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### **Re: changes in body weight and body fat distribution as risk factors for clinical diabetes in US men**

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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 A<sub>1c</sub>, 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.

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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 unfa-

vorable 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

a lower risk of diabetes. Second, adipose tissue secretes many signaling proteins and cytokines with broad biologic activity and critical functions. Some of these adipokines may be involved in the development of insulin resistance in obesity (12). Because the secretory functions of adipose tissue are probably subject to regional variation (13), the different associations of abdominal and femoral fat with metabolic variables may be mediated by differential secretion of adipokines by these fat depots.

We think these considerations are relevant additional explanations for the intriguing findings of Koh-Banerjee et al. (1).

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## THREE AUTHORS REPLY

We thank Snijder et al. (1) for their insightful comments regarding our article (2). They direct our attention to an additional potential explanation for the association we observed between smaller hip circumference and increased risk of type 2 diabetes mellitus. In particular, they argue that the hazards posed by a smaller hip circumference may be attributed to a reduction in leg fat mass in addition to peripheral muscle wasting.

We agree that there is mounting evidence to support such associations and that the leg fat depot, unlike the truncal fat depot, may confer protection against metabolic disturbances due to regional differences in the regulation of lipolysis (3) as well as to variation in adipokine secretion and function deriving from these depots (4). However, the studies that linked baseline leg fat depot to a more favorable metabolic profile were cross-sectional (4–6). These studies did not quantify the *relative* degree of change in the fat versus fat-free depots at particular circumference sites in the same population, which may more strongly explain changes in diabetes risk. It is in the context of our original study aims that these questions are important, since we examined how 9-year changes in circumference predicted subsequent 4-year risk (2).

To our knowledge, one prospective study to date has documented the relation of magnitude of change in appendicular and trunk circumferences to regional changes in fat and fat-free tissue (7). In that study, mean thigh circumference significantly decreased by 2.4 cm (standard deviation, 2.9) among men and 4.5 cm (standard deviation, 4.4) among women over an average of 9.4 years. With the use of computed tomography in a subset of men, the investigators determined that the decline in thigh area was explained entirely by the decrease in muscle area, whereas subcutaneous fat area remained unchanged (7). Such findings support the greater emphasis we placed on diminishing peripheral muscle mass versus declining leg fat in explaining the decrease in hip circumference over time among the men. The fact that skeletal muscle is the main target organ and site of insulin resistance (8), coupled with the high degree to which gluteal/femoral muscle mass accounts for total skeletal muscle, supports the hypothesis of an independent role of peripheral muscle atrophy in the progression to diabetes, which we and other investigators have postulated (8, 9).

Further data are needed to assess whether the reduction in hip girth signifies a predominant loss of muscle mass and whether it may serve as an independent correlate of insulin resistance in predicting diabetes risk. Moreover, whether the quality of muscle mass affects insulin resistance, with respect to changes in fiber type and/or increased infiltration of intramuscular fat mass, is unknown. In the meantime, our data provide further support for recommending regular physical activity and avoidance of excess energy intake, which