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Cardiometabolic Syndrome

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1. Introduction

The term "Metabolic Syndrome" is generally used to indicate a clinical entity of substantial heterogeneity, represented by the co-occurrence of hypertension, impaired glucose tolerance, atherogenic dyslipidemia, central fat accumulation, insulin resistance, as well as prothrombotic and inflammatory states[1]. This multiple metabolic and cardiovascular disorders clusters together in the same individual more often than might be expected by chance, leading to an increased probability of suffering from cardiovascular disease and type 2 diabetes mellitus[2], [3].

Notwithstanding the controversial concept[4], data from large prospective population-based studies, such as the Framingham offspring study[5], the Botnia study[2], the Kuopio Ischemic heart Disease study[3], the Italian study [6], and the Atherosclerosis Risk in Communities (ARIC) study[7], [8], confirmed that the presence of the metabolic syndrome was significantly associated with an increased risk of cardiovascular disease morbidity and mortality, thus providing substantial support for the metabolic syndrome hypothesis[1]. One important justification cited for the utility of the syndrome is that it changed medical perspective from a single-risk factor to the multiple-risk factors paradigm [9], [10].

During the last decade, this multiplex cardiometabolic disorder has progressively become a major worldwide public health problems, because of its association with increased risk of type 2 diabetes mellitus, atherosclerotic cardiovascular disease and all-cause mortality[2], [3], [1]. More than 100 million individuals suffer from this syndrome in the world. this number is set to increase rapidly, fuelled by the increase in obesity and diabetes epidemics[11]. The pathogenesis of the metabolic syndrome is complex and so far incompletely understood but the interaction of obesity, sedentary lifestyle, dietary, environmental and genetic factors are known to contribute to its development[12], [13], [14].

This chapter constitutes a review of the state-of-the-art of the metabolic syndrome, as regards the historical evolution of the concept, the debated key points and the evolution towards a new concept of global cardiometabolic risk. The last section provides an overview of the worldwide epidemiology of the metabolic syndrome, in terms of prevalence variation and determinants.

2. Historical evolution of the metabolic syndrome concept

Regardless of the disagreement about who first described the metabolic syndrome in the medical literature, its basic concept existed for at least 80 years[15]. According to a group of researchers[11], the constellation of metabolic disturbances was initially described in 1920s by Kylin, and later by Vague in 1947. The latter drew the attention to upper body adiposity (android or male-type obesity), as a metabolic abnormality commonly associated with type 2 diabetes and cardiovascular disease [16,17]. However, the frequent simultaneous presence of obesity, hypertension, diabetes and hyperlipidemia was described in 1965 by Avogaro et al, and then by Haller et al in 1977, who described their association with atherosclerosis[11].

Ten years later, the clinical importance of the syndrome was highlighted by Reaven who introduced the concept of Syndrome X, as a clustering of disturbances in glucose and insulin metabolism, dyslipidemia and hypertension. Reaven suggested that insulin resistance was a fundamental "disorder" associated with a set of metabolic abnormalities which not only increased the risk of type 2 diabetes but also contributed to the development of cardiovascular disease before the appearance of hyperglycemia. He emphasized that insulin resistance was at the centre of a cluster of metabolic abnormalities, which include hypertriglyceridemia, low high-density lipoprotein (LDL) cholesterol level, increased glycemia, and elevated blood pressure[13].

Following this early conceptual contribution, numerous studies have confirmed that insulin resistance was indeed associated with metabolic abnormalities that increase the risk of both diabetes and cardiovascular disease [18,19]. Syndrome X was also called Reaven's Syndrome, Insulin Resistance Syndrome, deadly quartet, and is now widely known as metabolic syndrome. A later key conceptual advance was the recognition of the central role of abdominal obesity [20] in the diagnosis of the metabolic syndrome, and its introduction as a clinically easy-measurable entity. This second hallmark put the abdominal obesity on the front line to diagnose the metabolic syndrome.

3. Debated key points

After a plethora of international publications, the metabolic syndrome concept is still ill-defined with many unanswered questions[11], [21]. So far, evidence-based outcomes concerning the components and cut-off values are limited and based principally on expert consensus[22].

3.1 Diversity of definitions

During the last decade, several definitions of the metabolic syndrome were suggested by a number of expert groups. Although these definitions were similar in their focus on basic criteria as obesity, dyslipidemia, hyperglycemia, and hypertension, substantial differences remained concerning the insulin resistance.

3.1.1 WHO definition

In an attempt to provide a tool for clinicians and researchers, the "WHO Working Group on Diabetes" proposed a set of criteria to define the metabolic syndrome [23]. The consensus was published on the WHO website in 1999, but reported clearly that the definition would be

modified as new information became available about the components and their predictive power. The WHO definition, stated that diabetes type 2 or impaired glucose tolerance (IGT), together with at least 2 of 4 other factors (hypertension, hyperlipidemia, obesity and microalbuminuria) define the metabolic syndrome. In case of normal glucose tolerance, the evidence of insulin resistance is needed; this is defined as the lowest quartile of measures of insulin sensitivity. The definition of obesity is based either on overall obesity assessed by body mass index (BMI), or on central obesity assessed by waist-to-hip ratio (WHR)[23] (Table 1).

WHO definition of the metabolic syndrome 1999[23]
Glucose intolerance, Impaired Glucose Tolerance (IGT) or Diabetes mellitus and/or insulin resistance together with two or more of the following criteria listed below:
1. Obesity: BMI > 30 kg/m^2 and / or Waist-to-hip ratio > 90 cm in men or > 85 cm in women
2. Dyslipidaemia: serum triglycerides ≥ 150 mg/dl and/or HDL-C < 35 mg/dl in men and < 39 mg/dl in women
3. Urinary albumin excretion rate ≥ 20 μg/min or albumin: creatinine ratio ≥ 30 mg/g
4. Hypertension: Blood pressure ≥ 140/90 mmHg

Table 1. WHO definition of the metabolic syndrome 1999

The potential disadvantage of the WHO criteria is that special testing of glucose status, beyond routine clinical assessment, is necessary to diagnose the metabolic syndrome, for example: oral glucose tolerance test (OGTT) and insulin resistance measurement by hyperinsulinemic euglycemic clamp. Since insulin clamp evaluation was impractical, most epidemiological studies used hyperinsulinemia as a surrogate for insulin resistance[24], [3]. Another weak point was related to the non-reliable measurement of obesity by the BMI, especially in the elderly, due to the changes in height with advancing age compared to younger adults[25]. In addition, for any given BMI tertile, subjects in the top waist tertile had a worse risk factor profile than individuals with the same BMI but with lower waist circumference measures, meaning that the BMI and waist circumference did not predict the risk of metabolic disturbances equally[11]. The greater truncal adipose tissue was distinguished as the real risk factor for the metabolic syndrome [25]. Moreover, the frequency of microalbuminuria in non-diabetic individuals is very low and, therefore, this criterion was relevant only in the presence of diabetes[11].

3.1.2 EGIR definition

In 1999, the European Group for the Study of Insulin Resistance (EGIR) proposed an alternative definition[26], which was called the insulin resistance syndrome. While the WHO definition required an evaluation of insulin resistance under euglycemic hyperinsulinemic conditions and was applied alike to diabetic and non-diabetic subjects, the EGIR definition excluded the diabetic population and relied on fasting insulin as a surrogate marker of insulin resistance. The EGIR definition retained insulin resistance, as an essential component and major etiological determinant of the metabolic syndrome. However, waist circumference was used as surrogate for obesity measured by the BMI; this represented a major deviation in the conceptual development of the metabolic syndrome. In addition, the impaired glucose tolerance was not necessary for the recognition of the metabolic syndrome (Table 2).

EGIR definition of the metabolic syndrome1999[27]
Hyperinsulinaemia defined as fasting insulin concentration above the upper quartile for the non-diabetic subjects* (age and sexes combined) in addition to two or more of the following components:
1. Central obesity: waist circumference ≥ 94 cm in men or ≥ 80 cm in women
2. Dyslipidemia: serum triglycerides (TG) >180 mg/dl and/or HDL-C < 40 mg/dl and/or drug treatment for dyslipidemia
3. Hypertension: systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg and/or drug treatment for hypertension
4. Fasting plasma glucose ≥ 110 mg/dL,
* The EGIR insulin resistance syndrome was defined only for non-diabetic subjects.

Table 2. EGIR definition of the metabolic syndrome1999

3.1.3 NCEP-ATPIII definitions

Two years later, the National Education Program's Adult Treatment Panel III (NCEP-ATPIII) formulated another definition, designed to have clinical utility. The ATPIII did not find enough evidence to recommend routine measurement of insulin sensitivity or the 2-hour post-challenge glucose intolerance, but included simply a fasting glucose testing[28]. Additionally, the cut-off points for each component of the cluster and the way of combining them to define the metabolic syndrome differed from the two previous definitions[28]. The ATPIII definition is based on a simple set of common clinical measures and diagnostic criteria, including waist circumference to identify central obesity, raised triglycerides (TG), reduced HDL-C, elevated blood pressure (BP) and raised fasting plasma glucose level. The metabolic syndrome diagnosis was established, when 3 out of 5 listed characteristics were present (Table 3). The ATPIII criteria were widely used in both clinical practice and epidemiological studies. This definition had the advantage of excluding the specific measure of insulin sensitivity, and treated all components with equal importance by avoiding the emphasis on a single cause [29].

NCEP-ATIII definition of the metabolic syndrome 2001[30]
Any 3 of 5 following criteria constituted the diagnosis of metabolic syndrome
1. Central obesity: waist circumference ≥ 102 cm in men or ≥ 88 cm in women
2. Hypertriglyceridamia: serum TG ≥ 150 mg/dl
3. Low HDL-C < 40 mg/dl in men and < 50mg/dl in women
4. Hypertension: SBP ≥ 130 mmHg or DBP ≥ 85 mmHg
5. Fasting plasma glucose ≥ 110 mg/dL

Table 3. NCEP-ATIII definition of the metabolic syndrome 2001

Subsequently, various modifications of the ATPIII definition were developed later by the American Heart Association/National Heart, Lung, Blood Institute (AHA/NHLBI) including adjustment of waist circumference to lower thresholds particularly in ethnic groups, for instance, the Asian American, who are more susceptible to insulin resistance. In addition, TG, HDL-C levels, and BP were counted as abnormal when a person was taking

drug treatment for these factors. The threshold for elevated fasting plasma glucose was reduced from ≥ 110 mg/dL to ≥ 100 mg/dL, in accordance with the American Diabetes Association's guidelines [29] (Table 4).

Revised ATPIII definition of the metabolic syndrome 2005[29]
Any 3 of 5 criteria listed below constitute the diagnosis of metabolic syndrome
1. Elevated waist circumference ≥102 cm in men or ≥ 88 cm in women
2. Elevated TG ≥ 150 mg/dl and/or drug treatment for elevated TG*
3. Reduced HDL-C < 40 mg/dl in men and < 50 mg/dl in women and/or drug treatment for reduced HDL-C
4. Elevated BP ≥ 130 mmHg systolic BP or ≥ 85 mmHg diastolic BP or drug treatment for hypertension
5. Elevated fasting plasma glucose ≥ 100 mg/dL and/or drug treatment for elevated glucose
*Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-C. Patients taking 1 of these drugs were presumed to have high TG and low HDL

Table 4. Revised ATPIII definition of the metabolic syndrome 2005

3.1.4 IDF definition

In parallel, a consensus group, comprising members of the International Diabetes Federation (IDF) and representatives from organizations which contributed to the previous definitions, was formed in 2005 to establish a unified definition for the metabolic syndrome that would be suitable for use in both epidemiological and clinical practice. A major issue for the IDF consensus was that central (abdominal) obesity was a prerequisite risk factor for the diagnosis of the syndrome. The IDF provided, for the first time, different obesity cut-off points for different ethnic groups (Table 5 & 6). Waist circumference was a well accepted proxy measurement for abdominal obesity and served as the first screening test for the metabolic syndrome. The added advantage is that insulin resistance which is difficult to measure in routine clinical practice was not an essential requirement[31].

The IDF definition of the metabolic syndrome 2005[31]
Central obesity (defined as waist circumference with ethnicity specific values) plus any 2 of the following 4 factors:
1. Raised serum TG ≥ 150 mg/dl or specific treatment for this lipid abnormality
2. Reduced HDL-C < 40 mg/dl in men and < 50 mg/dl in women and/or specific treatment for this lipid abnormality
3. Elevated BP ≥ 130 mmHg systolic BP or ≥ 85 mmHg diastolic BP and/or treatment of previously diagnosed hypertension
4. Elevated fasting plasma glucose ≥ 100 mg/dL or previously diagnosed type 2 diabetes.
If Fasting plasma glucose was above 100 mg/dL, oral glucose tolerance test (OGTT) was strongly recommended but was not necessary to define the presence of the metabolic syndrome.

Table 5. The IDF definition of the metabolic syndrome 2005

The underlying principle behind the ethnic-specific thresholds was that for a given waist circumference, Asians, Blacks, Caucasians showed different levels of intra-abdominal adiposity, putting the subjects at different risk levels of cardiovascular disease and diabetes[32].

Country/Ethnic group		Waist circumference
Europids In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes	Male	≥ 94 cm
	Female	≥ 80 cm
South Asians Based on a Chinese, Malay and Asian-Indian population	Male	≥ 90 cm
	Female	≥ 80 cm
Chinese	Male	≥ 90 cm
	Female	≥ 80 cm
Japanese	Male	≥ 90 cm
	Female	≥ 80 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available	

Table 6. Ethnic specific values for waist circumference

3.1.5 Last Joint Interim Statement

In 2009, a Joint Interim Statement (JIS) of the IDF Task force on Epidemiology and prevention (National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of obesity) was published, in an attempt to harmonize the definition. The new definition is also known as Revised IDF 2005. Unlike the first IDF definition, the abdominal obesity should not be an obligatory criterion, though the waist circumference was agreed to be a useful preliminary screening tool. The remaining 4 diagnostic criteria were essentially identical to those provided by the R-ATPIII and IDF. The presence of 3 components out of 5 establishes the diagnosis of metabolic syndrome (Table 7).

This new definition recognizes that the risk associated with a particular waist measurement varies in different populations and ethnic groups. The WHO identified 2 levels of abdominal obesity in European population depending on risk for metabolic complications[34]. An increased risk occurs at waist circumferences of ≥ 94 cm in men or ≥ 80 cm in women, but risk is substantially higher at ≥ 102 cm in men or ≥ 88 cm in women. Until more data from research work become available, it was suggested to use national or regional cut-off points for waist circumference.

To sum up, the abundance of widely varying data, comparing the prevalence of metabolic syndrome by using different criteria across different populations reinforced the need for a

standardized definition internationally. Now after the release of the JIS, the current question is whether this new definition is the last word or whether the scientific community needs further reconciliation.

Joint Interim Statement definition of the metabolic syndrome 2009 [33]
Any 3 of 5 criteria listed below constitute the diagnosis of metabolic syndrome
1. Elevated waist circumference according to population- and country-specific definitions (either the IDF or AHA/NHLBI cut points for people of European origin)
2. Elevated TG ≥ 150 mg/dl or drug treatment for elevated TG
3. Reduced HDL-C < 40 mg/dl in men and < 50 mg/dl in women or drug treatment for reduced HDL-C
4. Elevated BP ≥ 130 mmHg systolic BP or ≥ 85 mmHg diastolic BP and/or drug treatment for hypertension
5. Elevated fasting plasma glucose ≥ 100 mg/dL or drug treatment for elevated glucose

Table 7. Last Joint Interim Statement definition of the metabolic syndrome 2009

3.2 Ambiguous pathophysiologic mechanism

The pathogenesis of the metabolic syndrome is currently a subject of crucial discussion. The criteria of metabolic syndrome are interrelated, but the pathophysiology of their relation is not yet fully understood. The long-standing debate about how to define this syndrome led to the appearance of two distinct schools of thought: the insulin resistance-based and the ectopic fat deposition-based hypothesis. So far, both suggested mechanisms remain equivocal and debated.

The basic scientists and endocrinologists support the point of view that the insulin resistance and compensatory hyperinsulinemia are squarely responsible for the metabolic syndrome [13], [21], [35]. According to this group, obesity is thought to exacerbate insulin resistance and thus increase the likelihood of an associated adverse clinical condition. However, the obesity is not considered as a fundamental component of the syndrome, as the clustering of risk factors can occur in insulin resistant individuals of normal weight[36], [37]. The primary goal of this pathophysiological approach is to alert physicians to the idea that patients with insulin resistance are not only at risk for cardiovascular disease, but also to other multiple adverse clinical conditions such as polycystic ovarian syndrome, nonalcoholic fatty liver disease, breast cancer, sleep apnoea. Cardiovascular disease is just one of these important conditions. This group of researchers do not seek strict clinical definition for the metabolic syndrome[38].

In opposition, the other group consists of cardiologists and clinical epidemiologists. This group support the term "metabolic syndrome" and seek to assemble a set of related metabolic risk factors for cardiovascular prevention perspectives. In line with this viewpoint, obesity is considered as a core component of the metabolic syndrome rather than a modulator of the effects of insulin resistance[39]. The primary clinical goal of this school of thought is to suggest an operational tool to be used for long-term risk stratification of atherosclerosis patients [40], [29]. This group supports the idea that the abdominal obesity is the predominant driving force behind the metabolic syndrome and is a particularly detrimental factor in persons who have concomitant metabolic susceptibility from other causes.

Chronologically, the pathophysiological "Insulin Resistance Syndrome" transmuted into clinical "Metabolic Syndrome" in the 1990s[41]. This shift happened to help the scientists to translate science into practice in an area of major medical and public health concern. As insulin resistance was difficult to be measured by the glucose clamp technique, at the population level, fasting plasma insulin levels was used as a proxy to prompt the research for cheap, easy surrogates of insulin resistance[41]. However, this introduced a confusion because of the partial difference in the physiology of hyperinsulinemia and insulin resistance[42], as well as a lack of measurement standardization across studies[41].

Thereafter, anthropometric measures were suggested to replace insulin resistance in new definitions of the metabolic syndrome. The NCEP-ATPIII and particularly the IDF, took the position that obesity (especially abdominal obesity) is a dominant factor behind the multiplication of risk factors. According to the NCEP, the onset of obesity elicits a clustering of risk factors in persons who are metabolically susceptible[40].

In sum, the metabolic susceptibility has many contributing factors, including genetic forms of insulin resistance, increased abdominal fat, ethnic and racial influences, physical inactivity, advancing age, endocrine dysfunction, and genetic diversity[43]. However, the relevance of this application has not yet exclusively been established by the research[41].

3.3 Uncertain clinical utility

Although the suggested definitions provided some uniformity to researchers, a considerable confusion about the precise clinical utility of the "metabolic syndrome" exists and remains controversial.

The major polemic emerged in 2005 when a joint committee of the American Diabetes Association (ADA) and from the European Association for the Study of Diabetes (EASD) published a critical appraisal of the metabolic syndrome concept, and of its diagnostic utility in clinical practice[22]. This group of researchers opposed extending the concept of the metabolic syndrome to clinical practice and objected to characterize the metabolic syndrome as a risk factor for heart disease or diabetes[22], [44]. The claim was that the primary clinical emphasis should remain on treating the individual risk factors and that aggregating them into a syndrome has little clinical utility. Moreover, creating a diagnostic category of the metabolic syndrome was criticized by Reaven himself who was a pioneer in systemizing the concept of a risk factor syndrome. Reaven believed that this effort had little clinical or pedagogic utility and if necessary the WHO approach was the most rational one[44]. In this line, the WHO Expert Consultation, who edited the first definition 10 years earlier, released in 2009 a Position Statement, pertaining to evaluate the relevance and the clinical utility of the metabolic syndrome concept[38]. The statement critically concluded that though the metabolic syndrome may be considered useful as an educational concept, it has limited practical utility as a diagnostic or management tool.

The counter arguments, represented principally by the IDF and AHA, advocated that the diagnosis of the metabolic syndrome helps physicians to discover persons at increased lifetime risk for cardiovascular disease [45], [46]. They believe that the metabolic syndrome is a simple useful tool to call attention to patients who are at high lifetime risk for both atherosclerotic cardiovascular disease and diabetes; such persons deserve increased attention in clinical management and monitoring[23], [26], [29], [22],[44]. Grundy was the scientist who most

thoroughly advocated the clinical utility of the metabolic syndrome, by linking the importance of clinical metabolic syndrome recognition to an "iceberg phenomenon"[43]. He explained that identifying the metabolic syndrome provides a simple means of recognising the risk, submerged in a tangle of metabolic derangement[43]. According to Grundy, seeing the tip of the iceberg can be lifesaving because most of the danger lies below. The same is true in case of finding aggregated metabolic signs such as high TG, low HDL-C, impaired fasting plasma glucose, and mildly elevated BP in a patient with an increased waist circumference [43].

Although the metabolic syndrome seemed to provide little advantage over the available risks scores (Framingham or European SCORE)[47], [22], several clinicians believe that the clinical diagnosis is useful because it determines the therapeutic strategy in patients at higher risk[43]. Moreover, the application of the available cardiovascular disease risk scores is still cumbersome and not routinely used in clinical practice. The metabolic syndrome may thus represent a simple convenient alternative tool to identify individuals at increased risk of atherosclerotic cardiovascular disease or type 2 diabetes mellitus[48], [46]. Beyond risk assessment, the presence of the metabolic syndrome can alert clinicians to the likelihood of related pathological conditions, e.g. obstructive sleep apnoea, fatty liver, cholesterol gallstones, and polycystic ovarian disease[45]. In addition, it helps to recognize that patients with a clustering of measured risk factors usually have several hidden metabolic risk factors, e.g, a prothrombotic state, a proinflammatory state, and multiple lipoprotein abnormalities[29], [46].

3.4 Debated therapeutic strategies

Globally, there are two viewpoints about the best therapeutic strategy for patients with the metabolic syndrome. One conventional approach holds that each of the metabolic risk factors should be singled out and treated separately. However, the concern about this prescription is that it may lead to an aggressive use of medications at the expense of lifestyle therapies, particularly, weight reduction and increased exercise[43]. Alternatively, the other view emphasizes the global approach that aims to implement lifestyle therapies to reduce all risk factors simultaneously. It targets multiple risk factors together by striking at the underlying causes. Treating the underlying causes does not rule out the management of individual risk factors, but it may reinforce the control of multiple risk factors[43]. In practice, there is a tendency to switch from a vertical approach (by speciality) to a multidisciplinary horizontal approach, which enables early detection of the combination of risk factors, sometimes without obvious illness, as measure of effective prevention. So far, there is no proof that the lifestyle modification interventions targeting the metabolic syndrome are superior to those targeting the individual components[22], [48]. Recently, a new study published in 2010 analyzed data from the INTERHEART study, a case-control study of incident acute myocardial infarction that involved 12 297 cases and 14 606 controls from 52 countries. The results suggested that patients with metabolic syndrome are not at higher risk of future myocardial infarction than those with diabetes or hypertension alone[49]. The results strongly suggested that treating the individual risk factors is rather better than focusing on the metabolic syndrome, supporting therefore, the individual risk-factor approach.

3.5 Predictability of the metabolic syndrome to cardiovascular risk

One of the most important criticisms addressed to the concept of the metabolic syndrome was its efficiency to properly evaluate the global cardiovascular disease risk in clinical

practice. The plethora of epidemiological, metabolic and clinical studies, published over the last 2 decades, have demonstrated that the different definitions of the metabolic syndrome were able to identify subgroups of patients at greater risk of type 2 diabetes[50] and at increased relative risk of coronary heart disease[51], [52]. Nevertheless, none of these definitions can properly assess global cardiovascular disease risk [32].

Many prospective studies documented the relation of metabolic syndrome to cardiovascular risk, particularly to cardiovascular morbidity, mortality as well as all-cause mortality. In the Kuopio Ischemic Heart Disease Risk Factor Study, a population-based, prospective cohort study of 1209 Finnish men aged 42 to 60 years, the 10-year cardiovascular disease risk was increased 2.1- and 2.5-fold with the ATP III and WHO definitions, respectively[3]. The same study found that the risk of death from cardiovascular disease was increased by 2.6–3 times, and the risk of all-cause mortality was increased 1.9–2.1 times with the presence of metabolic syndrome. The DECODE project, based on 11 prospective European cohort studies, comprising 6156 men and 5356 women, aged from 30 to 89 years reported that the overall hazard ratios for all-cause and cardiovascular mortality in non-diabetic persons with the metabolic syndrome were 1.44 and 2.26 in men and 1.38 and 2.78 in women, respectively[12]. In the WOSCOPS (West of Scotland Coronary Prevention) Study, a modified NCEP definition predicted CHD events, in the multivariate model incorporating conventional risk factors (hazard ratio=1.30). Men with 4 or 5 features of the metabolic syndrome had a 3.7-fold increase in risk for CHD and a 24.5-fold increase for diabetes compared with men without the syndrome [53]. In Botnia study, carried out on 4483 subjects, aged 35-70 years, followed for 7 years in Finland and Sweden, the risk for coronary heart disease and stroke was increased 3-fold in subjects with the WHO defined metabolic syndrome. Cardiovascular mortality was also markedly increased in subjects with the syndrome compared to those without it (12.0% vs. 2.2%, $P < 0.001$)[2].

In sum, the use of different definitions of the metabolic syndrome led to inconsistent results on its association with the risk of cardiovascular disease [51]. Systematic research reviews showed that the cardiovascular risk, conferred by the different definitions, varied between populations; in most studies, it was lower with the IDF definition as compared to other alternatives[54], [51]. In addition, two recent meta-analyses of longitudinal studies, showed that the relative risk of cardiovascular disease associated with the metabolic syndrome was higher in women compared to men[52], and higher in studies that used the WHO definition compared to studies that used the NCEP-ATP III definition[51].

3.6 Predictability of the metabolic syndrome to type 2 diabetes

The most important clinical dimension of the metabolic syndrome is its association with the risk of development of type 2 diabetes. Several prospective studies indicated that the metabolic syndrome predicts type 2 diabetes[24], [55], [56]. People with the syndrome were over 4 times as likely to develop type 2 diabetes compared with subjects who did not have it[1], although without excluding the diabetic subjects, this might not be surprising, since impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are components of the WHO definition[16]. In addition, neither the ATP III nor the IDF criteria excluded hyperglycaemia as 1 of the 5 criteria for the diagnosis of the metabolic syndrome. By these criteria, most patients with type 2 diabetes mellitus have the metabolic syndrome. In the San Antonio Heart Study, the NCEP definition of the metabolic syndrome predicted diabetes

better than the WHO definition, independently of other factors. It was suggested therefore to lower the fasting glucose cut-off points to improve the diabetes prediction [55].

Despite the above data, there is an ongoing controversy as to whether the metabolic syndrome is associated with increased cardiovascular and diabetes risk or is simply a sum of the risk of the associated components: glucose tolerance, elevated blood pressure, dyslipidemia, and abdominal obesity[9]. According to a recent research review, aimed to examine the ability of the metabolic syndrome to predict vascular events and incident diabetes, the number of existing studies appeared limited to draw definite conclusions[54] and the metabolic syndrome predicts diabetes much more efficiently in non-diabetic individuals[57].

4. Evolution toward a new global "cardiometabolic risk" concept

The traditional risk assessment algorithms (Framingham, PROCAM or European SCORE, etc.) take into account classical risk factors such as age, sex, family history, blood pressure, smoking, cholesterol (both LDL and HDL), and diabetes. However, these risk assessment tools do not capture the risk of abdominal obesity and the related abnormalities of the metabolic syndrome. This is especially important with the recent sweeping epidemic of abdominal obesity, where many individuals are at increased risk of cardiovascular disease because of the presence of a constellation of metabolic abnormalities. It has been suggested that the cardiovascular disease risk of abdominal obesity and/or metabolic syndrome may be independent from or go beyond the risk predicted by traditional risk factors [32]. Moreover, the Framingham risk score does not assess properly lifetime risk particularly among young adults with abdominal obesity and metabolic syndrome who may not be considered at elevated risk of cardiovascular disease because of their young age[45]. Therefore, the existing cardiovascular disease risk assessment tools proved cumbersome in clinical practice and were not sufficient to adequately capture the additional risk related to the metabolic syndrome, such as the abdominal obesity, insulin resistance and related complications [32].

On the other hand, the metabolic syndrome as a clinical entity could not improve prediction of risk of cardiovascular disease [47], [22], because it did not incorporate important traditional risk factors, such as smoking, age and gender[45]. The current recommendations stress the need to focus on the assessment of the total burden of risk, the so-called global risk profile, rather than on individual or particular risk factor. This is because, the absolute risk of an acute coronary event depends on the totality of interacting risk determinants; some associated with adult lifestyle, others operating from early childhood[58].

On the whole, the presence of metabolic syndrome alone cannot predict global cardiovascular disease risk, nor do the available risk scores. Meanwhile, better risk assessment algorithms are needed to quantify diabetes and cardiovascular disease risk on a global scale[59]. This unremitting debate, as to whether the metabolic syndrome increases cardiovascular disease risk beyond the risk posed by traditional cardiovascular disease risk factors, has spurred the creation of a new concept named the global "cardiometabolic risk (CMR)". In order to move the field forward, a multidisciplinary International Chair on CMR was created, at the end of 2005, to provide a platform to discuss the concepts of abdominal obesity, metabolic syndrome, and global cardiovascular disease risk[32].

Global CMR is defined as the risk of cardiovascular disease resulting from the presence of traditional risk factors along with features of the metabolic syndrome [32], [59]. Under this model, CMR encompasses the overall cardiovascular disease risk, resulting from traditional risk factors (age, sex, smoking, hypertension, LDL cholesterol, HDL cholesterol, diabetes) and from the additional risks of intra-abdominal obesity or related features of the metabolic syndrome [32]. Under this working model, the metabolic syndrome is one of the potentially modifiable cardiovascular disease risk factors, besides smoking (Figure 1). It has been suggested that the cardiovascular risk of abdominal obesity/metabolic syndrome may be independent of or go beyond the risk predicted by traditional risk factors.

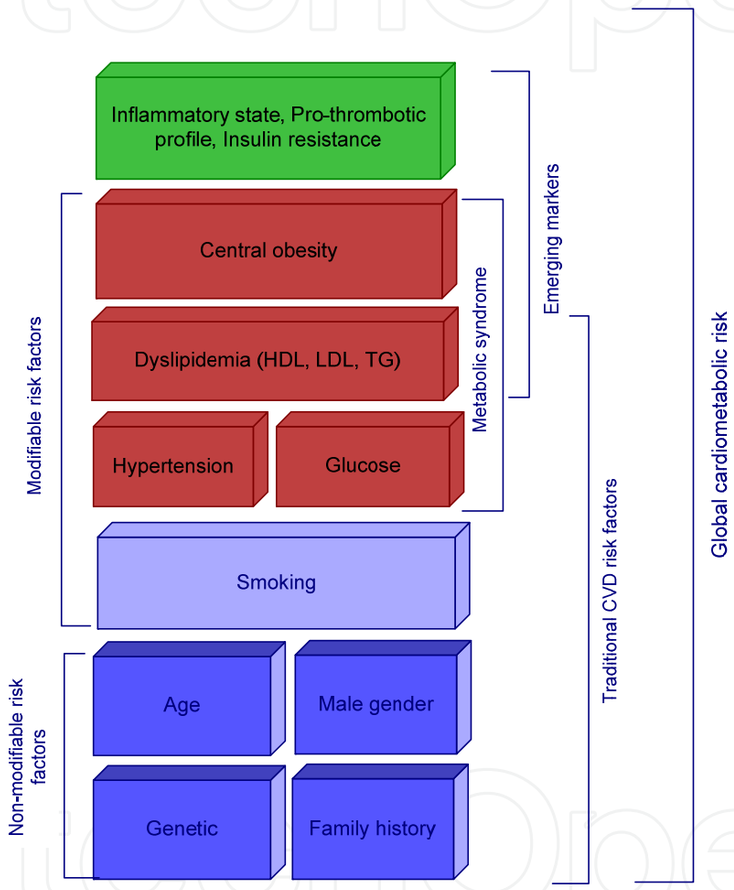

Fig. 1. The "building blocks" of global cardiometabolic risk, with adaptation from Després et al[32].

5. Epidemiology of metabolic syndrome

The metabolic syndrome is a cluster of cardiovascular risk factors associated with an increased risk of type 2 diabetes mellitus and cardiovascular morbidity and mortality[3]. This section aims to shed light on the current state-of-art with regards to the prevalence of the metabolic syndrome worldwide and its key determinants. Understanding the epidemiology of the metabolic syndrome, as regards the variation of its frequencies and its potential determinants, are essential pre-requisites to addressing public health needs.

5.1 Prevalence of metabolic syndrome

The multiplicity of prevalence data suggest that the metabolic syndrome is common worldwide, especially among older people and in certain ethnic populations[15]. The syndrome will undoubtedly become even more common over time, in parallel with the exploding epidemic of obesity and type 2 diabetes[60]. In addition, the worldwide increase in the prevalence of metabolic syndrome among children and adolescents[61], constitutes a greater public health concern, as emerging evidence has suggested that children with the metabolic syndrome increase their risk of developing adverse cardiovascular events later in life[62].

In this setting, the present section describes and compares the metabolic syndrome prevalence rates reported in different studies, carried out during the current decade, in various countries all over the world. A thorough literature search for publications, documenting the prevalence of the metabolic syndrome according to the existing definitions, was conducted with an emphasis on international prevalence comparison. The reported worldwide prevalence rates of the metabolic syndrome are depicted in Table 8 (A-D).

Globally, the prevalence of the metabolic syndrome was different across the countries in terms of gender, age groups and ethnicity, regardless of the definition used. In US population, the IDF definition led to a higher prevalence estimate (39%) than that based on the R-ATPIII criteria (34.5%)[63]. A spectacular increase in the prevalence was recorded among the same population, from 24% in 1988[63] to 34.5% in 2002[64], by using the NCEP-ATPIII definition. This raise was attributed to the increase in the prevalence of obesity between 1988 and 2000, as well as the aging of the population[65]. In European studies, the prevalence of the metabolic syndrome varied considerably between 18% in Italy[66] and 38% in Turkey[67]. The metabolic syndrome was also frequent in Middle Eastern countries[68] and India[69], although the lowest prevalence rates were recorded in Australia[70], and china[71]. Generally, the IDF criteria gave a higher prevalence rate as compared to the NCEP-ATPIII[60]. This was undoubtedly attributable to the lower waist circumference threshold to define the abdominal obesity criterion. The WHO criteria variably induced a higher prevalence rate when compared to the NCEP-ATPIII definition [60].

Irrespective of the criteria, studies were inconsistent regarding the gender-specific metabolic syndrome prevalence. While the metabolic syndrome was higher among men than women in France[72], [73], Germany[50], Ireland[74], Singapore[75], it was higher in Omani[68], Chinese[71] and Indian women[69]. In addition, accumulating evidence demonstrated that the prevalence of the metabolic syndrome was highly age-dependent, so as its individual components[15]. The prevalence increases with age through the sixth decade of life among men and seventh decade among women [76]. Race/ethnicity influenced also the prevalence of the metabolic syndrome. Some ethnic groups have a higher predisposition to central obesity than others: for example, the prevalence of central obesity is higher among South Asians than in Europeans. Asian populations have more metabolic abnormalities with the same obesity than do the Caucasians[71]. Thus, a modification of the waist circumference cut-off values of the NCEP-ATPIII definition has been proposed for Asian populations. By applying the European definition of waist circumference, the prevalence of metabolic syndrome was generally lower among Asian populations than among European populations, however, when modified Asian waist circumference criteria were used, the

prevalence of metabolic syndrome increased and became similar (Korean population)[77] to or even higher (urban Indians)[69] than European populations. In USA, NCEP ATPIII-defined metabolic syndrome is more prevalent in Mexican Americans (31.9%) than in Caucasian (23.8%) and African American (21.6%)[7]. Ford et al reported that the metabolic syndrome was more common in Black and Hispanic women than in both counterpart men, which contrasted with the similar gender prevalence for Whites [7].

Country, year of publication	Acronym, setting and period of data collection	Study design	Age group and subjects number	Definition	subject's characteristics	Age-adjusted Prevalence of metabolic syndrome
USA, 2002[7]	Third National Health and Nutrition Examination Survey (NHANESIII), 1988-1994	Cross-sectional population-based sample	≥20years (8814 subjects)	NCEP ATPIII	White	23.8%*
					Mexican American	31.9%*
					African American	21.6%*
					Other	20.3%*
USA, 2004[84]	Dearborn, Michigan, 2004	Cross-sectional, random sample	20-75years, (542 subjects)	NCEP ATPIII	Arab Americans population	23% *
				WHO		28% *
USA, 2003[64]	Third National Health and Nutrition Examination Survey (NHANESIII), 1988-1994	Cross-sectional, representative sample	≥ 20 years, (8608 participants)	NCEP ATPIII	Total	23.9%*
					Men	24.2% *
					Women	23.5%*
				WHO	Total	25.1%*
					Men	27.9%*
					Women	22.6%*
USA, 2005[63]	National Health and Nutrition Examination Survey (NHANES), 1999-2002	Cross-sectional population-based sample	≥ 20years (3601 subjects)	NCEP ATPIII	Total	34.5%
					Men	33.7%
					Women	35.4%
				IDF	Total	39%
					Men	39.9%
					Women	38.1%

*Non age-adjusted prevalence rate
A Prevalence of the metabolic syndrome in USA

Table 8. Prevalence of the metabolic syndrome in different countries.

In fact, the cross-sectional and longitudinal epidemiological studies provided markedly different prevalence and incidence rates of the metabolic syndrome, because of the lack of internationally agreed-upon criteria to define the syndrome. The NHANES III surveys carried out in USA, aimed at comparing the prevalence of the metabolic syndrome according to the WHO and NCEP-ATPIII definitions, demonstrated a substantial discordance for gender and ethnicity[64]. The IDF definition, led generally to higher estimates of the prevalence, in all ethnic groups, especially among Mexican American men

[63]. An elevated IDF prevalence of the metabolic syndrome was similarly observed in other international studies[70], [78], [79], [66], [80], [67], [81]. In 8 European cohorts (DECODE Study), the metabolic syndrome prevalence rate defined according to the WHO, NCEP-ATPIII and EGIR varied widely among countries; the WHO definition showed particularly a wide gender-specific difference[82]. In Bruneck Italian Study, the prevalence of metabolic syndrome was significantly higher and almost doubled with the WHO criteria as compared to those of the NCEP (34.1% vs 17.8% respectively)[46].

Apart from definitions diversity, the wide variation of published data made direct international comparisons exceedingly difficult, because of important methodological differences with respect to the characteristics of target population, the study design, the sample selection, and the year of conduct.

In sum, the emerging prevalence data from population-based studies suggest that the metabolic syndrome is a quite common cardiometabolic disorder worldwide with a wide gender discrepancy. A very consistent finding was that the prevalence of the metabolic syndrome increased dramatically with age and varied considerably across ethnic groups. Racial/ethnic waist circumference component heterogeneity gave rise to substantial racial/ethnic variation in the prevalence of the metabolic syndrome itself. The use of different definitions in diverse populations resulted in wide ranging prevalence rates, thus highlighting the urgent need for a unified definition[83]. Moreover, only a few international studies reported age-adjusted prevalence rates, to enable meaningful comparison.

Australia, 2005[70]	Adelaide, south Australia study,	Random household sample	≥ 18 years, (4060 subjects)	NCEP ATPIII	Total	15%
					Men	15.7%
					Women	14.4%
				IDF	Total	22.8%
					Men	26.4%
					Women	19.4%

B Prevalence of the metabolic syndrome in Australia

Table 8. Prevalence of the metabolic syndrome in different countries.

Country, year of publication	Acronym, setting and period of data collection	Study design	Age group and subjects number	Definition	Subject's characteristics	Age-adjusted Prevalence rate
Europe, 2005[82]	The DECODE Study Group, 1991, except in Spain (1996-1997)	Seven cross-sectional European population-based studies	30-77years, (9140 subjects), Non-diabetic Europeans	WHO	Men	26.9%
					Women	19.5%
				EGIR	Men	17.9%
					Women	16.5%
				NCEP ATPIII	Men	22.7%
					Women	23.1%
Germany, 2008[50]	The European Prospective	Multi-centre, prospective cohort study	35-65years, (2796 subjects)	Revised NCEP ATPIII	Total	22.5% *
					Men	29.1%*
					Women	18.5%*

Country, year of publication	Acronym, setting and period of data collection	Study design	Age group and subjects number	Definition	Subject's characteristics	Age-adjusted Prevalence rate
	Investigation into Cancer and Nutrition-Potsdam Study (EPIC) Potsdam, 1994-1998			IDF	Total	28.3% *
					Men	33.2%*
					Women	25.2% *
France, 2006[72]	D.E.S.I.R Study, centre-western France, 1994-1996	Volunteered for health check-up	5446 subjects, 30-64 years	Revised NCEP ATPIII	Men	15%
					Women	10.1%
France, 2003[73]	Centre IPC (Investigation Préventives et Cliniques), Paris, 1999-2002	Volunteered for health check-up	62000 subjects, (mean age 53.2+/-9.1years)	Revised NCEP ATPIII	Men	11.8%*
					Women	7.6%*
Norway, 2007[78]	Nord-Trondelag Heart Study(HUNT 2), 1995-1997	Cross-sectional population-based sample	20-89 years, (10206 subjects	Revised NCEP ATPIII		25.9%*
				IDF		29.6%*
Finland, 2007[79]	The Cardiovascular risk in Yong Finns Study, 1986-2001	Population-based follow-up study	2182 subjects, 24-39 years	Revised NCEP ATPIII	Total	13%
				EGIR		9.8%
				IDF		14.3%
Ireland, 2003[74]	Primary care setting in the South of Ireland.	Random sample of attended subjects for screening from 17 general practice lists	50–69 years, (1,018 subjects)	WHO	Total	21%*
					Men	24.6%*
					Women	17.8%*
				NCEP-ATPIII	Total	20.7%*
					Men	21.8%*
					Women	21.5%*
Italy, 2003[46]	Bruneck Study, 1990	Prospective population-based survey	40–79 years, 888 subjects	WHO		34.1%*
				NCEP ATPIII		17.8%*
Italy, 2007[66]	FIBAR study,	Sample of individuals enrolled in a	2,945 subjects, mean age	Revised NCEP ATPIII	Total	16.6%*
				IDF		29.7%*

Country, year of publication	Acronym, setting and period of data collection	Study design	Age group and subjects number	Definition	Subject's characteristics	Age-adjusted Prevalence rate
		screening program for diabetes	55.2+/-11.5 years			
Spain, 2003[85]	Nutritional Survey of the Canary Islands (ENCA), 1997-1998)	Population–based study	18-74 years, 578 adults	NCEP ATPIII	Total	24.4%*
Spain, 2007	Province of Albacete	Cross-sectional, Population–based study	40-70 years, 425 subjects	Adapted NCEP ATPIII	Total	20.9%
Greece, 2007[86]	Greece	cross-sectional, a representative sample	adults, 9669 subjects	NCEP-ATP-III		23.3%
				Revised NCEP ATPIII		22.6%
				IDF		18.3%
Portugal, 2007[80]	Porto	Representative random sample, Population-based study	18-92 years,1433 subjects	WHO	adult residents	26.4%
				NCEP ATPIII 2001		24%
				IDF		41.9%
				AHA/NHLBI 2005		37.2%
Portugal, 2008[87]	VALSIM Study	Primary health care users	18-96 years, 16,856 subjects	NCEP ATPIII	total	27.5%
					Alentejo region	30.99%
					Algrave region	24.42%
Turkey, 2007[67]	Turkish Heart Study, 2003	Cross-sectional population-based sample	mean age 45± 13 years, (1568 subjects)	WHO	General adult population	19%
				EGIR		20%
				NCEP ATPIII		38%
				IDF		42%
Luxembourg, 2011[88]	ORISCAV-LUX survey, Luxembourg, 2007-2008	Cross-sectional population-based sample	18-69 years, 1432 subjects	R-ATP III	General adult population	24.7%*
				JIS (94/80cm)		28.0%*

C Prevalence of the metabolic syndrome in European countries

Table 8. Prevalence of the metabolic syndrome in different countries

Country, year of publication	Acronym, setting and period of data collection	Study design	Age group and subjects number	Definition	subject's characteristics	Age-adjusted Prevalence rate
Oman, 2003[68]	Nizwa study, 2001	Cross-sectional population-based sample	≥ 20years, (1419 subjects)	NCEP ATPIII	Total	21%
					Men	19.5%
					Women	23%
Chile, 2008[81]	Talca city study, year of data collection not mentioned	Probabilistic sample	18-74 years, (1007 subjects)	Revised NCEP ATPIII		29.5%
				IDF		36.4%
China, 2006[71]	The Chinese Multiprovincial Study, 1992	Prospective cohort study	35-64 years, (26972 subjects)	ATPIII according to Asian criteria of waist circumference	Men (≥ 90cm)	14.4%
					Women (≥ 80cm)	20%
				IDF according to Asian criteria of waist circumference	Men (≥ 90cm)	9.8%
					Women (≥ 80cm)	16.6%
South Korea, 2004[77]	Mokdong Study of Diabetes Prevalence, 1997	Random cluster sample	30-80 years, (1804 subjects)	ATPIII based on Asia-Pacific guidelines	Men (≥ 90cm)	29%*
					Women (≥ 80cm)	16.8%*
				ATPIII	Men (≥ 102 cm)	16%*
					Women ≥ 88cm)	10.7%*
South Korea, 2006[89]	Korean National Health and Nutrition Examination survey, 1998	Stratified multistage probability sampling design	20-80 years, (6824 subjects)	IDF (with specific waist circumference cut-off points)	Men (≥ 90cm)	13.5%
					Women (≥ 85cm)	15%
India, 2004[69]	Urban Indian population study	Population-based study	>20 years, (1123 subjects)	ATPIII	Total	24.9%
					Men	18.4%
					Women	30.9%
Seychelles (Indian Ocean, African region), 2008[90]	Seychelles Heart Study III, 2004	Cross-sectional, Population-based study	25-64 years, (1218 subjects)	WHO	Men	25%*
					Women	24.6%*
				ATPIII	Men	24%*
					Women	32.2%*
				IDF	Men	25.1%*
					Women	35.4%*
Singapore, 2004[75]	Singapore National Health Survey, 1998	Population-based study	18-69 years, (4723 subjects)	NCEP	Men (all races)	13.1%
					Chinese	10.8%
					Malays	17.3%
					Asian Indians	21.7%
					Women (all races)	11%
					Chinese	8.3%

Country, year of publication	Acronym, setting and period of data collection	Study design	Age group and subjects number	Definition	subject's characteristics	Age-adjusted Prevalence rate
					Malays	20%
					Asian Indians	19.3%
				NCEP-Asian criteria (Waist circumference 90 cm in men and 80 cm in women)	Men (all races)	20.9%
					Chinese	18.1%
					Malays	24.7%
					Asian Indians	32.4%
					Women (all races)	15.5%
					Chinese	12.5%
					Malays	23.8%
					Asian Indians	25.8%

D Prevalence of the metabolic syndrome in Asian countries

Table 8. Prevalence of the metabolic syndrome in different countries

5.2 Potential determinants of the metabolic syndrome

At every stage of life, health is determined by complex interactions between a multitude of factors that influence a person's disease or health status. With regards to the metabolic syndrome, the determinants which are centrally involved in its multi-factorial causation can be categorized as: biological or genetic susceptibility; socio-economic; environmental and behavioural factors.

5.2.1 Biological or genetic susceptibility

Although twin and family studies showed a high heritability for each of the individual components [91], the genetic basis of the metabolic syndrome, as a composite phenotype, has not yet been thoroughly investigated. A number of researches indicated a genetic susceptibility of the metabolic syndrome. However, the associations were weak and the replication of findings was poor[92], [93]. While the prevalence of the metabolic syndrome has increased markedly in the last decades, the human genome has not changed. At present, no single gene or cluster of genes has been consistently replicated for the expression of this phenotype (metabolic syndrome) among different populations[94], [95], probably due to the complex interactions between gene and environment.

The 'thrifty genotype' hypothesis was proposed to explain the emergence of insulin resistance and diabetes in populations, shifted from vigorous activity to provide subsistence nutrition to sedentary life style with food abundance. In urban societies, the modern abundant food environment may be responsible for the elevated insulin levels and excessive energy stores in some type 2 diabetic individuals, leading in consequence to insulin resistance and obesity[96].

Genetic background can interact with habitual dietary fat composition, thereby affecting predisposition to the metabolic syndrome, and may also determine the individual's responsiveness to altered dietary fat intake[97]. Recent research indicates that currently ineffective therapeutic dietary recommendations may require a 'personalised nutrition'

approach, wherein the genetic profile may determine the responsiveness of patients to specific dietary fatty acid interventions[98].

5.2.2 Socio-economic determinants

Several prospective observational studies showed that low socio-economic position, measured as education level, income, or occupational class was associated with increased risk for type 2 diabetes[99] and coronary heart disease[100], [101]. Clinical features of the metabolic syndrome were more commonly observed among socio-economically disadvantaged individuals[102], in individuals with low education level[103], [104], and in those doing menial jobs[105]. There is increasing evidence that the distribution of the metabolic syndrome varies among different geographic and socioeconomic categories of the population, demonstrating notable health inequalities[106], [107], [108].

5.2.3 Behavioural or lifestyle determinants

Lifestyle choices imposed by modern civilization have been demonstrated to be centrally involved in the multi-factorial causation of severe atherosclerotic disease [108]. There has been an increasing body of evidence demonstrating that unhealthy behaviours were substantially responsible for epidemic prevalence and mortality of cardiovascular disease, diabetes and metabolic disorders[4], [5], [109]. In contrast, a healthy lifestyle including non-smoking, appropriate diet, satisfactory physical activity level and healthy weight provided substantial cardiovascular and metabolic benefits[110]. Among the major potentially modifiable risk factors for metabolic syndrome and its components are the following:

1. Smoking

Growing evidence pointed to smoking as an independent risk factor for metabolic syndrome and type 2 diabetes. Smoking is a strong risk factor for atherosclerotic cardiovascular disease, with a dose dependent relationship[111], [112]. Several population-based studies confirmed that cigarette smoking was independently associated with the metabolic syndrome [113], [114], [115], in particular in men[116]. The general belief is that insulin resistance or hyperinsulinemia is the main underlying mechanism. Increased insulin resistance may underlie the clustering of the metabolic and hemodynamic abnormalities that have potential atherosclerotic properties, designated the metabolic syndrome [14]. However, this hypothesis still needs to be tested in prospective studies.

2. Dietary habits

Although dietary intake has been linked to individual components of the metabolic syndrome [117], [118], [119], [97], the role of diet in its origin is not well understood[120]. Cross-sectional epidemiological studies demonstrated that dietary intake rich in whole-grain foods was linked to a lower prevalence of the metabolic syndrome [121], [122], although other study found no relation[123]. Dairy intake was inversely associated with the metabolic syndrome both prospectively and in cross-sectional studies [124,125]. Greater intakes of fruits and vegetables were associated with a lower prevalence of the metabolic syndrome [126]. Intakes of soft drinks were also positively associated with the prevalence of the metabolic syndrome, but the diet soda-metabolic syndrome incidence association was not yet hypothesized and needs further prospective studies [127].

Although various individual foods and nutrients were associated with the development or the progression of the metabolic syndrome, only a few studies examined the association with dietary patterns[128]. Prospective findings from Atherosclerosis Risk in Communities (ARIC) study suggested that consumption of a Western dietary pattern, meat, and fried foods promoted the incidence of the metabolic syndrome, whereas dairy consumption provided some protection[120].

Recently, dietary pattern analysis has emerged as an alternative and complementary approach to examine the relationship between diet and the risk of chronic diseases. Instead of looking at individual nutrients or foods, pattern analysis examines the effects of overall diet. Conceptually, dietary patterns address the effect of the diet as a whole and thus may provide a broader picture of food and nutrient consumption, and may thus be more predictive of disease risk than individual foods or nutrients[129], [130].

3. Alcohol consumption

Across the literature, the association between alcohol consumption and the metabolic syndrome is controversial and influenced by several factors, due to broad overlap of alcohol consumption with different components of metabolic syndrome. Protective and detrimental associations were reported between alcohol consumption and the metabolic syndrome, due to variations in drinking patterns and different alcohol effects on the metabolic syndrome components[131]. Mild to moderate alcohol consumption is associated with a lower prevalence of the metabolic syndrome, with a favourable influence on lipids, waist circumference, and fasting insulin. This association was strongest among whites and among beer and wine drinkers[132].

A recent meta-analysis study, aiming to support the evidence available regarding the relationship between alcohol consumption and the metabolic syndrome, as well as to identify the gender-specific dose-response, showed that alcohol consumption of less than 40 g/day in men and 20 g/day in women significantly reduced the prevalence of metabolic syndrome [133].

4. Physical activity

In agreement with the notion that physical inactivity is a risk factor of diabetes, obesity, dyslipidemia and hypertension[134], [135], [136], the prevalence of the metabolic syndrome was higher in subjects with poor physical activities[46], [137].

Sedentary behaviour is an important potential determinant of the metabolic syndrome. Several studies demonstrated that physical activity was inversely associated with the prevalence of the metabolic syndrome[138], [139], notably among those who spend much time in sedentary activity as watching television or video or using a computer[137]. The adverse effect of excess television watching on obesity and other cardiovascular risk factors is thought to be attributed, in part, to decreased energy expenditure and, in other pat, to increased energy intake. Therefore, understanding how sedentary behaviour relates to the metabolic syndrome may provide new opportunities for clinical and public health approaches in its prevention and control.

5. Psychosocial factors

Accumulating evidence implied that psychological mechanisms were possibly underlying the development of the metabolic syndrome. The syndrome appeared to be triggered by adverse

psycho-social circumstances[140], certain chronic psychological pathologies[141,142] and chronic stress[102]. Individuals who had hostile personality and certain behaviour traits, were particularly predisposed to develop the metabolic syndrome [102]. Such factors might interact with others to encourage the development of metabolic syndrome. The stress is exacerbated by lack of social support and/or poor coping skills. As a vicious cycle, the negative psychological behaviours may induce unhealthy lifestyle and/or adverse social circumstances[143]. A large population study demonstrated a higher incidence of the metabolic syndrome among young women, but not in men, with a history of depression after controlling for other associated factors [141]. Features of the metabolic syndrome also appeared more common among women experiencing social anxiety [144]. These findings suggest the possibility of different gender-specific causal pathways to the metabolic syndrome development.

5.2.4 Environmental factors

Recently, the scientific evidence linking air pollution to heart attacks, strokes and cardiovascular death, has been substantially supported, especially for the fine particulate matter (PM). The major source of PM is fossil fuel combustion from industry, traffic, and power generation. Biomass burning, heating, cooking, indoor activities and forest fires may also be relevant sources, particularly in certain regions[145].

Several interrelated pathophysiologic mechanisms underlying the observed short-term and long-term [146]adverse cardiac effects of ambient air pollution have been elucidated[147], for instance, the pivotal role of vascular inflammation in pathogenesis and progression of atherosclerosis and coronary heart disease. Systemic inflammatory response to inhaled ambient particles has emerged as an important mediator of the PM-associated acute cardiac effects[148]. However, human data are still scant and conflicting with respect to the pathophysiologic mediators of cardiovascular disease associated with long-term exposure to fine PM. Researchers hypothesized that long-term exposure is associated with increased systemic inflammation, and that people with metabolic syndrome have a higher degree of inflammatory responses to PM.

5.2.5 Emergent factors

In a recent research study, a growing number of other factors, called “emerging or novel risk factors”, have been described and linked with features of the metabolic syndrome. Several new bio-markers or candidate cardiovascular risk factors have been proposed as significant predictors of the atherosclerotic disease and its complications. These include inflammatory-, hemostasis or thrombosis-, lipid-related markers, oxidative stress, hormonal factors and infectious agents [149], [150], [151], [152], [153], [154]. Over the past few years, the concept of atherosclerosis as an inflammatory disorder has been substantially established[155]. However, the role of systematic inflammation needs further exploration. The novel bio-markers, psychological and environmental determinants are outside the scope of the present chapter and hence will not be further detailed.

6. Conclusion

The metabolic syndrome is a multi-factorial disorder and its development is the result of interactions between biological, behavioural and environmental factors. Despite

disagreement over the relevance and clinical utility of the metabolic syndrome, most investigators agree that the clustering of metabolic risk factors is a real and relatively common phenomenon[60]. Around the world, the metabolic syndrome is now considered as one of the major public health challenges of the 21st century, associated with a 5-fold and 2- to 3-fold increase in type 2 diabetes and cardiovascular disease, respectively [32]. In consequence, the related premature morbidity and mortality could overcharge the health care system budgets of both developed and developing countries[16].

The introduction of the metabolic syndrome concept was a stimulus for a large number of epidemiological, metabolic, and genetic studies that moved up the scientific research field. In addition, the metabolic syndrome constitutes a comprehensive public health message and an easily educational tool for patients and health professionals, focusing on the multi-factorial nature of the atherosclerotic diseases. This approach recommends the same prevention and management strategies for both metabolic syndrome and its individual components (e.g., a healthy diet, regular physical activities, smoking cessation, weight loss and control, plus pharmacological intervention where necessary)[38].

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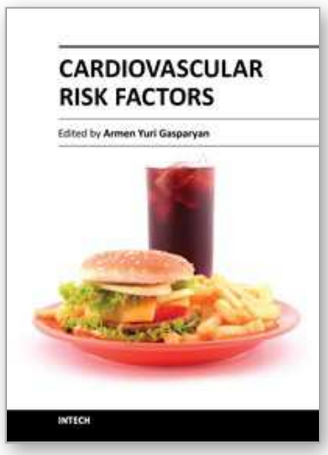

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Cardiovascular risk factors contribute to the development of cardiovascular disease from early life. It is thus crucial to implement preventive strategies addressing the burden of cardiovascular disease as early as possible. A multidisciplinary approach to the risk estimation and prevention of vascular events should be adopted at each level of health care, starting from the setting of perinatology. Recent decades have been marked with major advances in this field, with the emergence of a variety of new inflammatory and immune-mediated markers of heightened cardiovascular risk in particular. The current book reflects some of the emerging concepts in cardiovascular pathophysiology and the shifting paradigm of cardiovascular risk estimation. It comprehensively covers primary and secondary preventive measures targeted at different age and gender groups. Attention is paid to inflammatory and metabolic markers of vascular damage and to the assessment of vascular function by noninvasive standardized ultrasound techniques. This is a must-read book for all health professionals and researchers tackling the issue of cardiovascular burden at individual and community level. It can also serve as a didactic source for postgraduate medical students.

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