Can Folic Acid Prevent AMD?

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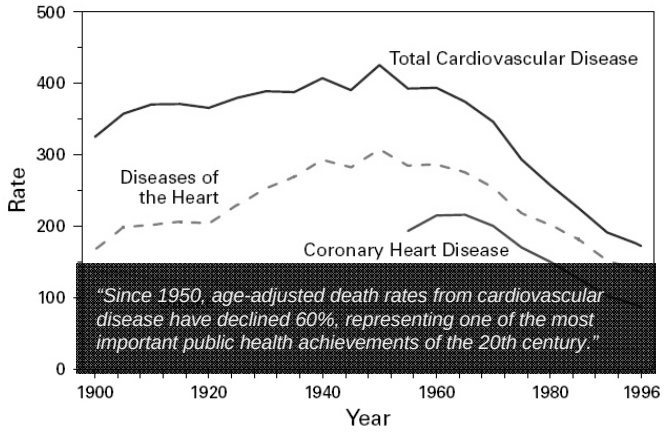
Folate and B-vitamin fortification of the food supply began in the 1950s and 1960s

Heart Disease and Stroke — Continued

FIGURE 1. Age-adjusted death rates* for total cardiovascular disease, diseases of the heart, coronary heart disease, and stroke,† by year — United States, 1900–1996



"Since 1950, age-adjusted death rates from cardiovascular disease have declined 60%, representing one of the most important public health achievements of the 20th century."

*Per 100,000 population, standardized to the 1940 U.S. population.
†Diseases are classified according to *International Classification of Diseases* (ICD) codes in use when the deaths were reported. ICD classification revisions occurred in 1910, 1921, 1930, 1939, 1949, 1958, 1968, and 1979. Death rates before 1933 do not include all states. Comparability ratios were applied to rates for 1970 and 1975.

Heart disease has been the leading cause of death in the United States since 1921, and stroke has been the third leading cause since 1938; together they account for approximately 40% of all deaths.

We have witnessed a dramatic decline in vascular disease mortality in the United States to less than one-half the peak incidence

Death rates from cardiovascular disease (CVD) peaked in 1955 and have since declined 60%, representing one of the most important public health achievements of the 20th century.

None of the traditional risk factors, such as changes in dietary fats, blood cholesterol concentrations, smoking, hypertension, exercise, or coronary care units could explain this dramatic decline

One possible explanation is increased consumption of folic acid due to fortification of grains beginning in the 1950s, and later mandated by the FDA.

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THE EFFECT OF FOLIC ACID FORTIFICATION ON PLASMA FOLATE AND TOTAL HOMOCYSTEINE CONCENTRATIONS

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ABSTRACT

Background In 1996, the Food and Drug Adminis-

IN 1996, the Food and Drug Administration (FDA) issued a regulation, to be effective by Jan-

"Folic acid fortification was undertaken to reduce the risk of neural-tube defects, but it may also have a beneficial effect on vascular disease…"

fifth examination (January 1991 to December 1994)

ble of becoming pregnant should consume 0.4 mg of

Fortification provides about 70-120 µg of FA/day for middle-aged and older adults

The mean Hcy concentration decreased from 10.1 to 9.4 µmol/l (P<0.001), and the prevalence of high homocysteine concentrations (>13 µmol/l) decreased from 18.7 to 9.8% (P<0.001). *Cut in half!*

Lowering of blood homocysteine concentrations by the addition of vitamin B-6 and folic acid to the US diet may explain in part the **dramatic decline in vascular disease mortality in the United States to less than one-half the peak incidence**.

This statement would seem to confirm the "homocysteine hypothesis" - that the amino acid hcy is a cause of cardiovascular dx

- In the 1950s and 1960s, vitamin B-6 was added to cereals
- In the 1960s, synthetic folic acid was also added to the food supply
- In 1996, the FDA issued a regulation, to be effective by January 1998, requiring that all enriched flour, rice, pasta, cornmeal, and other grain products contain 140 µg of folic acid per 100 g to decrease the risk of **spina bifida** and other neural tube birth defects

The Homocysteine Hypothesis

- 1962: Homocystinuria
  - Genetic defect causing inborn error of Hcy metabolism
  - Blood and urine testing reveals very high levels of the amino acid homocysteine (Hcy)
  - Premature death from stroke or heart disease
  - Autopsy reveals widespread arteriosclerosis
- 1969: Suggested that elevated Hcy may cause arteriosclerosis in the general population

McCully K. Am J Pathol. 1969;56:111-128.

Hcy hypothesis grew out of research into homocystinuria

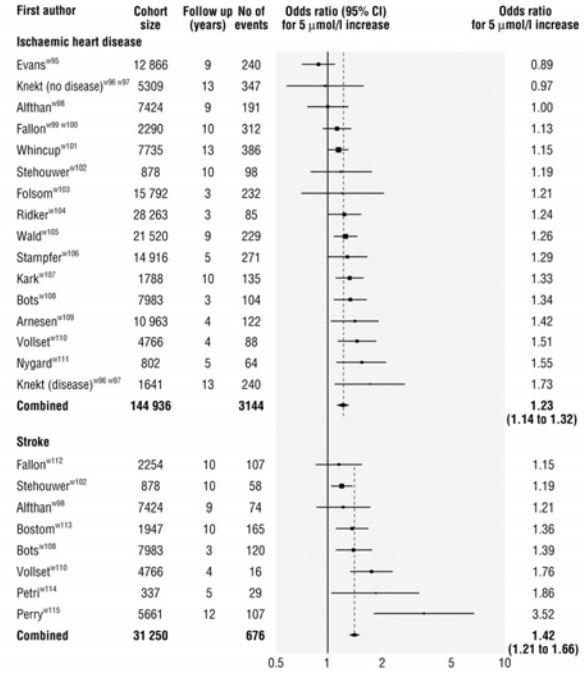
Extensive AS in young people with extremely high hcy due to inborn error of hcy metabolism

If extremely high hcy can cause precocious AS in persons with HCU, then moderately elevated hcy may cause AS in the general population

Meta-analysis of observational studies investigating association of serum Hcy level and risk of ischemic heart disease and stroke

Epidemiologic studies find that elevated Hcy is associated with increased risk of heart attack and stroke

3 μmol/l decrease in serum Hcy (achievable with folic acid) would reduce the risk of heart attack by 10% and stroke by 20%



Wald DS, et al. BMJ 2002;325:1202-1206

Numerous studies have investigated the relation between CVD and hcy levels

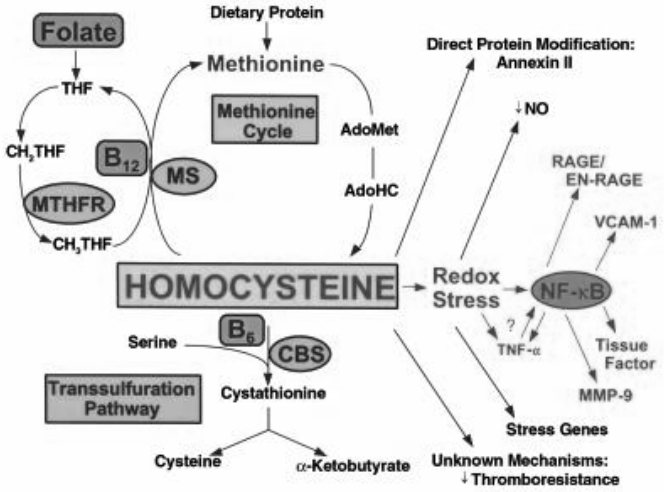
Observational studies have found a strong relation between elevated hcy levels and elevated risk of CVD

- 20% increased risk of IHD
- 40% increased risk of stroke

Folic acid can decrease hcy by 3 μmol/l, and this corresponds to:

- 10% lower risk of heart attack
- 20% lower risk of stroke

Homocysteine



What exactly is hcy?

Hcy is a non-protein forming amino acid formed as an intermediate in the conversion of one amino acid to another (methionine to cysteine)

Hcy is pro-oxidant and pro-inflammatory

Conversion of hcy to cysteine requires vitamin B6 and is irreversible, but hcy can be converted back into methionine using FA and B12

So the amount of hcy in the body is largely dependent upon the availability of FA, vitamins B6 and B12

Hyperhomocysteinemia

- Serum Hcy upper limits of normal
  - 12 µmol/l with folic acid fortified diet (North America)
  - 10% of general population
- Determinants of serum Hcy
  - Age impaired vitamin absorption (1 µmol/l / decade)
  - Diet deficient in folic acid and B vitamins
  - Lifestyle smoking, alcohol, coffee
  - Genetics congenital 25% elevation of Hcy (10% gen pop)
- Reduction of serum Hcy
  - 0.8 mg folic acid lowers serum Hcy by 3 µmol/l

Clarke R. Am J Clin Nutr 2005; 82: 806-812

Elevated hcy is a common problem

- **10% general pop** in countries with folic acid fortification
- 20% in countries without fortification
- More common in the elderly
- Largely influenced by diet and lifestyle factors

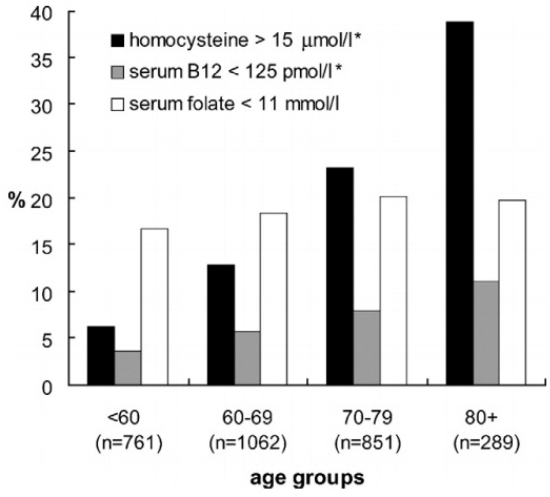
Genetic polymorphisms effecting various enzymes in the methionine/cysteine pathway can lead to a congenital elevation of hcy

- HCU: complete absence of the ability to metabolize hcy. RARE
- Mild impairment of the ability to metabolize hcy is common (**10% of gen pop**)

Folic acid is a **safe, cheap and highly effective** means to lower hcy

Hyperhomocysteinemia

Prevalence of serum homocysteine >15 µmol/l, by age groups in the Blue Mountains Eye Study population (3,509 patients aged 49+ years)



Am J Ophthalmol 2007;143:344–346

BMES = Australia

No folic acid fortification in Australia until 2009

Note strong age-related prevalence of HHC

If elevated Hcy is associated with increased risk of cardiovascular disease,

And

Folic acid lowers Hcy levels,

Then

Folic acid should decrease the risk of cardiovascular disease. Right?

IF ELEVATED HCY IS ASSOCIATED WITH CVD, AND

FOLIC ACID LOWERS HCY LEVELS, THEN

FOLIC ACID SUPPLEMENTS SHOULD DECREASE THE RISK OF CVD,

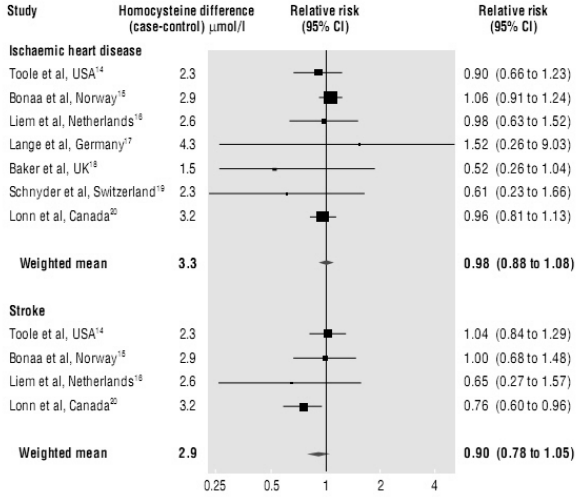
RIGHT???

WRONG!!!

The Homocysteine Paradox

Meta-analysis of interventional studies of folic acid supplementation for IHD and stroke

Randomized controlled trials have found no benefit of folic acid supplementation on heart attack, and a marginally significant benefit for stroke in patients with established cardiovascular disease



Wald DS. BMJ 2006:333;1114-1117

Very few studies have found any benefit of FA supplementation in the treatment of patients with cardiovascular dx

When a benefit is found, it tends to be more for stroke than heart dx

The failure of hcy-lowering tx to benefit pts with **established** cardiovascular dx has been labeled the hcy paradox

The Homocysteine Paradox

- Why does folic acid supplementation fail to prevent heart attack and stroke?
  1. Lowering Hcy may be more important in primary prevention than secondary prevention
  2. Elevated Hcy may be a consequence of vascular disease, not a cause
  3. Folic acid may have deleterious effects that mask the benefit of Hcy lowering
  4. Clinical trials failed to detect a benefit because they were too small, too short, or failed to lower Hcy sufficiently

Several possible explanations have been proposed for the hcy paradox

1. MOST LIKELY (my favorite)

- corollary: hcy is more important in cerebrovascular dx than in coronary artery dx
- final reason: **hcy more important in primary prevention of stroke than in secondary prevention on ischemic heart dx**

2. Disputed by fortification and HCU experience

3. Possible. FA has many roles in the body unrelated hcy metabolism

4. True. But larger, longer trial will probably not be funded. Meta-analysis has failed to reveal a significant benefit

Vascular Model of AMD

- Close relationship between AMD and CVD
  - Common risk factors
    - Smoking, Obesity, High dietary fat, HTN, CRP
  - Common antecedents:
    - Inflammation, Oxidative stress, Vascular endothelial dysfunction, Genetics
  - Common interventions
    - Fish oil, heart-healthy diet, exercise, weight loss, etc
- Speculation: AMD and CVD are two manifestations of a single underlying chronic inflammatory disease of aging
- Hypothesis: If Hcy is assoc with CVD, and if CVD is assoc with AMD, then Hcy may be assoc with AMD

There is a **clear, strong, probably causal** relation between hcy and vascular dx

There is a **clear, strong, probably causal** relation between vascular dx and AMD

Given the demonstrated relation between hcy and CVD, it is reasonable to suspect that hcy may also be related to AMD

Genetics: apolipoprotein E gene

Homocysteine and AMD

- Observational evidence
  - Studies finding AMD associated with elevated Hcy
    1. Axer-Siegel (2004) wet AMD only
    2. Nowak (2005) wet AMD only
    3. Vine (2005) wet and dry AMD
    4. Coral (2006) wet AMD only
    5. Kamburoglu (2006) wet and dry AMD
    6. Seddon (2006) intermediate or advanced AMD
    7. Rochtchina (2007) advanced AMD in persons <75yo
    8. Ates (2009) wet AMD only
  - Studies not finding an association
    1. Heuberger (2002) NHANES, few late AMD cases, non-fasting
    2. Wu (2007) BMES, few late AMD cases

Sure enough… 8 studies to date have found AMD is associated with elevated hcy

- 4/8 studies only studied wet AMD
- 4/8 studies examined both wet and dry AMD

2/10 studies found no assoc between AMD and hcy, but these are population-based studies that have few advanced AMD cases

On the basis of observational studies we can conclude that **elevated Hcy is a risk factor for AMD**, at least for advanced/wet AMD

Folic Acid & AMD Prevention

- Interventional study: Christen (2009)
  - Substudy of the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS)
    - RCT of women at high risk for CVD evaluating whether antioxidant vitamins and/or folic acid can prevent CVD
  - 5205 women without AMD at baseline randomized to receive folic acid or placebo for 7.3 yrs
    - 2.5 mg folic acid, 50 mg vitamin B_6, 1 mg vitamin B_{12}
  - 137 cases of AMD appeared during follow-up, including 70 visually significant (20/30 or worse)

Christen WG. Arch Intern Med. 2009;169(4):335-341

We have one, and only one, interventional study investigating the efficacy of folic acid in the primary prevention of AMD

- This study represents a potential major breakthrough in AMD prevention

Folic Acid & AMD Prevention

	TOTAL AMD 137 cases	VS AMD 70 cases
Folic Acid	55 cases	26 cases
Placebo	82 cases	44 cases
Relative Risk	0.66 (35% lower risk)	0.59 (40% lower risk)
95% CI	0.47-0.93	0.36-0.95
P	0.02	0.03

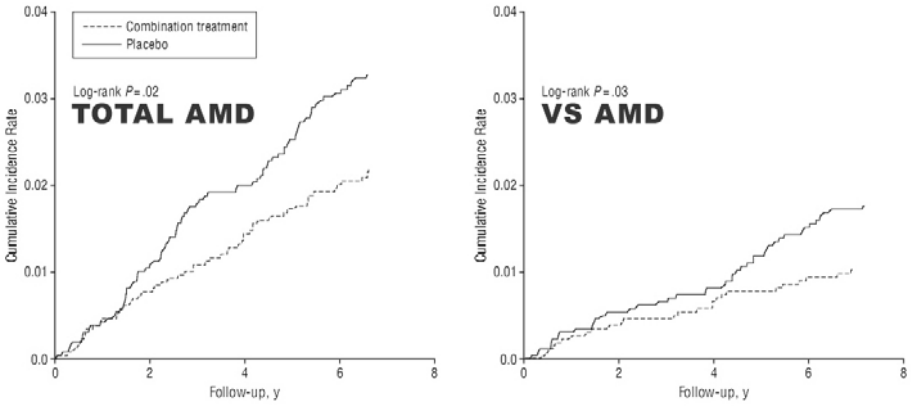
Christen WG. Arch Intern Med. 2009;169(4):335-341

Any AMD: drusen, pigmentary changes

Visually significant AMD: BVA of 20/30 or worse attributable to AMD

Statistical significance: less than 5% probability that something would occur by chance

Folic Acid & AMD Prevention



Christen WG. Arch Intern Med. 2009;169(4):335-341

Survival curves

Total AMD: benefit begins to emerge 1 yr after supplementation

VS AMD: benefit begins to emerge after 4 yrs

Folic Acid & AMD Prevention

- Folic acid is the first identified means, other than cigarette avoidance, to prevent the onset of AMD
- Folic acid decreases the risk of developing AMD by 35-40% in women at increased risk of CVD
  - Future studies needed to determine whether these findings can be generalized

Christen WG. Arch Intern Med. 2009;169(4):335-341

Question ability to generalize findings

HOWEVER

Because folic acid is a relatively safe and inexpensive nutritional supplement; and AMD is an incurable potentially blinding disease, the risk benefit analysis would seem to favor recommending folic acid supplementation at the present time despite the incomplete research evidence supporting its use

No reason to expect men to respond differently to FA

Should I Prescribe Folic Acid?

- Primary prevention, not progression
  - Only recommended for prophylaxis against AMD
- Women vs. Men
  - Evidence is currently stronger for women
  - No reason to expect men to respond differently
- Balance megadoses with vitamin B_{12}
  - If daily intake of folic acid exceeds 1 mg, balance with at least 100% RDA of B12
- Should be avoided by cancer patients
  - Facilitates growth & multiplication of cancer cells

So, if you are still awake and paying attention, you are probably asking yourself whether you should be prescribing FA supplementation

Some things to keep in mind regarding prescribing FA:

1. Primary prevention only

- no evidence to support its use in pts with established AMD

2. Women vs men

- Evidence is currently stronger for women than men

3. Balance megadoses of FA with B12

- If total daily FA intake exceeds 1mg, make sure pt is getting at least 100% RDA of B12

4. Dual effect on cancer

- FA decreases risk of carcinogenic mutations, but facilitates growth multiplication of ca cells
- **avoid prescribing FA to pts battling cancer**

Should I Prescribe Folic Acid?

- What should I prescribe?
  - Maximum Hcy-lowering effect: 0.8mg *200% RDA*
    - RDA: 0.4 mg *(400 mcg)*
  - Tolerable upper intake level: 1mg
    - From all sources (food, supplements)
    - B_{12} not required if upper limit not exceeded
  - WAFACS supplement not commercially available
    - 2.5 mg folic acid, 50 mg vitamin B_6, 1 mg vitamin B_{12}
  - Recommendation: ≥200% folic acid RDA plus ≥100% B_{12} RDA (2.5 mcg)

Fortification provides about 0.1 mg of FA/day for middle-aged and older adults

WAFACS: 2.5 mg folic acid, 50 mg vitamin B6, 1 mg vitamin B12

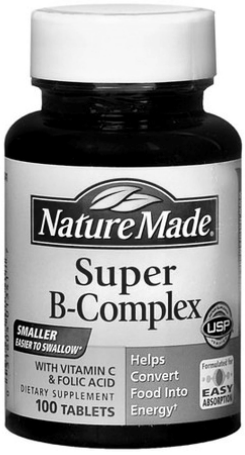
If you want to prescribe the WAFACS supplement: 5 pills/day

You will probably need to do it this way: 3 separate supplements, 5 pills daily

800 mcg x 3 pills = 2.4 mg (very close to 2.5 mg in WAFACS)

3 x folic acid
1 x B6
1 x B12 (hard to find 1 mg B12, may need multiple pills)

Total: 5 pills minimum



Supplement Facts

Serving Size 1 Caplet

Amount Per Caplet	% Daily Value
Vitamin C 500 mg	833%
Thiamin (Vitamin B1) 50 mg	3333%
Riboflavin (Vitamin B2) 50 mg	2941%
Niacin 50 mg	250%
Vitamin B6 50 mg	2500%
Folate 400 mcg	100%
Vitamin B12 50 mcg	833%
Biotin 50 mcg	17%
Pantothenic Acid 50 mg	500%

WAFACS: 2.5 mg folic acid, 50 mg vitamin B6, 1 mg vitamin B12

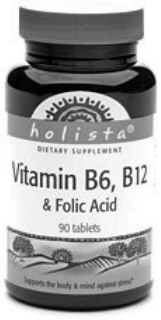
Simplest for patient: 2 pills/day B-complex supplement.

Look for 200% RDA of folic acid (RARE – almost always contains 100%).

Pt will have to take 2 pills/day to get max Hcy-lowering dosage (800 mcg)

B-complex: combination of all B vitamins

- It was once thought B vitamin was a single vitamin
- Later research uncovered that B vitamin was actually about a dozen different chemicals, and each was given a number



Supplement Facts

Serving Size:	1 Tablet	
Servings Per Container:	90	
	Amount per Serving	% Daily Value
Vitamin B6 as pyridoxine hydrochloride	50 mg	2500%
Folate,Folic Acid,Folacin	1000 mcg	250%
Vitamin B12	125 mcg	2080%
Calcium as dicalcium phosphate	33 mg	3%

* Daily Value not established.

WAFACS: 2.5 mg folic acid, 50 mg vitamin B6, 1 mg vitamin B12

1 pill/day

If you are lucky, your pt may find a single pill that contains everything you need

Thank You!