# The Exercise Pillar of Lifestyle Medicine: Emerging Evidence, Novel Modalities, Molecular Mechanisms, and Pharmacological Synergies.


## Abstract

Background: Physical activity, one of the six foundational pillars of lifestyle medicine, is arguably the most potent non-pharmacological intervention available for the prevention and management of non-communicable diseases (NCDs). Recent years have witnessed transformative evidence—from landmark randomized controlled trials demonstrating exercise-driven cancer survival benefits to the discovery of novel ultra-short activity paradigms and exercise-derived molecular mediators—that collectively redefine the scope and practice of exercise prescription within lifestyle medicine.

**Objective**: This narrative review synthesizes emerging and paradigm-shifting evidence on the exercise pillar of lifestyle medicine, focusing on four interconnected frontiers: (1) Exercise is Medicine and exercise prescription for NCDs, (2) novel exercise modalities including vigorous intermittent lifestyle physical activity (VILPA) and exercise snacking, (3) the gut-brain axis, exerkines, and molecular mechanisms of exercise, and (4) exercise as an adjunct to pharmacotherapy, particularly with GLP-1 receptor agonists and antidepressants.

**Methods**: A structured literature search was conducted in PubMed, Scopus, and Google Scholar using keywords including "exercise prescription," "lifestyle medicine," "VILPA," "exercise snacking," "exerkines," "Lac-Phe," "myokines," "GLP-1 exercise," and "exercise oncology," with emphasis on publications from 2022 through March 2026.

**Results**: Level 1 evidence from the CHALLENGE trial (NEJM, 2025) demonstrates that structured exercise after adjuvant chemotherapy for colon cancer reduces cancer recurrence by 28% and death by 37%, rivaling many approved drug therapies. VILPA research from the UK Biobank reveals that as little as 1.2–3.4 minutes per day of vigorous incidental activity reduces major cardiovascular events by 30–45% in non-exercising women. The exerkine Lac-Phe, identified as the most exercise-responsive metabolite, opens new avenues for biomarker-guided exercise prescription and pharmacological adjuncts. Meanwhile, the synergy between

structured exercise and GLP-1 receptor agonists addresses the critical clinical challenge of lean mass preservation during pharmacological weight loss.

**Conclusion**: The exercise pillar of lifestyle medicine is undergoing a scientific renaissance. Integrating traditional exercise prescription with novel modalities, molecular biomarkers, and pharmacological synergies offers an unprecedented opportunity to personalize and optimize physical activity interventions across the spectrum of chronic disease.

**Keywords:** *lifestyle medicine, exercise prescription, VILPA, exercise snacking, exerkines, Lac-Phe, GLP-1 receptor agonists, exercise oncology, physical activity, non-communicable diseases*

## 1. Introduction

Physical inactivity is recognized as the fourth leading risk factor for global mortality, contributing to an estimated 3.2 million deaths annually and approximately 7.2% of the global burden of disease [1, 2]. Despite decades of public health messaging and accumulating evidence, more than one-quarter of the world's adult population—approximately 1.4 billion people—remain insufficiently active [3]. This global inactivity pandemic imposes an enormous and growing burden on healthcare systems, economies, and individual well-being.

Lifestyle medicine, defined as the evidence-based practice of assisting individuals and families in adopting and sustaining healthful behaviors, is organized around six foundational pillars: a whole food, plant-predominant eating pattern; regular physical activity; restorative sleep; stress management; positive social connectedness; and avoidance of risky substances [4, 5]. Among these pillars, physical activity occupies a uniquely central position, not only because of its direct health benefits but also because of its documented positive influence on all other pillars—including sleep quality, stress resilience, dietary behavior, and substance avoidance [6].

The years 2024–2026 have been transformative for the exercise pillar. A phase 3 randomized trial published in the New England Journal of Medicine provided the first definitive level 1 evidence that structured exercise reduces cancer recurrence and extends survival [7, 8]. Simultaneously, wearable technology-enabled research has identified vigorous intermittent lifestyle physical activity (VILPA)—activity bouts as short as one minute—as a potent and accessible health intervention [12–14]. The discovery of exercise-induced metabolites (exerkines) such as N-lactoyl-phenylalanine (Lac-Phe) has opened molecular windows into

how exercise communicates health benefits across organ systems [24, 26]. And the rapid expansion of GLP-1 receptor agonist prescriptions for obesity has created an urgent clinical need for exercise strategies that preserve lean mass during pharmacological weight loss [39–41].

This narrative review synthesizes these converging frontiers to provide a comprehensive, clinically actionable overview of the exercise pillar as it stands in 2026—and where it is heading.

## 2. Exercise is Medicine: From Prescription to Precision

### 2.1 The Polypill Analogy and Exercise Prescription

The concept of exercise as a 'polypill'—a single intervention with simultaneous benefits across multiple organ systems—is now firmly established [34]. Systematic reviews consistently demonstrate that regular physical activity reduces all-cause mortality by 30–35%, cardiovascular mortality by 20–35%, incident type 2 diabetes by 25–40%, depression by 20–30%, and the risk of at least 13 cancer types by 10–20% [2, 6, 55]. A landmark metaepidemiological study by Naci and Ioannidis found that exercise interventions achieved mortality reductions comparable to drug therapies for coronary heart disease, stroke rehabilitation, and heart failure [62].

Despite this evidence, exercise remains the most underutilized intervention in medicine. The Exercise is Medicine (EIM) initiative, launched by the American College of Sports Medicine and the American Medical Association, advocates for the systematic integration of physical activity assessment and prescription into routine clinical care [53, 54]. The EIM framework uses the FITT principle (Frequency, Intensity, Time, Type) to guide individualized prescriptions, aligned with the WHO 2020 guidelines recommending 150–300 minutes per week of moderate-intensity or 75–150 minutes per week of vigorous-intensity activity [11].

The paradigm is now shifting from generic population-level recommendations toward precision exercise prescription—tailoring modality, intensity, duration, and timing to individual patient characteristics, comorbidities, genomic profiles, and biomarker responses. This evolution parallels the broader trajectory of precision medicine and represents a critical advancement for lifestyle medicine practice.

### 2.2 The CHALLENGE Trial: Exercise as Cancer Medicine

Perhaps the most consequential development in exercise science in 2025 was the publication of the CHALLENGE trial in the New England Journal of Medicine [7]. This phase 3, multicenter, randomized trial enrolled 889 patients with resected stage II–III colon cancer who had completed adjuvant chemotherapy, assigning them to either a 3-year structured exercise program with behavioral support or a health-education control group.

At a median follow-up of 7.9 years, the structured exercise group demonstrated a 28% reduction in the composite endpoint of disease recurrence, new primary cancer, or death (HR 0.72; 95% CI, 0.55–0.94; P=0.02). The 5-year disease-free survival was 80.3% in the exercise group versus 73.9% in the control group. More remarkably, the 8-year overall survival was 90.3% versus 83.2%, representing a 37% reduction in all-cause mortality (HR 0.63; 95% CI, 0.42–0.96) [7].

As eloquently noted in the accompanying editorial, if exercise were a pill producing these effect sizes, it would receive FDA priority review and headline every oncology conference [8]. The CHALLENGE trial represents definitive level 1 evidence that structured exercise is not merely supportive care but a therapeutic intervention with survival benefits comparable to established pharmacotherapies.

For lifestyle medicine practitioners, this trial validates the clinical urgency of integrating exercise prescription into post-cancer survivorship care and provides a scalable model—involving periodic consultations with physical activity consultants and individualized exercise prescriptions—that is feasible across healthcare settings [9].

### 2.3 Exercise and Cognitive Decline: The POINTER Trial

The US-POINTER trial, published in JAMA in 2025, examined the effects of a 2-year multicomponent lifestyle intervention—with exercise as a core component—on cognitive trajectories in older adults at risk for dementia [10]. The trial demonstrated that structured physical activity, combined with dietary counseling and cognitive training, significantly slowed cognitive decline compared to a health-education control, adding to the growing evidence that exercise is among the most effective strategies for preserving brain health in aging populations.

Importantly, a 2025 systematic review and meta-analysis demonstrated that fitness level—assessed by objective exercise testing—is a more powerful predictor of cardiovascular and all-cause mortality than body mass index. Fit individuals showed no statistically significant

increase in mortality regardless of BMI category, fundamentally challenging the notion that weight alone determines cardiometabolic risk [68].

## 3. Novel Exercise Modalities: Rethinking the Dose-Response

### 3.1 Vigorous Intermittent Lifestyle Physical Activity (VILPA)

Perhaps the most paradigm-shifting development in physical activity research is the emergence of VILPA—vigorous intermittent lifestyle physical activity. Defined as brief, sporadic bouts (up to 1–2 minutes) of vigorous-intensity physical activity performed as part of daily living—such as brisk stair climbing, carrying heavy shopping, uphill or power walking, or playing energetically with children—VILPA requires no dedicated exercise time, equipment, or facility access [12, 13].

Using wrist-worn accelerometry data from the UK Biobank, Stamatakis et al. demonstrated in a landmark 2022 Nature Medicine publication that a median of 4.4 minutes of daily VILPA was associated with a 26–30% reduction in all-cause and cancer mortality and a 32–34% reduction in cardiovascular mortality among non-exercising adults [13]. Subsequent studies have extended these findings: VILPA was associated with lower cancer incidence across 13 cancer types (JAMA Oncology, 2023) [15], and a 2025 Circulation study established dose-response relationships between incidental physical activity and cardiovascular events [16].

A particularly striking 2025 study in the British Journal of Sports Medicine revealed pronounced sex differences in VILPA responses. Among non-exercising women aged 40–79, as little as 1.2–1.6 minutes of daily VILPA was associated with a 30% lower risk of major adverse cardiovascular events, a 33% lower risk of myocardial infarction, and a 40% lower risk of heart failure. Women averaging 3.4 minutes daily achieved a 45% reduction in total cardiovascular events and a 67% reduction in heart failure risk [14]. These effect sizes are remarkable for such minimal time investment and have profound implications for exercise prescription in populations unable or unwilling to engage in structured exercise.

A 2025 pilot RCT in adults transitioning to retirement demonstrated that a 12-week VILPA intervention was feasible, acceptable, and associated with increases in total physical activity, self-reported health, and functional fitness [21]. VILPA-based interventions are now being replicated in US cohorts using NHANES data, confirming the generalizability of these findings to nationally representative populations [17].

### 3.2 Exercise Snacking and Micro-Workouts

Complementing the VILPA paradigm, the concept of 'exercise snacking'—brief, isolated bouts of structured exercise interspersed throughout the day—has gained traction as a practical strategy for metabolically inactive populations [18]. Unlike VILPA, which is incidental and unplanned, exercise snacks are deliberate but ultra-short: typically 20–60 seconds of intense activity (stair climbing, squats, jumping jacks) performed 2–3 times daily.

Both VILPA and exercise snacking challenge the traditional assumption that meaningful health benefits require sustained, moderate-to-vigorous activity sessions of 10 minutes or more. The 2020 WHO guidelines already removed the previous 10-minute minimum bout requirement, acknowledging that every minute of movement counts [11]. VILPA and exercise snacking operationalize this principle in ways that are particularly relevant for time-poor, sedentary, or mobility-limited populations—precisely those most in need of lifestyle medicine interventions.

### 3.3 High-Intensity Interval Training (HIIT) and Reduced-Volume Protocols

High-intensity interval training (HIIT) continues to evolve as an evidence-based, time-efficient alternative to moderate-intensity continuous training. Systematic reviews confirm that HIIT produces comparable or superior improvements in cardiorespiratory fitness ($VO_2max$), glycemic control, body composition, and endothelial function relative to traditional exercise, while requiring 40–60% less time commitment [18, 19].

Reduced-volume HIIT protocols—involving as few as 3 × 20-second maximal efforts within a 10-minute session—have demonstrated meaningful improvements in insulin sensitivity and mitochondrial capacity in both healthy and clinical populations. For lifestyle medicine practitioners, HIIT represents a pragmatic tool for addressing the perennial barrier of time scarcity, provided that appropriate screening, contraindication assessment, and progressive programming are applied.

## 4. The Molecular Language of Exercise: Exerkines and the Gut-Brain Axis

### 4.1 Exerkines: Exercise as Molecular Medicine

One of the most exciting developments in exercise science is the recognition that skeletal muscle—comprising 40–50% of body mass—functions as a major endocrine organ, releasing hundreds of bioactive molecules during contraction [23, 25]. These exercise-induced

signaling molecules, collectively termed 'exerkines,' include muscle-derived myokines (e.g., irisin, IL-6, BDNF, cathepsin B), liver-derived hepatokines, adipose-derived adipokines, and circulating metabolites [24].

Exerkines mediate the inter-organ communication that underpins the systemic benefits of exercise: metabolic regulation, immune modulation, neuroprotection, anti-inflammation, and tissue repair [24, 25]. Over 200 distinct myokines have been catalogued, constituting what has been termed the 'myokinome' [32]. The therapeutic implications are profound: understanding the exerkine profile of exercise could enable biomarker-guided exercise prescription, identification of non-responders, and development of pharmacological adjuncts that enhance or mimic exercise responses.

### 4.2 N-Lactoyl-phenylalanine (Lac-Phe): A Paradigm-Shifting Exerkine

Among recent exerkine discoveries, N-lactoyl-phenylalanine (Lac-Phe) stands out as the most significantly exercise-responsive metabolite identified through untargeted metabolomics in both mice and humans [26]. Lac-Phe is a conjugate of lactate and phenylalanine, synthesized by the enzyme CNDP2. A pivotal 2022 Nature paper demonstrated that Lac-Phe suppresses food intake and reduces obesity in mouse models, providing a molecular explanation for exercise-induced appetite regulation [26].

Subsequent research has established that Lac-Phe levels are exercise-intensity-dependent, rising most dramatically after vigorous activity, and that higher post-exercise Lac-Phe predicts greater adipose tissue loss during endurance training in overweight humans [27]. Beyond appetite regulation, Lac-Phe has been shown to exert anti-inflammatory effects, with a 2025 study demonstrating amelioration of experimental colitis through suppression of M1 macrophage polarization via NF-κB signaling inhibition [28].

Intriguingly, metformin—a drug with established exercise-mimetic properties—also elevates circulating Lac-Phe levels, suggesting convergent molecular mechanisms between pharmacological and exercise-induced metabolic pathways [29]. Lac-Phe may serve dual roles as both a biomarker for personalizing exercise intensity prescriptions and a therapeutic target for populations unable to exercise.

### 4.3 Irisin, SPARC, and the Expanding Myokine Landscape

Irisin, a PGC-1α-dependent myokine cleaved from the FNDC5 precursor during exercise, promotes browning of white adipose tissue, enhances thermogenesis, and exerts neurotrophic

effects including support for hippocampal neurogenesis and BDNF expression [31]. Its role as a mediator of the exercise-brain connection continues to attract research interest, particularly in neurodegenerative and psychiatric disorders.

SPARC (secreted protein acidic and rich in cysteine), recently highlighted as the myokine that increases most significantly following exercise, has been proposed as a leading candidate for exercise-mimicking therapeutic development [30]. Unlike narrowly acting myokines, SPARC confers broad, multi-tissue effects spanning tissue remodeling, angiogenesis, and tumor suppression, and its endogenous nature may minimize adverse effect risk [30].

### 4.4 The Gut-Brain Axis and Exercise

Emerging evidence connects physical activity to the gut microbiome, with regular exercise associated with increased microbial diversity, enrichment of short-chain fatty acid (SCFA)-producing bacteria, and improved intestinal barrier integrity. The gut-brain axis—bidirectional communication between enteric and central nervous systems—provides a mechanistic framework linking exercise-induced microbiome changes to improvements in mood, cognition, and neuroinflammation.

The discovery that exercise-derived metabolites like Lac-Phe also modulate intestinal inflammation [28] suggests that the exerkine concept extends to gut-brain signaling, creating a 'muscle-gut-brain axis' that may partially explain the antidepressant, anxiolytic, and neuroprotective effects of physical activity. This area is rapidly evolving and holds promise for informing both exercise prescription and dietary/probiotic adjunctive strategies within the lifestyle medicine framework.

## 5. Exercise as Adjunct to Pharmacotherapy

### 5.1 Exercise and GLP-1 Receptor Agonists: The Muscle Preservation Imperative

The rapid global expansion of GLP-1 receptor agonist (GLP-1 RA) prescriptions for obesity and type 2 diabetes has created one of the most pressing clinical questions in contemporary lifestyle medicine: how to preserve lean body mass during pharmacological weight loss [39, 40]. Clinical evidence consistently shows that weight reduction with GLP-1 RAs is accompanied by loss of lean mass accounting for 15–40% of total weight lost, raising significant concerns about therapy-induced sarcopenia, particularly in elderly patients and those with pre-existing muscle wasting [39, 41].

Structured resistance training is emerging as the cornerstone strategy for mitigating GLP-1 RA-associated muscle loss. A landmark NEJM trial demonstrated that combination of exercise with liraglutide achieved superior weight loss maintenance compared to either intervention alone, while better preserving lean mass [42]. A subsequent study confirmed that combined exercise and GLP-1 RA treatment reduces the severity of metabolic syndrome, abdominal obesity, and systemic inflammation more effectively than either alone [43].

A 2025 JAMA Internal Medicine perspective emphasized that integrating diet and physical activity when prescribing GLP-1s is not optional but essential, and that lifestyle factors remain crucial regardless of pharmacological intervention [44]. For lifestyle medicine practitioners, this represents both a clinical imperative and a professional opportunity: the GLP-1 era does not diminish the importance of the exercise pillar but rather amplifies it.

Emerging pharmacological approaches—including myostatin inhibitors (e.g., bimagrumab), activin receptor antagonists, and exercise mimetics such as ERR agonists—are being investigated as adjuncts to preserve or enhance muscle mass during GLP-1 RA therapy [45, 46, 47]. The convergence of exercise science, pharmacology, and lifestyle medicine in this space is likely to define a major frontier of clinical practice in the coming decade.

### 5.2 Exercise and Antidepressant Therapy: The Muscle-Brain Axis

Exercise is a potent antidepressant, with meta-analyses demonstrating effect sizes comparable to pharmacotherapy and psychotherapy for mild-to-moderate depression [35, 37]. A comprehensive 2023 overview of systematic reviews in the British Journal of Sports Medicine confirmed that physical activity interventions effectively reduce depression, anxiety, and psychological distress across diverse populations, with vigorous-intensity activities yielding the largest benefits [37].

However, a cruel paradox of depression is that the illness itself often robs patients of the motivation, energy, and psychomotor capacity to initiate physical activity [36]. A 2026 Molecular Psychiatry paper by Fabiano et al. proposed exercise mimetics as unexplored therapeutics for depression, leveraging the 'muscle-brain axis'—the biochemical signaling from contracting muscle to brain—to deliver antidepressant effects pharmacologically [36].

The authors proposed that exercise mimetics could serve as a 'pharmacological bridge,' providing sufficient AMPK–PGC-1α activation and downstream myokine release to overcome the motivational paralysis of severe depression, enabling patients to gradually re-

engage with physical activity and behavioral activation [36]. This framework complements, rather than replaces, both traditional antidepressant pharmacotherapy and exercise prescription.

For lifestyle medicine practice, this emerging evidence supports the integration of exercise prescription with psychiatric pharmacotherapy—using antidepressants or exercise mimetics to lower the threshold for physical activity engagement, and using physical activity itself as a therapeutic multiplier that enhances medication efficacy, promotes neuroplasticity, and builds long-term resilience.

### 5.3 Exercise Mimetics: Complementing the Exercise Pillar

The nascent field of exercise mimetics—pharmacological agents that activate molecular pathways normally triggered by exercise—is increasingly relevant to lifestyle medicine [47, 48, 50]. Candidate compounds include AICAR (AMPK activator), GW501516 (PPARδ agonist), SLU-PP-332 (ERR pan-agonist), resveratrol, metformin, urolithin A, and NAD+ precursors [46, 47].

While a 2025 comprehensive review persuasively argued that no pill can fully replicate the complex, multisystemic 'exercise milieu'—encompassing hemodynamic, mechanical, neuroendocrine, and psychosocial stimuli [46]—exercise mimetics may serve important roles in specific clinical contexts: as adjuncts for patients who cannot exercise due to paralysis, severe frailty, or acute illness; as enhancers of suboptimal exercise responses; and as muscle-protective agents during GLP-1 RA therapy or cancer cachexia.

For lifestyle medicine practitioners, exercise mimetics should not be viewed as competitors to the exercise pillar but as potential allies—extending the reach of physical activity's benefits to populations currently unreached by conventional exercise prescription.

## 6. Integrating the Exercise Pillar: A Lifestyle Medicine Framework

The exercise pillar does not operate in isolation. Physical activity synergizes with every other lifestyle medicine pillar: it improves sleep architecture, reduces stress biomarkers and cortisol reactivity, enhances dietary self-regulation through exerkine-mediated appetite control, supports smoking cessation by modulating reward circuitry, and strengthens social connectedness through group-based activities [5, 6, 22].

A 2025 BMC Medicine study by Stamatakis et al. examined minimum and optimal combined variations in sleep, physical activity, and nutrition in relation to all-cause mortality, finding that the combination of adequate physical activity with sufficient sleep and reasonable dietary quality was associated with substantially lower mortality than any single pillar alone [22]. This underscores the importance of the holistic, multi-pillar approach that distinguishes lifestyle medicine from single-intervention strategies.

Practically, lifestyle medicine clinicians can leverage the 2026 payment landscape, which increasingly recognizes exercise prescription through new billable services, prevention-aligned CMS models (e.g., MAHA Elevate, ACCESS), and quality measures that reward physical activity counseling and outcome tracking [67]. The convergence of scientific evidence, clinical tools, and reimbursement policy creates an unprecedented opportunity to mainstream exercise prescription within healthcare delivery.

## 7. Future Directions

Several frontier areas warrant investment and investigation. First, precision exercise prescription—using wearable-derived data, exerkine biomarker profiles (e.g., Lac-Phe response), genetic polymorphisms, and machine learning algorithms to individualize activity prescriptions—represents the natural evolution of the Exercise is Medicine paradigm. Second, VILPA-based public health interventions, now supported by robust epidemiological evidence, need validation in large-scale randomized trials across diverse populations.

Third, the integration of exercise prescription with GLP-1 RA therapy requires evidence-based clinical guidelines specifying optimal exercise type (resistance vs. aerobic vs. combined), intensity, timing relative to medication administration, and monitoring protocols for lean mass preservation. Fourth, the clinical translation of exerkine science—including Lac-Phe-guided exercise intensity titration and SPARC-based therapeutic development—offers exciting possibilities for bridging exercise physiology and pharmacology.

Finally, implementation science research is needed to scale effective exercise prescription models—such as the CHALLENGE trial's physical activity consultant approach—across diverse healthcare systems, including low-resource and primary care settings where lifestyle medicine is most needed and potentially most impactful.

## 8. Conclusion

The exercise pillar of lifestyle medicine is experiencing a scientific renaissance. Level 1 evidence now establishes exercise as a survival-extending therapeutic intervention in cancer. Ultra-short activity paradigms such as VILPA democratize the benefits of vigorous exercise for non-exercising populations. The molecular revolution of exerkines provides mechanistic understanding and biomarker-guided precision for exercise prescription. And the GLP-1 era underscores, rather than undermines, the indispensable role of physical activity in comprehensive chronic disease management.

For lifestyle medicine practitioners, these developments collectively argue that exercise prescription is not a supplementary recommendation but a core clinical competency—as essential as pharmacological prescribing and perhaps more impactful. The evidence is clear: movement is medicine, and it is time for healthcare systems worldwide to prescribe it accordingly.

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