cannot be causally explained by the factors contained in its current diagnostic criteria. The latter serves to identify the presence of higher risk condition but does not necessarily represent the sole targets of therapy for the condition.

SCOTT M. GRUNDY, MD, PHD[1,2,3]

From the [1]Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, Texas; the [2]Department of Clinical Nutrition and Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas; and the [3]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas.

Address correspondence to Scott M. Grundy, MD, PhD, Center for Human Nutrition and Departments of Clinical Nutrition and Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Y3.206, Dallas, TX 75390-9052. E-mail: scott.grundy@utsouthwestern.edu.

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The Metabolic Syndrome (Emperor) Wears No Clothes

Response to Kahn

Kahn (1) pointed out that metabolic syndrome is associated with many uncertainties and inconsistencies, which could easily misdirect care, mislead patients, and lead to unnecessary health care costs. The risk of cardiovascular disease (CVD) associated with the syndrome is no greater than that explained by the presence of its components, and it is possible to create an almost infinite number of scenarios in which individuals who do not meet the diagnostic criteria for metabolic syndrome would be at greater risk of CVD than would those who do, as noted by Reaven (2).

What if, among the diagnostic components of metabolic syndrome, waist circumference, which is one of the anthropometric markers of obesity, was substituted by high-sensitivity C-reactive protein (CRP)? CRP is a sensitive marker of subclinical systemic inflammation and positively relates to leptin (3) and insulin resistance (4) and negatively relates to adiponectin (5), even in people with normal BMI (excluding those with diabetes). Reaven (2) pointed out that only about one-third of the most insulin-resistant individuals were actually obese, and the degree of correlation between insulin-mediated glucose uptake and BMI, waist circumference, and visceral obesity were almost equal. Neither abdominal obesity nor metabolic syndrome, as defined by the National Cholesterol Education Program Adult Treatment Panel III criteria, were a significant independent risk factor for CVD in multiple regression analyses (6,7), while very low levels of CRP were useful for risk prediction among women with calculated 10-year Framingham risks <10% (8). Previously, we propose a CRP value of 0.65 mg/l as the cut point for metabolic syndrome (9) instead of ethnic-specific controversial cut points of waist circumference. Whether the new clothes fit the emperor should be revealed by reanalyses of existing epidemiological studies including CRP data.

EIJI ODA, MD

From the Department of Internal Medicine, Niigata Prefectural Yoshida Hospital, Niigata, Japan.

Address correspondence to Eiji Oda, MD, Department of Internal Medicine, Niigata Prefectural Yoshida Hospital, Yoshida-Daibochou 32-14, Tsubame, Niigata, 959-0242, Japan. E-mail: ijie@venus.sannet.ne.jp.

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The Metabolic Syndrome (Emperor) Wears No Clothes

Response to Oda

The possible inclusion of C-reactive protein (CRP) in the metabolic syndrome algorithm highlights the problems of the construct itself. If the syndrome is supposed to be a predictive tool for future cardiovascular events, then we should indeed test the benefit of adding CRP, along with age, sex, race, adiponectin, homocysteine, etc. If the utility of the syndrome is to call attention to obesity, then there is no need for expensive laboratory tests. If the virtue is to predict diabetes, then a measure of glucose intolerance alone is better. If the syndrome is supposed to identify those with insulin resistance, then there are simpler ways to do so; however, measuring CRP might be helpful.

Dr. Oda (1) seems to have one purpose for the construct; others have different perspectives. The problem is that no one, not even the proponents themselves (2–4), have conveyed the exact utility of the syndrome and shown that it is better than or even equal to other approaches, and the critical issue, therefore, is why clinicians should even bother diagnosing metabolic syndrome in the first place.

RICHARD KAHN, PHD

From the American Diabetes Association, Alexandria, Virginia.

Address correspondence to Richard Kahn, PhD,

American Diabetes Association, 1701 N. Beauregard St., Alexandria, VA 22311. E-mail: rkahn@diabetes.org.

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A Strong Dose-Response Relation Between Serum Concentrations of Persistent Organic Pollutants and Diabetes: Results From the National Health and Nutrition Examination Survey 1999–2002

Response to Lee et al.

Lee et al. (1) and *Diabetes Care* deserve praise for publishing what may be the first study worldwide to analyze, in a sample of a general population, serum concentrations of persistent organic pollutants (POPs) and plasma fasting glucose. The main implication of the study is that POPs stored in the adipose tissue may be a key player in the etiopathogenesis of type 2 diabetes. It is even rational to speculate that POPs might be, if not "the single factor" (2), then one factor linking some core components of the metabolic syndrome.

In the study by Lee et al. and other studies (3,4), it seems likely that a relationship exists between diabetes and POPs. Hence, patients, clinicians, and other health professionals may need to cope with the possible fact that on average, diabetic subjects have higher concentrations of POPs and may thus be more likely to suffer the adverse effects of POPs. The mechanistic, clinical, and public health implications of the study by Lee et al. are potentially high (1,3–5). However, several questions remain unanswered regarding the nature of the relationship between prevalence of diabetes and population distribution of POPs (6,7). Therefore, I would appreciate it if Lee et al. could address the following issues.

1) What is the direction of the relationships with the poverty income ratio? For example, in Table 1, did wealthier individuals have lower concentrations of DDE and higher concentrations of PCB153 after adjusting for confounders?

2) Many of the estimates (e.g., in Table 2) were adjusted for age, sex, race, income, lipids, BMI, and waist circumference. This is coherent with several aims (e.g., to "isolate" the effect of POPs from that due to obesity, age, race, or income). However, adjusting by BMI and waist circumference may also be an overadjustment, since fat intake is the most common source of exposure to POPs (1,5) and since the body burden of some of these lipophilic chemicals, but not all and not always, increases with increasing BMI (8,9). Thus, crude or less adjusted odds ratios (ORs) would also be relevant for determining the prevalence of diabetes in people with specific concentrations of POPs. Could the authors provide some crude ORs?

3) The finding that there was no association between obesity and diabetes among subjects with nondetectable levels of POPs is highly surprising and calls for additional results to be presented. A figure may be warranted.

4) Also crucial is what we may call "the changes in BMI-POPs relationship." Could the authors please comment on the possible influence upon BMI measurements of the cross-sectional design of the study? Could they suggest possible consequences upon findings of weight gain and weight loss in diabetic and nondiabetic participants?

5) High-prevalence ORs were found for the summary or composite of the six POPs with the highest concentrations. Are the results similar if the joint effects of multiple POPs are assessed through alternative methods?

6) Finally, the authors state that "reverse causality is unlikely." Indeed, evidence supporting the hypothesis that diabetes increases accumulation of POPs seems scarce (4). Do the authors know of studies on the toxicokinetics of POPs in diabetic subjects demonstrating that they accumulate POPs more than nondiabetic subjects?

MIQUEL PORTA, MD, MPH, PHD

From the School of Medicine, Universitat Autònoma de Barcelona and Institut Municipal d'Investigació Mèdica, Barcelona, Catalonia, Spain.

Address correspondence to Prof. Miquel Porta, School of Medicine, Universitat Autònoma de Barcelona and Institut Municipal d'Investigació Mèdica, Carrer del Dr Aiguader 80, E-08003 Barcelona, Catalonia, Spain. E-mail: mporta@imim.es.

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