Effect of Preventive Supplementation on Young Children in Niger

To the Editor: In their randomized controlled trial, Ms Isanaka and colleagues[1] found that providing children younger than 5 years with ready-to-use therapeutic food during periods of food insecurity can prevent cases of malnutrition. However, their study presents 2 important methodological difficulties.

First, the authors used different reference distributions to define malnutrition at inclusion in the study (National Center for Health Statistics/World Health Organization [NCHS/WHO], 1978) and at inclusion in the analysis (WHO Child Growth Standards, 2006). A proportion of participants were thus excluded from the analysis on the grounds that they were already malnourished at recruitment according to the WHO reference.[2] This proportion was likely substantial and would be expected to consist mainly of children younger than 24 months because the 2 references yield different diagnoses principally in that age range.[2] Unfortunately, this age range has the highest risk of malnutrition.[3] This compromises the internal validity of the study, and extrapolation of results to children aged 6 to 60 months requires caution. The problem could be amplified by the interaction of the intervention with child age at baseline ($P = .07$), a result not fully discussed by the authors.

Second, the authors chose purposively a small number of villages that experienced a high prevalence of wasting during the 2005 food crisis. This crisis was an extreme manifestation of a long-term problem, including weak markets, land degradation, and poor access to health services.[4] As a result, the study villages were likely to differ from other villages by a number of key characteristics, putting the external validity of the study in question. In addition, it indicates that without addressing the causal complexity of malnutrition any intervention will have limited impact on malnutrition. The intervention in the study by Isanaka et al reduced the rate of wasting by only 36%.

Dominique Roberfroid, MD, MSc, MPhil
droberfroid@itg.be
Institute of Tropical Medicine
Antwerp, Belgium

Lieven Huybregts, MSc
Ghent University
Ghent, Belgium

Patrick Kolsteren, MD, PhD
Institute of Tropical Medicine

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To the Editor: Ms Isanaka and colleagues[1] conducted a cluster randomized trial to evaluate the effect of ready-to-use therapeutic foods on various measures of nutritional status, morbidity, and mortality in children in Niger. The cluster randomized trial design is a very useful one for this setting because of logistical constraints. However, such a design leads to analytic complications.

There are 2 levels of correlation in the study that need to be accounted for in the analysis. The first is that the children were clustered within households. This is shown in Figure 1 of the article, which indicates 1671 children from 647 households in the intervention group and 1862 children from 760 households in the control group. This leads to use of mixed-effects models in which correlation is accounted for at the village, household, and individual levels.

However, the survival analyses are more problematic in this setting. The authors employed a marginal modeling approach, in which the population-averaged effect of treatment on the time to event was modeled, adjusting for other covariates.[2] For this approach, the correlation at multiple levels is not accounted for in the estimation of the adjusted hazard ratios. It is instead adjusted for in the estimates of the variance of the adjusted hazard ratios, which are reflected in the estimated 95% confidence intervals presented in Tables 2 and 3.

However, validity of this estimation procedure requires that the number of truly statistically independent sampling units be large.[2] In this study, the sampling units are the villages, of which there are 12. Such a small number calls into doubt the validity of the standard errors used in computing the 95% confidence intervals in the adjusted hazard ratios in

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Tables 2 and 3. The issue of how to properly model survival data in a group-randomized trial setting is still very much an open question, although some recent proposals have been made.[3]

Debashis Ghosh, PhD
ghoshd@psu.edu
Department of Statistics
Penn State University
University Park, Pennsylvania

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In Reply: Dr Roberfroid and colleagues have highlighted that different reference populations were used and that this may affect the internal validity of this study. We note, however, that the NCHS reference was used to determine eligibility for preventive supplementation or treatment in the local nutritional program and not to determine inclusion in the study's surveillance activities. Anthropometric data were collected on and available for all children in the study villages. In the survival analyses, children were only excluded if, according to the WHO growth standards, the outcome was present at baseline. Use of the WHO growth standards in the analysis was chosen to facilitate comparison with future studies in which the WHO standards will be increasingly adopted. As the WHO growth standards have been shown more inclusive in classifying children as malnourished than the NCHS reference,[1] this decision resulted in the exclusion of a greater number of children from the analysis than if the NCHS reference population were used. This decision does not introduce a bias or reduce the internal validity of the study but rather limits the generalizability of the preventive effect of ready-to-use therapeutic foods to children classified as nonmalnourished by the WHO growth standards.

We agree with Roberfroid et al that the villages in this study likely differ from those in other settings and that the impact of preventive strategies using ready-to-use therapeutic foods may differ depending on the population and context. We strongly encourage other groups to perform similar studies in other contexts to add to the evidence base. We also agree on the underlying complexity of malnutrition and the importance of better understanding it to improve current interventions.

The comments by Dr Ghosh highlight the need to further develop appropriate techniques for the analysis of clustered survival data. We agree that survival analyses of clustered data can be problematic and look forward to further methodological advances in this area. We acknowledge that the marginal model approach is not able to account for the correlation at both the village and households levels. However, the mixed-effects analyses that account for multiple levels of correlation yield qualitatively similar results as those from the marginal survival models.

Sheila Isanaka, BA
sisanaka@hsph.harvard.edu
Department of Epidemiology
Harvard School of Public Health
Boston, Massachusetts

Rebecca F. Grais, PhD
Epicentre
Paris, France

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Nutritively Sweetened Beverages and Obesity

To the Editor: In their Commentary questioning the relationship between sugar-sweetened beverages and obesity, Drs Allison and Mattes[1] cited our randomized controlled pilot study.[2] We would like to clarify 2 points regarding this study: the nature of the counseling provided as part of the intervention and the relevance of effect modification by baseline body mass index (BMI).

First, the intervention involved delivery of noncaloric beverages to the homes of adolescents who reported consuming at least 1 serving per day of sugar-sweetened beverage as a strategy to decrease consumption. In addition, we contacted adolescents in the treatment group by telephone on a monthly basis throughout the 25-week intervention period to encourage adherence. We disagree with Allison and Mattes that this "extra counseling . . . most likely confounded the study" because the telephone calls focused strictly on beverage consumption, without conveying other dietary or lifestyle messages, thereby serving to enhance rather than compromise treatment fidelity. Indeed, process data indicated a significant decrease in sugar-sweetened beverage consumption among adolescents in the treatment group and no change in the control group. By way of comparison, there were no differences between groups in physical activity level, television viewing, or media time.

Second, an a priori aim of our study was to examine the effects of reducing consumption of sugar-sweetened beverages across a range of baseline BMI. As hypothesized, the effects were greatest among the heaviest children—those in most need of dietary intervention—providing a basis for targeting this high-risk population in future studies.

Cara B. Ebbeling, PhD
David S. Ludwig, MD, PhD
david.ludwig@childrens.harvard.edu
Children's Hospital
Boston, Massachusetts

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