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A CRITICAL INTEGRATIVE MINI REVIEW

From Prescribed Exercise to Realized Adaptation: Dose, Specificity, Context, and Transfer Across Health and Performance

Goran Sporiš[1], Aida Mohammadi[2], Navid Moravej[3], Parham Jalali[4]

[1]Department of General and Applied Kinesiology, Faculty of Kinesiology, University of Zagreb, Zagreb, Croatia, [2]Sport and Health Promotion Program, Department of Experimental Medicine and Surgery, University of Rome Tor Vergata, Rome, Italy, [3]Islamic Azad University, Iran, [4]Wellness, Sport and Health Program, University of Bologna, Rimini Campus, Rimini, Italy

Abstract

Exercise prescriptions are commonly summarized by mode, intensity, frequency, and duration, yet the same nominal prescription can yield markedly different biological, functional, and performance outcomes. This critical integrative review examined a predefined corpus of 34 full-text evidence syntheses spanning resistance and endurance training, rehabilitation, cardiometabolic and respiratory disease, neurodegeneration, musculoskeletal conditions, athletic performance, injury prevention, and nutritional or respiratory adjuncts. Rather than re-pooling overlapping primary trials, we used cross-review integration to identify recurring conditions that alter the pathway from prescribed exercise to meaningful outcome. Five themes converged. First, dose is multidimensional and outcome-specific: higher volume or intensity can improve some adaptations, but plateaus, thresholds, and minimum effective doses are common. Second, specificity acts as a transfer gate; adaptations are strongest when the training stimulus, tissue demand, and outcome test share relevant mechanical or metabolic features. Third, baseline state changes the meaning of a given dose, with initial fitness, sarcopenia, inspiratory weakness, disease severity, and training status repeatedly modifying response. Fourth, adjuncts are not inherently additive. Protein and creatine can augment selected resistance-training outcomes, respiratory support can enable greater training tolerance in severe chronic obstructive pulmonary disease, and concurrent aerobic training can coexist with hypertrophy and maximal-strength development, yet some adjuncts show little added value and close-proximity concurrent training may attenuate explosive-strength gains. Fifth, statistical improvement does not guarantee clinically or practically meaningful transfer; several reviews reported small effects, failure to reach minimal clinically important differences, uncertain quality-of-life effects, or limited durability. We integrate these findings into a Realized Adaptation Cascade in which prescription is translated through internal exposure, biological adaptation, task-specific transfer, and meaningful outcome, while baseline state, adjunct exposures, recovery, and measurement architecture modify each transition. The practical implication is not to maximize exercise dose indiscriminately, but to identify a minimum sufficient, context-matched stimulus and verify that the desired adaptation transfers to the outcome that matters.

Keywords: *exercise prescription; dose-response; specificity; resistance training; aerobic training; rehabilitation; performance; adaptation; precision exercise; clinical relevance*

Correspondence:

G. Sporiš
Department of General and Applied Kinesiology, Faculty of Kinesiology, University of Zagreb, Zagreb, Croatia Sporiš
Email: goran.sporis@kif.unizg.hr

Key Messages

• A training label is not a biological dose: volume, intensity, frequency, sequence, recovery, and task mechanics determine the realized stimulus.

• More is not universally better. Across resistance, endurance, rehabilitation, and nutritional evidence, thresholds and plateaus coexist with positive dose-response relationships.

• Specificity governs transfer. A physiological or tissue adaptation is not equivalent to improved sport performance, physical function, cognition, quality of life, or clinically meaningful change.

• Baseline state and active constraints matter. The same external prescription can represent a different internal challenge in a trained athlete, an older adult with sarcopenia, or a patient with severe COPD.

• Adjuncts should be used to relieve a limiting constraint rather than assumed to add benefit automatically.

• Exercise prescription should be treated as a feedback process: define the target, select a minimum sufficient context-matched dose, verify the realized response, and adapt the program only when the outcome supports change.

Introduction

Exercise is one of the most versatile interventions in health and performance, but versatility creates a persistent translation problem. Terms such as resistance training, aerobic training, high-intensity interval training, plyometrics, pulmonary rehabilitation, or multicomponent exercise are useful categories, yet they do not uniquely specify the stimulus delivered to a tissue or the adaptation required for a target outcome. Across the present evidence corpus, changes in strength, muscle morphology, mitochondrial content, running economy, gait, cognition, pain, cardiometabolic markers, and quality of life varied not only between exercise modes but also within the same nominal mode as a function of volume, intensity, frequency, sequence, baseline status, outcome definition, and adjunct exposure [1-34].

This variability is often discussed as heterogeneity, but heterogeneity is not merely statistical noise. Several reviews show that it contains decision-relevant information. In resistance training, weekly set volume displays a graded relationship with strength, yet training to repetition failure is not required for strength or hypertrophy [20,27]. In older adults, resistance-training intensity, training period, time under tension, and frequency contribute differently to strength and morphology, while sarcopenic populations show distinct dose-response patterns and uncertainty for muscle-mass indices [3,4,28]. In endurance-related adaptation, similar average increases in mitochondrial content can arise from endurance training, high-intensity training, or sprint-interval training, although their time efficiency differs and capillary responses are not identical [23]. In Parkinson's disease, modeled optimal doses differ by exercise modality, yet statistically favorable walking-speed responses did not reach the estimated minimal clinically important difference [32]. These patterns argue against a single hierarchy of "best" exercise and instead favor outcome-specific matching.

The same problem appears when laboratory adaptation is expected to transfer to performance or daily function. High-load and plyometric training can improve running economy, but their effects depend on running speed and athlete characteristics [21]. Different physical-training methods improve jump outcomes with distinct task-specific profiles [22]. Neck exercise can alter electromyographic behavior, but the neuromuscular adaptation depends on the trained task [14]. After total knee arthroplasty, resistance-oriented rehabilitation improves some measures of walking speed, timed function, knee power, flexion range, and pain, while other functional tests remain unchanged [31]. Thus, an intervention can be biologically effective without transferring uniformly across outcomes.

A further complication is that exercise rarely occurs in isolation. Nutritional intake, supplements, respiratory assistance, and concurrent training modify the environment in which adaptation occurs. Protein supplementation can modestly augment resistance-training-induced muscle and strength gains, but benefits diminish beyond a total intake near 1.6 g/kg/day in healthy adults [24]. Whey protein during resistance exercise in sarcopenic older adults shows small benefits with low-to-very-low certainty and changes that may not exceed clinical importance [11]. Creatine increases fat-free mass most clearly when paired with resistance or combined training, but dose and loading strategy do not provide a simple universal optimization rule [26]. Conversely, periodized carbohydrate restriction does not reliably improve endurance performance in trained athletes despite plausible metabolic signaling advantages [18]. In severe COPD, noninvasive positive-pressure ventilation can increase tolerance of pulmonary-rehabilitation exercise by reducing an active respiratory constraint [7]. These findings suggest a general principle: adjunct value depends on whether the adjunct relieves a constraint that remains limiting after the training stimulus and baseline state are considered.

The purpose of this critical integrative review is therefore to move beyond modality labels and synthesize a context-sensitive model of exercise adaptation. The distinctive contribution of the synthesis is the Realized Adaptation Cascade: a framework linking prescribed external stimulus to realized internal exposure, biological adaptation, task-specific transfer, and clinically or practically meaningful outcome. We use the 34-source bounded evidence corpus to examine five recurring questions: how dose behaves across outcomes; when specificity determines transfer; how baseline state alters response; when concurrent or adjunct exposures add value; and why statistical efficacy may fail to produce meaningful real-world benefit.

Review Design and Evidence Provenance

Review design and rationale

This article was designed as a critical integrative review rather than a systematic review. The evidence base was a predefined, author-curated corpus of 34 unique full-text publications [1-34]. The corpus was intentionally broad and consisted predominantly of systematic reviews and meta-analyses, including network meta-analyses, dose-response meta-analyses, meta-regressions, and one umbrella review. It spanned sport performance, healthy ageing, sarcopenia, musculoskeletal rehabilitation, cardiometabolic disease, respiratory disease, neurodegenerative disease, mental health, injury prevention, and nutritional or respiratory adjuncts.

No de novo bibliographic database search, PRISMA screening process, duplicate-removal workflow, formal review registration, new risk-of-bias assessment, new GRADE assessment, or statistical re-pooling of primary trials was conducted for the present manuscript. Such procedures would be inappropriate to invent for a corpus selected in advance. Where source reviews reported risk-of-bias, GRADE, CINeMA, PEDro, or other certainty judgments, those judgments were retained as properties of the source review rather than reclassified as a new formal assessment.

Evidence organization and cross-review synthesis

For each source, the synthesis considered population, study design, intervention mode, dose variables, comparator, intervention duration, key outcomes, moderators, reported statistical uncertainty, reported methodological limitations, and the relation of the findings to other reviews in the corpus. Evidence was organized by inferential role rather than by disease name alone. Four principal roles emerged: dose architecture, specificity and transfer,

biological or clinical state, and concurrent or adjunct exposures. A fifth domain, measurement and meaningfulness, was used to distinguish physiological change from task performance, clinical function, quality of life, or minimal clinically important change.

Because several source reviews likely contain overlapping primary trials, their effect sizes were not combined into a new umbrella estimate. Instead, convergence was inferred only when reviews addressing different outcomes or populations independently supported the same conditional principle. Discordant and null findings were deliberately retained. Network rankings were treated cautiously when based largely on indirect evidence, sparse nodes, or low-certainty comparisons. Mechanistic interpretations were limited to mechanisms directly measured or explicitly supported within the source corpus; biological plausibility was not treated as proof of efficacy.

Scope and limitations of the corpus

The corpus is broad enough to identify recurring translational patterns but is not a representative census of all exercise science. It over-represents evidence syntheses and therefore inherits the eligibility decisions, reporting limitations, and overlap of the underlying reviews. Some domains are supported by many randomized trials, whereas others rely on small networks, indirect comparisons, or highly heterogeneous interventions. The review should therefore be read as a bounded conceptual synthesis of the provided evidence, not as a universal clinical guideline or a substitute for population-specific systematic review.

The Realized Adaptation Cascade

Across the corpus, exercise effects can be organized as a sequence of five linked stages: (1) the prescribed external stimulus; (2) the realized internal exposure; (3) the biological adaptation; (4) task-specific transfer; and (5) a meaningful functional, clinical, or performance outcome. Failure can occur at any transition. A prescription may be inadequately dosed, an individual may be unable to realize the intended internal load, a biological change may not transfer to the target task, or a statistically detectable task improvement may remain too small to matter clinically.

The prescribed external stimulus includes mode, intensity, volume, frequency, duration, sequence, and recovery. The realized internal exposure is the physiological and neuromuscular challenge that actually reaches the individual. Severe ventilatory limitation in COPD can prevent a nominally appropriate exercise prescription from becoming a tolerable training exposure; respiratory support can therefore change the realized dose without changing the external exercise task [7,19]. In contrast, a trained athlete may complete the same external session with a lower relative physiological disruption than an untrained individual, and initial fitness repeatedly predicts the magnitude of mitochondrial, capillary, and aerobic adaptation [23].

Biological adaptation is the change in tissue or system capacity produced by repeated exposure. Examples include strength, muscle mass, mitochondrial content, capillarization, neuromuscular activation, and cardiorespiratory fitness [4,14,23,26-29]. Task-specific transfer asks whether those adaptations improve the performance or function of interest. The final stage asks whether the magnitude is meaningful: faster gait, less disability, better quality of life, lower cardiometabolic risk, improved sport performance, or a change that exceeds an accepted clinical threshold. The distinction between these stages prevents mechanistic enthusiasm from being mistaken for practical efficacy.

Table 1. Recurring evidence patterns across the bounded corpus

Principle	Representative domains	Integrated finding	Practical interpretation	Key refs
Dose architecture	Resistance training; aerobic/interval training; metabolic syndrome; Parkinson disease; sarcopenia	Positive dose-response relationships coexist with minimum sufficient doses, thresholds, plateaus, and outcome-specific optima.	Do not escalate volume or intensity without identifying the target outcome and fatigue cost.	[4,10,13,20,23,27,28,32]
Specificity and transfer	Running economy; vertical jump; injury prevention; neck neuromuscular function; TKA	Training effects depend on movement mechanics, contraction behavior, test speed, and the functional outcome assessed.	Choose training and testing that share the mechanical/metabolic features of the desired task.	[2,14,21,22,31]
Baseline state	Initial fitness; inspiratory weakness; sarcopenia phenotype; disease severity; training status	The same external prescription produces different marginal benefit depending on the dominant baseline constraint.	Screen for decision-relevant constraints rather than personalizing every variable.	[7,8,19,23,24,28]
Adjunct/ concurrent exposure	Protein; whey; creatine; carbohydrate availability; respiratory support; concurrent training	Adjuncts can add value, have no additive effect, or alter a specific outcome depending on the active bottleneck and scheduling.	Use adjuncts to relieve a limiting process; avoid assuming automatic synergy.	[7,11,18,24,26,29]
Meaningful outcome	PD walking; cognition; TKA rehabilitation; limb amputation; quality of life	Statistical effects may fail to reach MCID, may be short-lived, or may not transfer to participation/QoL.	Predefine clinical or performance meaningfulness and follow-up duration.	[1,6,9,11,12,16,31,32,34]
Measurement architecture	Body composition; gait tests; cognition scales; network rankings	The choice of test can change the apparent effect; surrogate and task-specific endpoints are not interchangeable.	Match the measure to the stage of the adaptation cascade being tested.	[4,9,12,21,26,31-34]

Dose Is Multidimensional, Outcome-Specific, and Frequently Nonlinear

Resistance training: volume, intensity, frequency, and failure are not interchangeable

Resistance-training evidence provides the clearest demonstration that dose is multidimensional. In healthy older adults, resistance training produces large gains in strength and smaller changes in muscle morphology, while meta-regression indicates that training period, intensity, and time under tension can influence strength response [4]. Independent analyses in that review suggested effective configurations around two weekly sessions, two to three sets per exercise, and moderate-to-high relative loads, but the authors emphasized heterogeneity and the inability to define a single general dose-response relationship [4]. In a separate meta-analysis, medium and high weekly set volumes produced marginally greater strength gains than low weekly volume, supporting a graded relationship for strength [27].

Yet greater effort within each set does not obey the same rule. Training to repetition failure did not produce superior overall gains in strength or hypertrophy compared with non-failure training [20]. When training volume was not equated, non-failure training even favored strength, whereas a small hypertrophy advantage for failure appeared in resistance-trained participants [20]. The implication is that "dose" cannot be reduced to effort proximity alone: weekly volume, loading, fatigue accumulation, and training status interact.

The Nordic hamstring literature reinforces the distinction between minimum sufficient dose and maximal dose. Low-volume and high-volume Nordic hamstring programs produced similarly large changes in eccentric strength and biceps femoris architecture after sufficiently long interventions, suggesting that reducing prescribed volume may preserve key adaptations while potentially improving adherence [10]. In sarcopenic older adults, resistance training improves grip strength and physical performance, but the modeled relationship between frequency, intensity, and outcome differs from that observed in healthy older adults, and effects on skeletal muscle mass index remain uncertain [28]. Secondary sarcopenia adds further heterogeneity because comorbid conditions modify the response to the same training category [8].

Aerobic and cardiometabolic dose: thresholds, efficiency, and plateaus

Endurance and cardiometabolic evidence likewise rejects a universal dose. In skeletal muscle, endurance training, high-intensity training, and sprint-interval training produced broadly similar percentage increases in mitochondrial content after covariate adjustment, but sprint-interval training generated greater improvement per hour of exercise [23]. Capillary outcomes were more mode-dependent: capillaries per fiber increased across modes, whereas capillaries per square millimeter increased after endurance and high-intensity training but not clearly after sprint-interval training [23]. Training frequency and initial fitness strongly modified the magnitude of adaptation, demonstrating that time efficiency and absolute adaptation are separate questions.

In coronary artery disease, high-intensity interval training outperformed moderate-intensity continuous training for peak oxygen uptake and 6-minute walk distance, but not for left-ventricular ejection fraction, end-diastolic volume, or systolic blood pressure [17]. Cardiac rehabilitation after myocardial revascularization improved physical performance overall, with larger pooled effects in aerobic or combined programs and in interventions lasting approximately 8-12 weeks [5]. In type 2 diabetes, combined aerobic and resistance exercise ranked more favorably for HbA1c than either supervised mode alone, while aerobic or resistance training showed different strengths for other cardiometabolic outcomes [25]. These findings illustrate outcome-specific superiority rather than a single best modality.

A 2025 dose-response network meta-analysis in metabolic syndrome provides a useful example of nonlinearity. Clinically relevant lipid improvements appeared at relatively modest volumes for LDL cholesterol and triglycerides, while modeled benefits tended to plateau above approximately 900 MET-min/week; combined aerobic-resistance exercise and HIIT performed well across moderate-to-high dose ranges, whereas mind-body exercise rankings were sensitive to sparse evidence [13]. The precise numerical thresholds should not be generalized beyond the included trials, but the structural message is robust: a dose-response curve may contain an effective threshold, a productive range, and a plateau rather than a simple linear relation.

Neurodegenerative conditions: modeled optima versus meaningful change

Parkinson's disease demonstrates why modeled optimal doses require clinical interpretation. A Bayesian dose-response network meta-analysis identified different estimated optimal doses for aerobic, multicomponent, sensory, resistance, and mind-body exercise for walking velocity [32]. However, no exercise type at the analyzed dose achieved the estimated minimal clinically important difference. A much larger network meta-analysis of 250 trials similarly showed that the "best" mode depended on the outcome: power training ranked highly for motor symptoms and strength, body-weight-supported treadmill training for balance and gait outcomes, robotic-assisted gait training for freezing of gait, dance for depression, yoga for anxiety, and resistance training for sleep and cognition, with overall certainty of evidence remaining low [33].

Dose must therefore be interpreted in relation to the target construct. More weeks or more sessions may improve one symptom cluster without producing equivalent effects on another. In Alzheimer's disease, aerobic exercise improved pooled cognitive scales and quality of life, and subgroup patterns favored interventions longer than 16 weeks for several outcomes; however, cognitive evidence was rated very low and heterogeneity was high [34]. In COPD, exercise may improve global cognition, but the small number and heterogeneity of trials prevent a confident prescription of a specific cognitive dose [12].

Specificity Is the Gate Between Adaptation and Transfer

Sport performance: transfer depends on mechanics and test conditions

Strength gains are not synonymous with sport-performance gains. In middle- and long-distance runners, high-load strength training, plyometrics, and combined methods improved running economy, whereas submaximal-load and isometric approaches were less consistently effective [21]. The effect was conditional on running speed and athlete aerobic capacity: high-load training appeared especially useful at higher speeds and higher VO2max, whereas plyometric benefits were more apparent at lower running speeds [21]. The training stimulus therefore interacted with the speed at which economy was assessed.

Jump performance shows a related pattern. Plyometric, resistance, and complex training can all improve vertical-jump outcomes, but the most favorable method depends on the jump task; complex training was particularly effective for countermovement-jump performance, while resistance training strongly improved vertical and squat-jump outcomes [22]. The injury-prevention literature in youth team sport similarly suggests that lower-body concentric and eccentric work, core tasks, movement mechanics, and stability components can reduce overall and lower-extremity injury incidence, yet effects are not uniform across anatomical regions and knee findings remain contradictory [2].

Table 2. Context-matched exercise prescription workflow

Step	Decision	Operational example
1. Define the target	Specify the outcome and timescale.	Peak VO2, race-speed running economy, knee power, gait speed, cognition, HbA1c, QoL.
2. Identify the dominant constraint	Measure baseline variables that can plausibly limit adaptation or tolerance.	Initial fitness, inspiratory weakness, sarcopenia, disease severity, training status.
3. Select a minimum sufficient stimulus	Choose mode, intensity, volume, frequency, progression, and sequence based on target specificity.	Avoid unnecessary failure, excessive volume, or high-frequency exposure when lower doses produce the required adaptation.
4. Manage modifiers	Add support or adjuncts only when they address a remaining limitation.	Respiratory support in severe COPD; protein/creatine when relevant; separate concurrent sessions if explosive strength is a priority.
5. Verify adaptation	Measure the capacity expected to change.	Strength, mitochondrial content, peak VO2, neuromuscular activation, body composition.
6. Verify transfer and meaningfulness	Test the target task and compare with clinically/practically relevant thresholds.	Walking, stair climbing, sport performance, quality of life, MCID, long-term durability.
7. Iterate selectively	Modify the variable most likely to be limiting; avoid indiscriminate complexity.	Increase dose, change specificity, alter scheduling, or add adjunct only when evidence and response support the change.

Specificity therefore extends beyond exercise mode to movement pattern, contraction behavior, speed, and the failure mechanism targeted by the intervention.

Rehabilitation: local adaptation and functional transfer can diverge

Clinical rehabilitation provides direct evidence that local impairment improvement does not guarantee broad functional transfer. After total knee arthroplasty, active lower-limb resistance exercise improved knee extension and flexion power, maximal walking speed, Timed Up and Go performance, flexion range of motion, and pain, but did not significantly improve 6-minute walking distance, stair-climb performance, or extension range in the same meta-analysis [31]. Earlier post-discharge physiotherapy evidence showed short-term improvements in function and pain but no durable long-term advantage and little difference between outpatient and home-based provision [1]. Outcome selection therefore determines whether an intervention is judged successful.

In chronic neck pain, exercise targeting the neck produces neuromuscular adaptation, including altered electromyographic activation, but the pattern depends on the specific training task [14]. Therapeutic exercise can improve forward-head posture, rounded shoulders, and thoracic kyphosis in upper-crossed syndrome, yet pooled categories encompass different strengthening, stretching, shoulder-focused, and comprehensive programs [30]. For lower-limb amputation, exercise improves several physiological and mobility outcomes, but quality-of-life effects remain inconclusive and intervention heterogeneity prevents a single protocol from being recommended across amputation levels and causes [6]. These examples support a practical distinction: impairment-specific success, task performance, participation, and quality of life are related but non-equivalent endpoints.

Baseline State Changes the Meaning of the Same Prescription

The largest response to a nominal dose often occurs where the relevant capacity is most constrained. In the skeletal-muscle meta-regression, lower initial fitness was associated with larger percentage gains in mitochondrial content, capillarization, and VO-2max, while the ability to adapt was maintained across age, sex, and disease categories [23]. In COPD, inspiratory-muscle training improved inspiratory strength, endurance, dyspnea, functional exercise capacity, and quality of life, with patients who had greater baseline inspiratory weakness appearing to benefit more when inspiratory training was added to general exercise [19]. This is a direct example of constraint matching: an intervention has greater marginal value when the targeted limitation is present.

Disease severity can also alter whether the prescribed task is realizable. During pulmonary rehabilitation in stable severe COPD, respiratory support—especially noninvasive positive-pressure ventilation—improved exercise-capacity and physiological outcomes relative to unsupported exercise in a network meta-analysis, although evidence quality was limited by sparse direct comparisons and heterogeneous protocols [7]. The external exercise task may be unchanged, but reducing ventilatory load can increase the internal dose that the locomotor system can tolerate.

Sarcopenia further demonstrates state dependence. In healthy older adults, resistance training reliably improves strength and morphology [3,4]. In secondary sarcopenia, resistance training improves muscle strength and mass, yet physical-function effects are less certain and comorbidity type appears to modify the magnitude of response [8]. In primary sarcopenia, training frequency and intensity predict selected strength and performance outcomes, but not all body-composition measures [28]. Thus, age alone is an insufficient modifier; diagnosis, comorbidity, baseline impairment, and target outcome all alter the interpretation of dose.

Concurrent and Adjunct Exposures: Add Value Only When They Relieve a Limiting Constraint

Nutrition and supplementation

Protein and creatine provide a useful contrast between established ergogenic effects and context-specific marginal benefit. Across healthy adults performing prolonged resistance exercise training, protein supplementation produces statistically significant but modest additional gains in strength, fat-free mass, and muscle size. The effect on fat-free mass decreases with age and appears larger in resistance-trained individuals, while intakes above approximately 1.6 g/kg/day do not show further gains in fat-free mass [24]. This is not evidence that 1.6 g/kg/day is a universal physiological ceiling; it is a pooled breakpoint within the included healthy-adult trials. In sarcopenic older adults, whey protein added to resistance training improved muscle mass and handgrip strength, but effect sizes were small, grip-strength change did not exceed the minimally important clinical difference, and certainty was low to very low [11].

Creatine supplementation increases body mass and fat-free mass modestly, particularly when creatine monohydrate is combined with resistance or concurrent training [26]. The evidence

does not support a simple claim that higher dose, loading, longer duration, or alternative creatine forms reliably generate larger body-composition benefits. Some apparent fat-free-mass gain may also reflect changes in body water, which complicates interpretation when body composition rather than direct muscle morphology is the outcome [26]. The appropriate inference is therefore adjunct-specific: creatine can support training adaptation, but its effect depends on what is measured and whether the training stimulus is capable of exploiting the added phosphagen availability.

Periodized carbohydrate restriction illustrates the opposite case. Training with low carbohydrate availability can amplify selected metabolic signals in acute studies, yet a meta-analysis in well-trained endurance athletes did not show a significant overall performance advantage over training with normal carbohydrate availability [18]. Mechanistic plausibility and performance efficacy therefore occupy different stages of the adaptation cascade. An intervention that magnifies a signaling pathway may still reduce training quality or fail to improve the task that ultimately matters.

Concurrent training and interference

Concurrent aerobic and strength training is often framed as globally antagonistic, but the pooled evidence is more selective. Compared with strength training alone, concurrent training did not materially compromise maximal strength or muscle hypertrophy, yet explosive-strength development was modestly attenuated [29]. The interference was more apparent when aerobic and strength training occurred within the same session and was not evident when sessions were separated by at least three hours [29]. Thus, interference is not an all-or-none property of combining modalities; it is outcome- and schedule-specific.

This distinction matters because many clinical programs deliberately combine modalities. In type 2 diabetes, combined aerobic and resistance training can improve glycemic control more than either supervised mode alone [25]. Cardiac rehabilitation likewise benefits from aerobic and combined approaches [5]. The objective should therefore determine whether potential interference is relevant. For metabolic control, preserving two complementary stimuli may be advantageous; for rapid force production in an athlete, session proximity may deserve greater attention.

Statistical Efficacy Is Not Equivalent to Meaningful Benefit

Several reviews explicitly separate statistical significance from clinical or practical relevance. In Parkinson's disease, dose-response models predicted significant walking-speed improvements, yet no analyzed exercise-dose combination achieved the estimated minimal clinically important difference [32]. In sarcopenic older adults, adding whey protein to resistance training improved handgrip strength statistically, but the mean difference did not exceed the clinically important threshold and the evidence was low to very low certainty [11]. In Alzheimer's disease, pooled cognitive effects were statistically favorable, but the certainty for MMSE and ADAS-cog outcomes was very low and heterogeneity was high [34].

Table 3. Priority research gaps generated by the synthesis

Gap	Why it matters	Recommended design feature
True dose-response coverage	Primary trials cluster around similar doses, making modeled thresholds unstable.	Multi-arm or adaptive trials spanning low-to-high exposure; report full dose vector and adherence.
Direct comparative evidence	Network rankings often rely on indirect comparisons.	Head-to-head trials of leading modalities at matched exposure and clearly specified outcomes.
Baseline effect modification	Disease severity, fitness, weakness, and training status are inconsistently modeled.	Pre-specified interaction analyses and stratified randomization.
Adaptation-to-transfer linkage	Mechanistic or impairment outcomes are often disconnected from function/performance.	Measure proximal adaptation, task transfer, and meaningful endpoint in the same trial.
Clinical meaningfulness	Statistical significance is often emphasized without MCID or responder analysis.	Report MCID attainment, responder distributions, and confidence intervals for individual benefit.
Adjunct synergy	Bundled interventions cannot identify whether the adjunct truly modifies training response.	Factorial designs with dietary/training control and interaction testing.
Durability	Many rehabilitation and cognitive studies have short follow-up.	Long-term follow-up with maintenance, detraining, adherence, and participation outcomes.

Durability is another form of meaningfulness. Post-discharge exercise after total knee replacement improves short-term function and pain, but the earlier evidence base did not demonstrate long-term benefits [1]. In limb amputation, physiological and mobility outcomes improve more consistently than quality of life [6]. In depression, exercise produced a small improvement in working memory but not clear benefits for inhibition or cognitive flexibility, with few high-quality studies [9]. In Parkinson's disease, a small pooled global-cognition effect remains very uncertain because of small samples, heterogeneous exercise programs, and different comparators [16].

These examples suggest a hierarchy for interpretation. First ask whether the outcome changed. Then ask how large and precise the change was, whether it exceeds a clinically or practically relevant threshold, whether it transfers to the target activity, and whether it persists. A framework that stops at statistical significance risks recommending interventions that change a surrogate measure without changing the person's function or the athlete's performance.

Measurement Architecture Determines What the Intervention Appears to Do

Outcome measurement is not a neutral final step; it shapes the apparent efficacy of an intervention. Running-economy effects vary with the speed at which economy is tested [21]. Resistance-training effects differ between one-repetition maximum, isometric force, muscle morphology, explosive strength, and regional body-composition measures [4,20,26,29]. After knee arthroplasty, maximal walking speed and Timed Up and Go may improve while 6-minute walking distance or stair climbing does not [31]. Parkinson's exercise rankings change depending on whether the outcome is motor symptoms, balance, gait velocity, freezing, depression, anxiety, cognition, sleep, strength, or concern about falling [33].

Measurement also changes the certainty of inference. Body-composition methods cannot always separate tissue accretion from hydration shifts after creatine [26]. Cognitive reviews combine different scales and domains, producing high heterogeneity and low certainty [9,12,16,34]. Network meta-analyses can rank treatments despite sparse direct comparisons, but a high ranking should not be interpreted as high certainty [7,13,33]. For prescription science, measurement should therefore be selected before the intervention and should match the stage of the cascade being tested: biological adaptation, task transfer, or meaningful outcome.

Clinical and Practical Implications: A Context-Matched Prescription Workflow

The integrated evidence supports a parsimonious workflow rather than a universal exercise hierarchy. Step 1 is to define the target outcome precisely. "Improve fitness" is less actionable than improve peak oxygen uptake, walking tolerance, knee-extensor power, running economy at race-relevant speed, or executive function. Step 2 is to identify the dominant baseline constraint. Inspiratory weakness, sarcopenia, poor aerobic fitness, low muscle strength, disease severity, or high training status change what the same external dose means [3,7,8,19,23,28].

Step 3 is to select the minimum sufficient stimulus with the greatest specificity for the target. The evidence for Nordic hamstring training, repetition failure, protein intake, and several dose-response analyses shows that maximal fatigue or maximal volume is not a prerequisite for adaptation [10,20,24,27]. Step 4 is to manage modifiers that can prevent the intended exposure from being realized. These may include respiratory support in severe COPD, appropriate nutritional intake during resistance training, or spacing of concurrent aerobic and strength sessions when explosive strength is a priority [7,24,26,29]. Step 5 is to verify the realized dose using an outcome that directly represents the adaptation of interest. Step 6 is to test transfer and meaningfulness rather than assuming them. If a biomarker improves but gait, quality of life, or performance does not, the prescription has succeeded at one stage of the cascade but failed at a later one.

This workflow does not imply that every program must be individually optimized with complex testing. It implies the opposite: personalization should be selective and decision-relevant. Modify only variables that are plausible bottlenecks for the chosen outcome, and avoid adding volume, supplements, or modalities merely because they can produce an additional biological signal.

Critical Discussion

The strongest cross-domain signal in this corpus is conditionality. Exercise is effective across many populations, but the magnitude and meaning of the effect depend on how the stimulus is constructed and where in the adaptation cascade success is measured. This explains why apparently contradictory findings can coexist. High weekly resistance-training volume may produce somewhat greater strength gains, while lower Nordic hamstring volume preserves eccentric-strength and architectural adaptation; the contradiction disappears when the target, exercise, and fatigue cost are distinguished [10,27]. High-intensity interval training can outperform moderate continuous training for selected cardiorespiratory outcomes in coronary disease without improving every cardiac measure [17]. Combined training can be useful for glycemic control while same-session concurrent training can attenuate explosive-strength gains [25,29].

The framework also clarifies why adjuncts show inconsistent value. An adjunct can only add meaningful benefit if the process it targets remains limiting. Protein supplementation has greater marginal value when total protein intake is not already sufficient and appears less effective for fat-free-mass gain with increasing age [24]. Whey protein in sarcopenia provides only small incremental benefit over resistance training in a low-certainty evidence base [11]. Creatine produces modest body-composition benefits, most clearly when training is present, but protocol escalation does not generate a universal dose-response advantage [26]. Respiratory support has a more obvious rationale in severe COPD because ventilatory limitation directly constrains exercise tolerance [7]. In this sense, adjunct efficacy is a bottleneck problem rather than a product-ranking problem.

A major limitation is that the corpus consists largely of evidence syntheses rather than primary mechanistic trials. The present review can integrate recurring physiological patterns but cannot establish new molecular causal pathways. The overlap of primary studies across reviews may also create an illusion of replication. For example, one trial can contribute to several meta-analyses examining different outcomes or subgroups. This is why the present manuscript does not count repeated inclusion as independent confirmation and does not produce a pooled umbrella effect.

Another limitation is uneven certainty. Some conclusions are supported by dozens or hundreds of trials, while other apparent rankings depend on sparse nodes, small samples, or indirect network comparisons [7,13,16,33]. Exercise intensity is inconsistently reported in several clinical reviews, and intervention labels often conceal substantial variation in progression, supervision, adherence, and movement execution [2,12,14,34]. These limitations are not peripheral: they directly constrain the precision with which exercise can be prescribed.

Finally, the corpus contains relatively little direct implementation science. A few findings have practical implications—lower-volume Nordic hamstring training may facilitate compliance, and home-based post-knee-replacement exercise can perform similarly to outpatient care for several outcomes—but the corpus does not justify broad claims about access, behavior, health-system delivery, or long-term adherence [1,10]. Those domains require dedicated evidence rather than extrapolation from efficacy-focused reviews.

Future Research Directions

Future trials should be designed to identify why an intervention works, for whom, and at what stage of the adaptation cascade benefit is lost. First, exercise dose should be reported as a vector rather than a single variable: mode, relative intensity, set or interval structure, total work, frequency, session duration, progression, recovery, and sequence. Dose-response analyses are most informative when primary trials populate a broad exposure range rather than clustering around similar prescriptions.

Second, direct head-to-head comparisons are needed where network rankings currently depend mainly on indirect evidence. This is particularly relevant in Parkinson's disease, respiratory-support strategies, and multicomponent exercise, where treatment rankings can appear precise despite limited direct contrast [7,32,33]. Third, baseline state should be pre-specified as a potential effect modifier. Initial fitness, training status, inspiratory weakness, sarcopenia phenotype, disease severity, and comorbidity should be measured before treatment rather than inferred post hoc [8,19,23,24,28].

Fourth, trials should bridge adaptation and transfer by measuring at least one proximal mechanism or capacity, one task-specific outcome, and one patient- or performance-relevant endpoint. For example, a strength intervention could quantify muscle or neuromuscular adaptation, a functional transfer task, and a clinically meaningful activity outcome. Fifth, minimal clinically important differences and responder distributions should be reported more consistently so that statistical efficacy is not mistaken for practical relevance [11,32].

Sixth, adjunct trials should use factorial designs that can test whether the adjunct changes the response to training rather than merely comparing two bundled programs. Dietary intake, training work, and hydration should be controlled when evaluating protein or creatine, and training quality should be quantified when carbohydrate availability is manipulated [18,24,26]. Finally, longer follow-up is required to determine whether short-term gains persist, especially in rehabilitation and neurodegenerative conditions [1,6,12,31,34].

Conclusions

Across 34 evidence syntheses, no single exercise mode, intensity, volume, frequency, or adjunct emerges as universally optimal. The most reproducible principle is that exercise efficacy is conditional. Dose must be matched to the target adaptation; specificity determines whether adaptation transfers; baseline state determines the internal meaning of an external prescription; adjuncts add value when they relieve a genuine bottleneck; and measurement determines whether success is biological, functional, or meaningful.

The Realized Adaptation Cascade offers a practical way to interpret these findings. A prescription should be judged sequentially: Was the intended external stimulus delivered? Was the internal exposure sufficient and tolerable? Did the relevant system adapt? Did the adaptation transfer to the target task? Was the final change large enough to matter? The evidence favors a minimum sufficient, context-matched dose combined with targeted modifiers and explicit verification of transfer, rather than indiscriminate escalation of training load or adjunct use. This framework is hypothesis-generating and should be tested prospectively, but it provides a defensible structure for moving exercise prescription from nominal labels toward outcome-specific, context-sensitive practice.

Evidence Provenance and Scope Statement

This critical integrative review is based on a bounded corpus of 34 unique full-text publications provided for the project. The corpus was not generated by a de novo systematic search conducted for this manuscript. The source set was used to support cross-domain conceptual integration, not to estimate a new pooled treatment effect. All numerical values and study-specific claims in the manuscript should be interpreted as originating from the cited source reviews, which retain responsibility for their own primary-study selection, risk-of-bias judgments, and statistical analyses.

Declarations

Data availability

No new datasets were generated or statistically analyzed for this review. All evidence discussed in the manuscript derives from the cited literature. A structured evidence map can be retained as an internal supplementary audit file if the authors choose to share it.

Use of generative AI and AI-assisted technologies

Generative AI (ChatGPT, OpenAI) was used in this project for evidence organization, cross-study synthesis, structural development, drafting, language editing, table generation, figure-concept development, and document formatting. AI is not an author and does not assume responsibility for scientific conclusions. Before submission, the human authors must independently verify all scientific claims, numerical values, references, and journal-specific wording and take full responsibility for the final manuscript.

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