abdominal obesity, high BMI, high fasting triacylglycerol concentrations, low HDL concentrations, small dense LDLs, decreased insulin sensitivity, and high blood pressure. Now, let us suppose that on further examination this individual also has elevated liver enzymes but does not drink alcohol. Fatty liver is suspected and progression to nonalcoholic steatohepatitis is a possibility. A recommendation to follow a low-fat, high-carbohydrate diet for weight loss and to reduce heart disease risk might exacerbate the overproduction of fatty acids via de novo lipogenesis and thus worsen the hypertriglyceridemia in this individual.

The metabolic environment is highly dynamic, and it is necessary to document and annotate all particulars that might affect any given measurement. For instance, the follicular phase of the menstrual cycle is different from the luteal phase in terms of blood lipid profiles in women, and the time of day influences the concentrations of certain compounds that are secreted according to a diurnal rhythm. Approaches that measure and analyze many endpoints simultaneously provide a more complete picture of system functioning and the possible underlying disorders involved in a particular disease state. In effect, the measurement of multiple endpoints adds resolution to the metabolic profile.

Measure more, more often

In light of the points discussed above, we propose that individual variability among people should be a prominent component of the diagnosis of metabolic syndrome and other metabolic disorders. A move away from a one-size-fits-all approach in diagnosis and toward a more individualized approach that recognizes the variability among people is necessary. As Grundy points out, the clustering of metabolic factors that defines the metabolic syndrome is a step toward recognition that the metabolic diseases of today are complex and require different solutions than do diseases that have one clear cause.

The authors had no conflicts of interest.

Angela M Zivkovic

Department of Nutrition
One Shields Avenue
University of California
Davis, CA 95616
E-mail: mzivkovic@ucdavis.edu

J Bruce German

Nestle Research Centre
Lausanne
Switzerland
E-mail: jbgerman@ucdavis.edu

REFERENCES

1. Reaven GM. The metabolic syndrome: is this diagnosis necessary? Am J Clin Nutr 2006;83:1237–47.
2. Grundy SM. Does a diagnosis of metabolic syndrome have value in clinical practice? Am J Clin Nutr 2006;83:1248–51.
3. Lai CQ, Corella D, Demissie S, et al. Dietary intake of n−6 fatty acids modulates effect of apolipoprotein A5 gene on plasma fasting triglycerides, remnant lipoprotein concentrations, and lipoprotein particle size: the Framingham Heart Study. Circulation 2006;113:2062–70.
4. Ordovas JM. Genetic interactions with diet influence the risk of cardiovascular disease. Am J Clin Nutr 2006;83(suppl):443S–6S.

Reply to AM Zivkovic and JB German

Dear Sir:

In their letter, Zivkovic and German argue that the metabolic syndrome should be viewed from the perspective of systems biology. This view could aid in the understanding of individual variation in the risk-factor expression of the syndrome. Systems biologists attempt to understand how complex biological systems function in light of multiple interconnected pathways (1). It represents an integrative or synthetic approach to biological phenomena. Zivkovic and German contend that the metabolic syndrome is an example par excellence of a biological system gone astray. I am sympathetic to the systems biology approach to the metabolic syndrome. It may hold considerable promise for a better understanding of the syndrome.

As Zivkovic and German point out, some investigators, such as Reaven (2), have set forward the hypothesis that a single underlying factor—insulin resistance—dominates the causation of the syndrome. Although this is a powerful and useful hypothesis, it does not adequately account for variable expression of the risk factors associated with the syndrome. I contend that ≥3 levels of causation must be considered to account for the great variation in manifestations of the syndrome (3). First, most persons with the metabolic syndrome are either overweight or obese. A nutrient energy overload, manifest by obesity, places a strain on metabolic processes and sets the stage for development of the syndrome. However, obesity alone is not sufficient. Because many obese persons do not have the syndrome, metabolic susceptibility must also be a factor. One form of susceptibility is systemic and is characterized by a generalized metabolic dysfunction; in my view, this dysfunction is what many investigators call insulin resistance, although the overall derangement may involve pathways other than insulin signaling pathways. There also can be risk-factor specific dysregulation that modifies the responses in each risk factor. It seems to me that this model of the pathogenesis of the metabolic syndrome better accounts for individual variability than does the insulin-resistance model.

One question that is repeatedly asked about the metabolic syndrome is whether its whole is more than its parts. Presumably, the question being asked is whether the syndrome confers a greater risk of cardiovascular disease (CVD) than does its component risk factors. Zivkovic and German contend that a major message of systems approaches is that the whole is always greater than its parts. This thought is contained in the concept of *emergence*, which implies that new entities, such as living systems, emerge out of complex combinations of simple units (4). It is on this concept that Zivokvic and German seemingly base their conclusion that the metabolic syndrome embodies more risk than would be embodied by the sum of its risk components.

One argument supporting the view that the CVD risk accompanying the metabolic syndrome is greater than its component parts is the observation that risk factors are multiplicative, ie, their combined effect on risk is greater than the sum of the risk of individual risk factors. Presumably, risk factors are synergistic in their actions on the arterial wall. The multiplicative nature of CVD risk factors is well established in epidemiology and presumably is an example of "systems biology at work."

Even if the risk associated with the metabolic syndrome were to equate to the sum of the component risk factors, the issue remains whether all of the risk components can actually be identified. Because atherogenesis is a chronic condition, it is difficult to define the relative contributions of each of the components of the syndrome. Two of the metabolic risk factors, elevated blood pressure and reduced HDL-cholesterol concentrations, are most strongly associated with atherosclerotic CVD events in epidemiologic studies, but these

risk factors are not necessarily the only causes of clinical disease in patients with the syndrome. Because of colinearity with the other factors, predictive power does not always equate to causality. The contributions of elevated triacylglycerol-rich lipoproteins, a prothrombotic state, a proinflammatory state, and insulin resistance tend to be hidden behind blood pressure and HDL cholesterol, although considerable evidence exists that these 2 factors increase the risk of atherosclerotic CVD events.

Finally, the metabolic syndrome is progressive, ie, its risk factors tend to worsen with advancing age. For this reason, risk is compounded over time. Long-term risk rises progressively so that lifetime risk exceeds that which would be extrapolated from short-term risk projections.

On the whole, I essentially agree with Zivkovic and German that both the pathogenesis and accompanying risk of the metabolic syndrome should be viewed as a problem of systems biology. I encourage them to continue to explore this concept because it has implications beyond the metabolic syndrome, ie, to the entire field of risk prediction for disease.

The author had no conflict of interest.

Scott M Grundy

Center for Human Nutrition
University of Texas Southwestern
5325 Harry Hines Boulevard
Dallas, TX 75390
E-mail: scott.grundy@utsouthwestern.edu

REFERENCES

1. Ideker T, Galitski T, Hood L. A new approach to decoding life: systems biology. Annu Rev Genomics Hum Genet 2001;2:343-72.
2. Reaven GM. The metabolic syndrome: is this diagnosis necessary? Am J Clin Nutr 2006;83:1237-47.
3. Grundy SM. Does a diagnosis of metabolic syndrome have value in clinical practice? Am J Clin Nutr 2006;83:1248-51.
4. Emmeche C, Køppe S, Stjernfelt F. Explaining emergence: towards an ontology of levels. J Gen Philosophy Sci 1997;28:83-119.

Severe pneumonia research and the problem of case definition: the example of zinc trials

Dear Sir:

We read with great interest the report by Bose et al (1) of their randomized controlled trial of zinc supplementation in young children with severe pneumonia in southern India—they are to be commended for making an important contribution to a little-studied question. Mixed evidence from a small number of trials leaves unresolved the question of the role of zinc in severe pneumonia (2, 3).

One problem that attends research in childhood pneumonia, to which the authors refer, is that of case definition. The World Health Organization's clinical definition of pneumonia, a modified version of which was used in the study of Bose et al, does not attempt to distinguish between pneumonia and bronchiolitis. However, clinicians have long recognized that these are in fact 2 distinct conditions (albeit with a degree of clinical overlap) whose prognosis and clinical features are different. Bronchiolitis tends to be viral, self-limiting, and associated with wheezing, whereas pneumonia tends to be bacterial (especially in the developing world; 4), to have a significant mortality, and not to have associated wheezing. The reliable detection of wheezing is problematic in primary care settings in the developing world, and thus in a pneumonia study including children with wheezing may enhance the study's generalizability to these settings. However, the danger is that what is intended to be a study of pneumonia becomes a study of bronchiolitis. That may have been the case in the study of Bose et al: nearly two-thirds of patients had wheezing, and therefore they are likely to have had bronchiolitis (or possibly asthma), which is consistent with the very low reported case fatality (1 death in 300 participants; 0.3% case fatality rate). We suggest, therefore, that the ability to exclude bronchiolitis from the analysis is helpful to the meaningful study of pneumonia. Practical options for doing this include designing and powering studies to detect a difference in the nonwheezing subgroup, excluding wheezers altogether, or including radiologically confirmed pneumonia only.

Bose et al speculated that zinc may be harmful in bacterial pneumonia, at the same time that they acknowledged the limitations of the subgroup analysis on which the speculation was based. They showed prolongation of recovery (risk ratio in the placebo group: 0.60; $P = 0.015$) in a subgroup of 97 participants in the hot season, when nonwheezing apparently is more common. However, it is notable that no difference in recovery time was found between wheezers and nonwheezers in the study, which would be expected if the etiology of the pneumonia accounted for the difference in treatment effect by season. In contrast, Brooks et al (2) showed more rapid recovery from signs of severe disease in a nonwheezing subgroup of 164 participants (risk ratio: 0.61; 95% CI: 0.4, 0.92).

It is not clear whether the population studied by Bose et al was zinc deficient or not. Although the 3 completed trials were conducted in South Asia, soil and food zinc content could be substantially lower in deltaic Bangladesh and West Bengal than in southern India, which would make Bangladeshi children more likely than children from the other regions to benefit from zinc supplementation.

We agree with Bose et al that more studies are needed in a variety of populations before rational policy recommendations can be made on the role of zinc in the treatment of severe pneumonia. We know of 4 studies in progress, 2 in Africa [Tanzania (Clinical Trials.gov identifier NCT00133432) and Gambia (Current Controlled Trials registration no. ISRCTN335484593)] and 2 in Nepal (Clinical Trials.gov identifiers NCT00252304 and NCT00148733). In all of these trials, as in the trial of Bose et al, the possibility exists that the study group may not be zinc deficient and thus would show no benefit from zinc supplementation. The Gambian study (our study) is seeking to determine zinc status by measuring linear growth and immune status, in addition to plasma zinc concentrations, in a subgroup supplemented with zinc or placebo for 6 mo. As far as case definition goes, the Tanzanian study addresses the problem by including radiologic criteria, and the Gambian study does so by excluding wheezers, whereas the Nepali studies use definitions similar to those used by Bose et al. It is to be hoped that, with the completion of these studies, the picture will become clearer.

None of the authors had a personal or financial conflict of interest.

Stephen Howie
Syed MA Zaman
Osaretin Omoruyi
Richard Adegbola

Medical Research Council Laboratories
PO Box 273
Banjul