



## Is the metabolic syndrome a real syndrome?

### *Metabolic Syndrome*

#### *Is It a Syndrome? Does It Matter?*

Richard Kahn, PhD



To provide useful answers to the title questions, the first issue to resolve is what is meant by the term “metabolic syndrome.” If it is supposed to refer to a loose clustering of signs that are associated with cardiovascular disease (CVD) and type 2 diabetes mellitus, which can largely be ascribed to what we conceptually call “insulin resistance,” then the term may have some utility. However, if the term represents a very specific algorithm that should be used to diagnose a unique disease, it is highly misleading and ineffective. Unfortunately, many proponents of the term write about and discuss it as if both meanings are interchangeable, and as a result, they effectively blur all the problems that have arisen when referring to the term, confuse practitioners who are unable to easily understand the distinction, and do clinical medicine a great disservice. Let’s look closely at the issues.

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#### Response by Beaser and Levy p 1811

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##### **The Syndrome as a Concept**

For several decades, we have had many terms that represented a clustering of signs related to CVD and diabetes mellitus that seemed to occur more often than chance would dictate. Certainly, an aggregate of signs associated with a morbid process that together constitute the picture of a disease may be rightly called a syndrome. In the early days, many investigators put a name to the condition that reflected its

“metabolic”<sup>1-3</sup> or “insulin resistance”<sup>4</sup> origin. At that time, the cluster referred to the presence of obesity, hyperglycemia, hypertension, hyperlipidemia, and sometimes hyperuricemia. Reaven, in his now classic publication,<sup>5</sup> provided an elegant explanation for how insulin resistance and its compensatory hyperinsulinemia could predispose individuals to the above conditions and thus was the underlying cause of much CVD and, of course, diabetes mellitus. Among its many attributes, Reaven’s publication opened the door to considerably more research documenting the clustering and its relationship to insulin resistance.

Of note, however, all of the studies that examined this relationship have shown that only about half to two thirds of those people with the diagnosis of the metabolic syndrome are indeed insulin resistant, and a smaller proportion of those with insulin resistance meet the criteria for metabolic syndrome.<sup>6-9</sup> As to the relationship between each component of the cluster and insulin resistance, what few data we have suggest that overweight/obesity often gives rise to insulin resistance, and type 2 diabetes mellitus virtually always requires the presence of insulin resistance. Thus, we have a ready explanation for why these 2 signs often occur together.

On the other hand, when hypertension and dyslipidemia occur by themselves or in the absence of diabetes mellitus and obesity, they are far less frequently associated with insulin resistance. Making the story more complicated is the

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fact that insulin resistance is defined as defective insulin-mediated glucose disposal and is itself the subject of much uncertainty as to its molecular origin. All told, one can easily appreciate that at this time, the precise pathobiology of the clustering beyond the association between diabetes mellitus and obesity remains uncertain.

In addition, the list of signs that should fall into the bucket called the metabolic syndrome is also uncertain. First, as mentioned above, obesity is not a result of insulin resistance but a cause of it,<sup>5,10</sup> and only about half of those who are obese are insulin resistant.<sup>6</sup> Some investigators have proposed adding albuminuria,<sup>11</sup> elevated C-reactive protein,<sup>12</sup> decreased adiponectin levels,<sup>13,14</sup> and a list of other poorly described “underlying,” “major,” and “emerging” CVD risk factors<sup>15</sup> to those that constitute the original group of metabolic syndrome signs.

The difficulty deciding what signs constitute the syndrome is a direct result of the uncertainty about its underlying cause. If we are uncertain as to what to attribute the clustering, we do not know what to add that is associated with the core problem. Also, no studies exist that present an argument for how much clustering above chance alone is sufficient for a factor to enter the syndrome, or whether the factor must cluster with all or some of the existing syndrome components. Finally, no study has systematically examined in different populations the prevalence of each combination of the 5 key signs, and thus, we do not know much beyond “they tend to occur together.” We also do not know the general order in which they appear, nor whether any must appear within a certain timeframe to be considered part of the syndrome. Thus, to the question, “Does the use of the term metabolic syndrome as defined by explicit cut points for a proscribed set of markers provide a better understanding of the cause or pathogenesis of CVD or diabetes mellitus?” we must answer no.

### The Value of the Syndrome as a Concept

Despite these uncertainties, sufficient evidence exists to conclude that diabetes mellitus, hypertension, high triglycerides, low high-density lipoprotein cholesterol, and obesity, taken 2, 3, 4, or 5 at a time, occur more often than chance would dictate. The obvious utility of this knowledge is that the identification of 1 of these CVD risk factors in a patient should prompt a search for the others. Equally important, the clustering should continue to stimulate research into the underlying biology of each risk factor as it relates to the biology of the other risk factors. For example, a subject of much current research is how adipose tissue affects insulin action, and thus, we should understand one day soon why type 2 diabetes mellitus and obesity almost always occur together. Should we one day also understand the genetic basis for the clustering or develop a test that discriminates between competing causes of the clustering, we will be in a much better position to understand its underlying source.

All the above should make us comfortable with the concept that a syndrome exists associated with insulin resistance, or a

syndrome associated with a handful of factors that portend CVD and whose origin includes and extends beyond insulin resistance. After all, many other syndromes exist in the medical literature that are also defined as a loose array of signs and/or symptoms, with no clear order or combination preference, and that in part have an unclear pathophysiology.<sup>16</sup>

But looking at the syndrome as a concept only may leave some feeling that the “glass is half empty.” That is, nearly all syndromes in the medical literature come into being because the clustering of specific signs and symptoms suggests a unique disease or condition, or because the presence of a syndrome dictates a specific therapy, rules out unnecessary therapies, or predicts a prognosis that would otherwise not occur. Without any pathogenic reason to use the term “syndrome,” and with the great unlikelihood that any single unifying cause will emerge to explain it all, we are left with the need to question its clinical utility.

### Is the Metabolic Syndrome a Good Predictor of Diabetes Mellitus or CVD?

To diagnose the metabolic syndrome, one has to know what to look for, and to know what to look for requires that a clinician know which CVD risk factors tend to cluster. Thus, it is the concept of the clustering per se that is the critical teaching point, not necessarily the knowledge that someone has the metabolic syndrome.

On the other hand, a compelling reason for deciding that an abnormality constitutes a unique disease is that the diagnosis signals an explicit warning or action that would otherwise not occur. In the circumstances in which the metabolic syndrome is diagnosed, we must ask, what is gained by doing so (other than the possibility that the clinician looked for the relevant associations that he/she should have already known could exist)?

Innumerable articles have been written showing that the presence of the syndrome is a good predictor of diabetes mellitus or CVD. Proponents of the syndrome extoll this virtue as if it were really something novel or particularly unique.<sup>17–20</sup> Yet, what would be really remarkable is if the presence in a patient of any major risk factor for diabetes mellitus (eg, obesity or glucose intolerance) or many risk factors for CVD did not herald an increased risk for these diseases. Indeed, many have recently questioned whether the construct does anything to improve prediction of future diabetes mellitus or CVD risk above that of its individual components or relative to other risk prediction tools.<sup>10,21–26</sup>

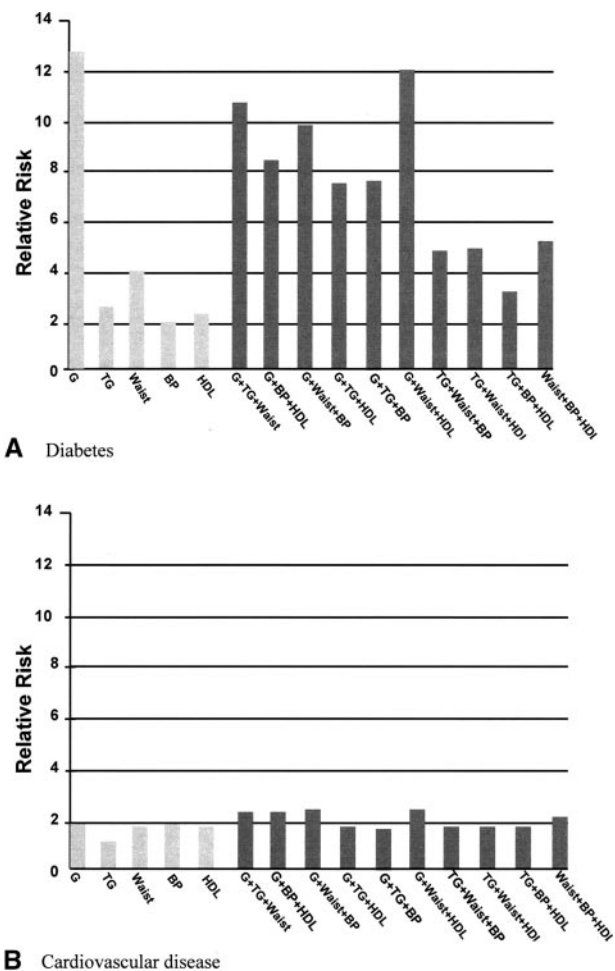
In addition, one might suppose that having a somewhat complex, very explicit construct must have as its origin a body of literature that describes the sensitivity, specificity, and positive predictive value of the definition, and how other definitions, however similar or different, were less or more satisfactory. Such evidence is, remarkably, nowhere to be found. Despite many thousands of articles written about the syndrome, there do not appear to be any experimental data

published that ordained the specifics of the definition.<sup>15,19,27</sup> For example, why do we have only 5 risk factors and not others; why must there be 3 of 5, or 1 mandatory and 2 optional instead of an entirely different algorithm? Should we be concerned that the algorithm appears not to be driven by hard data? And when various groups have inaugurated a new definition, on what basis should it be presumed to reflect some improvement over the old definition?

It could be blind luck that yielded a construct of great value. Here too, however, the literature suggests that the syndrome is no better than other tools that can be used to predict diabetes mellitus or CVD,<sup>28–32</sup> and no report exists that provides data showing that the risk imparted by the syndrome is higher than the risk imparted by the component factors themselves. Quite to the contrary, many reports document that the risk of CVD associated with the syndrome is explained entirely by the presence of its components.<sup>33–39</sup> In addition, the metabolic syndrome in the absence of diabetes mellitus or clinical CVD is a much weaker CVD risk predictor than either diabetes mellitus or clinical CVD.

Moreover, the study by Wilson and colleagues<sup>31</sup> showed that fasting plasma glucose is a far better predictor of diabetes mellitus than any of the combinations of factors that denote the presence of the metabolic syndrome (Figure 1A). In addition, they showed that the relative risk of CVD was essentially the same when the 5 metabolic syndrome factors were taken 1 or even 3 at a time (Figure 1B). This study dramatically highlights what has been reported by many, that is, the clinical benefit that results from diagnosis of the metabolic syndrome appears to be of little to no added value above that which can be gleaned in many other ways.

Thus, proponents of the syndrome have only been able to present the circular argument that CVD risk factors predict CVD. However, a recent post hoc analysis of the Treat to New Targets data concluded that patients with the metabolic syndrome get added cardiovascular protection by high-dose statin treatment.<sup>40</sup> This finding suggested that the presence of the metabolic syndrome may help select patients who should be taking a high-dose statin. However, earlier studies have shown that whereas low-density lipoprotein (LDL) cholesterol levels are unrelated to the metabolic syndrome, LDL particle number is directly related.<sup>41</sup> Thus, the results of the Treat to New Targets subanalysis can also be interpreted to indicate that the presence of the metabolic syndrome can be a surrogate marker for elevated LDL particle number. Because LDL particle number or apolipoprotein B levels may be a much better measure of CVD risk than is LDL cholesterol,<sup>42–45</sup> one could perhaps even better select patients who would benefit from a high-dose statin by quantifying LDL particle number and/or apolipoprotein B, both of which approaches are likely to be more informative than the metabolic syndrome.

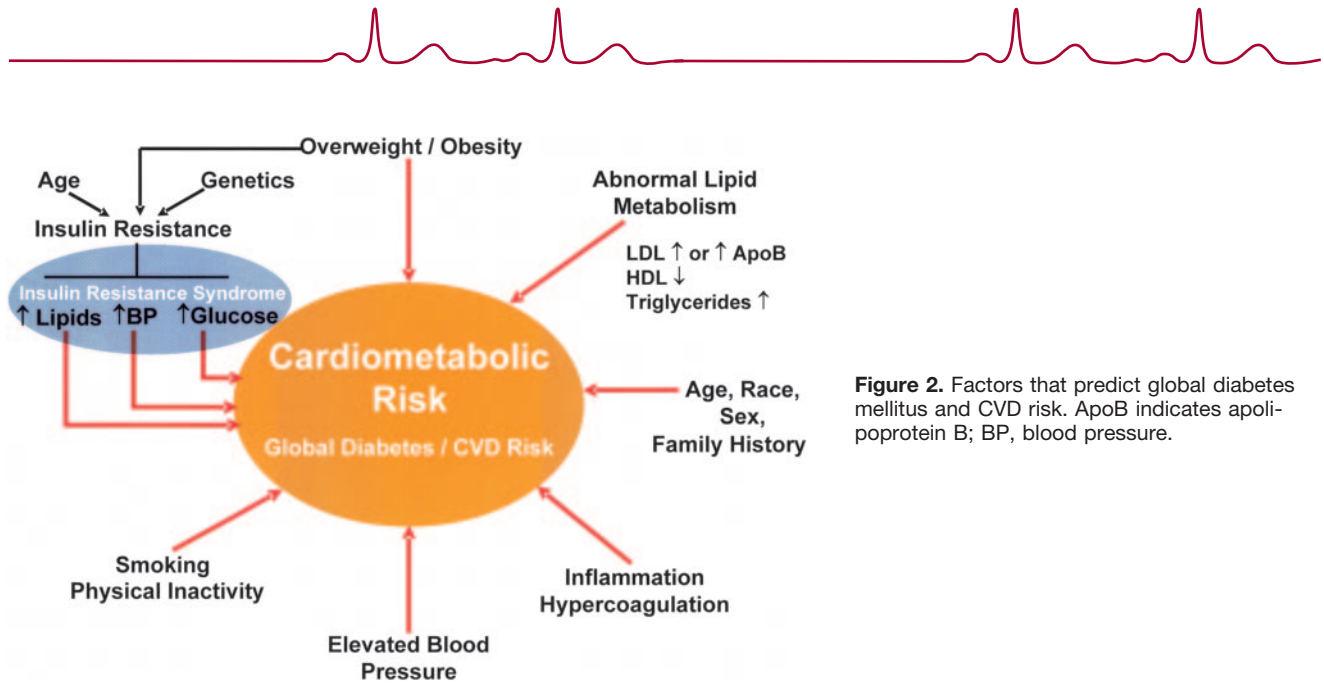


**Figure 1.** Metabolic syndrome and risk of diabetes mellitus or CVD. Relative risk of (A) diabetes mellitus and (B) CVD among participants in the Framingham Offspring Study. G indicates elevated fasting plasma glucose; TG, elevated triglycerides; BP, elevated blood pressure; HDL-C, low high-density lipoprotein cholesterol; and Waist, enlarged waist circumference. Adapted from Wilson et al,<sup>31</sup> with permission of the publisher. Copyright © 2005, The American Heart Association, Inc.

### Does the Diagnosis Trigger a Unique Action?

Proponents of the syndrome suggest that the diagnosis somehow raises awareness of the need to recommend lifestyle modification.<sup>15,19,20</sup> It would seem obvious, however, that all the components of the syndrome occurring alone or in any combination merit such treatment. Moreover, if a patient has hypertension, dyslipidemia, or hyperglycemia, it should be treated. Thus, no treatment of the syndrome exists that is in any fashion different from that for its component parts.

Alternatively, if the label somehow stimulates patients to take action or is somehow useful for patients, it would be helpful for this benefit to be documented, but no such study appears to have been published.<sup>21,26</sup> It would also be remarkable if a mere mention to a patient (“you have the metabolic syndrome”) yielded significant weight loss that was maintained. This accomplishment would be quite impressive given



**Figure 2.** Factors that predict global diabetes mellitus and CVD risk. ApoB indicates apolipoprotein B; BP, blood pressure.

the countless, far more intensive interventions that have failed to achieve such success.

### An Alternative to the Metabolic Syndrome

As reviewed in many articles,<sup>21–26</sup> a number of concerns have been raised about the metabolic syndrome that have yet to be resolved. Chief among the issues are that (1) no unifying cause of the syndrome has been identified, (2) no clear basis exists for the algorithm that defines the construct, (3) the CVD or diabetes risk prediction associated with the syndrome is no greater than the sum of its parts and is no better than various simpler and less expensive alternatives, and (4) treatment of the syndrome is no different from the treatment of each of its components.

These concerns, however, do not in any fashion suggest that clinicians should pay less attention to all the factors that contribute to diabetes mellitus and CVD, particularly overweight/obesity. This mandate was highlighted in a recent call to action from the American Diabetes Association and the American Heart Association.<sup>46</sup> Such cardiometabolic risk factors are depicted in Figure 2. Obesity is a major driving force, both directly increasing cardiometabolic risk and often leading to insulin resistance. Insulin resistance can be an underlying cause of a syndrome that can result in hyperglycemia, dyslipidemia, or hypertension. Conversely, these abnormalities can occur independently of insulin resistance. We have no ability to diagnose the insulin resistance syndrome, because no sensitive and specific method yet exists to do so. Advancing age, family history, and lifestyle factors also increase cardiometabolic risk. All of these factors have been integrated into a well-validated global risk assessment tool, now available at the World Wide Web site [diabetes.org/phd](http://diabetes.org/phd).

### Conclusions

It is time to put aside the metabolic syndrome as a unique disease that has diagnostic value. When the full nature of the

risk factor clustering reflected in the metabolic syndrome concept becomes known and we then understand the underlying pathophysiology, our knowledge may provide instructive information to clinicians. Insulin resistance, in the context of a syndrome, describes much, but not all, of the clustering and could itself have multiple causes. Perhaps to simplify terminology, we should rename the risk factor clustering “Reaven’s syndrome.” At the very least, we would no longer have a term whose usage has been blurred to denote either the concept of risk factor clustering due in part to insulin resistance or a complex clinical construct that denotes a unique disease. In this suggested paradigm, Reaven’s syndrome denotes the concept that, as intended,<sup>5,10</sup> should be a stimulus for much research; it is the often-seen clustering of some of the modifiable cardiometabolic risk factors (see Figure 2) that can be treated clinically.


Thus, clinicians should focus on ascertaining all well-known diabetes mellitus and CVD risk factors, and they should appreciate that the occurrence of one may portend the presence of others. All abnormalities should be treated according to current guidelines, and clinicians should actively counsel patients who are overweight/obese or sedentary.

### Disclosures

None.

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## Response to Kahn

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The major differences in the positions on the metabolic syndrome do not appear to result from the construct's imperfection nor from the call for more investigation into common causes and clinical implications. In fact, possibly no optimal clinical pattern will be identified, because varied genetics produce differing manifestations and risk profiles. The key proponent argument is the value of functionality, targeting the cluster for clinical and academic purposes despite its imperfections. The mere presence of these articles in this journal demonstrates that the controversy has stimulated discussion and forced reflection on imperfections in hopes of refining or resolving them. Arguably, promoting this cluster as a syndrome has stimulated clinicians to treat its components and initiate preventive strategies. The argument against the benefit of the widely recognized syndrome label cannot be substantiated. In the absence of a comparative control group of physicians unaware of the title but aware that individual risk factors need treatment, we will never know the true impact of the clustering as a call to therapeutic action. Regardless of whether the treatment is the same if we target the individual components or a syndrome, and regardless of whether arguing the semantics of "syndrome" versus a "cluster" is valid, the more important goal to keep sight of is optimally stimulating intervention. It remains for the academic community to set evidence-based boundaries on the use of this construct so that actual decisions are based on science and not conjecture. Yet, having the construct as a focus of attention has tremendous value for both clinician and patient and, we argue, also for the academics.