Metabolically Healthy Obesity—Heterogeneity in Definitions and Unconventional Factors

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Abstract: The concept of heterogeneity among obese individuals in their risk for developing metabolic dysfunction and associated complications has been recognized for decades. At the origin of the heterogeneity idea is the acknowledgement that individuals with central obesity are more prone to developing type 2 diabetes and cardiovascular disease than those with peripheral obesity. There have been attempts to categorize subjects according to their metabolic health and degree of obesity giving rise to different obese and non-obese phenotypes that include metabolically unhealthy normal-weight (MUHNW), metabolically healthy obese (MHO), and metabolically unhealthy obese (MUO). Individuals belonging to the MHO phenotype are obese according to their body mass index although exhibiting fewer or none metabolic anomalies such as type 2 diabetes, dyslipidemia, hypertension, and/or unfavorable inflammatory and fibrinolytic profiles. However, some authors claim that MHO is only transient in nature. Additionally, the phenotype categorization is controversial as it lacks standardized definitions possibly blurring the distinction between obesity phenotypes and confounding the associations with health outcomes. To add to the discussion, the factors underlying the origin or protection from metabolic deterioration and cardiometabolic risk for these subclasses are being intensely investigated and several hypotheses have been put forward. In the present review, we compare the different definitions of obesity phenotypes and present several possible factors underlying them (adipose tissue distribution and cellularity, contaminant accumulation on the adipose tissue, dysbiosis and metabolic endotoxemia imposing on to the endocannabinoid tone and inflammasome, and nutrient intake and dietary patterns) having inflammatory activation at the center.

Keywords: adipocyte hypertrophy; metabolic inflammation; obesity phenotypes; metabolically healthy obese phenotype; metabolically unhealthy normal-weight phenotype; metabolically unhealthy obese phenotype; persistent organic pollutants; gut microbiota; inflammasome; endocannabinoid system

1. Introduction

Obesity, defined by the World Health Organization (WHO) as abnormal or excessive fat accumulation that may impair health, constitutes a rising threat to public health and welfare [1] and has become an epidemic in both developed and developing countries. Obesity is not only intimately associated with the prevalence of chronic low-grade inflammation, underlying systemic
metabolic dysfunction, but also linked to an elevated risk of premature death as a result of type 2 diabetes (T2DM), non-alcoholic fatty liver disease (NAFLD), cardiovascular diseases (CVD), and certain types of cancer [2–11].

In recent years, the existence of heterogeneity among obese subjects in what regards their cardiometabolic risk has come to light, with a subgroup of these individuals being reported to be more resilient to metabolic, inflammatory, and/or fibrinolytic dysfunctions and its associated complications [3,6,7,9,12–17]. Remarkably, a subset of non-obese subjects, on the other hand, may present metabolic, inflammatory, and/or fibrinolytic abnormalities commonly found in the obese [18]. Definitions of different obesity and normal-weight phenotypes have emerged and will be discussed here. Although they are still a matter of debate, these definitions have practical consequences. In addition to high health care costs, obesity and cardiometabolic dysfunction also lead to economic and social burden explained by lost work days, lower productivity at work, and higher disability and mortality [19]. Therefore, it becomes pivotal to allocate rational resources tailored for the prevention and treatment of according to the health phenotype [7,11,16,20,21]. Obesity and cardiometabolic dysfunction are diseases with a very complex management due to their multifactorial nature involving environmental, genetic, and psychosocial factors interacting through intricate networks [22].

Obesity closely associates with a chronic low-grade inflammation, triggered by metabolic surplus [23]. Expansion of adipose tissue (AT) is considered a central element in obesity-related inflammation, with other organs and tissues being pivotal sources of inflammatory mediators during obesity. For instance liver, pancreas, and muscle can simultaneously contribute to the inflammatory milieu and be affected by it [24,25]. Adipose-originated metabolic inflammation has a close relationship with insulin resistance, being a determinant player for metabolic syndrome development, and has been under investigation for decades [25]. Inflammation and insulin resistance have been considered by many the main instigators of metabolic syndrome [26,27], being hallmarks of AT dysfunction. The list of triggers for AT inflammation is continuously growing and extends far beyond positive energy balance. This inflammatory signaling centered on the AT, with many possible culprits, leads to a vicious cycle that perpetuates AT dysfunction, hinders metabolic adaptation [28,29], and may be at the basis of unhealthy, opposed to healthy, obesity.

2. The Diverse Weight-Metabolic Phenotypes

Despite the presence of cardiometabolic disturbances in a vast majority of obese individuals, a considerable amount of people with a high body mass index (BMI) and excessive AT lack most of the metabolic, inflammatory, or fibrinolytic abnormalities and comorbidities typically associated with obesity although experiencing the same mechanical complications observed in other obese subjects [3,6,7,9,12,14,15,30–32]. Compared with age- and BMI-matched metabolically unhealthy counterparts, the metabolically healthy subjects have a lower risk of cardiovascular and liver diseases, may present normal insulin sensitivity and glucose metabolism regardless of the excessive amount of body fat [33]. On the other hand, a subset of normal-weight individuals who are metabolically unhealthy was identified in the 1980s by Ruderman et al., who suggested to characterize them according to certain parameters such as hyperinsulinemia, insulin resistance, hypertriglyceridemia, and coronary heart disease [18]. More recently, postmenopausal women who are metabolically unhealthy were associated with increased risk for breast cancer regardless of normal BMI, when compared to healthy counterparts [34]. Obese and non-obese phenotypes that include metabolically unhealthy normal-weight (MUHNW), metabolically healthy obese (MHO), and metabolically unhealthy obese (MUO) have been widely reported within clinical and epidemiological studies (see below). In MUHNW and MHO individuals, obesity is not linked to its usual metabolic, inflammatory, and/or fibrinolytic consequences, offering insight into risk factors that are largely independent of overall obesity (MUHNW) or risk factors associated with obesity that are largely independent of adiposity-induced abnormalities (MHO) [35]. Still, the phenotype categorization remains a matter of debate as it lacks standardized definitions (discussed below).
2.1. The Metabolically Unhealthy Normal-Weight Phenotype

The MUHNW phenotype is characterized by a normal BMI (18.5–25 kg/m$^2$) associated with reduced lean body mass and increased levels of adiposity and ectopic fat distribution, with augmented visceral AT (vAT) and abdominal subcutaneous AT (sAT) which is a distinctive feature of this category [36,37]. MUHNW individuals tend to neglect prevention or clinical treatment, thus presenting an increased prevalence of clinical aspects often found in metabolic syndrome, such as low insulin sensitivity, increased blood pressure, decreased high density lipoprotein (HDL)-cholesterol, and high levels of triglycerides and systemic inflammatory markers [38–40]. In addition to the risk of developing metabolic syndrome, the MUHNW phenotype is characterized by increased risk of T2DM and CVD. Moreover, elderly people presenting this phenotype show a higher risk of CVD-related and all-cause mortality [41]. A standardized definition of MUHNW is still lacking, thus compromising an early diagnosis of this condition necessary for a suitable risk management [42] and preventive measures. During a prospective cohort study, Lee et al. proposed a triglyceride-glucose index (ln (fasting triglycerides [mg/dL] × fasting plasma glucose [mg/dL])/2) to be used as simple diagnostic criterion for MUHNW (above 8.82 for men and 8.73 for women) among normal weight people [41].

2.2. The Metabolically Healthy Obese Phenotype

Andres and Sims pioneered the proposal of the existence of MHO subjects, although without completely characterizing this clinical entity [12,43,44]. Most articles suggest that individuals belonging to the MHO phenotype are obese with BMI over 30 kg/m$^2$ not exhibiting metabolic anomalies such as T2DM, dyslipidemia, hypertension, and/or unfavorable inflammatory and fibrinolytic profiles [3,7,11,12]. The absence of a unique widely universal definition and the inconsistencies in the criteria used between studies for the MHO concept explain the variability found in the prevalence of MHO phenotype, ranging from 6% to 75% of the obese population, as summarized by Rey-López et al. [16,45]. Noteworthy, Kuk et al. proposed MHO is a rare phenotype, suggesting it accounts for only 1.3% of the U.S. population [46].

Several underlying factors have been proposed to explain the healthier profile in individuals with MHO, among which are lower vAT and ectopic fat accumulation (including decreased hepatic steatosis) when compared to the more expandable subcutaneous fat depots [13]. A low inflammatory degree and low immune cell infiltration into AT is also a feature of MHO, as further discussed ahead [8,47]. Although MHO subjects present preserved high insulin sensitivity, a favorable lipid profile (e.g., reduced levels of triglycerides), increased levels of adiponectin and/or absence of hypertension and, so, a reduced risk of developing T2DM and CVD, there is no evidence protection is permanent [5,35–37,42,48,49]. For instance, Marini et al. showed that a group of 20 MHO women presented a less positive metabolic profile compared with a control group of 80 non-obese women [40]. These MHO women had significantly increased blood pressure and carotid artery intima-media thickness and lower concentrations of HDL-cholesterol, which could represent early signs of atherosclerosis [40]. Oflaz et al. further revealed that 24 MHO women, although showing a normal metabolic profile, presented signs of deteriorated endothelial function and atherosclerotic changes when compared with their healthy lean counterparts (n = 14) [50]. Additionally, Meigs et al. reported that insulin-sensitive obese individuals present a three-times higher risk of T2DM (after 11 years of follow up of 2902 men and women) when compared to insulin-sensitive normal-weight subjects, pointing towards the diabetogenic nature of obesity even in the initial absence of insulin resistance [35]. In the same line, a study comprising 6011 men and women from the Third National Health and Nutrition Examination Survey (NHANES III), with public-access mortality data linkage, showed that, in the absence of metabolic abnormalities, obesity is associated with augmented all-cause mortality risk [46]. From the community-based Uppsala Longitudinal Study of Adult Men, comprising 1675–1758 participants, Arnlöv et al. observed that overweight or obese middle-aged men without metabolic syndrome were at increased risk for diabetes after 20 years of follow up [49]. After more than 30 years of follow up, the same subjects also presented increased risk for cardiovascular events and all-cause mortality [46].
mortality [5]. More recently, Espinosa De Ycaza et al. conducted a retrospective cohort involving 1805 MHO and 3047 metabolically healthy normal-weight (MHNW) adults with a median follow-up of 15 years and concluded that MHO individuals are more likely to develop metabolic complications than MHNW, with this difference being accentuated when MHO gained weight [51].

In the following section we will discuss the multiple different definitions for MHO from several sources aiming to show that there is heterogeneity in them, possibly blurring the distinction between obesity phenotypes and confounding the associations with health outcomes. Stratification of obese individuals taking into consideration their metabolic health phenotype is relevant for the establishment of the most suitable (even personalized) lifestyle, therapeutic and/or surgery strategies [7,11,20,52,53].

The Multiple Definitions of Metabolically Healthy Obesity

There are more than a few distinct definitions of the concept of MHO (also named as benign or uncomplicated obesity), which identify subpopulations of obese individuals presenting different levels, in a more favorable profile, of metabolic, inflammatory, and fibrinolytic activity as well as immune and liver function abnormalities. Some authors argue that the distinct MHO definitions support the concept that (a) MHO does not describe a biologically fixed, defined, or stable phenotype and (b) MHO represents the extreme healthier phenotype of continuous associations between increased obesity and several diverse metabolic, inflammatory, and/or fibrinolytic activity dysfunctions along with immune and/or liver function impairments. Some authors claim that MHO provides short- but not long-term protection against obesity-associated comorbidities, what supports its transient nature. Different definitions of MHO identify different subgroups of obese individuals what is suggestive of distinctive etiologies for this phenotype. Despite a multitude of studies focusing on MHO and its characteristics, a large disparity both in the criteria used to define this phenotype and in the health outcomes analyzed still exists, hence leading to a difficult comparison among published data [6,7,11,16,20,30–32,42,52–68]. Additionally, variables that include lifestyle (diet (food groups and macro- and micronutrients intakes), smoking status, alcohol consumption, physical activity (for example motor activity, sedentary behavior, and exercise)), physical fitness (cardiorespiratory fitness, functional capacity, muscular strength, etc.), psychosocial stress, ethnicity, gender, pubertal development, or age account for the complexity in evaluating MHO although they are not included in current MHO definitions [6,7,9,11,16,55–57,60,62–64,67,69,70].

MHO definitions differently include the parameters that are presented in Table 1. Additionally, distinct cut-off values (sometimes not based on an established value but instead dependent on the population being studied) and number of inclusion criteria considered for the setting of the MHO phenotype are used [3,5–7,9–12,15,16,20,30–32,35,38,40,42,46,48,52–59,61–65,68–89].

In order to define MHO, the aforementioned parameters have been organized bearing in mind the following [16,30–32,35,42,53,56,59,66]: (1) metabolic syndrome criteria; (2) a combination of metabolic syndrome criteria and insulin sensitivity; (3) a combination of metabolic syndrome criteria and inflammatory markers (C-reactive protein) (Table 2, [52,61,75,80]); (4) a combination of metabolic syndrome score, insulin sensibility/homeostasis, and inflammatory markers (C-reactive protein, fibrinogen and/or white blood cell (WBC) count) (Table 2, [12,54,59,77,86]); and (5) insulin sensitivity/glucose homeostasis. The MHO definition most frequently used relies on four metabolic syndrome components: HDL-cholesterol, triglycerides, and glucose levels in addition to blood pressure values [16]. With or without some modification or expansion, the metabolic syndrome definition included in the MHO classification is based on the guidelines by the International Diabetes Federation, National Cholesterol Education Program Expert Panel and the American Heart Association/National Heart, Lung and Blood Institutes (in 2005) as well as the joint guidelines of major International Organizations (in 2009) [7,9,10,12,16,30–32,35,48,52,56,61,63,65,75,76,79,81,82,84,86,88–102] (some examples of their use were included in the references).
The relevance of MHO definition harmonization has been discussed and the aim of obtaining a unique MHO definition has been disclosed [11,16,32,53,55–57,59]. Interestingly, a combination of obesity and absence of components of the metabolic syndrome (in some definitions with the exception of waist circumference) has been suggested as a potential MHO definition and is already in use [55–58,64]. Table 2 presents some examples of MHO definitions that include inflammatory parameters.

Table 1. Parameters used in the multiple metabolically healthy obesity definitions.

| Parameters Used in the Multiple MHO Definitions | References |
|-----------------------------------------------|------------|
| CVD diagnosis                                 | [12,55]    |
| Evaluation of insulin sensitivity (determined by euglycemic-hyperinsulinemic clamp, homeostatic model assessment-insulin resistance (HOMA-IR), Matsuda index, insulin suppression test, glucose disposal rate, triglyceride glucose index, and oral glucose tolerance test) | [3,5–7,10–12,15,16,30–32,35,38,40,42,46,48,53,56,59,64,68,71,72,74,77–79,84–87,89] |
| Determination of systolic and diastolic blood pressure (including information on antihypertensive drug treatment) | [5–7,9–12,16,30–32,35,38,42,46,48,52–59,61,64,68–70,73,75,76,79–84,86–89] |
| Circulating lipid profile (apolipoprotein B, triglycerides and total-, low density lipoprotein (LDL)-, and HDL-cholesterol as well as triglycerides/HDL-cholesterol, total-cholesterol/HDL-cholesterol, and % of LDL particles with diameter <255 Å; plus data on associated medication treatment) | [3,5–7,9–12,16,30–32,35,38,42,46,48,52–59,61,64,68–70,73,75–77,79–84,86–89] |
| Circulating glucose levels and related parameters (glycated hemoglobin and history/diagnosis of T2DM as well as use of blood glucose lowering agents/T2DM treatment) | [5–7,9–12,16,30–32,35,38,42,46,48,52,53,55–59,61,64,68–70,73,75,76,79–84,86–89] |
| Circulating insulin levels                     | [12,16,32,54,56,68] |
| Circulating inflammatory profile (C-reactive protein, fibrinogen and white blood cell count) | [6,11,12,16,31,32,42,52–54,56,59,68,75,77,80,83,86,89] |
| Uric acid levels                              | [12,16]    |
| Waist circumference                           | [6,10,11,16,30–32,35,52,53,56,61,64,68,69,79,81,82,88,89] |
| Assessment of cardiorespiratory fitness       | [56,89]    |
Table 2. Examples of metabolically healthy obese (MHO) definitions that include inflammatory parameters.

| Parameter | Definition Details |
|-----------|--------------------|
| Glucose   | Diagnosis of incident T2DM during follow-up |
| Blood pressure | SBP/DBP ≥ 130/85 mm Hg or antihypertensive medication use |
| HDL-C     | <50 mg/dL or lipid lowering medication use |
| Triglycerides | ≥150 mg/dL |
| Other lipid parameters | - |
| Insulin sensitivity | - |
| Inflammatory markers | (Distribution of CRP levels and stratification for CRP ≥ 3.0 mg/dL vs. <3.0 mg/dL) |
Table 2. Cont.

| Other parameters | WC > 88 cm | WC > 102 cm in men and >88 cm in women | WC > 102 cm in men and >88 cm in women | WC > 102 cm in men and >88 cm in women | WC > 102 cm in men and >88 cm in women | WC > 102 cm in men and >88 cm in women |
|------------------|------------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|
| MHO definition   | <3 cardiometabolic abnormalities | <3 cardiometabolic abnormalities | <3 cardiometabolic abnormalities | <2 cardiometabolic abnormalities | <2 cardiometabolic abnormalities | All these criteria |
|                  | <3 cardiometabolic abnormalities | <3 cardiometabolic abnormalities | <3 cardiometabolic abnormalities | <2 cardiometabolic abnormalities | <2 cardiometabolic abnormalities | All these criteria |
| Ridker et al. 2003 [61] | Song et al. 2007 [75] | Khan et al. 2011 [80] | Hamer et al. 2012a [83] | Hamer et al. 2012b [52] | Iacobellis et al. 2005 [12] | St-Pierre et al. 2005 [54] |
|                  |                 |                                      |                                       |                                       |                                       |                                      |
|                  |                 |                                      |                                       |                                       |                                       |                                      |
|                  |                 |                                      |                                       |                                       |                                       |                                      |

Uric acid < 5.6 mg/dL in women and <7.0 mg/dL in men; no clinically significant abnormalities on physical examination, no lipid-lowering, hypoglycemic, or antihypertensive drugs, normal thyroid function, no history of metabolic, cardiovascular, respiratory, or other systemic diseases and normal ECG

Nondiabetic individuals free of ischemic heart

MHO definition

ApoB, apolipoprotein B; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiogram; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL%, percentage of LDL particles with diameter lower than 255 Å; LDL-C, low-density lipoprotein cholesterol; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides; WBC, white blood cell count; WC, waist circumference. To convert mg/dL to mmol/L, multiply by 0.0259 for HDL-C and LDL-C and by 0.0113 for triglycerides (from Wildman et al. 2008 and http://www.onlineconversion.com/cholesterol.htm).
2.3. The Metabolically Unhealthy Obese Phenotype

At last, the MUO phenotype is defined by a BMI over 30 kg/m² and body fat percentage over 30% [103–105]. MUO patients typically reveal an ectopic fat distribution with excessive accumulation of vAT and are considered at risk to develop major health problems (including metabolic syndrome progression, T2DM, and CVD) and, consequently, present higher mortality [33,105,106]. Given the dissimilarities observed in metabolic profiles among people within the same categories of BMI, several authors considered that instead of the amount of AT other factors such as composition and distribution of body fat are determinants of metabolic function [107–109].

3. Metabolic Inflammation

Nowadays, although it is well-established that inflammation is a major contributor for the development of obesity-related metabolic disorders (e.g., insulin resistance and T2DM), the underlying molecular mechanisms leading to the inflammatory state in AT remain only partially understood [22,110].

The first report establishing a link between inflammation and obesity revealed augmented levels of tumor necrosis factor α (TNFα) in AT of obese mice compared with lean controls [111]. Since then, a wealth of studies focusing on inflammation in obesity revealed a growing list of proinflammatory cytokines produced by adipocytes and infiltrating macrophages that are increased in obese when compared to lean subjects, such as interleukin (IL) 6, IL1β, IL18, leptin, CC-chemokine ligand 2 (CCL2), and resistin [110,112,113].

In obesity, inflammatory responses present a chronic low-grade condition, distinct from the features observed in classical inflammation elicited by infection, cancer, or injury [114]. The terms “meta-inflammation”, signifying metabolically-triggered inflammation [114], or “para-inflammation” for an intermediate state between basal and full inflammatory states [115], were proposed to name the inflammatory state observed in obesity. Both metabolic and immune systems are highly interdependent, with common cellular machinery and sharing modulators and regulators, that include hormones, cytokines, signaling protein mediators, transcription factors, and bioactive lipids [24,116].

Besides functioning as energy reservoir, thermal regulator, and mechanical protector for internal organs, AT is a central metabolically active endocrine organ. This tissue plays a role in energy homeostasis and insulin sensitivity through secretion of a wide range of molecules, such as adipokines, cytokines, hormones, and growth factors [117,118].

Inflammatory processes in the AT are now regarded as contributors to obesity-related metabolic disorders [24,119]. The energy surplus in AT has been shown not only to induce proinflammatory responses but also to lead to endoplasmic reticulum stress, hypoxia, mitochondrial defects, and ultimately, to systemic insulin resistance [119–121]. Augmenting lipid and carbohydrate substrates results in a higher demand on the mitochondrial electron transport chain. The increased demand for nutrient oxidation along with the augmented hypoxia, due to insufficient AT vascularization, generate abnormally high amounts of reactive oxygen species [22,122]. Oxidative stress leads to activation of major inflammatory kinases, such as c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinases (MAPK), and inhibitor of kappa B kinase (IKK), that may directly interfere with insulin signaling, or indirectly via induction of the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), and increase of proinflammatory cytokine and chemokine production [22,123].

Understanding fully how metabolic homeostasis deteriorates and relates to inflammation and pinpointing triggering factors for inflammation in obesity still poses an extremely hard challenge.

Adipose Tissue Inflammation and Pathogenesis of Obesity

Adipose Tissue Cellularity, Remodeling, and Inflammation

White AT (wAT) plays a key role in mediating the systemic inflammation observed in certain obesity phenotypes. Chronic nutrient overload results in excessive fat accumulation and implicates
hyperplasia (increase in adipocyte number) and adipocyte hypertrophy (increase in cell size) [110,124]. Growing adipocyte size requires a constant remodeling in the extracellular matrix of the AT, that, if insufficient will lead to vascularization and innervation deficits [124,125].

Srdic et al. found that MUHNW subjects reveal higher adipocyte hypertrophy in vAT when compared to healthy counterparts [89,125,126]. In the same line, MHO subjects were associated with smaller adipocytes relative to MUO controls [89,125]. O’Connell et al. reported a significant increase of the mean omental adipocyte size in MUO when compared to MHO. Adipocyte size strongly correlates with metabolic parameters, such as insulin resistance, triglyceride levels, hepatic steatosis, and fibrosis. A higher degree of steatosis was found in MUO (43%) than in MHO (3%). The size of adipocytes was suggested to be more relevant than the actual size of fat depot [127]. Later, O’Connell revealed AT in MHO individuals presented lower levels of preadipocyte factor-1 (Pref-1), a known inhibitor of preadipocyte differentiation, and a more favorable inflammatory profile, with lower numbers of macrophages, lower levels of TNFα, monocyte chemotactic protein-1 (MCP1), and granulocyte colony-stimulating factor, and higher levels of adiponectin [128]. Consistently, McLaughlin et al. reported that an expanded population of subcutaneous small adipose cells together with lower expression of preadipocyte differentiation markers (e.g., peroxisome proliferator-activated receptor γ (PPARγ) 1 and 2, glucose transporter type 4 (GLUT4), adiponectin) are linked to insulin resistance, thus suggesting impaired cell differentiation in this tissue may contribute to obesity-associated insulin resistance [74]. The importance of adipocyte size could potentially be explained by the overflow hypothesis that suggests adipocytes have a limit to store lipids. When this limit is reached, reminiscent fatty acids start to “overflow” to ectopic locations such as muscle, heart or liver, leading to cardiovascular and metabolic risk (e.g., hepatic insulin resistance) [127,129–131]. Overall, the capacity to recruit new or small adipocytes seems to be associated with a better metabolic health status [31,89,125–128].

Adipose Tissue Macrophages

Adipocyte hypertrophy, followed by augmented release of proinflammatory cytokines, promotes AT infiltration with immune cells and phenotypic changes in resident immune cells [110,125]. Weisberg et al. reported an increase of AT proinflammatory macrophages in obese individuals, accompanied by overexpression of TNFα, IL6, inducible nitric oxide synthase, transforming growth factor β1, and C-reactive protein (CRP), among others [121]. Additionally, Xu et al. showed an upregulation of multiple inflammation and macrophage-specific genes in wAT of genetic and high-fat-induced obesity mouse models. The observed upregulation preceded the increase in serum insulin levels. Furthermore, authors reported a significant infiltration of macrophages in histological samples of wAT in obese mice and proposed AT infiltrating macrophages and their inflammatory pathways to be major contributors to the pathogenesis of obesity-induced insulin resistance [120]. Diet-induced obesity has been shown to provoke a phenotypic switch in AT macrophage polarization into the proinflammatory M1-state, which relates to insulin resistance [132]. Interestingly, AT resident macrophages were reported to be higher in vAT when compared to sAT [133], which could relate with the worse metabolic risk profile observed in subjects with vAT accumulation [134]. Consistently, vAT adiposity was reported to have a central role in the development of insulin resistance and inflammation [125,135,136].

MHO has been linked to a low inflammatory degree, with reduced WBC counts and low levels of TNFα, IL6, and CRP identified in the plasma [8,47]. Additionally, a normal adipose function associated with lower immune cell infiltration into AT and a normal adipokine secretion pattern was reported in MHO individuals [137].

Patterns of Adipose Tissue Distribution

Vague firstly reported a distinct fat deposition between sexes, with a worse metabolic profile being related to the android (male) when compared to the gynoid (female) body type [138,139]. These two terms are used to classify obesity in terms of fat distribution. In the android fat distribution, individuals present accumulation of AT mainly around the trunk and upper body (e.g., abdomen,
chest). This central obesity pattern often named “apple-shaped” is more commonly found in men. In the gynoid fat pattern, AT is mainly deposited around the hips, thighs, and lower trunk, leading to a “pear-shaped” shape more often found in premenopausal women, also referred to as peripheral obesity [139–141].

Even in the absence of obesity, accumulation of abdominal and central AT, has been related to metabolic and CVD risk in healthy adults in multiple cohort studies [142–144]. Additionally, Fu et al. confirmed that higher central fat and central/peripheral fat ratio are significantly associated with increased metabolic risks in adult Chinese women [144]. Furthermore, in children aged 7–13 years old, the central/peripheral ratio was closely positively linked to both insulin resistance and dyslipidemia. This ratio was suggested to be a good predictor for metabolic and CVD risk in normal weight, overweight, and obese children [145].

The association of vAT with metabolic deterioration and cardiometabolic risk, regardless of BMI, has been at the basis of the definition of the MUHNW phenotype [36–40]. Accordingly, multiple studies demonstrated that MUHNW, and also MUO, both associating with poorer metabolic function and inflammatory status, show increased vAT when compared to MHO [3,125,146,147].

Distinct fat compartments within the abdominal AT also lead to different metabolic risk factors. Fox et al. showed that, although both vAT and sAT abdominal compartments are associated with metabolic risk factors, vAT seems to be more strongly correlated with cardiometabolic risk factors [148]. vAT depots show an increased secretion of proinflammatory cytokines (e.g., TNFα) and a reduced secretion of adiponectin, a hormone positively related with whole-body insulin sensitivity. Furthermore, abdominal vAT adipocytes, in comparison to abdominal sAT adipocytes, are more sensitive to catecholamine-induced lipolysis which translates into a greater release of free fatty acids (FFA) into the portal venous system and consequently, to increased lipotoxic effects, mainly in the liver and skeletal muscle. In addition, vAT accumulation was correlated with insulin resistance and hyperinsulinemia. Hence, vAT is nowadays considered as an independent risk factor for T2DM [149,150]. Altogether, the vAT adipocyte profile could explain the deleterious effects observed in vAT accumulation [140,151]. Noteworthy, peripheral fat appears to be concomitant with a lower metabolic risk, which could derive from the less inflammatory nature of the lower-body AT [144,152,153]. As already stated, among the factors underlying the healthier profile found in individuals with MHO are a lower vAT and ectopic fat accumulation (including decreased hepatic steatosis) and more expandable subcutaneous fat depot [13].

Interestingly, and demonstrating how much vAT contributes to determining obesity phenotypes, a novel mathematical model, the visceral adipose index (VAI), was proposed to assess visceral adiposity based on anthropometric and lipid profiles. VAI calculation is assessed by equations comprising waist circumference, BMI, and levels of both low-density lipoprotein (LDL)-cholesterol and triglycerides. Kang et al. showed VAI to be a good predictive tool in determining the conversion of MHO to the more unfavorable MUO phenotype, in both genders [154].

Endocrine Disrupting Chemicals: Adipose Tissue Persistent Organic Pollutants and Plastic-Associated Chemicals

Other potential contributors to obesity and metabolic syndrome have been investigated. Among them, are persistent organic pollutants (POPs) that accumulate in AT. These heterogeneous compounds of both natural and anthropogenic origin are highly persistent and present endocrine-disrupting properties [155]. POPs have been studied for their adverse effects on human health. In 2014, Gauthier et al. demonstrated the relationship of POPs with the variation in metabolic risk observed among obese individuals showing that the MHO phenotype is associated with lower plasma levels of POPs as compared with MUO subjects [156]. Although POP accumulation in AT may prevent the systemic effects of these compounds, this tissue can also be a target of their disruptive effects [156]. POP levels, either in sAT and vAT, have been shown to be higher in subjects with evidence of metabolic abnormalities. This pattern was especially evident for vAT, supported by higher vAT POP levels in patients with
increased aggregation of metabolic syndrome components and higher 10-year cardiovascular risk based on the Framingham score [157].

Owing to this association, a paradigm shift of the view of POPs as mere obesogen compounds towards their acknowledgement as markers of dysmetabolic obesity was proposed [158]. Indeed, Teixeira et al. showed that the presence of xenoestrogens, such as hexachlorocyclohexane, in vAT and plasma in premenopausal women correlate positively with levels of the proinflammatory chemokine MCP1, thus contributing to a more proinflammatory status [159]. In accordance, it was demonstrated that xenoestrogens affect human peripheral blood-derived M1 and M2 macrophage migration, cytokine release, and estrogen-related signaling pathways. These effects were shown to be mediated by either estrogen receptor (ER) α or ERβ and were simultaneous to modulation of NFκB, activator protein-1, JNK, or extracellular signal-regulated kinase signaling pathways [160]. Additionally, Pestana et al. reported exposure to p,p’-dichlorodiphenylchloroethylene (p,p’-DDE) in male Wistar rats to be linked to impaired vAT normal function (e.g., decreased tissue development-related genes) and a reduction of the dynamic response to energy surplus, thus translating into exacerbated metabolic syndrome complications [161]. Smink et al. reported an association between prenatal exposure to hexachlorobenzene and increased BMI and weight in children aged 6.5 years in a study involving 482 children [162]. Finally, Lee et al., conducting a 20-year follow-up prospective cohort study with a group of 90 T2DM-free individuals, revealed that p,p’-DDE most consistently predicted higher BMI, triglycerides, and HOMA–IR and lower HDL-cholesterol at year 20, when compared to other organochlorine (OC) pesticides. Oxychlordane, trans-nonachlor, and hexachlorobenzene could also predict higher triglycerides. Persistent polychlorinated biphenyls with ≥7 chlorides similarly predicted higher BMI, triglycerides, and HOMA-IR and lower HDL-cholesterol at year 20. Accordingly, authors suggested low dose organochlorine pesticides and polychlorinated biphenyls may contribute to obesity, dyslipidemia, and insulin resistance [163]. In the same line, a systematic review and meta-analysis by Cano-Sancho et al. identified prospective associations between exposure to p,p’-DDE and increased adiposity from seven epidemiological studies. Two in vivo studies were identified as evidence for positive associations between exposure to p,p’-DDT and increased adiposity in rodents. Furthermore, 19 in vivo studies and seven in vitro studies were reported to support the obesogenic effects of the pesticide p,p’-DDT and its metabolite p,p’-DDE [164]. Very recently, Daniels et al. described 3–9-fold and 9–30-fold higher levels of OC pesticides, respectively, in 120 South Asians of Tamil and Telugu descent, when compared to 120 European Caucasians. Since T2DM is augmented in South Asians and occurs at a lower body weight, blood lipid level, and age in relation to other ethnic populations, one possible explanation for this particular vulnerability is that South Asians have a higher exposure to OC pesticides, according to the same authors [165].

Compared to POPs, plastic-associated chemicals (PACs) such as phthalates and bisphenol A (BPA) are quickly metabolized [166–168]. However, these compounds are part of the most produced chemicals worldwide and are present in a very broad range of products such as toys, medical devices, food packaging, personal-care products, and building materials. Due to their ubiquitous nature it is expected that virtually everyone is persistently exposed to these compounds [169,170]. Over the last two decades, multiple studies detected measurable amounts of phthalates, BPA and their metabolites in human samples (e.g., urine, blood, breast milk, amniotic fluid, feces, etc.). Although there is increasing evidence on the involvement of these chemicals in the causation, progression, and susceptibility to metabolic disturbances, it is still a matter of debate and not fully understood [169–172].

The potential mechanisms of phthalates and BPA action on obesity and glucose metabolism disruption were reviewed by Stojanoska et al. Nuclear receptors seem to be the primary target of these PACs that act as either agonists (complete or partial) or antagonists thus altering regulatory pathways involved in energy homeostasis and metabolism. These nuclear receptors comprise the PPARs α,γ (with a role in adipocyte differentiation and adipogenesis, lipid metabolism, and glucose homeostasis), the estrogen receptors (ERα,β) (with a role in lipid accumulation and adipocyte differentiation), the estrogen-related receptors (ERRγ) (with a role in the regulation of energy homeostasis), the pregnant
X receptor (PXR) (with a protective role in the endocrine system by detoxifying against xenobiotics), and the thyroid hormone receptors (TRα,β) (with a role in energy and glucose homeostasis). Besides binding to nuclear receptors, phthalates and BPA exposure was described to increase the orexigenic neuropeptide Y (NPY). Additionally, phthalates were reported to increase reactive oxygen species while BPA associates with the release of inflammatory cytokines IL6 and TNFα [170].

According to cross-sectional analysis of the NHANES 2003–2006 (survey representative of the general adult population of the United States), higher urinary BPA levels were positively associated with the prevalence of T2DM [173] and general and central obesity [174]. Additionally, a study exploring the association between urinary phthalate metabolite concentrations and diabetes among a group of 2350 women who participated in the cross-sectional study NHANES 2001–2008, found that the presence of some phthalates, such as mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono-benzyl phthalate (MBzP), mono-(3-carboxy propyl) phthalate (MCPP), and three di-(2-ethylhexyl) phthalate metabolites (ΣDEHP), was associated with the prevalence of diabetes [175]. In a cross-sectional study by Hong et al., 296 nondiabetic, reproductive-aged women living in South Korea, were enrolled to explore the relationship between BPA and phthalates levels and insulin resistance and obesity. BPA levels were significantly associated with BMI and waist circumference after adjusting for confounding variables. Consistently, fasting insulin and HOMA-IR were also significantly related to urinary BPA concentration. Authors further reported an increase in BPA levels among metabolically unhealthy women compared to metabolically healthy women. Phthalates were not associated with any of the metabolic parameters [176]. In a pilot study conducted by Piecha et al., the urine levels of bisphenol A and phthalate metabolites were assessed in 168 patients presenting metabolic syndrome with or without, dyslipidemia, hypertension, and T2DM. Four metabolites, mono-n-butyl phthalate (MBP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) had significantly higher levels in diabetic compared to non-diabetic patients. The differences remained significant after adjustment for hypertension, dyslipidemia, age, and BMI [177]. Recently, Shim et al. found a positive association between the concentration of one phthalate metabolite in the urine, MEHHP, and the metabolic syndrome status, involving 5251 participants from the Korean National Environmental Health Survey II (2012–2014), after adjustment for demographic variables. Nevertheless, the authors could not explain the reported association, claiming that chemical properties and health effects of each phthalate metabolite are not well known [178]. Milošević et al. analyzed the presence of 10 different phthalate metabolites in the urine samples of 305 participants of both genders (mono-ethyl phthalate (MEP), mono-(2-ethylhexyl) phthalate (MEHP), mono-methyl phthalate (MMP), mono-n-propyl phthalate (MPP), mono-n-butylphthalate (MBP), mono-iso-allyl phthalate (MiAP), mono-nallylphthalate (MnAP), mono-cyclohexyl phthalate (MCHP), MBzP, and mono-n-octyl phthalate (MOP)). Authors found that exposure to even one phthalate metabolite was associated with an increase in glucose serum levels in all phthalate positive subjects enrolled and divided by three groups: obese, T2DM, and non-obese non-diabetic. Furthermore, they argued phthalate exposure may increase susceptibility for NAFLD development [179]. In a case-control study including 320 children and adolescents (divided into four groups, with or without excess weight and with or without cardiometabolic risk factors), Mansouri et al. found that serum MEHP concentration was associated with higher odds ratio of cardiometabolic risk factors in participants, independently of their weight status. The serum MBP concentration increased the odds ratio of cardiometabolic risk factors only in the normal weight group. Additionally, in young individuals without cardiometabolic risk factors, serum MMP, and MEHP levels were significantly associated with increased risk of excess weight [171]. Martínez-Ibarra et al. found positive correlations between urinary levels of some phthalates and expression levels of serum miRNAs linked to gestational diabetes mellitus. In particular, MBzP and MEHP levels in urine were associated miR-16-5p and miR-29a-3p expression levels, respectively [180].
Despite the emerging evidence on the role of phthalates and BPA in the development of metabolic syndrome components, a cause-effect relationship between exposure and manifestation of disease remains to be solved as there are still many conflicting results [169,170,172].

Besides all the evidence so far revealing associations between adiposity, TD2M, metabolic disruption, and inflammation, among other effects, further longitudinal and experimental studies are needed to provide firm evidence and confirm whether POPs and PACs are contributors for the metabolic abnormalities observed in MUO or MUHNW phenotypes.

Gut Microbiota, Endocannabinoid System, and Inflammasome

The gut microbiota, a diverse microbial community composed of trillions of bacteria, has been recognized as a major environmental factor affecting host metabolic balance and, therefore, is being considered as a virtual endocrine organ [181,182].

Multiple studies comparing obese and lean human subjects revealed significant alterations on gut microbiota composition, notably showing a reduction of Bacteroidetes phylum and a related increase of Firmicutes phylum [183–187]. The reduced Bacteroidetes:Firmicutes ratio has been linked to a more efficient hydrolysis of non-digestible carbohydrates and subsequent increased absorption of calories by the host.

In particular, Turnbaugh et al. identified an increase in Bacteroidetes in individuals losing weight while undergoing a low-calorie diet [185]. Additionally, Jumpertz et al. concluded that nutrient load can affect gut microbiota by showing an association between an augmented energy harvest of ≈150 kilocalories and a 20% increase in Firmicutes associated with a corresponding decrease in Bacteroidetes [188]. Nevertheless, other human studies did not corroborate the association between Bacteroidetes:Firmicutes ratio and obesity [189–192]. Multiple reports analyzing the microbiota of populations from different regions of the world have started to pinpoint which species, genera, or phyla are altered in individuals with obesity and metabolic disease. Results vary largely between studies and underscore the marked interindividual variations in the gut microbiota composition with genetics, diet, or surrounding environment, for instance [193,194].

Changes in the normal gut microbial composition caused by external factors (e.g., high-fat diet) can lead to dramatic alterations of the symbiotic relationship between the gut microbiota and the host. The microbial imbalance can drive an increase of the intestinal permeability, thus promoting translocation of bacterial products that results in a systemic low-grade elevation in bacterial derived endotoxin lipopolysaccharide (LPS). This condition is termed metabolic endotoxemia [195–197]. Increased circulating LPS levels activate the pattern recognition receptor toll-like receptor 4 (TLR4) and trigger proinflammatory and oxidative cascades that contribute to the development of metabolic imbalances observed in obesity and T2DM [196].

For instance, Cani et al. showed that metabolic endotoxemia can dysregulate the inflammatory tone and trigger body weight gain and T2DM in mice [198]. Creely et al. suggested LPS can activate an innate immune response in human AT in T2DM and obesity [199]. In the same line, a population-based cohort study comprising 7169 subjects showed endotoxemia is tightly bound to increased risk of incident T2DM [200]. Finally, a 6-year follow-up study with 2529 middle-aged and older Chinese men and women revealed elevated plasma LPS-binding protein levels correlate significantly with an increased risk of developing metabolic syndrome by triggering the activation of proinflammatory pathways, such as NFκB in macrophages [201]. Noteworthy, Akkermansia muciniphila, one of the most abundant single species in the human intestinal microbiota, was reported as a main beneficial bacterium to reduce gut barrier disruption [202,203]. Although the mechanisms of action are not yet fully uncovered, very recently, this effect was attributed to the regulation of tight junction proteins expression by the extracellular lipid bilayer vesicles secreted by A. muciniphila [204]. Interestingly, this bacterium is inversely associated with obesity, T2DM, cardiometabolic disease, and low-grade inflammation in humans and there is growing evidence that it may provide protection against certain abnormalities associated with low-grade inflammation [203,205,206]. Noteworthy, very recently a proof-of-concept
randomized exploratory study demonstrated, for the first time, that the oral supplementation of \textit{A. muciniphila} (either alive or pasteurized) in obese and overweight volunteer humans for a 3-month period was associated with improvement of several metabolic parameters (e.g., insulin resistance, visceral adiposity, circulating lipids, systemic inflammation markers) \cite{207}. In line, the use of the antidiabetic drug metformin and bariatric surgery have been both correlated with a significant increase in the abundance of \textit{A. muciniphila} \cite{203,208,209}.

Obesity and associated inflammatory disorders are related to a dysregulation of the endocannabinoid (eCB) system which, in turn, contributes to an aggravation of the inflammatory tone. Changes in the gut eCB system are involved in the dysregulation of LPS levels and intestinal permeability as well as development of chronic inflammation and dysbiosis of gut microbiota \cite{210–213}. Noteworthy, the blockade of the cannabinoid receptor type-1 (CB1) was shown to attenuate insulin resistance, glucose intolerance, dyslipidemia, diet-induced obesity, inflammation, and cardiometabolic risk factors \cite{214–216}.

Recently, Mehrpourya-Bahrami et al. added that the blockade of CB1 in mice attenuates both diet-induced obesity and metabolic disorders and induces alterations in the gut microbiota, namely by increasing the relative abundance of \textit{A. muciniphila} \cite{216}. In the opposite direction, Muccioli et al. showed gut microbiota can modulate endocannabinoid levels in the gut and AT by regulating levels of either cannabinoid receptors agonists such as anandamide (N-arachidonoyl-ethanolamine, AEA) or enzymes needed for their biosynthesis, such as N-acyl-phosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD). Furthermore, authors found that activation of some components of the eCB system in the intestine by an altered gut microbiota increases gut permeability and plasma LPS amount as well as exacerbates gut barrier disruption and peripheral eCB system tone in both the intestinal and ATs. During obesity, the elevated eCB tone and LPS levels are involved in the dysregulation of adipogenesis \cite{217}. Additionally, Liu et al. showed LPS induces a strong production of endogenous ligands of cannabinoid receptors (in particular, AEA) in murine AT macrophages, thus contributing to exacerbation of chronic inflammation in visceral fat, hyperglycemia, and insulin \cite{213}. Importantly, Everard et al. reported that administration of \textit{A. muciniphila} in high-fat diet-fed mice ameliorated the metabolic profile by reversing fat-mass gain, metabolic endotoxia, AT inflammation, and insulin resistance. \textit{A. muciniphila} administration increases intestinal levels of endocannabinoids that control inflammation (e.g., 2-arachidonoylglycerol (2-AG)) and improves the gut-barrier function \cite{205}. 2-AG was proposed to be an important gate keeper promoting gut barrier function \cite{205}. The associations between dysbiosis, metabolic endotoxia, and changes in eCB tone as well as inflammasome activation are illustrated in Figure 1.

Apart from the distinction between lean and obese subjects, the gut microbiota is also now identified as a determining factor in the pathogenesis of the MUO phenotype and related comorbidities through increased endotoxia, intestinal and systemic inflammation, as well as insulin resistance. In accordance, recent studies suggested that a healthy-like gut microbiota profile may contribute to the MHO phenotype \cite{218}. For instance, it remains unanswered whether probiotic bacteria such as \textit{A. muciniphila} could be a factor involved in the differences observed between MHO and MUO.

The multiprotein signaling complex nucleotide-binding oligomerization domain-like receptor (NLRP) 3 inflammasome, which recognizes a wide range of microbial, stress, and damage signals, leads to the activation of caspase-1 and subsequent production of potent proinflammatory cytokines, such as IL1β. Noteworthy, NLRP3 inflammasome components as well as caspase-1 were found to be increased in adipose and liver tissues of obese mice and humans \cite{219}. Vandanmagsar et al. reported a prominent role of NLRP3 inflammasome in inducing obesity and insulin resistance. NLRP3 inflammasome ablated mice do not show obesity-induced inflammasome activation in both fat depots and liver and present better insulin signaling \cite{219}.
Figure 1. Imbalances in the composition of the gut microbiota can lead to an altered gut-barrier function, and are often observed in several conditions including obesity, related metabolic disorders, and type 2 diabetes. A dysfunctional or “leaky” intestinal tight junction barrier allows augmented translocation of luminal gut-microbiota-derived components, such as LPS, into the blood stream. Increased circulating LPS levels activate the pattern recognition receptor TLR4 and trigger proinflammatory and oxidative cascades that contribute to insulin resistance, macrophage infiltration, secretion of pro-inflammatory cytokines, and lipid accumulation in several organs and tissues, including the AT. The probiotic *Akkermansia muciniphila* preserves the integrity of intestinal barrier function and reduces endotoxemia, possibly by regulating expression of endocannabinoids such as 2AG (augmented), which has been considered as a “gate keeper”, and AEA (decreased), considered a “gate-opener”. During obesity, AT expansion can be mediated by hypertrophy, hyperplasia, or both. MHO individuals are associated with an enhanced adipogenic capacity in comparison to MUO, therefore hyperplasia could potentially be the preferred expansion mechanism of fat tissue in the former individuals. The molecular mechanisms controlling both hyperplasia and hypertrophy have not been fully disclosed so it would be of interest to explore if microbiota and gut-barrier function have any role in regulating the AT expansion during obesity and if this could explain the distinct health profile between MHO and MUO. 2AG, 2-arachidonoylglycerol; AEA, anandamide; AT, adipose tissue; CD14, cluster of differentiation 14; IKK, I kappa B kinase; JNK, c-Jun N-terminal kinase; LBP, lipopolysaccharide binding protein; LPS, lipopolysaccharide; M1, classically activated macrophages; M2, alternatively-activated macrophages; MHO, metabolic healthy obesity; MUO, metabolic unhealthy obesity; NFκB, factor nuclear kappa B; TLR4, Toll-like receptor 4; TNFα, tumor necrosis factor-α.
In spite of the potential role of the NLRP3 inflammasome in metabolic syndrome, activation of this pathway in fat occurs in a late phase of obesity, thus suggesting that NLRP3 inflammasome is actually not a primary etiologic factor in the disease [219,220]. Yet, Esser et al. revealed that MUO phenotype appears to be related to an increased activation of the NLPR3 inflammasome in macrophages infiltrating vAT, and a less favorable inflammatory profile compared with the MHO phenotype [221]. In the opposite direction, NLRP1 inflammasome was described to prevent obesity and metabolic syndrome through IL18 production. Murphy et al. found that mice lacking the NLRP1 inflammasome develop spontaneous obesity due to lipid accumulation. The same effect was observed in mice lacking IL18 [222].

Nutrient Intake and Dietary Pattern

In 2017, a large 7-year prospective cohort study using data from 135,335 adults from 18 countries and five continents (Prospective Urban Rural Epidemiology, PURE) concluded that a higher carbohydrate intake was associated with a higher risk of total mortality, in opposition to the intake of total fat and each type of fat (saturated, monounsaturated and polyunsaturated) that were linked to lower risk of total mortality. Additionally, authors reported total fat and saturated and unsaturated fats were not significantly associated with risk of myocardial infarction or CVD mortality [223]. These surprising results are at the basis of a paradigm shift concerning the dietary impact of macronutrients in human disease and mortality. Such conclusions cast doubts on the classical dietary guidelines recommending a substantial reduction of total fat intake, therefore, this subject remains highly controversial [223,224]. Additionally, the majority of studies have been conducted in Western countries (Europe and North America) where nutrition excess is more likely, so it is unsolved whether they are applicable to other populations [223]. Although there is still a major discussion on the impact of each macro- and micronutrient in health, it is well established that the Mediterranean diet is the gold standard of healthy nutrition. Here, the whole is greater than the sum of its parts [225,226]. The Mediterranean diet comprises a balanced combination of fruit, vegetables, fish, cereals, polyunsaturated fats, and a moderate amount of meat and dairy products. Multiple studies have been consensual in associating this diet with decreased morbidity and mortality (mainly from cardiovascular causes). Its health benefits have been attributed to (a) elevated consumption of monounsaturated fat instead of a low fat intake in general; (b) high complex carbohydrate intake, mostly grains and legumes, and (c) high fiber intake, mainly from vegetables and fruit [227]. Micronutrients such as polyphenols and alpha-linolenic acid, may also provide additional cardioprotective effects [227,228]. During a prospective cohort study, the association between Mediterranean diet, metabolic phenotypes, and mortality risk was explored for 1739 adults from the NHANES III survey. Participants were classified as MHO or MUO phenotypes and Mediterranean Diet Scores (MDS) were created to assess the adherence to Mediterranean diet. During a median follow-up of 18.5 years, 12.9% of MHO and 27.1% of MUO subjects died. Noteworthy, a 41% reduction in the risk of all-cause mortality was observed in the MHO phenotype (but not in the MUO phenotype) upon adherence to Mediterranean diet [229]. Very recently, Arenaza et al. examined the adherence to the Mediterranean dietary pattern (MDP) in MHO and MUO phenotypes in European adolescents. In this cross-sectional study comprising 137 overweight/obese adolescents, authors found that adherence to MDP seems to be beneficial to maintaining metabolic health among overweight/obese adolescents [230].

4. Conclusions

Whatever the trigger for obesity-related inflammation, it is undisputable that it plays a central role in the pathogenesis of obesity comorbidities. Here we report that the inflammatory status associated with adipocyte hypertrophy, proinflammatory AT macrophages, vAT, POPs accumulating in the AT, PACs, and metabolic endotoxemia elicited by an unfavorable gut microbiota along with a subsequent dysregulation of the endocannabinoid tone and the increased activation of the NLPR3 inflammasome may explain why a subset of obese subjects are more prone to develop metabolic disturbances, while
others on the opposite side of this spectrum, remain with relatively preserved metabolic function (Figure 2). Meanwhile, the gold standard Mediterranean diet, composed of a diverse group of foods such as fruits, vegetables, whole grains, among others, and with restricted amounts of red meat, sweets, and processed foods, seems to play a major role in preserving the metabolic function. Nevertheless, one cannot ignore that the prognosis for the MHO phenotype remains a matter of intense debate and multiple prospective cohort studies provide evidence that MHO, when compared to their non-obese counterparts, are at higher risk to develop hypertension, T2DM, and metabolic syndrome [38,231]. Still, risk is lower when compared to MUO and MUHNW. Keeping in mind that inflammation may be at the crossroads between obesity phenotypes, interventions aiming to target metabolic inflammation may show promise in counteracting obesity metabolic comorbidities.

Figure 2. Interplay between factors contributing to inflammatory activation and adipose tissue dysfunction that may underlie the different obesity and metabolic phenotypes. Presence of the depicted possible triggers of inflammation may favor development of hypertrophic dysfunctional adipose tissue, with M1 macrophage recruitment, while impeding adipose tissue growth through hyperplasia with resident M2 macrophages, more prone to metabolic adaptation. M1, classically activated; M2, alternatively activated; MHO, metabolically healthy obese; MUHNW, metabolically unhealthy normal-weight; MUO, metabolically unhealthy obese.

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References
1. WHO. Obesity and Overweight; WHO: Geneva, Switzerland, 2017.
2. Mokdad, A.H.; Ford, E.S.; Bowman, B.A.; Dietz, W.H.; Vinicor, F.; Bales, V.S.; Marks, J.S. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 2003, 289, 76–79. [CrossRef] [PubMed]
3. Shin, M.-J.; Hyun, Y.J.; Kim, O.Y.; Kim, J.Y.; Jang, Y.; Lee, J.H. Weight loss effect on inflammation and LDL oxidation in metabolically healthy but obese (MHO) individuals: low inflammation and LDL oxidation in MHO women. Int. J. Obes. 2006, 30, 1529–1534. [CrossRef] [PubMed]
4. Huang, H.-L.; Lin, W.-Y.; Lee, L.-T.; Wang, H.-H.; Lee, W.-J.; Huang, K.-C. Metabolic syndrome is related to nonalcoholic steatohepatitis in severely obese subjects. Obes. Surg. 2007, 17, 1457–1463. [CrossRef] [PubMed]
5. Arnlov, J.; Ingelsson, E.; Sundstrom, J.; Lind, L. Impact of Body Mass Index and the Metabolic Syndrome on the Risk of Cardiovascular Disease and Death in Middle-Aged Men. Circulation 2010, 121, 230–236. [CrossRef] [PubMed]
6. Phillips, C.M. Metabolically healthy obesity: Definitions, determinants and clinical implications. Rev. Endocr. Metab. Disord. 2013, 14, 219–227. [CrossRef]
7. Blüher, M. Are metabolically healthy obese individuals really healthy? Eur. J. Endocrinol. 2014, 171, R209–R219. [CrossRef]
8. Phillips, C.M.; Perry, I.J. Does Inflammation Determine Metabolic Health Status in Obese and Nonobese Adults? J. Clin. Endocrinol. Metab. 2013, 98, E1610–E1619. [CrossRef]
9. Ortega, F.B.; Lee, D.; Katzmarzyk, P.T.; Ruiz, J.R.; Sui, X.; Church, T.S.; Blair, S.N. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. Eur. Heart J. 2013, 34, 389–397. [CrossRef]
10. Manu, P.; Ionescu-Tîrgoviste, C.; Tsang, J.; Napolitano, B.A.; Lesser, M.L.; Correll, C.U. Dysmetabolic Signals in “Metabolically Healthy” Obesity. Obes. Res. Clin. Pract. 2012, 6, e9–e20. [CrossRef]
11. Phillips, C.M.; Dillon, C.; Harrington, J.M.; McCarthy, V.J.C.; Kearney, P.M.; Fitzgerald, A.P.; Perry, I.J. Defining Metabolically Healthy Obesity: Role of Dietary and Lifestyle Factors. PLoS ONE 2013, 8, e76188. [CrossRef]
12. Iacobellis, G.; Ribaudo, M.C.; Zappaterreno, A.; Iannucci, C.V.; Leonetti, F. Prevalence of Uncomplicated Obesity in an Italian Obese Population. Obes. Res. 2005, 13, 1116–1122. [CrossRef] [PubMed]
13. Blüher, M. The distinction of metabolically ‘healthy’ from ‘unhealthy’ obese individuals. Curr. Opin. Lipidol. 2010, 21, 38–43. [CrossRef]
14. Karelis, A.D. Obesity: To be obese—does it matter if you are metabolically healthy? Nat. Rev. Endocrinol. 2011, 7, 699–700. [CrossRef] [PubMed]
15. Calori, G.; Lattuada, G.; Piemonti, L.; Garancini, M.P.; Ragogna, F.; Villa, M.; Mannino, S.; Crosignani, P.; Bosi, E.; Luzi, L.; et al. Prevalence, Metabolic Features, and Prognosis of Metabolically Healthy Obese Italian Individuals: The Cremona Study. Diabetes Care 2011, 34, 210–215. [CrossRef] [PubMed]
16. Rey-López, J.P.; de Rezende, L.F.; Pastor-Valero, M.; Tess, B.H. The prevalence of metabolically healthy obesity: a systematic review and critical evaluation of the definitions used. Obes. Rev. 2014, 15, 781–790. [CrossRef]
17. Mongraw-Chaffin, M.; Foster, M.C.; Anderson, C.A.M.; Burke, G.L.; Haq, N.; Kalyani, R.R.; Ouyang, P.; Sibley, C.T.; Tracy, R.; Woodward, M.; et al. Metabolically Healthy Obesity, Transition to Metabolic Syndrome, and Cardiovascular Risk. J. Am. Coll. Cardiol. 2018, 71, 1857–1865. [CrossRef]
18. Ruderman, N.B.; Schneider, S.H.; Berchtold, P. The “metabolically-obese” normal-weight individual. J. Am. Clin. Nutr. 1981, 34, 1617–1621. [CrossRef]
19. Tremmel, M.; Gerdtham, U.-G.; Nilsson, P.; Saha, S. Economic Burden of Obesity: A Systematic Literature Review. Int. J. Environ. Res. Public Health 2017, 14, 435. [CrossRef]
20. Blüher, M. Are there still healthy obese patients? Curr. Opin. Endocrinol. Diabetes Obes. 2012, 19, 341–346. [CrossRef]
21. Mutie, P.M.; Giordano, G.N.; Franks, P.W. Lifestyle precision medicine: the next generation in type 2 diabetes prevention? BMC Med. 2017, 15, 171. [CrossRef]
22. Monteiro, R.; Azevedo, I. Chronic inflammation in obesity and the metabolic syndrome. Mediat. Inflamm. 2010, 2010, 1–10. [CrossRef] [PubMed]
23. Trayhurn, P.; Wood, I.S. Adipokines: inflammation and the pleiotropic role of white adipose tissue. Br. J. Nutr. 2004, 92, 347. [CrossRef] [PubMed]
24. Monteiro, R.; Teixeira, D.; Calhau, C. Estrogen signaling in metabolic inflammation. Mediat. Inflamm. 2014, 2014, 615917. [CrossRef]
25. Gregor, M.F.; Hotamisligil, G.S. Inflammatory Mechanisms in Obesity. Annu. Rev. Immunol. 2011, 29, 415–445. [CrossRef]
26. González, A.S.; Guerrero, D.B.; Soto, M.B.; Díaz, S.P.; Martínez-Olmos, M.; Vidal, O. Metabolic syndrome, insulin resistance and the inflammation markers C-reactive protein and ferritin. Eur. J. Clin. Nutr. 2006, 60, 802–809. [CrossRef]
27. Wannamethee, S.G.; Lowe, G.D.O.; Shaper, A.G.; Rumley, A.; Lennon, L.; Whincup, P.H. The metabolic syndrome and insulin resistance: relationship to haemostatic and inflammatory markers in older non-diabetic men. Atherosclerosis 2005, 181, 101–108. [CrossRef]
28. Goossens, G.H.; Blaak, E.E. Adipose tissue dysfunction and impaired metabolic health in human obesity: a matter of oxygen? Front. Endocrinol. (Lausanne) 2015, 6, 55. [CrossRef]
29. Bremer, A.A.; Jialal, I. Adipose Tissue Dysfunction in Nascent Metabolic Syndrome. J. Obes. 2013, 2013, 1–8. [CrossRef]
30. Durward, C.M.; Hartman, T.J.; Nickols-Richardson, S.M. All-Cause Mortality Risk of Metabolically Healthy Obese Individuals in NHANES III. J. Obes. 2012, 2012, 460321. [CrossRef]
31. Boonchaya-anant, P.; Apovian, C.M. Metabolically Healthy Obesity—Does it Exist? *Curr. Atheroscler. Rep.* 2014, 16, 441. [CrossRef]
32. Roberson, L.L.; Aneni, E.C.; Maziak, W.; Agatston, A.; Feldman, T.; Roussef, M.; Tran, T.; Blaha, M.J.; Santos, R.D.; Sposito, A.; et al. Beyond BMI: The “Metabolically healthy obese” phenotype & its association with clinical/subclinical cardiovascular disease and all-cause mortality—A systematic review. *BMC Public Health* 2014, 14, 14.
33. Dobson, R.; Burgess, M.I.; Sprung, V.S.; Irwin, A.; Hamer, M.; Jones, J.; Daousi, C.; Adams, V.; Kemp, G.J.; Shojaee-Moradie, F.; et al. Metabolically healthy and unhealthy obesity: differential effects on myocardial function according to metabolic syndrome, rather than obesity. *Int. J. Obes.* 2016, 40, 153–161. [CrossRef] [PubMed]
34. Park, Y.-M.M.; White, A.J.; Nichols, H.B.; O’Brien, C.R.; Weinberg, C.R.; Sandler, D.P. The association between metabolic health, obesity phenotype and the risk of breast cancer. *UICC Int. J. Cancer IJC* 2017, 140, 2657–2666. [CrossRef] [PubMed]
35. Meigs, J.B.; Wilson, P.W.F.; Fox, C.S.; Vasan, R.S.; Nathan, D.M.; Sullivan, L.M.; D’Agostino, R.B. Body Mass Index, Metabolic Syndrome, and Risk of Type 2 Diabetes or Cardiovascular Disease. *J. Clin. Endocrinol. Metab.* 2006, 91, 2906–2912. [CrossRef] [PubMed]
36. Cembrowska, P.; Staﬁna, A.; Odrowarz-Sypniewska, G. Obesity phenotypes: normal-weight individuals with metabolic disorders versus metabolically healthy obese. *Med. Res. J.* 2017, 1, 95–99. [CrossRef]
37. Mathew, H.; Farr, O.M.; Mantzoros, C.S. Metabolic health and weight: Understanding metabolically unhealthy normal weight or metabolically obese patients. *Metabolism.* 2016, 65, 73–80. [CrossRef]
38. Aung, K.; Lorenzo, C.; Hinojosa, M.A.; Haffner, S.M. Risk of Developing Diabetes and Cardiovascular Disease in Metabolically Unhealthy Normal-Weight and Metabolically Healthy Obese Individuals. *J. Clin. Endocrinol. Metab.* 2014, 99, 462–468. [CrossRef]
39. Dvorak, R.V.; DeNino, W.F.; Ades, P.A.; Poehlman, E.T. Phenotypic characteristics associated with insulin resistance in metabolically obese but normal-weight young women. *Diabetes* 1999, 48, 2210–2214. [CrossRef]
40. Marini, M.A.; Succurro, E.; Frontoni, S.; Hribal, M.L.; Andreozzi, F.; Lauro, R.; Perticone, F.; Sesti, G.; Pedro-Botet, J. Metabolically healthy but obese women have an intermediate cardiovascular risk profile between healthy nonobese women and obese insulin-resistant women. *Diabetes Care* 2007, 30, 2145–2147. [CrossRef]
41. Lee, S.-H.; Han, K.; Yang, H.K.; Kim, H.-S.; Cho, J.-H.; Kwon, H.-S.; Park, Y.-M.; Cha, B.-Y.; Yoon, K.-H. A novel criterion for identifying metabolically obese but normal weight individuals using the product of triglycerides and glucose. *Nutr. Diabetes* 2015, 5, e149. [CrossRef]
42. Muñoz-Garach, A.; Cornejo-Pareja, I.; Tinhalones, F.J. Does Metabolically Healthy Obesity Exist? *Nutrients* 2016, 8, 320. [CrossRef] [PubMed]
43. Andres, R. Effect of obesity on total mortality. *Int. J. Obes.* 1980, 4, 381–386. [PubMed]
44. Sims, E.A.H. Are there persons who are obese, but metabolically healthy? *Metabolism* 2001, 50, 1499–1504. [CrossRef] [PubMed]
45. Lin, H.; Zhang, L.; Zheng, R.; Zheng, Y. The prevalence, metabolic risk and effects of lifestyle intervention for metabolically healthy obesity: a systematic review and meta-analysis: A PRISMA-compliant article. *Medicine (Baltimore)* 2017, 96, e8838. [CrossRef]
46. Kuk, J.L.; Ardern, C.I. Are metabolically normal but obese individuals at lower risk for all-cause mortality? *Diabetes Care* 2009, 32, 2297–2299. [CrossRef] [PubMed]
47. Marques-Vidal, P.; Velho, S.; Waterworth, D.; Waeber, G.; von Känel, R.; Vollenweider, P. The association between inflammatory biomarkers and metabolically healthy obesity depends of the definition used. *Eur. J. Clin. Nutr.* 2012, 66, 426–435. [CrossRef]
48. Bobbioni-Harsch, E.; Pataky, Z.; Makoundou, V.; Laville, M.; Disse, E.; Anderwald, C.; Konrad, T.; Golay, A. RISC Investigators From Metabolic Normality to Cardiometabolic Risk Factors in Subjects With Obesity. *Obesity* 2012, 20, 2063–2069. [CrossRef]
49. Arnlov, J.; Sundstrom, J.; Ingelsson, E.; Lind, L. Impact of BMI and the Metabolic Syndrome on the Risk of Diabetes in Middle-Aged Men. *Diabetes Care* 2011, 34, 61–65. [CrossRef]
50. Oflaz, H.; Ozbay, N.; Mantar, F.; Genchellac, H.; Mercanoglu, F.; Sencer, E.; Molvalilar, S.; Orhan, Y. Determination of endothelial function and early atherosclerotic changes in healthy obese women. *Diabetes Nutr. Metab.* 2003, 16, 176–181.
51. Espinosa De Ycaza, A.; Donegan, D.; Jensen, M.D. Long-term metabolic risk for the metabolically healthy overweight/obese phenotype. Int. J. Obes. 2018, 42, 302–309. [CrossRef]
52. Hamer, M.; Stamatakis, E. Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. J. Clin. Endocrinol. Metab. 2012, 97, 2482–2488. [CrossRef] [PubMed]
53. Jung, C.H.; Lee, W.J.; Song, K.-H. Metabolically healthy obesity: a friend or foe? Korean J. Intern. Med. 2017, 32, 611–621. [CrossRef] [PubMed]
54. St-Pierre, A.C.; Cantin, B.; Mauri...dislipidemia. Metabolism 2019, 92, 71–81. [CrossRef]
55. Iacobini, C.; Pugliese, G.; Blasetti Fantauzzi, C.; Federici, M.; Menini, S. Metabolically healthy versus metabolically unhealthy obesity. Metabolism 2019, 92, 51–60. [CrossRef]
56. Beh, S. Is metabolically healthy obesity a useful concept? Diabet. Med. 2019, 36, 539–545. [CrossRef]
57. Katzmarzyk, P.T.; Church, T.S.; Janssen, I.; Ross, R.; Blair, S.N. Metabolic syndrome, obesity, and mortality: impact of cardiorespiratory fitness. Diabetes Care 2005, 28, 391–397. [CrossRef]
58. Cadenas-Sanchez, C.; Ruiz, J.R.; Labayen, I.; Huybrechts, I.; Manios, Y.; Gonzalez-Gross, M.; Breidenassel, C.; Kafatos, A.; De Henauw, S.; Vanhelst, J.; et al. Prevalence of Metabolically Healthy but Obese Phenotype and Its Association With Sedentary Time, Physical Activity, and Fitness. J. Adolesc. Health 2017, 61, 107–114. [CrossRef]
59. Karelis, A.D.; Brochu, M.; Rabasa-Lhoret, R. Can we identify metabolically healthy but obese individuals (MHO)? Diabetes Metab. 2004, 30, 569–572. [CrossRef]
72. Karelis, A.D.; Faraj, M.; Bastard, J.-P.; St-Pierre, D.H.; Brochu, M.; Prud’homme, D.; Rabasa-Lhoret, R. The Metabolically Healthy but Obese Individual Presents a Favorable Inflammation Profile. *J. Clin. Endocrinol. Metab.* 2005, 90, 4145–4150. [CrossRef] [PubMed]

73. Daly, C.A.; Hildebrandt, P.; Bertrand, M.; Ferrari, R.; Remme, W.; Simoons, M.; Fox, K.M. EUROPA investigators Adverse prognosis associated with the metabolic syndrome in established coronary artery disease: data from the EUROPA trial. *Heart* 2007, 93, 1406–1411. [CrossRef] [PubMed]

74. McLaughlin, T.; Sherman, A.; Tsao, P.; Gonzalez, O.; Yee, G.; Lamendola, C.; Reaven, G.M.; Cushman, S.W. Enhanced proportion of small adipose cells in insulin-resistant vs insulin-sensitive obese individuals implicates impaired adipogenesis. *Diabetologia* 2007, 50, 1707–1715. [CrossRef] [PubMed]

75. Song, Y.; Manson, J.E.; Meigs, J.B.; Ridker, P.M.; Buring, J.E.; Liu, S. Comparison of usefulness of body mass index versus metabolic risk factors in predicting 10-year risk of cardiovascular events in women. *Am. J. Cardiol.* 2007, 100, 1654–1658. [CrossRef]

76. Aguilar-Salinas, C.A.; García, E.G.; Robles, L.; Riaño, D.; Ruiz-Gomez, D.G.; García-Ulloa, A.C.; Melgarejo, M.A.; Zamora, M.; Guillen-Pineda, L.E.; Mehta, R.; et al. High Adiponectin Concentrations Are Associated with the Metabolically Healthy Obese Phenotype. *J. Clin. Endocrinol. Metab.* 2008, 93, 4075–4079. [CrossRef]

77. Karelis, A.D.; Rabasa-Lhoret, R. Inclusion of C-reactive protein in the identification of metabolically healthy but obese (MHO) individuals. *Diabetes Metab.* 2008, 34, 183–184. [CrossRef]

78. Stefan, N.; Kantartzis, K.; Machann, J.; Schick, F.; Thamer, C.; Rittig, K.; Balletshofer, B.; Machicao, F.; Fritsche, A.; Häring, H.-U. Identification and Characterization of Metabolically Benign Obesity in Humans. *Arch. Intern. Med.* 2008, 168, 1609. [CrossRef]

79. Hosseinpanah, F.; Barzin, M.; Sheikholeslami, F.; Azizi, F. Effect of Different Obesity Phenotypes on Cardiovascular Events in Tehran Lipid and Glucose Study (TLGS). *Am. J. Cardiol.* 2011, 107, 412–416. [CrossRef]

80. Khan, U.I.; Wang, D.; Thurston, R.C.; Sowers, M.; Sutton-Tyrrell, K.; Matthews, K.A.; Barinas-Mitchell, E.; Wildman, R.P. Burden of subclinical cardiovascular disease in “metabolically benign” and “at-risk” overweight and obese women: the Study of Women’s Health Across the Nation (SWAN). *Atherosclerosis* 2011, 217, 179–186. [CrossRef]

81. Park, J.; Kim, S.H.; Cho, G.-Y.; Baik, I.; Kim, N.H.; Lim, H.E.; Kim, E.J.; Park, C.G.; Lim, S.Y.; Kim, Y.H.; et al. Obesity phenotype and cardiovascular changes. *J. Hypertens.* 2011, 29, 1765–1772. [CrossRef]

82. Voulgari, C.; Tentolouris, N.; Dilaveris, P.; Tousoulis, D.; Katsilambros, N.; Stefanadis, C. Increased Heart Failure Risk in Normal-Weight People With Metabolic Syndrome Compared With Metabolically Healthy Obese Individuals. *J. Am. Coll. Cardiol.* 2011, 58, 1343–1350. [CrossRef] [PubMed]

83. Hamer, M.; Batty, G.D.; Kivimaki, M. Risk of future depression in people who are obese but metabolically healthy: the English longitudinal study of ageing. *Mol. Psychiatry* 2012, 17, 940–945. [CrossRef] [PubMed]

84. Bervoets, L.; Massa, G. Classification and clinical characterization of metabolically “healthy” obese children and adolescents. *J. Pediatr. Endocrinol. Metab.* 2016, 29, 553–560. [CrossRef]

85. Al Masri, M.; Romain, A.J.; Boegner, C.; Maimoun, L.; Mariano-Goulart, D.; Attalin, V.; Leprieur, E.; Picandet, M.; Avignon, A.; Sultan, A. Vitamin D status is not related to insulin resistance in different phenotypes of moderate obesity. *Appl. Physiol. Nutr. Metab.* 2017, 42, 438–442. [CrossRef]

86. Wildman, R.P.; Muntner, P.; Reynolds, K.; McGinn, A.P.; Rajpathak, S.; Wylie-Rosett, J.; Sowers, M.R. The Obese Without Cardiometabolic Risk Factor Clustering and the Normal Weight With Cardiometabolic Risk Factor Clustering. *Arch. Intern. Med.* 2008, 168, 1617. [CrossRef]

87. Sánchez-Ingó, L.; Navarro-González, D.; Fernández-Montero, A.; Pastrana-Delgado, J.; Martínez, J.A. Risk of incident ischemic stroke according to the metabolic health and obesity states in the Vascular-Metabolic CUN cohort. *Int. J. Stroke* 2017, 12, 187–191. [CrossRef]

88. Lassale, C.; Tzoulaki, I.; Moons, K.G.M.; Sweeting, M.; Boer, J.; Johnson, L.; Huerta, J.M.; Agnoli, C.; Freisling, H.; Weiderpass, E.; et al. Separate and combined associations of obesity and metabolic health with coronary heart disease: A pan-European case-cohort analysis. *Eur. Heart J.* 2018, 39, 397–406. [CrossRef]

89. Stefan, N.; Häring, H.-U.; Hu, F.B.; Schulze, M.B. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. *Lancet Diabetes Endocrinol.* 2013, 1, 152–162. [CrossRef]
90. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001, 285, 2486–2497.

91. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002, 106, 3143–3421.

92. Grundy, S.M.; Cleeman, J.I.; Bairey Merz, C.N.; Brewer, H.B.; Clark, L.T.; Hunninghake, D.B.; Pasternak, R.C.; Smith, S.C.; et al. Diagnosis and Management of the Metabolic Syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Diabetes Care* 2009, 32, 89–97. [CrossRef] [PubMed]

93. Grundy, S.M.; Brewer, H.B.; Cleeman, J.I.; Smith, S.C.; Lenfant, C. American Heart Association; National Heart, Lung, and Blood Institute Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation* 2004, 109, 433–438. [CrossRef] [PubMed]

94. Grundy, S.M.; Cleeman, J.I.; Daniels, S.R.; Donato, K.A.; Eckel, R.H.; Franklin, B.A.; Gordon, D.J.; Krauss, R.M.; Savage, P.J.; Smith, S.C.; et al. Harmonizing the Metabolic Syndrome: A Joint Interim Statement from the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Diabetes Federation. *Diabetes Care* 2007, 30, 105–109. [CrossRef] [PubMed]

95. Jolliffe, C.J.; Janssen, I. Development of Age-Specific Adolescent Metabolic Syndrome Criteria That Are Linked to the Adult Treatment Panel III and International Diabetes Federation Criteria. *J. Am. Coll. Cardiol.* 2007, 49, 891–898. [CrossRef] [PubMed]

96. Alberti, K.G.M.M.; Zimmet, P.; Shaw, J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet. Med.* 2006, 23, 469–480. [CrossRef] [PubMed]

97. Delavari, A.; Forouzanfar, M.H.; Alikhani, S.; Sharifian, A.; Kelishadi, R. First Nationwide Study of the Prevalence of the Metabolic Syndrome and Optimal Cutoff Points of Waist Circumference in the Middle East: The National Survey of Risk Factors for Noncommunicable Diseases of Iran. *Diabetes Care* 2009, 32, 1092–1097. [CrossRef]

98. Ford, E.S.; Giles, W.H.; Dietz, W.H. Prevalence of the metabolic syndrome among US adults: Findings from the Third National Health and Nutrition Examination Survey. *J. Am. Med. Assoc.* 2002, 287, 356–359. [CrossRef]

99. Grundy, S.M.; Cleeman, J.I.; Bairey Merz, C.N.; Brewer, H.B.; Clark, L.T.; Hunninghake, D.B.; Pasternak, R.C.; Smith, S.C.; Stone, N.J. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004, 110, 227–239. [CrossRef]

100. Grundy Erratum: Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines (Circulation (July 13, 2004) 110 (227-239)). *Circulation* 2004, 110, 763.

101. Alberti, K.G.M.M.; Zimmet, P.; Shaw, J. IDF Epidemiology Task Force Consensus Group The metabolic syndrome—A new worldwide definition. *Diabetes Care* 2007, 8, 299–306. [CrossRef] [PubMed]

102. De Lorenzo, A.; Soldati, L.; Sarlo, F.; Calvani, M.; Di Lorenzo, N.; Di Renzo, L. New obesity classification criteria as a tool for bariatric surgery indication. *World J. Gastroenterol.* 2016, 22, 681–703. [CrossRef] [PubMed]

103. Saltevo, J.T.; Sundvall, J.; Vanhala, M.; et al. Metabolically healthy and unhealthy obesity phenotypes in the general population: the FIN-D2D Survey. *BMC Public Health* 2011, 11, 754. [CrossRef]
107. Björntorp, P. Metabolic implications of body fat distribution. *Diabetes Care* 1991, 14, 1132–1143. [CrossRef]
108. Manolopoulos, K.N.; Karpe, F.; Frayn, K.N. Gluteofemoral body fat as a determinant of metabolic health. *Int. J. Obes.* 2010, 34, 949–959. [CrossRef]
109. Jensen, M.D. Role of body fat distribution and the metabolic complications of obesity. *J. Clin. Endocrinol. Metab.* 2008, 93, S57–S63. [CrossRef]
110. Makki, K.; Froguel, P.; Wolowczuk, I. Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. *ISRN Inflamm.* 2013, 1, 1–12. [CrossRef]
111. Hotamisligil, G.S.; Arner, P.; Caro, J.F.; Atkinson, R.L.; Spiegelman, B.M. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J. Clin. Invest.* 1995, 95, 2409–2415. [CrossRef]
112. Ouchi, N.; Parker, J.L.; Lugus, J.J.; Walsh, K. Adipokines in inflammation and metabolic disease. *Nat. Rev. Immunol.* 2011, 11, 85–97. [CrossRef] [PubMed]
113. Schmidt, F.M.; Weschenfelder, J.; Sander, C.; Minkwitz, J.; Thormann, J.; Chittka, T.; Mergl, R.; Kirkby, K.C.; Faßhauer, M.; Stumvoll, M.; et al. Inflammatory cytokines in general and central obesity and modulating effects of physical activity. *PLoS ONE* 2015, 10, e0121971. [CrossRef]
114. Sun, S.; Ji, Y.; Kersten, S.; Qi, L. Mechanisms of inflammatory responses in obese adipose tissue. *Annu. Rev. Nutr.* 2012, 32, 261–286. [CrossRef] [PubMed]
115. Medzhitov, R. Origin and physiological roles of inflammation. *Nature* 2008, 454, 428–435. [CrossRef] [PubMed]
116. Wellen, K.E.; Hotamisligil, G.S. Inflammation, stress, and diabetes. *J. Clin. Invest.* 2005, 115, 1111–1119. [CrossRef] [PubMed]
117. Kershaw, E.E.; Flier, J.S. Adipose Tissue as an Endocrine Organ. *J. Clin. Endocrinol. Metab.* 2004, 89, 2548–2556. [CrossRef]
118. Prins, J.B. Adipose tissue as an endocrine organ. *Best Pract. Res. Clin. Endocrinol. Metab.* 2002, 16, 639–651. [CrossRef]
119. Kim, J.I.; Huh, J.Y.; Sohn, J.H.; Choe, S.S.; Lee, Y.S.; Lim, C.Y.; Jo, A.; Park, S.B.; Han, W.; Kim, J.B. Lipid-overloaded enlarged adipocytes provoke insulin resistance independent of inflammation. *Mol. Cell. Biol.* 2015, 35, 1686–1699. [CrossRef]
120. Xu, H.; Barnes, G.T.; Yang, Q.; Tan, G.; Yang, D.; Chou, C.J.; Sole, J.; Nichols, A.; Ross, J.S.; Tartaglia, L.A.; et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J. Clin. Invest.* 2003, 112, 1821–1830. [CrossRef]
121. Weisberg, S.P.; McCann, D.; Desai, M.; Rosenbaum, M.; Leibel, R.L.; Ferrante, A.W., Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J. Clin. Invest.* 2003, 112, 1796–1808. [CrossRef]
122. Rudich, A.; Kanety, H.; Bashan, N. Adipose stress-sensing kinases: linking obesity to malfunction. *Trends Endocrinol. Metab.* 2007, 18, 291–299. [CrossRef]
123. Qatanani, M.; Lazar, M.A. Mechanisms of obesity-associated insulin resistance: many choices on the menu. *Genes Dev.* 2007, 21, 1443–1455. [CrossRef]
124. Mulder, P.; Morrison, M.C.; Verschuren, L.; Liang, W.; van Bockel, J.H.; Kooistra, T.; Wielinga, P.Y.; Kleemann, R. Reduction of obesity-associated white adipose tissue inflammation by rosiglitazone is associated with reduced non-alcoholic fatty liver disease in LDLr-deficient mice. *Sci. Rep.* 2016, 6, 31542. [CrossRef] [PubMed]
125. Badoud, F.; Perreault, M.; Zulyniak, M.A.; Mutch, D.M. Molecular insights into the role of white adipose tissue in metabolically unhealthy normal weight and metabolically healthy obese individuals. *FASEB J.* 2015, 29, 748–758. [CrossRef] [PubMed]
126. Srdić, B.; Stokić, E.; Korać, A.; Ukropina, M.; Veličković, K.; Breberina, M. Morphological Characteristics of Abdominal Adipose Tissue in Normal-Weight and Obese Women of Different Metabolic Profiles. *Exp. Clin. Endocrinol. Diabetes* 2010, 118, 713–718.
127. O’Connell, J.; Lynch, L.; Cawood, T.J.; Kwasnik, A.; Nolan, N.; Geoghegan, J.; McCormick, A.; O’Farrelly, C.; O’Shea, D. The Relationship of Omental and Subcutaneous Adipocyte Size to Metabolic Disease in Severe Obesity. *PLoS ONE* 2010, 5, e9997. [CrossRef]
128. O’Connell, J.; Lynch, L.; Hogan, A.; Cawood, T.J.; O’Shea, D. Preadipocyte Factor-1 Is Associated with Metabolic Profile in Severe Obesity. *J. Clin. Endocrinol. Metab.* 2011, 96, E680–E684. [CrossRef] [PubMed]
129. Unger, R.H. Lipid overload and overflow: metabolic trauma and the metabolic syndrome. *Trends Endocrinol. Metab.* 2003, 14, 398–403. [CrossRef] [PubMed]
130. Sniderman, A.D.; Bhopal, R.; Prabhakaran, D.; Sarrafzadegan, N.; Tchernof, A. Why might South Asians be so susceptible to central obesity and its atherogenic consequences? The adipose tissue overflow hypothesis. *Int. J. Epidemiol.* 2007, 36, 220–225. [CrossRef] [PubMed]

131. Neeland, I.J.; Poirier, P.; Després, J.-P. Cardiovascular and Metabolic Heterogeneity of Obesity. *Circulation* 2018, 137, 1391–1406. [CrossRef]

132. Lumeng, C.N.; Bodzin, J.L.; Saltiel, A.R. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J. Clin. Invest.* 2007, 117, 175–184. [CrossRef] [PubMed]

133. Neeland, I.J.; Poirier, P.; Després, J.-P. Metabolic phenotypes in a working population: results from the Icaria study. *BMC Public Health* 2011, 11, 207–215. [CrossRef] [PubMed]

134. Okura, T.; Nakata, Y.M.; Masuda, I.; Higashiyama, A.; Takegami, M.; Nishimura, K.; Watanabe, M.; Ohkubo, T.; Okamura, T.; Miyamoto, Y. Risk for metabolic diseases in normal weight individuals with visceral fat accumulation: a cross-sectional study in Japan. *BMJ Open* 2017, 7, e013831. [CrossRef] [PubMed]

135. Goday, A.; Calvo, E.; Vázquez, L.A.; Caveda, E.; Margallo, T.; Catalina-Romero, C.; Reviriego, J. Prevalence and clinical characteristics of metabolically healthy obese individuals and other obese/non-obese metabolic phenotypes in a working population: results from the Icaria study. *BMC Public Health* 2016, 16, 248. [CrossRef]

136. Bastien, M.; Poirier, P.; Lemieux, I.; Després, J.-P. Overview of Epidemiology and Contribution of Obesity to Cardiovascular Disease. *Prog. Cardiomed. Dis.* 2014, 56, 369–381. [CrossRef]

137. Goossens, G.H. The Metabolic Phenotype in Obesity: Fat Mass, Body Fat Distribution, and Adipose Tissue Function. *Obes. Facts* 2017, 10, 207–215. [CrossRef]

138. Vague, J. Sexual differentiation. A determinant factor of the forms of obesity. 1947. *Obes. Res.* 1996, 4, 201–203. [CrossRef]

139. Vague, J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculus disease. *Am. J. Clin. Nutr.* 1956, 4, 20–34. [CrossRef]

140. Kyrou, I.; Randeva, H.S.; Weickert, M.O. Clinical Problems Caused by Obesity. *BMJ Open* 2011, 6, e27694. [CrossRef] [PubMed]

141. Fu, X.; Song, A.; Zhou, Y.; Ma, X.; Jiao, J.; Yang, M.; Zhu, S. Association of regional body fat with metabolic risks in Chinese women. *Public Health Nutr.* 2014, 17, 2316–2324. [CrossRef] [PubMed]

142. Messier, V.; Karelis, A.D.; Robillard, M.-È.; Bellefeuille, P.; Brochu, M.; Lavoie, J.-M.; Rabasa-Lhoret, R. Metabolically healthy but obese individuals: relationship with hepatic enzymes. *Metabolism* 2010, 59, 20–24. [CrossRef]

143. Ohkubo, T.; Okamura, T.; Miyamoto, Y. Risk for metabolic diseases in normal weight individuals with visceral fat accumulation: a cross-sectional study in Japan. *BMJ Open* 2017, 7, e013831. [CrossRef] [PubMed]

144. Samsell, L.; Regier, M.; Walton, C.; Cottrell, L. Importance of android/gynoid fat ratio in predicting metabolic and cardiovascular disease risk in normal weight as well as overweight and obese children. *J. Obes.* 2014, 2014, 846578. [CrossRef]

145. Brochu, M.; Tchernof, A.; Dionne, I.J.; Sites, C.K.; Eltabbakh, G.H.; Sims, E.A.H.; Poehlman, E.T. What Are the Physical Characteristics Associated with a Normal Metabolic Profile Despite a High Level of Obesity in Postmenopausal Women? *J. Clin. Endocrinol. Metab.* 2001, 86, 1020–1025.

146. Fox, C.S.; Massaro, J.M.; Hoffmann, U.; Pou, K.M.; Maurovich-Horvat, P.; Liu, C.-Y.; Vasan, R.S.; Murabito, J.M.; Meigs, J.B.; Cupples, L.A.; et al. Abdominal Visceral and Subcutaneous Adipose Tissue Compartments: Association With Metabolic Risk Factors in the Framingham Heart Study. *Circulation* 2007, 116, 39–48. [CrossRef]

147. Basat, Ö.; Ucak, S.; Ozkurt, H.; Basak, M.; Seber, S.; Altuntas, Y. Visceral Adipose Tissue as an Indicator of Insulin Resistance in Nonobese Patients with New Onset Type 2 Diabetes Mellitus. *Exp. Clin. Endocrinol. Diabetes* 2006, 114, 58–62. [CrossRef]
150. Sam, S.; Haffner, S.; Davidson, M.H.; D’Agostino, R.B.; Feinstein, S.; Kondos, G.; Perez, A.; Mazzone, T.; Mazzone, T. Relationship of abdominal visceral and subcutaneous adipose tissue with lipoprotein particle number and size in type 2 diabetes. Diabetes 2008, 57, 2022–2027. [CrossRef]

151. Montague, C.T.; O’Rahilly, S. The perils of portliness: causes and consequences of visceral adiposity. Diabetes 2000, 49, 883–888. [CrossRef]

152. Snijder, M.B.; Visser, M.; Dekker, J.M.; Goodpaster, B.H.; Harris, T.B.; Kritchevsky, S.B.; De Rekeneire, N.; Kanaya, A.M.; Newman, A.B.; Tylavsky, F.A.; et al. Low subcutaneous thigh fat is a risk factor for unfavourable glucose and lipid levels, independently of high abdominal fat. The Health ABC Study. Diabetologia 2005, 48, 301–308. [CrossRef]

153. Pinnick, K.E.; Nicholson, G.; Manolopoulos, K.N.; McQuaid, S.E.; Valet, P.; Frayn, K.N.; Denton, N.; Min, J.L.; Zondervan, K.T.; Fleckner, J.; et al. Distinct Developmental Profile of Lower-Body Adipose Tissue Defines Resistance Against Obesity-Associated Metabolic Complications. Diabetes 2014, 63, 3785–3797. [CrossRef] [PubMed]

154. Kang, Y.M.; Jung, C.H.; Cho, Y.K.; Jang, J.E.; Hwang, J.Y.; Kim, E.H.; Lee, W.J.; Park, J.-Y.; Kim, H.-K. Visceral adiposity index predicts the conversion of metabolically healthy obesity to an unhealthy phenotype. PLoS ONE 2017, 12, e0179635. [CrossRef]

155. Moully, T.A.; Toms, L.-M.L. Breast cancer and persistent organic pollutants (excluding DDT): a systematic literature review. Environ. Sci. Pollut. Res. 2016, 23, 22385–22407. [CrossRef] [PubMed]

156. Gauthier, M.-S.; Rabasa-Lhoret, R.; Prud’homme, D.; Karelis, A.D.; Geng, D.; van Bavel, B.; Ruzzin, J. The Metabolically Healthy But Obese Phenotype Is Associated With Lower Plasma Levels of Persistent Organic Pollutants as Compared to the Metabolically Abnormal Obese Phenotype. J. Clin. Endocrinol. Metab. 2014, 99, E1061–E1066. [CrossRef] [PubMed]

157. Pestana, D.; Faria, G.; Sá, C.; Fernandes, V.C.; Teixeira, D.; Norberto, S.; Faria, A.; Meireles, M.; Marques, C.; Correia-Sá, L.; et al. Persistent organic pollutant levels in human visceral and subcutaneous adipose tissue in obese individuals—Depot differences and dysmetabolism implications. Environ. Res. 2014, 133, 170–177. [CrossRef] [PubMed]

158. Teixeira, D.; Pestana, D.; Calhau, C.; Monteiro, R. Letter to the Editor: Adipose tissue persistent organic pollutants as possible markers of dysmetabolic obesity. J. Clin. Endocrinol. Metab. 2014. Available online: http://press.endocrine.org/e-letters/10.1210/jc.20 (accessed on 22 December 2019).

159. Teixeira, D.; Pestana, D.; Santos, C.; Correia-Sá, L.; Marques, C.; Norberto, S.; Meireles, M.; Faria, A.; Silva, R.; Faria, G.; et al. Inflammatory and cardiometabolic risk on obesity: role of environmental xenoestrogens. J. Clin. Endocrinol. Metab. 2015, 100, 1792–1801. [CrossRef]

160. Teixeira, D.; Marques, C.; Pestana, D.; Faria, A.; Norberto, S.; Calhau, C.; Monteiro, R. Effects of xenoestrogens in human M1 and M2 macrophage migration, cytokine release, and estrogen-related signaling pathways. Environ. Toxicol. 2016, 31, 1496–1509. [CrossRef]

161. Pestana, D.; Teixeira, D.; Meireles, M.; Marques, C.; Norberto, S.; Sá, C.; Fernandes, V.C.; Correia-Sá, L.; Faria, A.; Guardaño, L.; et al. Adipose tissue dysfunction as a central mechanism leading to dysmetabolic obesity triggered by chronic exposure to p,p′-DDE. Sci. Rep. 2017, 7, 2738. [CrossRef]

162. Smink, A.; Ribas-Fito, N.; Garcia, R.; Torrent, M.; Mendez, M.A.; Grimalt, J.O.; Sunyer, J. Exposure to hexachlorobenzene during pregnancy increases the risk of overweight in children aged 6 years. Acta Paediatr. 2008, 97, 1465–1469. [CrossRef]

163. Lee, D.-H.; Steffes, M.W.; Sjödin, A.; Jones, R.S.; Needham, L.L.; Jacobs, D.R. Low Dose Organochlorine Pesticides and Polychlorinated Biphenyls Predict Obesity, Dyslipidemia, and Insulin Resistance among People Free of Diabetes. PLoS ONE 2011, 6, e15977. [CrossRef] [PubMed]

164. Cano-Sancho, G.; Salmon, A.G.; La Merrill, M.A. Association between Exposure to p,p′-DDT and Its Metabolite p,p′-DDE with Obesity: Integrated Systematic Review and Meta-Analysis. Environ. Health Perspect. 2017, 125, 096002. [CrossRef] [PubMed]

165. Daniels, S.I.; Chambers, J.C.; Sanchez, S.S.; La Merrill, M.A.; Hubbard, A.E.; Macherone, A.; McMullin, M.; Zhang, L.; Elliott, P.; Smith, M.T.; et al. Elevated Levels of Organochlorine Pesticides in South Asian Immigrants Are Associated With an Increased Risk of Diabetes. J. Endocr. Soc. 2018, 2, 832–841. [CrossRef] [PubMed]

166. Warner, G.R.; Flaws, J.A. Bisphenol A and Phthalates: How Environmental Chemicals Are Reshaping Toxicology. Toxicol. Sci. 2018, 166, 246–249. [CrossRef] [PubMed]
167. Johns, L.E.; Cooper, G.S.; Galizia, A.; Meeker, J.D. Exposure assessment issues in epidemiology studies of phthalates. *Environ. Int.* **2015**, *35*, 27–39. [CrossRef] [PubMed]

168. Hauser, R.; Calafat, A.M. Phthalates and human health. *Occup. Environ. Med.* **2005**, *62*, 806–818. [CrossRef]

169. Gore, A.C.; Chappell, V.A.; Fenton, S.E.; Flaws, J.A.; Nadal, A.; Prins, G.S.; Tappari, J.; Zoeller, R.T. EDC-2: The Endocrine Society’s Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocr. Rev.* **2015**, *36*, 1–150. [CrossRef]

170. Stojanoska, M.M.; Milosevic, N.; Milic, N.; Abenavoli, L. The influence of phthalates and bisphenol A on the obesity development and glucose metabolism disorders. *Endocrine* **2017**, *55*, 666–681. [CrossRef]

171. Mansouri, V.; Ebrahimpour, K.; Poursafa, P.; Riahi, R.; Shoshtari-Yeganeh, B.; Hystad, P.; K elishadi, R. Exposure to phthalates and bisphenol A is associated with higher risk of cardiometabolic impairment in normal weight children. *Environ. Sci. Pollut. Res.* **2019**, *26*, 18604–18614. [CrossRef]

172. Sargis, R.M.; Simmons, R.A. Environmental neglect: endocrine disruptors as underappreciated but potentially modifiable diabetes risk factors. *Diabetologia* **2019**, *62*, 1811–1822. [CrossRef]

173. Melzer, D.; Rice, N.E.; Lewis, C.; Henley, W.E.; Galloway, T.S. Association of urinary bisphenol A concentration with heart disease: Evidence from NHANES 2003/06. *PLoS ONE* **2010**, *5*, e8673. [CrossRef] [PubMed]

174. Carwile, J.L.; Michels, K.B. Urinary bisphenol A and obesity: NHANES 2003-2006. *Environ. Res.* **2011**, *111*, 825–830. [CrossRef] [PubMed]

175. James-Todd, T.; Stahlhut, R.; Meeker, J.D.; Powell, S.G.; Hauser, R.; Huang, T.; Rich-Edwards, J. Urinary phthalate metabolite concentrations and diabetes among women in the national health and nutrition examination survey (NHANES) 2001-2008. *Environ. Health Perspect.* **2012**, *120*, 1307–1313. [CrossRef] [PubMed]

176. Hong, S.H.; Sung, Y.A.; Hong, Y.S.; Ha, E.; Jeong, K.; Chung, H.; Lee, H. Urinary bisphenol A is associated with insulin resistance and obesity in reproductive-aged women. *Clin. Endocrinol. (Oxf.)* **2017**, *86*, 506–512. [CrossRef] [PubMed]

177. Piecha, R.; Svačina, Š.; Malý, M.; Vrbik, K.; Lacinová, Z.; Haluzík, M.; Pavloušková, J.; Vavrouš, A.; Matějková, D.; Müllerová, D.; et al. Urine levels of phthalate metabolites and bisphenol a in relation to main metabolic syndrome components: Dyslipidemia, hypertension and type 2 diabetes a pilot study. *Cent. Eur. J. Public Health* **2016**, *24*, 297–301. [CrossRef] [PubMed]

178. Shim, Y.H.; Ock, J.W.; Kim, Y.J.; Kim, Y.; Kim, S.Y.; Kang, D. Association between Heavy Metals, Bisphenol A, volatile organic compounds and phthalates and metabolic syndrome. *Int. J. Environ. Res. Public Health* **2019**, *16*, 671. [CrossRef] [PubMed]

179. Milošević, N.; Milanović, M.; Sudji, J.; Bosić Živanović, D.; Stojanoski, S.; Vuković, B.; Milić, N.; Medić Stojanoska, M. Could phthalates exposure contribute to the development of metabolic syndrome and liver disease in humans? *Environ. Sci. Pollut. Res. Res.* **2019**, *27*, 1–13. [CrossRef]

180. Martínez-Ibarra, A.; Martín-Razo, L.D.; Vázquez-Martínez, E.R.; Martínez-Cruz, N.; Flores-Ramírez, R.; García-Gómez, E.; López-López, M.; Ortega-González, C.; Camacho-Arroyo, I.; Cerbón, M. Unhealthy levels of phthalates and bisphenol a in mexican pregnant women with gestational diabetes and its association to altered expression of miRNAs involved with metabolic disease. *Int. J. Mol. Sci.* **2019**, *20*, 3343. [CrossRef]

181. Fosti, D.; Schiumerini, R.; Eusebi, L.H.; Marasco, G.; Taddia, M.; Colecchia, A. Gut microbiota and metabolic syndrome. *World J. Gastroenterol.* **2014**, *20*, 16079–16094. [CrossRef]

182. Brown, J.M.; Hazen, S.L. The gut microbial endocrine organ: bacterially derived signals driving cardiometabolic diseases. *Annu. Rev. Med.* **2015**, *66*, 343–359. [CrossRef]

183. Ley, R.E.; Turnbaugh, P.J.; Klein, S.; Gordon, J.I. Microbial ecology: Human gut microbes associated with obesity. *Nature* **2006**, *444*, 1022–1023. [CrossRef] [PubMed]

184. Santacruz, A.; Collado, M.C.; García-Valdés, L.; Segura, M.T.; Martín-Lagos, J.A.; Anjos, T.; Martí-Martínez, R.; Lopez, R.M.; Florido, J.; Campoy, C.; et al. Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. *Br. J. Nutr.* **2010**, *104*, 83–92. [CrossRef]

185. Turnbaugh, P.J.; Ley, R.E.; Mahowald, M.A.; Magrini, V.; Mardis, E.R.; Gordon, J.I. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* **2006**, *444*, 1027–1131. [CrossRef] [PubMed]

186. Ley, R.E.; Bäckhed, F.; Turnbaugh, P.; Lozupone, C.A.; Knight, R.D.; Gordon, J.I. Obesity alters gut microbial ecology. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11070–11075. [CrossRef]

187. Turnbaugh, P.J.; Ley, R.E.; Mahowald, M.A.; Magrini, V.; Mardis, E.R.; Gordon, J.I. Obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* **2006**, *444*, 1027–1131. [CrossRef] [PubMed]

188. Ley, R.E.; Bäckhed, F.; Turnbaugh, P.; Lozupone, C.A.; Knight, R.D.; Gordon, J.I. Obesity alters gut microbial ecology. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11070–11075. [CrossRef] [PubMed]
187. Million, M.; Maraninchi, M.; Henry, M.; Armougom, F.; Richet, H.; Carrié, P.; Valero, R.; Raccah, D.; Vialles, B.; Raoult, D. Obesity-associated gut microbiota is enriched in Lactobacillus reuteri and depleted in Bifidobacterium animalis and Methanobrevibacter smithii. *Int. J. Obes.* 2012, 36, 817–825. [CrossRef]

188. Jumpertz, R.; Le, D.S.; Turnbaugh, P.J.; Trinidad, C.; Bogardus, C.; Gordon, J.I.; Krakoff, J. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *Am. J. Clin. Nutr.* 2011, 94, 58–65. [CrossRef]

189. Karlsson, C.L.J.; Önnerfält, J.; Xu, J.; Molin, G.; Ahném, S.; Thorngren-Jerneck, K. The Microbiota of the Gut in Preschool Children With Normal and Excessive Body Weight. *Obesity* 2012, 20, 2257–2261. [CrossRef]

190. Hu, H.-J.; Park, S.-G.; Jang, H.B.; Choi, M.-G.; Park, K.-H.; Kang, J.H.; Park, S.I.; Lee, H.-J.; Cho, S.-H. Obesity Alters the Microbial Community Profile in Korean Adolescents. *PLoS ONE* 2015, 10, e0134333. [CrossRef]

191. Zhang, H.; DiBaise, J.K.; Zuccolo, A.; Kudrma, D.; Braido, M.; Yu, Y.; Parmeswaran, P.; Crowell, M.D.; Wing, R.; Rittmann, B.E.; et al. Human gut microbiota in obesity and after gastric bypass. *Proc. Natl. Acad. Sci. USA* 2009, 106, 2365–2370. [CrossRef]

192. Duncan, S.H.; Lobley, G.E.; Holtrop, G.; Ince, J.; Johnstone, A.M.; Louis, P.; Flint, H.J. Human colonic microbiota associated with diet, obesity and weight loss. *Int. J. Obes.* 2008, 32, 1720–1724. [CrossRef]

193. Ramakrishna, B.S. Role of the gut microbiota in human nutrition and metabolism. *J. Gastroenterol. Hepatol.* 2013, 28, 9–17. [CrossRef] [PubMed]

194. Khan, M.J.; Gerasimidis, K.; Edwards, C.A.; Shaikh, M.G. Role of Gut Microbiota in the Aetiology of Obesity: Proposed Mechanisms and Review of the Literature. *J. Obes.* 2016, 2016, 7353642. [CrossRef] [PubMed]

195. Kim, K.-A.; Gu, W.; Lee, I.-A.; Joh, E.-H.; Kim, D.-H. High Fat Diet-Induced Gut Microbiota Exacerbates Inflammation and Obesity in Mice via the TLR4 Signaling Pathway. *PLoS ONE* 2012, 7, e47713. [CrossRef] [PubMed]

196. Boutagy, N.E.; McMillan, R.P.; Friesal, M.; Hulver, M.W. Metabolic endotoxemia with obesity: Is it real and is it relevant? *Biochimie* 2016, 124, 11–20. [CrossRef]

197. Erridge, C.; Attina, T.; Spickett, C.M.; Webb, D.J. A high-fat meal induces low-grade endotoxemia: evidence of a novel mechanism of postprandial inflammation. *Am. J. Clin. Nutr.* 2007, 86, 1286–1292. [CrossRef]

198. Cani, P.D.; Amar, J.; Iglesias, M.A.; Poggi, M.; Knauf, C.; Bastelica, D.; Neyrinck, A.M.; Fava, F.; Tuohy, K.M.; Chabo, C.; et al. Metabolic Endotoxemia Initiates Obesity and Insulin Resistance. *Diabetes* 2007, 56, 1761–1772. [CrossRef]

199. Creely, S.J.; McTernan, P.G.; Kusminski, C.M.; Fisherff, M.; Da Silva, N.F.; Khanolkar, M.; Evans, M.; Harte, A.L.; Kumar, S. Lipopolysaccharide activates an innate immune system response in human adipose tissue and type 2 diabetes. *AJP Endocrinol. Metab.* 2006, 292, E740–E747. [CrossRef]

200. Hussin, P.J.; Havulinna, A.S.; Lehto, M.; Sundqvall, J.; Salomaa, V. Endotoxemia Is Associated With an Increased Risk of Incident Diabetes. *Diabetes Care* 2011, 34, 392–397. [CrossRef]

201. Liu, X.; Lu, L.; Yao, P.; Ma, Y.; Wang, F.; Jin, Q.; Ye, X.; Li, H.; Hu, F.B.; Sun, L.; et al. Lipopolysaccharide binding protein, obesity status and incidence of metabolic syndrome: a prospective study among middle-aged and older Chinese. *Diabetologia* 2013, 57, 1834–1841. [CrossRef]

202. Collado, M.C.; Derrien, M.; Isolauri, E.; de Vos, W.M.; Salminen, S. Intestinal Integrity and Akkermansia muciniphila, a Mucin-Degrading Member of the Intestinal Microbiota Present in Infants, Adults, and the Elderly. *Appl. Environ. Microbiol.* 2007, 73, 7767–7770. [CrossRef]

203. Cani, P.D.; de Vos, W.M. Next-Generation Beneficial Microbes: The Case of Akkermansia muciniphila. *Front. Microbiol.* 2017, 8, 1765. [CrossRef] [PubMed]

204. Chelakkot, C.; Choi, Y; Kim, D.-K.; Park, H.T.; Ghim, J.; Kwon, Y.; Jeon, J.; Kim, M.-S.; Jee, Y.-K.; Gho, Y.S.; et al. Akkermansia muciniphila-derived extracellular vesicles influence gut permeability through the regulation of tight junctions. *Exp. Mol. Med.* 2018, 50, e450. [CrossRef] [PubMed]

205. Everard, A.; Belzer, C.; Geurts, L.; Ouwerkerk, J.P.; Druart, C.; Bindels, L.B.; Giotu, Y.; Derrien, M.; Muccioli, G.G.; Delzenne, N.M.; et al. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc. Natl. Acad. Sci. USA* 2013, 110, 9066–9071. [CrossRef] [PubMed]

206. Derrien, M.; Van Baarlen, P.; Hooi, V.; Norin, E.; Müller, M.; de Vos, W.M. Modulation of Mucosal Immune Response, Tolerance, and Proliferation in Mice Colonized by the Mucin-Degrador Akkermansia muciniphila. *Front. Microbiol.* 2011, 2, 166. [CrossRef]
207. Depommier, C.; Everard, A.; Druart, C.; Plovier, H.; Van Hul, M.; Vieira-Silva, S.; Falony, G.; Raes, J.; Maiter, D.; Delzenne, N.M.; et al. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. *Nat. Med.* 2019, 25, 1096–1103. [CrossRef]

208. Yan, M.; Song, M.-M.; Bai, R.-X.; Cheng, S.; Yan, W.-M. Effect of Roux-en-Y gastric bypass surgery on intestinal *Akkermansia muciniphila*. *World J. Gastrointest. Surg.* 2016, 8, 301. [CrossRef]

209. de la Cuesta-Zuluaga, J.; Mueller, N.T.; Corrales-Aguadelo, V.; Velásquez-Mejía, E.P.; Carmona, J.A.; Abad, J.M.; Escobar, J.S. Metformin is Associated With Higher Relative Abundance of Mucin-Degrading *Akkermansia muciniphila* and Several Short-Chain Fatty Acid–Producing Microbiota in the Gut. *Diabetes Care* 2017, 40, 54–62. [CrossRef]

210. Côte, M.; Matias, I.; Lemieux, I.; Petrosino, S.; Alméras, N.; Després, J.-P.; Di Marzo, V. Circulating endocannabinoid levels, abdominal adiposity and related cardiometabolic risk factors in obese men. *Int. J. Obes.* 2007, 31, 692–699. [CrossRef]

211. Bluher, M.; Engeli, S.; Knölling, N.; Berndt, J.; Fasshauer, M.; Batkai, S.; Pacher, P.; Schon, M.R.; Jordan, J.; Stumvoll, M. Dysregulation of the Peripheral and Adipose Tissue Endocannabinoid System in Human Abdominal Obesity. *Diabetes* 2006, 55, 3053–3060. [CrossRef]

212. Engeli, S.; Böhnke, J.; Feldpausch, M.; Gorzelniak, K.; Janke, J.; Batkai, S.; Pacher, P.; Harvey-White, J.; Luft, F.C.; Sharma, A.M.; et al. Activation of the peripheral endocannabinoid system in human obesity. *Diabetes* 2005, 54, 2838–2843. [CrossRef]

213. Liu, J.; Batkai, S.; Pacher, P.; Harvey-White, J.; Wagner, J.A.; Cravatt, B.F.; Gao, B.; Kunos, G. Lipopolysaccharide Induces Anandamide Synthesis in Macrophages via CD14/MAPK/Phosphoinositide 3-Kinase/NF-kB Independently of Platelet-activating Factor. *J. Biol. Chem.* 2003, 278, 45034–45039. [CrossRef] [PubMed]

214. Nam, D.H.; Lee, M.H.; Kim, J.E.; Song, H.K.; Kang, Y.S.; Lee, J.E.; Kim, H.W.; Cha, J.J.; Hyun, Y.Y.; Kim, S.H.; et al. Blockade of Cannabinoid Receptor 1 Improves Insulin Resistance, Lipid Metabolism, and Diabetic Nephropathy in db/db Mice. *Endocrinology* 2012, 153, 1387–1396. [CrossRef] [PubMed]

215. Lu, D.; Dopart, R.; Kendall, D.A. Controlled downregulation of the cannabinoid CB1 receptor provides a promising approach for the treatment of obesity and obesity-derived type 2 diabetes. *Cell Stress Chaperones* 2016, 21, 1–7. [CrossRef] [PubMed]

216. Mehrpoury-Bahrami, P.; Chitra, K.N.; Ganewatta, M.S.; Tang, C.; Murphy, E.A.; Enos, R.T.; Velazquez, K.T.; McCellan, J.; Nagarkatti, M.; Nagarkatti, P. Blockade of CB1 cannabinoid receptor alters gut microbiota and attenuates inflammation and diet-induced obesity. *Sci. Rep.* 2017, 7, 15645. [CrossRef]

217. Muccioli, G.G.; Naslain, D.; Bäckhed, F.; Reigstad, C.S.; Lambert, D.M.; Delzenne, N.M.; Cani, P.D. The endocannabinoid system links gut microbiota to adipogenesis. *Mol. Syst. Biol.* 2010, 6, 392. [CrossRef]

218. Rial, S.A.; Karelis, A.D.; Bergeron, K.F.; Druart, C.; Plovier, H.; Van Hul, M.; Vieira-Silva, S.; Falony, G.; Raes, J.; Maiter, D.; Delzenne, N.M.; et al. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. *Nat. Med.* 2019, 25, 1096–1103. [CrossRef]

219. Vandanmagsar, B.; Youm, Y.-H.; Ravussin, A.; Galgani, J.E.; Stadler, K.; Mynatt, R.L.; Ravussin, E.; Lu, D.; Dopart, R.; Kendall, D.A. Controlled downregulation of the cannabinoid CB1 receptor provides a promising approach for the treatment of obesity and obesity-derived type 2 diabetes. *Cell Stress Chaperones* 2016, 21, 1–7. [CrossRef] [PubMed]

220. Esser, N.; L’homme, L.; De Roover, A.; Kohen, L.; Scheen, A.J.; Moutschen, M.; Piette, J.; Legrand-Poels, S.; Paquot, N. Obesity phenotype is related to NLRP3 inflammasome activity and immunological profile of visceral adipose tissue. *Diabetologia* 2013, 56, 2487–2497. [CrossRef]

221. Murphy, A.J.; Kraakman, M.J.; Kammoun, H.L.; Dragoljevic, D.; Lee, M.K.S.; Lawlor, K.E.; Wentworth, J.M.; Vasanthakumar, A.; Gerlic, M.; Whitehead, L.W.; et al. IL-18 Production from the NLRP1 Inflammasome Prevents Obesity and Metabolic Syndrome. *Cell Metab.* 2016, 23, 155–164. [CrossRef]

222. Depommier, C.; Everard, A.; Druart, C.; Plovier, H.; Van Hul, M.; Vieira-Silva, S.; Falony, G.; Raes, J.; Maiter, D.; Delzenne, N.M.; et al. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. *Nat. Med.* 2019, 25, 1096–1103. [CrossRef]

223. Dehghan, M.; Mente, A.; Zhang, X.; Swaminnathan, S.; Li, W.; Mohan, V.; Iqbal, R.; Kumar, R.; Wentzel-Viljoen, E.; Rosengren, A.; et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet* 2017, 389, 2050–2062. [CrossRef]

224. Timóteo, A.T. Diet in patients with metabolic syndrome: What is the ideal macronutrient composition? *Rev. Port. Cardiol.* 2018, 37, 1001–1006. [CrossRef] [PubMed]

225. Martinez-Gonzalez, M.A.; Martín-Calvo, N. Mediterranean diet and life expectancy; Beyond olive oil, fruits, and vegetables. *Curr. Opin. Clin. Nutr. Metab. Care* 2016, 19, 401–407. [CrossRef]
226. Karamanos, B.; Thanopoulou, A.; Angelico, F.; Assaad-Khalil, S.; Barbato, A.; Del Ben, M.; Dimitrijevic-Sreckovic, V.; Djordjevic, P.; Gallotti, C.; Katsilambros, N.; et al. Nutritional habits in the Mediterranean Basin. The macronutrient composition of diet and its relation with the traditional Mediterranean diet. Multi-centre study of the Mediterranean Group for the study of diabetes (MGSD). Eur. J. Clin. Nutr. 2002, 56, 983–991. [CrossRef]

227. Di Daniele, N.D.; Noce, A.; Vidiri, M.F.; Moriconi, E.; Marrone, G.; Annicchiarico-Petruzzelli, M.; D’Urso, G.; Tesauro, M.; Rovella, V.; De Lorenzo, A.D. Impact of Mediterranean diet on metabolic syndrome, cancer and longevity. Oncotarget 2017, 8, 8947–8979. [CrossRef]

228. Billingsley, H.E.; Carbone, S. The antioxidant potential of the Mediterranean diet in patients at high cardiovascular risk: An in-depth review of the PREDIMED. Nutr. Diabetes 2018, 8, 1–8. [CrossRef]

229. Park, Y.-M.; Steck, S.E.; Fung, T.T.; Zhang, J.; Hazlett, L.J.; Han, K.; Merchant, A.T. Mediterranean diet and mortality risk in metabolically healthy obese and metabolically unhealthy obese phenotypes. Int. J. Obes. 2016, 40, 1541–1549. [CrossRef]

230. Arenaza, L.; Huybrechts, I.; Ortega, F.B.; Ruiz, J.R.; De Henauw, S.; Manios, Y.; Marcos, A.; Julián, C.; Widhalm, K.; Bueno, G.; et al. Adherence to the Mediterranean diet in metabolically healthy and unhealthy overweight and obese European adolescents: the HELENA study. Eur. J. Nutr. 2019, 58, 2615–2623. [CrossRef]

231. Bell, J.A.; Kivimaki, M.; Hamer, M. Metabolically healthy obesity and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies. Obes. Rev. 2014, 15, 504–515. [CrossRef]