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Do *trans* fatty acids increase the incidence of type 2 diabetes?[1,2]

M Tom Clandinin and Michaelann S Wilke

Salmerón et al (1) suggested, based on a reanalysis of data from the Nurses' Health Study, that an increase in polyunsaturated fatty acid intake and a decrease in *trans* fatty acid intake will substantially reduce the risk of type 2 diabetes in women. Specifically, these authors estimate that replacing 2% of energy from *trans* fatty acids with polyunsaturated fatty acids would lead to a 40% reduction in the incidence of type 2 diabetes. There is evidence from animal and human studies indicating that linoleic acid (18:2n−6) will improve insulin responsiveness and that eicosapentaenoic acid (20:5n−3) will reduce plasma triacylglycerol concentrations. The influence of dietary *trans* fatty acids on insulin resistance has not been studied and thus the hypothesis proposed by Salmerón et al is novel with important implications. Epidemiologic evidence relating diabetes to *trans* fatty acid intake is lacking. If the authors' conclusion that a decrease in *trans* fatty acid consumption will substantially reduce the risk of type 2 diabetes is correct, the implications for the food supply are serious. For example, the publicity that will result from these conclusions and the identification of foods in the diet that provide *trans* fatty acids will affect consumer choices and manufacturing practices. Therefore, it is important to assess the confidence that can presently be vested in the conclusions of Salmerón et al.

Over the past 20 y, Beaton et al published a variety of articles addressing limitations in the use of dietary methods to characterize the effect of change in an individual's usual intake or the usual intake of a population of individuals. Beaton et al made many important points, such as *1*) "those who use dietary data for secondary analyses must be conscious of the limitations inherent in the dietary data as a result of the original methodological decision" (2) and *2*) "regression and correlation analyses are generally undertaken in population data with the intent of asking 2 questions: (i) is there an association between variables…and (ii) what are the nature and the strength of the relationship? Methodologic decisions can impact on the answers to both of the questions" (3).

To evaluate the conclusions of Salmerón et al in the context of these points, one has to address a variety of fundamental questions, the first being what are the limitations inherent in the dietary data? The Nurses' Health Study was a longitudinal study, originally designed to relate diet and lifestyle factors to chronic disease incidence in female registered nurses. The 84 204 women who had filled out a questionnaire in 1980 were followed for 14 y. The original 61-item food-frequency questionnaire was subsequently expanded in 1984 to include 116–136 items, and nutrient intake was estimated by multiplying frequency by nutrient content of portions. Fat composition was updated in 1984, 1986, and 1990 and correlated with the earlier questionnaires for total and specific types of fat. The authors used this pool of information post hoc to make inferences about fat intake and risk of type 2 diabetes. Use of a food-frequency questionnaire to assess fat and polyunsaturated fatty acid intakes results in a large CV that is not likely to measure a change in fat intake at an intake of 2% of energy. Basically, the conclusions of Salmerón et al attempt to characterize the effect of change in an individual's usual intake when the method is only capable of characterizing the usual intake of a population of individuals. We are reminded by Beaton et al that "any source of variability in the data that cannot be attributed to true differences between individuals presents a problem…If there is a systematic error recurring in the same direction, it may generate a change in the mean as well as contributing to variance" (4), and "It is important to recognize from these questions that an increase in group size does not eliminate in any way the problems produced by a high intraindividual variance in the estimation of correlations or in regression analyses. Only an increase in the reliability of the estimate of usual intake by the individual, obtained by increasing the number of observations of that intake (*n*), can reduce the problem and appreciably improve the estimate" (4).

There is a distinct possibility of bias and error when assessing *trans* fat intakes and the *trans* fatty acid content of foods. For example, one should question whether the *trans* fatty acid content of foods consumed in 1980 is the same as in similar brands analyzed for updates occurring in 1984, 1986, and 1990. During this period, the processing technology for fats and oils improved and changed rapidly, with major fatty acid compositional changes occurring in the same brand of product. The analyses of *trans* fatty acids also changed dramatically during this period. The most important determinants of *trans* fatty acids at baseline specified in the Nurses' Health Study were intakes of margarine; beef, pork, or lamb as a main dish; cookies; and white bread. The 1980 and 1984 questionnaires only distinguished margarine as "stick or tub," which is not sufficient to determine *trans* fatty acid composition. Beef, pork, and lamb can only be considered minor sources of naturally occurring *trans* fatty acids, and cookies vary tremendously in their *trans* fatty acid content. Were other sources

[1] From the Nutrition and Metabolism Research Group, the Department of Agricultural, Food and Nutritional Science and the Department of Medicine, 4-10 Agriculture/Forestry Centre, University of Alberta, Edmonton, Canada.

[2] Address reprint requests to MT Clandinin, Nutrition and Metabolism Research Group, Department of Agricultural, Food and Nutritional Science and Department of Medicine, 4–10 Agriculture/Forestry Centre, University of Alberta, Edmonton, Canada T6G 2P5. E-mail: tclandin@ualberta.ca.

included on the questionnaire? Processed foods such as flour tortillas, peanut butter, nondairy creamer, and baked goods contain variable but substantial amounts of *trans* fatty acids. For instance, one 10-inch (25.4 cm) tortilla contains ≈1.53 g *trans* fatty acids, whereas 1 tbsp (15 mL) partially hydrogenated margarine may contain up to 2 g. A critical miscalculation of intake could easily result from food items such as these being overlooked, misestimated, or not listed. Quantifying *trans* fatty acid intake with any precision is difficult, even when using a questionnaire designed specifically with a comprehensive database.

Many of the highly processed foods containing *trans* fatty acids also contain high amounts of refined carbohydrates, which are known to exacerbate the insulin-resistant state. The high-fructose corn syrups found in hydrogenated fat–containing snacks stimulate lipogenesis and increases serum triacylglycerol concentrations. Therefore, when assessing the role of *trans* fatty acids in the disease-risk relation, there are issues beyond the usual inherent errors that occur in retrospective nutritional analyses. One must also consider the relatively small amount of *trans* fatty acids in the diet, the variability and specificity of food items containing *trans* fatty acids, the accuracy of the food composition data used in the analysis, and the likely associations of *trans* fatty acids with other nutrients.

The second fundamental question concerns the statistical analyses. For example, is there an association between variables? On a food composition basis there is clearly a relation between the intakes of different fatty acids, hence, one might argue that each are not independent variables in any statistical analysis. There is still no known functional or physiologic relation apparent to connect *trans* fatty acids and disease mechanisms involved in type 2 diabetes, thus indicating that the conclusions of Salmerón et al still represent another hypothesis to be tested.

Nutritional data are not without inherent bias and error. Salmerón et al recognize that there may be imprecise measurement and residual confounding factors and state that some findings may need confirmation because "the positive associations with *trans* fatty acids and dietary cholesterol were observed primarily among obese and less physically active women" (1). The authors speculate that the "effects of *trans* fatty acids and dietary cholesterol are not sufficient to cause diabetes, but in the presence of underlying insulin resistance may increase the probability of developing clinical disease" (1). It is important to note that the variables involved are not discreet or independent and, although some of the multiple interactions can be considered in statistical analyses, many are extraordinarily complex and not clearly defined in a free-living population. This context is complicated in the instance of small changes in fat composition, particularly because one type of fatty acid may counteract the increase in disease risk caused by another fatty acid. Thus, there are inherent limitations in the observations by Salmerón et al, but their conclusions should be taken into consideration to design studies that address this important public health problem.

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