

Strategies for exercise intervention in obesity: an integrated perspective from molecular mechanisms to public health implementation

Abstract

Obesity and its associated complications have emerged as a significant global public health challenge, placing substantial strain on healthcare systems worldwide. As a cost-effective and non-pharmacological strategy, exercise intervention has evolved from generalized recommendations to precise, individualized, and scalable approaches within obesity prevention and management frameworks. This article provides a systematic review of recent advances in exercise-based interventions for obesity, with an in-depth analysis across four key dimensions: novel insights into molecular mechanisms, optimization of personalized precision exercise prescriptions, public health implementation strategies, and considerations for special populations. Specifically, newly identified molecular pathways such as the FOXO1-KLF10 feedback loop and the CD47 signaling target are discussed in detail. Furthermore, evidence-based precision strategies—including optimized combinations of maximal fat oxidation intensity (FATmax) training, high-intensity interval training (HIIT), and moderate-intensity continuous training (MICT), as well as synergistic interventions combining exercise with intermittent fasting—are critically examined. The paper also highlights practical experiences from national-level science and technology initiatives that leverage artificial intelligence and interdisciplinary collaboration to innovate obesity prevention and control. By integrating cutting-edge scientific evidence with actionable insights, this review aims to offer clinicians and public health professionals a comprehensive and practically relevant framework for implementing effective exercise interventions.

Keywords: obesity, exercise intervention, precision prescription, molecular mechanism, public health, fatmax

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Introduction

The global prevalence of obesity has risen steadily in parallel with socioeconomic development and shifts in lifestyle patterns. According to the World Health Organization (WHO), the worldwide obesity rate has increased nearly threefold since 1975, with over 650 million adults currently affected.¹ The epidemiological burden is similarly pronounced in China: the *Report on Nutrition and Chronic Diseases among Chinese Residents (2020)* reports that the overweight and obesity prevalence among Chinese adults exceeds 34% and 16%, respectively.² Consequently, obesity—and its associated metabolic comorbidities—has emerged as a critical public health challenge threatening national health security and sustainable healthcare systems.

Obesity is not merely a chronic metabolic disorder in its own right but also a well-established risk factor for type 2 diabetes mellitus, hypertension, dyslipidemia, non-alcoholic fatty liver disease, cardiovascular diseases, and multiple malignancies.³ Moreover, obesity-related morbidity imposes substantial economic strain on both individuals and society. Recent estimates indicate that obesity-attributable medical expenditures account for more than 6% of China's total national health expenditure.⁴ Within comprehensive obesity prevention and control frameworks, exercise intervention remains a cornerstone strategy—valued for its non-invasiveness, safety profile, high cost-effectiveness, and broad-spectrum health benefits. Yet conventional “one-size-fits-all” multimodal exercise recommendations have demonstrated limited efficacy, largely due to insufficient personalization and mechanistic precision. In recent

years, advances in molecular biology have catalyzed a paradigm shift in exercise-based obesity management: from generalized protocols toward mechanism-informed, individualized interventions; from isolated exercise prescriptions to integrative, multi-domain approaches (e.g., combining exercise with nutritional, behavioral, or digital health modalities); and from clinical settings to scalable, evidence-based community and population-level implementation. This review systematically synthesizes contemporary advances in exercise intervention for obesity—from molecular mechanisms to translational public health applications—and proposes a multilevel, integrated strategic framework to support evidence-informed, practical decision-making by health promotion professionals, clinicians, and public health practitioners.

Physiological basis and mechanisms of exercise intervention in obesity management

Classical physiological models posit that exercise mitigates obesity primarily through energy deficit induction, favorable modulation of body composition (e.g., increased lean mass and reduced adiposity), elevation of resting metabolic rate, enhanced adipose tissue metabolism, and regulation of appetite signaling and central energy homeostasis. In parallel, rapid progress in molecular biology and omics technologies has substantially deepened our understanding of the underlying molecular pathways—such as exercise-induced adaptations in skeletal muscle mitochondrial biogenesis, adipose tissue browning, gut microbiota remodeling, and hypothalamic inflammation resolution—thereby furnishing a robust mechanistic foundation for next-generation, precision-targeted interventions.

Emerging molecular insights into exercise-mediated regulation of energy metabolism

The conventional paradigm posits that exercise-induced weight loss is primarily attributable to increased energy expenditure. However, emerging evidence indicates that exercise exerts multifaceted and highly coordinated regulatory effects on systemic energy metabolism—extending well beyond simple caloric deficit. Notably, physical activity modulates mitochondrial quality control (MQC), facilitating the selective removal of dysfunctional mitochondria via mitophagy and stimulating *de novo* mitochondrial biogenesis, thereby restoring cellular bioenergetic capacity.⁵

Furthermore, exercise influences extracellular matrix (ECM) remodeling and enhances insulin sensitivity,⁶ contributing to the maintenance of tissue homeostasis by mitigating inflammation, fibrosis, and structural damage. Collectively, these adaptations—including amelioration of metabolic dysregulation, anti-inflammatory and antioxidant actions, autophagic flux modulation, mitochondrial functional recovery, stem cell activation, and suppression of aberrant apoptosis—synergistically optimize whole-body energy metabolism.⁷

The FOXO1–KLF10 feedback loop: a central regulatory switch for adipose lipolysis

Transcriptional regulation constitutes a pivotal mechanism underlying exercise-induced metabolic adaptation. A landmark study by Professor Guo Liang's team at Shanghai University of Sport identified KLF10 as a critical adipocyte-intrinsic effector mediating the anti-obesity and metabolic benefits of exercise. Specifically, exercise activates the SIRT1/FOXO1 signaling axis, leading to upregulated KLF10 expression in mature adipocytes. KLF10 forms a transcriptionally active ternary complex with FOXO1 and KDM4A, directly binding to and transactivating the promoters of two rate-limiting lipolytic enzymes—adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL)—thereby enhancing lipolysis.⁸ In diet-induced obese mice, synergistic metabolic improvements were observed upon combined exercise intervention and adipose-specific KLF10 overexpression. Importantly, this FOXO1–KLF10 axis also promotes white-to-beige adipocyte transdifferentiation. Beige adipocytes exhibit multilocular lipid droplets, high mitochondrial density, robust uncoupling protein 1 (UCP1) expression, and potent thermogenic activity—features functionally analogous to classical brown adipose tissue. This finding provides mechanistic validation for the dual benefit of exercise: not only reducing adipose mass but also improving adipose tissue quality and functionality. Consequently, adipose KLF10 represents a promising therapeutic target for obesity and associated metabolic disorders.

CD47: A novel molecular target for exercise mimetics

For individuals with severe obesity, musculoskeletal limitations, or other contraindications to physical activity, pharmacological agents capable of recapitulating the systemic metabolic benefits of exercise—termed “exercise mimetics”—represent a frontier in translational metabolism research. In 2025, a collaborative study led by Professors Li Weida and Gao Shaorong at Tongji University, published in *Cell Reports Medicine*, identified CD47—a ubiquitously expressed transmembrane glycoprotein—as a key molecular mediator of exercise-induced metabolic adaptation.⁹ Although historically characterized for its role in immune checkpoint regulation (“don't eat me” signal), this study revealed that acute and chronic exercise significantly downregulates CD47 expression in skeletal muscle. Critically, CD47 suppression is indispensable for exercise-triggered

AMPK activation and subsequent mitochondrial biogenesis. Leveraging this insight, the authors developed a neutralizing anti-CD47 monoclonal antibody. In preclinical models, CD47 blockade faithfully recapitulated hallmark exercise effects—including skeletal muscle AMPK pathway activation, enhanced mitochondrial respiration, and significant reduction in adiposity—without requiring physical exertion.⁹ Notably, unlike conventional weight-loss interventions, CD47 antibody treatment preserved lean muscle mass while promoting fat loss—effectively circumventing the catabolic trade-off of sarcopenic adiposity. Mechanistically, CD47 inhibition reduces HSP90 α phosphorylation, thereby allosterically activating AMPK without direct pharmacological stimulation—thus avoiding off-target consequences such as cardiac hypertrophy associated with pan-AMPK agonists. These findings establish CD47 as a highly specific, druggable node for next-generation exercise mimetics, offering a viable therapeutic strategy for mobility-limited populations.

The exercise–gut microbiota–metabolism axis

Physical activity represents a critical non-pharmacological intervention for modulating the composition and functional profile of the gut microbiota in adults.¹⁰ A bidirectional, interdependent relationship exists between physical activity and the gut microbiota, characterized by a well-documented dose–response relationship. Consistent engagement in moderate-intensity exercise has been shown to support gut microbial diversity, enhance beneficial microbial metabolite production (e.g., short-chain fatty acids), and promote overall intestinal microecological homeostasis. In contrast, chronic excessive or exhaustive exercise—particularly without adequate recovery—may induce dysbiosis, compromise intestinal barrier integrity, and adversely affect both host health and athletic performance.¹¹

Moderate exercise exerts a beneficial influence on the gut microbiota by enhancing microbial diversity, promoting the proliferation of beneficial bacterial taxa, and increasing the production of health-promoting metabolites. Cross-sectional evidence indicates that professional athletes exhibit significantly greater gut microbial alpha-diversity compared with sedentary controls. Notably, exercise-associated enrichment is observed in probiotic-relevant genera—including *Ruminococcus* and *Akkermansia*—which ferment dietary fiber to generate substantial quantities of short-chain fatty acids (SCFAs). Among these, butyrate serves as the primary energy substrate for colonic epithelial cells, reinforces intestinal barrier integrity, and mediates potent anti-inflammatory effects—partly through inhibition of histone deacetylases. Furthermore, *Veillonella*—a genus consistently enriched in endurance athletes—is capable of metabolizing exercise-induced lactate into propionate, thereby suggesting a direct microbiota–host metabolic crosstalk that may contribute to enhanced exercise capacity and recovery.

The mechanisms underlying the beneficial effects of moderate exercise on intestinal microbiota composition and function are multifaceted. At the metabolic level, exercise enhances the production of short-chain fatty acids (SCFAs) by commensal gut bacteria; these SCFAs enter systemic circulation and activate AMP-activated protein kinase (AMPK)—a central regulator of cellular energy homeostasis in skeletal muscle—thereby improving whole-body glucose homeostasis and insulin sensitivity. At the immunological level, acute exercise induces transient secretion of myokines—including interleukin-6 (IL-6)—which subsequently stimulate the release of anti-inflammatory cytokines such as IL-10. This cascade not only facilitates skeletal muscle fat oxidation and glucose uptake but also establishes a systemic anti-inflammatory milieu conducive to the proliferation and functional

activity of beneficial gut microbes. Furthermore, chronic exercise promotes intestinal secretory immunoglobulin A (sIgA) production and modulates bile acid metabolism. Specifically, exercise-induced alterations in bile acid profiles enhance signaling through nuclear receptors such as the farnesoid X receptor (FXR), thereby fine-tuning host lipid metabolism, energy expenditure, and insulin sensitivity.

Conversely, when exercise intensity and duration exceed physiological tolerance thresholds, the gut-microbiota relationship shifts from symbiotic to dysbiotic. Prolonged high-intensity endurance exercise induces marked sympathetic nervous system activation, resulting in profound splanchnic vasoconstriction and intestinal ischemia. Subsequent oxidative stress damages epithelial tight junctions, increasing intestinal permeability. Concurrently, physical and psychological stress activates the hypothalamic–pituitary–adrenal (HPA) axis, elevating circulating cortisol levels –which further compromises epithelial barrier function. This compromised barrier facilitates translocation of bacterial lipopolysaccharide (LPS) into the bloodstream, initiating low-grade systemic inflammation via Toll-like receptor 4 (TLR4) signaling.¹² Such inflammation exacerbates metabolic dysfunction and fatigue. Microbial community analysis reveals concomitant dysbiosis: a marked reduction in the phylum *Bacteroidetes*, coupled with expansion of the potentially pathogenic phylum *Proteobacteria*, reflecting broad ecological destabilization. This transient post-exercise state –termed the “open window” of immune vulnerability –is associated with heightened infection risk among elite athletes. Consequently, in competitive sports settings, evidence-informed periodization of training load and exploration of targeted microbiome interventions –including precision probiotics, prebiotics, or postbiotics –are essential strategies to preserve gastrointestinal health and sustain performance.

In summary, exercise influences gut microbiota composition and function through integrated metabolic, immunological, neuroendocrine, and biomechanical pathways. Therefore, designing individualized, scientifically grounded exercise regimens represents a cornerstone strategy for optimizing both health promotion and athletic outcomes. Looking ahead, microbiota-targeted interventions hold significant promise as a novel paradigm for enhancing performance, accelerating recovery, and safeguarding long-term athlete health.

Precision strategies for individualized exercise prescription in obesity management

Building upon advances in the physiological and molecular understanding of exercise interventions for obesity, the development of individualized exercise prescriptions has become increasingly evidence-based and scientifically rigorous. Contemporary prescription frameworks have evolved beyond the conventional FITT (Frequency, Intensity, Time, Type) model to adopt the FITT-VP paradigm –incorporating two additional dimensions: Total Volume and Progression. This refinement enhances both the dynamism and personalization of exercise programming, aligning more closely with interindividual variability in metabolic response and functional capacity.

Precision regulation of exercise intensity via fatmax: mechanisms and empirical evidence

Exercise intensity is a pivotal determinant of fat oxidation efficiency; thus, its precise titration represents a central objective in optimizing exercise prescriptions for individuals with obesity. Training at the intensity eliciting maximal fat oxidation (FATmax) has emerged

as a physiologically grounded, individualized strategy, supported by accumulating empirical evidence. A PRISMA-compliant systematic review and meta-analysis integrating data from 64 studies retrieved across EBSCOhost, PubMed, and Scopus provided robust validation for FATmax-guided training.¹³ The analysis focused specifically on adults with obesity –defined as male body fat percentage >25% or female >35% –and systematically characterized the intensity and volume parameters required to elicit peak fat oxidation. Results revealed substantial interindividual variability in FATmax-derived intensity. Among individuals with obesity, FATmax typically occurs at 61–66% of peak heart rate (HR_{peak}); however, this range is modulated by adiposity: individuals with body fat ≥35% exhibit FATmax within 61–66% HR_{peak}, whereas those with body fat <35% demonstrate FATmax at 57–64% HR_{peak}. Notably, relative heart rate –as an intensity metric –exhibits significantly lower interindividual coefficient of variation compared with relative oxygen uptake (%VO_{2peak}),¹⁴ indicating superior reproducibility, feasibility, and clinical utility in real-world settings.

Multiple biological and biomechanical determinants collectively influence the magnitude and kinetics of fat oxidation. First, age exerts a pronounced effect: adolescents demonstrate inherently higher fat oxidation capacity than adults, who consequently require greater training volume to achieve comparable metabolic adaptations. Second, exercise modality matters: treadmill walking consistently yields higher fat oxidation rates than cycle ergometry under matched relative intensities. Third, body composition and cardiorespiratory fitness serve as independent modifiers –specifically, body mass index (BMI), body fat percentage, and peak oxygen uptake (VO_{2peak} ≤ 43 mL·kg⁻¹·min⁻¹) each correlate significantly with fat oxidation efficiency.

With regard to long-term outcomes, a subsequent meta-analysis –including 11 randomized controlled trials sourced from PubMed, Scopus, EBSCOhost, and ScienceDirect –evaluated the effects of 8–20 weeks of FATmax-targeted training on body composition and cardiorespiratory function in adults with obesity. Results demonstrated statistically significant reductions in body weight, total body fat mass, and waist circumference, alongside improvements in VO_{2peak}. Critically, lean body mass remained unchanged, suggesting selective fat loss without concomitant muscle catabolism.¹⁵ Although FATmax typically falls within the moderate-intensity domain (~40–50% VO_{2max}), the marked interindividual heterogeneity in its absolute and relative expression precludes substitution with generic moderate-intensity protocols. Sensitivity analyses –excluding studies involving adolescents or exclusively male cohorts –confirmed consistent effect sizes, underscoring the robustness and generalizability of these findings.

From a pragmatic standpoint, FATmax-guided training demonstrates high feasibility and adherence. A randomized trial conducted among Chinese adults with obesity reported significantly higher 12-week intervention completion rates and greater participant satisfaction in the FATmax group compared with a fixed-intensity control group.¹⁶ Collectively, these findings support a paradigm shift in clinical exercise prescription for obesity –from broad, population-level recommendations (e.g., “moderate-intensity exercise”) toward precision prescriptions anchored to individual FATmax, with heart rate monitoring serving as the preferred, operationally reliable intensity surrogate (Figure 1). Future research should prioritize longitudinal, methodologically rigorous randomized controlled trials to further elucidate underlying molecular mechanisms and refine implementation protocols for diverse clinical populations.

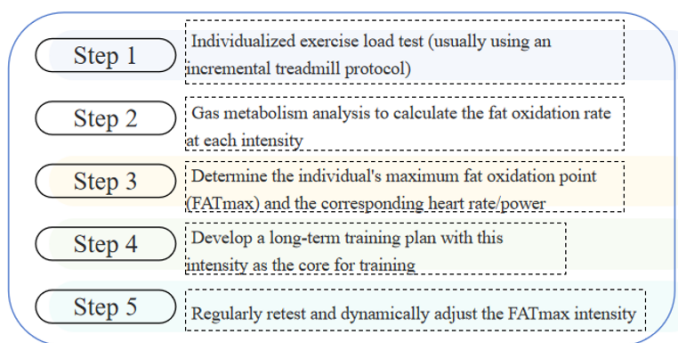


Figure 1 The process of formulating FATmax precise exercise prescriptions.

Optimization of exercise modalities: integrating aerobic, resistance, and high-intensity interval training

Different exercise modalities exert distinct physiological effects on body composition and metabolic health; therefore, evidence-informed integration of these modalities is essential to maximize therapeutic outcomes.

Aerobic exercise serves as the cornerstone for enhancing cardiorespiratory fitness and promoting fat oxidation. A network meta-analysis evaluating the efficacy of various exercise interventions in individuals with obesity demonstrated that aerobic training yielded the greatest reduction in visceral adipose tissue volume.¹⁷ Resistance training primarily modulates energy balance indirectly –by preserving or increasing lean body mass –and is consistently identified as the most effective modality for augmenting skeletal muscle mass.¹⁷ Notably, resistance training confers unique metabolic benefits, particularly in improving insulin sensitivity –a mechanism potentially mediated by upregulated expression of glucose transporter type 4 (GLUT4) in skeletal muscle and enhanced muscle quality.¹⁸ High-intensity interval training (HIIT) has gained prominence owing to its time efficiency and pronounced post-exercise oxygen consumption (EPOC), which contributes to sustained energy expenditure. However, current evidence indicates that HIIT does not surpass moderate-intensity continuous training (MICT) in overall weight loss efficacy. A comprehensive meta-analysis encompassing 42 randomized controlled trials reported that although HIIT achieves greater fat loss per unit time, its effect on visceral fat reduction is statistically equivalent to that of MICT.¹⁹ The principal advantages of HIIT lie in its favorable impact on insulin sensitivity and time economy; however, its elevated biomechanical and cardiovascular demands render it less appropriate as an initial intervention for sedentary or obese novice exercisers.¹⁹

Joint training –defined as the concurrent integration of aerobic and resistance exercise –is widely recognized as the most efficacious strategy for optimizing body composition and enhancing metabolic health. A recent meta-analysis demonstrated that joint training yields significantly greater improvements in key physiological parameters –including body fat percentage, visceral adipose tissue area, and insulin sensitivity –compared with either aerobic or resistance training performed in isolation.²⁰

Synergistic effects of exercise and adjunct interventions: intermittent fasting as a complementary strategy

Monotherapy approaches to metabolic health improvement are inherently limited in scope and sustainability. In contrast, multimodal interventions demonstrate substantially enhanced efficacy and durability. As illustrated in Figure 2, the integration of structured

exercise with intermittent fasting represents a particularly promising combinatorial paradigm. A meta-analytic synthesis confirmed that the combined protocol of “regular exercise plus intermittent fasting” produced statistically and clinically superior outcomes relative to either intervention alone, with significant improvements observed in fat mass reduction, waist circumference, fasting blood glucose concentration, and insulin resistance index.²¹ Mechanistically, this synergy may be mediated through coordinated activation of AMP-activated protein kinase (AMPK), modulation of autophagic flux, and favorable remodeling of gut microbiota composition. Notably, follow-up data revealed that participants in the combined-intervention group exhibited a significantly higher weight maintenance rate at the 6-month post-intervention assessment compared with those receiving single-modality treatment –suggesting that this integrative approach may mitigate the risk of weight regain and support long-term metabolic stability.²²

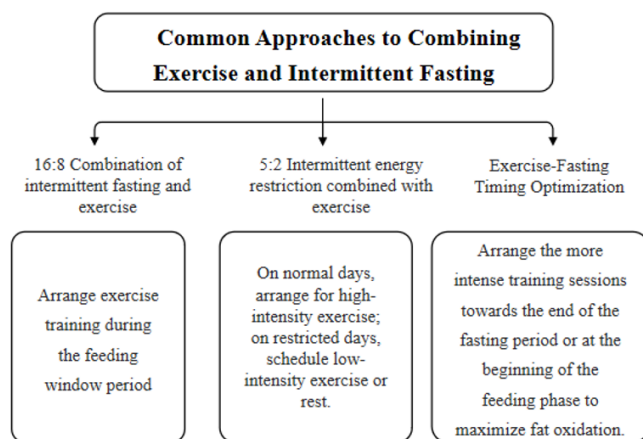


Figure 2 Common combinations of exercise and intermittent eating.

Temporal biological considerations in exercise interventions

Emerging evidence indicates that the timing of exercise –relative to an individual’s circadian rhythm –significantly modulates its metabolic effects. Specifically, chronic low-intensity exercise performed in the evening (i.e., prior to habitual sleep onset) has been associated with superior outcomes in weight management, skeletal muscle contractile function, and glucose tolerance compared with morning exercise following wakefulness. These time-dependent effects are mechanistically linked to core circadian regulators –such as BMAL1 and CLOCK –in skeletal muscle tissue.²³ Collectively, these findings underscore the potential value of incorporating chronobiological parameters into precision exercise prescription frameworks. While evidence-based temporal guidelines remain under development, integrating circadian timing represents a promising frontier for optimizing exercise efficacy in clinical and public health contexts.

Scaling evidence-based exercise interventions for public health impact

Bridging the translational gap between rigorously validated exercise prescriptions –developed in controlled research and clinical settings –and real-world population-level implementation is essential to mitigating the global obesity epidemic. Precision interventions tailored to individual physiological and behavioral risk profiles complement, rather than compete with, population-level public health

strategies; their synergistic application enhances both reach and effectiveness. Experiences from China offer instructive models in this domain.

National-level strategic design and digital enabling infrastructure

The national innovation-driven initiative on “Four Major Chronic Diseases” exemplifies a systems-level approach to scalable exercise intervention. Its primary objective is to develop, validate, and disseminate standardized yet adaptable exercise-based obesity prevention and management models across diverse regional and demographic contexts.²⁴ A defining feature of this initiative is the integration of artificial intelligence (AI) into a unified digital health platform, which dynamically generates fully individualized exercise and lifestyle plans. Intervention delivery follows a phased, longitudinal framework –comprising “exercise adaptation,” “progressive intensity optimization,” and “sustained behavior consolidation” –to support long-term adherence and physiological benefit (Figure 3).²⁴

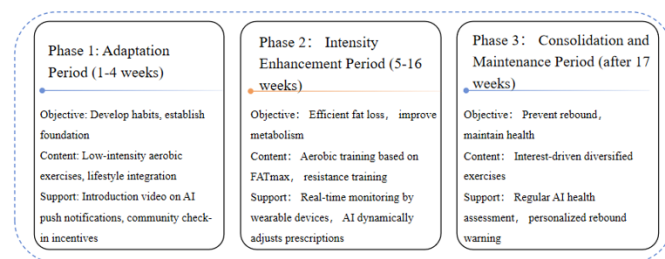


Figure 3 Three-stage practice model of AI-enabled obesity exercise intervention.

The project is characterized by four core attributes: (1) multidisciplinary integration, (2) dynamic adaptability, (3) deep technological embedding, and (4) economic sustainability. First, it synthesizes domain-specific expertise from clinical medicine, sports science, nutrition, psychology, and behavioral science to construct a holistic, evidence-informed intervention framework. Second, it incorporates real-time responsiveness –intervention protocols are iteratively refined based on longitudinal participant data, including physiological metrics, behavioral feedback, and adherence patterns. Third, it leverages a synergistic digital infrastructure comprising wearable biosensors, mobile health platforms, and cloud-based remote monitoring systems to enable end-to-end digital health management. Fourth, it embeds rigorous cost-benefit and scalability analyses throughout the design and implementation phases, ensuring fiscal prudence and translational feasibility across diverse healthcare settings.

Localized model development and comparative validation

Within the overarching national framework, regional sub-centers have pursued context-sensitive implementation strategies aligned with local resource capacities and infrastructural conditions. As a representative case, five districts in Chongqing concurrently piloted three distinct intervention models: (i) the *Professional Empowerment Model*, delivered by hospital-based multidisciplinary teams (e.g., physicians, registered dietitians, and rehabilitation specialists), designed for complex, comorbid cases and optimized for tertiary care environments; (ii) the *Community Collaboration Model*, implemented primarily by trained community health workers and certified physical activity instructors, emphasizing operational efficiency, affordability, and scalability within primary care and

community-based settings; and (iii) the *Family-Centered Self-Management Model*, which empowers participants and caregivers through interoperable mobile applications and smart health devices to support autonomous goal setting, progress tracking, and behavioral reinforcement. These parallel implementations constitute a pragmatic, quasi-experimental comparative evaluation aimed at generating robust, real-world evidence on model-specific effectiveness, cost-efficiency, and contextual fit –thereby informing differentiated policy recommendations for regions with heterogeneous resource endowments. Preliminary findings indicate comparable short-term (3-month) weight reduction outcomes across all three models ($p > 0.05$); however, at 12 months, the Professional Empowerment Model demonstrates superior long-term weight maintenance and metabolic parameter improvement (e.g., HbA1c, systolic BP), albeit at significantly higher per-capita cost. In contrast, the Community Collaboration Model achieves the most favorable incremental cost-effectiveness ratio (ICER), supporting its prioritization for large-scale public health deployment.²⁵

Policy enablers and health ecosystem integration

Sustained scaling of exercise-based interventions necessitates deliberate alignment with enabling policy structures and systemic health ecosystem reforms. Four interdependent strategies are proposed: (i) reforming health insurance reimbursement mechanisms to formally recognize and reimburse evidence-based exercise prescription and supervised physical activity counseling; (ii) institutionalizing sport-medicine convergence through standardized certification pathways for “Exercise Prescription Specialists,” thereby bridging professional silos and regulatory fragmentation; (iii) strengthening the built environment for physical activity –such as expanding accessible public recreation facilities, redesigning pedestrian- and cyclist-friendly urban infrastructure, and integrating movement-promoting design into community planning; and (iv) fostering a regulated innovation ecosystem for digital health tools, including evidence generation requirements, interoperability standards, and post-market surveillance frameworks. Empirical evidence from urban China corroborates the foundational role of environmental enablers: multivariate analysis revealed that objective measures of neighborhood walkability (e.g., street connectivity, land-use mix, sidewalk quality) were positively associated with residents’ weekly moderate-to-vigorous physical activity levels ($\beta = 0.32, p < 0.001$) and inversely associated with age- and sex-adjusted obesity prevalence (OR = 0.78, 95% CI: 0.69–0.88), underscoring the critical importance of ecological, rather than solely individual-level, approaches to obesity prevention and control.²⁶

Exercise intervention strategies for priority populations

Given the substantial heterogeneity observed among individuals with obesity, tailored exercise intervention strategies must be developed to address the distinct physiological, metabolic, and behavioral characteristics of specific subpopulations.

For older adults with obesity –particularly those presenting with sarcopenic obesity–a comprehensive, evidence-informed intervention integrating moderate caloric restriction with multimodal exercise is strongly recommended. This approach encompasses aerobic training, progressive resistance exercise, and balance-focused activities, and is designed not only to support sustainable weight management but also to preserve skeletal muscle mass and bone mineral density, enhance functional mobility, and ameliorate systemic inflammation.²⁷ Specifically, current guidelines advise accumulating 150–200 minutes per week of moderate-intensity aerobic activity, complemented by two

to three weekly sessions of moderate-to-vigorous resistance training and at least two sessions of structured balance training to mitigate age-related muscle loss and reduce fall risk.²⁸

In children and adolescents with obesity, interventions should prioritize engagement, sustainability, and ecological validity. Strategies emphasizing enjoyable physical activities—including interactive sports games, team-based movement programs, and family-involved lifestyle coaching—combined with evidence-based screen time regulation, have demonstrated superior long-term adherence and more consistent improvements in adiposity, cardiometabolic health, and psychosocial well-being.²⁹

For individuals with obesity and coexisting chronic conditions, exercise prescriptions require careful clinical customization: patients with osteoarthritis or other weight-bearing joint limitations are advised to engage in low-impact modalities such as aquatic exercise and stationary cycling; individuals with hypertension should avoid Valsalva maneuvers and high-intensity resistance efforts, and instead emphasize sustained aerobic activity with gradual progression; and persons with diabetes must integrate real-time glycemic monitoring, strategic timing of physical activity relative to meals and pharmacotherapy (including insulin), and individualized hypoglycemia prevention protocols to ensure safety and efficacy.

Challenges and future directions

Despite notable advances in exercise-based obesity management, several persistent challenges impede widespread implementation and long-term effectiveness: high rates of weight regain following initial loss, suboptimal adherence to prescribed regimens, marked interindividual variability in physiological and metabolic responses to exercise, a critical shortage of qualified exercise professionals trained in clinical obesity care, and fragmented integration of exercise interventions within broader healthcare delivery systems.

Future progress will hinge on five converging translational priorities: (i) advancing precision exercise medicine through discovery and validation of molecular, physiological, and digital biomarkers to inform individualized exercise dosing and modality selection; (ii) developing pharmacological or neuromuscular “exercise mimetics” capable of replicating key metabolic and anti-inflammatory adaptations in individuals with absolute or relative contraindications to physical activity; (iii) leveraging artificial intelligence, remote monitoring, and wearable biosensors to enable dynamic, real-time risk stratification, adaptive feedback, and personalized behavior support; (iv) embedding empirically validated behavior change techniques—including motivational interviewing, habit formation frameworks, and social accountability mechanisms—into scalable intervention models to sustain engagement across the lifespan; and (v) adopting a life-course perspective that informs developmentally appropriate, context-sensitive strategies—from preconception and early childhood through adolescence, adulthood, and advanced aging—to build resilient, equitable, and system-wide obesity prevention and management infrastructure.

Conclusion

Exercise remains a cornerstone, non-pharmacologic strategy in the global response to obesity—yet its full potential can only be realized through rigorously evidence-based, systematically implemented, and human-centered intervention design. This review synthesizes recent scientific advances across multiple levels of analysis, culminating in an integrated framework spanning molecular mechanisms, individual

clinical practice, and population-level public health action. Key insights include: at the molecular level, identification of regulatory axes such as the FOXO1–KLF10 feedback loop and emerging therapeutic targets including CD47 opens new avenues for mechanism-driven intervention and drug discovery; at the individual level, approaches such as FATmax-guided aerobic training, concurrent aerobic-resistance programming, and synergistic combinations of exercise with time-restricted eating demonstrate enhanced efficacy for fat oxidation, metabolic flexibility, and body composition remodeling; at the population level, nationally coordinated initiatives—complemented by locally adapted, community-engaged implementation models—have accelerated the translation of exercise science into scalable, real-world practice; and for vulnerable subgroups—including older adults—clinically nuanced, comorbidity-aware, and musculoskeletal-preserving exercise prescriptions are essential. Ultimately, an optimal exercise intervention ecosystem rests upon three foundational pillars: a robust, continuously updated evidence base; precision-tailored clinical prescriptions grounded in individual phenotyping and longitudinal monitoring; and a coordinated, multisectoral public health infrastructure-supported by policy, technology, environmental redesign, and cross-disciplinary workforce development. Achieving meaningful impact on the obesity pandemic demands deeper synergy between clinical science and public health practice, sustained investment in implementation research, and unwavering commitment to equity, accessibility, and person-centered care.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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