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Rethinking obesity management through a sex-specific lens: A narrative review

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Abstract

Obesity remains widely treated as a sex-neutral condition, despite decades of evidence revealing distinct sex-specific metabolic and behavioral trajectories between men and women. This neutrality perpetuates unequal outcomes: Men often achieve faster initial weight loss, whereas women face greater early resistance but display superior long-term resilience. The question persists: Why do men and women respond differently to the same intervention? The answer lies not in a single mechanism, but in the complex interplay among body composition, hormonal and neuroendocrine regulation, adaptive thermogenesis, and sociocultural determinants. To address this gap, this review proposes an integrative four-axis model encompassing: (i) Body composition and fat distribution, (ii) hormonal and neuroendocrine control, (iii) energy efficiency and adaptive thermogenesis, and (iv) sociocultural determinants. Drawing on literature from the past 25 years, it synthesizes physiological and behavioral evidence to explain how biological sex and menopausal status influence weight-loss responses. The narrative approach bridges clinical and experimental findings to offer a conceptual framework capable of guiding personalized strategies in obesity care. By integrating metabolic, hormonal, and psychosocial domains, the proposed model underscores that obesity cannot be reduced to a mere caloric equation. Recognizing sex-based dimorphism is essential for improving equity, sustainability, and precision in treatment outcomes. This framework invites a paradigm shift, from calorie-centered to complexity-informed medicine, where management is tailored to the distinct physiological and social realities of men and women.

Keywords: Obesity; Obesity management; Women; Men; Body composition

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1. Introduction

Obesity continues to be addressed in most clinical guidelines as a sex-neutral condition, despite decades of evidence demonstrating sex-specific trajectories between men and women.[1-3] This apparent neutrality contributes to unequal outcomes: Men generally exhibit faster and more pronounced early weight loss, whereas women experience greater initial difficulty but ultimately achieve more sustainable long-term results.[4]

The central question is clear: Why do men and women respond differently to weight loss? The answer does not reside in a single factor but rather in the complex interplay among body composition, hormonal and neuroendocrine regulation, energy adaptations, and sociocultural determinants.[5-7]

Moreover, the absence of stratification by sex and menopausal status in large-scale clinical trials perpetuates overgeneralized conclusions, thereby limiting the clinical applicability of their findings. Studies indicate that women remain underrepresented in recent randomized controlled trials (RCTs), particularly in older age groups, highlighting the need for differentiated approaches.[8,9]

In this context, the present study proposes an integrative four-axis model—(i) body composition and fat distribution; (ii) hormonal and neuroendocrine control; (iii) energy efficiency and adaptive thermogenesis; and (iv) sociocultural determinants—as a practical framework to reinterpret metabolic dimorphism and inform personalized strategies in obesity management.

2. Review methodology

This study was conducted as an integrative narrative review with a descriptive and thematic focus. Although systematic search and selection strategies were employed, the review was not pre-registered, and the PRISMA checklist was not fully applied, given its conceptual and opinion-based nature. The primary objective is to integrate and critically interpret the main evidence on sex-based differences in weight loss and their clinical implications, synthesizing findings from physiological, hormonal, and sociocultural perspectives.

A comprehensive search was performed using three major databases: PubMed/MEDLINE, Scopus, and SciELO, from their inception to August 2025, complemented by manual reference screening of key articles. These databases were selected because, together, they encompass the principal biomedical and Latin American scientific literature relevant to obesity research, providing broad coverage across experimental, clinical, and sociocultural domains. Other platforms, such as Web of Science and Embase, were not included due to their substantial overlap with the selected databases and to ensure methodological consistency.

Search terms were applied in English, Spanish, and Portuguese for SciELO, and in English for PubMed and Scopus. The keywords included "obesity," "weight loss," "sex differences," "estrogen," "menopause," "adaptive thermogenesis," and "sociocultural determinants," applied individually and in Boolean combinations (AND/OR). The initial search identified 702 articles (PubMed: n = 110; Scopus: n = 562; and SciELO: n = 30). After removing approximately 20% duplicates, 562 titles and abstracts were screened, followed by 200 full-text assessments.

Inclusion criteria encompassed RCTs, large observational studies, systematic reviews, meta-analyses, and translational or mechanistic research addressing physiological or clinical mechanisms of metabolic dimorphism in adults. Exclusion criteria included pediatric populations, animal models lacking translational relevance, non-English, Spanish, or Portuguese publications, and studies lacking sex-specific analyses. Additional references were incorporated through manual bibliography searches.

Two reviewers independently conducted the selection and data extraction processes, resolving divergences through discussion until consensus was reached. Extracted data included study design, population, interventions or exposures, comparators, outcomes, and limitations.

The synthesis was descriptive and organized according to the four conceptual axes proposed in this review. No meta-analysis was conducted due to the methodological heterogeneity among studies, and no formal risk-of-bias assessment was performed, in accordance with the narrative scope of the work. The reported numbers are approximate and intended to ensure transparency in methodological reporting. In total, 68 studies were selected and integrated into the final synthesis supporting the development of the proposed four-axis model.

3. The four-axis model

The synthesis of the reviewed evidence revealed consistent and complementary patterns across biological, hormonal, and behavioral dimensions. Men exhibit greater lipolysis and visceral adiposity, enabling faster mobilization of fat stores, whereas women preserve gluteofemoral depots that are more resistant to caloric deficit but exert a cardiometabolic protective effect.

Differences are also evident in substrate utilization: Men tend to oxidize carbohydrates, whereas women preferentially oxidize lipids, an effect partially mediated by estradiol. Over time, weight loss naturally reaches a physiological plateau, the hallmark of adaptive thermogenesis, where energy expenditure falls beyond what can be explained by body composition alone. This adaptive process tends to persist longer in men, whereas women demonstrate greater long-term metabolic resilience.

The menopausal transition represents a critical turning point. The abrupt decline of estradiol leads to visceral fat redistribution, insulin resistance, and loss of lean mass, establishing a specific window of metabolic vulnerability.

Several interventions have demonstrated effectiveness in this context. Intermittent energy restriction has shown benefits for enhancing weight loss, whereas resistance training remains essential for preserving lean mass. Pharmacotherapy with glucagon-like peptide-1 (GLP-1) receptor agonists or dual glucose-dependent insulinotropic polypeptide/GLP-1 agonists has also shown consistent efficacy in reducing weight and improving cardiometabolic outcomes. Psychobehavioral strategies, including motivational interviewing, mindfulness, and cognitive behavioral therapy, have proven effective in improving adherence and reducing emotional eating, increasingly supported by digital and hybrid care models.

These consistent findings across biological and behavioral domains reinforce the concept of metabolic duality between the sexes and introduce the integrative framework proposed in this review, the four-axis model, which seeks to explain why men and women respond differently to weight loss and how these differences can inform personalized treatment strategies.

3.1. Axis 1: The male advantage is initial but not sustainable

Is the male advantage in weight loss truly sustainable, or merely an initial illusion? Fat-free mass (FFM) is the principal determinant of resting energy expenditure (REE). In men, the greater amount of FFM supports higher absolute values of basal metabolic rate (BMR) and REE. However, not only the quantity but also the quality of FFM is decisive. Metabolically active organs, such as the liver, kidneys, brain, and heart, although representing only about 5% of body weight, account for up to 80% of REE. Differences in the proportion of these tissues help explain both individual and sex-related variation in resting metabolism.[10]

In addition, adipose tissue distribution adds a critical dimension. The visceral compartment, predominant although not exclusive in men, exhibits greater density of β-adrenergic receptors, favoring rapid lipolysis and fat mobilization in response to adrenergic stimulation or caloric deficit, and remains relatively resistant to suppression even under hyperinsulinemia or postprandial states.[1] In contrast, the female gluteofemoral depot, characterized by α2-adrenergic receptors with antilipolytic effects and by adiponectin secretion, is more resistant to mobilization but functions as a "metabolic safe reservoir," associated with cardiovascular protection and lower risk of insulin resistance.[3,11]

These differences extend to substrate metabolism during exercise. During moderate-intensity aerobic activity, men preferentially oxidize carbohydrates, whereas women utilize lipids to a greater extent and spare muscle glycogen. This pattern may be partially influenced by a higher proportion of type I muscle fibers in women, but also by estradiol, as the same lipolytic effect has been observed when estradiol was administered to men. Importantly, this sex effect appears to attenuate in elite athletes, suggesting that intensive training reduces the hormonal influence on substrate selection.[11-13]

Another relevant aspect is the adaptation to energy deficit. Several studies have reported declines in REE (the energy required to maintain vital physiological functions at rest) greater than those predicted by the loss of body mass, a phenomenon known as adaptive thermogenesis. During weight-loss programs, reductions of 20–25% below the expected expenditure for the weight lost have been described, contributing to the clinical plateau observed particularly in men.[14,15] Interestingly, in women, this effect tends to be more transient, with REE returning to the expected value after weight stabilization, whereas in men, the reduction may be more pronounced and persistently maintained below the expected level. This indicates that women generally display superior adaptive capacity and that the apparent male advantage due to higher FFM is counterbalanced over time by their greater long-term metabolic resilience.

Regarding brown adipose tissue (BAT), translational studies suggest sex differences in its activity, but findings in humans remain inconclusive. BAT should therefore be considered a potential modulator of energy efficiency, though not yet an established determinant.[16]

In summary, men present an initial advantage in weight loss, reflected in a faster clinical response. However, this advantage is transient and often limited to the short term. Women, although losing weight more gradually, demonstrate more enduring metabolic resilience, supported by protective peripheral fat depots and adaptive energy mechanisms. This contrast introduces the central conceptual opposition of the proposed model and sets the stage for the hormonal and neuroendocrine factors that will be examined in Axis 2.

3.2. Axis 2: Estradiol as the metabolic guardian of women

Estradiol plays a central regulatory role in energy expenditure and intake. In experimental models, activation of estrogen receptor (ER)-α in steroidogenic factor (SF)-1 neurons of the ventromedial hypothalamus inhibits AMP-activated protein kinase, elevates sympathetic tone, and stimulates thermogenesis in BAT.[13] The specificity of this circuit is crucial: deletion of ERα in SF-1 neurons produces a marked reduction in metabolism, decreased

thermogenesis, and accumulation of visceral fat, whereas impaired ERα signaling in pro-opiomelanocortin (POMC) neurons induces hyperphagia without directly reducing energy expenditure.[17] Recent reviews consolidate this functional segregation: SF-1 circuits regulate thermogenesis and energy expenditure, whereas POMC circuits regulate satiety in both sexes.[13,17] Clinically, menopause—through the abrupt decline of estradiol—favors central fat redistribution, insulin resistance, and lean mass loss, creating a window of female metabolic vulnerability, representing a period in which women are essentially thrust into a "menopausal metabolic syndrome," irrespective of their will.[13,17,18]

In contrast, testosterone exerts direct anabolic effects on muscle through androgen receptor (AR) activation, promoting satellite cell proliferation and protein synthesis, thereby preserving FFM and enhancing lipid oxidation.[19] Mechanistically, testosterone and dihydrotestosterone inhibit adipogenesis in 3T3-L1 cells in a dose-dependent manner via AR activation, with nuclear translocation of β-catenin independent of Wnt binding. Once in the nucleus, β-catenin binds to T-cell factor 4/lymphoid enhancer factor, blocking CAAT/enhancer binding protein-α and peroxisome proliferator-activated receptor-γ, thereby preventing preadipocyte differentiation; AR antagonists reverse this effect.[20] Clinical trials of testosterone replacement in elderly men have demonstrated increased lean mass, reduced fat mass, and enhanced lipid oxidation, though without consistent improvements in insulin sensitivity as measured by clamp techniques.[21] Complementarily, narrative reviews emphasize the anti-inflammatory effects of testosterone, reinforcing its potential metabolic contribution.[22]

During the menopausal transition, elevated follicle-stimulating hormone (FSH) exerts direct effects on adipocytes through its Gαi-coupled receptor, promoting Ca^{2+} influx, cAMP response element-binding protein activation, and expression of lipogenic genes. As a result, lipid biosynthesis increases, fat accumulates, and adipokine secretion, including leptin and adiponectin, is altered.[23] In pre-clinical models, pharmacological blockade of FSH with neutralizing antibodies has demonstrated opposite effects: it activated thermogenesis in brown and beige adipose tissue, increased uncoupling protein 1 expression, and induced beiging, thereby reducing fat mass.[24] Although still experimental, such findings suggest that FSH acts as an active regulator of energy efficiency and that its blockade may represent a future therapeutic pathway.

Clinically, menopausal hormone therapy is associated with metabolic improvements, including reduced homeostatic model assessment of insulin resistance, fasting glucose, and fasting insulin, as well as a lower incidence of type 2 diabetes, supporting the concept of a therapeutic window for intervention.[25]

The liver communicates with the hypothalamus primarily through fibroblast growth factor 21, mediated by the co-receptor βKlotho. Fibroblast growth factor 21 increases sympathetic activity, which in turn enhances uncoupling protein 1 expression, and also exerts direct effects on BAT by promoting energy expenditure.[26] This exemplifies a multihormonal integration in which estradiol functions as a coordinator of energy balance via the central nervous system.

Women tend to have higher circulating leptin levels for the same degree of adiposity, reflecting a relative resistance to this hormone.[27] Estradiol acts as a sensitizer, potentiating the anorexigenic action of leptin in POMC neurons via the cofactor Cited1, which bridges ERα and signal transducer and activator of transcription-3, and amplifies anorexigenic transcription.[28] In contrast, progesterone, particularly in the luteal phase, may further elevate leptin levels but attenuates its central satiety effects, leading to increased food intake.[29,30] Thus, leptin, which could act as an anorexigenic signal, functions primarily as an energy storage marker during specific phases of the female cycle.

In parallel, ghrelin levels rise under caloric deficit, and the response appears more pronounced in women, complicating dietary adherence.[31] Experimental models indicate that estradiol exerts a dual modulation: on the one hand, it maintains circulating levels while attenuating ghrelin-induced hunger; on the other hand, evidence in humans suggests that under hypoestrogenic conditions, the orexigenic action of ghrelin is amplified.[32]

3.3. Axis 3: Plateau, the clinical failure to recognize adaptation

If the weight-loss plateau is physiological and predictable, why does clinical practice still interpret it as a patient's failure rather than an expression of intrinsic energy adaptation?

The weight-loss plateau represents the clinical face of adaptive thermogenesis: a disproportionate reduction in total energy expenditure (TEE), greater than what would be expected from the loss of fat and lean mass alone. Studies demonstrate that maintaining a loss of ≥10% of body weight can reduce TEE by approximately 20–25%, of which up to 15% exceeds the value predicted based on body composition changes.[14] This represents a biological brake imposed by physiology itself, rather than a lack of patient discipline.

The mechanisms are multifactorial: Reduced BMR; declines in non-exercise activity thermogenesis (NEAT),

which may account for up to 300 kcal/day—approximately half of the reduction in TEE;[33] increased muscular efficiency during exercise;[34] and hormonal shifts, including decreases in leptin and peptide YY alongside increases in ghrelin. Together, these changes not only slow weight loss but also create a subjective sense of chronic hunger and demotivation. This is precisely where many protocols fail: they ignore that the body does not "play on the patient's team."

Clinical practice often insists on linear strategies, as if simply cutting calories indefinitely were sufficient. Such a view is naïve and reductionist. The body does not surrender to prolonged caloric deficit; it economizes energy, prioritizes essential functions, and protects stores. The result is predictable—frustration, abandonment, and relapse.

Another mechanism involves peripheral thyroid hormone conversion. Animal studies have shown increased expression of iodothyronine deiodinase type (DIO)-3 and decreased expression of DIO2 in skeletal muscle during caloric restriction, reducing local T3 and promoting the shift from fast-twitch to slow-twitch fibers. These slow fibers, relying predominantly on oxidative metabolism, display greater mechanical efficiency and lower energy cost per contraction, contributing to the energy conservation observed in adaptive thermogenesis.[35]

The duration of this adaptation remains debated. In bariatric surgery, it tends to normalize within 24 months; however, in intensive weight-loss programs, such as the "Biggest Loser" competition, it can persist for up to 6 years, even after regaining two-thirds of the weight lost.[36] Pro-hunger hormones (e.g., ghrelin, peptide YY, cholecystokinin, insulin, leptin, amylin, pancreatic polypeptide, and gastric inhibitory polypeptide) remain altered for at least 12 months, contributing to sustained subjective hunger.[37]

Aging adds further layers of adaptation. There is progressive loss of lean mass, mitochondrial dysfunction, and reduced ATP production due to increased oxidative damage and mtDNA depletion, resulting in diminished oxidative capacity, lower VO_2max, and impaired glucose tolerance.[38] This is accompanied by chronic low-grade inflammation ("inflammaging"), which shares pathways with obesity-related meta-inflammation and is largely influenced by alterations in the gut microbiota.[39]

In men, testosterone declines "gradually and imperceptibly" across decades, independent of obesity, smoking, alcohol consumption, or disease, predisposing to sarcopenia.[40] In women, the menopausal transition is abrupt, marked by a decline in estradiol, which intensifies visceral fat redistribution, insulin resistance, and muscle loss. Longitudinal studies have reported selective increases in visceral and trunk fat,[41] reductions of approximately 200 kcal/day in energy expenditure (with an 8% drop in sleeping metabolic rate), and decreases of up to 32% in lipid oxidation during the menopausal transition.[42,43]

Meta-analyses confirm that chronological aging increases total adiposity, but menopause specifically promotes central redistribution, with greater waist circumference, trunk and visceral fat, and reductions in peripheral fat.[6] Observational studies suggest that hormone therapy may partially attenuate this pattern, reducing visceral and android fat, though without consistently preserving lean mass and with no lasting effect after discontinuation.[18]

Post-menopausal women also show reduced lipid oxidation during submaximal exercise, associated with elevated visceral adiposity and insulin resistance.[43] According to the EWGSOP2 consensus, after age 50, women lose 1–2% of leg muscle mass and 1.5–5% of strength per year, a process accelerated by estrogen deficiency.[44] Mechanistically, estradiol deficiency compromises multiple organs: It reduces muscle glucose uptake through insulin receptor (IR)/IR substrate-1/phosphoinositide 3-kinase/protein kinase B pathway, increases hepatic gluconeogenesis through forkhead box protein O1, promotes hypertrophy of visceral adipocytes and oxidative stress, decreases pancreatic insulin secretion, and worsens endothelial function, culminating in inflammatory insulin resistance.[45]

Genetic factors modulate energy efficiency and display sex dimorphism. Polymorphisms in the *FTO* and *MC4R* influence total adiposity, whereas genes such as *RSPO3/KREMEN1*, *TBX15-WARS2*, *HOXC*, *VEGFA*, *GRB14/ADAMTS9*, and *LYPLAL1* are linked to higher waist-to-hip ratio in women.[46] Variants in leptin receptor (Q223R) increase leptin and body mass index in adolescent females, whereas MC4R polymorphisms (rs17782313) are associated with reduced satiety perception and hyperphagia, compounded by slower gastric emptying.[47,48]

At the epigenetic level, estrogen regulates adipogenesis and thermogenesis in a sex- and depot-specific manner, activating genes such as *ADRB3* and *DIO2* in animal models, favoring beiging and greater thermogenic activity.[49] In humans, estrogen and progesterone regulate modifications in Hox clusters, which determine regional fat distribution, as well as in long non-coding RNAs (e.g., HOTAIR), capable of remodeling chromatin and modulating adipogenesis and inflammation, thereby explaining sex-specific metabolic differences, particularly after menopause.[50]

Fetal programming also plays a role. Evidence from the developmental origins of health and disease studies indicates that gestational diabetes can induce hypomethylation of genes such as *LEP*, *ADIPOQ*, *ABCA1*, and *NR3C1*.[51] These epigenetic alterations predispose to obesity in adulthood by programming early metabolic and

hormonal pathways linked to fat storage, satiety, and stress response. Under suboptimal conditions, such as maternal obesity or intrauterine growth restriction, alterations in microRNA (miRNA) expression may affect pathways that produce structural changes in the liver, pancreas, and skeletal muscle—the latter directly influencing GLUT4 expression and glucose metabolism.[52] In BAT, molecular regulators including SIRT1, PRDM16, and miRNAs act as critical modulators of formation and thermogenic activity, suggesting potential future therapies.[16] However, in humans, BAT assessment still relies on fluorodeoxyglucose–positron emission tomography/computed tomography, and no pharmacological therapies are currently validated, opening a window of opportunity for research.

To interpret the plateau as a patient's failure is to perpetuate a clinical injustice. Recognizing metabolic adaptation as a critical turning point is not optional—it represents the dividing line between protocols destined to fail and a practice of medicine that truly respects human biology.

3.4. Axis 4: The invisible barrier of society in female weight loss

The trajectory of weight loss is not defined solely by biology and hormones. Social and cultural determinants profoundly shape adherence and outcomes, creating an unequal landscape between men and women. Ultimately, is it biology or society that exerts a stronger influence on female weight loss?

Studies show that men are more likely to engage in resistance and strength-based exercise, whereas women tend to participate less in strength activities. Moreover, individuals with obesity—particularly women—face additional barriers such as weight stigma, ridicule, and esthetic pressure, all of which contribute to discontinuation of physical activity and to a higher prevalence of emotional eating.[5] These external pressures often lead women to adopt extremely hypocaloric diets, frequently without professional guidance and without regard for the importance of maintaining muscle mass. During the COVID-19 pandemic, these disparities were amplified. Women, especially mothers, accumulated domestic and caregiving responsibilities, which reduced time available for self-care and intensified stress.[53]

Such external and internal pressures are reflected in early dropout from weight-loss programs. Some studies indicate higher dropout rates among women, although the association with gender is not consistent across the literature.[54] In addition, the higher prevalence of eating disorders among women—such as anorexia, bulimia, and binge eating disorder—is associated with stigma and body dissatisfaction, fueling cycles of frustration, relapse, and withdrawal.[55] Within this context, adherence proves more important than the specific dietary approach, as demonstrated by randomized clinical trials.

Systematic reviews confirm that men and women do not respond equally to interventions; men generally lose more body weight. However, the differences are modest and usually favor men.[4] This dynamic reinforces a contrast: In men, the prevailing cycle is results–motivation–adherence, whereas in women, the prevailing cycle often becomes effort–frustration–abandonment.

Axis 4 proposes that weight loss cannot be explained solely by physiology. Stigma, social overload, mental health, and cultural norms operate as invisible barriers that weigh more heavily on women. To ignore them is to perpetuate inequities in metabolic health. This axis expands the integrative model by situating weight loss as a phenomenon that is also socially determined, thereby setting the stage for the clinical and policy implications discussed in the following section. These sex-based contrasts are summarized in Table 1.

Table 1. Summary of sex differences in weight loss across biological, hormonal, and sociocultural dimensions

Dimension	Men	Women
FFM and RMR[10]	Higher FFM, higher absolute RMR	Lower FFM, lower absolute RMR, but greater long-term metabolic resilience
Fat distribution[1,3,56]	Predominantly visceral fat, higher β-adrenergic receptor density, faster lipolysis	Predominantly gluteofemoral fat, α2-adrenergic receptors, more resistant to mobilization, but cardioprotective
Substrate utilization during exercise[11,12]	Preferential carbohydrate oxidation	Preferential lipid oxidation, partly estradiol-mediated
Adaptive thermogenesis[14,15]	More persistent, RMR remains below expected after weight loss	More transient, RMR recovers after weight stabilization
Sex hormones[13,19,41]	Testosterone preserves muscle mass, inhibits adipogenesis	Estradiol regulates satiety and thermogenesis; an abrupt decline in menopause results in visceral fat gain, insulin resistance
Clinical response[4]	Faster and greater initial weight loss	Slower, but long-term resilience and metabolic adaptation
Sociocultural barriers[5,53]	Lower stigma, greater adherence to resistance training	Higher stigma, greater psychological burden, more eating disorders, and lower adherence

Abbreviations: FFM: Fat-free mass; RMR: Resting metabolic rate.

4. Clinical implications

Weight-loss interventions still insist on reducing obesity to a mere caloric equation. This reductionism is ineffective, blind to biological sex, and perpetuates predictable inequalities. The four-axis model reveals the shortcomings of this paradigm and offers a pathway toward personalized medicine.

4.1. Axis 1: Body composition

Aggressive caloric restriction destroys lean mass, reduces energy expenditure, and precipitates the plateau. Muscle is not an accessory; it is the true metabolic engine. The absence of resistance training and adequate protein intake transforms traditional protocols into promoters of relapse. Robust evidence shows that strength training combined with protein intake of 1.6–2.2 g/kg of body weight per day preserves lean mass and enhances fat loss.[57,58] The clinical error lies in treating these strategies as optional when they should be the core of treatment.

4.2. Axis 2: Hormonal

Estradiol is the true metabolic guardian of women. Its abrupt decline at menopause triggers a metabolic inflection point, marked by central fat redistribution, insulin resistance, and accelerated sarcopenia. It is at this moment that female risk surges. Menopause is the critical point of metabolic dimorphism, the dividing line between resilience and vulnerability. However, protocols remain neutral, ignoring the necessity of stratifying by menopausal status. Hormone therapy, when appropriately indicated, can remodel this scenario,[18] yet it remains underutilized in the vast majority of cases.

4.3. Axis 3: Metabolic adaptation

To interpret the plateau as a failure of character is a clinical and scientific error. The plateau is, in itself, proof that the body is fighting for survival. Linear protocols are destined to fail. Strategies such as scheduled maintenance breaks, dietary periodization, intensive resistance training, protein adjustment, and judicious use of incretin therapies are tools to mitigate this limitation. For women, particularly for post-menopausal women, recognizing estradiol as a central modulator is the dividing line between a practice that fails and one that liberates.

4.4. Axis 4: Sociocultural

Axis 4 highlights the invisible societal barriers to female weight loss. Weight stigma, domestic overload, and esthetic pressure are not merely background factors; they are clinical forces shaping adherence, relapse, and prognosis. Women face unrealistic expectations of body and beauty while simultaneously bearing family and professional responsibilities. This dual burden produces predictable dropout rates.[5,53] Cultural and climatic factors further shape dietary choices and food availability, influencing macronutrient preferences, seasonal eating patterns, and adherence to weight-loss strategies. These environmental contexts amplify the social gradient of obesity, particularly among women in warmer or economically constrained regions. Men benefit from a positive cycle of results–motivation–adherence, whereas women are often trapped in the cycle of effort–frustration–abandonment, perpetuated by social structures that devalue their self-care.

The clinical impact of these barriers is as real as any biomarker. Adjusting calories is insufficient if the social environment undermines adherence. To interpret relapse as a "lack of willpower" is to ignore the role of stigma and gender inequality in metabolic health. Psychological interventions, such as cognitive behavioral therapy, acceptance and commitment therapy, and mindfulness, reduce emotional eating and enhance cognitive flexibility,[59] but they must be delivered in non-judgmental environments where women are not forced to negotiate between dignity and treatment.

Group-based and hybrid programs (in-person and digital) show higher adherence rates than individual care, primarily due to social support and mutual reinforcement.[60,61] Likewise, digital self-monitoring tools and continuous feedback provide modest but sustainable benefits, provided they are accompanied by structured clinical support.[61,62] This clearly demonstrates that ignoring social determinants condemns women to inequality in metabolic health. Addressing them is integral to treatment, not an optional add-on.

5. Discussion

The four-axis model highlights the difficulty of weight loss not as an individual failure but as the outcome of interactions among biological, hormonal, adaptive, and sociocultural factors. This multidimensional perspective challenges the reductionist paradigm that equates obesity with caloric imbalance alone, providing a framework that better explains the faster initial response often observed in men and the slower yet more resilient metabolic trajectory typically seen in women.[14,41,42]

The menopausal transition emerges as a decisive inflection point. The abrupt decline in estradiol promotes visceral fat redistribution, exacerbates insulin resistance, and accelerates muscle loss, transforming weight management into a disproportionate challenge for women.[6,18] These vulnerabilities remain underrecognized

in universal protocols, highlighting the need to stratify interventions by sex and menopausal status.

Another critical dimension is the weight-loss plateau, frequently misinterpreted in clinical practice as a lack of adherence. In reality, it represents the physiological manifestation of adaptive thermogenesis, characterized by disproportionate reductions in REE, lower NEAT, and altered hormonal signaling.[33,37] Recognizing this adaptation as biological rather than behavioral is essential for designing humane and sustainable strategies.

Finally, the sociocultural domain reveals barriers that disproportionately affect women. Weight stigma, gendered role overload, and the higher prevalence of eating disorders compromise adherence and perpetuate cycles of relapse.[5,53,55] Addressing these determinants is as critical as correcting caloric intake, since neglecting them perpetuates inequalities in metabolic health. As this study is a narrative review, it did not systematically assess bias or exhaustively screen the literature, and available evidence remains heterogeneous. The gaps in the literature on sex-based dimorphism in weight loss are outlined in Table 2.

There is a pressing need for trials stratified by sex, menopausal status, and sociocultural determinants, ideally integrating molecular biomarkers, longitudinal designs, and translational models that validate menopause as a critical metabolic turning point.[49]

Table 2. Key gaps in the literature on sex-based dimorphism in weight loss

Area	Gap identified	Clinical/scientific implication
Randomized controlled trials[8,9]	Lack of sex stratification and menopausal status reporting	"Neutral" protocols yield unequal clinical outcomes
Menopause transition[6,41,42]	Underrepresentation of peri- and post-menopausal women	Failure to capture the metabolic inflection point of estradiol decline
Anti-obesity pharmacotherapy[63-65]	Few sex-specific analyses with GLP-1 and dual GIP/GLP-1 agonists	Uncertainty on efficacy and safety in post-menopausal women
Exercise interventions[57]	Predominance of male samples; low female adherence to resistance training	Limited evidence to guide sex-specific exercise prescriptions
Psychosocial factors[5,54]	Few studies integrating stigma, caregiving, and mental health	Underestimation of sociocultural determinants of female dropout
Epigenetics and DOHaD[51,52]	Fragmented data on sex-dependent fetal programming	Difficulty translating epigenetic findings into preventive strategies

Abbreviations: DOHaD: Developmental origins of health and disease; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1.

The four-axis model is not merely an academic construct but a critical lens through which the complexities of weight-loss responses are interpreted. Men and women do not share identical metabolic pathways nor face equivalent social barriers. Recognizing these differences is a prerequisite for building fairer, more effective, and sustainable interventions.

6. Conclusion

The current paradigm remains overly reductionist and clinically limited. Future models should integrate biological sex, menopausal status, and sociocultural determinants as central variables in both research and clinical practice. Adoption of the four-axis model is not merely an academic exercise; it represents a necessary step toward overcoming the inequities in outcomes between men and women. Menopause, in particular, is not destiny but rather an opportunity. It represents a pivotal moment that, if recognized and treated properly, can redefine the female metabolic trajectory.

Although it is well established that men and women respond differently to weight-loss interventions, sex-neutral protocols persist, highlighting the limitations of a reductionist paradigm that frames obesity as a simple caloric equation.

Metabolic dimorphism in weight loss must be recognized as a multidimensional phenomenon. The preservation of lean mass, the central role of hormones—particularly estradiol during the menopausal transition—the inevitability of metabolic adaptation, and the decisive influence of sociocultural determinants must be understood as interconnected elements of a single process. When treated in isolation, these dimensions fragment the therapeutic approach and limit long-term effectiveness.

The proposed four-axis model illustrates that only an integrative strategy encompassing biological, hormonal, energetic, and social domains can truly capture the complexity of obesity and reduce sex-based disparities. Clinically, this model provides a conceptual foundation for developing personalized interventions that align with biological sex, hormonal status, and psychosocial context, while also guiding future research toward stratified trials and translational validation.

To treat obesity without acknowledging its complexity is to perpetuate failure. To integrate it in its entirety is to advance toward a more effective, sustainable, and equitable medicine. Future studies should validate and refine

this framework, bridging the gap between conceptual understanding and clinical practice.

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References

1. Wahrenberg H, Lönnqvist F, Arner P. Mechanisms underlying regional differences in lipolysis in human adipose tissue. *J Clin Invest*. 1989;84:458-467.

   doi: 10.1172/JCI114187

2. Lovejoy JC. The menopause and obesity. *Prim Care*. 2003;30:317-325.

   doi: 10.1016/s0095-4543(03)00012-5

3. Jensen MD. Role of body fat distribution and the metabolic complications of obesity. *J Clin Endocrinol Metab*. 2008;93:S57-S63.

   doi: 10.1210/jc.2008-1585

4. Williams RL, Wood LG, Collins CE, Callister R. Effectiveness of weight loss interventions--is there a difference between men and women: A systematic review. *Obesity Rev*. 2015;16:171-186.

   doi: 10.1111/obr.12241

5. Pearl RL, Wadden TA, Jakicic JM. Is weight stigma associated with physical activity? A systematic review. *Obesity (Silver Spring)*. 2021;29:1994-2012.

   doi: 10.1002/oby.23274

6. Ambikairajah A, Walsh E, Tabatabaei-Jafari H, Cherbuin N. Fat mass changes during menopause: A meta-analysis. *Am J Obstet Gynecol*. 2019;221:393-409.e50.

   doi: 10.1016/j.ajog.2019.04.023

7. Hopkins M, Gibbons C, Blundell J. Fat-free mass and resting metabolic rate are determinants of energy intake: Implications for a theory of appetite control. *Phil Trans R Soc B Biol Sci*. 2023;378:20220213.

   doi: 10.1098/rstb.2022.0213

8. Wallach JD, Sullivan PG, Trepanowski JF, Steyerberg EW, Ioannidis JPA. Sex based subgroup differences in randomized controlled trials: Empirical evidence from Cochrane meta-analyses. *BMJ*. 2016;355:i5826.

   doi: 10.1136/bmj.i5826

9. Daitch V, Turjeman A, Poran I, *et al*. Underrepresentation of women in randomized controlled trials: A systematic review and meta-analysis. *Trials*. 2022;23:1038.

   doi: 10.1186/s13063-022-07004-2

10. Wang Z, Heshka S, Gallagher D, Boozer CN, Kotler DP, Heymsfield SB. Resting energy expenditure-fat-free mass relationship: New insights provided by body composition modeling. *Am J Physiol Endocrinol Metab*. 2000;279:E539-E545.

    doi: 10.1152/ajpendo.2000.279.3.E539

11. Cano A, Ventura L, Martinez G, *et al*. Analysis of sex-based differences in energy substrate utilization during moderate-intensity aerobic exercise. *Eur J Appl Physiol*. 2022;122:29-70.

    doi: 10.1007/s00421-022-04961-z

12. Tarnopolsky MA. Sex differences in exercise metabolism and the role of 17-beta estradiol. *Med Sci Sports Exerc*. 2008;40:648-654.

    doi: 10.1249/MSS.0b013e31816212ff

13. Martínez De Morentin PB, González-García I, Martins L, *et al*. Estradiol regulates brown adipose tissue thermogenesis via hypothalamic AMPK. *Cell Metab*. 2014;20:41-53.

    doi: 10.1016/j.cmet.2014.03.031

14. Rosenbaum M, Leibel RL. Adaptive thermogenesis in humans. *Int J Obes (Lond)*. 2010;34:S47-S55.

    doi: 10.1038/ijo.2010.184

15. Doucet E, St-Pierre S, Alméras N, Després JP, Bouchard C, Tremblay A. Evidence for the existence of adaptive thermogenesis during weight loss. *Br J Nutr*. 2001;85:715-723.

    doi: 10.1079/bjn2001348

16. Carpentier AC, Blondin DP, Haman F, Richard D. Brown adipose tissue-a translational perspective. *Endocr Rev*. 2023;44:143-192.

    doi: 10.1210/endrev/bnac027

17. Xu Y, Nedungadi TP, Zhu L, *et al*. Distinct hypothalamic neurons mediate estrogenic effects on energy homeostasis and reproduction. *Cell Metab*. 2011;14:453-465.

doi: 10.1016/j.cmet.2019.04.006. Erratum for: *Cell Metab*. 2011;14(4):453-465.

doi: 10.1016/j.cmet.2011.08.009

18. Papadakis GE, Hans D, Rodriguez EG, *et al*. Menopausal hormone therapy is associated with reduced total and visceral adiposity: The osteolaus cohort. *J Clin Endocrinol Metab*. 2018;103:1948-1957.

doi: 10.1210/jc.2017-02449

19. Allan CA, Strauss BJG, Burger HG, Forbes EA, McLachlan RI. Testosterone therapy prevents gain in visceral adipose tissue and loss of skeletal muscle in nonobese aging men. *J Clin Endocrinol Metab*. 2008;93:139-146.

doi: 10.1210/jc.2007-1291

20. Singh R, Artaza JN, Taylor WE, Gonzalez-Cadavid NF, Bhasin S. Androgens stimulate myogenic differentiation and inhibit adipogenesis in C3H 10T1/2 pluripotent cells through an androgen receptor-mediated pathway. *Endocrinology*. 2003;144:5081-5088.

doi: 10.1210/en.2003-0741

21. Frederiksen L, Højlund K, Hougaard DM, Brixen K, Andersen M. Testosterone therapy increased muscle mass and lipid oxidation in aging men. *AGE (Dordr)*. 2012;34:145-156.

doi: 10.1007/s11357-011-9213-9

22. Bianchi VE. The anti-inflammatory effects of testosterone. *J Endocr Soc*. 2019;3:91-107.

doi: 10.1210/js.2018-00186

23. Liu X, Chan HC, Ding G, *et al*. FSH regulates fat accumulation and redistribution in aging through the Gαi/Ca$^{(2+)}$/CREB pathway. *Aging Cell*. 2015;14:409-420.

doi: 10.1111/acel.12331

24. Sponton CH, Kajimura S. Burning fat and building bone by FSH blockade. *Cell Metab*. 2017;26:285-287.

doi: 10.1016/j.cmet.2017.07.018

25. Mauvais-Jarvis F, Manson JE, Stevenson JC, Fonseca VA. Menopausal hormone therapy and type 2 diabetes prevention: Evidence, mechanisms, and clinical implications. *Endocr Rev*. 2017;38:173-188.

doi: 10.1210/er.2016-1146

26. Owen BM, Ding X, Morgan DA, *et al*. FGF21 acts centrally to induce sympathetic nerve activity, energy expenditure, and weight loss. *Cell Metab*. 2014;20:670-677.

doi: 10.1016/j.cmet.2014.07.012

27. Kelesidis T, Kelesidis I, Chou S, Mantzoros CS. Narrative review: The role of leptin in human physiology: Emerging clinical applications. *Ann Intern Med*. 2010;152:93-100.

doi: 10.7326/0003-4819-152-2-201001190-00008

28. González-García I, García-Clavé E, Cebrian-Serrano A, *et al*. Estradiol regulates leptin sensitivity to control feeding via hypothalamic Cited1. *Cell Metab*. 2023;35:438-455.e7.

doi: 10.1016/j.cmet.2023.02.004

29. Hirschberg AL. Sex hormones, appetite and eating behaviour in women. *Maturitas*. 2012;71:248-256.

doi: 10.1016/j.maturitas.2011.12.016

30. Salem AM. Variation of leptin during menstrual cycle and its relation to the hypothalamic-pituitary-gonadal (HPG) axis: A systematic review. *Int J Womens Health*. 2021;13:445-458.

doi: 10.2147/IJWH.S309299

31. Cummings DE, Weigle DS, Frayo RS, *et al*. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med*. 2002;346:1623-1630.

doi: 10.1056/NEJMoa012908

32. Smith A, Woodside B, Abizaid A. Ghrelin and the control of energy balance in females. *Front Endocrinol (Lausanne)*. 2022;13:904754.

doi: 10.3389/fendo.2022.904754

33. Levine JA. Nonexercise activity thermogenesis (NEAT): Environment and biology. *Am J Physiol Endocrinol Metab*. 2004;286:E675-E685.

doi: 10.1152/ajpendo.00562.2003

34. Rosenbaum M, Goldsmith R, Bloomfield D, *et al*. Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. *J Clin Invest*. 2005;115:3579-3586.

doi: 10.1172/JCI25977

35. De Andrade PBM, Neff LA, Strosova MK, *et al*. Caloric restriction induces energy-sparing alterations in skeletal muscle contraction, fiber composition and local thyroid hormone metabolism that persist during catch-up fat upon refeeding. *Front Physiol*. 2015;6:254.

doi: 10.3389/fphys.2015.00254

36. Hall KD. Metabolic adaptations to weight loss. *Obesity (Silver Spring)*. 2018;26:790-791.

doi: 10.1002/oby.22189

37. Sumithran P, Prendergast LA, Delbridge E, *et al*. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med*. 2011;365:1597-1604.

doi: 10.1056/NEJMoa1105816

38. Short KR, Bigelow ML, Kahl J, *et al*. Decline in skeletal muscle mitochondrial function with aging in humans. *Proc Natl Acad Sci USA*. 2005;102:5618-5623.

doi: 10.1073/pnas.0501559102

39. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: A new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol*. 2018;14:576-590.

doi: 10.1038/s41574-018-0059-4

40. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR, Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab*. 2001;86:724-731.

doi: 10.1210/jcem.86.2.7219

41. Greendale GA, Sternfeld B, Huang M, *et al*. Changes in body composition and weight during the menopause transition. *JCI Insight*. 2019;4:e124865.

doi: 10.1172/jci.insight.124865

42. Lovejoy JC, Champagne CM, De Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. *Int J Obes (Lond)*. 2008;32:949-958.

doi: 10.1038/ijo.2008.25

43. Abildgaard J, Pedersen AT, Green CJ, *et al*. Menopause is associated with decreased whole body fat oxidation during exercise. *Am J Physiol Endocrinol Metab*. 2013;304:E1227-E1236.

doi: 10.1152/ajpendo.00492.2012

44. Cruz-Jentoft AJ, Bahat G, Bauer J, *et al*. Sarcopenia: Revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48:16-31.

doi: 10.1093/ageing/afy169

45. De Paoli M, Zakharia A, Werstuck GH. The role of estrogen in insulin resistance: A review of clinical and preclinical data. *Am J Pathol*. 2021;191:1490-1498.

doi: 10.1016/j.ajpath.2021.05.011

46. Heid IM, Jackson AU, Randall JC, *et al*. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat Genet*. 2010;42:949-960.

doi: 10.1038/ng.685

47. Acosta A, Camilleri M, Shin A, *et al*. Association of melanocortin 4 receptor gene variation with satiation and gastric emptying in overweight and obese adults. *Genes Nutr*. 2014;9:384.

doi: 10.1007/s12263-014-0384-8

48. Álvarez-Martín C, Caballero FF, De La Iglesia R, Alonso-Aperte E. Association of *MC4R* rs17782313 genotype with energy intake and appetite: A systematic review and meta-analysis. *Nutr Rev*. 2025;83:e931-e946.

doi: 10.1093/nutrit/nuae075

49. Bjune JI, Strømland PP, Jersin RÅ, Mellgren G, Dankel SN. Metabolic and epigenetic regulation by estrogen in adipocytes. *Front Endocrinol (Lausanne)*. 2022;13:828780.

doi: 10.3389/fendo.2022.828780

50. Lumish HS, O'Reilly M, Reilly MP. Sex differences in genomic drivers of adipose distribution and related cardiometabolic disorders: Opportunities for precision medicine. *Arterioscler Thromb Vasc Biol*. 2020;40:45-60.

doi: 10.1161/ATVBAHA.119.313154

51. El Hajj N, Schneider E, Lehnen H, Haaf T. Epigenetics and life-long consequences of an adverse nutritional and diabetic intrauterine environment. *Reproduction*. 2014;148:R111-R120.

doi: 10.1530/REP-14-0334

52. Deodati A, Inzaghi E, Cianfarani S. Epigenetics and in utero acquired predisposition to metabolic disease. *Front Genet*. 2020;10:1270.

doi: 10.3389/fgene.2019.01270

53. OECD. Caregiving in crisis: Gender inequality in paid and unpaid work during COVID-19. In: *OECD Policy Responses to Coronavirus (COVID-19)*. Paris: OECD Publishing; 2021.

doi: 10.1787/3555d164-en

54. Moroshko I, Brennan L, O'Brien P. Predictors of dropout in weight loss interventions: A systematic review of the literature. *Obes Rev*. 2011;12:912-934.

doi: 10.1111/j.1467-789X.2011.00915.x

55. Keski-Rahkonen A, Mustelin L. Epidemiology of eating disorders in Europe: Prevalence, incidence, comorbidity, course, consequences, and risk factors. *Curr Opin Psychiatry*. 2016;29:340-345.

doi: 10.1097/YCO.0000000000000278

56. Karastergiou K, Smith SR, Greenberg AS, Fried SK. Sex differences in human adipose tissues - the biology of pear shape. *Biol Sex Differ*. 2012;3:13.

doi: 10.1186/2042-6410-3-13

57. Lopez P, Taaffe DR, Galvão DA, *et al*. Resistance training effectiveness on body composition and body weight outcomes in individuals with overweight and obesity across the lifespan: A systematic review and meta-analysis. *Obes Rev*. 2022;23:e13428.

doi: 10.1111/obr.13428

58. Morton RW, Murphy KT, McKellar SR, *et al*. A systematic review, meta-analysis and meta-regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in healthy adults. *Br J Sports Med*. 2018;52:376-384.

doi: 10.1136/bjsports-2017-097608corr1

59. Chew HSJ, Chng S, Rajasegaran NN, Choy KH, Chong YY. Effectiveness of acceptance and commitment therapy on

weight, eating behaviours and psychological outcomes: A systematic review and meta-analysis. *Eat Weight Disord*. 2023;28:6.

doi: 10.1007/s40519-023-01535-6

60. Abbott S, Smith E, Tighe B, Lycett D. Group versus one-to-one multi-component lifestyle interventions for weight management: A systematic review and meta-analysis of randomised controlled trials. *J Hum Nutr Diet*. 2021;34:485-493.

doi: 10.1111/jhn.12853

61. Tate DF, Lutes LD, Bryant M, *et al*. Efficacy of a commercial weight management program compared with a do-it-yourself approach: A randomized clinical trial. *JAMA Netw Open*. 2022;5:e2226561.

doi: 10.1001/jamanetworkopen.2022.26561

62. Pujia C, Ferro Y, Mazza E, Maurotti S, Montalcini T, Pujia A. The role of mobile apps in obesity management: Systematic review and meta-analysis. *J Med Internet Res*. 2025;27:e66887.

doi: 10.2196/66887

63. Wilding JPH, Batterham RL, Calanna S, *et al*. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384:989-1002.

doi: 10.1056/NEJMoa2032183

64. Jastreboff AM, Aronne LJ, Ahmad NN, *et al*. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387:205-216.

doi: 10.1056/NEJMoa2206038

65. Lincoff AM, Brown-Frandsen K, Colhoun HM, *et al*. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389:2221-2232.

doi: 10.1056/NEJMoa2307563