The recent paper by Hoffmann et al. (1) raises a very important methodological issue in nutritional epidemiologic research. The investigation of dietary patterns in disease risk analyses is a necessary step away from the reductionist approach of studying single nutrients as disease predictors. The suggestion of Hoffmann et al. to substantially improve the hitherto-applied statistical procedures in dietary pattern analysis by employing a method that uses an actual data set and prior knowledge about nutrient-disease relations is to be greatly appreciated. However, I would like to comment on some further limitations of that approach which were not sufficiently considered in the article.

The main criticism raised about dietary quality scores, an approach to the characterization of food-related effects on health and disease, was that they focus on selected aspects of diet—based on prior knowledge—but do not take the correlation structure of food and nutrient intake into account. In contrast, principal-components analysis and factor analysis use the actual data to derive dietary patterns but ignore prior knowledge of nutrient-disease relations. Although Hoffmann et al. convincingly argue that reduced rank regression (RRR) overcomes these limitations, this is only partly true.

RRR uses disease-specific response variables to determine combinations of foods that explain a maximum amount of response variation. Two prerequisites here might not be present in all instances. First, there needs to be a clear picture of the underlying biologic mechanism relating nutrients or dietary factors to the development of a specific disease. Second, data on the nutrient or dietary factor must be available in food composition tables. The case of fruit and vegetable intake and the glycemic effect of foods on blood glucose and insulin levels illustrates these issues very well.

A high fruit and vegetable intake has been found to be protective against many diseases (2, 3). However, this protective effect has been ascribed to a range of different nutrients and nonnutritive components in fruits and vegetables that could be independently or jointly responsible for the apparent reduction in disease risk. Given this lack of clarity, RRR cannot be any more informative than a dietary pattern analysis like the suggested RRR, the resulting patterns, as presented by Hoffmann et al. (1), have only limited meaning.

RRR does not overcome the limited knowledge about the relations among food intake, dietary factors, and disease risk. If the underlying biologic mechanisms remain to be elucidated, RRR can only work on the basis of current knowledge or hypotheses. This is quite often the case and is not an extreme case, as Hoffmann et al. (1) stated in their Discussion section. Therefore, the results can only provide answers within the current theoretical framework.

**REFERENCES**


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**THE AUTHORS REPLY**

We thank Dr. Kroke for her comments (1) on the application of reduced rank regression (RRR) in nutritional epidemiology. We agree that using nutrients as response variables in RRR requires both adequate data from food composition tables and prior knowledge of an association between nutrient intake and disease. However, we do not agree that a clear picture of the underlying biologic mechanism is a prerequisite for RRR analysis. For deriving disease-related patterns, the RRR method is already more powerful than principal-components analysis if variation in intake of the selected nutrients is more relevant for disease development than the unspecified variation in intake of all foods. This weaker assumption seems to be fulfilled for the ratio of poly-
unsaturated fat intake to saturated fat intake, fiber intake, magnesium intake, and alcohol consumption, which were chosen as response variables in our study of diabetes mellitus (2).

The RRR method does not require that the response variables be nutrients or other dietary chemicals. Rather, any continuous variables that are affected by diet and are predictive for the disease are possible responses. For example, biomarkers that are on the causal pathway from diet to disease are predestined for RRR response sets. In a recent application of RRR, five biomarkers of coronary artery disease (high density lipoprotein cholesterol, low density lipoprotein cholesterol, lipoprotein(a), C-peptide, and C-reactive protein) were chosen as response variables (3). The first RRR pattern was strongly associated with the incidence of coronary artery disease (3). A high pattern score corresponded to a biomarker profile of high concentrations of C-reactive protein and C-peptide and low concentrations of high density lipoprotein cholesterol; this profile is a known risk factor for cardiovascular disease. Similarly, in a diabetes study, blood measurements of certain factors, such as glucose, hemoglobin A1c, and C-peptide, could be considered as response variables in an RRR analysis to reflect the overall glycemic response to diet.

The aim of an RRR analysis is not to discover the nutrients or nonnutritive components of a specific food group—for example, fruits and vegetables—that might account for the positive health effects of this food group in observational studies. Rather, starting from the hypotheses that some dietary components or intermediate variables are related to a specific disease, a dietary pattern will be derived by explaining maximal variation in these variables. RRR is limited to studies for which knowledge about important dietary components or intermediate variables exists. In addition, the study of RRR patterns and disease risk should be considered an approach that is complementary to the study of individual nutrients or food components, individual foods, and behavioral dietary patterns. Clearly, it may happen that no appropriate response variables are available at all. In this case—which is an extreme case from the theoretical point of view, regardless of whether or not it is rare—classical principal-components analysis should be the preferred method for obtaining dietary patterns.

REFERENCES


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RE: “CHANGES IN BODY WEIGHT AND BODY FAT DISTRIBUTION AS RISK FACTORS FOR CLINICAL DIABETES IN US MEN”

We read with great interest the paper recently published in the Journal by Koh-Banerjee et al. (1), who prospectively studied the relations between changes in body weight and body fat distribution (1986–1996) and subsequent risk of diabetes mellitus (1996–2000) among 22,171 Caucasian men. Weight gain was associated with increased risk of type 2 diabetes, whereas weight loss was related to decreased risk, independently of baseline body mass index, changes in fat distribution, and potential lifestyle confounders. Even more interesting were the relations with changes in fat distribution. As expected, an increase in waist circumference was associated with increased risk of diabetes independently of weight changes. However, increased risk was also observed for persons with a decrease in hip circumference.

Koh-Banerjee et al. assumed the higher risk of diabetes associated with decreased hip circumference to be caused by wasting of leg muscle mass (1). Indeed, a decrease in peripheral muscle mass is a well-known phenomenon of aging. We would like to emphasize another possible underlying mechanism which is in line with several studies that also found an independent relation of smaller hip circumference with more unfavorable glucose and lipid levels (2, 3) and future risk of diabetes (4–6).

Until recently, it was not clear whether the relation between smaller hips and increased health risk was due to smaller muscle mass at the hips, smaller fat mass, or both. A number of recent investigations used dual-energy x-ray absorptiometry to distinguish muscle and fat mass in the legs (7–10). These studies showed that, apart from lower muscle mass, a lower fat mass in the legs was independently related to unfavorable glucose and lipid levels (7–9) and progression of aortic calcification (10).

Several mechanisms may explain why leg fat seems to confer protection against metabolic disturbances. First, because the femoral fat depot is relatively insensitive to lipolytic stimuli and highly sensitive to antilipolytic stimuli, the femoral-gluteal fat depot may play a protective role by acting as a “sink” for circulating free fatty acids (11). This uptake of free fatty acids prevents ectopic fat storage in the liver, skeletal muscle, and pancreas, which causes insulin resistance and beta-cell dysfunction. In other words, if a person is more capable of storing lipids in femoral-gluteal adipose tissue (which results in larger hips), circulatory lipid levels will be lower and therefore cause less damage to organs, resulting in...