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The Metabolic Syndrome: in need of a global mission statement.

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Aims The value of clinical definitions of the metabolic syndrome has been questioned, with confusion surrounding their intended use and purpose. Our aim was to construct a mission statement that outlines the value of the metabolic syndrome in clinical and public health settings.

Methods Case studies have been used to demonstrate three key points.

Results We argue here for recognition of obesity as being a crucial element within the metabolic syndrome but perhaps even more important before its development. We also contend that the concept does indeed have a role as a risk prediction tool, and that it could provide a useful metric for the scale and progress of the looming global epidemic of diabetes and cardiovascular disease.
**Conclusions** Through appreciation of its purpose, and recognition of both its limitations and those attributes that make it unique and valuable, we believe we have demonstrated here that the metabolic syndrome deserves its place in the global toolbox of diabetes and CVD prevention.

The metabolic syndrome has suffered from a lack of clarity regarding its intended use and raison d’etre. This has led some to question its value in clinical practice and as a public health tool.[1, 2] The major stated rationale for the main definitions of the syndrome is to identify patients at high risk of clinical atherosclerotic disease and type 2 diabetes mellitus in order to institute preventive measures to reduce these risks.[3, 4] In addition, the International Diabetes Federation (IDF) definition of the metabolic syndrome, in particular, was designed to be useful globally in primary as well as specialist care, and in resource poor settings.

Recent reports indicate that even though the metabolic syndrome does independently predict both cardiovascular disease and type 2 diabetes, it is not necessarily the most effective tool for this purpose.[5-8] Doubt about the utility of the syndrome in clinical practice means that it is timely to consider whether the current high level of interest in the metabolic syndrome is misplaced, or if it does indeed deserve an important place in the global fight against diabetes and cardiovascular disease (CVD).

We propose here that the attributes of the metabolic syndrome that make it a potentially valuable global public health tool are the emphasis it places on central obesity (although we contend that this emphasis requires a subtle shift), its ability to identify high risk individuals at a young age and the possibilities provided by its dichotomous structure.
Obesity: important in the metabolic syndrome, more important before the syndrome develops

We will begin our explanation of this view by focusing on obesity and its role in the syndrome.

A thirty year old male has a waist circumference of 130cm (and a BMI of 35kg/m²) and is therefore markedly obese, but doesn’t (yet) have the hypertension, dyslipidaemia or elevated blood glucose characteristic of the metabolic syndrome.

**Q.** What is his risk of diabetes using available calculators?

**A. Low** (using the Finnish diabetes risk score,[9] even if he also does no exercise and never eats fruit or vegetables (but is without a family history of diabetes), his **10 year** diabetes risk is described as only “slightly elevated”. Using the San Antonio Heart study diabetes prediction model,[10] with a fasting plasma glucose of 5.0 mmol/L and normal blood pressure and HDL cholesterol readings, he has a **7.5 year** risk of developing diabetes of <5%)

**Q.** What is his risk of coronary heart disease using available calculators?

**A. Negligible.** (Even with a substantial risk factor burden, **10 year** CHD risk estimates in young men have been shown to remain low.[11] In this case, it is only 1%.[12])

**Q.** Those calculators all estimate only short term risk (10 years or less). Is he at high lifetime risk of these conditions?

**A. Absolutely** (Obesity is a major risk factor for diabetes, and its strong relationship with CHD morbidity and mortality becomes apparent with longer-term followup.[13-15])
Q. Does his low short term risk and the fact that he does not meet the criteria for the metabolic syndrome mean that he does not need to try to reduce his risk?

A. Absolutely not. His extreme obesity at such a young age means a very high lifetime risk of developing the other components of the MetS, and subsequent CHD and diabetes. Indeed, his young age means a longer time at risk and the potential for greater expense, disability and suffering. His childhood and early adulthood were actually the best time to intervene when behaviour is more modifiable. But better late than never.

This example serves to highlight the importance of recognizing that obesity is a risk factor in its own right, and one that can often be present before the appearance of the metabolic syndrome proper.

The emphasis on obesity in a definition of the metabolic syndrome is perhaps less important than acknowledging that obesity is the most important modifiable risk factor before the metabolic syndrome even develops. Our recent research supports this view, demonstrating that central obesity precedes deterioration in each of the components that constitute the metabolic syndrome.[16] As a metaphor, obesity can be thought of as the sea retreating before the tsunami of metabolic syndrome, then diabetes and CVD roll in. The important role of obesity in the metabolic syndrome is as a warning sign for future disease, not as a correlate for disease that is already present. The Japanese government has clearly understood this, recently announcing laws requiring all companies and local governments to measure waistlines of their 40-74 year old employees annually (44% of the entire Japanese population).[17] We suggest that definitions of the metabolic syndrome need to acknowledge this important point, recognising the importance of
obesity in the metabolic syndrome, but placing greater emphasis on the role of obesity before the metabolic syndrome has even developed. Having said this, it is also important to recognize that a sub-population of obese patients may exist who will remain metabolically healthy despite their excess body fat, and who may be protected against obesity-related metabolic complications.[18]

The metabolic syndrome: a CVD and type 2 diabetes risk prediction tool after all

Q. If this young man from our earlier example also had hypertension (systolic BP 150mmHg) and total cholesterol of 6.5mmol/L and met the criteria for the metabolic syndrome, which of the metabolic syndrome or a CVD risk algorithm would identify him as someone at high future CVD risk?

A. His 10 year calculated risk of CHD[12] is still only 1%, and even if he was also a smoker, this would still be less than 10%. By meeting the criteria for the metabolic syndrome, however, this individual is clearly identified as someone at high lifetime risk of CVD and diabetes. Indeed, Sundstrom et al. recently demonstrated the long term value of the metabolic syndrome in predicting total and cardiovascular mortality independently of age, smoking, diabetes, hypertension and cholesterol.[19]

Because of the influence of age in risk prediction models and the fact that they only predict short term risk, the importance of risk factors such as obesity in younger people is often ignored. The opportunity for preventive intervention is ripe well before most people will qualify as “high risk” on risk prediction models, which are often difficult to use and interpret.[20] It is the high lifetime risk which is more important than the comparatively low 10 year risk. The absence of an age criterion in definitions of the metabolic
syndrome, while reducing its overall predictive ability, means that it goes some way to recognizing that those with signs of serious metabolic deterioration at a young age are at very high lifetime risk of diabetes and CVD.

It has now become clear that the metabolic syndrome is not the best predictor of global cardiovascular or diabetes risk and misses those persons whose risk is not mediated by metabolic syndrome parameters.[21, 22] For these reasons, and because clinical definitions do not acknowledge increasing numbers or severity of components as an even greater risk, the arguments we have made for the value of the syndrome need to be kept in context. In isolation, the metabolic syndrome is an imperfect tool for the identification of those at high risk of future CHD or diabetes. In combination with the knowledge that other risk factors for these conditions are also important, and used in combination with good clinical judgment and other appropriate tools, the metabolic syndrome does, however, have an important clinical function. It highlights the role obesity often plays in metabolic deterioration. It can help patients understand the inter-related nature of the syndrome’s components and finally, when present it suggests the need for intensive intervention to prevent diabetes and CVD. Just as measurement of obesity in itself is not the optimal tool for CHD or diabetes risk prediction, neither is the metabolic syndrome (or any other risk prediction device). Each, however, has characteristics that make them important clinical and public health tools.

**The metabolic syndrome: more than just risk prediction**

We conclude by suggesting that the debate surrounding the metabolic syndrome’s risk prediction qualities has meant that other important features of the syndrome have been ignored. We demonstrate the public health value of the metabolic syndrome by answering some of the key questions relating to its mission statement, and by suggesting an alternative perspective on the utility of the concept.
Q. Was the metabolic syndrome designed to be the optimal short to medium term risk prediction device for CVD or diabetes?

A. No, as we discussed earlier, it is obvious that other risk factors specific to these two conditions (as well as age and sex) would be required to determine risk optimally. It is important to acknowledge, however, that all available risk prediction devices have flaws and none can be used as the sole basis for clinical decisions. The metabolic syndrome as currently defined was never intended as an absolute risk indicator – rather as an early warning system.

Q. Does a diagnosis of the metabolic syndrome actually identify a population at high risk of CVD and diabetes?

A. Yes, as has been repeatedly shown.[23]

Q. Other than predicting absolute CVD and type 2 diabetes risk (for which it, as well as all other available risk prediction devices, are imperfect), are there other features of the metabolic syndrome that provide further value?

A. We contend that in addition to the important clinical attributes identified earlier, an under-recognised use for the metabolic syndrome is a global metric that identifies a looming epidemic of CVD and diabetes.

Q. How will the coming global diabetes epidemic (most of which will occur in developing countries)[24] and the resultant CVD be prevented?

A. Identification of those at high short term risk of diabetes and CVD and intensive medical intervention can only be a small part of the solution, particularly in developing countries. Population level lifestyle modification requires a big picture approach that addresses the structural and environmental causes of an obesogenic environment and is reliant on support of all levels of government, the public as well as health care providers.
We explain below how the metabolic syndrome helps each of these stakeholders do just this.

Two pieces of information that will help any country appreciate the urgency of implementing measures to prevent diabetes and CVD, and chart their progress toward that aim, are the prevalence of obesity (the warning of a tsunami to come), and the prevalence of the metabolic syndrome (how much of the tsunami has already arrived). As a metric, the metabolic syndrome allows comparisons of the scale of the tsunami both between countries (at least those of similar ethnicity) and across time, with all of its elements being modifiable through lifestyle alteration. Although often under-appreciated, quantifying the magnitude of a problem and how it changes over time is crucial for public and political awareness, and to inform funding decisions and preventive measures. Over the previous few decades, tracking the trends in smoking, hypertension and cholesterol might have been a good way of predicting future changes in CVD. As the importance of CVD risk factors shifts to metabolic abnormalities and obesity, the metabolic syndrome may have a valuable role to play in predicting future disease burden, and one that cannot be filled by other risk prediction models.

In conclusion, the metabolic syndrome was not designed to be a tool that optimally predicts absolute risk of future CVD and type 2 diabetes. It is clear, however, that those with the metabolic syndrome do constitute a population at high risk of both. We have demonstrated here that a diagnosis of the metabolic syndrome can add valuable information regarding future risk, particularly among the young, and should therefore be seen as an additional device in the toolbox of diabetes and CVD prevention. As a metric allowing comparison of the scale of an impending epidemic between countries or
population groups and across time, the metabolic syndrome differentiates itself as a unique tool for the global prevention of diabetes and CVD. The emphasis on central obesity in the metabolic syndrome should be as a pre-cursor to the development of the syndrome itself, not as a correlate for disease that is already present, with lifestyle intervention being important as soon as obesity is present, particularly in the young.

To build on the considerable awareness of the metabolic syndrome and achieve the potential we have identified, a single global definition (with appropriate consideration of ethnic differences) is imperative. By ensuring that obesity is recognised as an important warning sign before the metabolic syndrome even appears, and recognising and appreciating those attributes that make the concept unique and valuable, the metabolic syndrome should be a much needed tool in the campaign to prevent the devastating consequences of a global diabetes and CVD epidemic.

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References


