homocysteine levels lower than 12 μ mol/L and more than 33% for people starting with homocysteine levels higher than 12 μ mol/L.

Table 2. Assumptions About Homocysteine Reduction and Coronary Heart Disease

In our model, we assumed 100% compliance with therapy for the primary simulations. For sensitivity analyses of compliance, we assumed that everyone would continue to receive homocysteine screening and prescriptions for vitamin supplementation (thus accruing all costs), but only a reduced percentage would take the supplements and accrue benefit.

Effect of Change in Homocysteine Level on CHD Event Rates

We assumed that the relative risk reduction (RRR) from homocysteine-lowering therapy was equivalent for both primary and secondary prevention. We derived summary odds ratios (ORs) for changes in CHD event rates from homocysteine level modification using a standard random-effects model [57](#) to combine results from studies of homocysteine and CHD. [2-3, 5, 8, 10-11, 58-70](#) The summary OR was 0.63 per 5- μ mol/L (0.68-mg/L) decrease in total homocysteine level (95% confidence interval [CI], 0.55-0.71). This did not differ by sex, and there were no data supporting an interaction of the risk relationship with age. For the baseline analysis, we used the conservative bound (0.71 per 5 μ mol/L [0.68 mg/L], a 29% RRR) as our primary estimate because cross-sectional studies often overestimate the strength of the risk relationship compared with prospective studies and clinical trials. For sensitivity analyses, we used a range from 0.55 to 0.91 (45% to 9% RRR), based on the upper bound of the 95% CI of the random effects model including only prospective studies in the meta-analysis [2-3, 5, 8, 10-11](#) and the lower bound of the full

random effects model ([Table 2](#)). We did not model any adverse effects of vitamin supplementation.

Fortification of Cereal Grain With Folic Acid

Based on FDA projections, we assumed that fortified cereal grain would increase the folic acid intake of the average US consumer by 100 µg/d. [71](#) We did not model differential increases in folic acid consumption by age and sex. The effect of increasing folic acid intake by 100 µg on total homocysteine level was estimated with the same analysis of covariance model [56](#) used for modeling vitamin supplementation above, limited to clinical trials using supplements containing less than 200 µg of folic acid. [26, 32](#) Grain fortification was estimated to decrease a basal homocysteine level of 12 µmol/L (1.62 mg/L) to 10.7 µmol/L (1.45 mg/L), an 11% reduction. Sensitivity analyses evaluated a reduction as low as 5%. Our estimates virtually replicated the drop in homocysteine levels in the Framingham cohort: the geometric mean homocysteine level was 10.1 µmol/L (1.37 mg/L) before grain fortification was mandated and declined to 9.4 µmol/L (1.27 mg/L) after fortification. [42](#) Our model predicts that the group mean would decrease from 10.1 to 9.37 µmol/L (1.37-1.27 mg/L). These lower homocysteine levels were used as the starting point for all subsequent models of primary and secondary prevention.

Secondary Prevention

Our secondary prevention models assumed that persons with clinically manifest CHD (the population of the disease history submodel) would take a daily supplement containing 1 mg of folic acid and 0.5 mg of cyanocobalamin in addition to cereal grain fortification.

Primary Prevention

Primary prevention was modeled as an incremental strategy to secondary prevention. As CHD would become manifest in those untreated, they were assumed to have started receiving supplements. Two strategies were modeled: treat everyone with no known CHD with a daily supplement containing 1 mg of folic acid and 0.5 mg of cyanocobalamin or measure everyone's homocysteine level and treat only those with a homocysteine level greater than 10 µmol/L (>1.35 mg/L). These strategies were evaluated separately for men and women. For each sex, 5 different age cutoffs were modeled beginning with individuals aged 75 years or older. Younger people were added in 10-year increments. The strategies for each sex were then compared. We assumed that everyone would have had an increased folic acid intake at baseline due to grain fortification.

Time Frame

Both primary and secondary prevention strategies were modeled to begin in the year 2001 and were run through 2010. Flour fortification with folic acid was assumed to have begun on January 1, 1998. Our projections assumed that treatment with vitamin therapy, including flour fortification, had a 2-year delay before affecting CHD event rates, analogous to clinical data used to model cholesterol-lowering therapy in prior studies. [72](#) This approach biases the model against effectiveness in the youngest individuals

because they would miss quality-adjusted life-years (QALYs) that they would accrue due to the intervention well after the year 2010.

Cost Considerations

The cost of the vitamin therapy was estimated to be \$20.29 per year based on the median *1997 Red Book* average wholesale price of 1 mg folic acid supplements plus the median value of 0.5 mg cyanocobalamin supplements. [54](#) A range from \$10 to \$30 was used for sensitivity analyses. We did not assume any extra costs for office visits to implement vitamin therapy since this expense was treated as a routine part of health care maintenance requiring less than 1 minute of time. The cost of the homocysteine assay (\$26.32) reflected the 1997 Health Care Financing Administration reimbursement for an amino acid assay (CPT-4 code 8213190) and blood specimen handling. [55](#)

All costs were converted to 1997 dollars using the Medical Care Component of the Consumer Price Index. The cost effectiveness (CE) ratio was expressed in 1997 dollars per QALY. A 3% discounting rate for costs and benefits was used for the primary projections. [73](#) The discounting rate was varied from 0% to 5% in sensitivity analyses ([Table 2](#)). Costs were calculated using a health care perspective. Patient-time costs, lost productivity, and other non-health care costs were not considered in these models, but the costs of CHD events, hospitalizations, revascularization procedures, and outpatient therapy were included. Before calculating CE ratios, we eliminated strategies that were less effective and either more expensive (dominated) or have a higher incremental CE ratio (fail by extended dominance). [74](#)

RESULTS

Cereal Grain Fortification With Folic Acid

Using baseline estimates, the model predicted that flour fortification would lead to a 13% reduction in myocardial infarctions in men and an 8% reduction in women with comparable reductions in CHD mortality ([Table 3](#)). Using our most conservative assumptions, the estimated reductions in annual CHD mortality rates were 1% to 3%.

Percentage Reduction in Homocysteine Level, $\mu\text{mol/L}$ [*]	Percentage Reduction in Risk of CHD [†]	Percentage Decrease in Myocardial Infarctions		Percentage Decrease in CHD Deaths	
		Men	Women	Men	Women
11	29	13.0	7.6	12.8	8.7
5	29	6.9	3.9	6.7	4.5
11	9	2.8	1.8	2.8	2.1
5	9	1.4	0.9	1.4	1.0

*Reduction in homocysteine levels standardized at 12 $\mu\text{mol/L}$. To convert homocysteine from $\mu\text{mol/L}$ to mg/L divide by 7.397.

†Reduction in risk of CHD for each 5- $\mu\text{mol/L}$ reduction in homocysteine level, 2-year delay in clinical effect.

Table 3. Predicted Decline in Annual Coronary Heart Disease (CHD) Events Over 10 Years Due to US Food and Drug Administration Mandated Folic Acid Fortification Based on 4 Scenarios

Secondary Prevention: Folic Acid and Cyanocobalamin Supplementation Plus Grain Fortification

If, in addition to grain fortification, all patients with known CHD were treated with 1 mg of folic acid and 0.5 mg of cyanocobalamin as supplements to lower their homocysteine levels, it was projected that approximately 310 000 fewer CHD deaths would occur over a 10-year period compared with grain fortification alone ([Table 4](#)). The estimated absolute reduction in deaths would be greatest in the older age groups in whom mortality from CHD and initial homocysteine levels tend to be higher. Because the baseline homocysteine levels at all ages are higher in men and because age-specific CHD mortality is also higher in men, they were expected to benefit more than women. Treating everyone with known CHD with a vitamin supplement was predicted to save money as well as lives in all age and sex subgroups.

Group, Age, y	No. of Myocardial Infarctions Prevented	No. of CHD Deaths Averted	Savings, US \$ Million†
Men			
75-84	41 000	62 000	1600
65-74	66 000	74 000	5300
55-64	57 000	50 000	6400
45-54	27 000	21 000	4400
35-44	5600	4300	1100
Total	196 600	211 300	18 800
Women			
75-84	28 000	48 000	1000
65-74	25 000	33 000	1800
55-64	14 000	15 000	1700
45-54	5300	4700	780
35-44	1100	840	140
Total	73 400	101 540	5420

* Vitamin supplementation was compared with folic acid grain fortification alone for those aged 75 through 84 years; extending supplementation to each younger 10-year age group was compared with supplementation in the older group.

† Costs are the expense of treatment with vitamin supplements minus the savings from CHD events prevented.

Table 4. Secondary Prevention: Incremental Benefit Over 10 Years of Folic Acid and Cyanocobalamin Supplementation in US Adults With Coronary Heart Disease (CHD)*

Primary Prevention: Folic Acid and Cyanocobalamin Supplementation Plus Grain Fortification

In men, the model predicted that each of the 10 primary prevention strategies would save lives and money compared with men who would consume fortified grain alone (Figure 1). Screening men aged 45 years or older with no known CHD and treating those whose homocysteine levels were higher than 10 $\mu\text{mol/L}$ (1.35 mg/L) was predicted to maximize cost savings. Providing vitamin supplementation beyond grain fortification to all men aged 45 years or older was projected to cost \$9000/QALY saved compared with screening for elevated homocysteine levels (screen and treat). Extending supplementation to men aged 35 through 44 years had an incremental CE ratio of nearly \$100 000/QALY and, thus, generally would not be recommended.

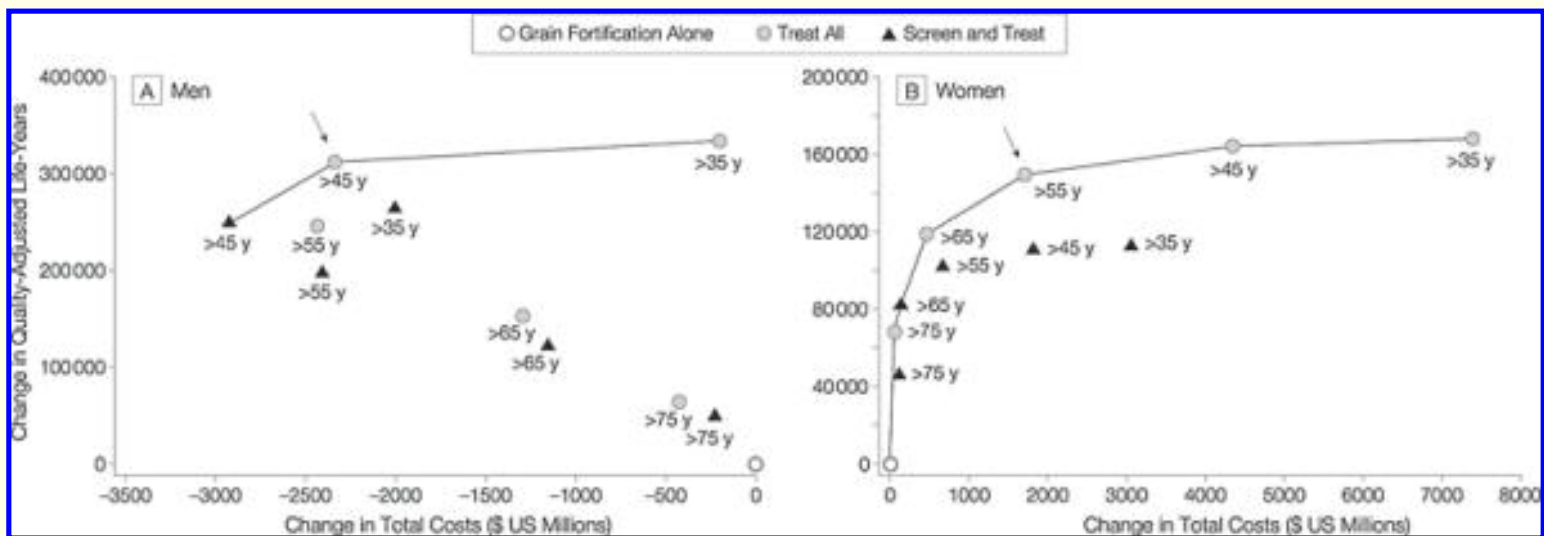


Figure. Incremental Cost-effectiveness of Primary Prevention With Folic Acid and Cyanocobalamin Supplementation. The strategies along the solid line dominate the other strategies. The slope of each line segment represents the incremental cost-effectiveness ratio between 2 prevention strategies. The arrow points to the strategy with the greatest quality-adjusted life-years (QALYs) and a cost-effectiveness ratio below that conventionally considered cost-effective (<\$40 000/QALY).

In women aged 75 years or older without CHD, vitamin supplementation was predicted to have an incremental CE ratio of \$1200/QALY vs grain fortification alone. Screening women aged 65 through 74 years and treating those with elevated homocysteine levels had an incremental CE ratio of \$5500/QALY vs treating all women aged 75 years or older. Extending treatment to all women aged 65 years or older was predicted to have an incremental CE ratio of \$8800/QALY vs the screen-and-treat strategy. Treating all women aged 55 through 64 years had an incremental CE ratio of \$39 000/QALY, which is in the range of other commonly recommended therapies. Routine treatment of all women aged 45 years or older (\$180 000/QALY) or all women aged 35 years or older (\$830 000/QALY) would be too expensive for routine recommendation.

Primary Prevention With Folic Acid and Cyanocobalamin Supplementation: Sensitivity Analyses

If the RRR of vitamin supplementation is 9% rather than 29%, the primary prevention strategies of treating everyone without measuring homocysteine levels would remain attractive at less than \$40 000/QALY saved for men aged 55 years or older and women aged 75 years or older. A 2-way sensitivity analysis assuming less effective lowering of homocysteine values by vitamin therapy (26%) and the weaker association between homocysteine and CHD risk (RRR 9%) demonstrated that the screen-and-treat strategy would cost \$29 000/QALY saved for men aged 45 years or older and \$42 000/QALY saved for women aged 65 years or older. If the cost of the vitamin supplement decreased to \$10 per year in the prior analysis, the screen-and-treat strategy would save costs and lives in men aged 45 years or older and would cost less than \$10 000/QALY gained for women aged 65 years or older. If compliance with vitamin supplementation is only 50%, the treat-all strategy's incremental CE ratios remain less than \$50 000/QALY gained for men aged 45 years or older and women aged 65 years or older.

COMMENT

The primary parameter that determines the benefit of homocysteine-lowering therapy for any person or group is their absolute risk of having a CHD event. Age is the single strongest predictor of CHD risk [75](#) and is readily available to clinicians when making decisions about whether to screen for hyperhomocysteinemia or recommend vitamin supplementation for CHD prevention. Furthermore, homocysteine increases with age in both men and women. At any given age, both CHD risk and homocysteine levels are lower in women, so sex differences were also considered.

There is always uncertainty in the assumptions used to project cost and effectiveness. We performed a systematic literature review to find the best available data. The risk estimates were based on multivariate analyses of data from the Framingham Heart Study, a source of data demonstrated to be accurate. [76-77](#) The model's simplifying use of categories to summarize risk factors has been shown to be comparable to what would be obtained by considering each risk factor on a continuous scale. [78](#) Furthermore, future projections based on the Coronary Heart Disease Policy Model have been proven consistently accurate in comparison with subsequent prospective trials. For example, the model's analyses of the cost-effectiveness of cholesterol reduction in patients after experiencing myocardial infarction [72](#) are similar to those calculated from the results of randomized trials. [79-81](#) The Coronary Heart Disease Policy Model also carries the limitation of any state-transition model—the so-called Markov assumption or limited memory for previous states. This problem has been addressed primarily by creating states in the model to account for prior events (myocardial infarction, cardiac arrest, or coronary artery bypass graft surgery) that influence subsequent CHD event rates. Prior analyses using the model [43-44](#) suggest that this is not a significant problem.

The major limitation of our projections is the absence of clinical trial data on the effect of homocysteine-lowering therapy on disease rates. Data from a cohort of patients with homocystinuria treated with vitamin therapy provide evidence for biological plausibility. Compared with historical controls, up to a 90% reduction in catastrophic cardiovascular events has been reported. [82](#) Our conservative baseline estimate of the association between change in homocysteine level and risk of CHD events was equivalent to the lower bound of the 95% CI in the meta-analysis by Boushey et al. [53](#) It was also more conservative (closer to an OR of 1) than the summary odds ratio in a recent meta-analysis of prospective observational trials. [10](#) Sensitivity analyses assuming one fourth the effect size of the baseline estimates projected an attractive CE ratio for men aged 55 years or older and women aged 75 years or older.

We decided not to model benefits for diseases other than CHD despite evidence that elevated homocysteine levels are associated with increased risk for stroke and peripheral vascular disease. [83-89](#) Therapy with folic acid and cyanocobalamin may also decrease the incidence of pernicious anemia, dementia, and other clinical manifestations of deficiency of these vitamins.

We also did not model any negative consequences of vitamin supplementation. Both folic acid and cyanocobalamin are water-soluble vitamins with very low potential for adverse effects. One concern frequently raised when considering population-based folic acid therapy is the potential to accelerate the neurologic sequelae of vitamin B₁₂ deficiency. [90-92](#) However, a recent clinical trial demonstrated that oral cyanocobalamin was as effective as parenteral cyanocobalamin in treating multiple etiologies of cyanocobalamin deficiency. [93](#)

The observational evidence supporting high homocysteine levels as a risk factor for CHD events is strong. [94](#) Furthermore, clinical trial data demonstrate that homocysteine levels can be lowered by inexpensive and safe doses of folic acid and cyanocobalamin. Nevertheless, recent clinical trials of beta carotene, vitamin E, and hormone replacement therapy have contradicted strong evidence for benefit demonstrated in multiple prospective observational studies. [95-99](#) Ultimately, we would recommend homocysteine-lowering therapy routinely only if ongoing clinical trials demonstrate that vitamin therapy reduces clinically important CHD events. In the meantime, since combined therapy with folic acid and cyanocobalamin is well tolerated, it is reasonable to consider routine therapy in men older than 45 years and women older than 55 years.

Author Contributions: *Study concept and design:* Tice, Ross, Rosenberg, Weinstein, Hunink, Williams, L. Goldman.

Acquisition of data: Tice, Ross, Coxson, Rosenberg, P. Goldman, Williams.

Analysis and interpretation of data: Tice, Ross, Coxson, L. Goldman.

Drafting of the manuscript: Tice.

Critical revision of the manuscript for important intellectual content: Tice, Ross, Coxson, Rosenberg, Weinstein, Hunink, P. Goldman, Williams, L. Goldman.

Statistical expertise: Tice, Ross, Williams.

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Study supervision: Rosenberg, L. Goldman.

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Coronary Heart Disease; Coronary Disease; Cost Effectiveness; Cost-Benefit Analysis; Folic Acid; Food, Fortified; Homocysteine; Preventive Medicine

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