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SYSTEMATIC REVIEWS AND META-ANALYSES

Early identification of metabolic syndrome risk: A review of reviews and proposal for defining pre-metabolic syndrome status

Eva Gesteiro [a,*], Ana Megía [b,c,d], Amelia Guadalupe-Grau [a], Sonia Fernandez-Veledo [b,c], Joan Vendrell [b,c,d], Marcela González-Gross [a,e]

[a] ImFINE Research Group, Department of Health and Human Performance, Universidad Politécnica de Madrid, Madrid, Spain
[b] Hospital Universitari de Tarragona Joan XXIII-Institut d'Investigació Sanitària Pere Virgili (IISPV), Tarragona, Spain
[c] CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM)-Instituto de Salud Carlos III, Madrid, Spain
[d] Rovira i Virgili University, Tarragona, Spain
[e] CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN)-Instituto de Salud Carlos III, Madrid, Spain

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Risk score

Abstract *Aims:* a) To analyze the relationship of known and emerging biomarkers/indicators for early risk identification of cardiometabolic health risk; b) to identify early risk markers to be used in both clinical and nonclinical settings; and c) to propose a definition of early risk identification in terms of pre-metabolic syndrome (PreMetSyn).
Data synthesis: Pubmed/Medline, Web of Science, Embase, and Cochrane were searched for Systematic Reviews and Meta-analysis. Selected studies were evaluated, and relevant data were extracted and synthesized.
Conclusions: Serum uric acid is a good predictive biomarker of metabolic syndrome (MetSyn) and has been associated with non-alcoholic liver fat disease (NAFLD) and type 2 diabetes. NAFLD emerges as an early risk indicator of PreMetSyn by itself. Muscle strength should also be included as an early risk marker of cardiometabolic health. High serum triglycerides and waist circumference confirm their predictive value regarding MetSyn. Indicators related to an inflammatory/pro-inflammatory status usually linked to MetSyn showed limited evidence as robust biomarkers for PreMetSyn. Authors suggest defining PreMetSyn related to cardiometabolic risk. It is also necessary to determine how close people are to the cut-off point of MetSyn components, including emerging indicators proposed by our review. Some biomarkers could be used as indicators of PreMetSyn, before any of the MetSyn components appear, allowing early health interventions to prevent its development. Defining a PreMetSyn status might consider both emerging indicators and those variables already included in the definition of MetSyn. New indicators should be considered to create a new risk score specifically meant for PreMetSyn.

* Corresponding author. Facultad de Ciencias de la Actividad Física y del Deporte-INEF, Universidad Politécnica de Madrid, C/ Martín Fierro 7, 28040, Madrid, Spain.
E-mail addresses: eva.gesteiro@upm.es (E. Gesteiro), amelia.guadalupe@upm.es (A. Guadalupe-Grau).

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Introduction

Cardiometabolic diseases are among the leading morbidity and mortality causes in both developed and developing countries. In 2016, more than 1900 million adults, ≥18 years old, were overweight (39%). Of these over 650 million were obese (13%) [1]. The prevalence of type 2 diabetes mellitus (T2DM) was estimated in 500 million people worldwide [2], around 60 million in Europe [3]. Cardiovascular (CV) diseases (CVDs) are the number one cause of death globally, taking an estimated 17.9 million lives each year. CVDs are a group of disorders of the heart and blood vessels and include coronary heart disease (CHD), cerebrovascular disease, rheumatic heart disease, and other conditions. Four out of 5 CVD deaths are due to heart attacks and strokes, and one-third of these deaths occur prematurely in people under 70 years of age [4].

There is a quite large amount of literature addressing the topic about the causes and consequences of a "bad metabolic health" on different endpoints for a plentiful of diseases, including CVDs, obesity, T2DM, nonalcoholic fatty liver disease (NAFLD), sleep apnea, hypertension, stroke, and cancer among others. However, there is scarce scientific evidence about what we can consider a "normal metabolic health status" in a convincing way that can be assumed without discussion by the scientific community. The insulin resistance (IR) classification has been one of the main drivers around which an attempt was made to build a definition of a healthy metabolic status in humans. The absence of IR or low subclinical inflammation (usually determined by C-reactive protein (CRP) levels) in combination with the presence of fewer than 2 parameters associated with metabolic syndrome (MetSyn) are claimed as the gold standard for a metabolically healthy (MH) status in a wide number of studies [5,6]. However, estimation of IR and subclinical inflammation are usually absent or roughly defined in most of the studies, and more importantly, there are no studies awarding the same pathophysiological mechanisms for the risk factors in lean people than in obese population in terms of metabolic derangements.

In a recent report trying to define the phenotypes to identify the people at risk of having a "bad metabolic health" the authors claim about the existence of a lipodystrophy-like phenotype in the general population. In order to unify criteria to define a MH status, Stefan et al. (2017) proposed cut-off values for the most frequent criteria associated with metabolic disturbances, suggesting that fewer than two should be given to define subject as MH [7]. In the opposite side of the spectrum, we found the MH obese (MHO) subjects who despite the presence of obesity appear to be in a MH status. The main concern of this scenario is the absence of a clear definition of this condition, including more than 30 different criteria used to identify these subjects. This led to a high variability in the prevalence of MHO in the literature ranging from 10 to 45% [8,9].

Early risk identification has been a priority for clinicians and researchers for a long time. Kylin already described what we call now MetSyn in 1923 [10]. MetSyn is an artificial construction defined by the most frequent association of pathology that is accompanied by greater CV morbidity and a higher prevalence in the onset of T2DM. In fact, its definition is not considered based on a particular pathophysiological mechanism, but rather a pragmatic approach to obtain a final clinical benefit, trying to improve its components based on a healthy lifestyle and a healthy improvement in the variables associated with it.

IR was initially proposed as the common driver in the components of MetSyn (high blood pressure, obesity, dyslipidemia, and hyperglycemia), even when it does not represent a pathology itself. On the contrary, WHO and EGIR include IR among the MetSyn criteria [11].

Scientific societies (International Diabetes Foundation (IDF), National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII), American Heart Association (AHA), World Heart Organization (WHO), etc.) have taken part in the matter and agreed on criteria for defining MetSyn (obesity, high triglyceride (TG) levels, low HDLc, hypertension, IR/hyperglycemia), but without strong evidence on the weight of each of them over the rest [11]. Very interesting is the view that Reaven offers on MetSyn and the determinants that are considered part of it [12]. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) did the same in a joint communication [13]. Independently of disagreements, it is a fact that they all agree on the markers but mainly disagree on the cut-off values for increased risk or the combination of those.

However, it is known that other determinants, such as chronic inflammation, may have a predictive capacity like that of IR or to the components of MetSyn themselves, in the onset of both T2DM and CV events [14]. While as is often the case, not all studies link these markers with increased risk of MetSyn and/or CV events [15,16].

It is a fact that currently there seems to be more predictable factors for cardiometabolic-related diseases than those included in the MetSyn definitions. Therefore, the aims of this review were: a) to analyze the relationship of known and emerging biomarkers/indicators for early risk identification of cardiometabolic health risk; b) to identify early risk marker that could be used in both clinical and nonclinical settings; c) to propose a new definition of early risk identification in terms of pre-metabolic syndrome (PreMetSyn).

Methods

Literature search

A systematic-similar approach considering PRISMA indications was followed. Pubmed/Medline, Web of Science, Embase, and Cochrane were searched for Systematic Reviews and Meta-analysis according to the following Medical Subject Headings (MeSH) terms: >Prehypertension OR Diastolic blood pressure OR Systolic blood pressure OR Heart rate OR Insulin resistance OR Hyperglycemia OR Impaired glucose tolerance OR Impaired fasting glucose OR

Glucose intolerance/Glucose tolerance OR Prediabetes OR Hyperinsulinism OR Waist circumference (WC) OR Waist-to-hip ratio (WHR) OR Body mass index (BMI) OR Overweight OR Abdominal obesity OR Abdominal fat OR Adiposity OR Thinness OR Hypertriglyceridemia OR High low-density lipoprotein cholesterol (HDL-c) OR Low high-density lipoprotein cholesterol (LDL-c) OR Triglycerides (TG) OR Physical fitness OR Cardiorespiratory fitness OR Strength OR Physical function and performance>. Selected titles and abstracts were reviewed at least by two researchers and selected articles were agreed among all authors.

Additional suitable studies and other relevant reviews were included from the reference lists of selected papers.

Inclusion and exclusion criteria

Inclusion criteria are as follows: systematic reviews and meta-analysis published between 2012 and 2020 including European data; adults aged 20 to 45.

Analysis of each study was performed by one researcher, and final data included in the table in annex followed an analysis and consensus of the research group. Data in this Table are focused on the new biomarkers related to Pre-MetSyn found and their relationship with the already known components of MetSyn. The linkage to PreMetSyn is commented, as well as the type of study and the supporting references.

Results and discussion

Search results

From the first search, 9866 studies were obtained and 298 were initially selected, and finally, 95 systematic reviews and meta-analysis were included (Fig. 1). Those systematic reviews that fitted better the aims of our research are analyzed in the table in Appendix. In the RESULTS and Discussion section only those with at least evidence are commented.

Indicators related to anthropometric and clinical variables

There are some anthropometrical measurements useful in determining some MetSyn components [17,18]. Bellou et al. (2018) performed an umbrella-review about risk factors for T2DM, finding that high BMI, waist circumference (WC), waist-to-hip ratio, waist-to-height ratio, and low hip circumference were associated with high risk of T2DM, supported by a highly suggestive evidence [19]. Waist-to-height ratio seems to be also a good tool in assessing adiposity and obesity in the elderly [20]. Neck circumference is an easy-to-obtain measurement, and it has shown positive associations with some MetSyn-related parameters such as WC, blood pressure, fasting glucose, BMI, total cholesterol (TC), and LDLc, and negative

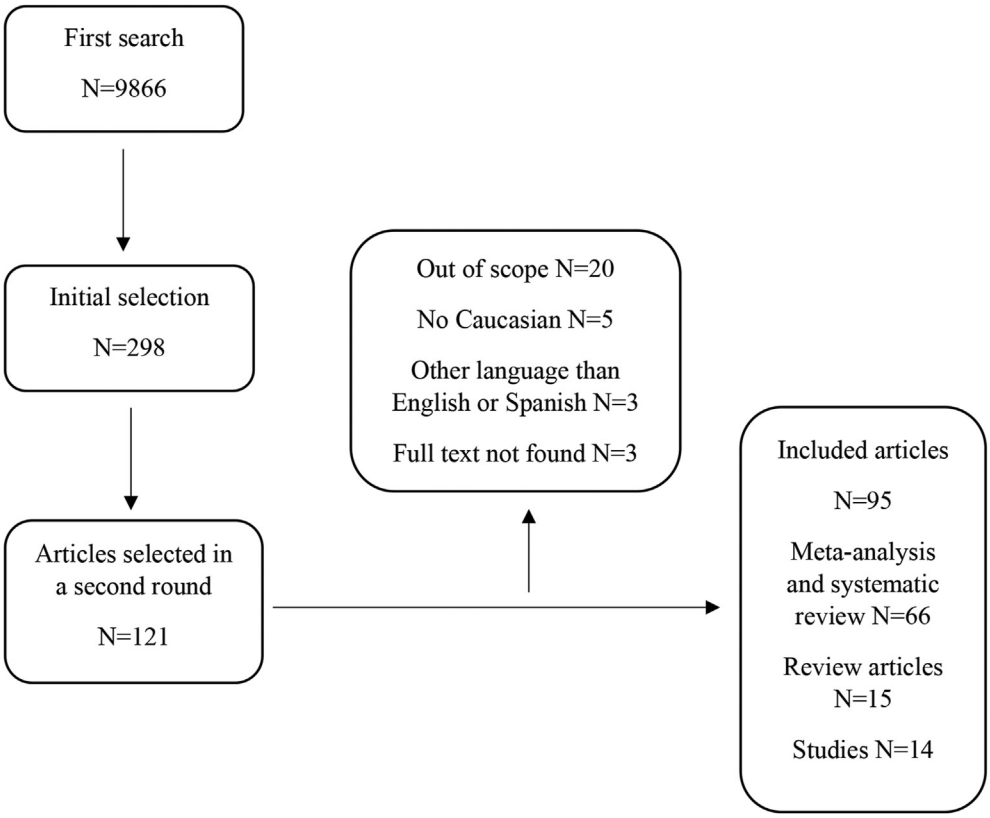

Figure 1 Flow diagram.

with high-density lipoprotein cholesterol (HDLc). Although there is a large heterogeneity between studies, the triglyceride-glucose index (TyG index) (a novel parameter leading to predict MetSyn) is related to great risk of T2DM [21]. Sánchez-García et al. (2020) found that the TyG index had moderate to low evidence to detect the presence of IR [22]. People presenting high neck circumference showed two-fold risk of hypertriglyceridemia [23].

Handgrip strength is a good predictor for CHD. In prehypertensive men, medium and high levels of muscular strength reduced the risk of hypertension. Individuals presenting lower muscular fitness may gain more age-related weight and adiposity. Contrasting, muscular strength showed no benefits on lipid profile [24]. Muscle strength seems to be a sensitive indicator of MetSyn, considering each component individually and/or combinations of MetSyn components [25].

Some clinical variables are also related to MetSyn components. For instance, there have been described associations of high systolic blood pressure or resting heart rate (RHR) with higher risk of T2DM [19,26] and low insulin sensitivity. Cardiorespiratory fitness (CRF) improvement can prevent T2DM, thus for each metabolic equivalent (MET) higher CRF, the risk of T2DM decreases by 8% [27]. Accordingly, Lee et al. (2020) observed that obesity increases the risk of MetSyn even in people with high CRF compared with those with normal weight. They also showed that a minimum of CRF level of 8.39 METs is necessary to have low risk of MetSyn [28]. Regarding muscle strength, there is an inverse association with the risk of T2DM [29]. In line with this, Tarp et al. (2019) found that for each standard deviation (SD) increase in muscular strength, the risk of T2DM decreased by 13% [27].

Risk of MetSyn can be estimated using some of the above-mentioned indicators. Thus, there is a linear relationship between RHR and risk of MetSyn, where for each 10-bpm increase, there is a 28% higher risk of MetSyn [26]. Moreover, the carotid intima-media thickness has shown higher values in MetSyn [30]. There is an inverse association between MetS risk and muscular strength, and a protective effect of CRF and muscular strength has been found among overweight and obese men. Muscular strength is inversely associated with MetSyn in low and moderate CRF but not in high CRF men [24].

Indicators related to physiological processes

There are some physiological processes that have been associated with metabolic health such as sleep, menopause, or stress among others. Sleep quality, quantity, or complaints are associated with MetSyn. Thus, the risk of MetSyn increases with the bad quality of sleep, with difficulties in falling asleep and in maintaining sleep, but there is no association with early morning awaking or awaking during the night [31]. Regarding the sleep quantity, there is a dose–response relationship between short sleep duration and MetSyn risk, being the odds of MetSyn 1.5 for <5h sleep [32]. In South Korea, the findings about the sleep duration in women have shown that comparing >8 h/d with <6 h/d, there was a 2.13-fold increased prevalence of MetSyn. A sleep duration of more than 10 h/d compared with <6 h/d in females showed a higher odds ratio (OR) for MetSyn (1.4), and some of its components (higher WC (1.14), increased TG (1.41), lower HDLc (1.24) and higher fasting glucose (1.39)) [32].

Postmenopausal women are more prone to develop MetSyn than premenopausal ones; they become physically inactive and are more likely to be overweight and develop CVD and T2DM [33]. Thus, they have higher odds for high fasting glucose and TG levels, blood pressure and WC, and for lower HDLc [34].

Sarcopenia is linked to aging when a skeletal muscle mass loss occurs. Sarcopenia increases the risk of MetSyn, thus prevalence of MetSyn among sarcopenic was 22.8% among middle-aged adults [35], while prevalence of sarcopenia among obese was >40% [36]. Even when there are few longitudinal studies about the effects of sarcopenic obesity in health, Khadra et al. (2019) found that sarcopenic obesity increased the risk of T2DM in 38% [36].

Tenk et al. (2018) studied the relationship between perceived stress and different MetSyn components, finding positive correlations between perceived stress and WC, BMI, TG and diastolic blood pressure, and negative correlation with HDLc [37]. These results show that perceived stress could be considered as a MetSyn predictor.

Indicators related to associated diseases/syndromes

There are some diseases that may have potential utility in predicting the future risk of developing MetSyn in patients who suffer from them. Some authors suggest that NAFLD can be considered the hepatic manifestation of the MetSyn. However, the liver affects the pathogenesis of the MetSyn and its complications [38]. The meta-analysis performed by Ballestri et al. (2016) suggested that NAFLD significantly increases the risk of incident T2DM and MetSyn over a median 5-year follow-up [39].

People suffering psoriasis disease have higher risk of T2DM, independently of BMI, while IR relates to psoriasis severity [19]. There is a positive and strong correlation between psoriasis and MetSyn (pooled OR: 2,14) [40,41] and in Latin American population it is nearly 3-fold higher [40]. Those patients who were recently diagnosed showed a lower risk of MetSyn than those with chronic disease (pooled OR: 1.5). The association between MetSyn and psoriasis was stronger in studies performed using the ATPIII criteria than in those using the IDF criteria (pooled OR: 3.97) [40]. Likewise, a recent meta-analysis observed that the incidence of CVD is greater in people with psoriasis as well as with single components of the MetSyn including hypertension disease associated with psoriasis [42].

Although numerous studies have indicated a relationship between Obstructive Sleep Apnea (OSA) and MetSyn, a

systematic review failed to find causality between these two factors [43]. Recently, Peres et al. (2019) have shown that some circulating biomarkers such as inflammatory markers, adhesion molecules, and vascular proteins are associated with the presence of cardiometabolic disease in patients with OSA but this finding does not support enough the possibility of OSA being an indicator for MetSyn [44].

Periodontitis (PD) has also been proposed as a comorbidity associated with MetSyn. Indeed, a meta-analysis revealed a positive association between MetSyn and PD and suggested that individuals with MetSyn are 38% more likely to have PD than individuals without MetSyn [45,46]. Accordingly, Muñoz-Aguilera et al. (2020) observed a positive association between hypertension and periodontitis leading to an increase in the risk of high systolic and diastolic blood pressure and hypertension [47]. This finding has recently been confirmed by a case–control study [48]. Therefore, the conclusion could be that PD is more frequent in MetSyn patients, but that PD is not an indicator of MetSyn by itself.

Rosacea is cutaneous chronic inflammation affecting adults [49]. Li et al. (2020) observed that is not associated with CVD [49]; however, Cheng et al. (2020) found that rosacea is associated with hypertension and high levels of LDL and low HDL [50]. Furthermore, people presenting lichen planus (LP), which is an idiopathic inflammatory dermatosis, are more likely to be affected by MetSyn [51].

One study from Pal et al. (2018) regarding the relative risk (RR) of progression from mild cognitive impairment (MCI) to dementia in people with and without MetSyn or T2DM, concluded that diabetes and MetSyn were both associated with an increased incidence of dementia when co-existing with MCI. Indeed, an intensive CV risk reduction and lifestyle changes for patients are presenting MCI and diabetes, prediabetes or MetSyn may be important in reducing the incidence of dementia in this high-risk population [52]. Therefore, similarly to what happens with PD, the conclusion is that there is increased incidence of dementia in patients with MetSyn but dementia is not an indicator of MetSyn. In reference to migraines, which are considered a risk factor for dementia, they have not been associated with MetSyn [53].

Regarding hormonal disorders, Fazleen et al. (2018) performed a systematic review and meta-analysis in adolescents with polycystic ovarian syndrome (PCOS), supporting that the risk of MetSyn is greater in adolescents with PCOS than in normal population [54]. More recently, Misitzis et al. (2019) reviewed the relationships of sex hormones with components of MetSyn, such as IR and dyslipidemia, in pre- and postmenopausal women. High testosterone, low sex hormone-binding globulin (SHBG), and low estrogen levels increase the risks of MetSyn and T2DM in women. In this study, several diseases mediated by sex hormones, including PCOS, acanthosis nigricans, acne vulgaris, and pattern alopecia, were associated with IR and increased risk for MetSyn [55]. Furthermore, Weeker et al. (2020) found that females with PCOS could be affected by higher risk of cardiometabolic syndrome [56].

In view of the evidence commented above, the best and reliable “disease associated marker” to be considered as a good predictive biomarker of MetSyn is the existence of PCOS.

Indicators related to blood biomarkers

There are a huge number of serum biomarkers that have been explored as potential predictors of a “bad metabolic health”, and in turn, associated with components of MetSyn or with MetSyn itself.

Uric acid is formed when purines break down. It is a normal body waste product; high circulating levels can lead to gout and has also been associated with several components of MetSyn. There is a large body of evidence suggesting that higher circulating uric acid levels lead to an increased risk of MetSyn regardless of the study characteristics, with a linear dose–response relationship. A RR of 1.3 is reported by Yuan et al. (2015) [57]. Furthermore, increased levels of uric acid have been associated with a high prevalence of NAFLD and T2DM (but not causal association) [11,19,58].

Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate levels. Furthermore, Vitamin D is involved in cell growth, immune function, and modulation of inflammation. Low levels of Vitamin D have been associated with a higher prevalence of NAFLD [59,60], PCOS [61,62], prediabetes [63], T2DM [62,64] and higher BMI, WC, abdominal obesity [65], and blood pressure [62] but no evidence has been provided of increased risk of MetSyn and hypertension in Caucasian population. In addition, Zhang et al. (2020) did not also observe an association between hypertension and Vitamin D supplementation [66]. Observational, and prospective studies suggest an increased risk for MetSyn components in Asian population, although different results were observed for abdominal obesity and Vitamin D in Asian compared to other races [65].

Alanine amino transferase (ALT), Gamma glutamyl transferase (GGT), and bilirubin. ALT and GGT are liver enzymes measured clinically as part of liver functionality and integrity. ALT is considered the most specific indicator of hepatic damage in NAFLD [19], but GGT was a better predictor of MetSyn. RR for MetSyn in the pooled analysis for GGT levels comparing individuals in the top *vs* bottom thirds of baseline GGT levels was 1.88 (95% confidence interval (CI): 1.49–2.38) [67].

For bilirubin, a meta-analysis of nine cross-sectional studies, analyzing the pooled OR for MetSyn according to extreme tertiles of serum bilirrubin showed a protective effect (0.70–95% CI: 0.62–0.78); however, in prospective studies this association was not confirmed. T2DM was also associated with decreased levels of bilirubin [68].

Inflammatory/anti-inflammatory and pro and antioxidant parameters (CRP, PAI-1, IL-6, TNFα, OxLDL, IL-10,

PON-1, and lutein). The evidence of the association between high levels of circulating inflammatory/pro-oxidant parameters is mainly based on literature reviews but not on formal meta-analysis considering MetSyn or any of its components. In general, it is accepted that inflammatory parameters are increased, and anti-inflammatory ones are decreased [11]. Higher serum lutein was associated with a lower risk of MetSyn (pooled RR: 0.75; 95% CI: 0.60, 0.92) for the highest compared with the lowest tertile. However, lutein might be beneficial for atherosclerosis and inflammatory markers, but there were inconsistent associations with blood pressure, adiposity, IR, and blood lipids [69].

Adipokines (resistin, leptin, and adiponectin). Resistin circulating levels show a wide variability in the associative observational studies with some components of MetSyn such as blood pressure, TG, and HDLc. No final conclusions can be drawn. Adiponectin can improve glucose and lipid metabolism, and it has been suggested that high levels of circulating adiponectin can protect against atherosclerosis [70]. Leptin and adiponectin go in an opposite sense, and some works include the leptin/adiponectin ratio (LAR) as a marker of MetSyn. Higher LAR is a better biomarker for MetSyn diagnosis criteria than leptin and adiponectin separately. High molecular weight adiponectin (<2.5 μg/ml) can be the most reliable biomarker for MetSyn diagnosis criteria. The results are based on observational studies, not in meta-analysis data [11,71].

Ferritin is a protein that stores iron and serves as a buffer against iron deficiency and iron overload and can be used as an indirect marker of the total amount of iron stored in the body. Furthermore, it is a biomarker of iron-dependent oxidation, which is involved in dyslipidemia, impaired metabolism of glucose and hypertension [33]. High circulating levels have been associated with increased risk of MetSyn with an OR around 1.7. Among MetSyn components, high TG (OR 1.96) and high glucose levels (OR 1.60) were the stronger associated variables with increased ferritin [72].

Magnesium is essential for the energy cellular production and plays a role in the active transport of calcium and potassium ions across cell membranes, being necessary for maintaining a proper function of the neurologic and CV systems. We have identified two meta-analyses in which there is consensus about an inverse association between magnesium levels and MetSyn with an OR near 0.7 [73,74]. But more prospective studies controlling for other nutrient factors are highly recommended.

Fibroblast growth factor 21 (FGF21) is a signaling protein involved in cell differentiation, morphogenesis, proliferation, and metabolism. In a meta-analysis of 28 studies, the risk of MetSyn was increased (Hazard Ratio (HR): 1.70; 95%CI: 1.35–2.15; $P < 0.0001$ $I2 = 24\%$) and circulating levels predicted T2DM incidence or progression (HR: 1.35; 95% CI: 1.06–1.72, $P < 0.05$, $I2 = 69\%$) [75].

Osteocalcin is a protein secreted by the fibroblasts and has the capacity to stimulate adiponectin in fat cells and promotes energy availability and utilization in muscle. The risk estimates comparing individuals in the higher *vs* lower quartile of circulating levels of serum total osteocalcin were 0.39 (95% CI 0.27–0.56; $P < 0.001$) for MetSyn from cross-sectional evidence. Both cross-sectional and cohort studies support inverse associations of serum total osteocalcin with the risk of adverse metabolic outcomes [67]. A recent meta-analysis suggest that low concentration of osteocalcin is associated with low BMI and fat mass [76].

Mean Platelet Volume (MPV) is a measurement of the average size of the platelets. It has been associated with some inflammatory diseases. The study is related with NAFLD and standardized mean difference in MPV between NAFLD and controls was 0.457 (95%CI: 0.348–0.565, $P < 0.001$) using fixed effects model and 0.612 (95%CI: 0.286–0.938, $P < 0.001$) using random effects model. No references to MetSyn were analyzed [77].

Sodium. A meta-analysis showed that participants with highest dietary/urinary or serum sodium levels had 37% higher chance of developing MetSyn when compared with participants with the lowest sodium levels (OR = 1.37; 95%CI: 1.31–1.42; $I2 = 86.9$) [78].

Triglycerides. Elevated TG levels are already included as a component of the definition of MetSyn. There are also evidences about the value of fasting TG as a biomarker of CVD [79,80]. Nonfasting TG has been explored as a marker for increased CV risk. The Copenhagen City Heart Study demonstrated that stepwise increasing levels of nonfasting TC and nonfasting TG were similarly associated with stepwise increasing risk of myocardial infarction (MI), ischemic heart disease, and death in men and women. The best predictor of MI in women was nonfasting TG, while in men was nonfasting TC. Only increasing levels of nonfasting TG were associated with total mortality, whereas increasing TC levels were not [81,82].

Circulating amino acids (AA): According to a meta-analysis on 20 circulating AA, 12 circulating AA, namely, Ala, Val, Lys, Glu, Pro, Ile, Leu, Tyr, Phe, Trp, His, and Met, were significantly higher while 4 circulating AA, namely, Ser, Gly, Gln, and Asn were significantly lower in MetSyn patients than in non-MetSyn subjects [83]. Ahola-Olli also found a higher risk of T2DM associated with both branched-chain and aromatic AA [84].

Androgens (Testosterone) and SHBG: Men with low concentrations of total testosterone (TT), SHBG, or free testosterone (FT) were more likely to have prevalent MetSyn (ORs per quartile decrease were 1.69 (95%CI: 1.60–1.77), 1.73 (95%CI: 1.62–1.85), and 1.46 (95%CI: 1.36–1.57) for TT, SHBG, and FT, respectively) and incident MetSyn [85]. This association was also observed in women (not in a meta-analysis) [55]. In perimenopausal and postmenopausal women, androgenic markers (testosterone and SHBG) are more important than estrogens in the assessment of MetSyn. FT is positively correlated with BMI and WC in postmenopausal women [33].

Cortisol: Pooled results showed no significant difference in basal cortisol levels between subjects with and without MetSyn (standardized mean difference [SMD] = 0.02, 95%CI = −0.11–0.14) [86].

n-3 polyunsaturated fatty acids (PUFAs): A higher plasma/serum n-3 PUFAs was associated with a lower

MetSyn risk (pooled OR = 0.63; 95%CI: 0.49–0.81). The plasma/serum n-3 PUFAs in controls was significantly higher than that in cases (weighted mean difference (WMD): 0.24; 95% CI: 0.04–0.43), especially docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA). However, no significant association was found between dietary intake of n-3 PUFAs or fish and MetSyn risk [87].

Glutamate as a product of the catabolism of branched-chain amino acids is positively correlated with visceral adipose tissue accumulation and WC. There is only one observational study that cannot be considered a strong evidence to consider glutamate a good biomarker of metabolic risk [88].

Microbiota: Gut microbiota is an emerging new field of research in many metabolic diseases including obesity, T2DM, NAFLD, and MetSyn [89,90]. However, up to now, there is no evidence for a strong association between a specific microbiome signature and the increased prevalence of MetSyn [91]. Several systematic reviews support that there is a wide heterogeneity, and the variability between studies and microbiota is difficult to assess with different ways to analyze (by urine, feces, or serum samples) [92–94].

Pre-metabolic syndrome approach

There is no well-established definition of PreMetSyn and a few studies have used different criteria to identify this entity. Considering that MetSyn is the combination of three or more CV risk factors, all these studies have defined PreMetSyn as having less than the required numbers of components of MetSyn, with or without one mandatory component required, such as BMI [95–97]. Yin et al. (2013) defined PreMetSyn as having no less than two components of MetSyn but did not meet the criteria for the diagnosis of MetSyn [98].

The authors propose to define PreMetSyn in the sense of cardiometabolic risk. Therefore, instead of considering the number of components of MetSyn that are present, our proposal is to take into account how close subjects are of getting to the cut-off point of the variables already included in the definition of MetSyn and the emerging indicators proposed by our review.

Conclusion

This review has addressed indicators and how they are linked to PreMetSyn. Some of them have low evidence to be a robust biomarker for MetSyn. They are markers for an inflammatory/pro-inflammatory status that is usually accompanying the “low grade chronic inflammation” that takes place in MetSyn or in its individual components. High TG in serum and WC are variables already included in the definition of MetSyn, and therefore, a good biomarker to be considered. Uric acid serum levels have a constant and quite good consistence in many studies as a predictive biomarker of MetSyn and have been linked in an associative manner with NAFLD and T2DM. NAFLD emerges as an early risk indicator of PreMetSyn by itself. Finally, muscle strength should be also included as an early risk marker of cardiometabolic health.

After this review, new indicators could be considered to create a new risk score specifically meant for PreMetSyn in European population. A clear definition of PreMetsyn would help to establish public health policies in order to reduce the incidence of MetSyn in European population.

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Author’s contribution

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Declaration of competing interest

None declared

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Appendix

New biomarkers related to Pre-MetSyn found and their relationship with the already known components of MetSyn.

Biomarker	Indicator of MetSyn	Linkage to PreMetSyn	Comments/strengths	Supporting References
Anthropometric/clinical variables				
Body mass index (BMI)	Risk of type 2 diabetes mellitus (T2DM)	↑ BMI associated with ↑ risk of T2DM. (Obese *vs* lean, overweight *vs* lean and per 1SD increase)	Review of meta-analysis. Supported by highly suggestive evidence.	Bellou et al. (2018) [19]
Waist circumference (WC)		↑ WC associated with ↑ risk of T2DM.		
Hip circumference (HC)		↓ HC associated with ↑ risk of T2DM.		
Waist-to-hip ratio		↑ waist to hip ratio associated with ↑ risk of T2DM.		
Waist-to height ratio (WHtR)		↑ WHtR associated with ↑ risk of T2DM.		
	Obesity	WHtR very useful in assessing adiposity in the elderly. Findings ranking WHtR as the best index with good discriminatory power.	10/16 studies concluded WHtR is a valid anthropometric measure to diagnose obesity in the elderly	Corrêa et al. (2016) [20]
Systolic blood pressure (SBP)	Risk of T2DM	↑ SBP associated with ↑ risk of T2DM.	Review of meta-analysis. Supported by highly suggestive evidence.	Bellou et al. (2018) [19]
Resting heart rate (RHR)	Metabolic syndrome (MetSyn)	Linear ↑ risk of MetSyn with ↑ RHR (28% ↑ per 10 bpm ↑)	Meta-analysis	Liu et al. (2017) [26]
	Risk of T2DM	RHR independently associated with ↑ risk of T2DM	2/17 European, 14/17 Asian. RHR a new target of clinical intervention. No publication bias.	
Neck circumference (NC)	WC	Positive association (r = 0.85; 95%: 0.75, 0.95)	Systematic review of 19 articles. Included studies that examined the association of NC with risk of MetSyn, or at minimum, one of its components as outcomes	Namazi et al. (2018) [23]
	Triglycerides (TG)	↑ NC have 2x risk for hypertriglyceridemia. Positive association (OR: 1.87)		
	Diastolic blood pressure (DBP)	Positive association (r: 0.20, 95%CI: 0.16, 0.23)		
	Fasting glucose	Positive association (r: 0.20, 95%CI: 0.16, 0.24)		
	High density lipoprotein cholesterol (HDLc)	Negative association (r:-0.21; 95% CI: −0.26, −0.15)		
	BMI	Positive association (r:0.88; 95%CI: 0.74, 0.91)		
	Total cholesterol (TC)	Positive association (r:0.14; 95%CI: 0.05)		
	Low density lipoprotein cholesterol (LDLc)	Positive association (r: 0.18; 95%CI: 0.07, 0.29)		
	Hypertension	positive association (OR: 1.94)		
	SBP	positive association (r: 0.21, 95%CI: 0.19, 0.23)		
Carotid intima-media thickness	MetSyn	Greater in MetSyn *vs* without it (788 ± 47 μm vs 727 ± 44 μm), SD = 0.28 ± 0.06 (p = 0.00003)	8 studies. Carotid intima-media thickness paralleled by a higher prevalence of plaques	Cuspidi et al. (2018) [30]
Cardiorespiratory fitness (CRF)	Risk of T2DM	1 MET higher CRF↓ 8% RR for T2DM	Meta-analysis. 22 studies CRF, 13 studies strength. 4–21% new T2DM cases in people aged 45-64 y could be prevented by changing CRF.	Tarp et al. (2019) [27]
		1 MET higher CRF, RR of T2DM = 0.95 (95% CI: 0.93, 0.98; p = 0.003)	Meta-analysis 8 prospective studies	Zaccardi et al. (2015) [99]
		HR for T2DM per 1-MET higher CRF = 0.93 (95%CI: 0.84, 1.02; p = 0.109)	Mean age: 53 y.	
		Each 1-MET ↑ in CRF was associated with a 5% ↓ in diabetes events.	High heterogeneity, small sample, CRF only at baseline.	
	Cardiovascular disease (CVD)	Each 1-MET ↑ in CRF was associated with a 15% ↓ in CVD events (95% CI: 12, 18).		
	MetSyn	Obesity ↑ the risk of MetSyn even in people with high CRF compared with normal weight = 4.87 (95% CI: 2,92–8,14; p < 0.01)	8 observational Studies: 1 European, 3 Asian, 2 USA	Lee J et al. (2020) [28]
		Low CRF + obesity, higher risk of MetSyn than high CRF + normal weight = 7.17 (95% CI: 4.32–11.90; p < 0.01).		

Muscle strength	CVD (Coronary heart disease, (CHD))	Handgrip strength best predictor for CHD. Knee extension strength best predictor for intracerebral and subarachnoid hemorrhage.	1 Study (>1 mill participants during 24 y)	Artero et al. (2012) [24]
	Hypertension	Middle and high levels of muscular strength reduced the hypertension risk in prehypertensive but not in normotensive men.	1 study (19 y follow-up, >4000 men)	
	Obesity	Age-related weight and adiposity gain may be higher among individuals with lower muscular fitness	2 studies (>500 participants during 20 y; >3500 participants 8 y)	
	MetSyn	Inverse association between MetSyn risk and muscular strength in men and women. Protective effect of muscular strength and CRF among overweight and obese men. Muscular strength inversely associated with MetSyn in low and moderate CRF but not in high CRF in men.	4 studies	
	Dyslipidemia	No benefits of muscular strength on TC, TG, LDLc, HDLc.	1 study (>6500 participants)	
	T2DM	Inverse association between T2DM and grip strength. ↑ muscle mass and strength may be related to ↓ T2DM risk. 1 SD higher muscular strength ↓ 13% RR for T2DM	SNP analysis. European population	Yeung et al. (2019) [29] Tarp et al. (2019) [27]
Physiological processes				
Sarcopenia (skeletal muscle mass index)	MetSyn	Prevalence MetSyn among sarcopenic was 36,45%. (22,81% in middle-aged). Sarcopenia ↑ risk of MetSyn (OR = 2,01). Association sarcopenia and MetSyn. Non obese.	Systematic review and meta-analisis. 12 studies in adults (>50 y) (1 North America, 11 Asia). No publication bias; small cohorts; difficult to establish with DXA; includes handgrip; MetSyn - ATP III and IDF. The only study with handgrip - no clear association	Zhang et al. (2018) [35]
	Obesity	Prevalence of sarcopenia among obese > 40%. Sarcopenic obesity (SO) indicates ↑ risk for T2DM of 38% *vs* those without SO	Systematic review and meta-analysis. 11 studies, 6 in elderly (>60 y), 5 in young adults (<60 y). Higher prevalence of sarcopenia reported in studies that accounted BMI. Lack of evidence if so may lead to T2DM as there are few longitudinal studies about the effects of SO on health.	Khadra et al. (2019) [36]
	Hypertension	No association in the sub analysis of Euroepean studies and sarcopenia	Sarcopenia was associated with hypertension, but no correlation was found between handgrip strength and hypertension in older adults.	Bai et al. (2020) [100]
Menopause	MetSyn	MetSyn ↑ in postmenopausal women and > premenopausal women. ↑ fasting glucose (OR 3.51), ↓HDLc (OR 1.45), Hypertension (OR 3.95), ↑ TG (OR 3.2), and ↑ WC (OR 2.75) were all postmenopausal > premenopausal women.	Prevalence of MetSyn varied according to the criteria. Individual components were ↑ in all studies. Systematic review and meta-analysis. Few studies in European countries and no one when comparing individual components of MetSyn	Hallajzadeh et al. (2018) [34]
Sleep quality Sleep complains	MetSyn	Bad quality associated with ↑ risk of MetSyn (1.37 (1.15−1.64)) Difficulty in falling sleep ↑ in MetSyn (1.18 (1.05−1.33)) Difficulty in maintaining sleep ↑ in MetSyn (1.15 (1.02−1.30)) No association with early morning awakening or awakening during the night	Systematic review and meta-analysis of observational studies. Different criteria to define sleep quality.	Lian et al. (2019) [31]
Sleep quantity		Short sleep ↑ MetSyn <7 h sleep OR = 1.23; <5 h OR = 1,51; 5−6 h OR = 1,28; 6−7 h OR = 1.16. Sleep duration <5 h had 1.5 higher odds of MetSyn	Meta-analysis. 14 cross-sectional studies. Different MetSyn definitions. Dose−response relationship between short sleep duration and MetSyn	Iftikhar et al. (2015) [32]
Perceived stress	WC BMI TG HDLc DBP	Positive correlation (Effect Size 1.84 (95% CI 0.79, 2.89) Positive correlation (Effect Size 0.65 (95% CI 0.16,1.14) Positive correlation (Effect Size 7.52 (95% CI 0.07,14.96) Negative correlation (Effect Size −0.83 (95% CI -2.13, 0.46) Positive correlation (ES 1.04 mmHg with 95% CI 0.18, 1.89)	Systematic review of 17 studies. Stress level assessed by stress scales (such as Perceived Stress Scale (PSS)	Tenk et al. (2018) [37]

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Biomarker	Indicator of MetSyn	Linkage to PreMetSyn	Comments/strengths	Supporting References
Associated diseases/syndromes				
Polycystic ovary syndrome (PCOS)	MetSyn	Odds for MetSyn in adolescents with PCOS > healthy adolescent controls in population and non-population based onstudies (OR 4.7; OR 6.1, respectively). In adults there were no differences in population-based studies.	Different criteria for PCOS diagnosis. Meta-analysis. 44 full- text articles. Some studies used various PCOS/MetSyn diagnostic criteria or different age groups with various methods of confounder control	Behboudi-Gandevani et al. (2018) [101]
	Hypertension	Increased risk 1.75 (1.42−2.15)	Observational and retrospective studies. All continents. More than half European. Different diagnostic criteria for PCOS	Weeker et al. (2020) [56]
	T2DM	Increased risk 3.0 (2.56−3.51)		
	Low HDLc	Increased risk with lower HDLc (−2.45 (−4.51 to −0.38)		
	TG	No association		
Obstructive sleep apnea (OSA)	MetSyn	OSA is shown to be associated with MetSyn, although causality is not demonstrated.	Systematic review of 15 cross-sectional and 5 case −control studies. Future cohort and randomized controlled studies are needed	Xu et al. (2015) [43]
		Association with C reactive preotein (CRP), chitinase-3- like-1 (YKL-40), glycated hemglobin (HbA1c), Resistin, HDLc, TG, Glucose	Systematic review 10 studies. Identify biomarkers of cardiometabolic risk. Different criteria for diagnosis OSA. Small sample sizes, great heterogeneity.	Peres et al. (2019) [44]
	CVD	Association with CRP, YKL-40, Interleukin (IL)-8, Regulated on Activation Normal T Expressed and Secreted protein (RANTES), Tumour Necrosis Facror alpha (TNF-a), IL-1Ra, Soluble Intercellular Adhesion Molecule (sICAM), soluble fms-like tyrosinkinase 1 (sFlt-1), soluble endoglin (sEng), LDLc, Glucose		
Worms	MetSyn	Protective association between previous helminth infections and prevalence of MetSyn (OR:0.36)	Meta-analysis. 4 cross sectional studies. China, Indonesia, Australia. 3 mechanisms proposed: nutrition, gut microbiota, and immunomodulation. Short sample. Selection bias.	Tracey et al. (2016) [102]
Non-alcoholic fat liver disease (NAFLD)	T2DM	NAFLD associated with ↑ risk of incident T2DM. RR depends on the diagnosis (Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma glutamyl transferase (GGT).	Meta-analysis. NAFLD significantly ↑ risk of incident T2DM and MetSyn over a median 5-year follow-up.	Ballestri et al. (2016) [39]
	MetSyn	NAFLD associated with ↑ risk of incident MetSyn. RR depends on the diagnosis (AST, ALT, GGT)		
Psoriasis disease	Risk of T2DM	↑ risk of T2DM, independently of BMI. Insulin resistance (IR) relates to psoriasis severity	Review of meta-analyses. Supported by highly suggestive evidence	Bellou et al. (2018) [19]
	MetSyn	Positive and strong correlation between psoriasis and MetSyn (pooled OR: 2,14).	Meta-analysis. 35 observational studies. OR for MetSyn in psoriasis > general population. Publication bias detected.	Singh et al. (2017) [41]
		MetSyn risk psoriasis > general population (OR:1,42)	Meta-analysis. 14 studies. MetSyn risk in Middle East (OR:1,76) > Europe (OR:1,40). Publication bias.	Rodríguez-Zúñiga & García-Perdomo. (2017) [40].
	Obesity	Association with WC in European studies	Includes middle east, Asian and European studies	Choudhary et al. (2020) [42]
Periodontitis (PD)	MetSyn	Association: 1.38 (1.26−1.51) in patients with partial and/or complete periodontal examination, and for each Diagnostic criterion of MetSyn. The weakest association, despite significant is with AACE 2003 criteria, and the strongest with IDF 2009	Systematic review: 26 studies included. Different criteria for MetSyn diagnosis. Most cross-sectional. Considers types of periodontal examination and analyzes diagnostic criteria	Dautd et al. (2018) [45]
	Hypertension	Moderate-severe PD OR = 1.22; 95% CI: 1.10, 1.35] and severe PD (OR = 1.49; 95% CI: 1.09, 2.05) were associated with hypertension. Patients with PD exhibited higher mean SBP [WMD of 4.49 mmHg; 95% CI: 2.88, 6.11] and DBP (2.03 mmHg; 95% CI: 1.25, 2.81) when compared with non-PD.	All countries. 26 studies. Moderate 1.22 (1.10−1,35); severe: 1.49 (1.09 −2.05); PD treatment and improvement of blood pressure, inconclusive	Muñoz-Aguilera et al. (2020) [47]
	MetSyn	Crude and adjusted ORs were 1.99 (95% CI: 1.75, 2.25) and 1.46 (95% CI: 1.31, 1.61).	All continents. 32 cross-sectional studies, 8 case −control studies, and 3 cohort studies	Gobin et al. (2020) [46]

Rosacea	Blood pressure/ Hypertension	RR 1.20 (1.08–1.32)	Most retrospective studies. 70% women. Only 3/13 studies from Europe. Most Asian (8 studies)	Cheng et al. (2020) [50]
	Dyslipidemia	RR of dyslipidemia 1.32 (1.10–1.58); ↑ TG, no differences in HDLc	No association with CVD or T2DM. Only 2 of 10	
	T2DM	Higher fasting glucose, but not higher prevalence of T2DM	European. High heterogeneity. Results not very	
	Blood pressure/ Hypertension	OR = 1.17; 95%CI (1.02–1.35)	conclusive	Li et al. (2020) [49]
	Dyslipidemia	OR = 1.34; 95%CI (1–1.79)		
	MetSyn	OR = 1.72; 95%CI (1.09–2.72)		
Lichen planus	MetSyn	RR: 2.281 (1.79–4.41)	12 studies, 2 European, 6 Asian, 4 African. No publication bias. Heterogeneity in the studies. Strong association with IDF criteria	Ying et al. (2020) [51]
Helicobacter pylori	MetSyn	Significant association between *H. pylori* and MetSyn (pooled OR = 1.34). *H. pylori* associated with↑ TG, fasting glucose, BMI, Homeostatic model assessment for insulin resistance (HOMA-IR), SBP and ↓ HDLc.	Meta-analysis. 6 observational studies.	Upala et al. (2016) [103]
Migraine	MetSyn	Major gaps in knowledge and weaknesses in research were identified. MetSyn incidence of 21.8% in migraineurs with aura, 16.8% in migraineurs without aura and 14.5% in subjects without headaches.	Systematic literature review of observational studies. Valid data to link migraine with MetSyn	Andreeva et al. (2019) [53]
Subclinical hypothyroidism (SCH)	MetSyn	Significant association between SCH and ↑ risk of MetSyn (pooled OR = 1.31)	Meta-analysis. 9 observational studies. Subgroup analyses by countries (Asian *vs* non-Asian). IDF and NCEP-ATPIII criteria	Yang et al. (2016) [104]
		No significant difference in MetSyn prevalence between SCH and euthyroid individuals	Meta-analysis. 8 studies. Only ATPIII criteria. No publication biases.	Eftekharzadeh et al. (2016) [105]
	Central obesity	Prevalence of central obesity significantly ↑ in SCH than euthyroid (OR = 1.43)		
	Hypertriglyceridemia	↑ TG more prevalent in the female only SCH subgroup		
Serum biomarkers				
Uric acid (SUA)	MetSyn	↑ 1 mg/dl SUA associated with MetSyn risk (RR: 1.30) MetSyn incidence in highest *vs* lowest SUA (pooled HR: 1.55). HR = 1.05 per 1 mg/dl SUA increase	Meta-analysis of prospective studies. Consistency of the association. Publication bias cannot be discarded.	Yuan et al. (2015) [57]; Liu et al. (2015) [58];
	NAFLD	↑ 1 mg/dLSUA, ↑ NAFLD risk 21% (RR: 1.21) Highest SUA 40% greater risk of NAFLD. Dose–response increment of NAFLD = 1.03	SUA useful in screening metabolic disorders and causal factor of NAFLD risk.	Srikanthan et al. (2016) [11]
	Risk of T2DM	↑ levels associated (not causal) with ↑ risk of T2DM	Review of meta-analyses. Supported by convincing evidence	Bellou et al. (2018) [19]
Vitamin D	Risk of T2DM	↓ levels associated (non-causal) with ↑ risk of T2DM	Review of meta-analyses. Supported by convincing evidence	Bellou et al. (2018) [19]
	NAFLD	VitaminD in NAFLD < Vitamin D in no-NAFLD (−16.8 nmol/L)	Meta-analysis. Randomized-control, cohort, cross-sectional and case–control studies.	Akinyemi et al. (2019) [59]
		Vitamin D in NAFLD < Vitamin D in no-NAFLD (−0.36 ng/mL)	Meta-analysis. 17 studies included. Vitamin D in Western NAFLD participants < Eastern NAFLD.	Eliades et al. (2013) [60]
	PCOS	PCOS patients with Vitamin D deficiency (VDD) more prone to dysglycemia *vs* without VDD.	Meta-analysis. 30 studies.	He et al. (2015) [61]
	Prediabetes	Association between ↓ Vitamin D and prediabetes	Different criteria to diagnose VDD. Heterogeneous. No association IR, T2DM	Yu et al. (2020) [63]
	Obesity	Inverse relationship with abdominal obesity; ↑ 25 nmol/L Vitamin D is associated with 10% ↓ risk of abdominal obesity	Cross-sectional studies, population based, different criteria for abdominal obesity, a lot of heterogeneity even when considered Asian and non-Asian	Hajhashemy et al. (2020) [64]
	Hypertension	Between 75 and 130 nmol/L an ↑ in 25 nmol/L Vitamin D is associated with a RR 0.93 (0.89–0.98) of hypertension. No improvement with vitamin D treatment	Protection similar in Caucasian and non-Caucasian. No differences by sex	Zhang et al. (2020) [66]

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Biomarker	Indicator of MetSyn	Linkage to PreMetSyn	Comments/strengths	Supporting References
Vitamin C	Blood pressure	Inverse association between Vitamin C and blood pressure. Treatment with antihypertensive drugs, show consistent low values. A large variability in the other groups	Observational studies. No threshold points. Includes patients with and without Vitamin C supplementation, with and without antihypertensive treatment. Difficult to assess in our study	Ran et al. (2020) [106]
Amylase	T2DM	Mean difference compared to heatlthy individuals (−5.29 (−7.27 to −3.32)); 3.1-fold ↓ amylase	Heterogeneity	Ko et al. (2020) [107]
	Obesity	Mean difference compared to heatlthy individuals (−0.77 (−1.43 to -0.10)	No data on other diseases that may affect concentrations	
	MetSyn	Mean difference compared to heatlthy individuals (−5.07 (−6 to −4.13)		
ALT	Risk of T2DM	↑ levels are associated with ↑ risk of T2DM. Low-grade hepatic inflammation	Review of meta-analysis. Supported by convincing evidence	Bellou et al. (2018) [19]
	NAFLD	Most specific indicator of hepatic pathology in NAFLD		
CRP	Risk of T2DM	↑ CRP associated (not causal) with ↑ risk of T2DM. (Highest *vs* lowest category and per 1 log pm/mL)		
Cortisol	MetSyn	No association between basal cortisol levels and MetSyn	Systematic review and meta-analysis. Lower levels in saliva. No differences in serum/urine.	Garzez et al. (2018) [86]
Resisitin	Hypertension	↑ resistin in hypertension or positive correlation with blood presuure (11 studies)/No association or negative association (3 studies)	Strengths: literature review up to 2017; heterogeneity of results; Review -Physiopathology	Mostafazadeh et al. (2018) [108]
	HDLc	15 studies negative correlations/8 studies positive or no association		
	TG	14 studies positive correlation/5 studies negative or no association		
Ferritin	MetSyn	↑ Ferritin associated with MetSyn.	Meta-analysis. 27 studies (3 longitudinal/2 cross-sectional and longitudinal/22 cross-sectional - discrepancy between text and figures). Ferritin levels >200 in all studies, but different thresholds in the studies.	Suárez-Ortegón et al. (2018) [72]
	Glucose	↑ Ferritin associated with ↑ Glucose (OR = 1.60; 95%CI (1.40−1.82))		
	TG	↑ Ferritin associated with ↑ TG (OR = 1.96; 95%CI (1.65−2.32))		
	Hypertension	↑ Ferritin associated with HBP (OR = 1.13; 95%CI (1.04−1.23))		
	WC	↑ Ferritin associated with ↑ WC (OR = 1.51 95%CI(1.31−1.75))		
	HDLc	↑ Ferritin associated with ↓ HDLc (OR = 1.47 ;95%CI (1.30−1.66))		
	NAFLD	Association with NAFLD	9/30 studies in Europe. Limited value in our study	Pan et al. (2020) [109]
Magnesium (Mg) status	MetSyn	↓ Mg levels in MetSyn on the findings of observational studies.	Meta-analisis: 9 cross-sectional and 4 case−control studies. Different MetSyn classification. High heterogenicity. Mg levels in cases < controls in West Asia and Latin America, but not in East Asia or Europe/Oceania	La et al. (2016) [73]
		Significant but heterogeneous inverse association between serum Mg and MetSyn	Meta-analysis. 8 studies. The link between Mg status and MetSyn should be confirmed.	Sarrafzadegan et al. (2016) [74]
Fibroblast growth factor 21 (FGF-21)	Coronary artery disease (CAD)	↑ FGF-21 levels predict the incidence of CAD (HR: 1.29)	Review of 28 studies. Need to standardize the measurement assay for FGF21 and its cut-off points	Lakhani et al. (2018) [75]
	MetSyn	HR: 1.43		
	T2DM incidence or progression	HR: 1.35		
Total bilirubin	MetSyn	Negative association (OR= 0.70 (95% CI: 0.62, 0.78))	Randomized controlled trials, and cohort, case −control and cross-sectional studies. Inverse association between ORs of bilirubin levels and MetSyn in fully adjusted models is suggested, but no significant association with prospective evidence. Large-scale prospective studies needed	Nano et al. (2016) [68]
	T2DM	Negative association. (OR: 0.77 (95% CI: 0.67, 0.87))		

Lutein	CHD	↓ risk of CHD (pooled RR: 0.88) for highest *vs* lowest tertile of lutein blood concentration	Meta-analysis. Trials and cohort, case–control, and cross-sectional studies. Lutein might be beneficial for atherosclerosis and inflammatory markers. Inconsistent associations with blood pressure, adiposity, IR, and blood lipids	Leermakers et al. (2016) [69]
	Risk of T2DM	No significant association with T2DM (pooled RR: 0.97) for highest *vs* lowest tertile of lutein blood concentration		
	MetSyn risk	↑ lutein associated with ↓ risk of MetSyn (pooled RR: 0.75) for highest *vs* lowest tertile of lutein blood concentration		
Osteocalcin	T2DM	Inverse association of serum total osteocalcin with risk of T2DM.	Meta-analysis. 52 observational studies.	Kunutsor et al. (2015) [67]
	Obesity	Negative association with obesity and body fat mass	Observational cross-sectional, stronger in Caucasians, no differences between sex.	Liy et al. (2020) [76]
Mean platelet volume (MPV)	NAFLD	MPV in NAFLD > without NAFLD	Meta-analysis. 8 observational studies.	Madan et al. (2016) [77]
GGT	MetSyn	Baseline GGT positively and strongly associated with risk of MetSyn in a nonlinear dose–response manner.	Meta-analysis. 10 prospective cohort studies. No publication bias.	Kunustor et al. (2015) [67]
	Risk of T2DM	↑ GGT associated with ↑ risk of T2DM. Low-grade hepatic inflammation.	Review of meta-analysis. Supported by highly suggestive evidence.	Bellou et al. (2018) [19]
Leptin	MetSyn	Leptin ↑ in MetSyn group	Meta-analysis. 16 studies.	Falahi et al. (2015)
Adiponectin		Adiponectin ↓ in MetSyn group (<4 μg/ml)	↑ Leptin/Adiponectin ratio (LAR) is a better biomarker for MetSyn diagnosis criteria than leptin and adiponectin separately	[71] Srikanthan et al. (2016) [11]
High molecular weight (HMW) adiponectin		HMW adiponectin (<2.5 μg/ml) can be the most reliable biomarker for MetSyn diagnosis criteria.		
Circulating amino acids profile	Obesity T2DM MetSyn	Val, Ile, Glu and Pro ↑, while Gly↓ in all metabolic disorders.	Meta-analysis. 46 case–control studies. No publication bias.	Okekunle et al. (2017) [83]
Sodium (Na) status	MetSyn	Na levels in MetSyn > healthy controls. Na level ↑ with number of MetSyn components. Highest Na levels 37% higher chance of developing MetSyn *vs* lowest Na levels (OR:1.37).	Meta-analysis. 17 cross-sectional publications.	Soltani et al. (2019) [78]
Plasminogen activator inhibitor 1 (PAI-1)		All ↑ in MetSyn	Literature review	Srikanthan et al. (2016) [11]
IL-6		Correlated with number of components of MetSyn		
TNF-α				
Oxidized LDL				
Ghrelin		All ↓ in MetSyn		
IL-10				
Paraoxonase 1 (PON-1)				
Glutamate	WC	Potential biomarker of abdominal obesity. Good correlation.	Study. Mechanism not clear. Easier measurement of WC than circulating glutamate.	Maltais-Payette et al. (2019) [88]
	MetSyn	Potential biomarker of metabolic risk. Good correlation with TG, HDLc, HOMA-IR		
TG	CVD	Fasting TG associated with CVD and correlated well with non-fasting TG Non-fasting TG recommended for CVD risk prediction	Review. Drugs and genetic studies.	Sandesara et al. (2019) [80]
		Non-fasting TG necessary to evaluate CHD in IR patients. Correlates with remnant cholesterol. Involved in endothelial dysfunction.	Review. Important and residual risk factor when LDLc is lowered.	Nakamura et al. (2016) [79]
Triglyceride-glucose index (TyG)	T2DM	TyG index at risk values: increase T2DM RR: 3.12 (2.32–4.21)	Observational, longitudinal studies men follow-up 1.4 and 12 y. Heterogeneity in the results.	Da Silva et a. (2020) [21]
	IR	Poor association	Low quality and evidence	Sánchez-García et al. (2020) [22]

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Biomarker	Indicator of MetSyn	Linkage to PreMetSyn	Comments/strengths	Supporting References
Androgens (testosterone (T), dehidroepiandrosterone sulphate (DHEAS), sex hormone binding globulin (SHBG))	Obesity	Hyperandrogenism increased with BMI	Hyperandrogenic eumenorrheic *vs* PCOS women.	Torchen et al. (2020) [110]
	MetSyn	MetSyn risk ↑ in hyperandrogenic women (OR = 2.9)	Low SHBG may be the primary predictor.	
		↑SHBG levels associated with ↓ risk of MetSyn. Total and free levels of T are ↑ in women with MetSyn. T/estradiol ratio and its rate of change in menopause ↑ incidence of MetSyn.	Review. Only females.	Misitzis et al. (2019) [55]
		↓ T and SHBG associated with ↑ prevalence of MetSyn. (ORs per quartile decrease 1.69, 1.73 and 1.46 for TT, SHBG and free T (FT), respectively) and incident MetSyn (HRs per quartile decrease 1.25, 1.44 and 1.14 for TT, SHBG and FT, respectively).	Meta-analysis. 20 observational studies. Largest associations in non-overweight men: stronger associations with hypertiglyceridemia, abdominal obesity and hyperglycemia and weakest associations for hypertension.	Brand et al. (2014) [85]
	Dysglycemia	Dysglycemia risk ↑ in hyperandrogenic women (OR = 2.7)	Hyperandrogenic eumenorrheic *vs* PCOS woman. ↓ SHBG may be the primary predictor.	Torchen et al. (2020) [110]
		↓ SHBG associated with impaired glucose control	Review. Only females.	Misitzis et al. (2019) [55]
	CVD	↓ SHBG and ↑ free androgen index associated with CVD risk factors		
		↓ T/estrogens ratio associated with ↑ risk of CVD in postmenopausal women.	Review.	Morselli et al. (2017) [111]
	T2DM	↑ T in women ↑ risk of T2DM.	Review. Only females.	Misitzis et al. (2019) [55]
		↓ T associated with ↑ risk of T2DM in young men (<40y)	Review	Morselli et al. (2017) [111]
n-3 polyunsaturated fatty acids (PUFAs)	MetSyn risk	↑ circulating n-3 PUFAs associated with ↓ MetSyn risk. Stable biomarkers to predict MetSyn risk. No association with intake	Meta-analysis - n-3 PUFAs levels and intake. Considerable sample-size but low grade of evidence.	Guo et al. (2017) [87]
Microbiota	Obesity	Short chain fatty acids (SCFA) ↓ appetite and/or alter energy metabolism to promote healthy weight. Propionate and butyrate induce leptin expression from adipocytes. Fecal SCFA and propionate in obese > overweight and lean. Nucleotide-binding oligomerization domain leucine-rich repeat with caspase recruitment domain-2 protein (NLRC2) potentially beneficial pattern recognition receptor in the obesity-associated dysbiosis. Obese have lower bacterial diversity and higher Firmicutes/ Bacteroidetes (F/B) ratio than lean, reversible with weight loss. Bifidobacterial abundance ↓ in overweight. The composition of microbiota in obesity can impact and/or predict weight loss. Urinary hippurate is ↓ in obese but after weight loss approximated to those of lean.	Literature Review. Many studies in animal model. It remains uncertain whether the F/B is a useful biomarker for overweight or obesity. No consensus on specific patterns of gut bacteria involved in the etiology.	Shen et al. (2013) [91]
	IR	Gut microbiota has a role in the IR of obese humans.		
	T2DM	The amount of 16s rRNA gene in the blood may be a novel biomarker of T2DM risk. Gut dysbiosis characterized by ↑ opportunistic pathogens, ↑ capacity for SO4- reduction and ↓ SCFA producers is a hallmark of T2DM. There are also ↓ levels of butyrate-producing bacteria.		

Obesity	Differences in microbiota metabolites in obesity/overweight compared to normal weight	No intervention. Only observational. Different types of samples (urine, feces, serum). Describes different products. Difficult to assess in our project	Ehtahed et al. (2020) [94]
	Trimethylamine N-oxide (TMAO) associated with BMI in healthy individuals. ↑ TMAO was associated with ↑ BMI	High heterogeneity, observational studies, lack of control of potential confounders. Limited utility in our study	Dehghan et al. (2020) [93]
	F/B ratio associated with obesity. Firmicutes seem to be more associated with obesity, whereas Bacteroidetes ↓ in obesity	Systematic review. 32 articles, 13 in European countries. Difficult to define a standard for the gut microbiota composition.	Crovesy et al. (2020) [92]

AACE: American Association of Clinical Endocrinology; ATPIII: Adult Treatment Panel III; bpm: beats per minute; CI: confidence interval; DXA: dual X-ray absorptometry; HR: hazard ratio; IDF: International Diabetes Foundation; MET: metabolic equivalent task; NCEP: National Cholesterol Educational Program; OR: odds ratio; RR: Relative risk; SD: standard deviation; SNP: single nucleotide polimorphism; WMD: weighted mean difference.

References

[1] World Health Organization (WHO). Obesity and overweight. 2020. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. [Accessed 3 March 2020].

[2] Kaiser AB, Zhang N, Der Pluijm WV. Global prevalence of type 2 diabetes over the next ten years (2018-2028). Diabetes 2018;67:202.

[3] World Health Organization (WHO). Diabetes. Data and statistics. 2015. http://www.euro.who.int/en/health-topics/noncommunicable-diseases/diabetes/data-and-statistics. [Accessed 3 March 2020].

[4] World Health Organization (WHO). Cardiovascular diseases. 2019. https://www.who.int/health-topics/cardiovascular-diseases/#tab=tab_1. [Accessed 3 March 2020].

[5] Karelis AD, Rabasa-Lhoret R. Inclusion of C-reactive protein in the identification of metabolically healthy but obese (MHO) individuals. Diabetes Metab 2008;34:183–4.

[6] Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). Arch Intern Med 2008;168:1617–24.

[7] Stefan N, Schick F, Häring HU. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metabol 2017;26:292–300.

[8] Schulze MB. Metabolic health in normal-weight and obese individuals. Diabetologia 2019;62:558–66.

[9] Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: facts and fantasies. J Clin Invest 2019;129:3978–89.

[10] Kylin E. Studien uber das Hypertonie-Hyperglyka 'mie-Hyperurika' miesyndrom. Zentralbl Inn Med 1923;44:105–27.

[11] Srikanthan K, Feyh A, Visweshwar H, Shapiro JI, Sodhi K. Systematic review of metabolic syndrome biomarkers: a Panel for early detection, management, and risk stratification in the west virginian population. Int J Med Sci 2016;13:25–38.

[12] Reaven GM. The metabolic syndrome: requiescat in pace. Clin Chem 2005;51:931–8.

[13] Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal. Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2005;48:1684–99.

[14] Festa A, D'Agostino Jr R, Tracy RP, Haffner SM. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. Diabetes 2002;51:1131–7.

[15] Langenberg C, Bergstrom J, Scheidt-Nave C, Pfeilschifter J, Barrett-Connor E. Cardiovascular death and the metabolic syndrome: role of adiposity-signaling hormones and inflammatory markers. Diabetes Care 2006;29:1363–9.

[16] Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003;111:1805–12.

[17] Šoštarič A, Jenko B, Kozjek NR, Ovijač D, Šuput D, Milisav I, et al. Detection of metabolic syndrome burden in healthy young adults may enable timely introduction of disease prevention. Arch Med Sci 2019;15:1184–94.

[18] Suliga E, Ciesla E, Głuszek-Osuch M, Rogula T, Głuszek S, Kozieł D. The usefulness of anthropometric indices to identify the risk of metabolic syndrome. Nutrients 2019;11:2598.

[19] Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: an exposure-wide umbrella review of meta-analyses. PloS One 2018;13:e0194127.

[20] Corrêa MM, Thumé E, De Oliveira ER, Tomasi E. Performance of the waist-to-height ratio in identifying obesity and predicting non-communicable diseases in the elderly population: a systematic literature review. Arch Gerontol Geriatr 2016;65:174–82.

[21] da Silva A, Caldas APS, Rocha DMUP, Bressan J. Triglyceride-glucose index predicts independently type 2 diabetes mellitus risk: a systematic review and meta-analysis of cohort studies. Primary Care Diabetes 2020;14:584–93.

[22] Sánchez-García A, Rodríguez-Gutiérrez R, Mancillas-Adame L, González-Nava V, Díaz González-Colmenero A, Solis RC, et al. Diagnostic accuracy of the triglyceride and glucose index for insulin resistance: a systematic review. International Journal of Endocrinology 2020;2020:4678526.

[23] Namazi N, Larijani B, Surkan PJ, Azadbakht L. The association of neck circumference with risk of metabolic syndrome and its components in adults: a systematic review and meta-analysis. Nutr Metabol Cardiovasc Dis 2018;28:657–74.
[24] Artero EG, Lee DC, Lavie CJ, España-Romero V, Sui X, Church TS, et al. Effects of muscular strength on cardiovascular risk factors and prognosis. J Cardiopulm Rehabil Prev 2012;32:351–8.
[25] Rodrigues de Lima T, González-Chica DA, Santos Silva DA. Clusters of cardiovascular risk factors and its association with muscle strength in adults. J Sports Med Phys Fit 2020;60:479–85.
[26] Liu X, Luo X, Liu Y, Sun X, Han C, Zhang L, et al. Resting heart rate and risk of metabolic syndrome in adults: a dose-response meta-analysis of observational studies. Acta Diabetol 2017;54:223–35.
[27] Tarp J, Støle AP, Blond K, Grøntved A. Cardiorespiratory fitness, muscular strength and risk of type 2 diabetes: a systematic review and meta-analysis. Diabetologia 2019;62:1129–42.
[28] Lee J. Influences of cardiovascular fitness and body fatness on the risk of metabolic syndrome: a systematic review and meta-analysis. Am J Health Promot 2020;34:796–805.
[29] Yeung CHC, Au Yeung SL, Fong SSM, Schooling CM. Lean mass, grip strength and risk of type 2 diabetes: a bi-directional Mendelian randomisation study. Diabetologia 2019;62:789–99.
[30] Cuspidi C, Sala C, Tadic M, Gherbesi E, Grassi G, Mancia G. Association of metabolic syndrome with carotid thickening and plaque in the general population: a meta-analysis. J Clin Hypertens 2018;20:4–10.
[31] Lian Y, Yuan Q, Wang G, Tang F. Association between sleep quality and metabolic syndrome: a systematic review and meta-analysis. Psychiatr Res 2019;274:66–74.
[32] Iftikhar IH, Donley MA, Mindel J, Pleister A, Soriano S, Magalang UJ. Sleep duration and metabolic syndrome. An updated dose-risk metaanalysis. Ann Am Thorac Soc 2015;12:1364–72.
[33] Stefanska A, Bergmann K, Sypniewska G. Metabolic syndrome and menopause: pathophysiology, clinical and diagnostic significance. Adv Clin Chem 2015;72:1–75.
[34] Hallajzadeh J, Khoramdad M, Izadi N, Karamzad N, Almasi-Hashiani A, Ayubi E, et al. Metabolic syndrome and its components in premenopausal and postmenopausal women: a comprehensive systematic review and meta-analysis on observational studies. Menopause 2018;25:1155–64.
[35] Zhang H, Lin S, Gao T, Zhong F, Cai J, Sun Y, et al. Association between sarcopenia and metabolic syndrome in middle-aged and older non-obese adults: a systematic review and meta-analysis. Nutrients 2018;10.
[36] Khadra D, Itani L, Tannir H, Kreidieh D, El Masri D, El Ghoch M. Association between sarcopenic obesity and higher risk of type 2 diabetes in adults: a systematic review and meta-analysis. World J Diabetes 2019;10:311–23.
[37] Tenk J, Mátrai P, Hegyi P, Rostás I, Garami A, Szabó I, et al. Perceived stress correlates with visceral obesity and lipid parameters of the metabolic syndrome: a systematic review and meta-analysis. Psychoneuroendocrinology 2018;95:63–73.
[38] Dietrich P, Hellerbrand C. Non-alcoholic fatty liver disease, obesity and the metabolic syndrome. Best Pract Res Clin Gastroenterol 2014;28:637–53.
[39] Ballestri S, Zona S, Targher G, Romagnoli D, Baldelli E, Nascimbeni F, et al. Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. J Gastroenterol Hepatol 2016;31:936–44.
[40] Rodríguez-Zúñiga MJM, Cortez-Franco F, Quijano-Gomero E. Association of psoriasis and metabolic syndrome in Latin America: a systematic review and meta-analysis. Actas Dermosifiliogr 2017;108:326–34.
[41] Singh S, Young P, Armstrong AW. An update on psoriasis and metabolic syndrome: a meta-analysis of observational studies. PloS One 2017;12:e0181039.
[42] Choudhary S, Patel R, Pradhan D, Deval R, Singh H, Thomas G, et al. Psoriasis and cardiovascular disorders: association or epiphenomenon? Meta-analysis of observational studies. 3 Biotech 2020;10:104.
[43] Xu S, Wan Y, Xu M, Ming J, Xing Y, An F, et al. The association between obstructive sleep apnea and metabolic syndrome: a systematic review and meta-analysis. BMC Pulm Med 2015;15:105.
[44] Peres BU, Hirsch Allen AJ, Fox N, Laher I, Hanly P, Skomro R, et al. Circulating biomarkers to identify cardiometabolic complications in patients with Obstructive Sleep Apnea: a systematic review. Sleep Med Rev 2019;44:48–57.
[45] Daudt LD, Musskopf ML, Mendez M, Remonti LLR, Leitão CB, Gross JL, et al. Association between metabolic syndrome and periodontitis: a systematic review and meta-analysis. Braz Oral Res 2018;32:e35.
[46] Gobin R, Tian D, Liu Q, Wang J. Periodontal diseases and the risk of metabolic syndrome: an updated systematic review and meta-analysis. Front Endocrinol 2020;11.
[47] Muñoz Aguilera E, Suvan J, Buti J, Czesnikiewicz-Guzik M, Barbosa Ribeiro A, Orlandi M, et al. Periodontitis is associated with hypertension: a systematic review and meta-analysis. Cardiovasc Res 2020;116:28–39.
[48] Campos JR, Costa FO, Cota LOM. Association between periodontitis and metabolic syndrome: a case-control study. J Periodontol 2020;91:784–91.
[49] Li Y, Guo L, Hao D, Li X, Wang Y, Jiang X. Association between rosacea and cardiovascular diseases and related risk factors: a systematic review and meta-analysis. BioMed Res Int 2020;2020:7015249.
[50] Chen Q, Shi X, Tang Y, Wang B, Xie H-f, Shi W, et al. Association between rosacea and cardiometabolic disease: a systematic review and meta-analysis. J Am Acad Dermatol 2020;83:1331–40.
[51] Ying J, Xiang W, Qiu Y, Zeng X. Risk of metabolic syndrome in patients with lichen planus: a systematic review and meta-analysis. PloS One 2020;15:e0238005.
[52] Pal K, Mukadam N, Petersen I, Cooper C. Mild cognitive impairment and progression to dementia in people with diabetes, prediabetes and metabolic syndrome: a systematic review and meta-analysis. Soc Psychiatr Psychiatr Epidemiol 2018;53:1149–60.
[53] Andreeva VA, Galan P, Julia C, Fezeu L, Hercberg S, Kesse-Guyot E. A systematic literature review of observational studies of the bidirectional association between metabolic syndrome and migraine. Diabetes Metab 2019;45:11–8.
[54] Fazleen NE, Whittaker M, Mamun A. Risk of metabolic syndrome in adolescents with polycystic ovarian syndrome: a systematic review and meta-analysis. Diabetes Metab Syndr 2018;12:1083–90.
[55] Misitzis A, Cunha PR, Kroumpouzos G. Skin disease related to metabolic syndrome in women. Int J Womens Dermatol 2019;5:205–12.
[56] Wekker V, van Dammen L, Koning A, Heida KY, Painter RC, Limpens J, et al. Long-term cardiometabolic disease risk in women with PCOS: a systematic review and meta-analysis. Hum Reprod Update 2020;26:942–60.
[57] Yuan H, Yu C, Li X, Sun L, Zhu X, Zhao C, et al. Serum uric acid levels and risk of metabolic syndrome: a dose-response meta-analysis of prospective studies. J Clin Endocrinol Metab 2015;100:4198–207.
[58] Liu Z, Que S, Zhou L, Zheng S. Dose-response relationship of serum uric acid with metabolic syndrome and non-alcoholic fatty liver disease incidence: a meta-analysis of prospective studies. Sci Rep 2015;5:14325.
[59] Akinyemi OA, Lanham-New SA, Darling AL. Vitamin D and non-alcoholic fatty liver disease: a systematic review and meta-analysis. Proc Nutr Soc 2019;78:E28.
[60] Eliades M, Spyrou E, Agrawal N, Lazo M, Brancati FL, Potter JJ, et al. Meta-analysis: vitamin D and non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2013;38:246–54.
[61] He C, Lin Z, Robb SW, Ezeamama AE. Serum vitamin D levels and polycystic ovary syndrome: a systematic review and meta-analysis. Nutrients 2015;7:4555–77.
[62] Marquina C, Mousa A, Scragg R, de Courten B. Vitamin D and cardiometabolic disorders: a review of current evidence, genetic determinants and pathomechanisms. Obes Rev 2019;20:262–77.
[63] Yu L, Zhai Y, Shen S. Association between vitamin D and prediabetes: a PRISMA-compliant meta-analysis. Medicine 2020;99.
[64] Angellotti E, Pittas AG. The role of vitamin D in the prevention of type 2 diabetes: to D or not to D? Endocrinology 2017;158:2013–21.
[65] Hajhashemy Z, Shahdadian F, Ziaei R, Saneei P. Serum vitamin D levels in relation to abdominal obesity: a systematic review and

dose–response meta-analysis of epidemiologic studies. Obes Rev 2021;22:e13134. Epub 2020 Sep. 3.
[66] Zhang K, Yang W, Dai H, Deng Z. Cardiovascular risk following metformin treatment in patients with type 2 diabetes mellitus: RESULTS from meta-analysis. Diabetes Res Clin Pract 2020;160: 108001.
[67] Kunutsor SK, Apekey TA, Laukkanen JA. Association of serum total osteocalcin with type 2 diabetes and intermediate metabolic phenotypes: systematic review and meta-analysis of observational evidence. Eur J Epidemiol 2015;30:599–614.
[68] Nano J, Muka T, Cepeda M, Voortman T, Dhana K, Brahimaj A, et al. Association of circulating total bilirubin with the metabolic syndrome and type 2 diabetes: a systematic review and meta-analysis of observational evidence. Diabetes Metab 2016;42: 389–97.
[69] Leermakers ETM, Darweesh SKL, Baena CP, Moreira EM, Melo van Lent D, Tielemans MJ, et al. The effects of lutein on cardiometabolic health across the life course: a systematic review and meta-analysis1,2. Am J Clin Nutr 2016;103:481–94.
[70] Yanai H, Yoshida H. Beneficial effects of adiponectin on glucose and lipid metabolism and atherosclerotic progression: mechanisms and perspectives. Int J Mol Sci 2019;20.
[71] Falahi E, Khalkhali Rad AH, Roosta S. What is the best biomarker for metabolic syndrome diagnosis? Diabetes Metab Syndr 2015;9: 366–72.
[72] Suárez-Ortegón MF, Ensaldo-Carrasco E, Shi T, McLachlan S, Fernández-Real JM, Wild SH. Ferritin, metabolic syndrome and its components: a systematic review and meta-analysis. Atherosclerosis 2018;275:97–106.
[73] La SA, Lee JY, Kim DH, Song EL, Park JH, Ju SY. Low magnesium levels in adults with metabolic syndrome: a meta-analysis. Biol Trace Elem Res 2016;170:33–42.
[74] Sarrafzadegan N, Khosravi-Boroujeni H, Lotfizadeh M, Pourmogaddas A, Salehi-Abargouei A. Magnesium status and the metabolic syndrome: a systematic review and meta-analysis. Nutrition 2016;32:409–17.
[75] Lakhani I, Gong M, Wong WT, Bazoukis G, Lampropoulos K, Wong SH, et al. Fibroblast growth factor 21 in cardio-metabolic disorders: a systematic review and meta-analysis. Metabolism 2018;83:11–7.
[76] Liu X, Liu Y, Mathers J, Cameron M, Levinger I, Yeap BB, et al. Osteocalcin and measures of adiposity: a systematic review and meta-analysis of observational studies. Archives of Osteoporosis 2020;15:145.
[77] Madan SA, John F, Pitchumoni CS. Nonalcoholic fatty liver disease and mean platelet Volume: a systemic review and meta-analysis. J Clin Gastroenterol 2016;50:69–74.
[78] Soltani S, Kolahdouz Mohammadi R, Shab-Bidar S, Vafa M, Salehi-Abargouei A. Sodium status and the metabolic syndrome: a systematic review and meta-analysis of observational studies. Crit Rev Food Sci Nutr 2019;59:196–206.
[79] Nakamura K, Miyoshi T, Yunoki K, Ito H. Postprandial hyperlipidemia as a potential residual risk factor. J Cardiol 2016;67: 335–9.
[80] Sandesara PB, Virani SS, Fazio S, Shapiro MD. The forgotten lipids: triglycerides, remnant cholesterol, and atherosclerotic cardiovascular disease risk. Endocr Rev 2019;40:537–57.
[81] Langsted A, Freiberg JJ, Tybjaerg-Hansen A, Schnohr P, Jensen GB, Nordestgaard BG. Nonfasting cholesterol and triglycerides and association with risk of myocardial infarction and total mortality: the Copenhagen City Heart Study with 31 years of follow-up. J Intern Med 2011;270:65–75.
[82] Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. Jama 2007;298: 299–308.
[83] Okekunle AP, Li Y, Liu L, Du S, Wu X, Chen Y, et al. Abnormal circulating amino acid profiles in multiple metabolic disorders. Diabetes Res Clin Pract 2017;132:45–58.
[84] Ahola-Olli AV, Mustelin L, Kalimeri M, Kettunen J, Jokelainen J, Auvinen J, et al. Circulating metabolites and the risk of type 2 diabetes: a prospective study of 11,896 young adults from four Finnish cohorts. Diabetologia 2019;62:2298–309.
[85] Brand JS, Rovers MM, Yeap BB, Schneider HJ, Tuomainen T-P, Haring R, et al. Testosterone, sex hormone-binding globulin and the metabolic syndrome in men: an individual participant data meta-analysis of observational studies. PloS One 2014;9: e100409.
[86] Garcez A, Leite HM, Weiderpass E, Paniz VMV, Watte G, Canuto R, et al. Basal cortisol levels and metabolic syndrome: a systematic review and meta-analysis of observational studies. Psychoneuroendocrinology 2018;95:50–62.
[87] Guo XF, Li X, Shi M, Li D. n-3 polyunsaturated fatty acids and metabolic syndrome risk: a meta-analysis. Nutrients 2017;9.
[88] Maltais-Payette I, Allam-Ndoul B, Pérusse L, Vohl M-C, Tchernof A. Circulating glutamate level as a potential biomarker for abdominal obesity and metabolic risk. Nutr Metabol Cardiovasc Dis 2019;29: 1353–60.
[89] Augustyn M, Grys I, Kukla M. Small intestinal bacterial overgrowth and nonalcoholic fatty liver disease. Clin Exp Hepatol 2019;5: 1–10.
[90] Mitev K, Taleski V. Association between the gut microbiota and obesity. Open Access Maced J Med Sci 2019;7:2050–6.
[91] Shen J, Obin MS, Zhao L. The gut microbiota, obesity and insulin resistance. Mol Aspect Med 2013;34:39–58.
[92] Crovesy L, Masterson D, Rosado EL. Profile of the gut microbiota of adults with obesity: a systematic review. Eur J Clin Nutr 2020;74: 1251–62.
[93] Dehghan P, Farhangi MA, Nikniaz L, Nikniaz Z, Asghari-Jafarabadi M. Gut microbiota-derived metabolite trimethylamine N-oxide (TMAO) potentially increases the risk of obesity in adults: an exploratory systematic review and dose-response meta- analysis. Obes Rev 2020;21:e12993.
[94] Ejtahed H-S, Angoorani P, Soroush A-R, Hasani-Ranjbar S, Siadat S-D, Larijani B. Gut microbiota-derived metabolites in obesity: a systematic review. Bioscience of Microbiota Food and Health 2020.
[95] Cherqaoui R, Kassim TA, Kwagyan J, Freeman C, Nunlee-Bland G, Ketete M, et al. The metabolically healthy but obese phenotype in African Americans. J Clin Hypertens 2012;14:92–6.
[96] Okosun IS, Boltri JM, Davis-Smith M, Ndirangu M. Premetabolic syndrome and clustering of cardiometabolic risk factors in White, Black and Mexican American adults. Diabetes & Metabolic Syndrome. Clin Res Rev 2009;3:143–8.
[97] Tomiyama H, Yamada J, Koji Y, Yambe M, Motobe K, Shiina K, et al. Heart rate elevation precedes the development of metabolic syndrome in Japanese men: a prospective study. Hypertens Res 2007;30:417–26.
[98] Yin Q, Chen X, Li L, Zhou R, Huang J, Yang D. Apolipoprotein B/apolipoprotein A1 ratio is a good predictive marker of metabolic syndrome and pre-metabolic syndrome in Chinese adolescent women with polycystic ovary syndrome. J Obstet Gynaecol Res 2013;39:203–9.
[99] Zaccardi F, O'Donovan G, Webb DR, Yates T, Kurl S, Khunti K, et al. Cardiorespiratory fitness and risk of type 2 diabetes mellitus: a 23-year cohort study and a meta-analysis of prospective studies. Atherosclerosis 2015;243:131–7.
[100] Bai T, Fang F, Li F, Ren Y, Hu J, Cao J. Sarcopenia is associated with hypertension in older adults: a systematic review and meta-analysis. BMC Geriatr 2020;20:279.
[101] Behboudi-Gandevani S, Amiri M, Bidhendi Yarandi R, Noroozzadeh M, Farahmand M, Rostami Dovom M, et al. The risk of metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Clin Endocrinol 2018;88:169–84.
[102] Tracey EF, McDermott RA, McDonald MI. Do worms protect against the metabolic syndrome? A systematic review and meta-analysis. Diabetes Res Clin Pract 2016;120:209–20.
[103] Upala S, Jaruvongvanich V, Riangwiwat T, Jaruvongvanich S, Sanguankeo A. Association between Helicobacter pylori infection and metabolic syndrome: a systematic review and meta-analysis. J Dig Dis 2016;17:433–40.
[104] Yang L, Lv X, Yue F, Wei D, Liu W, Zhang T. Subclinical hypothyroidism and the risk of metabolic syndrome: a meta-analysis of observational studies. Endocr Res 2016;41:158–65.
[105] Eftekharzadeh A, Khamseh ME, Farshchi A, Malek M. The association between subclinical hypothyroidism and metabolic syndrome as defined by the ATP III criteria. Metab Syndr Relat Disord 2016;14:137–44.

[106] Ran L, Zhao W, Tan X, Wang H, Mizuno K, Takagi K, et al. Association between serum vitamin C and the blood pressure: a systematic review and meta-analysis of observational studies. Cardiovascular Therapeutics 2020;2020:4940673.
[107] Ko J, Cho J, Petrov MS. Low serum amylase, lipase, and trypsin as biomarkers of metabolic disorders: a systematic review and meta-analysis. Diabetes Res Clin Pract 2020;159:107974.
[108] Mostafazadeh M, Haiaty S, Rastqar A, Keshvari M. Correlation between resistin level and metabolic syndrome component: a review. Horm Metab Res 2018;50:521–36.
[109] Pan X, Kaminga AC, Chen J, Luo M, Luo J. Fetuin-A and fetuin-B in non-alcoholic fatty liver disease: a meta-analysis and meta-regression. Int J Environ Res Publ Health 2020;17.
[110] Torchen LC, Tsai JN, Jasti P, Macaya R, Sisk R, Dapas ML, et al. Hyperandrogenemia is common in asymptomatic women and is associated with increased metabolic risk. Obesity 2020;28:106–13.
[111] Morselli E, Santos RS, Criollo A, Nelson MD, Palmer BF, Clegg DJ. The effects of oestrogens and their receptors on cardiometabolic health. Nat Rev Endocrinol 2017;13:352–64.