Cost-effectiveness of vitamin therapy to lower plasma homocysteine levels for the prevention of coronary heart disease: effect of grain fortification and beyond

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The fortification of grain with folic acid (140 microg per 100 g), to lower plasma homocysteine levels in order to prevent coronary heart disease (CHD), was examined. Additional vitamin supplementation (with folic acid and cyanocobalamin) for CHD prevention was a further intervention under evaluation.

Type of intervention
Primary and secondary prevention.

Economic study type
Cost-utility analysis.

Study population
The study modelled the entire US population of men and women aged 35 to 85 years. Population numbers were derived from US census data and risk factor distributions from nationally representative samples of the US population.

Setting
The setting considered in the analysis was not explicitly stated. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1987 and 1998. No dates relating to resource consumption were reported. The price year was 1997.

Source of effectiveness data
The effectiveness evidence came from a review of published studies and the authors' assumptions.

Modelling
A published state-transition (Markov) model, the Coronary Heart Disease Policy Model (see Other Publications of Related Interest), was used to estimate the costs and CHD events in a hypothetical cohort of adults aged 35 to 84 years. The model contained three sub-models. The disease epidemiologic sub-model based new CHD events on four risk factors (smoking status, diastolic blood pressure, high-density lipoprotein levels and total serum cholesterol levels). The bridge sub-model estimated the events occurring during the first 30 days following a primary CHD event. The disease history sub-model was used to predict subsequent events in those who survived the initial CHD event. Both primary and secondary prevention strategies were modelled to begin in 2001, and were run until 2010.

Outcomes assessed in the review
A group of health outcomes was derived from published studies. These were:

- the distribution of smoking status, diastolic blood pressure, high-density lipoprotein levels, and total serum cholesterol levels;
- the number of US residents who entered the model;
- age- and gender-specific relative risk coefficients for CHD incidence and all-cause mortality;
- non-cardiac disease mortality;
- data on angina, myocardial infarction, cardiac arrest, incidence and case-fatality rates of recurrent coronary events;
- the age- and gender-specific risk of non-coronary death.

A review of the literature was also conducted to estimate the pre-treatment and post-treatment homocysteine levels. Also, to estimate the odds ratio for changes in CHD event rates from homocysteine level modification.

**Study designs and other criteria for inclusion in the review**
The inclusion criteria for the literature review were not reported. The design of only a few primary studies was mentioned.

**Sources searched to identify primary studies**
MEDLINE was searched from 1966 to February 1999 using the keywords "homocysteine", "folic acid", "vitamin B12" and "cardiovascular disease".

**Criteria used to ensure the validity of primary studies**
Not stated.

**Methods used to judge relevance and validity, and for extracting data**
Not stated.

**Number of primary studies included**
It seems that approximately 60 references, reported as primary studies, have provided the effectiveness evidence used in the decision model.

**Methods of combining primary studies**
An analysis of variance was used to pool the estimates extracted from the primary studies.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
In men, the age-specific homocysteine levels ranged from 10.3 to 12.7 micromol/L depending on age class before grain fortification, from 9.52 to 11.2 micromol/L after grain fortification, and from 7.47 to 8.18 micromol/L after grain fortification and a daily supplement.

The corresponding age-specific homocysteine levels in women ranged from 8.60 to 11.2 micromol/L before grain
fortification, from 8.31 to 10.1 micromol/L after grain fortification, and from 6.96 to 7.74 micromol/L after grain fortification and a daily supplement.

The decline in homocysteine levels with vitamin therapy was 33% (range: 26 - 38). The relative risk reduction per 5-micromol/L decrease of homocysteine levels was 29% (range: 9 - 45%. The odds ratio was 0.63 (95% confidence interval: 0.55 - 0.71) per 5-micromol/L decrease in total homocysteine levels.

Grain fortification decreased homocysteine levels by 11%.

Other data were not reported.

Methods used to derive estimates of effectiveness
The authors made some assumptions used in the decision model.

Estimates of effectiveness and key assumptions
It was assumed that there was 100% compliance, and that the relative risk reduction from homocysteine-lowering therapy was equivalent for both primary and secondary prevention. It was also assumed that fortified cereal grain would increase the folic acid intake of the average US consumer by 100 microg/day. Other assumptions were also reported in the article.

Measure of benefits used in the economic analysis
The summary benefit measure used in the economic analysis was the quality-adjusted life-years (QALYs). These were calculated by combining survival data from the decision model with published utility data, which were obtained in a prior study using the time trade-off approach. Short-term quality of life adjustments were made. The benefits were discounted using a rate of 3%. The decrease in CHD deaths was also reported as a model outcome.

Direct costs
A 3% annual discount rate was applied to the estimated costs because of the long time horizon of the decision model. The unit costs were only reported separately from the quantities of resources for vitamin therapy and homocysteine assay. The health services included in the economic analysis were vitamin therapy, treatment of CHD events, hospitalisations, revascularisation procedures and outpatient therapy. The cost/resource boundary adopted in the study was that of the health care system. The costs were estimated using Medicare data and the Acute Myocardial Infarction Patient Outcome Research Team. For details of other cost data utilised in the model see “Other Publications of Related Interest” below. All of the costs were inflated to 1997 prices using the Medical Care Component of the Consumer Price Index.

Statistical analysis of costs
No statistical test was conducted on the costs.

Indirect Costs
The indirect costs were not included in the economic evaluation.

Currency
US dollars ($).

Sensitivity analysis
One-way and two-way sensitivity analyses were conducted on several model inputs to evaluate the robustness of the
estimated costs and benefits. Some of the assumptions made in the model were also tested. The ranges reported in the literature were used for the sensitivity analysis.

**Estimated benefits used in the economic analysis**
The number of QALYs gained with the study intervention was not reported. The decrease in CHD deaths due to cereal grain fortification with folic acid was 12.8% for men and 8.7% for women using baseline estimates. In patients with known CHD (secondary prevention), the intervention with folic acid and vitamin supplements over 10 years resulted in 186,600 myocardial infarctions prevented and 211,300 CHD deaths averted in men. The corresponding values in women were 73,400 (myocardial infarctions prevented) and 101,540 (CHD deaths averted), respectively.

**Cost results**
The estimated total costs were not reported.

In patients with known CHD, the cost-savings (expense of treatment with vitamin supplements minus the savings from CHD events prevented) were $18,800 for men and $5,420 for women.

**Synthesis of costs and benefits**
An incremental cost-effectiveness ratio was calculated to combine the costs and QALYs of the alternative strategies evaluated in the analysis.

In primary prevention, the use of vitamin supplementation in men older than 45 years cost $9,000 per QALY saved, compared with the option of fortified grain alone in men. The treatment of men with homocysteine levels higher than 10 micromol/L was predicted to maximise the cost-savings.

In women aged 75 years or older without CHD, vitamin supplementation had an incremental cost-utility ratio of $1,200 per QALY saved, compared with grain fortification alone. Compared with treating all women aged 75 years or older, screening all women aged 65 to 74 years and treating only those with elevated homocysteine levels had an incremental cost-utility ratio of $5,500 per QALY saved.

Other scenarios were also reported. However, the most cost-effective strategies for primary prevention were providing vitamin supplements in addition to grain fortification to all men aged at least 45 years and to all women older than 55 years.

In secondary prevention, the treatment of all patients with known CHD with vitamin supplements was the dominant strategy because it was more effective (fewer CHD events) and cheaper (cost-savings) than the option of no treatment.

These results held constant under most of the scenarios considered in the sensitivity analyses.

**Authors' conclusions**
The combined therapy with folic acid and cyanocobalamin for the prevention of coronary heart disease (CHD) was cost-effective in men older than 45 years and women older than 55 years.

**CRD COMMENTARY - Selection of comparators**
The authors compared each alternative strategy with the option of no intervention, which was appropriate because it represented the standard practice. The strategies under evaluation were then compared to each other. You should decide whether this represents a valid basic comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence came from data derived from the literature. Separate reviews of the literature were conducted to identify the relevant studies that provided data on the outcomes used in the decision model. However, the
methods and conduct of the reviews were unclear and the inclusion criteria were not explicitly stated. It was not clear whether the evidence came exclusively from randomised trials, and the quality of the primary studies was not discussed. Other information used in the model was selectively identified. The authors used specific pooling methods to combine the data extracted from the studies, but they did not comment on differences between the primary studies. Some assumptions were also made and the authors stated that conservative hypotheses were used to bias the model against the study interventions. Most of the model inputs and the assumptions were varied in the sensitivity analysis, which used ranges derived from the literature, where feasible.

**Validity of estimate of measure of benefit**
QALYs were used as the summary benefit measure in the economic analysis. Their use appears to have been appropriate because the study intervention had an impact on both survival and quality of life. The use of QALYs also facilitates comparisons with the benefits of other interventions. QALYs were calculated using a validated decision model. Appropriate discounting was applied.

**Validity of estimate of costs**
The perspective adopted in the study was reported, but a detailed breakdown of the costs was not provided. Overall, few details on the cost analysis were given. The unit costs and the quantities of resources used were not analysed separately. The price year was reported, thus facilitating reflation exercises in other settings. However, the total estimated costs were not reported and the source of the resource use data was not given. Some of the costs were varied in the sensitivity analyses using ranges observed in the literature. These issues indicate that the generalisability of the cost results to other settings is low.

**Other issues**
The authors did not compare their findings with those reported in other studies. They also did not address the issue of the generalisability of the study results to other settings. Although some sensitivity analyses were conducted, the overall external validity of the analysis was low. The authors stated that the main limitation of the analysis was the lack of clinical trial data on the effects of homocysteine-lowering therapy on disease rates. The analysis was appropriately split between primary and secondary prevention strategies.

**Implications of the study**
The authors stated that they would recommend routine homocysteine-lowering therapy, only if the results of the ongoing clinical trial confirm the conclusions of the present study.

**Source of funding**
Not stated.

**Bibliographic details**

**PubMedID**
11509058

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Aged; Coronary Disease /blood /economics /epidemiology /prevention & control; Cost-Benefit Analysis; Dietary Supplements /economics; Edible Grain; Female; Folic Acid /administration & dosage; Food, Fortified /economics; Homocysteine /blood; Humans; Male; Middle Aged; Quality-Adjusted Life Years; United States; Vitamin B 12 /administration & dosage

**AccessionNumber**
22001008214

**Date bibliographic record published**
31/01/2004

**Date abstract record published**
31/01/2004