Implications of Total Energy Intake for Epidemiologic Analyses

Chapter 11

Total Energy Intake

Importance:
- Level of energy intake may important as a primary determinant of disease
- Individual differences in total energy intake may be extraneous, a source of error.
- If energy intake is associated with disease, but not a direct cause, total energy intake may be a confounder

Energy Utilization

\[
\text{energy expenditure} = \text{BMR} + \text{thermogenic effect of food} + \text{physical activity} + \text{adaptive thermogenesis}
\]

Figure 11-1: Percent of total energy expenditure

Variation in energy intake is caused by:

1. Body size
2. Metabolic efficiency
3. Physical activity
4. Weight Change

Often height and weight are used as alternatives to direct measurement of energy intake.
Intakes of most nutrients are positively correlated with total energy intake (Table 11-2).

Composition of diet may vary by level of total energy intake (Table 11-3).

**Adjustment for energy intake:**

1. absolute amount of nutrient (crude)
2. nutrient in relation to total caloric intake
   - what is biology of nutrient
   - what is public health consideration
3. nutrient in relation to body size (intake/kg body weight)

**Consequences of Not Controlling for caloric intake**

If total caloric intake is associated with disease, it may be serious if you fail to account for total energy intake.

**e.g.** Table 11-4 diet and coronary heart.

Crude intake is lower for 11 nutrients, but heart disease cases have lower caloric intake, thus lower nutrient intakes.
Variations in caloric intake reflects:

- physical activity
- Body size
- metabolic efficiency
- weight change

Fact: any nutrient disease association is not likely to be important in disease etiology if the association is merely a result of differences in caloric intake.

Rule 1: If caloric intake has an important relationship with outcome, then crude nutrient intakes are not instructive.

Rule 2: If caloric excess or deficiency is a primary cause of disease then nutrients that contribute to calories (protein, fat, CHO, alcohol) might be primary exposures and to control for calories might over control.

Correction for caloric intake:

Nutrient densities = nutrient value / total caloric intake or percent total caloric intake.

Problems:
- How to interpret a value that is related both to the nutrient intake and to the inverse of caloric intake.
- As the between person variance of the nutrient diminishes, the nutrient density approaches the inverse of caloric intake.

However:

- If energy intake is NOT related to disease can reduce variation in nutrient intake due to differences in size, physical activity and metabolic efficiency.

- If nutrient and calories are weakly related, can CREATE variation.

- If energy intake IS related to disease can alter direction of relationships (Table 11-4)
Example Table 11-5:
- Case control investigation of colon cancer.
- Cases caloric intake > controls
- Cases fat intake > controls
- When look at nutrient densities:
  1. Fat no association
  2. Fiber and vitamin C inverse association

To best study a nutrient and disease relationship:
Ideally we want a measure of nutrient intake that is INDEPENDENT of total calories especially if total calories are associated with disease.

Energy adjusted method:
Energy adjusted nutrient intakes are computed as the residuals from the regression model with total caloric intake as the independent variable and absolute nutrient intake as the dependent variable.

Model 1: Disease = \( b_1 \) nutrient residual
Note: be sure assumptions for regression are met

Model 2: Disease = \( b_1 \) nutrient residual + \( b_2 \) calories
Note: if calories are important in relation to the disease then add calories to the model

Model 3:
Standard multivariate model:
Disease = \( b_3 \) calories + \( b_4 \) calories

Note: \( b_3 \) now represents the relationship between calories and disease independent of nutrient
Problem: simultaneous inclusion of strongly correlated variables in the same model

Energy decomposition model:

Model 4:
Disease = \( b_5 \) calories from nutrient + \( b_6 \) calories from all other
Multivariate nutrient density model:

Model 5:
Disease = b₇ nutrient/calories + b₈ calories

How to present energy adjusted intakes using the residual method (Figure 11-5):

- Energy adjusted nutrient intakes are computed as the residuals from the regression model with total caloric intake as the independent variable and absolute intake as the dependent variable.
- Because residuals have a mean of zero you can add a constant; logical choice is the predicted nutrient intake for the mean energy intake of the study population or a rounded number of energy intake near the population mean (a+b) where a is the residual value.

Figure 11-6: Distribution of total fat intake with and without (dark line) adjustment for residual caloric intake. Data are based on four 1-week diet records completed by 176 Boston-area women aged 34 to 59 years. Calorie-adjusted values were calculated as a residual in the regression model. Data and error bars are from W. Willett and Sampson, 1988, reproduced with permission.

Correction for the effects of measurement error

Chapter 12

What is the effect of measurement error on the relationship under study?

- First: What is the type of error?
  - Random (day to day fluctuation) vs. systematic (tendency to deny or exaggerate food intakes or unclear questions)
  - In systematic error repeated measures do not approximate the mean.
- Secondly: What is the level of error?
  - Within person or between persons
  - Between person error random error will average out but the SD will be large
  - Systematic between person error is often the result of a poor measurement tool that omits a commonly eaten food.
Correction of Correlation and Regression coefficients, and RR are explained with examples

- A variety of methods exist to correct epidemiologic measures of association for error in the measurement of exposure
- Many of these methods are based on assumptions that should be reviewed (e.g. is the “true measure” really true)

Data Cleaning: Blanks and Outliers

- Prior to data collection a decision of what is to be considered acceptable data quality is important
- For example exclude data from subjects with X number of blank responses (e.g. 70/130)
- What are the allowable ranges for nutrient intakes (e.g. women 500-3500 kcal/day and men 800-4000 kcal/day)
Categorized versus Continuous Presentation of Independent Variables

- Many nutritional variables are categorized in order to present as rate ratios for levels of exposure.
  - Can use quartiles or quintiles
  - Use cut points with a priori biological rationale.
  - However there is greater statistical power with the continuous variables

Examination of foods and nutrients

- If a major nutrient is associated with the disease, examine foods to see if there is one major contributor.
- If you look at many foods, should you correct for multiple comparisons? Can you combine into food groups? How do you deal with supplement users? Are there subgroups that are differentially affected?

Ecologic studies:

mostly due to animal fat $r=0.83$ vs. vegetable fat $r=0.18$ (fig 16-1)

Potential confounders:

- lean body mass
- obesity
- sedentary lifestyle
- reproductive variables

Chapter 16: Dietary Fat and Breast Cancer

Ecologic studies:

mostly due to animal fat $r=0.83$ vs. vegetable fat $r=0.18$ (fig 16-1)

Potential confounders:

- lean body mass
- obesity
- sedentary lifestyle
- reproductive variables
Migrant studies

migrants from Japan to US: breast cancer rates in offspring are similar to US women.
migrants from Italy to Australia and Poland to US immediately attain rates of current homeland.

Special Populations:

lower in Seventh Day Adventists but confounded by SES.
no significant differences between vegetarian nuns and single British Women.
strong correlation between dietary fat intake and breast cancer rates in five ethnic groups in Hawaii (fig 16-3)

Secular trends:

dramatic changes in incidence rates within a country over time indicate that non-genetic factors are important
Iceland(figure 16-4) and Norway (Figure 16-5)

Case Control Studies

* Table 16-1
* Table 16-2
* No evidence of association between fat and breast cancer
* Howe- 12 case-control studies
  RR=1.35 for 1000 kcal from fat (energy decomposition)
  RR=1.07 (nutrient density)
Cohort Studies

- Largest was Nurses Health Study
  - n = 89,538
  - aged 34-35 in 1980
  - FFQ, 4 year follow-up 601 breast cancer cases.
  - NSD in fat, saturated fat, linoleic acid and cholesterol (Table 16-4).

Validation Component

- 28 days of diet records for fat intake
- N=173
- Lowest quintile 32% from fat
- Highest quintile 44% from fat
- No data on intake <30%

Comments

- Latent period between exposure and disease of 4 years was insufficient
- Childhood fat intake is important?
- Oldest age at diagnosis 59, need longer follow-up
Prospective Cohort Studies

- Table 16-5; 
- n=6 studies 
- NSD in breast cancer risk in high vs. low total fat and saturated fat.

### Table 16-5. Large prospective studies of total and saturated fat intake and risk of breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Total n.</th>
<th>Years of</th>
<th>NSD</th>
<th>High vs. low factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food (Physicians', 1986)</td>
<td>85,491</td>
<td>6</td>
<td>1.00</td>
<td>1.00 (0.87-1.15)</td>
</tr>
<tr>
<td>Canadian Study (Muir, 1990)</td>
<td>19,687</td>
<td>5</td>
<td>0.99</td>
<td>1.00 (0.83-1.18)</td>
</tr>
<tr>
<td>New York State Cohort (Dale, 1979)</td>
<td>17,416</td>
<td>7</td>
<td>1.00</td>
<td>1.00 (0.84-1.34)</td>
</tr>
<tr>
<td>Nurses' Health Study (Colditz, 1990)</td>
<td>22,904</td>
<td>4</td>
<td>0.98</td>
<td>1.00 (0.84-1.22)</td>
</tr>
<tr>
<td>Danish Diet, Nutrient Study (Gravlee, 1992)</td>
<td>66,731</td>
<td>4</td>
<td>0.97</td>
<td>1.00 (0.87-1.21)</td>
</tr>
<tr>
<td>Nurses' Health Study (Adams, 1994)</td>
<td>66,734</td>
<td>4</td>
<td>0.97</td>
<td>1.00 (0.86-1.20)</td>
</tr>
</tbody>
</table>

RR: relative risk; CI: confidence interval

No association between breast cancer and intake of total, saturated, mono, polyunsaturated fat (Table 16-6) 
- RR=1.02 (0.94 to 1.11)

**Figure 16-7. Relative risk of breast cancer by percentage of energy from fat in pooled analysis of prospective studies. (From Hunter et al., 1998; reprinted with permission, Copyright 1998 Massachusetts Medical Society. All rights reserved.)**

**Figure 16-6. Relative risk of breast cancer and 95% confidence intervals for quarters of energy-adjusted nutrient intake in the pooled analysis of cohort studies.**
Integration of findings

- Case control studies appear to be influenced by selection bias and recall bias
- Early influence of diet may be important
- Some suggestion that olive oil is protective.
- WHI may answer question with a randomized clinical trial

Why does the large international variation in breast cancer exist?

- Reproductive risk factors
- Selenium and other minerals
- Alcohol
- Specific vegetables
- Phytoestrogens
- HRT/ERT use
- Physical activity
- Height (figure 16-9)

Figure 16-6: Correlation of average adult height in women with breast cancer incidence for 30 countries, r = -0.8. (From Slonim, 1985, reprinted with permission.)