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# THE STATISTICAL PROBLEM OF RELATING DIET AND DISEASE

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- My **motivation**: fat intake and breast cancer
- The controversy
- Statistical Models
- Data
- Potential **implications**

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## THE CONTROVERSY

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- For some time, **nutrient fat intake** has been suspected of being a promotor of breast cancer.
- \* **Animal studies** show this clearly.
- **Ecological studies** show it clearly as well.
  - \* Countries with lower aggregate nutrient fat intake have lower rates of breast cancer.
  - \* Japanese women who move to the U.S. have higher rates of breast cancer, and higher nutrient fat intakes.
- **Case-control studies**, when pooled in a meta-analysis, also show a nutrient fat intake effect on breast cancer.

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## THE CONTROVERSY

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- The nutrition epidemiology group at Harvard has bitterly opposed the nutrient fat intake hypothesis.
  - \* This means that they also see as largely a **waste of funds** the nutrition experiment part of the WHI.
- One piece of evidence they cite is that no study that follows women *prospectively* has **ever** found a statistically significant effect of nutrient fat intake on breast cancer.
  - \* Prospective, nonrandomized studies have their own problems, but they are not subject to the potential confounding of ecological studies.
  - \* They are also not subject to the clear biases inherent in case–control studies.

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## SOME BACKGROUND IN MEASURING DIET

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- The goal is to measure “usual nutrient intake”, which I call  $T$  (“truth”).
  - \* This can only be defined **operationally**, as the average daily intake of a nutrient over a fixed period of time, e.g., one year.
  - \*  $T$  is **unobservable**. It is impossible to monitor non–confined populations for their diet.
- The simplest method to “measure” usual intake is the **food frequency questionnaire**, called  $Q$ .
  - \* It is cheap, fast, and simple.
  - \* This is important, because the typical prospective nonrandomized study will have many thousands of participants.

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## BASIC MODEL

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- Generally, people agree on certain properties of the FFQ (an old model of ours is used).
  - \* *Flattened slope*: People who eat large amounts of fat will under-report fat intake, and vice-versa.
  - \* *Measurement or reproduction error*: If you give a person an FFQ multiple times, you will not get the same answers.
  - \* *Equation error or Person-specific bias*: Two people with the same nutrient fat intake will not fill out the FFQ the same way, so that even if you administer the FFQ multiple times and average out the measurement errors, they won't agree exactly.
- The model then is

$$\text{FFQ} = \underbrace{\text{flattened slope}} + \underbrace{\text{Person-specific bias}} + \underbrace{\text{Measurement error}}$$

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## BASIC MODEL

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$$\underbrace{\text{FFQ}} = \underbrace{\text{flattened slope}} + \underbrace{\text{Person-specific bias}} \\ + \underbrace{\text{Measurement error}}$$

- In symbols, this becomes that the  $j$ th measurement on the  $i$ th person is

$$\underbrace{Q_{ij}} = \underbrace{\beta_0 + \beta_1 T_i} + \underbrace{r_i} + \underbrace{\epsilon_{ij}}$$

- Paradoxically, Food Recalls/Records (F) are called *reference instruments* and reference instruments are thought to be unbiased measures of usual intake.

$$\underbrace{\text{Records/Recalls}} = \underbrace{\text{Usual Intake}} + \underbrace{\text{Measurement error}}$$

$$\underbrace{F_{ij}} = \underbrace{T_i} + \underbrace{U_{ij}}$$

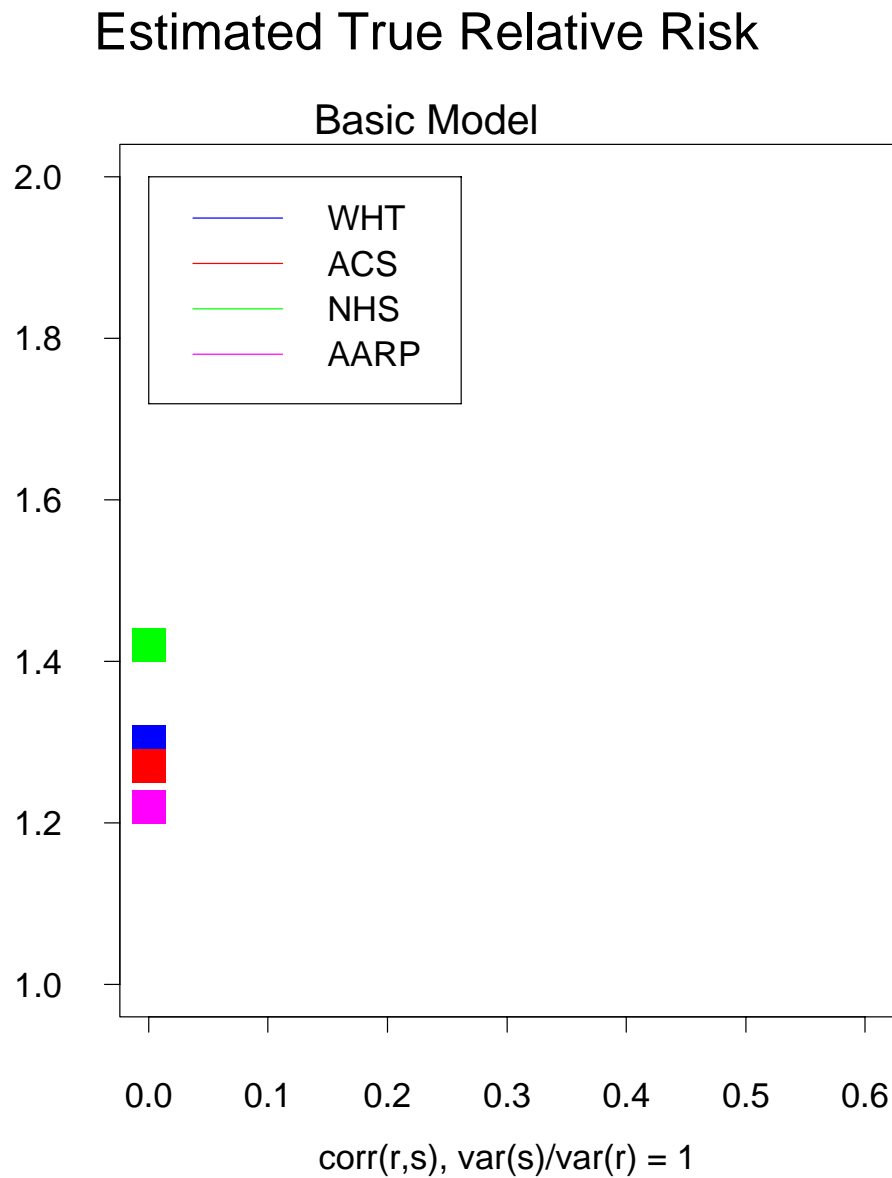


Figure 1: **Results of the Basic Model. Deattenuation from an observed relative risk of 1.10 for % Calories from Fat. Squares on the left are the results for the basic model. The relative risks are still fairly low.**

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## WHAT'S MISSING FROM THE BASIC MODEL

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$$\underbrace{\text{FFQ}} = \underbrace{\text{flattened slope}} + \underbrace{\text{Person-specific bias}} + \underbrace{\text{Measurement error}}$$

$$\underbrace{\text{Records/Recalls}} = \underbrace{\text{Usual Intake}} + \underbrace{\text{Measurement error}}$$

- You do not have to be in love with formulae to ask the question: *where is the flattened slope and the person-specific bias in records/recalls?*

\* Should the model not be:

$$\underbrace{\text{FFQ}} = \underbrace{\text{flattened slope}} + \underbrace{\text{Person-specific bias}} + \underbrace{\text{Measurement error}}$$

$$\underbrace{\text{Recalls}} = \underbrace{\text{flattened slope}} + \underbrace{\text{Person-specific bias}} + \underbrace{\text{Measurement error}}$$

- We think yes.

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## THE NEW MODEL

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- The new model has **flattened slope**, **person-specific bias** and **measurement error** for the FFQ and for records/recalls.
- We hypothesize that the person-specific biases are probably correlated, if they exist.
- There is a complication:
  - \* The four calibration data sets do not allow the estimation of all parameters (statisticians call this **non-identifiability**).
- We are thus reduced to a **sensitivity analysis**.
- For this sensitivity analysis, today we assume that
  - \* No flattened slope in recalls/records
  - \* Equal variances for person-specific biases
  - \* We vary the correlation between the person-specific biases.

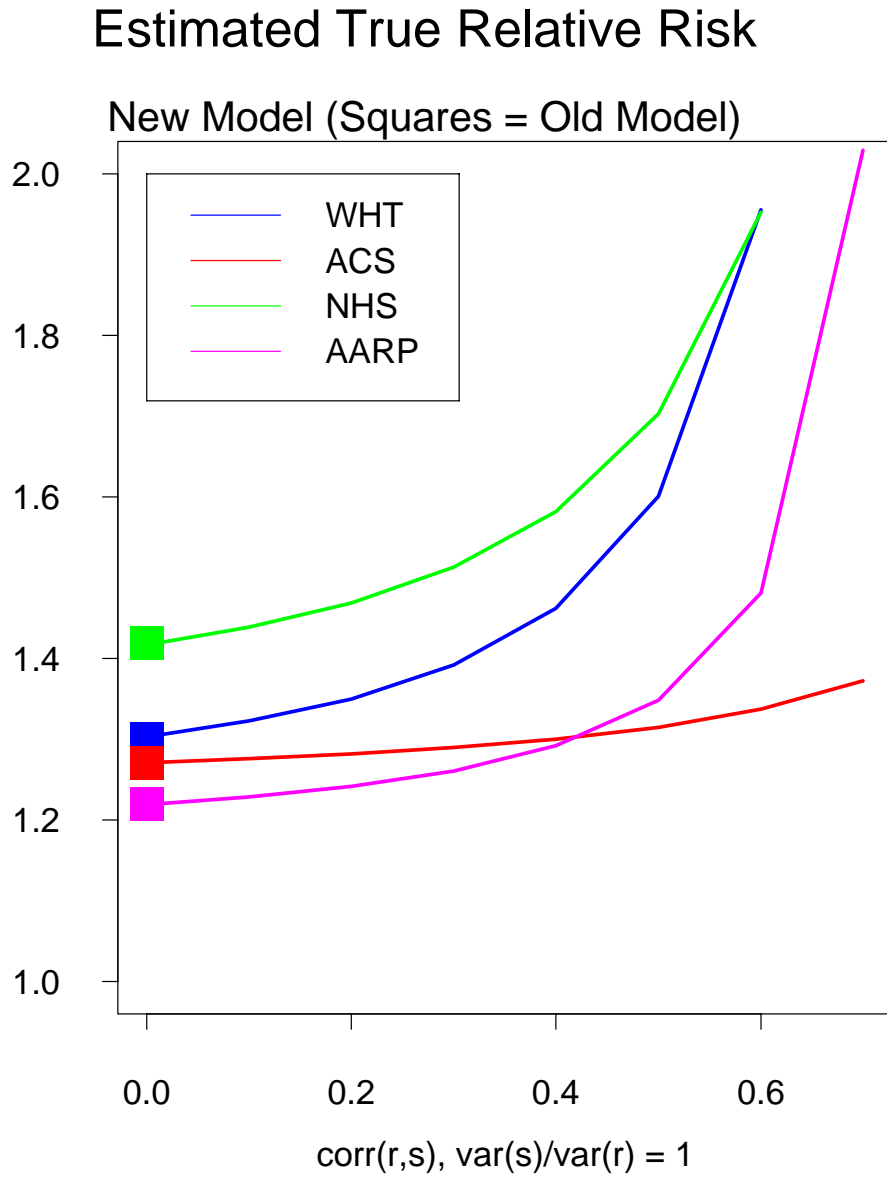


Figure 2: **Results of the New Model. Deattenuation from an observed relative risk of 1.10 for % Calories from Fat.**

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## BIOMARKERS

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- Energy (caloric intake), via double-labelled water (DLW) and Protein, via urinary nitrogen can, in principle, be measured without a flattened slope and without person-specific biases.
- **There is no biomarker for fat.** We can only infer from energy and protein.
- We recently received data from the **MRC** on 130 women: four weighed food records, four urinary nitrogens, one Willett-style FFQ.
  - \* We did model checking, and among all the models that have been proposed in the literature, **ours is the only one that fits the data: flattened slope, person-specific bias** and **correlation  $\geq 0.50$**  between the two person-specific biases all exist.

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## EVIDENCE FOR THE NEW MODEL

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- We used the MRC data, starting from an observed relative risk of 1.10.
  - \* **Old model**: true relative risk estimate of 1.35
  - \* **New model**: true relative risk estimate of 1.80.
- **These results thus suggest that the FFQ is a far less precise instrument for measuring protein–disease relationships than had been thought previously.**

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