

# Clinical use of evidence-based medicine: Studies used to assess harm

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## Does the Atkin's diet increase risk of cardiac morbidity and mortality in women?

### Patient

A 36-year-old obese woman with a past medical history of hyperlipidemia and tobacco abuse and a family history of early cardiac death presents to clinic for an annual physical exam. She is very motivated to lose weight and wants to try the Atkins diet.

### Clinical Question

In an obese woman with multiple cardiac risk factors, does following the Atkins diet increase the risk of cardiac morbidity and mortality?

### Search Strategy

1. Cochrane Database of Systemic Reviews and Database of Abstracts of Reviews of Effects (DARE) (search performed via Wiley Interscience February of 2007):
  - a. "Atkins" (keyword, title, abstract)
  - b. no matching articles
2. ACP Journal Club
  - a. "Atkins"
  - b. no matching articles
3. All years of Pubmed (search performed February of 2007)
  - a. "diet, carbohydrate-restricted" (MeSH heading)
  - b. "Cardiovascular diseases" (MeSH heading)
  - c. Combine (a) and (b)
  - d. Limit (c) to English
  - e. 19 matches, 2 applicable to our case:
    1. Halton et al. "Low Carbohydrate-Diet Score and the Risk of Coronary Heart Disease in Women."
    2. Truby et al. "Randomized controlled trial of four commercial weight loss programmes in the UK: initial findings from the BCC 'diet trials.'"

### Studies Assessing Harm

Studies assessing harm may be performed differently than studies assessing benefit. Ethical considerations often make it impos-

sible to perform randomized controlled trials, which are commonly used to evaluate therapies. Therefore, researchers often use cohort studies or case-control studies to evaluate harm.

In a cohort study, the investigators compare a group of subjects who have been exposed to a potentially harmful stimulus with a group of non-exposed subjects. The subjects are followed over time to see if they develop the disease of interest. Ideally, the non-exposed subjects should be similar to the exposed subjects in every way with the exception of the exposure. If there are differences between the groups, the investigators can use statistical techniques to adjust for the differences. Cohort studies are particularly helpful if the harmful outcomes are infrequent or it is unethical to randomize subjects to the exposure. However, unknown differences between the exposed and non-exposed groups can lead to bias.

Case-control studies are used to assess outcomes that are very rare or require an extended amount of time to develop. Investigators identify subjects who have already developed the outcome of interest (cases) and then choose a set of subjects who have not developed the outcome of interest, but who are otherwise similar to the cases (controls). In this way the investigators can assess the frequency of exposure in a retrospective fashion. The retrospective nature of case-control studies can introduce biases. One of these biases is recall bias; subjects who have developed the disease are more likely to remember being exposed than subjects who did not develop the disease. It is also difficult to determine definitively whether the exposure occurred before the disease started.

### Study Characteristics

Halton et al

- Prospective Cohort of 82,802 healthy female nurses between the ages of 30 and 55 years.
- Objective to determine if low carbohydrate diet increases the risk of coronary heart disease in women.
- Members of the Nurse's Health Study filled out semi-quantitative food frequency questionnaires every 2 to 4 years.
- Low carbohydrate diet score calculated for each subject .
- Patients were placed into groups based on frequency of carbohydrate consumption, and then each group's cardiovascular events were calculated.

Truby et al

- Randomized control trial.
- 293 volunteers between the ages of 18 and 65 years with a self reported BMI between 27 and 40.
- Volunteers were randomized to 4 different commercial diets

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(Atkins, Weight Watchers, Slim-Fast, and Rosemary Conley) and then followed over 1 year.

- Objective to determine weight loss, changes in cholesterol, and ability to maintain weight loss of 4 commercial diets.
- Weight and body fat changes over a period of 6 months were the main measured outcomes.

### Validity of Evidence

Halton et al

- The Low Carbohydrate/High Fat group had more risk factors for coronary artery disease (CAD) at baseline.
  - Researchers adjusted for many known risk factors (BMI, smoking status, postmenopausal hormone use, hours of physical activity per week, alcohol intake, aspirin use, hypertension, hypercholesterolemia, and family history of CAD).
- Diet determination was subjective.
  - Patients filled out questionnaires asking for food consumption over the past 2 years.
- Follow up was very long (20 years).
- Age range of patients at start was 30 to 55.
  - Some patients were only 50 years old at study conclusion.
- Overall, this is a very large study with a lot of potential biases.

Trudy et al

- Randomized properly.
- Patients made up of volunteers wanting to lose weight.
- Groups were similar at the start of the trial.
- Patients and study personnel not blinded.
- Intention to treat analysis performed.
- Very high dropout rate.
  - 28% of all patients withdrew by 6 months.
  - 35% of control group withdrew by 6 months.
- Randomized trial, but high dropout rate and lack of blinding could lead to bias.

### Results

Halton et al

- No increase in coronary events in low carbohydrate group when compared to the high carbohydrate group.
- Relative risk of myocardial infarction or death for low carbohydrate group when compared to high carbohydrate group is 1.29 (1.04-1.60).
- When adjusted for multiple confounders listed above, the relative risk is no longer significant at 0.94 (0.76 to 1.18).
- Subgroup analysis of 466 women showed no association between low carbohydrate diet score and total cholesterol, HDL, or LDL.

Trudy et al

- Atkins diet resulted in significantly higher weight loss in the first 4 weeks (mean of 4.4kg compared to 2.86kg in Weight Watchers, 2.68kg in Slim-Fast, and 3.17kg in Rosemary Conley).
- At 6 months, weight loss was not significantly different among the 4 diets.
- Cholesterol fell significantly compared with the control group only in the Weight Watchers group (0.55mmol/l with a *P*-value of 0.013).
- All diets resulted in a significant decrease in mean percent-

age of body fat (2.1%-3.6% depending on diet) and mean weight (4.9kg-7.3kg depending on diet) over 6 months.

- Groups did not differ significantly but loss of body fat and weight was greater in all groups that completed the study, compared with the control group.

### Applying the Evidence to the Patient

- Our patient fits within the age requirements of both studies.
- Our patient's BMI was higher than the women in the nurses health study.
- Women in the Nurses Health Study were not trying to lose weight.
- Our patient is much younger than the average age of the patients in the 2 studies.
- Our patient has significant dyslipidemia and the majority of the study patients did not.
- Our patient is very interested in losing weight and thinks the Atkins diet will be able to help her.

### Summary

Studies of harm are often carried out in cohort or case-controlled studies. We reviewed a prospective cohort study by Halton et al that assessed increased cardiovascular events in women on a low carbohydrate diet. This study did not show an increase in cardiovascular events. However, the diet assessment was very subjective, and the control group was dissimilar. The fact that these women were not trying to lose weight may have also affected the results. The randomized controlled trial by Trudy et al compared weight loss in 4 different commercially available diets and revealed similar weight loss in all 4 groups. Cholesterol levels did not increase in the Atkins group and systolic blood pressure decreased, although not significantly. Our patient will likely lose weight if she is able to continue with any of these diets. Although the evidence evaluating increased cardiovascular events in patients on the Atkins diet is not strong, the available evidence does not show that the Atkins diet increases this risk.

### Bottom Line

There is no evidence that the Atkins diet increases cardiac morbidity or mortality in women. However, the Atkins diet is not superior to other commercial diets in regard to weight loss, decrease in cholesterol, or decrease in fasting blood glucose. Weight Watchers may be more beneficial to our patient, given the lower incidence of drop out, but if our patient is motivated to try the Atkins diet the weight loss will likely cause more benefit than any potential harm. More research is needed in this area to clearly elucidate the potential risks of the Atkins diet.

### References

1. Halton TL, Willett WC, Liu S, et al. Low carbohydrate-diet score and the risk of coronary heart disease in women. *N Engl J Med.* 2006;355(19):1991-2001.
2. Levine M, Walter S, Lee H, et al. User's guides to the medical literature iv: how to use an article about harm. *JAMA.* 1994;271(20):1615-1619.
3. Truby H, Baic S, deLooy A, et al. Randomised controlled trial of four commercial weight loss programmes in the UK: initial findings from the BBC "diet trials." *BMJ.* 2006;332(7553):1309-1314.

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