Improving power with repeated measures

Dear Sir:

In their study, Marshall et al (1) found a significant relation between serum LDL cholesterol and saturated fat intake when random-effects models for longitudinal data were used. The model parameters were estimated by using data on 928 participants from the San Luis Valley of southern Colorado. Nutritional intakes were measured by the 24-h recall method; 2 observations were available for LDL cholesterol and nutrient intakes for most subjects. The models controlled for sex, age, body mass index, and energy intakes. The authors emphasized that significant associations were observed only in the 2 cases (models C and D) in which the statistical procedures took into account individual specific random effects.

The earliest studies by Keys et al (2, 3) emphasized the importance of the role of cholesterol intakes on serum cholesterol concentrations. Because of the poor fit of the model, intakes of saturated and polyunsaturated fats were also introduced; functional forms were empirically selected. In a subsequent study of 46 adults in the Boston area, Kushi et al (4) reported significant partial correlations between serum cholesterol and intakes of dietary cholesterol and saturated fat. Thus, a natural starting point for the statistical models estimated by Marshall et al would have been to also include intakes of dietary cholesterol and polyunsaturated fat in their regression models. Furthermore, because cholesterol intakes exhibit high within-subject variation (5), and because the authors relied on 24-h dietary recalls for measuring nutrient intakes, it is plausible that the reported coefficients of saturated fat intakes were not robust to changes in model specification. The authors should have reported results for a model that included saturated and polyunsaturated fat and cholesterol intakes as regressors. It would be interesting to see whether the results with such a model would support results obtained with the Keys equation, which is often used for approximating serum cholesterol concentrations in groups of individuals. From an estimation standpoint, it seems preferable to treat fat intakes as continuously measured variables. The estimated coefficients from the expanded model would show the relative importance of saturated fat and cholesterol intakes for serum LDL.

Second, because approximately half of cholesterol is endogenously produced, an individual's current serum cholesterol concentration is likely to depend heavily on the measurement in the previous period. Dynamic models, which allow the dependent variable (serum cholesterol) to depend on its previous value, can be estimated by the principle of maximum likelihood in the presence of time-varying covariates (6–8). These models also take into account individual specific random effects that are assumed to be multivariate and normally distributed; equation *2* in Marshall et al's article is a special case of the general formulation. Dynamic models and the "static" formulations used by Marshall et al are potentially useful for modeling serum cholesterol. However, because of the endogenous production of cholesterol, the underlying biological relations are perhaps better suited to dynamic modeling. With only 2 time observations available in the data used by Marshall et al, the empirical results from dynamic and static models are likely to be close. However, the model parameters have been interpreted differently. For example, it seems somewhat unlikely that serum LDL will decline immediately by 0.14 mmol/L after a 20-g decrease in saturated fat intakes on the day of a 24-h recall survey. Rather, there are complex delays underlying the relation between dietary intakes and serum LDL. One might be able to analyze these relations more systematically by using data from studies such as the Women's Health Trial Vanguard Study (9) and the Women's Health Trial Feasibility Study in Minority Populations (10), from which multiple observations on serum cholesterol and 4-d food records are available for relatively shorter time intervals.

Last, Marshall et al state that "parameter estimates for age were so different in models A and B than in models C and D" (models A and B did not allow for individual specific random effects). The authors attributed these differences to the underlying differences in LDL-cholesterol concentrations in different age cohorts. However, an alternative explanation would be that the subject-specific random effects partially reflected the age distribution of the sample. Because the authors apparently used discrete groups to represent age, the random effects are likely to further detect age differences in serum LDL cholesterol. This in turn would decrease the magnitude of the coefficient of age in models that include random effects. Evidently, this is the case when one compares the estimated coefficients of age in models A and B with those in models C and D in Table 3 (1).

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Reply to A Bhargava

Dear Sir:

Our study focused on the added power of random-effects models and we chose to use saturated fat for the purpose of illustration (1). Bhargava suggests that when serum cholesterol is modeled, results from models incorporating polyunsaturated fat and cholesterol intakes be reported. We used the Key's index as one indicator of an atherogenic diet in descriptive studies of this population (2) and we previously evaluated the relation of the index's components as predictors of serum lipid concentrations (3). We chose to use saturated fat because it was the strongest predictor and was relatively easy to interpret. When polyunsaturated fat and cholesterol intakes were added to model D, neither variable was significant and there was no improvement in the −2 log likelihood. Similarly, when saturated fat was replaced by the Key's index in model D, the index was a significant predictor, but again there was no improvement in the model. Dietary fat intake was treated continuously in all models.

Bhargava further suggests that dynamic models that adjust for prior serum lipid concentrations by adding a lag variable be explored. We agree that this procedure is unlikely to improve the model fit with only 2 observations. In addition, Bhargava references his own work in which observations were equally spaced and collected over days and not years. We do not have equally spaced data and the average interval between visits was 4.3 y. In model D, the inclusion of random subject effects modeled between-subject differences in serum cholesterol that may have been due to non-time-varying factors and may have included the endogenous production of cholesterol.

Bhargava assumed that we used discrete groups to represent age, but we modeled age as a continuous variable. Bhargava suggested that the different age effects may have "partially reflected the age distribution of the sample." However, given the relatively wide age range of the subjects (20–75 y; $\bar{x}$: 45 y) compared with the length of follow-up (4 y), it is unlikely that age differences in models A and B compared with models C and D explain these results. When age is separated into its cross-sectional and longitudinal components (4), serum LDL concentrations increase across age cohorts and decrease within subjects over time. This finding is consistent with patterns seen in national surveys collected over time (5). We appreciate Bhargava's analysis of our article and his effort to promote discussion.

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Nutritional status and energy metabolism in Crohn disease

Dear Sir:

We read with great interest the paper by Geerling et al (1) and the related editorial (2) regarding the usefulness of a comprehensive assessment of nutritional status in patients with inactive Crohn disease (CD). In Geerling et al's study, patients with inactive CD were found to have fat and fat-free mass contents (assessed by anthropometry and dual-energy X-ray absorptiometry) similar to those of control subjects. Our group previously reported the importance of studying CD patients during a remission phase because intercurrent factors related to inflammation can severely affect data measurement (3, 4). We found steroid treatment; the presence of clinical symptoms such as diarrhea, abdominal pain, and nausea; and the exclusion of patients who had undergone intestinal resection to be factors of primary importance for a correct evaluation of nutritional status in patients with inflammatory bowel disease (IBD). In addition, we suggested that the measurement of energy balance provides valuable information (5). We showed that CD patients with inactive disease had peculiar metabolic and body-composition features with respect to both control subjects and patients affected by ulcerative colitis

(UC), the other major form of IBD. In particular, regardless of disease localization (ileal, ileocolonic, or colonic), patients with inactive CD had reduced fat mass with good preservation of fat-free mass and an enhanced utilization of lipids as a fuel substrate (3–5). This lack of similarity between patients with different IBDs with the same intestinal localization seems to strengthen the hypothesis of peculiar metabolic features in CD (3–5).

The differences between our data and those of Geerling et al could be due to several factors. First, as Geerling et al stated in their methods section, 15 patients (47% of the population examined) had a Crohn's Disease Activity Index >150; thus, although the C-reactive protein value for these patients was within the normal range, they were presumably not in clinical or histologic remission. It would have been of interest to evaluate whether differences existed in any of the variables examined between patients with different disease activity indexes.

Second, to obtain a homogeneous group, none of our patients with inactive CD had undergone intestinal resections because we do not think that patients with or without small-bowel resections can be considered to be similar from nutritional and metabolic points of view. On the contrary, 27 patients in Geerling et al's study (84% of the patient population) underwent an average intestinal resection of 75 cm.

We were surprised by the high lipid intakes reported by CD patients in Geerling et al's study. Subjects with diseases of the gastrointestinal tract usually become able to identify food items that may give rise to intestinal symptoms, such as those containing high amounts of lipids, and avoid them in their diets. Nutritional deficiencies of micro- or macronutrients could then easily occur. In CD, because of major disease symptoms including abdominal pain and nausea, decreased intakes of nutrients have been reported (6). In particular, consumption of energy, calcium, iron, vitamin A, vitamin B-12, and folate was found to be poorest in patients with CD (7). The inclusion of patients with small-bowel resections may have created a bias in energy intake evaluation, independent of disease activity. Moreover, Geerling et al stated that 13 patients (41%) were taking an average daily dose of prednisone of 5 mg. Our group showed recently that glucocorticoid therapy is positively correlated with energy intake in patients with active CD (5).

Finally, according to the difference between energy intake and energy expenditure, which was computed only in mathematical equations by the authors, CD patients seemed to be in positive energy balance (610 kJ/d) whereas control subjects were in negative energy balance (−585 kJ/d). These data suggest that indirect calorimetry assessment of energy requirements along with the measurement of energy loss, essentially with stools, might be of great use in evaluating energy balance, especially in patients with an inflammatory disease characterized by intestinal malabsorption (5). Many patients in Geerling et al's study had liquid stools, indicating increased energy loss.

We therefore suggest that in addition to the measurements given by Geerling et al, a comprehensive assessment of nutritional status in CD patients should include the study of energy requirements, which can be safely done and is easy to perform even in children. The combination of these diagnostic tools would allow clinicians, surgeons, and nutritionists to better manage impairments of nutritional status in these patients and consequently to improve their quality of life (8). In addition, great care should be taken in defining current remission and in choosing a homogeneous group of patients.

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Reply to E Capristo et al

Dear Sir:

We read with pleasure the letter by Capristo et al and appreciate their comments on our study (1). In a recent study, Capristo et al (2) reported a lower fat mass in patients with Crohn disease (CD) during a remission phase than in control subjects or patients with ulcerative colitis, whereas fat-free mass did not differ significantly between groups. Indeed, we also found a significantly lower fat mass and percentage body fat (measured by dual-energy X-ray absorptiometry) in male patients with long-standing CD currently in remission, in contrast with female CD patients in whom body composition did not differ from that in control subjects. The observed sex differences are interesting and are not often described. Data suggest that there may be sex differences in the efficiency of energy metabolism under metabolic stress. It was reported that daily exercise reduces fat mass, protein mass, and body mass in male but not female rats despite a more negative energy balance in female rats (3).

There is no general agreement regarding the assessment of disease activity in CD. The clinical index most frequently used is the Crohn's Disease Activity Index (CDAI), but its value is widely disputed. Most studies continue to use the CDAI because of the lack of a better index. Many complications of CD elevate the CDAI yet do not reflect active inflammation (4); this was illustrated by the increased stool frequency after small-bowel resection observed in our study. As we pointed out, all patients had stable body weights, no significant acute phase response (ie, normal C-reactive protein values), and no change in medication during the 3 mo preceding the study. This indicated that the patients included in the study were clinically in remission.

Capristo et al suggested that patients with and without small-bowel resection should not be pooled to study nutritional or metabolic changes. However, we were interested in the nutritional status of a representative sample of patients with long-standing CD. Exclusion of patients with small-bowel resections would have greatly impaired the clinical value of such a study. Second, in our opinion there is no essential metabolic difference in small-bowel function between patients with small-bowel resections and those in whom a small-bowel segment has been destroyed as the result of a previous inflammation. In both cases, small-bowel function is impaired, eventually resulting in malnutrition.

In our study, absolute daily fat intake was not significantly different between CD patients (35.1% of energy intake) and matched control subjects (33.6% of energy intake). Patients were clinically in remission and were not anorexic, in contrast with the patients in the study of Rigaud et al (5) who lost weight and reported decreased food intake. Although we did not measure energy metabolism directly, the patients in our study were presumably in energy balance because they all had stable body weights during the 3 mo preceding the study. It would be interesting from a scientific point of view, however, to measure energy expenditure in these patients because this may further our understanding of the pathophysiology of malnutrition in CD. Because of possible differences in daily total energy expenditure between patients and control subjects as a result of quantitative and qualitative differences in daily activities, the predictive value of resting energy expenditure measured by indirect calorimetry is limited. Hence, in this respect, the doubly labeled water technique seems to be the most adequate method (6).

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My valedictory on the differences in biological potency between *RRR*-α-tocopheryl and *all-rac*-α-tocopheryl acetate

Dear Sir:

The paper by Burton et al (1), a collaborative study from 4 institutions, dealt with the relative biological values of *RRR*-α-tocopheryl acetate and *all-rac*-α-tocopheryl acetate, the 2 forms marketed in terms designated by the US Pharmacopoeia (2) as *d*-α-tocopheryl acetate and *dl*-α-tocopheryl acetate, respectively. On the basis of an assay in pregnant rats, 1 mg of the natural form *RRR*-α-tocopheryl acetate is officially considered to have 1.36 times the activity of 1 mg of the synthetic product *all-rac*-α-tocopheryl acetate. The excellent studies by Burton et al made use of deuterium labeling to show that when *RRR*- and *all-rac*-α-tocopheryl acetate were fed, amounts of *RRR*-α-tocopherol in the tissues of human subjects were much higher than amounts of *all-rac*-α-tocopherol. Burton et al concluded that the present official ratio of the biological activity of *RRR*-α-tocopheryl acetate to *all-rac*-α-tocopheryl acetate of 1.36:1 is erroneous. The last sentence of their report reads, "It seems highly improbable that the official biopotency ratio is relevant to human needs, which might be better served by thinking in terms of a 2:1 ratio, as was first suggested ≈18 y ago in this Journal" (3).

The relative biopotency of *RRR*- and *all-rac*-α-tocopheryl acetate has been controversial for many years. Very little vitamin E is required by adults (<8 mg/d) to prevent nutritional deficiency, and nutritional deficiency is rare. As an antioxidant, however, much more tocopherol is recommended to inhibit undesirable free radical reactions in the tissues. The current conflict regarding the relative potency of tocopherol compounds has produced strong disagreement that makes an interesting story, which I will try to summarize.

The original protocol of the fourth Elgin Project (4) sponsored by the Food and Nutrition Board of the National Research Council [the first 3 projects (5) dealt with thiamine, riboflavin, and niacin-tryptophan] was designed to determine whether vitamin E was required by humans. No consideration was given in the original protocol to use *all-rac*-α-tocopheryl acetate because almost pure *RRR*-α-tocopheryl acetate was already available. After some of the subjects had been consuming a controlled diet that contained ≈4 mg total tocopherols/d for 54 mo, the sponsoring committee approved supplementation of the remaining subjects. Two members of the committee insisted, against my preference, that the effects of *all-rac*-α-tocopheryl acetate as well as *RRR*-α-tocopheryl acetate be included in the study. Unexpectedly, the data obtained during 138 d of supplementation (6) showed that 15 mg *RRR*-α-toco-

pheryl acetate/d resulted in higher plasma concentrations than did 20 mg *all-rac*-α-tocopheryl acetate and that 50 mg *RRR*-α-tocopheryl acetate/d had much greater biological potency than 80 mg *all-rac*-α-tocopheryl acetate. To avoid controversy, I presented no analysis of these data in my summarizing presentation at a symposium on the role of vitamins in October 1959 (6). About 20 y later, when consumer use of vitamin E had grown considerably, I decided to report the data obtained after supplementation in greater detail (3).

To evaluate the conflicting evidence, a committee was organized by FT Perkins, who was then Chief of Biologicals at the World Health Organization. We met in Geneva in April 1981. In this meeting, the animal assays were given preference over data obtained in humans and no agreement was reached. Convinced that the human data were different from the data derived from experiments in pregnant rats, Coy Fitch, I, and others conducted a definitive experiment in 1983 on 20 healthy men and women (7). The design of the experiment was such that each of 5 different vitamin E compounds in gelatin capsules was tested sequentially in each of the subjects. Briefly, the subjects ingested 800 IU of a tocopherol compound plus 100 mL whole milk and serum tocopherol concentrations were measured at 0, 8, 24, and 48 h. The total lipid content of each serum sample was also measured because lipid concentrations strongly affect tocopherol concentrations in the blood (8). The protocol was blinded as much as possible. An experienced technician performed the analyses in a different department. Tocopherol concentrations in the 24-h serum samples increased twice as much after ingestion of *RRR*-α-tocopheryl acetate than after ingestion of *all-rac*-α-tocopheryl acetate. The largest difference between the 2 compounds was found in samples obtained 8 h after ingestion. Incidentally, *RRR*-α-tocopherol was absorbed faster than the acetates and higher concentrations were sustained in the serum, confirming previous studies in the literature.

The findings of Burton et al (1) should end the debate about the biological potency of the 2 vitamin E compounds most commonly purchased. Now in my 90th y, I doubt whether I will ever see the proper correction made in the official values of the tocopherols. Having introduced the term *equivalent* as used by committees of dietary allowance (9), I prefer that this designation be used to describe the potency of the tocopherols. In the recommended dietary allowances (10), l mg *RRR*-α-tocopherol has a biological value of 1.0 α-tocopherol equivalents. Accordingly, in modified US Pharmacopoeia vitamin E units, *RRR*-α-tocopherol should have a value of 1.0, *all-rac*-α-tocopherol a value of 0.5, *RRR*-α-tocopheryl acetate a value of 0.91, and *all-rac*-α-tocopheryl acetate a value of 0.455.

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Dietary determinants of iron homeostasis

Dear Sir:

A considerable amount of research over the past 50 y has contributed to our knowledge of iron bioavailability, particularly our understanding of the dietary determinants or variables that influence the iron status of individuals and populations. Studies of iron bioavailability have progressed from studies of single foods to studies of mixed meals and more recently of dietary intake over a given time period (1).The paper by Fleming et al (2), as stated in the accompanying editorial (3), is indeed a valuable contribution to this recent emphasis on the dietary determinants of iron homeostasis over prolonged time periods. Contrary to the findings of most earlier reports, dietary modulators of iron bioavailability influenced the serum ferritin concentration, one of the indexes of functional iron metabolism. The study, I suppose, brings to bear the concept of adaptive responses to iron absorption, metabolism, and balance. The subjects studied were a group of elderly, iron-replete persons whose dietary patterns varied. Iron homeostasis is known to be regulated by absorption from the gastrointestinal tract (4), in which absorption is inversely related to the stores of iron in the body. Consequently, iron bioavailability in humans can be adapted and regulated within a wide range of intakes to establish and maintain healthy iron status, particularly when the diet is varied. As adulthood is attained and in the elderly chosen for study, the physiologic demands for iron are minimal and adequate iron is absorbed to prevent iron deficiency (4) and maintain positive iron balance.

The authors stated 3 reasons that could account for the lack of correlation between dietary modulators and serum ferritin concentrations in previous studies: the need to take into account *1*) confounders of serum ferritin values, *2*) supplemental iron intake, and *3*) small sample sizes. The disparities in the duration of the studies might also account for the differences observed. Although the earlier studies were usually for periods of 4–6 mo (5), the study by Fleming et al (2) lasted ≈2 y. The effects of dietary factors might therefore be compensated for initially by adaptive responses in the gastrointestinal tract. After a period of adjustment, sustained variables in dietary composition could then exert influences on serum ferritin concentrations.

It might be useful for future studies to evaluate the time course of effects of dietary factors on serum ferritin.

The authors also reported that the study corroborated on a population basis the well-known superiority of meat in iron nutrition (6). Although this finding is unquestionable, it might be worth considering at this stage of nutrition research the issue of meat intake in the general nutrition of adults and the elderly. Public health recommendations now focus on not only reducing fat intake but also reducing red meat consumption (a superior source of highly available iron) and increasing consumption of whole-grain products and cereals (which contain factors that inhibit iron absorption). These public health recommendations are consistent with those for the prevention of other diet-related chronic diseases, such as cancer, diabetes, coronary artery diseases, and obesity. That is, the consumption of a variety of plants foods with greater emphasis on fruit and vegetables is advocated. Paradoxically, however, these nonheme iron sources contain ascorbic acid, an enhancer of iron bioavailability comparable in magnitude to the effect of meat. Ascorbic acid, however, does not seem to maintain this positive influence for long periods. One of the reasons for this, as suggested by Fleming et al (2), could be the compounding influences of supplemental ascorbic acid.

Perhaps the study by Fleming et al (2) confirms further the basis of these recommendations, especially for adults and the elderly. Although heme iron was correlated with high serum ferritin values and nonheme plant sources were associated with low serum ferritin values, the average figures fell within the normal reference range for both groups. Because the subjects were iron replete, the different dietary variables resulted in the maintenance of normal serum ferritin values. Although the specifications and recommendations for groups most vulnerable to iron deficiency would obviously be very different, it is hoped that dietary patterns and the nutrition issues considered in policy formulations would be amalgamated to promote the overall well-being and healthy status of adults and the elderly.

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