



## Can Energy Adjustment Separate the Effects of Energy from Those of Specific Macronutrients?

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Energy adjustment is used in nutritional epidemiology in an attempt to separate specific effects of macronutrients (carbohydrate, fat, and protein) from one another and from the generic effect of the total quantity of energy consumed. However, models in which the risk of disease is allowed to depend simultaneously on daily total energy consumption and separate components of energy that sum to the total are not identifiable: the specific effects of individual macronutrients and the generic effect of energy cannot be disentangled by multivariate analysis. The standard, residual, and partition methods exclude one or more macronutrients from consideration, thereby allowing estimation, but the parameters that are estimated no longer represent specific macronutrient or generic energy effects. Therefore, an interpretation of a regression coefficient from these methods as a specific effect of a macronutrient or as the generic effect of energy requires additional, almost always questionable, assumptions. For example, a conclusion based on data alone that there is a specific fat effect upon the development of breast cancer but no specific effects of other macronutrients and no generic energy effect is not possible. Notwithstanding these serious problems, some useful etiologic inference still can be made. *Am J Epidemiol* 1994;140:848-55.

biometry; caloric intake; diet; dietary carbohydrates; dietary fats; dietary proteins; epidemiologic methods; regression analysis

One aim of studies of the effects of macronutrients (carbohydrate, fat, and protein) and total energy on disease risk is to isolate the distinct effects of each of the macronutrients from one another and from the effects of total energy. We would like to be able to reach conclusions regarding the *specific* effects of different nutrients on the risk of disease, as well as the *generic* effect of the delivery of energy to the body. For example, we would like to learn the an-

swers to two separate questions: 1) Is the risk of breast cancer associated specifically with the consumption of fat? and 2) Does consumption of energy, regardless of source, increase disease risk? The main purpose of this paper is to point out that the energy-adjustment procedures in the literature (1, 2) cannot be used for inference at this level of detail from experimental or observational studies that relate dietary intake to disease outcome. For example, we show that the coefficient for calories in the residual approach is sensitive to the nutrient composition of the diet. However, the *overall* effect of consuming a particular nutrient—the sum of its generic and specific effects—and the *difference* between the specific effects of two nutrients can be estimated, as can the difference in risk be-

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Several energy-adjustment methods (1, 2) have been proposed, and the meaning of parameters in these approaches has been discussed (3–8). However, this debate has not revealed the full extent of the problems of interpretation that arise from each of these approaches. We argue below that parameters of the model of greatest etiologic interest are not estimable. Further,

when one macronutrient or more or total energy is omitted from the model, as in the standard (3), residual (1), and partition (2) approaches to energy adjustment, the interpretation of the new model does not address our main concern. Thus, we claim, contrary to common understanding, that it is not possible with any energy-adjustment method to address the distinct questions of whether intake of energy or a specific macronutrient causes disease.

#### AN ELEMENTARY MODEL INCLUDING SPECIFIC EFFECTS OF MACRONUTRIENTS AND A GENERIC EFFECT OF ENERGY

Energy-adjustment methods are based on the premise that a calorie from a particular macronutrient can have two distinct effects on the risk of disease: one generic, as a source of energy (1), and one specific to the particular macronutrient. If, for simplicity, we assume that only two macronutrients, namely, FAT and NONFAT, as well as total energy consumed ( $TOTAL = FAT + NONFAT$  when all variables are expressed in common units of energy) are important, we have three separate effects, or pathways to disease, that we seek to distinguish:

1. an effect specific to fat,
2. an effect specific to nonfat, and
3. an energy effect, common to all calories.

The simplest model that distinguishes among these effects is

$$\text{logit}[\text{Pr}(D|\mathcal{M})] = \beta_0 + \beta_F F + \beta_N N + \beta_T T \quad (1)$$

where  $\text{Pr}(D|\mathcal{M})$  means the probability of disease, given  $\mathcal{M}$ , the *macronutrient profile* with values  $F$  and  $N$  for variables FAT and NONFAT, respectively, and, by addition, value  $T = F + N$  for TOTAL. In this model,  $\beta_F$  and  $\beta_N$  are the specific effects of fat and nonfat, above and beyond their caloric content, and  $\beta_T$  is the generic energy effect. Thus, demonstrating a nonzero value for  $\beta_F$  or  $\beta_N$  implies the existence of an effect that cannot be attributed to caloric intake, thereby satisfying Willett's requirement for attributing causality to a macronutrient (9, p. 20).

Model 1 follows standard epidemiologic practice for distinguishing among several potential risk factors, since we have no better model based on our scientific understanding of disease etiology. Still, as shown in the appendix, we cannot estimate the regression coefficients because of nonidentifiability, the property of a model that more than one (here, infinitely many) sets of regression parameters fit the data equally well; the nonidentifiability here is a consequence of the fact that one regression variable,  $T$ , is the sum of two others,  $F$  and  $N$ . Deeper understanding of disease etiology, in addition to data consisting of individuals' dietary intake and disease status, is needed to distinguish among the separate pathways to disease.

Model 1 is a classical multivariate modeling approach to the problem of distinguishing among the effects of three variables. Alternatively, one might, following Willett and co-workers (1, 9), prefer a multivariate model with one overall effect combining the energy-related effects from all disease pathways and coefficients for new variables  $F^*$  and  $N^*$ , representing the nonenergy sources of risk from fat and nonfat. In this case,  $F$  and  $N$  from model 1 are replaced by  $F^*$  and  $N^*$ , defined as the residuals of the regressions of  $F$  and  $N$  on  $T$ , that is,  $F^* \equiv F - \alpha_0 - \alpha_1 T$  and  $N^* \equiv N + \alpha_0 + (\alpha_1 - 1)T = -F^*$  where

$\alpha_0$  and  $\alpha_1$  are the intercept and slope from the regression of  $F$  on  $T$ :

$$\text{logit}[\text{Pr}(D|\mathcal{M})] = \gamma_0 + \gamma_F F^* + \gamma_N N^* + \gamma_T T. \quad (2)$$

In model 2,  $\gamma_F$  and  $\gamma_N$  represent the nonenergy effects of FAT and NONFAT on the risk of disease, while  $\gamma_T$  represents the effect of energy from all sources, including pathways involving FAT and NONFAT. In terms of model 1, model 2 is

$$\begin{aligned} \text{logit}[\text{Pr}(D|\mathcal{M})] &= \gamma_0 + \gamma_F F^* + \gamma_N N^* + \gamma_T T \\ &= \gamma_0 + \gamma_F [F - \alpha_0 - \alpha_1 T] + \gamma_N [N + \alpha_0 - (1 - \alpha_1)T] + \gamma_T T \\ &= \gamma_0 + k + \gamma_F F + \gamma_N N + [\gamma_T - \alpha_1 \gamma_F + \alpha_1 \gamma_N - \gamma_N] T, \end{aligned}$$

where  $k$  is a constant equal to  $\alpha_0(\gamma_N - \gamma_F)$ . Thus,  $\beta_F = \gamma_F$ ,  $\beta_N = \gamma_N$ , and  $\beta_T = \gamma_T - \alpha_1 \gamma_F + \alpha_1 \gamma_N - \gamma_N$ , so models 1 and 2 are simply alternative parameterizations of the same model, yielding coefficients of  $T$  with different meanings, while the  $F$  and  $N$  coefficients and the fit of the data are exactly the same. All of the problems of model 1 are shared by model 2.

We deliberately made models 1 and 2 as simple as possible. *A fortiori*, adding confounders or other effect modifiers will not resolve the problem we raise, nor will removing NONFAT from the model and replacing it with CARBOHYDRATE and PROTEIN or any other combination summing to NONFAT. A model using the logarithmic or other nonlinear transformation of the independent variables will eliminate the nonidentifiability. However, we would not consider even the sign of the resulting estimate to be trustworthy unless there were sound biological justification for the particular transformation.

It is clear from the appendix that parameters from a model for disease risk that, like models 1 or 2, includes an effect of total energy as well as the specific effects of two or more disjoint sources of energy summing to the total are not identifiable. The interpretation of the parameters will change when the model is made identifiable by omitting a variable, thereby making an implicit assumption that the omitted variable has no effect. We now show that the commonly used energy-adjustment models are examples of this kind of simplification of models 1 or 2.

## ENERGY-ADJUSTMENT METHODS

We now show what the regression coefficients actually estimate in terms of the parameters of model 1.

### Standard and residual methods

In the standard method (3), risk is assumed to depend on FAT and TOTAL. Under equation 1, we observe

$$\begin{aligned} \text{logit}[\text{Pr}(D|\mathcal{M})] &= \beta_0 + \beta_F F + \beta_N N + \beta_T T \\ &= \beta_0 + \beta_F F + \beta_N (T - F) + \beta_T T \\ &= \beta_0 + (\beta_F - \beta_N) F + (\beta_N + \beta_T) T \end{aligned} \quad (3)$$

after gathering terms. Thus the coefficient for FAT equals  $\beta_F - \beta_N$ , the difference between two macronutrient-specific effects, and for TOTAL equals  $\beta_N + \beta_T$ , the sum of the specific and generic effects of NONFAT.

The residual method (1, 9) is similar to the standard (3), except that it is based on model 2 rather than model 1. So instead of using  $F$  to represent the fat variable, the residual

method uses  $F^*$ , the residual from the regression of  $F$  on  $T$ . Using the residual method and equation 1, we would observe

$$\begin{aligned} \text{logit}[\text{Pr}(D|\mathcal{M})] &= \beta_0 + \beta_F F + \beta_N(T - F) + \beta_T T \\ &= \beta_0 + (\beta_F - \beta_N)F + (\beta_N + \beta_T)T \\ &= \beta_0 + (\beta_F - \beta_N)(F^* + \alpha_0 + \alpha_1 T) + (\beta_N + \beta_T)T \\ &= \beta_0 + (\beta_F - \beta_N)\alpha_0 + (\beta_F - \beta_N)F^* + [\alpha_1\beta_F + (1 - \alpha_1)\beta_N + \beta_T]T. \end{aligned} \quad (4)$$

Thus, the coefficient for residualized FAT equals  $\beta_F - \beta_N$ , the difference between macronutrient effects, and the coefficient for TOTAL equals  $\alpha_1\beta_F + (1 - \alpha_1)\beta_N + \beta_T$ .

Note that in both equations 3 and 4, the regression coefficients do not represent a single parameter from the basic model 1. The coefficients for  $F$  and  $F^*$  are not macronutrient specific. For example, the fat coefficient in equations 3 and 4 is not equal to the fat-specific effect  $\beta_F$  but to the difference between fat and nonfat effects,  $\beta_F - \beta_N$ . Thus, the FAT coefficient addresses the question of whether a calorie from fat imparts greater risk than one from a nonfat source. However, the FAT coefficient is not a specific fat effect unless  $\beta_N = 0$ , that is, unless there is no nonfat-specific effect.

Since  $T$  and  $F^*$  are uncorrelated by definition of residual, the TOTAL coefficient  $\gamma_T$  in the univariate or crude regression of disease risk on  $T$ ,

$$\text{logit}[\text{Pr}(D|\mathcal{M})] = \gamma'_0 + \gamma_T T,$$

is approximately equal to the TOTAL coefficient in equation 4. However, the TOTAL coefficient does not equal  $\beta_T$  and *cannot be interpreted as the generic energy effect* under model 1 unless one assumes either 1) the specific effects of fat ( $\beta_F$ ) and nonfat ( $\beta_N$ ) are both zero, or 2)  $\alpha_1\beta_F = -(1 - \alpha_1)\beta_N$ , leaving only  $\beta_T$  as the coefficient for  $T$  in equation 4. Neither assumption is warranted *a priori*; the second assumption is quite unrealistic, because it requires an unlikely relation involving sets of unrelated parameters.

### Partition method

In the partition method (2), disease risk is assumed to depend on FAT and NONFAT, but not TOTAL. Under equation 1, one observes

$$\begin{aligned} \text{logit}[\text{Pr}(D|\mathcal{M})] &= \beta_0 + \beta_F F + \beta_N N + \beta_T(F + N) \\ &= \beta_0 + (\beta_F + \beta_T)F + (\beta_N + \beta_T)N. \end{aligned} \quad (5)$$

Thus, the fat and nonfat effects are both linked with the generic energy effect,  $\beta_T$ . Specific effects of fat or of nonfat cannot be estimated unless  $\beta_T$  is assumed to be zero.

### Substitution and addition effects

Analyses by the three energy-adjustment methods discussed above yield the same likelihoods when continuous covariates are used (3, 4). Table 1 summarizes the regression coefficients for the three methods in terms of the parameters of model 1. The four distinct expressions in table 1 correspond to substitution and addition effects; this relation was noted by Kipnis et al. (4), but without reference to the parameters representing specific and generic effects. We show in the appendix how both substitution and addition effects can be estimated in terms of these parameters from all three methods.

TABLE 1. Expected values for coefficients from three methods for analysis of macronutrient effects

Method	Expected values under model 1		
	FAT	TOTAL	NONFAT
Standard	$\beta_F - \beta_N$	$\beta_N + \beta_T$	
Residual	$\beta_F - \beta_N$	$\alpha_1 \beta_F + (1 - \alpha_1) \beta_N + \beta_T$	
Partition	$\beta_F + \beta_T$		$\beta_N + \beta_T$

### Energy effect

Can an energy effect be estimated? Table 1 shows that none of the three methods discussed above yields an estimate of the generic energy effect as formulated in equation 1. For example, a zero coefficient for TOTAL from the standard method could reflect either effects specific to nonfat and generic to energy that are in opposite directions, or zero generic energy and specific nonfat effects.

The TOTAL coefficient in the residual approach (equation 4) is commonly called the "energy effect." But the TOTAL coefficient *does not reflect a generic energy effect* unless  $\beta_F$  and  $\beta_N$  equal zero (table 1). Specifically, the TOTAL coefficient is sensitive to the pattern of macronutrient consumption: it will increase with the average proportion of calories from FAT when  $\beta_F > \beta_N$ . We therefore disagree with Willett's claim (10, p. 771) that the TOTAL coefficient "retains its biological meaning" in the residual method. Instead, we have shown that it shares the weakness he points out about the TOTAL coefficient in the standard model: that it "reflect[s] the . . . composition of the diet rather than the biological meaning of total energy" (10, p. 770). For the same reason, the suggestion of Howe et al. (2) to begin routinely with a univariate analysis of energy does not seem appropriate.

Howe et al. use the partition method to "elucidate the separate roles of calories and saturated fat" on the risk of colorectal cancer (2, p. 158). They find a null effect of energy sources other than saturated fat and conclude that there is "no evidence for any independent effect of caloric intake" (2, p. 159). While an interpretation of no generic energy effect is plausible, it is also possible that some macronutrient other than saturated fat (perhaps complex carbohydrates) has a negative effect on risk while the generic energy effect is positive.

### SCENARIOS

We have argued that etiologic inference is complicated by an inability to distinguish among specific effects of fat and nonfat and their generic energy effect. Nevertheless, some etiologic inferences can still be made and reasonable dietary advice can be given. We demonstrate this with two hypothetical scenarios.

#### Scenario 1

Some studies (e.g., Kushi et al. (8)) have found apparently discrepant results, where the effect of fat seems to differ depending on which method of analysis is used. Consider this hypothetical set of seemingly discrepant results:

- a FAT coefficient of 1 using the partition method
- a FAT coefficient of 0 using the residual method.

These results indicate that reducing consumption of fat reduces risk (partition), whereas substituting nonfat for fat does not reduce risk (residual). In other words, a reduction in energy consumption accompanying the reduction in fat is necessary to reduce risk. On the basis of the table, these results imply  $\beta_F + \beta_T = 1$  and  $\beta_F - \beta_N = 0$ , and therefore, by subtraction,  $\beta_N + \beta_T = 1$  (which is the partition coefficient of NONFAT). This suggests that reduction in fat, without compensatory increase in nonfat, will reduce risk either through a fat-specific effect or the generic energy effect or both. Similarly, reduction in nonfat (without re-

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## APPENDIX

In this appendix, we demonstrate three claims: 1) that the parameters in model 1 are not identifiable; 2) that substitution and addition effects can be estimated from the three methods, despite nonidentifiability; and 3) that the effect of any change in the macronutrient profile can be estimated.

Specifically, suppose that the values  $(\hat{\beta}_0, \hat{\beta}_F, \hat{\beta}_N, \hat{\beta}_T)$  fit the data best. Then, for any value of  $\nu$ , the right-hand side of model 1 for the set of values  $(\hat{\beta}_0, \hat{\beta}_F + \nu, \hat{\beta}_N + \nu, \hat{\beta}_T - \nu)$  equals

$$\begin{aligned} \hat{\beta}_0 + (\hat{\beta}_F + \nu)F + (\hat{\beta}_N + \nu)N + (\hat{\beta}_T - \nu)T &= \hat{\beta}_0 + \hat{\beta}_F F + \hat{\beta}_N N + \hat{\beta}_T T + \nu(F + N - T) \\ &= \hat{\beta}_0 + \hat{\beta}_F F + \hat{\beta}_N N + \hat{\beta}_T T + \nu(0) \\ &= \hat{\beta}_0 + \hat{\beta}_F F + \hat{\beta}_N N + \hat{\beta}_T T. \end{aligned}$$

Therefore,  $(\hat{\beta}_F, \hat{\beta}_N, \hat{\beta}_T)$  and  $(\hat{\beta}_F + \nu, \hat{\beta}_N + \nu, \hat{\beta}_T - \nu)$  fit the data identically, and the data cannot be used to distinguish among infinitely many sets of parameters.

We now show that both substitution and addition effects can be estimated from the standard, residual, and substitution methods. In model 3, the coefficient for  $F$  can be interpreted as the effect of changing  $F$  by one unit while holding  $T$  constant; implicitly,  $N$  must be reduced by one unit. Thus the coefficient for  $F$  is the difference  $\beta_F - \beta_N$ , that is, the effect of substitution of one fat calorie in place of one nonfat calorie. This difference can also be estimated directly from the residual method and by subtraction of the NONFAT from the FAT coefficients from the partition method. Similarly,  $\beta_F + \beta_T$  is the effect of increasing  $F$  by one calorie without changing  $N$ , that is, the regression coefficient for  $F$  in model 5. This effect is directly estimable from the partition method; by addition of the two

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coefficients from the standard method; or as the sum of the product of the fat coefficient times the known  $1 - \alpha_1$  plus the TOTAL coefficient from the residual method. Similarly,  $\beta_N + \beta_T$ , the aggregate effect of increasing NONFAT by one calorie, can be estimated directly from the standard and partition methods or as the difference between the TOTAL coefficient and  $\alpha_1$  times the FAT coefficient from the residual method.

The values of  $\beta_F - \beta_N$ ,  $\beta_F + \beta_T$ , and  $\beta_N + \beta_T$  do not depend on  $\nu$  and thus are estimable under model 1. For example,  $(\beta_F + \nu) - (\beta_N - \nu) = \hat{\beta}_F - \hat{\beta}_N$ . Similarly, the difference in risk between two individuals with different macronutrient profiles can be estimated unambiguously, since it does not depend on  $\nu$ . Thus, one can estimate the effect of any specific change of macronutrient profile.

**Example**

As an example, assume that the true values are  $\beta_F = 4$ ,  $\beta_N = 2$ , and  $\beta_T = 1$ . Then the left-hand side of equation 1 equals

$$4F + 2N + T = 4F + 2N + (F + N) = 5F + 3N + 0T.$$

Thus,  $\beta_F = 5$ ,  $\beta_N = 3$ , and  $\beta_T = 0$  gives the exact same model predictions as do the true values. Any of the three parameters can be fixed at a particular value, and still the same model predictions would be obtained. For example, if  $\beta_F = -1$ , then  $\beta_N = -3$  and  $\beta_T = 6$ . No amount of data will be able to distinguish among these three or among infinitely many other possible sets of parameter values.

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