Metabolic syndrome: an overview on its genetic associations and gene-diet interactions

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Abstract

Metabolic syndrome (MetS) is a cluster of cardio-metabolic risk factors that includes central obesity, hyperglycemia, hypertension, and dyslipidemias and whose inter-related occurrence may increase the odds of developing type 2 diabetes and cardiovascular diseases. MetS has become one of the most studied condition, nevertheless due to its complex etiology this has not been fully elucidated. Recent evidence describes that both genetic and environmental factors play an important role on its development. With the advent of genomic-wide association studies (GWAS), single nucleotide polymorphisms (SNPs) have gained special importance. In this review, we present an update of the genetics surrounding MetS as a single entity as well as its corresponding risk factors, considering SNPs and gene-diet interactions related to cardio-metabolic markers. Here, we focus on the conceptual aspects, diagnostic criteria as well as the role of genetics, particularly on SNPs and polygenic risk scores (PRS) for inter-individual analysis. In

addition, this review highlights future perspectives of personalized nutrition with regards to the approach of MetS and how individualized multi-omics approaches could improve the current outlook.

Introduction

In recent decades, chronic diseases, such as metabolic and cardiovascular disorders, have become particularly important worldwide. For almost a century now, a set of risk factors has been described to increase the risk of developing type 2 diabetes (T2D) and cardiovascular disease (CVD),[1] two of the top 10 worldwide diseases that cause mortality.[2] It is forecasted that by 2040, the metabolic risk factors of high blood pressure, high body mass index (BMI), and high fasting blood glucose will be among the five leading global risk factors for years of life lost (YLLs), and the differences between risk-attributable YLLs in the better/worse health scenarios will be at least 2.6 times.[3] The term "metabolic syndrome" (MetS) began to be used until earlies 1980s to identify cardiometabolic abnormalities and recognizing their deleterious synergistic role for health.[1,4] These factors include central obesity, insulin resistance, dyslipidemia and elevated blood glucose, characterized by an increase in triglyceride (TG) and a decrease of high-density lipoprotein cholesterol (HDL-C) serum levels, as well as high blood pressure. Later, a model with insulin resistance was proposed as the central axis of this condition, although the obesity factor was omitted, being called as "syndrome x".[5] Since its conceptualization, various definitions have been suggested for the diagnosis of metabolic syndrome. These include common clinical markers, although other biochemical markers associated with inflammation, cardiovascular risk and energy metabolism have been also described. [6,7]

Among the most common definitions (Table I), are those proposed by the world health organization (WHO) in 1989,[8] which highlighted the presence of insulin resistance (or its substitutes) as essential components. Subsequently, in 2001, the US National

Cholesterol Education Program: Adult Treatment Panel III (NCEP-ATPIII) published its diagnostic criteria, focusing on the detection of people with higher cardiovascular risk by giving an equal weighting to the presence of all markers.[9] In 2004, the International Diabetes Federation (IDF) proposed a definition that sought to be applicable for the detection of the risk of CVD and T2D worldwide in a simple manner.[10] Central obesity was included as an essential marker, establishing different cut-off points for waist circumference, specific to each ethnicity, in conjunction with at least two additional factors for diagnosis. Interestingly, the IDF mentioned additional criteria for future MetS research, such as tomographic evaluation of visceral and hepatic adiposity, adipose tissue biomarkers, apolipoprotein B (Apo B), low-density lipoprotein cholesterol (LDL-C) particle size, formal measurements of insulin resistance and glucose tolerance test, as well as inflammatory and thrombotic markers.[10]

There are other proposals for definitions such as the European Group for the Study of Insulin Resistance (EGIR),[11] the American Association of Clinical Endocrinologists (AACE),[12] the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI).[13] However, the efforts to harmonize definitions resulted in a consensus to use the IDF definition by Alberti *et al* in 2009.[14] Although these different diagnostic criteria for MetS vary in terms of the factor considered "central", all definitions include common clinical markers and have undeniably contributed to the detection of the increasing prevalence of MetS worldwide.[15]

Lately, the approach of concepts such as metabolic health and subphenotyping of metabolic risk has attracted attention to the scientific community. There is evidence which suggests that cardiometabolic risk stratification is not superior to established risk

prediction models. However, the addition of risk factors and the clustering approaches to identify subphenotypes might be informative to improve the prediction of cardiometabolic risk in subgroups of individuals with particular characteristics such as those in different BMI categories or with diabetes diagnosis. In addition, the communication of cardiometabolic risk to patients is easiest through the concept of metabolic health. Evidence is still missing with regards whether the allocation of individuals to a specific pathophysiological risk group could be helpful for prevention and treatment of cardiometabolic diseases.[16]

Due to the complex etiology behind the presence of each of the individual factors that comprise the MetS, its study as an interrelated entity becomes even more intricate. Its analysis across the '*omics*' sciences offers a picture of greater potential, by improving the ability of novel biomarkers to refine risk assessment for the disease.[17] Genetics and nutrigenetics stand out, explaining part of the interindividual variability in the presence of MetS and its relationship with dietary aspects. Although non-genetic factors such as diet and lifestyle remain the main trigger for the development of components of MetS linked to obesity, there is a growing evidence explaining how genetic variants, and their interaction with other environmental factors, modulate the risk of developing MetS.[18]

The aim of this review is to explore the most relevant and recent evidence on how genetic factors, particularly single nucleotide polymorphisms (SNPs) and their interaction with diet can determine an individual's risk for developing MetS or maintaining optimal cardiometabolic health. In turn, the pathway and challenges towards personalized nutrition in cardiometabolic health are discussed.

1. How do genetics affect cardiometabolic risk?

The risk components for MetS are complex entities, influenced by environmental factors such as diet, physical exercise, and lifestyle.[19] The so-called "obesogenic environment" that promotes an unhealthy diet, sedentary lifestyle, along with aspects of urbanization and difficult access to adequate nutrition, also affect the other markers of cardiometabolic risk. [20]

However, genetic variation remains an important force of phenotypic variation in MetS components.[21] In polygenic studies of disease, single nucleotide polymorphisms (SNPs) have been widely associated with an individual's predisposition to develop cardiometabolic abnormalities, including components of MetS.[22,23] The estimate of heritability of MetS as an entity varies between 10-30%.[24-26] On the other hand, as individual components, HDL-C is the trait with the highest heritability (30-80%), followed by waist circumference (30-70%), systolic blood pressure (20-71%), TG levels (30-72%), diastolic blood pressure (10-50%), and insulin levels (20-55%).[24,26]

Genome wide association studies (GWAS) and candidate gene studies have identified numerous SNPs significantly associated with the presence of MetS and its individual cardiometabolic components (Table II).

One of the most recent GWAS using data from the UK Biobank,[27] found 93 independent *loci* with a p-value $<5x10^{-8}$, associated with the MetS as a binary trait. Eighty out of these 93 variants had not been previously identified by their association with the trait; however, several variants had been associated with some of the individual components of the MetS. In a Korean population, 43 significantly associated *loci* were identified, in which 17

were novel.[28] Moreover, the rs662799 variant in the *APOA5* gene was associated with the presence of MetS, as previously reported in the Taiwanese population.[29] The authors also found significant association of the rs16944558 SNP in the *COLEC12* gene with the presence of MetS and an interaction with rs662799 in *APOA5* that promotes high levels of TG and low HDL-C.[29] Another study in India, comprising 10,093 individuals, reported two variants near the *CETP* gene, nominally associated with MetS, in addition to other modest signals reported for the first time.[30] On the other hand, in the Han Chinese population, two *loci* were identified in the *APOA5* and *ALDH2* genes, rs651821 and rs671, respectively, associated with the presence of MetS. In combined analyses they reported ORs and 95% CI of 1.28 (1.20, 1.36) and 0.71 (0.67, 0.76) for MetS risk, with the presence of C and A alleles in rs651821 and rs671 SNPs, respectively.[31]

There is evidence of the widely studied cluster region *APOA1/C3/A4/A5*, through the rs964184 SNP, associated with the presence of MetS and several lipid phenotypes in Finnish cohorts.[32] Also, in a population of European ancestry, 29 common variants associated with MetS (or at least with a couple of individual traits) were identified.[33] Some of the genes that showed the greatest significance were *LPL, CETP, APOA5, GCKR, LIPC, TRIB1,* among others.

Notably, most of evidence indicates that the top genetic signals are located mostly in genes related to lipid metabolism and obesity pathways.[34] Through metabolic and transcriptomic studies, it has been shown that most of the SNPs of greater association with MetS have shown significant association with various lipid metabolites such as very low-density lipoprotein cholesterol (VLDL-C),[33] intermediate-density lipoprotein cholesterol (IDL-C) and Apo B and none with glucose or glycoproteins,[32] which may

indicate that the genetic contribution to the development of MetS could be rather directed by the lipid component of this entity.

Regarding the approach of complex diseases such as MetS, it has been suggested to analyze their genetic etiology through polygenic risk scores (PRS), which include a series of risk alleles previously associated with the presence of MetS,[35] either as an entity or their individual traits, which added and weighted (beta or OR values) result in a score that can help to identify individuals with greater genetic susceptibility to develop the disease.

In the past, there were studies including PRS of tens of *loci* that conferred a higher risk of developing T2D compared to that of individual SNPs.[36] However, these marginally improved the predictive power of previously known clinical risk factors.[37] With the appearance of GWAS in larger cohort populations, the number of variants associated with MetS has increased, improving the predictive power of derived PRS.[38,39]

The aim of identifying and classifying risk groups at the extremes of the population distribution (i.e., those with highest percentiles) is becoming more popular due to the progress made in including a greater number of SNPs in the calculation of MetS PRS, as well as larger sample sizes.[40,41] However, the fact that greater inclusion of ethnically diverse populations, which are currently underrepresented in the GWAS is required, should not be overlooked.[42] This will allow in the future to improve the generalization and application of the indisputable benefits that PRS could bring to the clinical practice.

2. Genetic variants (SNPs) associated to cardiometabolic clinical markers

2.1 Obesity

Depending on the selected criteria, obesity can be one of the central components of MetS. However, due to its complexity, much of the etiology behind its origin is still unknown. Higher genetic susceptibility can increase the risk of obesity, although the impact of genes is greater when combined with the increasingly worsening obesogenic environment.[43] Recent evidence suggests that despite midlife obesity being independently associated with CVD, obesity influenced by genetic predisposition (i.e. individuals with genetically predicted high BMI) is less harmful than obesity influenced by environmental factors (i.e. individuals with obesity despite a genetically predicted low BMI). However, additional influencing factors such as other genetic variants could still affect these associations.[44]

Obesity is defined by an excessive accumulation of fat mass, however, there is large variability in the risk associated to metabolic disease according to different subphenotypes. Evidence suggests this could be partly due to the variability in fat distribution patterns.[45] The accumulation of visceral fat and an impaired ability to expand subcutaneous fat in the lower part of the body contributes to the increased incidence of cardiometabolic diseases.[46] In addition, genetic factors are a key determinant of fat distribution[47] with an heritability of 22-61%.[48] Within the last decade, hundreds of genetic variants associated to measures of fat distribution have been identified in GWAS,[49] mostly in European population. This is important since fat distribution patterns also differ among populations. For example, Asians have lower BMIs but higher total body fat and visceral fat accumulation than Europeans.[48]

The ratio of visceral adipose tissue (VAT) to subcutaneous adipose tissue (SAT) and the non-alcoholic fatty liver disease (NAFLD) lately named “metabolic dysfunction-associated

fatty liver disease" (MAFLD), play important roles in the increase of associated cardiometabolic diseases. VAT drains directly to the liver through portal circulation and contains a larger number of inflammatory and immune cells and a greater percentage of large and more metabolically active adipocytes, more sensitive to lipolysis and more insulin-resistant than SAT adipocytes.[50] Since most of the mechanisms of lipid metabolism are mediated by hormonal pathways,[51] and the adipose tissue is an endocrine organ itself, there is evidence that supports the association of adipokines to the development of metabolic diseases and T2D trough VAT augmentation. The chronic inflammation, neurohormonal activation and insulin resistance are among the proposed mechanisms involved in the progression of MetS and its comorbidities (Figure 1).[52] Notably, MAFLD is also an important cause of insulin resistance, its close relationship with visceral obesity conceals the role of fatty liver from VAT as the main pathomechanism of this relationship.[53] To this matter, the determination of major hepatokines and adipokines has been proposed to cluster insulin resistance in MAFLD and VAT in a pathomecanism-based way, i.e. attempt to differentiate the drivers of insulin resistance in metabolic dysregulation of white adipose tissue, skeletal muscle, or liver dysfunction.

Non-syndromic obesity can be classified as monogenic and polygenic, according to the participation of genes in its etiology. With regards the monogenic form, severe obesity (mainly early onset) is principally characterized by relative hyperphagia. Evidence suggests that around 5% of severe obesity cases in children can be attributed to this origin.[54] Four of the genes of the greatest association and study include the leptin (*LEP*), leptin receptor (*LEPR*), pro-opiomelanocortin (*POMC*) and melanocortin receptor-4 (*MC4R*).[55] These genes belong to the leptin/melanocortin pathway and play an important

role in the regulation of food intake since they encode proteins that act in the process at the hypothalamic level. These are centrally or peripherally produced molecules that influence appetite regulation.[56] Genetic variants in those genes have shown to be associated with variability on BMI and weight. For example, the variant Tyr35Ter (rs13447324) in *MC4R* has been associated with an excess of 7 kg of greater body weight in carriers (approximately 1 in 5,000 people).[57] However, despite being a mutation that results in the loss of total function (LoF) of *MC4R*,[58] it has been found to present incomplete penetrance, partly because normal-weight carriers of monogenic variants possess additional common variants that predispose them to a lower weight,[59] i.e., its low polygenic risk for obesity could compensate, at least in part, the risk caused by the mutation in *MC4R*.

In counterpart, obesity of polygenic origin, also called 'common obesity', represents the highest proportion of cases in the world, besides to being complex and exacerbated by the environment. The genetic component of common obesity is mostly given by the cumulative presence of multiple common genetic variants with little individual etiological contribution although, when added together, it can explain a greater proportion of the variability of body weight. The most studied variants for their abundance in the human genome are also SNPs. To date, more than 900 nearly independent SNPs associated with BMI,[60] and around 346 SNPs with body fat distribution.[49] To quantify the genetic predisposition of an individual, several PRS models have been proposed, including 12,[61] 20,[62] 32,[63] 56,[64] 97,[65] and 941 SNPs,[60] managing to explain a maximum proportion of the phenotypic variation of BMI of around 6%.[60] There are also several studies where these PRS have been replicated.[43] Furthermore, some genome-wide polygenic scores (GPS)

included 2.1 million genetic variants for the quantification of genetic predisposition to obesity over the life course of more than 300,000 people of European ancestry. [66] Longitudinally, a significant weight gradient was found between GPS deciles, which began in early childhood and reached a maximum difference of 12 kg at age 18. Notably, GPS allowed to identify 1.6% of the population with an increase in BMI like those with monogenic mutations. The model explained about 9% of the BMI variation, similarly to those results obtained in a Norwegian population.[67]

Despite the modest, but significant advances in the study of polygenic obesity, there is still a gap between BMI heritability that can be explained by SNPs (h^2_{SNPs}) according to the literature (21-30%).[65,68] However, the great potential of increasing the sample size of several populations in GWAS to detect a greater amount of common and rare associated *loci* and thus be able to explain more proportion of the total h^2_{SNP} is recognized.

Among the genes associated with obesity, the most widely studied is the fat mass and obesity-associated (*FTO*) gene.[69] In 2007, its polymorphisms were the first to be reproducibly associated with BMI.[70] Since then, the association of being a carrier of risk alleles in SNPs in the *FTO* gene has been replicated by several authors.[71] However, the contribution of these SNPs to BMI variability remains modest, with carriers of the rs9939609 risk allele estimated to weigh about 3 kgs more and being 1.67 times more likely to develop obesity compared to non-carriers.[70] Other genes identified by their association with obesity have been studied. Interestingly, many of them have been found to be involved in neurogenesis, central nervous system (CNS) development, and in signaling pathways related to appetite and dietary intake regulation.[60] A compendium of human genes that regulate eating behavior and body weight was published, including 578

genes which were ordered according to their biological role in the regulation of body weight and classified by their expression patterns or functional characteristics.[72]

Among the main genes whose *loci* have been identified and replicated by various studies for their association to body weight and BMI are *FTO* ,[70,73] *MC4R*,[74,75] *POMC*,[63,76] *BDNF*, [77,78] *TCF7L2*,[49,65,79] *LINC01875, TMEM18*,[80-82] *ADCY3*,[49,76,83] among many others.

Beyond genetic factors, some of the latest advances in obesity study have been directed to the identification of multiomic signatures of BMI. Despite the use of a single targeted metric (for example, BMI) or a single specific biomarker that provides useful information to quantify health and disease states, multiomic blood profiling which includes human genomes and longitudinal measurements of metabolomics, proteomics, clinical laboratory tests, gut microbiomes, physical activity, and health/lifestyle data, could help close the knowledge gaps between BMI and heterogeneous physiological states in a multifaceted manner. With regards to lifestyle interventions, the multiomic signatures can predict responses in a heterogeneous way; omics-inferred BMI behaves different than the actual BMI measurement in response to treatment. This highlights the fact that multiomic profiling could be a resource to quantify the changes in obesity status and metabolic health for predictive and preventive medicine.[84]

2.2. Insulin resistance and type 2 diabetes

Insulin resistance, defined as the inability of insulin to stimulate the use of glucose in the body that can eventually lead to T2D, is the central component of most pathophysiological models of MetS. For several authors, this represents the underlying factor for the development of this pathological entity. Insulin sensitivity/resistance is closely related to

coronary artery disease (CAD),[85] one of the main outcomes of MetS. Its presence has increased in recent years, with a current prevalence of 15.5-40% worldwide.[86]

Depending on the diagnostic criteria, insulin resistance may be represented by different biochemical concepts and parameters. The inclusion of easily accessible biochemical parameters associated with hyperglycemia and insulin resistance, such as plasma glucose measurements, arose from the need to have criteria that would allow a lower cost and affordable diagnosis, particularly in studies including large study populations.[87] According to the American Diabetes Association (ADA), diabetes could be diagnosed by a fasting plasma glucose ≥126 mg/dl (7.0 mmol/L) or a 2-h plasma glucose ≥200 mg/dl (11.1 mmol/L) during OGTT or A1C ≥6.5% (48 mmol/mol) or by classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).[88]

Insulin resistance has been studied through GWAS and association studies where common genetic variants involved in the presence of T2D as a phenotypic trait have been evaluated. To date, more than 240 *loci* associated with T2D have been found, corresponding to more than 400 genetic variants.[41] The vast majority of *loci* related to this pathology are those associated with insulin secretion and beta cell function in the pancreas and to a lesser extent with insulin resistance.[89] This has a possible explanation in the complex etiology and pathophysiology of T2D, as well as its close relationship with obesity and plasma lipid levels. Some of the genes that have shown association with IR and T2D are *PPARG*,[90] *IRS1*,[91] *ADAMTS9*,[92] *KLF14*,[93] *ARL15*,[94] *FTO*,[95] among others.

One of the genes with the greatest contribution to T2D susceptibility is *TCF7L2* ,[96] in which the risk allele has been related to insulin secretion.[97] These effects have been

replicated in various populations by GWAS,[83,98] with the SNP rs7903146 being one of the most relevant SNPs. This SNP, which is located in an intronic region, has similar allelic frequencies worldwide, with the exception of East Asia where the risk allele remains relatively rare.[99] The presence of the T allele in rs7903146 has been shown to strongly predict the development of T2D and it is associated with increased expression of *TCF7L2* in human islets, as well as altered insulin secretion both *in vitro* and *in vivo* studies.[100]

Another gene of great importance for its association with diabetes mellitus, insulin resistance and MetS is *HMGA1* which has among its functions the regulation of insulin receptor (*INSR*) gene expression. HMGA1 is a master regulatory factor for gluconeogenesis and glycogenolysis, as well as a positive regulator of insulin expression; [101] consequently, being associated with the presence of T2D in different populations.[102] One of the studies of greater collaborative effort aimed to elucidate the genetic architecture of T2D hypothesized that the heritability of T2D, not yet fully explained by common variants, could be given by low-frequency variants.[103] However, the associated variants that they found (approximately 126 variants) were mostly common and identified by previous studies.

2.3. Serum triglyceride and HDL cholesterol levels

The presence of MetS increases the risk of cardiovascular disease and atherosclerosis, however, alterations in lipid metabolism are an independent risk factor for CAD.[104] The lipid markers considered for MetS are TG and HDL-C levels. The presence of hypertriglyceridemia (HTG) alone, defined as an elevation of circulating TG levels, usually >150-175 mg/dL (1.71-2 mmol/L), or in conjunction with other abnormalities such as

decreased levels of HDL-C tend to cluster in families.[105] Genetic factors influencing plasma TG levels explain about 40% of interindividual variations, while 49% is explained on the variation of the TG/HDL-C index.[106]

In the postgenomic era, HTG, formerly classified as primary or secondary, is accepted as a complex ethology phenotype, except for the very rare familial chylomicronemia syndrome (FCS), with an autosomal recessive Mendelian inheritance. In most cases, their predisposition is given by the presence of common genetic variants of small effects that interact with rare heterozygous variants of great effect in genes that regulate the synthesis or catabolism of triglyceride-rich lipoproteins or with non-genetic factors, this can lead to the expression of more severe HTG phenotypes.[107]

GWAS studies have identified SNPs in at least 45 *loci* associated with plasma TG levels alone or in combination with other lipoproteins.[108,109] For example, the *locus* 1q21-23 has been associated with different lipid traits such as HTG, where the group of genes *APOA1/C3/A4/A5* is related to the presence of FCS.[110] Similarly, the *USF1* gene is related to various target genes related to glucose and lipid metabolism.[111]

The polygenic risk for HTG can be quantified by using PRS.[112,113] A recent study found that ~2% of patients with severe HTG had a high PRS (16 *loci*) compared to 9.5% of normolipemic controls.[107] However, the genotype-phenotype relationship is probabilistic and non-deterministic. Some of the *loci* belonging to this PRS are located in the *DOCK7*, *KLHL8*, *GALNT2*, *MLXIPL*, *LPL*, *FADS*, *APOA*, *CETP*, *SUGP1*, *PLTP* genes, among others. The results found by recent studies suggest that non-genetic factors may lead to the presence of HTG in people with genetic predisposition, either through a rare variant or a high polygenic risk, or both.

Low HDL-C levels are a widely discussed risk marker for CAD and its functionality has been reappraised in recent years. Its role is mainly affected by both the heterogeneity of this lipoprotein class and the extensive remodeling of the HDL size and lipid and protein content during their physiological maturation.[114] However, as a risk marker, represents the most common lipid abnormality in patients with CAD.[115] HDL particles have multiple antiatherogenic effects, mainly through the removal of cholesterol from peripheral tissues to the liver, this reverse transport of cholesterol prevents macrophages from arterial walls from turning into foamy cells, which are progenitors of atherosclerotic plaque.[116] Additionally, HDL has antioxidant, antithrombotic, and anti-inflammatory properties.[117]

As for the genetic factors associated with decreased HDL-C levels, there are monogenic forms that lead to extreme phenotypes; however, these causes are rare and explain a minimal portion (~1%) of low HDL-C cases. For example, *APOA1* deficiency causes HDL-C levels <5 mg/dl (0.13 mmol/L), normal LDL-C and TG levels .[118,119] Likewise, defects in genes such as *ABCA1*,[118,120] *LCAT,*[121] and *LPL*,[122] among others, cause deficiencies and familial syndromes causing extremely low HDL-C levels.

The most common genetic disorder causing low HDL-C levels is familial hypoalphalipoproteinemia (FHA)[123] but even in this case, studies suggest that most hereditary patterns for low HDL-C are polygenic.[124] Several studies have constructed PRS for the risk of low HDL-C in conjunction (or not) with other lipid traits and risk of CVD.[107,125]

Regarding the relationship of HDL-C levels and MetS, a 5-year longitudinal follow-up study showed that the incidence of MetS is higher in individuals with decreased HDL-C

levels.[126] The authors mention that this important factor appears to be a pre-existing phase of MetS and could be a crucial state for prevention.

2.4 High blood pressure

Hypertension (HTN) is characterized by high systolic and/or diastolic blood pressure, and is a major risk factor for heart failure, stroke, kidney disease, and cardiovascular death.[127]

Several studies, mostly GWAS have set out to reveal the genetic architecture of HTN, uncovering hundreds of novel common and rare variants in trans-ethnic study populations of hundreds of thousands individuals.[128,129] Additionally, most blood pressure-associated SNPs are non-coding and found in regulatory elements of the genome.[130]

However, being an extremely complex entity, the environment and gene-environment interactions have a contribution of great weight that is not taken into account in most current GWAS studies.[131] Within these elements of interaction, prenatal environmental factors such as intrauterine and parental[132] and other postnatal factors such as the living environment, lifestyle, age, sex, socioeconomic status, ethnicity, among others, are also considered.[133]

Environmental risk factors traditionally considered such as an excess sodium in the diet were adaptive traits for the hot, humid, salt-free environment of ancient Africa. From an evolutionary point of view, there is a discrepancy between the current lifestyle and that of ancestors, which results in a poor adaptation that can lead to an increased risk of developing HTN.[134]

In Figure 2, we present a summary of some of the genes most frequently mentioned in GWAS and candidate genes studies.

3. Gene-diet interactions associated to cardiometabolic markers.

The study of the genetic component, responsible for the variation in phenotypes associated with MetS, has managed to explain only a proportion of this variability. Part of this "lost heritability" could be given by the interactions between genes and the environment (GxE) of individuals.[135]

One of the most studied GxE with regards to the components of MetS are those of the *FTO* gene and its interaction with diet. For example, in a recent study in a Middle Eastern population, dietary fiber consumption was found to modulate the association of a PRS of 6 SNPs in relation to obesity, where people with a higher PRS but a consumption ≥14 g/day were less likely to develop obesity, compared to those with lower PRS but low fiber intake.[136] Previous studies also found similar interactions.[137,138]

Other interactions of the *FTO* gene with dietary patterns such as adherence to a Mediterranean diet have been studied, for example, modulating the risk of diabetes. The increased risk effect of diabetes in individuals with the common variant rs9939609 is neutralized with high adherence to the Mediterranean diet.[139]

Similarly, a study that included a PRS with 16 genetic variants previously associated with obesity found significant interaction between higher animal protein intake and higher body fat mass in people within the higher genetic risk group, and a protective effect of higher plant protein intake for people belonging to the lower genetic risk group.[140]

The consumption of fried food has also shown interaction in a PRS with 32 variants associated with BMI, where the greatest effect of genetic predisposition was observed in individuals with a high consumption (≥4 times per week) of fried foods, compared to those who consumed them less than 1 time per week, regardless of their high PRS.[141]

Sodium intake is a significant environmental factor in modifying blood pressure values, and unexplained blood pressure variability in GWAS may result from gene-environment interactions (GxE).[142,143] For example, sodium consumption has shown interaction with various *loci* in genes such as *CLGN*, *MKNK1*, *EPHA6* and *CASP4*,[143] among others; however, the mechanisms through which these regulate blood pressure are still unknown. Nevertheless, interesting interaction trends have been observed, where people with higher PRS are less sensitive to modifications in dietary sodium intake, denoting that apparently for them the greatest influence comes from genes.[144]

On the other hand, it has been postulated that dietary fatty acid consumption might not uniformly influence individuals' blood lipid levels. A recent publication showed evidence of interactions of variants such as rs5882 in the *CETP* gene, where a higher consumption of monounsaturated fatty acids in carriers of the main allele presented lower serum TG levels, as well as the rs13708 variant of the *LPL* gene whose interaction was observed in higher HDL-C levels when consuming a diet with higher lipid content.[145]

These findings may explain the variation in the effectiveness of certain dietary interventions for the prevention or treatment of obesity and other traits of MetS, highlighting the importance of a healthy diet and lifestyle, especially in people who might have a higher genetic susceptibility to develop MetS.

4. What is the future of personalized nutrition for the improvement of cardiometabolic health?

Personalized nutrition has its focus on the design of "tailored" nutritional recommendations and treatments, based on the individual genetic arrangement, to treat or prevent various pathologies and metabolic disorders.[146] Personalized nutrition is a strategy that can help individuals to adopt lasting changes in dietary behavior, which are beneficial to their health.[147]

As previously mentioned, several studies focused on gene-environment interaction have provided relevant results in the study of MetS and its components. These could be a key piece in the implementation of personalized interventions based on genetic arrangement. Additionally, the fact that nutrigenetics has improved from analyzing individual genetic variants to integrating PRS and looking for complex interactions with pathological states such as obesity, denotes the important and necessary evolution in this field.[148] However, what evidence do we have so far of its effectiveness and implementation in the clinical practice? Through the generation of PRS_{MetS} and their validation on big datasets it has been possible to test early prevention strategies in individuals with high genetic risk, demonstrating benefits, for example, in reducing cardiometabolic events such as atherosclerotic cardiovascular disease (Fig. 3).[149]

Furthermore, there are some studies that have evaluated the effectiveness of interventions based on personalized nutrition.[150-152] These results suggest that the use of this strategy offers advantages over generalized "one-size-fits-all" diets, improving clinical outcomes and achieving greater reductions in discretionary food intake, as well as, facilitating the change in people's dietary behavior and improving acceptance and

adherence to nutritional treatment. However, multiple questions remain, and it is not entirely clear which aspects of personalization offer the greatest advantage over generalized strategies.

Regarding cardiometabolic health, studies have revealed that different dietary patterns and macronutrient intake have weight in modifying and reversing the presence of MetS components.[153,154] For example, there have been revealed genetic variants that could be considered when referring to certain dietary treatments, such as the low-carbohydrate diet, whose results could be affected by the presence of SNPs such as rs694066 (*GAL*)[155] and rs5950584 (*AGTR2*),[156] where people carrying different alleles tend to lose more or less weight and body fat when following a ketogenic diet.

There are recent GWAS that have been shown evidence about the potential clinical utility in the assessment and treatment of MetS and other related cardiometabolic traits (Table III).[149,157]

However, it is necessary to consider other factors, not only genetic, but others such as epigenetics, metabolomics, microbiome, to name a few, in the study of such complex entities as MetS.[158] This leads to the advancement from personalized nutrition to precision nutrition, whose main goal is to efficiently anticipate people's response to dietary recommendations, by considering the greatest number of biological-environmental aspects associated with health and disease states.[159,160]

Conclusions

There is evidence of the important role of genetics on the development of MetS and its individual components, however, there is still an important gap in the clinical implementation of personalized nutrition, successfully achieving prevention and decreasing of the prevalence of this pathological entity around the world. The most current evidence mentions that the study of the interaction of genes with the growing obesogenic environment is possibly a key piece to unite this gap. The advance towards precision nutrition in cardiometabolic health issues is still in its infancy, however, its progress has been increased in the last decade with the growth of omics sciences.

Authors' contributions

DPO wrote the initial draft and ID and FFGG reviewed and contributed extensively to the manuscript writing.

Author Disclosure Statement

The authors declare that no conflict of interest exist.

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Table I. Diagnostic criteria for MetS, according to ATP III, WHO, IDF and AHA/NHLBI.

Risk factors	ATP III[9]	WHO[8]	IDF[14]	AHA/NHLBI[13]
Blood pressure	≥130/≥85 mmHg	≥160/≥90 mmHg	≥130/≥85 mmHg	≥130/≥85 mmHg or drug treatment
Glucose levels	Fasting: ≥110 mg/dL (6.1 mmol/L) or T2D	IGT or IFG orT2D and/or IR	≥100 mg/dL (5.6 mmol/L) or drug treatment or T2D	≥100 mg/dL (5.6 mmol/L) or T2D or drug treatment
Triglyceride levels	≥150 mg/dL (1.7 mmol/L)	≥150 mg/dL (1.7 mmol/L)	≥150 mg/dL (1.7 mmol/L) or drug treatment	≥150 mg/dL (1.7 mmol/L) or drug treatment
HDL-C	<40 mg/dL (1 mmol/L) M <50 mg/dL (1.7 mmol/L) W	<35 mg/dL (0.9 mmol/L) M <39 mg/dL (1 mmol/L) W	<40 mg/dL (1 mmol/L) M <50 mg/dL (1.7 mmol/L) W or drug treatment	<40 mg/dL (1 mmol/L) M <50 mg/dL (1.7 mmol/L) W or drug treatment
Abdominal obesity	WC >102 cm (40 in) M >88 cm (35 in) W	WHR >0.90 M >0.85 W and/or BMI >30 kg/m^2	Population- and country-specific definitions	WC ≥102 cm (≥40 in) M ≥88 cm (≥35 in) W
Microalbuminuria	-	Urinary excretion rate ≥20 μg min^{-1} or albumin:creatinine ratio ≥20 mg g^{-1}	-	-
Diagnosis of MetS:	≥ 3 risk factors	IFG, IGT or T2D and/or IR together with ≥2 additional risk factors	Abdominal obesity and ≥2 risk factors	≥ 3 risk factors

AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; ATP III, the Panel for the Treatment of Adults III; BMI, Body Mass Index; F, female; HDL-C, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; IFG, impaired fasting glucose, defined by WHO as fasting <110 mg/dL (<6.1 mmol/L) and 2-h post glucose load ≥110 mg/dL (≥6.7 mmol/L) <180 mg/dL (<10 mmol/L); IGT, impaired glucose tolerance, defined by WHO as fasting ≥100 mg/dL (≥5.6 mmol/L) <110mg/dL (<6.1 mmol/L) and 2-h <120 mg/dL (<6.7 mmol/L); IR, insulin resistance; M, male; MetS, metabolic syndrome; T2D, type 2 diabetes; WC, waist circumference; WHO, World Health Organization; WHR, waist-hip ratio.

Table II. Principal GWAS published with metabolic syndrome as associated trait.

Publication year	Title	Discovery sample and ancestry	Reference
2021	Genome-wide association analysis of metabolic syndrome quantitative traits in the GENNID multiethnic family study	1520 Multiethnic	[161]
2020	Genome-wide association study of metabolic syndrome in Korean populations.	7423 East Asian	[28]
2019	Genome-Wide Association Study of the Metabolic Syndrome in UK Biobank.	291107 European	[27]
2019	Genome-Wide Association Study of Metabolic Syndrome Reveals Primary Genetic Variants at CETP Locus in Indians.	2158 South Asian	[30]
2019	Identification of female-specific genetic variants for metabolic syndrome and its component traits to improve the prediction of metabolic syndrome in females.	4659 East Asian	[162]
2018	Multiple genotype-phenotype association study reveals intronic variant pair on SIDT2 associated with metabolic syndrome in a Korean population.	7198 East Asian	[163]
2018	New Common and Rare Variants Influencing Metabolic Syndrome and Its Individual Components in a Korean Population.	8373 East Asian	[164]
2017	Detection of susceptibility loci on APOA5 and COLEC12 associated with metabolic syndrome using a genome-wide association study in a Taiwanese population.	10300 East Asian	[29]
2017	Susceptibility loci for metabolic syndrome and metabolic components identified in Han Chinese: a multi-stage genome-wide association study.	1742 East Asian	[31]
2014	Pathway Analysis of Metabolic Syndrome Using a Genome-Wide Association Study of Korea Associated Resource (KARE) Cohorts.	8842 East Asian	[165]
2012	Genome-wide screen for metabolic syndrome susceptibility Loci reveals strong lipid gene contribution but no evidence for common genetic basis for clustering of metabolic syndrome traits.	10564 European	[32]
2011	A bivariate genome-wide approach to metabolic syndrome: STAMPEED consortium.	22161 European	[33]
2010	A genome-wide association study of the metabolic syndrome in Indian Asian men.	2554 South Asian	[166]

Table III. Evidence from recent large GWAS and PRS studies and their potential clinical utility in the assessment and treatment of MetS and other related cardiometabolic traits.

Author, year	Population studied	PRS model	Results	Conclusions	Potential Clinical utility
Song H et *al*., 2022	3 Korean cohorts of 28,445, 8840 and 4333 individuals.	PRS_{MetS}-ASCVD: construction of the most optimal combination of PRS's for prediction of ASCVD.	6.7% of the population was at high genetic risk with 3.3-fold (95% C.I. 1.7-6.1, p<0.001) higher risk for incident ASCVD.	The polygenic risk of metabolic disease independently predicts those at an increased risk of ASCVD, identifying those at a genetically high risk of incident ASCVD.	The combination of PRS_{MetS}-ASCVD and conventional risk factors (such as age, sex, BMI, smoking, hypertension, diabetes and hyperlipidemia) could provide a better performance for predicting ASCVD, especially in younger individuals.
Eva S. van Walree *et al*., 2022	3 cohorts of European and multi-ancestry representation	Polygenic risk score drafted from the MetS factor GWAS.	PRS predicts 5.9% of the variance in MetS. Of the 235 loci identified in the GWAS, 53 (22.5%) overlap with loci identified for two or more MetS components.	Genetic correlations are best captured by a genetic one factor model. The MetS components genetic overlapping indicates that this entity is a complex, heterogeneous disorder.	These results provide mechanistic insights into the genetics of MetS and suggestions for drug targets, especially fenofibrate, which has the promise of tackling multiple MetS components.
Hardy, D.S. *et al*., 2021	10,681 European Americans and African Americans.	PRS and its interaction with dietary patterns to increase MetS risk.	Among each racial group within PRS tertiles, the Western dietary pattern was associated with development and cycling of MetS status between visits, and the high-fat dairy pattern with being free from MetS (p < 0.017).	The influence of dietary patterns on MetS risk appears to differ by genetic predisposition and racial ancestry.	Dietary patterns assessment becomes more important, especially for individuals with higher genetic risk for MetS. Routinely clinical-nutritional consultations could provide a clearer image of the overall increased risk for MetS in some individuals.

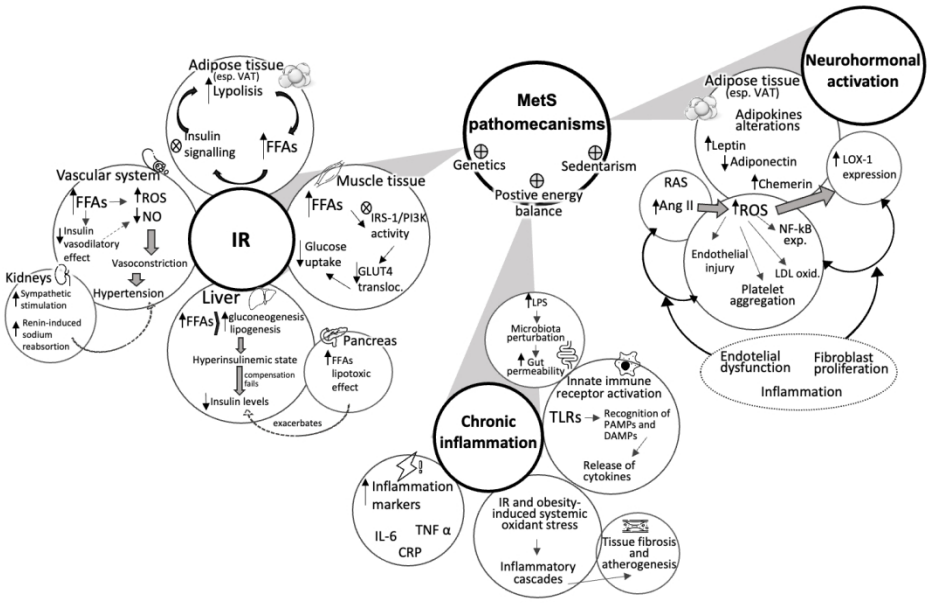
PRS, polygenic risk score; ASCVD, atherosclerotic cardiovascular disease; PRS_{MetS}-ASCVD, metabolic PRS to identify atherosclerotic cardiovascular disease incidence; BMI, body mass index; MetS, Metabolic syndrome; GWAS, Genome-wide association study.

Figure legends

Figure 1. Main pathomecanisms associated to the development of MetS.
Ang II, angiotensin II; CRP, C-reactive protein; DAMPs, damage-associated molecular patterns; FFAs, free fatty acids; GLUT4, glucose transporter type 4; IL-6, interleukin 6; IR, insulin resistance; IRS-1/PI3K, insulin receptor substrate-associated phosphoinositide 3-kinase activity; LDL, low density lipoprotein; LOX-1 lipoprotein receptor-1; LPS, lipopolysaccharides; MetS, metabolic syndrome; NF-kB, nuclear factor kappa-light-chain enhancer of activated B cells; NO, nitric oxide; PAMPs, pathogen-associated molecular patterns; RAS, renin–angiotensinogen system; ROS, reactive oxygen species; TLRs, Toll-like receptors; TNF α, tumor necrosis factor α; VAT, visceral adipose tissue.

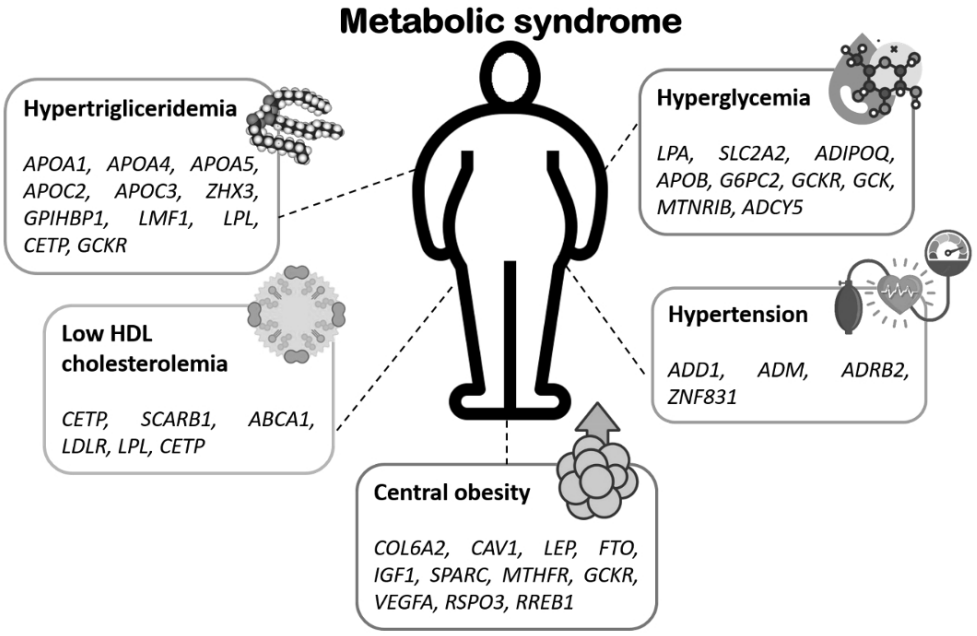
Figure 2. Main genes associated to the presence of MetS components.

Figure 3. Generation, validation, and application of PRS_{MetS} and its components.



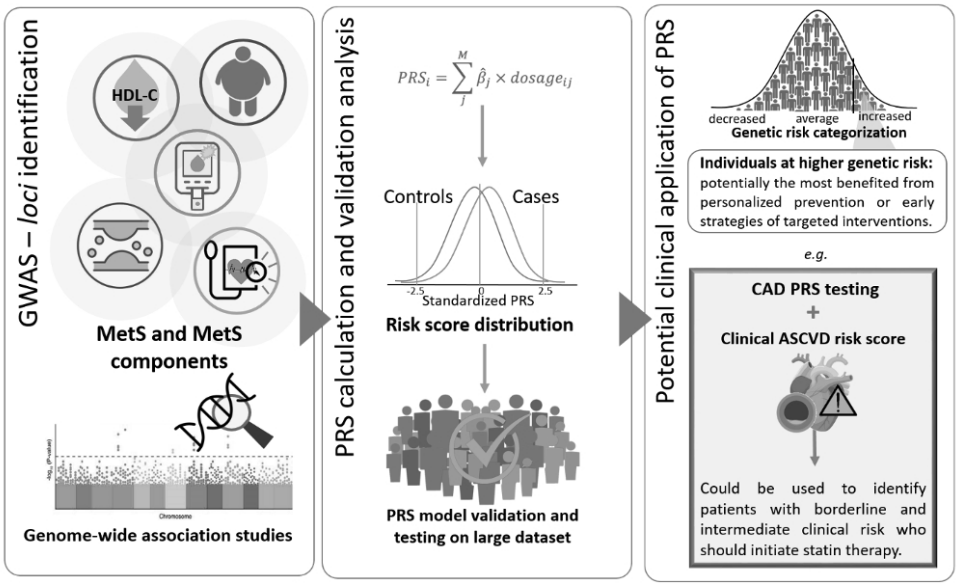
Main pathomecanisms associated to the development of MetS.
Ang II, angiotensin II; CRP, C-reactive protein; DAMPs, damage-associated molecular patterns; FFAs, free fatty acids; GLUT4, glucose transporter type 4; IL-6, interleukin 6; IR, insulin resistance; IRS-1/PI3K, insulin receptor substrate-associated phosphoinositide 3-kinase activity; LDL, low density lipoprotein; LOX-1 lipoprotein receptor-1; LPS, lipopolysaccharides; MetS, metabolic syndrome; NF-kB, nuclear factor kappa-light-chain enhancer of activated B cells; NO, nitric oxide; PAMPs, pathogen-associated molecular patterns; RAS, renin–angiotensinogen system; ROS, reactive oxygen species; TLRs, Toll-like receptors; TNF α, tumor necrosis factor α; VAT, visceral adipose tissue.

566x347mm (72 x 72 DPI)



Main genes associated to the presence of MetS components.

382x247mm (72 x 72 DPI)



Generation, validation, and application of PRSMetS and its components.

365x218mm (72 x 72 DPI)