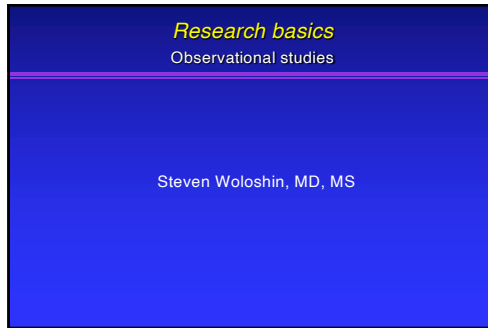


Highlighting cautions about observational studies  
Steven Woloshin



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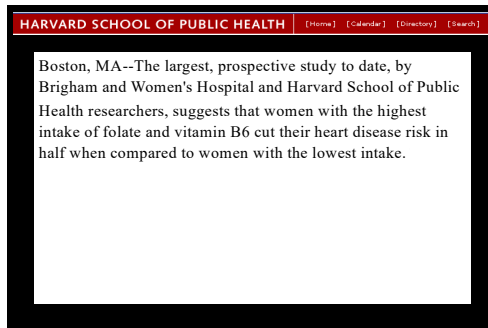
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# Highlighting cautions about observational studies

Steven Woloshin

**JAMA**  
Journal of the American Medical Association

**Folate and Vitamin B<sub>6</sub> From Diet and Supplements in Relation to Risk of Coronary Heart Disease Among Women**

**Context.**— Hyperhomocysteinemia is caused by genetic and lifestyle influences, including low intakes of folate and vitamin B<sub>6</sub>. However, prospective data relating intake of these vitamins to risk of coronary heart disease (CHD) are not available.

**Objective.**— To examine intakes of folate and vitamin B<sub>6</sub> in relation to the incidence of nonfatal myocardial infarction (MI) and fatal CHD.

**Design.**— Prospective cohort study.

**Setting and Patients.**— In 1980, a total of 80082 women from the Nurses' Health Study with no previous history of cardiovascular disease, cancer, hypercholesterolemia, or diabetes completed a detailed food frequency questionnaire from which we derived usual intake of folate and vitamin B<sub>6</sub>.

**Main Outcome Measure.**— Nonfatal MI and fatal CHD confirmed by World Health Organization criteria.

**Results.**— During 14 years of follow-up, we documented 638 incident cases of nonfatal MI and 281 cases of fatal CHD. After controlling for cardiovascular risk factors, including smoking and hypertension and intake of alcohol, fiber, vitamin E, and saturated, polyunsaturated, and trans fat, the relative risks (RRs) of CHD among women with the highest intake compared to the lowest intake were 0.69 (95% confidence interval [CI], 0.55–0.87) for folate (median intake, 496 µg/d vs 159 µg/d) and 0.55 (95% CI, 0.41–0.74) for vitamin B<sub>6</sub> (median intake, 4.6 mg/d vs 1.1 mg/d). Controlling for the same variables, the RR was 0.55 (95% CI, 0.41–0.74) among women with the highest intake of both folate and vitamin B<sub>6</sub> compared with the opposite extreme.

**Conclusion.**— These results suggest that intake of folate and vitamin B<sub>6</sub> above the current recommended dietary allowance may be important in the primary prevention of CHD among women.

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**Folate and Vitamin B<sub>6</sub> from diet and supplements in relation to risk of coronary heart disease among women (JAMA 1998)**

**Context.**— Hyperhomocysteinemia is caused by genetic and lifestyle influences, including low intakes of folate and vitamin B<sub>6</sub>. However, prospective data relating intake of these vitamins to risk of coronary heart disease (CHD) are not available.

**Objective.**— To examine intakes of folate and vitamin B<sub>6</sub> in relation to the incidence of nonfatal myocardial infarction (MI) and fatal CHD.

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**Conclusion.**— These results suggest that intake of folate and vitamin B<sub>6</sub> above the current recommended dietary allowance may be important in the primary prevention of CHD among women.

*What is the outcome?*

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**Part I Main result**

Quantify the exposure?	1. What is the exposure in the control group?	2. What is the exposure in the exposed group?
Folate (micrograms per day)	158	696
Vitamin B <sub>6</sub> (mgs per day)	1.1	4.6

3. What is the outcome?  
\_\_\_\_\_

4. What is the effect size?  
What is the relative risk? \_\_\_\_\_  
What are the absolute risks? \_\_\_\_\_

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### Number Needed to Eat

What you need to eat a day	1. What is the exposure in the control group?	2. What is the exposure in the exposed group?
Cups of orange juice	4	15
Cups of chicken	2	7

Probably need to take supplements  
not feasible to do with diet

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### Part I Main result

	1. What is the exposure in the control group?	2. What is the exposure in the exposed group?
	Lowest intake of both folate & B6	Highest intake of both folate & B6

3. What is the outcome?  
**Fatal and non-fatal heart**

But we just can't know exactly  
**\*\* Ask the researchers\*\***

4. What is the effect size?  
What is the relative risk? **0.55**

What are the absolute risks?

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    graph TD
      RR[0.55] --- AR1[1.4%]
      RR --- AR2[0.8%]
      AR1 --- AR3[1.2%]
      AR2 --- AR3[1.2%]
    
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It should be easy... but it's not  
Getting the absolute risks often requires work

Research BMJ

Ratio measures in leading medical journals: structured review of accessibility of underlying absolute risks  
Lisa M Schwartz, Steven Woloshin, Evan L. Deorn, H Gilbert Welch

We looked for absolute risks in 222 articles in leading medical journals which had ratio measures (e.g. relative risk) in the abstract.  
Absolute risks are not easily accessible in articles reporting ratio measures and sometimes are missing altogether

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**Guidance**  
*Expressing Cautions - observational*

1. Communicate exposure clearly: translate exposure into actual life activities. This serves 2 purposes:
  - clarify how extreme the 2 exposure groups are (what low vs. high intake means)
  - to help people understand whether the activity is worth the sacrifice.
2. Consider how likely confounding is to explain the results.
  - See if there is evidence the groups are different (Look at "Table 1").
  - Imagine other potential confounders which might explain the results (not in "Table 1").
  - **Advanced**: Consider what happens with adjustment.

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**Advanced Topic: Adjustment**

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Confounding

Vit B6 & Folate Exposure → Actual Observed effect → Heart attacks Outcome

**WARNING**  
Researchers can only adjust for things they have measured

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# Highlighting cautions about observational studies

Steven Woloshin

**Adjustment ...**

**makes effect stronger**  
(moves RR further away from 1)

**makes effect weaker**  
(moves RR closer to 1)

**makes little difference**

*Interpretation*

*Reassured there is a real effect*  
- because confounders minimized - rather than exaggerated the effect, even if other confounders exist – they would make effect stronger.

*More skeptical there is any real effect*  
- worried that other confounders exist which would eliminate the effect.

*It depends*  
- if you think the important confounders were included, you can be *reassured*.  
- if you think important confounders are missing, you should be *skeptical*.

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Compare the "crude" and adjusted results

What happens to the effect size with adjustment?

	RR <sub>crude</sub>	RR <sub>adjusted</sub>
Makes effect weaker (moves RR closer to 1)	0.50	0.90
	2.31	1.80
Makes effect stronger (moves RR further away from 1)	0.50	0.10
	1.20	2.10
Makes little difference	0.50	0.51
	1.07	1.09

**SUBJECTIVE JUDGMENT CALL**

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**Back to our vitamin story**

RR<sub>adjusted</sub> = 0.55

\*Adjusted for age; time period, body mass index, smoking, physical activity, hypertension, parental history of myocardial infarction before age 65 years, alcohol and quintiles of fiber, alcohol, and saturated, polyunsaturated and trans fat.

**Practice Quiz: Can you say it in a sentence**

After adjusting for age, smoking, etc., women with the highest folate and B6 intake had **0.55 times** the risk of heart attack as those with the lowest intake.

After adjusting for age, smoking, etc., women with the highest folate and B6 intake had **a 45% lower** risk than those with the lowest intake.

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Take home messages  
Adjustment

Adjustment doesn't make the findings true.  
Adjustment can only take care of variables you know about  
-- may miss known confounders or unknown confounders.  
You can be *reassured* if adjustment makes the effect stronger or hardly changes it (and includes the important confounders).  
You should be more *skeptical* when adjustment weakens the effect.

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Let's add even more caution

5. Did someone's choice (e.g. doctor, patient, etc) determine who was in which group?  
Yes No Maybe

6. Beside the exposure, are there other differences between the exposed and control groups that might explain the difference in outcome (i.e. potential confounders)?  
a. Differences reported in Table 1 of the article?  
**The two groups were different in many ways.  
Women reporting the highest folate and B6 intake had lower levels of several cardiac risk factors (less smoking, more regular exercise).**  
b. Other differences you imagine?

7. How worried are you that confounding might explain the results?  
Not at all A little Extremely

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Let's add even more caution

5. Did someone's choice (e.g. doctor, patient, etc) determine who was in which group?  
Yes No Maybe

6. Beside the exposure, are there other differences between the exposed and control groups that might explain the difference in outcome (i.e. potential confounders)?  
a. Differences reported in Table 1 of the article?  
**The two groups were different in many ways.  
Women reporting the highest folate and B6 intake had lower levels of several cardiac risk factors (less smoking, more regular exercise).**

7. How worried are you that confounding might explain the results?  
**Because adjustment for these factors weakened the observed effect, we are more worried about that there may be other unaccounted for differences between women in the 2 groups that make really explain the effect (like cholesterol levels)**  
**So we really don't know whether folate and B6 really lowered the risk of heart attack or if the women with the highest intake were just healthier to start.**

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Highlighting cautions about observational studies  
Steven Woloshin

**Bottom Line**  
What should people do (or believe) about these results

Based on this study, should people increase their intake of folate and vitamin B6?

**No. This study does NOT provide evidence to support changing behavior. To know whether high folate and B6 intake lowers heart attack risk requires a randomized trial.**

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How did 2 major newspapers handle the story?

The New York Times (1104 words, page A10)  
**High intake of 2 vitamins may lower coronary risk**

A high intake of two B vitamins found in fruits, vegetables and other common foods appeared to **reduce by nearly half** women's risk of suffering a heart attack, a study has shown. ....The study, conducted among more than 80,000 women who are nurses, is the first to **show a direct link** between these B vitamins, folate and B-6, and protection against coronary disease. It suggests that eating more fruits, vegetables and whole grains or getting these B vitamins from supplements is **as important as quitting smoking, lowering high cholesterol and controlling blood pressure in preventing premature death** from the nation's leading killer.

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How did 2 major newspapers handle the story?

The Washington Post (935 words, page A3)  
**Vitamins sharply reduce risk of heart attack**

Consuming large amounts of folic acid and vitamin B6 **may sharply reduce the risk** of heart attack, according to a major study released yesterday. The 14-year study found that women whose diets contain high levels of the two vitamins are **significantly less likely** to develop heart disease, the nation's leading killer. The findings suggest that the **nation's heart disease rate could be cut** if people simply ate more green leafy vegetables and other foods containing those nutrients.

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# Highlighting cautions about observational studies

Steven Woloshin

These are populations--ones where the absolute risks are higher--you would expect to see an effect if there was one.

Year	Population	Finding
2004	3,600 people with prior strokes	No effect on subsequent strokes or heart attacks
2006	5,500 people with diabetes and vascular disease	No effect on subsequent strokes or heart attacks
2008	3,100 people with heart disease or aortic valve disease	No effect on strokes, heart attacks or death
2010	12,064 with prior heart attack	No effect on strokes, heart attacks or death

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September 2014 PLOS ONE

### Association between B Vitamins Supplementation and Risk of Cardiovascular Outcomes: A Cumulative Meta-Analysis of Randomized Controlled Trials

Chi Zhang<sup>1\*</sup>, Zhi-Yong Wang<sup>2\*</sup>, Ying-Yi Qin<sup>3\*</sup>, Fei-Fei Yu<sup>4\*</sup>, Yu-Hao Zhou<sup>4\*</sup>

**B vitamin supplementation, when used for primary or secondary prevention is not associated with a reduction in MACE, total mortality, cardiac death, MI, or stroke.**

**Conclusion/Significance:** B vitamin supplementation, when used for primary or secondary prevention, is not associated with a reduction in MACE, total mortality, cardiac death, MI, or stroke.

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Now we know... findings of this observational study reflected confounding - NOT folate and B6

1. What is the exposure in the control group?	2. What is the exposure in the exposed group?
Lowest intake of both Folate & B6	Highest intake of both folate & B6

3. What is the outcome?  
Fatal and non-fatal heart attacks over 14 years

4. What is the effect size?  
What is the relative risk? 0.55

Where are the absolute risks?

1.44	0.79
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# Highlighting cautions about observational studies

Steven Woloshin

**CAUTION Guidance**  
*Observational studies*

Because confounding is always a potentially important problem. Every observational study needs an EXPLICIT caution.

**If the exposure is an intervention where a randomized trial is possible:**

"Because the study was not a true experiment, we cannot know whether changing [exposure] will change [outcome]. The differences may be explained by differences in the people who happened to be [exposed] rather than [drug/exposure]. A randomized trial is needed before widespread adoption of [intervention]."

**If the exposure is likely to be harmful so a randomized trial is NOT possible:**

"Because the study was not a true experiment, the findings may be explained by differences in the people who happened to be [exposed] rather than [drug/exposure]."

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