

The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation

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Abstract This article presents the conclusions of a WHO Expert Consultation that evaluated the utility of the ‘metabolic syndrome’ concept in relation to four key areas: pathophysiology, epidemiology, clinical work and public

health. The metabolic syndrome is a concept that focuses attention on complex multifactorial health problems. While it may be considered useful as an educational concept, it has limited practical utility as a diagnostic or management

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tool. Further efforts to redefine it are inappropriate in the light of current knowledge and understanding, and there is limited utility in epidemiological studies in which different definitions of the metabolic syndrome are compared. Metabolic syndrome is a pre-morbid condition rather than a clinical diagnosis, and should thus exclude individuals with established diabetes or known cardiovascular disease (CVD). Future research should focus on: (1) further elucidation of common metabolic pathways underlying the development of diabetes and CVD, including those clustering within the metabolic syndrome; (2) early-life determinants of metabolic risk; (3) developing and evaluating context-specific strategies for identifying and reducing CVD and diabetes risk, based on available resources; and (4) developing and evaluating population-based prevention strategies.

Abbreviations

ATP III	National Cholesterol Education Program Adult Treatment Panel III
CVD	Cardiovascular disease
IDF	International Diabetes Federation
NCD	Non-communicable disease

Introduction

Diabetes and cardiovascular disease (CVD) are, together with cancer and chronic respiratory disease, the world's biggest killers, causing an estimated 35 million deaths each year, 80% of which are in low- and middle-income countries [1]. Cost-effective strategies exist to control this growing burden, but non-communicable disease (NCD) programmes are drastically underfunded at the national and global levels, and prevention does not feature among current Millennium Development Goals [2]. The WHO recently developed an Action Plan for implementing the Global Strategy for the Prevention and Control of NCDs [1]. One of the objectives of this plan is to develop simple strategies to identify those at high risk, together with appropriate and cost-effective interventions. The metabolic syndrome has been advocated as both a simple clinical tool for predicting diabetes and CVD, and the conceptual basis for understanding at least part of the pathophysiological link between metabolic risk, future diabetes and CVD. This position paper examines the concept of the metabolic syndrome and considers its utility in the prevention and control of major NCDs.

The clustering of metabolic risk factors with CVD and diabetes has been recognised for more than 80 years, but the modern concept of the metabolic syndrome began when

Reaven proposed a conceptual framework which linked apparently unrelated biological events into a single pathophysiological construct [3]. This hypothesis argued that insulin resistance provided a common mechanism underlying the associated abnormalities of blood pressure, HDL-cholesterol, triacylglycerol and glucose tolerance. This pathophysiological concept was not intended for clinical or epidemiological use. Subsequently, a number of different definitions have been developed for this purpose by the WHO [4], the National Cholesterol Education Program Adult Treatment Panel III (ATP III) [5], the European Group for the Study of Insulin Resistance [6] and, most recently, the International Diabetes Federation (IDF) [7]. These definitions include the risk factors listed above, with the addition of (central) obesity, but rank them differently in order of importance and have sometimes used different cut-off points for the individual risk factors. More recently, the IDF and the modified ATP III definitions have become more concordant, with the remaining difference pertaining to waist measurement [8].

The rationale supporting use of the metabolic syndrome includes the following: (1) it provides a framework for research exploring a possible unifying pathophysiological basis for the observed cluster of risk factors; (2) it quantifies chronic disease risk within populations and facilitates between-country comparisons; (3) it can guide relative risk prediction and clinical management decisions; and (4) it provides an easily comprehensible public health message and reminds health professionals of the need to assess related risk factors when one risk factor is detected. Critics of the concept have pointed out that, despite an exponential increase in the number of research papers on the subject, no single unifying pathophysiological mechanism has been agreed, and the equivalence of the risk factors and their cut-off points across different populations has not been established [9]. The criteria used to diagnose the metabolic syndrome have major limitations including: the dichotomisation of risk factors; the attribution of relative as opposed to absolute risk; the differing predictive value of risk factor combinations; the inclusion of individuals with established diabetes and heart disease; and the omission of important risk factors for predicting diabetes and CVD. A formal diagnosis of the metabolic syndrome is rarely made in routine clinical practice, and the concept has not been widely adopted in national guidelines for the prediction of CVD or diabetes.

In summary, the metabolic syndrome is a widely recognised concept which focuses attention on important complex multifactorial health problems. While the concept has advantages in terms of professional and public education and awareness, critics argue that it has limitations and that its clinical utility has been over-interpreted. In light of this, a WHO Expert Consultation was undertaken in

November 2008 to review the concept and its utility in relation to four key areas: pathophysiology, epidemiology, clinical work and public health.

Pathophysiology

The pathogenesis of the clustering of risk factors referred to as the metabolic syndrome and its constituent elements remains unclear [10]. There is no accepted central underlying mechanism, although insulin resistance [3] and central obesity [11] have both been proposed in this role. Other central or contributory mechanisms that have been considered include: chronic activation of the immune system; disorders of the hypothalamic–pituitary–adrenal axis; altered glucocorticoid hormone action; chronic stress; and the contributions of cytokines, hormones and other molecules produced by adipocytes [10, 12]. Prenatal and early-life influences might play a role [13], as may multiple gene combinations [14], possibly explaining why current definitions encompass heterogeneous phenotypes in different ethnic groups.

In the absence of a clear mechanism, interim definitions of the metabolic syndrome can only be considered provisional rather than definitive. Furthermore, given that recent research has shown a link between metabolic syndrome and other clinical conditions including liver disease [15], sleep apnoea [16] and cancer [17], it is clear that our understanding of this complex set of risk factors is limited, and that further research is needed.

Epidemiology

A considerable amount of research has been undertaken to define the epidemiology of the metabolic syndrome in different populations, and it has identified wide variations in the prevalence of metabolic syndrome between the sexes and in different countries and ethnic groups [18]. The condition has strong lifestyle determinants, which are in turn influenced by socioeconomic status, cultural habits and country-specific educational opportunities. Metabolic syndrome has become increasingly common in many populations, particularly in the developing world, and has a changing phenotype, with an increasing prevalence in younger age groups [19, 20]. The existence of different definitions has, however, led to confusion when comparing prevalence figures and impact. Although the components of the two main versions of the metabolic syndrome are the same [5, 7], the specific weighting for those components that define an abnormality differs, and the manner in which they can be combined to make a positive diagnosis varies from version to version [21] (although this has recently

been resolved [8]). While there is agreement on four of the central components of metabolic syndrome and conformity in the measures used to define them, there is disagreement regarding the waist circumference to be used and how this should be adjusted for use in different ethnic groups. Similarly, while prevalence estimates reached by the different definitions in a single population are often similar, there are important differences between the subpopulations which are identified as having metabolic syndrome [22, 23] and rates vary from one ethnic group to another. The implications of these findings thus remain uncertain.

While the concept of the metabolic syndrome reminds us that NCDs are multifactorial in origin, the ability of the metabolic syndrome criteria to quantify CVD and diabetes risk within a population and facilitate between-country comparisons is limited. Given the confusion surrounding different past definitions of the metabolic syndrome and the different high-risk groups identified, we suggest that it is time to call a halt to studies in which different definitions of the metabolic syndrome are compared. Consistent use of a single definition worldwide would make global comparisons of metabolic risk more meaningful. Currently, however, there is little firm basis for such a definition. We therefore suggest that research efforts focus on elucidating the mechanisms underlying the clustering of metabolic risk factors, diabetes and CVD, and developing preventive strategies, rather than on developing new or revised definitions.

Clinical work

The metabolic syndrome has been proposed as a means of identifying people at increased risk of CVD and diabetes and to guide clinical management decisions. It has been shown to predict CVD morbidity, CVD mortality, type 2 diabetes and all-cause mortality in a number of populations worldwide [12]. Risk estimates differ according to the definition used and the population subgroup to which the definition is applied. They are usually modest for the association between metabolic syndrome and CVD, and stronger for the association between metabolic syndrome and type 2 diabetes [12, 24]. Metabolic syndrome criteria are, however, outperformed by traditional cardiovascular risk prediction algorithms, such as Framingham [25], and do not enhance risk prediction [22, 24]. This is unsurprising as the metabolic syndrome can only indicate relative risk. Similarly, the metabolic syndrome confers an elevated risk of incident diabetes, but not more than some of its individual components: e.g. fasting glucose conveys a greater risk of incident diabetes than the metabolic syndrome [26]. This has led critics to argue that the constellation of risk factors for the metabolic syndrome does not offer more than the sum of its parts in terms of

diagnosis and management [9]. Furthermore, current definitions are not very discriminating, and from 10% to almost half of the world's adult population will be identified as having the metabolic syndrome depending on which definition is used [22]. Finally, the clinical utility of the metabolic syndrome is confused by the existence of different definitions which identify different risk populations [22].

The construct of the metabolic syndrome diagnostic criteria has inherent limitations which impact on its clinical usefulness. Six are described below.

Dichotomisation of the diagnosis of metabolic syndrome and of risk factors used to define metabolic syndrome Dichotomisation is a common feature of diagnostic criteria for many diseases, including diabetes, and was employed in the metabolic syndrome for ease of use in primary care. However, the use of discrete thresholds to define abnormalities is artificial and discards crucial information about the magnitude of the risk factors [22]. The association of risk factors such as blood pressure and cholesterol with CVD is continuous and does not show any point at which risk clearly increases. Furthermore, the summation of components into a unitary diagnosis assumes that each dichotomised risk factor carries the same risk, yet some factors included in each definition are more strongly predictive of CVD than others.

Omission of established risk factors The metabolic syndrome does not include other important risk factors for predicting diabetes or CVD, such as age, sex, family history, socioeconomic status, ethnicity, current treatment, previous CVD events and LDL-cholesterol, or important behavioural variables such as smoking and physical activity.

Metabolic syndrome describes relative risk as opposed to absolute risk An individual's risk of developing diabetes or CVD is related to baseline risk. For example, a fourfold increase in relative risk in an individual with low baseline risk is likely to be less relevant than a twofold increase in absolute risk in an individual with high baseline risk. As such, absolute risk is a more useful measure in clinical practice. It should be noted that metabolic syndrome was not intended for use as an absolute risk predictor but rather as an indicator of relative risk.

Heterogeneity among individuals diagnosed with the metabolic syndrome There are 16 different ways to diagnose the metabolic syndrome using the ATP III definition and eleven different ways to diagnose the metabolic syndrome using the IDF definition. As such, there is inter-individual heterogeneity of the risk-factor components on

which a diagnosis of metabolic syndrome is made, and each combination identifies a different risk population [23].

Cardiovascular risk varies according to the risk factor combination used to diagnose metabolic syndrome in an individual The risk of CVD and diabetes is not equivalent across the different risk factor combinations which constitute a metabolic syndrome diagnosis [27]. This phenomenon is linked to the fact that although we often observe a clustering of risk factors, each component has multiple causes, some of which do not involve the metabolic syndrome but still increase risk for diabetes and CVD.

Defining obesity within metabolic syndrome criteria The IDF definition uses waist circumference as a useful criterion and entry point for further risk assessment, though there have been difficulties establishing ethnic-specific cut-off points. However, measurement of BMI and waist circumference often provide comparable estimates of the relationship between degree of adiposity and CVD risk [28], and each may make independent contributions in this regard [29]. Consequently, either measurement can provide a simple approach to identifying individuals at risk for developing the component parts of the metabolic syndrome that contribute to CVD risk.

The metabolic syndrome has not generally been adopted by national guidelines for the prediction of CVD or diabetes. Furthermore, a formal diagnosis of metabolic syndrome using any of the current definitions is rarely made in routine clinical practice, and the syndrome does not demand a specific treatment. There are currently no therapies—other than lifestyle modification—that specifically address the cluster of metabolic syndrome risk factors, and each individual risk factor requires separate treatment. Consequently, we emphasise that metabolic syndrome is a pre-morbid condition rather than a clinical diagnosis, and should thus exclude individuals with established diabetes or known cardiovascular disease. Although metabolic syndrome can predict diabetes and CVD, the construct was never intended for use as a detailed risk predictor, and there are other tools available which provide a measure of absolute risk within defined populations. In resource-poor settings, the use of WHO risk charts could be useful to inform risk stratification [30]. More developed health settings can adopt a pragmatic stepwise approach to risk stratification, where routine data or simple questionnaires are used to identify those at increased risk (without the need for laboratory measures). Individuals identified could then be invited for a short health assessment, including blood sampling, where absolute CVD risk can be quantified and appropriate preventive strategies recommended. As health information systems evolve, more sophisticated tools could be developed for risk stratification.

Public health

While there is very little research directly addressing the impact of metabolic syndrome on public health and/or health promotion activities, the introduction of the concept and the consequent surge of interest in the syndrome have stimulated valuable thinking and research across different disciplines [22]. Anecdotal evidence suggests that the metabolic syndrome concept has: (1) provided an easily comprehensible public health message; (2) educated health professionals on the importance of risk factor clustering and the need to assess related risk factors when one risk factor is detected; and (3) encouraged health professionals not to focus simply on diabetes or CVD. In Japan, for example, the Government recently introduced a national screening programme using the metabolic syndrome concept as a single point of entry to identify people at high risk who might benefit from an intervention to reduce CVD risk [31]. However, while many patients and practitioners still need educating on the multifactorial nature of NCDs, the same prevention and management strategies are recommended for both metabolic syndrome and its constituent parts (e.g. a healthy diet, regular physical activity, smoking cessation and weight loss/control, plus pharmacological intervention where necessary). Consequently, unless currently used in national or local public health campaigns, we do not encourage further introduction of the metabolic syndrome concept.

Effective lifestyle and pharmaceutical approaches to the prevention of diabetes and CVD in high-risk individuals are well established [32–35]. Each country should aim to develop context-specific policies for the identification and reduction of diabetes and CVD risk, based on the resources available. Although the cost-effectiveness of interventions to prevent and control non-communicable diseases remains unclear, a full range of options should be considered, including lifestyle modification and high-quality low-cost generic medications. While the metabolic syndrome and related risk stratification approaches focus attention on individuals at high risk of future disease, the importance of population-based prevention strategies should not be overlooked.

Conclusions

The metabolic syndrome is a concept that focuses attention on complex multifactorial health problems. While it may be considered useful as an educational concept, it has limited practical utility as a diagnostic or management tool. Further efforts to redefine it are inappropriate in the light of current knowledge and understanding, and epidemiological studies

in which different definitions of the metabolic syndrome are compared are of limited utility.

The metabolic syndrome should be considered a pre-morbid condition and should thus exclude individuals with established diabetes or known cardiovascular disease.

Metabolic syndrome should not be applied as a clinical diagnosis.

Each country should aim to develop cost-effective context-specific identification and reduction strategies for diabetes and CVD risk, based on available resources. These should be complemented with population-based prevention strategies focusing on the control and reduction of behavioural and metabolic risk factors by targeting their key determinants.

Future research should focus on: (1) further elucidation of common metabolic pathways underlying the development of diabetes and CVD, including those clustering within the metabolic syndrome; (2) early-life determinants of metabolic risk; (3) developing and evaluating context-specific identification and reduction strategies for diabetes and CVD risk, based on available resources; and (4) developing and evaluating population-based prevention strategies.

The consultation

The experts for the consultation were invited on the basis of their published work on the metabolic syndrome, with an attempt to ensure participation from all six WHO regions, to balance the sex distribution and represent different approaches of the authoritative national and international bodies. The conclusions were unanimously accepted by the participants. The list of experts invited to participate in the consultation is presented in Electronic supplementary material (ESM) Table 1.

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