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The Metabolic Syndrome: validity and utility of clinical definitions for cardiovascular disease and diabetes risk prediction

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Abstract

The purpose of clinical definitions of the metabolic syndrome is frequently misunderstood. While the metabolic syndrome as a physiological process describes a clustering of numerous age-related metabolic abnormalities that together increase the risk for cardiovascular disease and type 2 diabetes, clinical definitions include obesity which is thought to be a cause rather than a consequence of metabolic disturbance, and several elements that are routinely measured in clinical practice, including high blood pressure, high blood glucose and dyslipidaemia. Obesity is frequently a central player in the development of the metabolic syndrome and should be considered a key component of clinical definitions. Previous clinical definitions have differed in the priority given to obesity. Perhaps more importantly than its role in a clinical definition, however, is obesity in isolation before the hallmarks of metabolic dysfunction that typify the syndrome have developed. This should be treated seriously as an opportunity to prevent the consequences of the global diabetes epidemic now apparent. Clinical definitions were designed to identify a population at high lifetime CVD and type 2 diabetes risk, but in the absence of several major risk factors for each condition, are not optimal risk prediction devices for either. Despite this, the metabolic syndrome has several properties that make it a useful construct, in conjunction with short-term risk prediction algorithms and sound clinical judgement, for the identification of those at high lifetime risk of CVD and diabetes. A recently published consensus definition provides some much needed clarity about
what a clinical definition entails. Even this, however, remains a work in progress until more evidence becomes available, particularly in the area of ethnicity-specific waist cut-points.

**Introduction**

The term “metabolic syndrome” has developed to describe those individuals at increased risk of type 2 diabetes and cardiovascular diseases (CVD) due to the metabolic dysfunction commonly seen in individuals with insulin resistance. Clinical definitions of the metabolic syndrome have been developed in the last two decades, with a primary purpose being to assist in the identification of those at increased diabetes and CVD risk in order to put in place preventive measures that can reduce this risk.(1-5) As clinical constructs, these do not need to include all of the abnormalities associated with the metabolic dysfunction characteristic of the syndrome, and even include central obesity which is more often thought to be a cause rather than a consequence of metabolic dysfunction. Despite evidence supporting their ability to independently predict both type 2 diabetes and CVD, the various clinical definitions of the metabolic syndrome have been the subject of considerable controversy.(6-13) Commentators have questioned their validity and utility for use in clinical practice and as a public health tool because of the existence of multiple competing definitions and because other tools appear to be more useful for the prediction of CVD and type 2 diabetes. With the recent publication of a consensus definition of the metabolic syndrome,(5) it is timely to review the evidence for its use in the prediction of CVD and diabetes risk.

**Issues relating to clinical definitions for the metabolic syndrome**

The recent publication of a consensus statement on the definition of the metabolic syndrome, representing the views of six major organisations and societies, will hopefully prove to be a pivotal point in the development of the metabolic syndrome as a tool for clinical and public health use. (5)
major criticism levelled at the metabolic syndrome has been that multiple competing definitions are at best confusing, and at worst represent a syndrome which nobody knows how to define. The consensus definition (Table 1) represents a compromise of sorts between the previous International Diabetes Federation (IDF)(14) and American Heart Association/National Heart, Lung, and Blood Institute definitions(3). Previously, the only difference between these two commonly used definitions was the structure (any three of five abnormalities constituting a diagnosis for AHA/NHLBI; obesity plus two other abnormalities constituting a diagnosis for IDF), and the cut-points for obesity (lower and ethnicity-specific cut-points used in the IDF definition). The new consensus definition uses the structure of the American definition, with the IDF ethnicity-specific cut-points for obesity incorporated. No compromise was reached on obesity cut-points for Europid populations, however, with the recommendation that either the higher or lower waist circumference cut-points used in the previous definitions can be used based on the practical requirements of local (national) decision making groups. In research studies, results for both sets of cut-points should be reported. It is important to acknowledge that the new definition is an interim statement, with an acknowledgement that further evidence regarding the risk at waist thresholds in different ethnic groups should be taken into account in future iterations. Furthermore, the statement makes the point that both the World Health Organization and the American National Heart, Lung, and Blood Institute (NHLBI) are both re-considering the definition of the metabolic syndrome.(5) It can only be hoped that the present interim consensus statement will influence those organisations to come to an agreed definition.

The stronger link between the metabolic syndrome and type 2 diabetes compared to CVD is related to the composition of the clinical definitions. Of the five components of clinical metabolic syndrome definitions, all are stronger predictors for diabetes than CVD, with obesity and elevated glucose being particularly strong type 2 diabetes risk factors (Figure 1).(15) Impaired fasting glucose (IFG) is such a strong risk factor for diabetes that it has been shown to be the equal of the metabolic syndrome as a whole for prediction of incident diabetes.(16) The fact that the metabolic syndrome is
a far stronger predictor of type 2 diabetes than CVD is therefore unsurprising. Important risk factors for each of type 2 diabetes and CVD are absent (including smoking, age, family history, physical activity levels, LDL cholesterol, diet), meaning that risk prediction devices specific to each condition usually perform better than the metabolic syndrome.(16, 17)

The role of obesity in clinical definitions of the metabolic syndrome

Obesity is frequently cited as being a leading cause of the metabolic syndrome. In a review of the metabolic syndrome after menopause, Lobo commented that the increased prevalence of the metabolic syndrome among women post-menopause is a result chiefly of weight gain and obesity in this group.(18) The major difference between the IDF and AHA/NHLBI metabolic syndrome definitions is the priority given to obesity. In the IDF definition, one cannot be diagnosed without being obese. Critics of this definition will point out that a proportion of individuals with metabolic dysfunction are not obese, and these individuals are therefore excluded from this definition. In reality, however, the majority of individuals meeting the criteria for either the IDF or AHA/NHLBI definitions will also meet the obesity criteria, whether it is a required component or not. In an unpublished observation from the national and population representative Australian AusDiab study,(19) less than three percent of those not diagnosed by the IDF criteria would meet the criteria if obesity were not a required component.

Perhaps the most important point regarding the position of obesity in clinical metabolic syndrome definitions is that obesity is not simply important as a correlate of disease that is already present, but is a warning of the development of future disease. Our own research is in support of this view, demonstrating that central obesity (as measured using waist circumference) precedes the deterioration of the other components of the metabolic syndrome (dyslipidaemia, hyperglycaemia, hypertension and insulin resistance).(20) As a public health tool, obesity in isolation is an important target, as recognised by the Japanese government in their recent announcement of laws that require
the annual measurement of the waistlines of all 40 to 74 year old employees of all Japanese companies and local governments (44% of the entire Japanese population).(21) We have previously highlighted the importance of recognizing obesity in isolation as a significant risk for future metabolic deterioration(22) using the following example:

“A 30-year-old male has a waist circumference of 130 cm (and a body mass index of 35.0 kg/m²) and is therefore markedly obese, but does not (yet) have the hypertension, dyslipidaemia or elevated blood glucose characteristic of the metabolic syndrome.”

Using available risk calculators, this individual is classified as at low risk of both diabetes and coronary heart disease. With an otherwise normal metabolic profile, his risk of developing diabetes over the next 7.5 years, calculated using a diabetes-specific risk engine, is less than five percent.(23) His ten year risk of coronary heart disease is even lower at one percent.(24) The reason for such low levels of calculated risk is largely a result of risk prediction models generally providing only short term risk prediction (i.e. over the next 5-15 years). His lifetime risk, which is substantial purely because of his obesity at such a young age, is not accounted for in such models. Indeed, the ten year risk for coronary heart disease using the Framingham risk algorithm remains low even in those young men with a substantial risk factor burden. Longer term studies clearly show that the obesity-related risk of coronary heart disease morbidity and mortality only becomes fully apparent after many years of follow-up.(25-27) The fact that the case referred to above does not meet the criteria for the metabolic syndrome does not mean that he is at low lifetime risk of adverse outcomes, but rather highlights the importance of recognising that obesity is the important risk factor for the development of metabolic abnormalities well before they actually develop. The optimal time for intervention for such individuals was actually their infancy, childhood and early adulthood when behaviour patterns are becoming established, not when they finally develop the hallmarks of the metabolic syndrome.

As a final note on the importance of obesity, it is also worth acknowledging that a proportion of obese individuals will remain metabolically healthy despite high levels of body fat through their
genetic resilience to obesity-related metabolic complications. Likewise, a small proportion of those who develop metabolic dysfunction will do so despite remaining non-obese.

**The Metabolic syndrome as a tool for prediction of incident type 2 diabetes and CVD**

Numerous studies have quantified the risk for type 2 diabetes and CVD associated with clinical definitions of the metabolic syndrome. A recent meta-analysis of the studies examining risk for incident diabetes showed that for those definitions published prior to the recent consensus statement, the metabolic syndrome conferred a relative risk of between 3.1 and 5.1. (28) A similar meta-analysis focused on CVD showed that the metabolic syndrome is a comparatively poor predictor of CVD (estimated relative risk of 1.7 to 1.9) as well as all-cause mortality (estimated relative risk of 1.2 to 1.4). (29) While clearly a better predictor of diabetes than CVD, it is important to note that diabetes itself is a major risk factor for future CVD, with diabetes conferring a relative risk of between 2 and 4 for CVD (higher in women than men) (30) and some estimates suggesting that half to two thirds of deaths in people with diabetes are due to CVD. (30) Diabetes is considered a risk equivalent to previous coronary heart disease for development of future CVD events. (31) Most studies examining the risk between the metabolic syndrome and CVD are relatively short-term, and do not therefore capture the increase in CVD risk possible through first developing type 2 diabetes. An analysis of total and CVD mortality over a 33 year follow-up showed the metabolic syndrome to be a risk factor independent of other established risk factors, including smoking, hypertension, diabetes and cholesterol. This result may indicate the longer-term prognostic value of the metabolic syndrome for CVD over and above that achieved by short-term global risk calculators. (32) The heterogeneity of the metabolic syndrome is a problem when assessing risk for future diabetes and CVD. The level of risk has been shown to differ depending on what combination of abnormalities are present, (33) meaning that depending on the combination of abnormalities present, the diabetes or CVD risk may be higher or lower than the estimates for the syndrome considered as a whole.
Much of the diabetes risk associated with the metabolic syndrome is due to the presence of “prediabetic” fasting glucose in the definition. It is not at all surprising that a large proportion of those with already elevated glucose levels go on to develop frank diabetes. Research using the Australian AusDiab study and a comparable national study from Mauritius (among an ethnically South Asian and Creole population) have now shown that in fact simple measurement of fasting or 2-hour post load glucose may be at least as predictive of the development of diabetes compared with the metabolic syndrome as a whole.(16, 17) Similarly, the diabetes predicting model developed in the San Antonio Heart study was superior to dichotomous definitions of the metabolic syndrome.(16) A third predictive tool tested in the Australian study was the non-invasive FiNnish Diabetes Risk Score (FINDRISC), which incorporates self report of age, body mass index and waist circumference, physical activity, diet, family history of diabetes and previous diagnosis of elevated glucose levels (but not in the range for diabetes). The metabolic syndrome was found to be somewhat better than this score for identification of those who developed diabetes in this population.(16) This research supports a common criticism of the metabolic syndrome, in that it is no more useful than its collective component parts. A similar conclusion was reached in a Swedish study among a cohort of middle aged men looking at the metabolic syndrome and cardiovascular mortality. In this study, men were tested at ages 50 and 70 years, and followed up for a median of 29 and 9 years respectively for cardiovascular mortality. Unadjusted, the metabolic syndrome was a significant predictor (stronger at age 50 than age 70), however after adjustment for its component parts, this significant association was not seen. In contrast, at age 50, four of the five components of the metabolic syndrome remained significantly associated with CVD death even after adjustment for each other and the metabolic syndrome as a whole. The fifth component, elevated glucose, was only a significant predictor at age 70. These results remained consistent after the exclusion of those with pre-existing disease at baseline. The authors surmise that “if the results of the present study are confirmed in other samples, the metabolic syndrome might be viewed as a clinically handy summary measure of nontraditional risk factors rather than as a strong biological entity.”(34)
The scientific justification of the concept of the metabolic syndrome is that the clustering of abnormalities that it constitutes are actually representative of an underlying and separate metabolic disturbance (which may be insulin resistance, or could be related more to inflammation or obesity, although these hypotheses are not mutually exclusive). It might therefore be assumed that clinical definitions of the metabolic syndrome would identify an additional element of cardiometabolic risk. This assumption, however, does not fully take into account the purpose of clinical definitions of the metabolic syndrome. In fact, they were developed as summary measures that would identify a group of people who exhibit the hallmarks of metabolic dysfunction and would therefore be at increased risk of both type 2 diabetes and CVD, therefore being useful in the clinical setting and as a public health tool. The construction of the metabolic syndrome as a dichotomous (yes/no) diagnosis, with dichotomies also present for each of the constituent abnormalities, and with an absence of numerous type 2 diabetes and CVD risk factors has resulted in a fairly blunt, but still clinically useful definition. It is perhaps not surprising then, or even problematic, that such a definition does not fully capture the underlying risk factor responsible, and represent an independent risk factor.

As has previously been published, even though the metabolic syndrome was not designed as a tool that optimally predicts absolute risk of future CVD and type 2 diabetes, it certainly does identify a population at high future risk of both conditions. If nothing else, the ability to relay to a patient the interconnected nature of the multiple abnormalities for which they are being treated (and the fact that they can all be improved through lifestyle modification) is a useful feature of a clinical metabolic syndrome definition. Used in conjunction with the knowledge that it does not recognize some risk factors for type 2 diabetes, and with the use of other appropriate short-term risk prediction tools, the metabolic syndrome can certainly perform a useful clinical role.
Conclusions

The increase in the prevalence of obesity and the metabolic syndrome since the middle of the twentieth century is threatening to prevent achievement of the millennium development goals, with the increasing global burden of non-communicable diseases being described as the new agenda for global public health.(37) Clinical definitions of the metabolic syndrome, while therefore obviously important, have frequently been criticized for being sub-optimal in their ability to predict the development of type 2 diabetes and CVD. While clearly identifying a group at increased risk of both conditions, evidence suggests that the metabolic syndrome is not independent of its component parts, and is not the most effective predictor of short-term risk due to the absence of several disease-specific risk factors. The mission statement for clinical definitions of metabolic syndrome, however, is to identify those at high lifetime risk of both type 2 diabetes and CVD, and evidence is accumulating that it is highly useful for that purpose. The metabolic syndrome differentiates itself from short-term risk calculators in that it does not include age, and can therefore indicate high risk at any age. Furthermore, its dichotomous nature means it is useful for diagnostic purposes, for calculating the prevalence in a population, and for helping patients understand that the multiple abnormalities they present with are all related (and all potentially modifiable through lifestyle modification). Obesity is central to the concept of the metabolic syndrome, but is considered a cause rather than a symptom. Because obesity is important years before the development of the other abnormalities that together constitute the syndrome, it is important to recognise that obesity in isolation is the important risk factor for future metabolic deterioration. Clinical and public health interventions may be more effective in those who have not yet developed the full metabolic syndrome but are obese. The latest definition of the metabolic syndrome is a useful step forward toward a single, unified definition with a clear mission statement. While not the optimal device for diabetes and CVD risk prediction (none exist), the metabolic syndrome, used in conjunction with other shorter-term risk prediction algorithms and sound clinical judgement, should be considered a
useful tool for the prevention of the serious consequences of diabetes and CVD. Further refinement of the clinical definition (and in particular the obesity cut points it contains), using new evidence relating to the risk of CVD and type 2 diabetes as it becomes available, will further strengthen the concept and utility of the metabolic syndrome.

References


**Table 1.** Consensus criteria for clinical diagnosis of the metabolic syndrome.(5)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Categorical Cut Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference*</td>
<td>Population and country-specific definitions*</td>
</tr>
<tr>
<td>Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)</td>
<td>≥150 mg/dL (1.7 mmol/L)</td>
</tr>
<tr>
<td>Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)</td>
<td>&lt;40 mg/dL (1.0 mmol/L) in males; &lt;50 mg/dL (1.3 mmol/L) in females</td>
</tr>
<tr>
<td>Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)</td>
<td>Systolic ≥130 and/or diastolic ≥85 mm Hg</td>
</tr>
<tr>
<td>Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)</td>
<td>≥100 mg/dL</td>
</tr>
</tbody>
</table>

HDL-C indicates high-density lipoprotein cholesterol

*It is recommended that the IDF cut points be used for non-Europeans and either the IDF of AHA/NHLBI or points used for people of European origin until more data are available. (For a list of current recommended waist circumference in different ethnic groups, see the consensus statement).(5)

†The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High dose *-3 fatty acids presumes high triglycerides.

‡Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.
Table 2. The positives and negatives of the metabolic syndrome for prediction of future diabetes and CVD.

<table>
<thead>
<tr>
<th>Negative aspects of the Metabolic Syndrome for prediction of future diabetes and CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Several major risk factors for both diabetes and CVD not included in clinical definitions</td>
</tr>
<tr>
<td>- Different combinations of abnormalities confer different levels of risk</td>
</tr>
<tr>
<td>- Measurement of glucose alone may be just as good for diabetes risk prediction</td>
</tr>
<tr>
<td>- The metabolic syndrome may not be a risk factor that is independent of its component parts</td>
</tr>
<tr>
<td>- Cut-points for obesity in different ethnic groups not based on sound evidence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Positive aspects of the Metabolic Syndrome for prediction of future diabetes and CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Does not include age, so can identify young people as being at high risk, unlike most risk equations</td>
</tr>
<tr>
<td>- Is dichotomous, so allows measurement of changes in the proportion of a population at high risk over time</td>
</tr>
<tr>
<td>- Is useful for explaining to patients why the component conditions are all linked</td>
</tr>
<tr>
<td>- Is simpler to calculate than a complex risk equation</td>
</tr>
<tr>
<td>- Is related to a 3 to 5 fold greater risk of diabetes, and a 1.7 to 1.9 fold greater risk of CVD</td>
</tr>
<tr>
<td>- May be particularly useful for long-term risk prediction</td>
</tr>
</tbody>
</table>

Figure 1. Relative risk for CVD and diabetes associated with the metabolic syndrome. (Adapted from Wannamethee, 2008)(15)
Figure 2. Relative risk for CHD and diabetes associated with components of the metabolic syndrome. (Adapted from Wannamethee, 2008)(15)