



Is metabolically healthy obesity shaped by inflammation, gender differences, and fat distribution?

Davide Ramoni, Luca Liberale, Federico Carbone, Fabrizio Montecucco

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Davide Ramoni, Luca Liberale, Federico Carbone, Fabrizio Montecucco, Department of Internal Medicine, University of Genoa, Genoa 16132, Italy

Luca Liberale, Federico Carbone, Fabrizio Montecucco, First Clinic of Internal Medicine, Department of Internal Medicine, Italian Cardiovascular Network, IRCCS Ospedale Policlinico San Martino, Genoa 16132, Italy

Corresponding author: Fabrizio Montecucco, MD, PhD, Professor, Department of Internal Medicine, University of Genoa, Viale Benedetto XV 6, Genoa 16132, Italy.

fabrizio.montecucco@unige.it

Abstract

The obesity epidemic continues to challenge global cardiovascular (CV) health, but not all obesity is equal. Emerging evidence underscores that distinct obesity phenotypes – particularly metabolically healthy *vs* unhealthy profiles – confer differential CV risks. Recent large-scale studies have revealed that even metabolically healthy obesity (MHO) is associated with an increased risk of adverse CV events, particularly in the context of socioeconomic disadvantage. Central is the role of chronic low-grade inflammation, termed “metaflammation”, which can persist even in the absence of overt metabolic syndrome and is shaped by both gender and fat distribution. Epicardial and visceral adiposity contribute to this pro-inflammatory state and are strongly associated with conditions such as heart failure and atrial fibrillation. Notably, aging and hormonal changes, particularly in women, may destabilize MHO status, increasing CV vulnerability over time. This overview calls for a paradigm shift in cardiometabolic care, moving beyond anthropometric parameters toward a more refined assessment that incorporate inflammatory biomarkers, fat distribution and sex-specific factors. Recognizing these underlying biological and phenotypic differences enables more accurate CV risk stratification and supports the development of precision-based therapeutic strategies. Ultimately, understanding not just who is at risk, but why, is essential to improving prevention and outcomes across diverse populations facing the burden of obesity.

Key Words: Cardiovascular risk; Epicardial adipose tissue; Inflammation; Metabolically healthy obesity; Metaflammation; Obesity; Sex differences; Visceral fat

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Core Tip: Obesity is not a uniform condition but comprises multiple phenotypes with distinct cardiovascular (CV) risks. The concept of metabolically healthy obesity is increasingly challenged by evidence of low-grade inflammation, ectopic fat accumulation, and adipose dysfunction. Inflammation, particularly in visceral and epicardial fat, plays a central role in driving subclinical CV damage, even in the absence of overt metabolic disease. Postmenopausal women are especially vulnerable due to hormonal shifts and fat redistribution. Integrating fat phenotype, inflammatory biomarkers, and sex-specific factors is essential for precise cardiometabolic risk management and targeted prevention, moving beyond body mass index-based assessments.

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INTRODUCTION

Obesity is no longer viewed as a monolithic risk factor, but rather as a complex spectrum of phenotypes with diverse metabolic and cardiovascular (CV) implications. Among these, metabolically healthy obesity (MHO) has garnered considerable attention and debate. Although a universally accepted definition remains elusive, MHO generally refers to individuals who meet the clinical criteria for obesity but lack traditional metabolic disturbances such as hypertension, dyslipidemia, or diabetes. However, the assumption of "health" within this phenotype is increasingly questioned, as emerging research underscores the heterogeneous variability in CV risk among these individuals[1]. In their recent large-scale retrospective cohort study, Pingili *et al*[2] examined over 1.3 million hospitalized postmenopausal women, identifying 11.4% as MHO. Despite the absence of overt metabolic syndrome, these women exhibited an increased risk of major adverse cardiac and cerebrovascular events (MACCE) compared to their non-obese peers. The risk was particularly pronounced among African-American women and those in the lowest income quartile, suggesting the potential impact of socioeconomic disparities and biological differences. Crucially, the study invites a deeper exploration of inflammatory mechanisms underlying these observations. Even in the absence of classical metabolic abnormalities, inflammation may drive CV risk in MHO individuals[3]. The concept of "metaflammation" – a chronic, low-grade inflammatory state driven by metabolic excess – has been proposed to explain this phenomenon[4]. Elevated levels of inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α) have been observed in individuals with MHO[5]. A meta-analysis further confirmed that MHO individuals show significantly higher levels of inflammatory biomarkers compared to metabolically healthy normal-weight individuals, although lower than those with metabolically unhealthy obesity (MUO)[6]. This suggests that even "healthy" obesity may carry a pro-inflammatory burden capable of impairing vascular function. The picture becomes even more complex when considering sex-specific factors. Although men tend to accumulate more visceral fat earlier in life, postmenopausal women experience a marked increase in visceral adiposity, which is strongly associated with inflammation and endothelial dysfunction[7]. These changes, largely driven by declining estrogen levels, may heighten CV risk in aging women. Inflammatory responses and biomarker expression also differ by sex, adding complexity to risk prediction models[8]. Such findings highlight the need to re-evaluate the concept of "metabolically healthy" and incorporate gender, inflammatory biomarkers and fat distribution into CV risk stratification algorithms. MHO may, in fact, represent a transient or misleading state of apparent wellness, particularly in older women, where inflammation and hormonal fluctuations converge to amplify CV vulnerability[9].

FROM BMI TO FAT PHENOTYPES: RETHINKING CARDIOMETABOLIC RISK IN OBESITY

Overview and outlook

Over the past decade, understanding of obesity has evolved beyond the simplistic view of excess weight or a high body mass index (BMI). Nowadays, it is increasingly framed in terms of fat quality, distribution, and metabolic function[10]. Visceral and epicardial fat, in particular, have emerged as active players in cardiometabolic pathology[11]. These ectopic fat depots are metabolically active tissues that secrete pro-inflammatory cytokines, contribute to insulin resistance, and affect both cardiac and vascular structures[12]. Epicardial fat, due to its anatomical proximity to the myocardium and shared microcirculation, can exert local inflammatory effects, promoting arrhythmias and coronary artery disease. Abdominal visceral fat is closely linked to hepatic steatosis and metabolic-associated fatty liver disease, further fueling systemic inflammation[13]. Obesity-related CV risk is driven by a multitude of pathophysiological mechanisms. These include changes in cardiac structure (*e.g.*, left ventricular hypertrophy), functional abnormalities (diastolic dysfunction), neurohormonal imbalances (altered sympathetic activity and renin-angiotensin-aldosterone system activation) and pro-thrombotic states[14]. Many cardiometabolic alterations associated with obesity remain clinically silent for years, often going undetected until the disease has significantly progressed[15]. This silent cardiometabolic injury includes subclinical cardiac remodeling, endothelial dysfunction, and arterial stiffening, even in individuals without overt features of metabolic syndrome, contributing to underdiagnosis and delayed intervention[16,17]. Adipose tissue is now recognized not

merely as a fat reservoir, but as a dynamic endocrine and immune organ. Under conditions of overnutrition and cellular stress, particularly in visceral and epicardial depots, adipose tissue undergoes functional changes, becoming inflamed, insulin-resistant, and metabolically inflexible. This dysfunctional state, often referred to as adiposopathy, is characterized by increased secretion of pro-inflammatory cytokines (*e.g.*, TNF- α , IL-6), free fatty acids, and dysregulated adipokines, fueling systemic inflammation and vascular damage[18]. Crucially, these maladaptive changes can occur even in individuals with modest total fat mass but high visceral or ectopic fat burden. This highlights that adipose tissue function, rather than volume alone, is a key determinant of CV risk[19]. Moreover, dysfunctional adipose tissue disrupts the balance of key metabolic hormones. Elevated leptin levels, often accompanied by leptin resistance, enhance sympathetic activity and contribute to hypertension. In contrast, reduced adiponectin levels diminish anti-inflammatory and anti-atherogenic protection. These endocrine disruptions further link adipose dysfunction to CV pathology[20]. Importantly, not all fat behaves the same. While subcutaneous fat retains insulin sensitivity and a favourable adipokine profile, visceral depots exhibit hypoxia, immune cell infiltration, and impaired signalling. This depot-specific behaviour underscores the significance of adipose tissue biology, including its secretome, immune cell composition, and tissue-specific adaptability, particularly in individuals who may appear metabolically healthy by conventional standards[21]. Traditional metrics like BMI or waist circumference fail to capture these qualitative differences, leading to missed identification of high-risk individuals[22]. Future approaches should focus on assessing adipose tissue quality, through imaging, circulating biomarkers, and depot-specific profiling, to enhance early detection and refine risk stratification. Integrating adipose functionality into cardiometabolic assessments could represent a pivotal shift toward personalized, preventive strategies in obesity-related care.

Obesity phenotypes and fat depots

Epidemiological data have revealed a spectrum of obesity phenotypes with distinct metabolic and CV outcomes[23]. For instance, metabolically unhealthy normal-weight (MUNW) individuals present with hidden visceral fat and chronic inflammation despite a normal BMI, placing them at high CV risk[24]. In parallel with MUNW, another underrecognized but clinically significant phenotype is normal weight obesity (NWO)—a condition in which individuals maintain a normal BMI but exhibit excess body fat, especially visceral and ectopic fat, and display metabolic dysfunction akin to that seen in obesity. This phenotype, closely aligned with the MUNW category, challenges conventional risk stratification by highlighting hidden adiposity and systemic inflammation in seemingly lean individuals[25]. Recent evidence demonstrates that individuals with NWO are at significantly elevated risk for insulin resistance, type 2 diabetes, and CV disease, despite normal anthropometric readings[26,27]. The paradox of NWO lies in the fact that adipose dysfunction, not overall weight, drives metabolic disruption. These individuals often exhibit elevated inflammatory markers and impaired endothelial function, underscoring that metabolic health cannot be assumed based on BMI alone[28]. Inflammation appears to be a central pathophysiological mechanism, with NWO potentially representing a similarly unstable or transitional phenotype, particularly in aging populations and postmenopausal women. Conversely, MHO describes individuals with obesity who maintain relatively normal metabolic parameters. Although the prevalence of MHO varies significantly across populations, it tends to be more prevalent among younger individuals, women, and those with higher physical activity levels[29]. These individuals often possess a greater capacity for subcutaneous fat storage, exhibit smaller insulin-sensitive adipocytes and a more balanced inflammatory profile, with lower levels of TNF- α and IL-6[30]. However, the concept of MHO remains controversial. While some large-scale studies suggest that MHO individuals may have similar short-term risk for myocardial infarction or ischemic stroke as metabolically healthy normal-weight individuals, concerns persist regarding long-term outcomes. Despite their seemingly favorable profile, MHO individuals may still develop subclinical cardiac alterations and long-term CV complications such as heart failure[31,32]. The heterogeneity of MHO outcomes likely reflects the complexity of the phenotype itself. Despite this more benign profile, the MHO state appears to be unstable over time. Longitudinal data suggest that many individuals with MHO transition to MUO over time, especially with aging and hormonal changes[33]. For instance, postmenopausal women with MHO face a significantly higher risk of developing metabolic syndrome and MACCE[34]. MUO represents a particularly high-risk phenotype, often present with central fat dominance, ectopic lipid deposition, and hypertrophic, inflamed adipocytes[35]. What makes this phenotype particularly dangerous is its inability to store excess energy efficiently in subcutaneous depots, redirecting surplus lipids to ectopic sites such as the liver and skeletal muscle, triggering inflammation and systemic metabolic stress. This pathophysiological process underscores the role of dysfunctional fat tissue as a primary driver rather than a passive bystander of cardiometabolic disease[36]. A growing concern is sarcopenic obesity, particularly in older adults. This phenotype combines excess visceral fat mass with loss of muscle mass and strength, often resulting in reduced physical function, heightened insulin resistance, and increased susceptibility to heart failure with preserved ejection fraction (HFpEF) and frailty[37]. Given this complexity, reliance on anthropometric parameters alone is no longer sufficient for effective CV risk stratification. Precision approaches using artificial intelligence integration for advanced imaging, genomics and metabolic biomarkers assessment are essential[38]. Early detections of ectopic fat accumulation, especially in the liver and heart, can provide critical prognostic value. Among fat depots, epicardial adipose tissue (EAT) has gained attention due to its unique anatomical and physiological characteristics. Located between the myocardium and the visceral layer of the pericardium, EAT influence the coronary arteries and cardiac muscle through paracrine and vasocrine signaling. Sharing microcirculation with the underlying myocardium, EAT acts as a conduit for direct biochemical communication. EAT expansion has been strongly associated with coronary artery disease, HFpEF and atrial fibrillation (AF)[39]. In particular, greater EAT thickness appears to correlate with more vulnerable coronary plaque morphology and impaired coronary microvascular function, suggesting a role not only in disease initiation but also progression[40]. Importantly, EAT is not metabolically uniform. It displays beige fat characteristics, and a unique immune environment enriched in type 2 innate lymphoid cells, which are linked to thermogenic activity. However, this browning phenotype appears to decline with aging, obesity, and disease severity, potentially shifting the

balance toward a more pro-inflammatory state. These evolving insights underscore EAT's potential as both a biomarker and therapeutic target in obesity-related CV disease[41,42].

Nutritional overload, immune activation, and the inflammatory metabolism of obesity

Beyond energy storage, adipose tissue serves as a dynamic endocrine and immune organ, actively involved in the regulation of metabolic and inflammatory pathways. In obesity, chronic nutrient excess pushes the body into a sustained metabolic challenge, where physiological processes—such as the normal postprandial immune response—become exaggerated and pathological. This postprandial immune activation, normally involves in a release of inflammatory mediators as transient response to food intake, is amplified in individuals with obesity due to visceral fat accumulation and continuous exposure to nutrient-rich substrates[43]. As a result, immune cells within adipose depots, especially macrophages, undergo metabolic reprogramming, shifting from anti-inflammatory to pro-inflammatory phenotypes. Dysfunctional fat depots secrete elevated levels of inflammatory mediators like leptin, TNF- α , IL-6, and monocyte chemoattractant protein-1, contributing to chronic low-grade inflammatory microenvironments, even in the absence of classical metabolic disease[44]. Notably, adipocytes and macrophages share a significant functional overlap, both producing pro-inflammatory mediators, blurring the distinction between metabolic and immune cell functions in adipose tissue. Metaflammation, triggered not by infection but by continuous metabolic overload, is often worsened by age-related inflammaging, links nutrient overload to systemic CV risk. Together, elevated substrates and oxidative stressors fuel endothelial and metabolic dysfunction[45]. Recent studies have also linked metaflammation to altered adipokine profiles—notably, decreased adiponectin and elevated leptin levels—further modulate vascular inflammation and thrombosis. Moreover, in postmenopausal women, changes in estrogen levels worsen this inflammatory profile and promote visceral fat accumulation, compounding the effects of metaflammation[46]. Adding to this, chronic nutrient and growth signaling induces cellular senescence in hypertrophic adipocytes. These cells cease dividing but remain metabolically active, secreting a distinct set of inflammatory factors termed the senescence-associated secretory phenotype, compounding local and systemic inflammation and reinforcing the cycle of metabolic dysfunction[47]. The convergence of nutrient overload, immune reprogramming, cellular senescence, and oxidative stress forms a core mechanism linking obesity to cardiometabolic disease. This pathological state provides fertile ground for the development insulin resistance, vascular dysfunction, and atherosclerosis, often in individuals who appear metabolically "healthy" by conventional measures.

Gender differences in CV risk factors

As our understanding of obesity deepens, it is increasingly evident that gender differences critically shape the distribution and consequences of excess adiposity. Premenopausal women typically store fat subcutaneously, which is less metabolically active and offers temporary CV protection. Men accumulate more visceral fat earlier in life, a depot strongly pro-inflammatory and linked to CV events. However, during menopause and especially estrogen decline, women undergo a shift toward visceral fat accumulation and redistribution, which is associated with insulin resistance, endothelial dysfunction, and increased inflammatory signaling[48]. This transition can destabilize metabolically healthy profiles, making women more prone to developing MUO over time[49]. A central driver of this transition is inflammation. Postmenopausal women often exhibit elevated levels of CRP and adipokines, even when classical metabolic markers remain within normal ranges[50]. These subtle inflammatory shifts are not always captured by traditional diagnostic criteria but significantly elevate CV risk. Emerging evidence highlights that sex-specific molecular mechanisms further modulate risk of development and progression of cardiometabolic diseases. Women experience a sharper transition toward metabolically unhealthy states post-menopause, accompanied by a rise in visceral fat and an altered miRNA expression profile that may drive disease development, impacting CV remodeling and risk differently in men and women[51]. Moreover, circulating sex-biased miRNAs have been linked to endothelial dysfunction and HFpEF development in postmenopausal women, illustrating how molecular sex differences can modulate disease phenotypes. Moreover, conditions such as HFpEF and AF, closely associated with EAT, are more prevalent in women later in life. This may reflect both biological predisposition and the influence of adipose inflammation in close proximity to cardiac structures[52,53]. Further supporting this sex-specific risk, clinical data show that MUO increases long-term CV risk in men, while MUNW phenotypes confer higher risk in women, emphasizing the interplay between sex, body composition, and metabolic health[54]. Beyond biology, social and behavioral factors compound gender disparities. Women often face systemic barriers in healthcare, including underdiagnosis, limited access to advanced diagnostics, and underrepresentation in CV clinical trials[55]. These disparities are amplified in low-income settings, where caregiving responsibilities and limited health resources restrict opportunities for prevention. The World Health Organization identifies these disparities as a major concern for global health equity. Given this complexity, a sex-specific approach to obesity management is essential. Future models must evolve to incorporate fat distribution, hormonal profiles, inflammatory markers and sociocultural determinants of health. Tailored strategies can enable earlier detection, better prevention, and more personalized interventions for both women and men. Clinical guidelines and public health initiatives must adapt to these differences to ensure equity and precision across the lifespan.

GAPS IN KNOWLEDGE AND FUTURE RESEARCH DIRECTIONS

Despite growing insights into the heterogeneity of obesity phenotypes and their CV implications, major gaps remain. First, the long-term stability of the MHO phenotype is poorly understood, particularly in relation to aging, hormonal transitions, and inflammation-driven shifts. Large prospective studies are needed to clarify the temporal dynamics of

MHO and its transition to metabolically unhealthy states in both genders. Second, current risk stratification models often rely on anthropometric measures and fail to incorporate more nuanced parameters such as ectopic fat burden, inflammatory biomarkers, and adipose tissue functionality. Machine learning, radiomics, and omics-based profiling could provide greater resolution in identifying at-risk individuals before clinical disease manifests[56]. Therapeutically, the rise of anti-obesity medications offers promising avenues not only for weight loss but also for improving insulin sensitivity, reducing systemic inflammation, and potentially attenuating EAT volume[57]. An exciting frontier involves the study of EAT-derived extracellular vesicles, especially exosomes, which may serve as mediators of local myocardial inflammation or as circulating biomarkers of adipose dysfunction. Their molecular cargo, ranging from microRNAs to pro-inflammatory proteins, could illuminate new mechanisms of cardio-adipose communication and represent potential therapeutic targets[58]. Future research should prioritize sex-specific analyses, longitudinal cohort tracking, and interventional trials focused on inflammatory modulation to transform our current, often superficial, approach to obesity-related CV risk.

CONCLUSION

Obesity should no longer be assessed by anthropometric data alone but understood as a spectrum of fat phenotypes with distinct cardiometabolic risks. MHO often hides structural and inflammatory changes that raise CV risk, especially in aging women, despite a benign metabolic appearance. Future clinical strategies must integrate fat distribution, inflammatory profiles, and sex-specific variables to enable earlier detection and more personalized prevention of obesity-related CV outcomes.

FOOTNOTES

Author contributions: Montecucco F designed the drafting of the manuscript and supervised the work; Ramoni D performed the conceptualization and wrote the full manuscript; Liberale L and Carbone F reviewed and edited the final version; all authors have read and approve the final manuscript.

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Country of origin: Italy

ORCID number: Davide Ramoni 0009-0006-8457-9911; Luca Liberale 0000-0003-1472-7975; Federico Carbone 0000-0003-2957-4078; Fabrizio Montecucco 0000-0003-0823-8729.

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