Metabolic syndrome: a critical look from the viewpoints of causal diagrams and statistics

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Introduction

PubMed search for the words “metabolic syndrome” in the title of articles and letters has found 175 publications in 2002, 870 in 2005, and 1,431 in 2007. At the time of this writing, the trend might have reached a plateau, counting about 700 titles by mid 2008. Undoubtedly, the term “metabolic syndrome” has found a place of honor on the pages of scientific and medical journals, but has it also survived numerous attacks by critical minds? I am not so sure. Moreover, it is difficult to recall another example of a newly discovered, prevalent syndrome whose very existence had to be defended, repeatedly.

In this article I analyze the term "metabolic syndrome" from two related viewpoints: causal and statistical. To shed a new light on the debate, I rely on a simple tool called causal diagrams, formally known as directed acyclic graphs (DAG). Causal diagrams encode causal assertions unambiguously; mercilessly expose foggy causal thinking; and create a bridge between causal reality and statistical associations. In epidemiology, for example, causal diagrams proved to be a unified method to explain the key categories of bias: confounding, selection bias, and information bias.

The article is divided into two parts: The first part lays essential theoretical foundation. In the second part I analyze various aspects of the new syndrome.
Part I: Theoretical Foundation

Causal diagrams

The essence is simple. We write down the names of variables and draw arrows to connect them such that each arrow emanates from a cause and points to an effect. For example, “smoking status $\rightarrow$ lung cancer status” encodes the statement *smoking causes lung cancer*. The sequence “weight $\rightarrow$ insulin resistance $\rightarrow$ vital status” encodes the statement *weight affects survival through an intermediary variable called insulin resistance*. “HDL-cholesterol $\leftarrow$ gender $\rightarrow$ hemoglobin” encodes the statement *gender affects both HDL-cholesterol and hemoglobin*. The variables in question may be binary, nominal, ordinal, or continuous, but they must be *variables* and not *values* of variables. For example, formally we should not write “smoking $\rightarrow$ lung cancer” because “smoking” and “lung cancer” are not variables. We may draw arrows, however, to connect “smoking status” or “pack-years of smoking” with “lung cancer status”.

Causal diagrams assume an underlying causal structure, which percolates up to create the familiar statistical associations between variables. For instance, we observe a statistical association between smoking status and incident lung cancer because “smoking status $\rightarrow$ lung cancer status”. Most statistical associations, however, do not reflect the cause-and-effect of interest. One key explanation for observing an association between two variables is their sharing of a common cause. For example, fasting blood glucose and resting blood pressure are associated, at least in part, because weight affects both. And in general: a crude association between two variables contains both the effect of one on the other (if any) and the contribution of their common causes (if any). In causal inquiry, these common causes are called confounders.
Their contribution to the crude association is called confounding.

**Natural variables and derived variables**

Some variables are more natural than others in the sense that “nature has created their values through various causal mechanisms, and we just try to measure those values.” Fasting glucose level and weight may be examples of natural variables (although their *measured* version already contains the influence of human measurement.) Trisomy 21 (present, absent) is another example. At the other extreme we find human-made variables in the sense that “we, rather than nature, are the ultimate reason for their existence.” Body mass index (BMI), for instance, is not a natural variable because we create the content (values) of that variable from the measured version of two natural variables: weight and height. Stated differently, natural variables are measured, whereas their human-made counterparts are *derived* from natural variables (and sometimes from other derived variables.) The derivation could be carried out by an arithmetic expression (BMI=weight/height²) or by conditional statements (If fasting glucose<C, then diabetes status is “no diabetes”; otherwise diabetes is present). There are intermediate kinds of variables as well: “pack-years of smoking” is a natural variable, quantifying lifetime smoking exposure, but we typically derive it from the average number of cigarettes smoked per day and the number of years smoked.

Medicine is rich in human-made, derived variables, many of which originate in continuous variables. Take a measurement of a continuous trait, such as blood pressure, convert the result to a binary or an ordinal variable on the basis of some cutoff point(s), and you have created a human-made variable, perhaps “hypertension status”. Reporting the so-called upper limit of
normal, which is standard practice for many laboratory tests, is another example.

As will be illustrated later, deriving variables usually carries some penalty. Nonetheless, it seems that we can’t do without some of them, for a technical reason. Much of human life consists of categorical decisions—to act one way or another, or not to act—and we try to make those decisions on the basis of external information, which is often inherently continuous. If we wish to use such information, we must derive categorical variables because there is no other practical way to import continuous information into the realm of categorical decisions.

Consider a simple, familiar example: To prescribe an oral hypoglycemic drug to an asymptomatic patient, we rely on the level of blood glucose, which is a continuous variable. We must therefore draw a line between levels that “need treatment” and levels that “do not need treatment”. In other words, we must derive a binary variable (diabetes status) from a continuous trait. Blood pressure and hypertension treatment make up another well-known example, and there are many more. As a side note, it may be interesting to recall countless debates about the right way to chop up a continuous trait. Chopping is sometimes unnecessary and other times—a necessary evil. But it is almost never “right” for at least one reason: no matter where we draw the line, adjacent points on opposite sides of the line are forced to be very different, and that is rarely true, if ever.¹⁸

**Derived variables and causal diagrams**

When we think about cause-and-effect, we usually think about the relation between two natural variables where the values of one affect the values of the other. Set weight to be 300lb, rather
than 150lb, and chances are that fasting blood glucose will rise. But there is no reason to exclude derived variables from the domain of causal connections. In fact, their creation is a form of causation, just like the “creation” of fasting glucose by weight. Set the weight of a 5-foot person to be 300lb, rather than 150lb, and BMI will rise. The rules of causal diagrams, therefore, apply. We encode the expression “BMI=weight/height²” just as we encode any other causal relation between two causes and their common effect: “weight→BMI←height”. Similarly, “fasting glucose level→diabetes status” encodes the derivation of a variable called “diabetes status” according to conditionals about fasting glucose and cutoff points.

Relation of causes to their effect

There is one important empirical difference, however, between causal relations among natural variables and causal relations that involve derived variables. No set of causal variables will enable us to know the fasting glucose level (a natural variable) of any patient, either due to unknown causal variables or because causation is inherently indeterministic. In contrast, we can always tell the patient’s diabetes status (a derived variable) from his or her level of fasting blood glucose because we set up a causal mechanism—the derivation rule—to link the two. Likewise, no set of causal variables will precisely tell us anybody’s weight, but weight and height will precisely determine the value of BMI.

Which leads to the following conclusion: the information that is contained in a derived variable is usually present in the variables from which it was derived. Only under special causal circumstances, such as quadratic dose-response function or interaction, derived variables (U=V² or U=V₁*V₂) might carry new information and thereby predict something above and beyond
their makers. For other kinds of derivation, it is difficult to find theoretical arguments for incremental prediction—much less so for substituting a derived variable for the original information.\textsuperscript{19, 20}

\section*{Part II: Analysis}

\textbf{Deriving “metabolic syndrome status”}

For some writers the metabolic syndrome was discovered; for others it was defined; and for others it was made up of nothing. Technically, however, we should all agree that “metabolic syndrome status” is, undoubtedly, a derived variable. Actually, there are numerous derived variables that claim the title—as many as there are proposed definitions, or more correctly, as many as there are rules of derivation.\textsuperscript{21-28}

Almost every proposed derivation of metabolic syndrome status follows the same format.\textsuperscript{3} Let $V_1, V_2, \ldots, V_n$ denote a set of $n$ continuous variables, either natural or derived. For each variable, decide on a cutoff point and derive a binary variable (0, 1) on the basis of that cutoff point and a conditional. Next, add up the values of these binary variables to derive a summation variable, say, SUM. Finally, derive “metabolic syndrome status” from SUM using a cutoff point and a conditional: if $SUM < k$, then the metabolic syndrome is absent; otherwise, the metabolic syndrome is present.

Figure 1 shows the causal diagram of the process for $n=5$, which is a common number of input
variables for writers about the metabolic syndrome. Moving from left to right along the axis of
time, we find four generations of variables. Almost all of the variables in the first generation are
natural, but all subsequent generations are derived. As we see, the immediate cause of
“metabolic syndrome status” is SUM, whose causes are five derived binary variables.

That someone derived a variable indeed makes it exist, but existence *per se* is not a big
achievement in this case. Derived variables exist in the trivial sense that "we created them from
some other variables". No special insight is needed to follow the process shown in Figure 1: it
requires a group of variables, perhaps a group that has something in common, and a derivation
algorithm. For example, I have just derived a new variable from five other—smoking
intensity, caloric intake, physical activity, total fat intake, and saturated fat intake—and labeled it
the “behavioral syndrome”. All that I did was finding a group of variables that have
something in common (perhaps atherosclerosis-related behaviors). Then, I prescribed a cutoff
point for each one, and decided on a cutoff point for SUM. Moreover, I may even propose to
combine my variables with any set behind the metabolic syndrome, and call the newly derived
variable "behavioral-metabolic syndrome status”.

One matter may, therefore, be settled at this point. Regardless of whether *the one and only*
metabolic syndrome does exist (in some yet unclear sense), what surely exists are many derived
variables that claim the title.1 24 Rather than naming them after organizations that have endorsed
them, it is better to use numerical subscripts to indicate the chronology of the proposed
rules: “metabolic syndrome status1”, “metabolic syndrome status2”, “metabolic syndrome
status3”, and so on. The sequence has no meaningful order other than chronology, and may
continue indefinitely.
Clustering of risk factors

Almost every writer about the metabolic syndrome, whether a proponent or an opponent, mentions the clustering of risk factors as a key feature of the syndrome. For example, a group of proponents writes: "Five risk factors of metabolic origin (atherogenic dyslipidemia, elevated blood pressure, elevated glucose, a prothrombotic state, and a proinflammatory state) commonly cluster together". Likewise, a group of opponents writes: "The term 'metabolic syndrome' refers to a clustering of specific cardiovascular disease (CVD) risk factors..." What is clustering, however? What statistical idea underlies that powerful, emotive word, which invokes a sense of evil forces conspiring to cause harm?

A patient with high blood pressure is more likely to have a high level of blood glucose than a patient with low blood pressure, and a patient with low blood pressure is more likely to have a low level of blood glucose than a patient with high blood pressure. But no one would say that blood pressure and blood glucose cluster or "cluster together". We would say that these traits are correlated or associated. Even if we add a third variable, say plasma triglycerides, which correlates with both, we would still not use the word "cluster" because it is not used in the context of continuous variables. The word is reserved for categorical variables, selectively pointing to one aspect of a well-known statistical idea: association.

Let Binary V₁, Binary V₂,..., Binary Vₙ be a group of binary variables each taking the values of 1 ("bad, high risk") or 0 ("good, low risk"). Clustering is said to exist if patients with a value of 1 on any one variable are more likely to have a value of 1 on all others (than patients with a value of 0 on that variable). If that is the case, however, zero values cluster, too: patients with a
value of 0 on any one variable are more likely to have a value of 0 on all others (than patients with a value of 1 on that variable). Regardless of mechanism, patients who smoke are more likely to drink alcohol than patients who don’t and vice versa (clustering of smoking and drinking). Likewise, patients who don't smoke are more likely to not drink than patients who do and vice versa (clustering of no smoking and no drinking). In short, clustering is a word to describe a group of categorical variables, usually binary, where each variable is associated with all others. Of course, the latter description does not have the rhetorical power of "clustering of risk".

The phrase "clustering of risk" or “clustering of high risk” may be rhetorically helpful, but it is nonetheless poor scientific terminology for several reasons: First, why talk about clustering of one value of variables when the underlying statistical phenomenon is an association between variables? Second, the complement, favorable clustering of the other value ("low risk") is conveniently ignored—hardly an objective representation of statistical reality. Third, there is a better, core description of the phenomenon behind the metabolic syndrome: several natural, continuous variables are associated with each other (for reasons that will be discussed later).

Indeed, opponents of the syndrome have already reduced the "clustering" into common statistical jargon: "...certain 'metabolic' factors tend to associate with each other..."5 Similar, though less clear, expression may also be found in the writing of a proponent: "multiple risk factors that are metabolically interrelated".11 Surprisingly, however, numerous writers from both camps have also adopted a pseudo-statistical idea—that the observed clustering exceeds the clustering that would be expected by chance alone. Although we can estimate the magnitude of an association between variables and perhaps gather evidence against the claim of “no association”, no
statistical computation can tell us how strong of an association is expected by chance alone. (Chance alone could account for any association.) That erroneous idea can probably be traced to prevailing misinterpretation of a $P$-value as "the probability of observing this result by chance alone".

**Possible causal mechanisms behind "clustering"**

Having reduced the "clustering phenomenon" into multiple associations among derived, binary variables, we may now explore the scientific questions of interest: Why Binary V$_1$, Binary V$_2$, ..., Binary V$_5$ are all associated with each other? Which causal mechanisms have created these multiple associations? Why are they "interrelated" or plainly related?

As you may recall, two mechanisms contribute to an association between two variables: 1) one variable causes the other; 2) they both share at least one common cause. (There is a third mechanism, which will be mentioned later.) As we see in Figure 1, the first mechanism does not operate in that diagram: no causal arrow emanates from any binary variable and points to another—and rightly so. The only immediate causes of a derived variable are the variables from which it was derived. We may therefore conclude that the observed associations among the binary variables in Figure 1 must be attributed to their sharing of at least one common cause, which is missing from the figure. The causal diagram in Figure 1 must be incomplete.

Figures 2-4 show minimal causal structures that would create an association between each of the five binary variables behind metabolic syndrome status and the other four. To check the claim, we just need to verify that each pair shares at least one common cause. Indeed, if we pick any
two binary variables and follow their arrows “upstream” to their causes, we will always end up in a common cause. In Figure 2, the common cause is U; in Figure 3 it is U, too (as well as V₄
for the pair Binary V₄ and Binary V₅); and in Figure 4 it is V₁. Notice that in each case, the explanation for the associations among the binary variables has nothing to do with these variables per se; everything happened between natural variables at earlier stages of causation.

According to Figure 2 or Figure 3, one U will explain the “clustering of metabolic risk factors”, and it is not too difficult to name at least two candidates: age and maybe the amount of abdominal fat. As for Figure 4, one of the five continuous variables should assume the role of a common cause of all other. That variable may also be abdominal fat, whenever it is part of the derivation of metabolic syndrome status. The clustering mystery is finally and trivially solved.

Causal structures that cannot cause "clustering"

Figures 5-8 show examples of causal diagrams with no shared cause of all five binary variables. For reasons that are well-established in the theorems of causal diagrams,¹³,¹⁴ these causal structures will not create an association between every pair of the five binary variables. For example, Binary V₃ and Binary V₄ would not be associated in Figure 5; Binary V₂ and Binary V₄ would not be associated in Figure 6; Binary V₃ and Binary V₅ would not be associated in Figure 7; and Binary V₁ and Binary V₅ would not be associated in Figure 8.

Proponents of the metabolic syndrome state that no common cause is needed. Needed for what? No common cause is needed to derive any variable, including a variable called metabolic
syndrome status, but a causal structure with no common cause could not have created that “clustering”, which was the motivation for deriving metabolic syndrome status in the first place. Moreover, we have already realized that at least one common cause does exist (age) and maybe there are others.

**Spurious clustering**

Two variables that do not cause each other, nor share a common cause, may still be associated due to a third, less well-known mechanism called selection bias. In brief, selection bias arises from unnecessary manipulation of a common effect of the variables of interest. For example, two variables that are not associated at all will be associated within at least one stratum of a third variable, if that variable is their common effect. The association we would observe has no interesting causal meaning: it reflects neither cause-and-effect, nor confounding (a common cause).

As shown in Figures 1-8, "metabolic syndrome status" is a common effect of all preceding variables. Therefore, stratifying on this variable might create associations between components of the syndrome among patients who are classified as having the syndrome. Stated in the "clustering" jargon, part of the clustering of metabolic risk factors that we observe among patients who carry the label "metabolic syndrome" is likely spurious, attributable to stratification on the variable we have derived. Therefore, we should never look at the clustering in patients who received the label, or in patients who did not.
"The combined effect is more than the sum"

This loose idea shows up occasionally, usually referring to "summation" versus "multiplication" of the effects of the natural variables from which metabolic syndrome status is derived. The underlying concept is called interaction by statisticians, or effect modification by epidemiologists, and like other methodological topics, it is much deeper and more subtle than is usually appreciated.\textsuperscript{29-32} For example, the phenomenon depends on the scale on which we choose to measure associations and almost always exists on some scale.\textsuperscript{33, 34}

Regardless, the metabolic syndrome is neither the sum nor "more than the sum" of its components. There is no theoretical basis for the claim that deriving a binary variable from five continuous variables will somehow capture their combined effect, or a complex structure of multiplicative or additive interactions among them. Interactions among variables are modeled by interaction terms, not by reducing five continuous variables to one binary variable through cutoff points and derivation rules.

A predictor or a risk factor? Both or neither?

One contentious topic has been the ability of the metabolic syndrome to predict outcomes, or more precisely, the ability of a derived variable called "metabolic syndrome status" to predict outcome status, above and beyond components of the syndrome. Discussing stroke as a possible outcome, one writer has summarized the issue in two questions:\textsuperscript{35} Is the metabolic syndrome a risk factor for stroke? Does metabolic syndrome status help to predict stroke?
Figure 9 is a revision of Figure 2, adding stroke status as an outcome variable. The arrows pointing from V₁, V₂, V₃, V₄, and V₅ to stroke status correspond to prevailing theories: components of the metabolic syndrome are causes of stroke (or risk factors, in another jargon). Notice, however, that no arrow emanates from metabolic syndrome status and points to stroke status, because a derived variable cannot be a cause of a natural variable; it can only be a cause of another derived variable. Therefore, "metabolic syndrome status", in any of its versions, is not a risk factor for stroke. Any association between this variable and any outcome is due to confounding by their common causes—for example by V₁, V₂, V₃, V₄, V₅, and U (Figure 9).

Moreover, even if someone entertains a causal arrow between the two variables³⁵ (which is wrong, in my view), metabolic syndrome status would simply be an intermediary variable on five causal pathways from natural variables to stroke status. All of its "effect" on stroke is already contained in the effects of its causes. In fact, only part of their effects is captured by the metabolic syndrome because each of the five variables is also connected to stroke status through another causal pathway (Fig 9).

The terms "predictor" and "cause" (or "risk factor") are not synonyms, but the syndrome fails the prediction test, too. As we realized earlier, the information carried by a derived variable is usually contained in the variables from which it was derived, except for special causal circumstances. Therefore, metabolic syndrome status should not predict anything above and beyond its makers, as found empirically.³⁶ Components of the metabolic syndrome might predict stroke status better if we model interactions among them, but only a miracle would allow a single derived binary variable to reflect those interactions.
To sum up, a derived variable called metabolic syndrome status is not a risk factor for anything, nor should it predict anything above and beyond its makers, let alone as their substitute. Predictive information is lost at every step of the derivation chain which begins in several continuous natural variables and ends in a single binary variable.

**Circular causation**

The issue of circular causation is minor, but worth explaining, since it might be used to criticize the diagrams I presented here. Causal diagrams are formally called directed *acyclic graphs* because a cycle of causation is not permissible. We may not draw a diagram in which we can make a full cycle along a causal chain, returning to the cause from which we started. Self-causation does not exist because a future effect cannot be a cause of its cause in the past.

Although controversial, some writers raise the possibility of vicious cycles among components of the metabolic syndrome. For example, abdominal fat → insulin resistance → abdominal fat → insulin resistance, and so on. Nonetheless, the second showing of the variables "abdominal fat" and "insulin resistance" in that chain are new variables, and therefore the sequence requires subscripts to denote time-dependent variables: abdominal fat\(_1\) → insulin resistance\(_2\) → abdominal fat\(_3\) → insulin resistance\(_4\), and so on. The so-called circular causation is not circular at all: abdominal fat at time 1 affects insulin resistance at time 2 which affects abdominal fat at time 3, not abdominal fat at time 1. Measurements of time-dependent variables are often taken in longitudinal studies, allowing us to estimate effects in such causal chains.\(^{37}\)
What is a syndrome?

“Thus, if the metabolic syndrome is defined as multiple risk factors that are metabolically interrelated, then the syndrome certainly exists.”  

This argument is linguistically clever: the syndrome exists because it is defined as "multiple risk factors that are metabolically interrelated", which empirically exist. In other words, if something exists and I give it a name, then the name I just gave it exists, too. But the question remains: what is a syndrome?

As might be expected, online dictionaries offer numerous explanatory phrases. Most of the explanations, however, seem to share one key idea: a syndrome is more than a collection of symptoms, signs, or physiological traits—more than "metabolically interrelated" variables. Both dictionaries and common medical usage require that components of a syndrome would "indicate", "characterize", or "be characteristic of" a disease, a medical condition, a particular abnormality, and the like. It is not correlated components per se that make up a syndrome, as implied in the quote above, nor their sharing of a common effect. It is a meaningfully deeper abnormality which has caused them.

Sometimes, that deeper abnormality is a well-established cause of the syndrome (e.g., trisomy 21 behind Down syndrome; HIV infection behind AIDS). Other times the cause is a general pathological descriptor (acute myocardial ischemia behind acute coronary syndrome). In many instances no causal pathway or pathways are known yet, but even then we assume that some "interesting" causal mechanism has generated the syndrome and we hope to discover it some
day. For this reason, we don't call every set of aging related medical conditions, such as dementia, osteoporosis, and atherosclerosis—the "aging syndrome".

This cardinal feature of a syndrome is lacking in the so-called metabolic syndrome. Furthermore, an articulate proponent has stated that the term “does not commit to a particular pathogenesis” (and proposed an ambiguous causal distinction between “underlying causes and exacerbating factors”).11 Theoretically, he would not dump the name even if age alone underlies the associations among the various components. A name is just a name, of course, but the metabolic syndrome seems to propose a new meaning for the term "medical syndrome". Neither the "metabolic syndrome" nor the "behavioral syndrome" I coined earlier fit contemporary meaning of the term.

The metabolic syndrome vis-à-vis the insulin resistance syndrome

The origin of the metabolic syndrome is often traced to the insulin resistance syndrome, which was postulated long ago.38, 39 The idea was both clever and simple: perhaps resistance to the action of insulin is one of the determinants (causes) of several continuous physiological traits, such as glucose tolerance, blood pressure, plasma triglycerides, and HDL-cholesterol. That does not mean, of course, that every patient with unfavorable levels of these variables suffers from insulin resistance, but it does raise the possibility that some patients do. Unlike the metabolic syndrome, the name was not merely a reduction of natural continuous variables to a derived binary variable, nor was it a means for labeling patients. It was a scientific hypothesis to be tested, corroborated, refuted, or perhaps revised.40 If true, we have enriched our understanding of the pathogenesis of several risk factors for cardiovascular disease.
In contrast, deriving the metabolic syndrome variable offers nothing scientifically new—neither fresh insight into pathogenesis nor a new daring hypothesis. Not surprisingly, much of the debate centers on tangential matters: In what sense does the syndrome exist? What should we call it? What are the cutoff points? Whose definition will prevail? How do we promote another "worldwide definition"?21, 28, 41, 42

The merit of the derivation

What is left of the term? Are there any benefits to deriving that binary variable and deciding whether a patient "has it"?

Proponents argue that the label would motivate patients to change risky behaviors and cause doctors to pay greater attention to risk factor modification, certainly a reasonable hypothesis. Opponents argue that labeling would change nothing and that other patients, who missed the labeling, would have a sense of complacency and might do less to change their risk factor profile—another reasonable hypothesis. Unfortunately, it is difficult to imagine a study that would allow us to estimate the net effect.

I might propose two other merit-related questions for which no empirical answer is possible either: First, how many of the 1,431 publications in 2007 that contained the words "metabolic syndrome" in their titles would have been published if the term did not exist? Second, how much less we would have known today?
References

18. Greenland S. Dose-response and trend analysis in epidemiology: alternatives
Figure 1. A directed acyclic graph showing the causal structure behind the variable “metabolic syndrome status”
Figure 2. A directed acyclic graph showing a causal structure that would create an association between every pair of the five binary variables.
Figure 3. A directed acyclic graph showing a causal structure that would create an association between every pair of the five binary variables.
Figure 4. A directed acyclic graph showing a causal structure that would create an association between every pair of the five binary variables.
Figure 5. A directed acyclic graph showing a causal structure that would NOT create an association between every pair of the five binary variables.
Figure 6. A directed acyclic graph showing a causal structure that would NOT create an association between every pair of the five binary variables.
Figure 7. A directed acyclic graph showing a causal structure that would NOT create an association between every pair of the five binary variables.
Figure 8. A directed acyclic graph showing a causal structure that would NOT create an association between every pair of the five binary variables.
Figure 9. A directed acyclic graph showing several causal pathways to stroke status.