Comments on “Adjustment for total energy intake in epidemiologic studies”¹,²

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ABSTRACT Willett et al [Am J Clin Nutr 1997;65(suppl):1220S–8S] reviewed the case for energy adjustment in the analysis of nutritional studies and argued strongly for basing the main analysis on an energy-adjustment statistical model. They recommended focusing attention on a statistical association that represents the change in disease incidence associated with the substitution of energy from a specific nutrient for energy from other nutrient sources, while keeping total energy intake constant. Although we agree with many of the points made in their paper, we recommend assessing and reporting associations representing not only the substitution but also the addition of energy from the specific nutrient. For these “addition” associations, it is especially important to check for confounding with measures of body size and physical activity. Restricting analyses to substitution associations will confine investigators to estimating the relative effects of one nutrient to another and will preclude investigating the effects of increased intake of a specific nutrient. Am J Clin Nutr 1997;65(suppl):1229S–31S.

KEY WORDS Energy, epidemiology, methods, nutrient, nutritional, energy adjustment

INTRODUCTION

Since the publication of an article 10 y ago that proposed energy adjustment of nutrient intake in epidemiologic analyses (1), there has been considerable debate among nutritional epidemiologists over the most appropriate methods of analysis. In the preceding article, Willett et al (2) review energy adjustment and advocate adjustment of the association between disease and the intake of a specific nutrient for total energy intake (with use of the residual or multivariate density model) as the main analytic approach in nutritional epidemiology. This article is especially notable in view of the eminence of the authors and because the second author has previously advocated use of the partition model, which adjusts the association of disease with a specific nutrient for energy intake from other nutrient sources but does not adjust for total energy intake (3). The paper may therefore signal a complete switch to the use of adjustment by total energy intake in the published results of studies.

We comment here on the paper of Willett et al. We agree with a substantial number of the points they make and we especially endorse much of the content of the section “Risk models to account for total energy intake” and subsequent sections. With respect to the discussion in the first part of their paper, however, we recommend an approach to analysis that includes evaluating and reporting associations of specific macronutrients with disease, adjusted not only for total energy intake (with use of the residual or multivariate density model) but also for other macronutrients (with use of the partition model). In this commentary, we highlight areas of difference between our views and those expressed by Willett et al and indicate how these differences lead to the shift of emphasis in our conclusions.

REASONS FOR ENERGY ADJUSTMENT

Willett et al discuss three principal reasons for adjusting for total energy intake: control of confounding, removal of extraneous variation, and simulation of dietary intervention. We comment here on each of these rationales.

Control of confounding

Confounding is a serious problem in assessments of associations between the intakes of specific nutrients and disease incidence. The example of diet and coronary artery disease given by Willett et al highlights the problems and serves as a cautionary tale to those who would casually ascribe simple causal mechanisms to observed associations. Willett et al strongly advocate control of confounding by energy adjustment and mention that, in this regard, energy intake acts as a rough indicator of body size and physical activity. They prefer to use energy intake rather than body size and physical activity as the adjusting factor mainly because height and weight “do not reflect the directly relevant component of body size (lean body mass)” and because physical activity is poorly measured.

In our view, there is uncertainty about the relation between disease, energy intake, body size, and physical activity and additional uncertainty regarding the measurement errors that underlie reported values of energy intake and physical activity. Thus, when we use reported energy intake as a surrogate for

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body size and physical activity, we know little about how well we control for these variables and whether we may thereby be underadjusting or overadjusting the nutrient-disease association. Moreover, we have few or no data concerning measurement error on which to base a preference for using reported energy intake over a direct measure of physical activity. In truth, both are subject to considerable measurement errors but the relative magnitude and the nature of the errors are not known.

The consequence of always opting to use energy intake to control for confounding is that it shuts the door on addressing certain dietary hypotheses. Using energy intake as the adjusting variable leads to the adoption of one of three statistical models: the residual, the standard, or the multivariate nutrient density. As explained by Willett et al in this issue (2) and in previous publications (4), the coefficient of the nutrient of interest in these models has a substitution interpretation: it represents the change in disease incidence associated with substitution of that nutrient for an equivalent amount of energy from other nutrients. This interpretation contrasts with that of the nutrient coefficient in the partition model, because that coefficient represents the change in disease incidence associated with the additional intake of energy from that nutrient, while keeping the intakes of other nutrients fixed. In as far as they advocate adjusting for total energy to the exclusion of other analyses, Willett et al exclude the possibility of addressing hypotheses on the effects of increased intake of selected nutrients. With their preferred method, we can assess the effect of one nutrient only in relation to another. For example, we may be able to provide evidence that carbohydrate is more protective than fat intake or, equivalently, that fat increases risk more than does carbohydrate, but we would never be able to say whether the carbohydrate prevents or is the fat promotes disease.

We believe that questions about the effect of increased intake of fat or carbohydrate are important to public health. We agree with Willett et al that good answers to these questions are difficult to obtain because of potential confounding with physical activity and body size, but we think it is worth attempting to address them by using the partition model and including reported physical activity and body size directly in the model to adjust for confounding.

Removal of extraneous variation

Willett et al argue that even if total energy (and hence, by implication, physical activity and body size) is not related to disease incidence and is therefore not a confounder, it still contributes to the variation in nutrient intake among individuals and thereby weakens any observed relation between the nutrient and disease. This general statement requires some careful thought and analysis.

The relation between intake of a specific nutrient and total energy intake is one that always requires careful handling because one variable is a component of the other. The statement of Willett et al paraphrased above is predicated on an assumption that total energy has no association with disease. But that condition has immediate implications for the association of disease with intake of the specific nutrient relative to the disease’s association with intake of other nutrients. For if the specific nutrient has a positive association with disease, then by definition, intake of other nutrients has a negative association (otherwise, total energy intake could not have a null association with disease). Furthermore, the substitution of the specific nutrient for other nutrients will then have a stronger association with disease than the association with addition of intake of that nutrient. Hence, the condition of no association between total energy intake and disease necessitates, by logic, that the substitution association for any macronutrient be greater than the addition association. For this reason, adjustment for total energy intake (which leads to the substitution association) will more readily detect the association with disease than will adjustment for intake of other nutrients (which leads to the addition association).

One can also show, using similar reasoning, that the substitution association is greater than the crude unadjusted association. Thus, we concur with the conclusion of Willett et al (although for different reasons) that, under this condition, adjusting for total energy intake will generally lead to more sensitive testing of a disease-nutrient relation. It is worth noting, however, that the same logic does not follow from the null relation between physical activity and body size and disease because nutrient intake is not a component of these variables but is simply correlated with them. It is feasible that with diseases that are not related to physical activity or body size, the addition association of a specific nutrient is larger and more readily detected than the substitution association.

In general, because of the large amount of measurement error in total energy intake, it is possible for adjustment by total energy intake to weaken rather than strengthen observed nutrient-disease relations. Much depends on the correlations among different nutrients, the correlations among their errors in measurement, and the relative magnitudes of these correlations (5). Once again, we are confronted with a lack of knowledge about these errors, mainly because of the difficulty of obtaining reliable gold-standard measurements of nutrient intakes under field-study conditions. Theoretically, if the errors in total energy intake are only weakly correlated with the errors in intake of the nutrient and this correlation is much less than that between the “true” variables measured without error, then energy adjustment is particularly likely to weaken an observed nutrient-disease association. Thus, our concerns may be particularly relevant to the suggestion that even micronutrient intakes should be energy adjusted, but they also apply to nutrients that supply a small part of the total energy and are derived from a limited number of food items.

Simulation of dietary intervention

The third argument for energy adjustment advanced by Willett et al is that individuals do not make large changes in their total energy intake without also changing body size or physical activity. Therefore, for individuals who are not obese and who do not greatly alter their daily activity, any change in diet would involve a change in the components of the diet rather than in the amount eaten. Thus, energy-adjustment models address associations between disease incidence and the type of dietary change that would be of interest in a healthy population.

If physical activity levels and prevalences of obesity were uniform with time in different populations, then one might indeed conclude that the possibility of changing energy intake might be limited in any one group. However, because patterns of daily activity and cultural attitudes toward food can and do change, alterations in energy intake among individuals and populations do occur. If such changes are occurring, then it
certainly appears relevant to assess the effects of absolute changes in intake of certain nutrients, after adjusting for body size and physical activity. Thus, the partition model is still highly relevant. Mackerras (6) recently raised similar questions in relation to adjustment for total energy intake.

Summary

We do not disagree with examination of nutritional data by using adjustment for total energy but we consider exclusion or strong discouragement of other methods an unbalanced approach. Accordingly, addition associations derived from the partition model should continue to be used alongside substitution associations derived from the multivariate density or residual model. We agree, however, that it is particularly important to try to control for confounding by using body size and physical activity when using the partition model. Only with use of both types of association—substitution and addition—can a full understanding of the data be reached.

RISK MODELS TO ACCOUNT FOR TOTAL ENERGY INTAKE

Although we agree with most of the comments made by Willett et al on risk models, we think it is worthwhile to highlight a few points with which we do not fully concur.

In discussing the residual model, Willett et al describe the coefficient for total energy intake as “having its standard biological meaning.” We believe that this phrase is used by the authors to distinguish between the residual and standard models. In the standard model, the coefficient for total energy actually represents the change in disease incidence associated with an increase in intake of energy from sources other than the nutrient of interest, a surprising fact that often catches researchers unaware. In the residual model, this is no longer the case, but to say that the total energy coefficient has its “standard biological meaning” may still be misleading. In fact, the coefficient represents the change in incidence associated with an increase in total energy intake derived from a diet with a specific ratio of nutrient energy to other energy, and this ratio happens to be the slope of the linear regression of nutrient intake on total energy intake (4). Because the association between disease and total energy intake will generally depend on the constituents of the diet, it is difficult to speak of there being a standard biological definition of this association.

In discussing the choice of models, Willett et al mention that the nutrient coefficient in the residual model “represents the biologically specific effect of the nutrient beyond any effect due simply to its energy content.” For us, the coefficient simply represents the change in disease incidence associated with the substitution of nutrient for other energy. As discussed above, we are not convinced that total energy adjustment removes the “energy effect” because that effect is not well defined (7). The change in disease incidence associated with substitution of a nutrient for another energy depends as much on the effect of the other energy as it does on the nutrient.

Finally, with respect to categorization, we agree with Willett et al that, for categorized variables, the residual model is preferable to the standard model. However, we disagree with their statements regarding the choice between the residual and partition models. After categorization, there remains the question of whether one wishes to estimate a substitution or an addition association. Furthermore, whereas an addition association can be derived directly from the coefficients estimated from the continuous residual or standard model, this cannot be done after categorization. Therefore, after categorization, there is even more reason to consider carefully which type of association one wishes to examine. We think that investigators should continue to be interested in both addition and substitution associations.

REFERENCES