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Exercise as a multisystem signaling therapy: A hypothesis integrating inter-organ communication and membrane microdomain regulation in metabolic disease

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Abstract

Exercise is a powerful non-pharmacological intervention for metabolic diseases, yet current mechanistic explanations remain fragmented across individual organs. This review proposes that exercise may act as a multisystem signaling therapy, generating interdependent mechanical, endocrine, metabolic, inflammatory, and redox cues that integrate communication among skeletal muscle, adipose tissue, liver, endothelium, and the central nervous system. We introduce a conceptual model in which caveolae, cholesterol-rich membrane microdomains formed by caveolins and cavins, serve as a spatial platform that helps cells interpret and integrate these diverse extracellular signals into unified intracellular responses. Evidence already supports caveolar roles in mechanotransduction, insulin receptor organization, lipid handling, nitric oxide signaling, and membrane tension buffering. However, direct causal links between exercise-induced caveolar remodeling and whole-body metabolic adaptation remain limited. Rather than positioning caveolae as the sole regulator of exercise responses, this review synthesizes current findings across tissues, differentiates established mechanisms from emerging hypotheses, and evaluates how exercise modality, tissue context, and metabolic disease states may shape caveolae-dependent signaling. We outline experimental strategies capable of testing this framework and highlight key gaps that must be addressed before caveolae-targeted interventions can be translated clinically. By integrating systems physiology with membrane biology, this review provides a mechanistically grounded and testable model for understanding how exercise coordinates metabolic homeostasis through spatial regulation of cellular signaling.

Keywords: exercise, caveolae, mechanotransduction, exer kines, membrane microdomains, metabolic disease, exercise therapy, systems physiology

Introduction

Metabolic diseases, including obesity, type 2 diabetes mellitus (T2DM), β -cell dysfunction, metabolic dysfunction-associated steatotic liver

disease (MASLD), hypertension, and cardiovascular disease, have become major global health challenges^[1]. These disorders arise from complex interactions among impaired energy metabolism, chronic low-grade inflammation, endocrine

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dysregulation, vascular dysfunction, and altered communication among metabolically active organs. Although pharmacological therapies have improved disease management, lifestyle intervention, particularly regular physical exercise, remains the most effective strategy for improving metabolic health while simultaneously reducing cardiovascular morbidity and mortality.

Unlike pharmacological agents that typically target individual molecular pathways, exercise induces synchronized physiological responses throughout the body^[2]. Contracting skeletal muscle releases myokines, metabolites, extracellular vesicles, and other exercise-responsive factors (collectively termed exerkines) that influence liver metabolism, adipose tissue function, vascular physiology, immune responses, and brain activity, reviewed by Hah *et al*^[3]. Simultaneously, exercise generates substantial mechanical loading, vascular shear stress, transient oxidative signaling, and dynamic alterations in substrate availability, all of which contribute to adaptive remodeling across multiple organs. These responses occur over different temporal and spatial scales, and effectively produce systemic metabolic adaptations that cannot be fully explained by organ-specific mechanisms alone.

Exercise is increasingly recognized as a systems-level biological intervention rather than merely a means of increasing energy expenditure. Recent multi-organ molecular profiling studies have demonstrated that exercise remodels endocrine communication, immune regulation, lipid metabolism, mitochondrial function, extracellular matrix organization, and vascular biology simultaneously across numerous tissues^[4-5]. These findings suggest that the therapeutic benefits of exercise emerge from synchronized interactions among multiple signaling networks rather than isolated molecular pathways.

However, the existing literature has largely examined the major components of exercise adaptation as separate biological fields. Previous reviews have predominantly focused on exerkines and inter-organ communication, mechanotransduction and cellular responses to mechanical loading, caveolae and caveolin-dependent signaling, or membrane lipid composition and membrane organization. Although each of these areas has generated substantial mechanistic insight, their potential interactions during exercise have rarely been considered within a single integrated framework. The novelty of the present review therefore lies not in proposing a previously unknown function for any individual component, but in integrating these established areas, exercise-induced

endocrine signaling, mechanotransduction, caveolar biology, and membrane lipid regulation, into a unified systems-level framework. We propose that membrane spatial organization, particularly caveolar remodeling, may provide an important cellular interface through which the diverse mechanical, metabolic, endocrine, and lipid-derived signals generated during exercise are coordinated.

Despite growing recognition of exercise as a systems-level therapy, an important mechanistic question remains unresolved: how are the numerous biochemical and mechanical signals generated during exercise integrated within individual cells to produce coherent adaptive responses?

Multiple membrane-associated structures contribute to cellular signal integration, including receptor complexes (endothelial nitric oxide synthase, epidermal growth factor receptor, G protein-coupled receptors, insulin receptor, glucose transporter type 4, and Cluster of Differentiation 36, *etc.*), focal adhesions, integrins, cytoskeletal networks, primary cilia, lipid rafts, and membrane microdomains. Among these structures, caveolae have attracted increasing attention because of their unique ability to couple mechanical forces with biochemical signaling. Caveolae are flask-shaped plasma membrane invaginations enriched in cholesterol, sphingolipids, caveolins, and cavinins that participate in membrane tension buffering, mechanotransduction, lipid trafficking, receptor compartmentalization, and nitric oxide signaling^[6-7]. Their sensitivity to membrane lipid composition, mechanical deformation, and metabolic status makes them plausible candidates for coordinating multiple exercise-induced stimuli^[8-9]. Caveolae are emphasized because their mechanically deformable structure makes them uniquely capable of sensing membrane tension during exercise, a property not shared to the same extent by lipid rafts. They also serve as highly organized signaling hubs enriched in eNOS, AMPK, insulin receptors, and G-protein complexes, allowing rapid coordination of vascular and metabolic responses. While lipid rafts contribute to general membrane-signaling, caveolae have stronger experimental support for linking mechanical load to metabolic adaptation, particularly in endothelial mechanotransduction.

Although numerous independent studies have demonstrated critical roles for caveolae in mechanotransduction, insulin signaling, endothelial biology, lipid metabolism, and cellular adaptation to mechanical stress, direct evidence that exercise-induced caveolar remodeling causally drives whole-body metabolic adaptation remains limited. Most

available evidence derives from isolated cell systems, genetically modified animal models, or studies performed independently of exercise interventions. Therefore, the relationship between exercise physiology and caveolae biology currently remains inferential rather than definitively established.

Accordingly, this review does not propose caveolae as the exclusive regulator of exercise adaptation, nor does it suggest that existing evidence has established a causal mechanism. Instead, we propose a testable conceptual hypothesis in which caveolae represent one important membrane platform capable of integrating the diverse mechanical, metabolic, endocrine, and redox signals generated during exercise into orchestrated intracellular responses that contribute to systemic metabolic adaptation (*Fig. 1*).

This hypothesis generates several experimentally testable predictions. If caveolae contribute substantially to exercise-mediated metabolic adaptation, then genetic or pharmacological disruption of caveolar structure, for example through deletion of Caveolin-1 or cavin proteins, would be expected to attenuate at least some exercise-induced improvements in insulin sensitivity, endothelial function, lipid handling, or metabolic flexibility. Conversely, preservation of normal exercise adaptation despite substantial caveolar disruption would challenge the central role proposed in this framework. These predictions distinguish the present model from a purely descriptive narrative and provide a foundation for future experimental validation.

Throughout this review, we critically evaluate

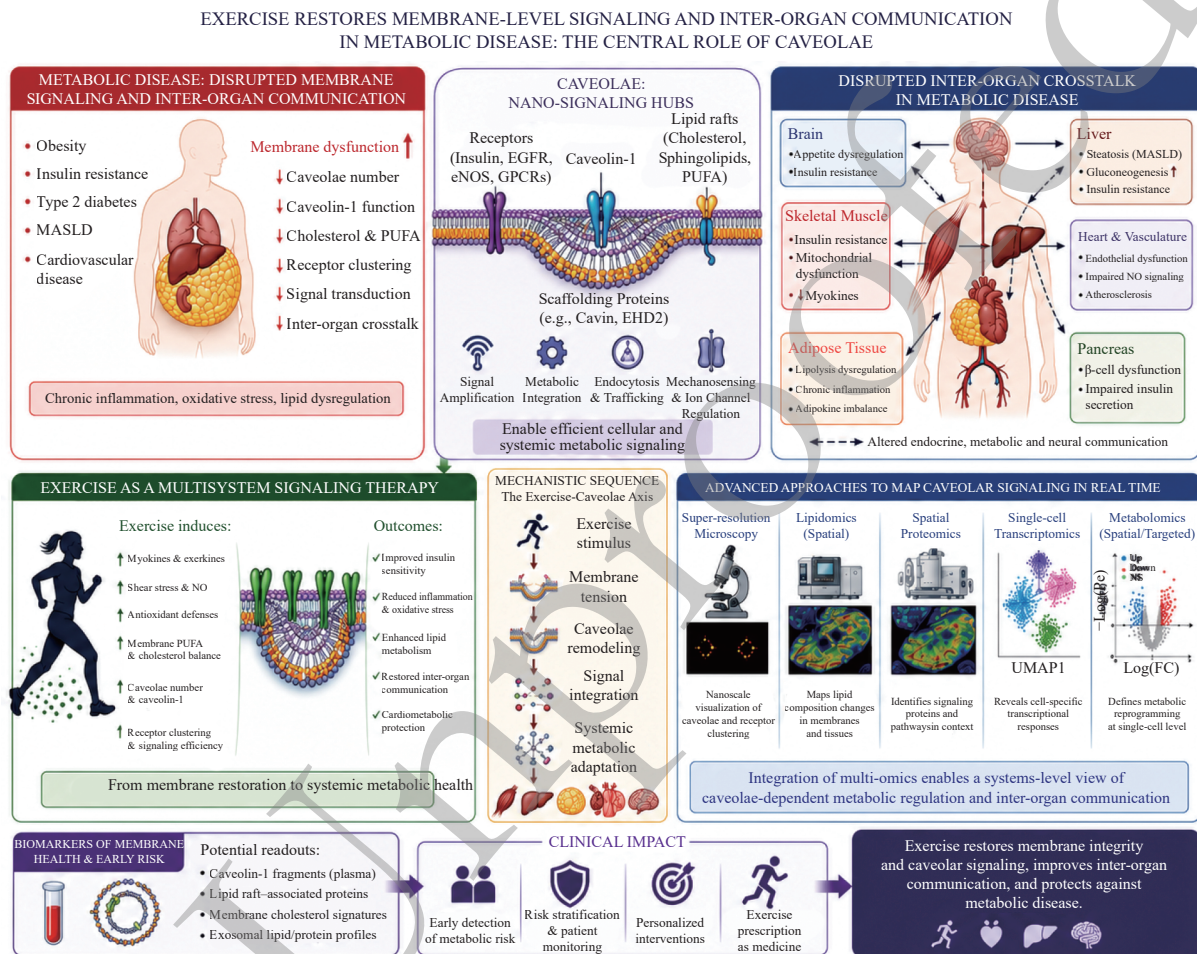


Fig. 1 proposed caveolae-centered framework for exercise-induced multisystem signaling in inter-organ communication and metabolic disease. Exercise generates a coordinated array of mechanical forces, endocrine mediators, metabolic cues, lipid remodeling events, inflammatory regulation, and localized redox signals across multiple organs. These signals shape the function of skeletal muscle, adipose tissue, liver, vascular endothelium, and the central nervous system through extensive inter-organ communication, ultimately influencing metabolic homeostasis and susceptibility to metabolic disease. Caveolae are proposed to act as a membrane-based signaling platform capable of spatially organizing subsets of these diverse extracellular stimuli through mechanotransduction, receptor compartmentalization, lipid microdomain regulation, and localized signal amplification. Current evidence most strongly supports caveolar mechanotransduction in vascular endothelium, whereas caveolar involvement in other tissues relevant to metabolic disease remains variable and requires further investigation. Accordingly, this model should be considered a hypothesis-generating conceptual framework rather than an established mechanism.

current evidence supporting interactions between exercise biology and caveolae across skeletal muscle, liver, adipose tissue, vascular endothelium, and the central nervous system. Particular emphasis is placed on distinguishing well-established mechanisms from emerging hypotheses, evaluating differences in evidence strength among tissues, and identifying important gaps that require direct experimental investigation. Rather than presenting a definitive mechanistic model, we aim to provide a hypothesis-driven framework that integrates systems physiology with membrane biology and that may guide future studies exploring how spatial organization of membrane-signaling contributes to the therapeutic benefits of exercise.

Literature search strategy

This conceptual review was designed to synthesize current evidence concerning exercise-induced inter-organ communication, membrane microdomain biology, mechanotransduction, and caveolae-dependent metabolic regulation. Literature searches were performed using PubMed, Web of Science, and Scopus for articles published through June 2026.

Search terms included combinations of exercise, exercise therapy, physical activity, caveolae, caveolin, cavin, mechanotransduction, membrane microdomains, lipid rafts, inter-organ communication, myokines, exerkines, endothelial shear stress, metabolic disease, insulin resistance, obesity, type 2 diabetes, MASLD, lipid remodeling, and exercise lipidomics. Additional relevant publications were identified through manual examination of reference lists from eligible articles.

Priority was given to original experimental studies, systematic reviews, and meta-analyses, particularly those investigating exercise physiology, membrane biology, mechanotransduction, caveolae function, and metabolic regulation. Narrative reviews and perspective articles were consulted primarily to identify relevant primary literature rather than as primary evidentiary support. Because direct studies linking exercise-induced caveolar remodeling with systemic metabolic adaptation remain limited, selected mechanistic evidence from complementary fields, including vascular biology, membrane biophysics, mechanotransduction, and lipid metabolism was incorporated to develop a hypothesis-generating conceptual framework. Throughout the review, established experimental findings are distinguished from proposed mechanisms and areas where direct evidence remains insufficient.

Exercise as a whole-body signaling network

Exercise represents a unique physiological intervention because it simultaneously activates mechanical, metabolic, endocrine, neural, immune, and vascular pathways across multiple organs^[10]. Unlike pharmacological therapies that typically target individual receptors or signaling cascades, exercise generates numerous concurrent stimuli that vary in magnitude, duration, and tissue specificity. These cooperated responses enable adaptation of whole-body metabolism while maintaining physiological homeostasis under increased energetic demand.

Skeletal muscle is the primary site of force generation during exercise, but it also functions as a major endocrine organ. Contracting muscle releases a diverse repertoire of biologically active molecules, including myokines, metabolites, nucleic acids, and extracellular vesicles, that communicate with distant tissues^[4,11–16]. Collectively termed exerkines^[17], these circulating mediators can influence hepatic glucose production, adipose tissue lipolysis, pancreatic hormone secretion, vascular function, immune activity, and central nervous system regulation. In parallel, reciprocal signals from adipose tissue^[18], liver^[19], vascular endothelium^[20], immune cells^[21], and the brain^[22] modify skeletal muscle metabolism, forming an interconnected network of bidirectional communication rather than a simple muscle-to-organ signaling axis.

Exercise also produces substantial mechanical stimulation^[23]. Muscle contraction generates membrane deformation and cytoskeletal tension, while increased cardiac output exposes vascular endothelial cells to elevated laminar shear stress. Simultaneously, repeated cycles of contraction and relaxation alter extracellular matrix loading, hydrostatic pressure, and tissue stiffness. These biomechanical signals regulate intracellular signaling independently of circulating hormones and therefore distinguish exercise from purely pharmacological interventions.

Metabolic perturbations provide an additional regulatory layer. ATP consumption, alterations in AMP/ATP ratios, calcium oscillations, transient hypoxia, changes in substrate availability, and reactive oxygen species (ROS) production activate multiple adaptive pathways, including AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α), mammalian target of rapamycin (mTOR), insulin signaling, and antioxidant defense systems^[24–30]. These responses occur concurrently with endocrine and mechanical

signaling, creating a highly incorporated physiological environment. These signals regulate hepatic glucose production, adipose tissue lipolysis, vascular function, and central energy balance, thereby coordinating substrate availability and utilization. For example, muscle-derived signals can suppress hepatic gluconeogenesis while enhancing lipid mobilization from adipose tissue, aligning systemic energy supply with increased demand^[31–33]. In addition to these feedforward mechanisms, peripheral organs generate feedback signals, such as hepatokines and adipokines, that modulate muscle metabolism and contribute to the fine-tuning of systemic homeostasis^[34–35], which is discussed further in the following section. This bidirectional communication is now recognized as a defining feature of exercise physiology, enabling rapid, consolidated adjustments across tissues.

Increasing evidence from multi-organ molecular profiling demonstrates that exercise-induced adaptations cannot be adequately explained by isolated pathways^[36]. Instead, exercise should be regarded as a systems-level signaling network in which multiple organs communicate through endocrine factors, metabolites, extracellular vesicles, immune mediators, vascular signals, and biomechanical forces. This systems' perspective raises an important mechanistic question: how are these diverse extracellular inputs harmonized within individual cells to generate coherent adaptive responses?

From exercise-derived signals to membrane signal integration

Although the systemic effects of exercise are increasingly well characterized, the intracellular mechanisms responsible for integrating multiple simultaneous exercise-derived signals remain incompletely understood. Individual cells are exposed simultaneously to circulating hormones, inflammatory mediators, metabolites, lipid species, extracellular vesicles, changes in membrane tension, oxidative signals, and mechanical loading. Rather than functioning independently, these stimuli frequently converge on common signaling pathways, including insulin receptor signaling, nitric oxide production, calcium homeostasis, AMPK activation, and cytoskeletal remodeling. Efficient cellular adaptation therefore requires structural mechanisms capable of spatially organizing these diverse inputs.

Several membrane-associated systems participate in signal integration, including receptor complexes, focal adhesions, integrins, primary cilia, lipid rafts,

cytoskeletal networks, and specialized membrane microdomains^[36]. These structures are not mutually exclusive but instead cooperate to coordinate cellular responses to complex extracellular environments.

Among these candidate integrative platforms, caveolae possess several characteristics that make them particularly relevant to exercise physiology. Caveolae are flask-shaped plasma membrane invaginations enriched in cholesterol, sphingolipids, caveolins, and cavinins that compartmentalize receptors, scaffold proteins, ion channels, lipid transporters, and signaling intermediates within organized membrane domains^[37]. Their ability to respond to mechanical forces while remaining sensitive to membrane lipid composition and metabolic state provides a potential mechanism for coordinating diverse exercise-derived stimuli.

Caveolae can undergo rapid structural remodeling in response to changes in membrane tension and mechanical loading, while their lipid composition and associated proteins influence receptor organization and intracellular signaling^[38–39]. They also contain or interact with signaling components involved in endothelial function, insulin signaling, lipid transport, and redox regulation. These properties provide a biologically plausible basis for considering caveolae as one membrane platform through which mechanical, metabolic, endocrine, and redox signals may be spatially aligned.

However, this interpretation remains a conceptual hypothesis. Although substantial evidence supports individual functions of caveolae in mechanotransduction, receptor organization, lipid metabolism, and endothelial biology^[40–41], direct evidence demonstrating that exercise-induced caveolar remodeling integrates these diverse signaling pathways *in vivo* remains limited. Consequently, caveolae should presently be regarded as one candidate integrative mechanism rather than the exclusive coordinator of exercise adaptation.

The subsequent sections therefore examine this hypothesis at the level of individual organ systems and inter-organ axes, with particular emphasis on the strength of experimental evidence and the distinction between established mechanisms and emerging possibilities.

Inter-organ communication during exercise: Current evidence

The therapeutic benefits of exercise depend upon harmonized communication among multiple metabolically active organs as reviewed by Kong, *et al.*^[42]. However, the strength of evidence supporting

caveolae involvement differs considerably across tissues. Distinguishing established mechanisms from emerging hypotheses is therefore essential when evaluating the proposed conceptual framework.

Skeletal muscle–liver communication

The skeletal muscle–liver axis plays a central role in maintaining glucose homeostasis during exercise. Contracting muscle increases glucose utilization while simultaneously releasing myokines and metabolites that influence hepatic glycogenolysis, gluconeogenesis, and lipid metabolism^[32,43]. Conversely, the liver secretes hepatokines that regulate skeletal muscle insulin sensitivity, substrate utilization, and mitochondrial metabolism^[44–45].

Recent evidence highlights that this axis is not merely metabolic but also involves membrane-level adaptations, including changes in hepatocyte spatial organization with caveolae that influence insulin receptor signaling^[46]. Evidence supporting endocrine communication between skeletal muscle and liver is extensive^[47–48]. But evidence directly linking caveolae to the coordination of this bidirectional communication remains relatively underdeveloped. Experimental studies demonstrate important roles for caveolae in hepatic insulin receptor organization and lipid trafficking, but whether exercise-induced remodeling of hepatic caveolae contributes directly to systemic metabolic adaptation has not yet been established.

Accordingly, current evidence may support an indirect role for caveolae within the muscle–liver axis while highlighting an important area for future investigation.

Skeletal muscle–adipose tissue communication

Communication between skeletal muscle and adipose tissue regulates substrate availability during exercise. Catecholamines stimulate adipocyte lipolysis, increasing free fatty acid availability for skeletal muscle oxidation^[49], while muscle-derived myokines influence adipocyte metabolism, inflammation, and endocrine activity^[33]. In turn, adipokines regulate skeletal muscle insulin sensitivity, mitochondrial function, and inflammatory signaling^[35]. This bidirectional axis is increasingly understood to depend on adipocyte membrane architecture, with caveolar dysfunction impairing lipid buffering and amplifying ectopic fat deposition^[50]. Chronic metabolic stress, including obesity, disrupts this bidirectional communication, leading to altered lipid handling and ectopic fat deposition^[51–52].

Compared with liver, stronger evidence supports an

important role for caveolae within adipocyte biology. Caveolae can contribute to lipid droplet expansion, fatty acid transport, membrane flexibility, and adipocyte mechanoadaptation. Experimental disruption of caveolar proteins can alter adipocyte morphology, lipid buffering, and insulin responsiveness, suggesting that membrane organization contributes to adipose tissue function^[53].

Whether exercise remodels adipocyte caveolae sufficiently to mediate systemic improvements in metabolic health remains incompletely understood. Current evidence therefore may support caveolae as plausible modulators of adipose adaptation but could not yet establish causality.

Skeletal muscle–vascular communication

Among all proposed organ systems, the vascular endothelium currently provides the strongest mechanistic support for the caveolae-centered model.

Increased blood flow and shear stress during exercise enhance endothelial function and nitric oxide production, facilitating nutrient delivery and waste removal as described by Laukkanen and Kunutsor^[54]. Muscle-derived signals further influence vascular tone and angiogenesis, promoting capillary density and tissue perfusion. Exercise markedly increases laminar shear stress, stimulating endothelial nitric oxide production, vascular remodeling, angiogenesis, and anti-inflammatory signaling^[55]. Endothelial caveolae contain numerous mechanosensitive signaling proteins, including caveolin-1, eNOS, Src-family kinases, and associated cytoskeletal components. Experimental studies demonstrate that caveolae rapidly respond to changes in membrane tension and shear stress through structural remodeling that influences downstream signaling^[56].

Although additional work is needed to determine how these responses contribute to whole-body metabolic adaptation, endothelial mechanotransduction represents the most experimentally supported example linking exercise-generated mechanical forces with caveolae-dependent signaling.

Skeletal muscle–brain communication

Exercise influences appetite regulation, autonomic activity, cognition, mood, and energy balance through extensive communication between peripheral tissues and the central nervous system (reviewed by Espinoza *et al.*^[57]). Myokines, metabolites, extracellular vesicles, and neural pathways all contribute to these adaptive responses. In parallel, central nervous system outputs regulate muscle function, substrate utilization, and

hormonal responses during exercise, described by Kong *et al*[42]. Extracellular vesicles released during exercise may deliver membrane-associated proteins and lipids to the brain, adding a structural dimension to muscle–brain communication, suggested by Moon and van Praag[58]. Because endothelial caveolae are primary mechanosensors for shear stress, this axis represents a key interface where mechanical forces and metabolic regulation converge. Impairment of this axis could be linked to endothelial dysfunction and cardiovascular disease.

Several studies suggest that extracellular vesicles may transport membrane-associated proteins and lipids capable of influencing neuronal function[59]. Nevertheless, direct evidence demonstrating caveolae-dependent regulation of exercise-induced brain signaling remains sparse. Much of the current literature derives from studies of neuronal membrane biology rather than exercise physiology.

Consequently, incorporation of the muscle–brain axis into the present conceptual framework should be regarded as hypothesis-generating rather than experimentally established.

Summary of tissue-specific evidence

The strength of evidence supporting caveolae as mediators of exercise-driven inter-organ communication is summarized in Tab-1 to distinguish well-established mechanisms from emerging hypotheses.

Collectively, current evidence may support substantial heterogeneity in the strength of evidence linking caveolae to exercise-mediated inter-organ communication.

The endothelial system presently provides the strongest experimental support because caveolae are well-established mechanosensors that respond directly to exercise-induced shear stress. Adipose tissue also possesses considerable evidence supporting caveolar regulation of lipid handling and membrane mechanics, although exercise-specific studies remain limited. Hepatic caveolae are increasingly recognized as important regulators of insulin signaling and lipid metabolism, but direct exercise evidence is relatively insufficient. Finally, caveolae-dependent mechanisms within the muscle–brain axis remain largely speculative.

Recognizing these differences is essential for avoiding overinterpretation of the available evidence. Rather than assuming equivalent support across all tissues, the proposed framework should be viewed as a graded conceptual model in which some components are strongly supported whereas others require

substantial experimental validation. This evidence-based perspective provides the foundation for the subsequent discussion of caveolae as candidate integrative membrane platforms capable of coordinating multisystem exercise signaling.

Caveolae as candidate integrators of exercise-induced signaling

The preceding sections demonstrate that exercise generates synchronized endocrine, mechanical, metabolic, vascular, and inflammatory signals across multiple organs. An unresolved question, however, is how these diverse extracellular stimuli are coordinated at the cellular level to produce coherent adaptive responses. We propose that caveolae represent one important membrane platform capable of facilitating such integration. This proposal is based on the convergence of independent lines of evidence from membrane biology, mechanotransduction, lipid metabolism, and vascular physiology rather than on direct experimental demonstrations of exercise-dependent caveolar remodeling. Consequently, the following sections distinguish well-supported mechanisms from emerging hypotheses.

Caveolae as dynamic membrane-signaling platforms

Caveolae are specialized plasma membrane invaginations approximately 50–100 nm in diameter that are particularly abundant in endothelial cells, adipocytes, skeletal muscle fibers, fibroblasts, and smooth muscle cells[41]. Their characteristic flask-shaped morphology is maintained by caveolin proteins (predominantly Caveolin-1 and Caveolin-3) together with cavin family proteins, cholesterol, sphingolipids, and interactions with the cortical cytoskeleton.

Initially regarded primarily as structural membrane domains, caveolae are now recognized as active signaling compartments that spatially organize membrane receptors, transport proteins, ion channels, and intracellular signaling molecules. Rather than functioning as static membrane structures, caveolae continuously assemble, disassemble, flatten, and reform in response to changes in membrane tension, lipid composition, and cellular metabolism[60].

Notably, caveolae should not be considered isolated signaling entities. They function alongside other membrane microdomains, focal adhesions, integrins, lipid rafts, and cytoskeletal networks to coordinate cellular responses. The present review therefore proposes that caveolae represent one component of a broader membrane-signaling architecture rather than

the exclusive regulator of exercise adaptation.

Mechanotransduction: The strongest evidence supporting the model

Among the various functions attributed to caveolae, mechanotransduction may provide the strongest experimental support for their potential involvement in exercise physiology.

Mechanical loading is an unavoidable consequence of physical activity. Skeletal muscle contraction repeatedly deforms the sarcolemma, while increased cardiac output during exercise substantially elevates laminar shear stress acting on vascular endothelial cells^[61]. Both conditions impose rapid alterations in membrane tension that require immediate cellular adaptation to preserve membrane integrity and maintain signaling fidelity.

Experimental studies have demonstrated that caveolae respond rapidly to increases in membrane tension through reversible flattening of the caveolar invagination^[61]. This process provides additional membrane surface area while simultaneously reorganizing caveola-associated signaling complexes. In endothelial cells, shear stress also modifies caveolar organization, influencing nitric oxide signaling, cytoskeletal remodeling, and vascular adaptation^[62].

These observations establish caveolae as authentic mechanosensitive membrane structures. However, whether exercise-induced mechanical remodeling of caveolae directly improves systemic insulin sensitivity, metabolic flexibility, or whole-body energy homeostasis remains unresolved, even though disruption of caveolar structure itself can precipitate metabolic disorders^[63]. Current evidence therefore may support a mechanistic role in cellular force sensing while leaving its contribution to organismal metabolic adaptation, an important question, for future investigation.

Lipid remodeling and membrane adaptation during exercise

Exercise induces substantial alterations in lipid metabolism at both systemic and cellular levels. Acute exercise mobilizes fatty acids from adipose tissue, whereas chronic exercise training remodels membrane phospholipid composition, cholesterol distribution, and mitochondrial lipid metabolism^[64]. These changes contribute to improved membrane fluidity, insulin responsiveness, mitochondrial function, and metabolic flexibility.

Because caveolae are highly enriched in cholesterol and sphingolipids, their structural integrity is closely linked to membrane lipid composition. Experimental

manipulation of membrane cholesterol rapidly alters caveolar morphology, receptor localization, and intracellular signaling^[65]. Similarly, changes in phospholipid composition may influence caveolar stability^[66], although the physiological significance of these alterations during exercise remains incompletely characterized.

Recent exercise-lipidomics studies demonstrate extensive remodeling of multiple phospholipid species following acute and chronic exercise interventions^[67]. These observations provide indirect support for the possibility that exercise modifies caveolar structure through alterations in membrane lipid composition. Nevertheless, few investigations have directly measured caveolar abundance or architecture alongside exercise-induced lipid remodeling. Therefore, the proposed relationship between membrane lipid adaptation and caveolar remodeling remains a plausible but currently unproven mechanism.

Caveolae and spatial organization of metabolic signaling

Efficient metabolic regulation depends not only on the presence of signaling molecules but also on their spatial organization within the plasma membrane. Caveolae concentrate numerous receptors and signaling proteins involved in glucose transport, insulin signaling, lipid metabolism, nitric oxide production, and ion transport. By organizing these molecules within confined membrane domains, caveolae may facilitate efficient signal propagation while minimizing inappropriate pathway activation.

For example, experimental studies have demonstrated that disruption of caveolar organization alters insulin receptor localization, glucose transporter trafficking, endothelial nitric oxide synthase activity, and cholesterol homeostasis as described by Paron *et al.*^[9] and Zhang^[68]. These observations support an important role for caveolae in regulating membrane-associated signaling.

Whether exercise actively remodels this spatial organization has not yet been established directly. It is therefore more appropriate to propose that exercise may influence membrane-signaling architecture through changes in caveolar organization rather than concluding that such remodeling has already been demonstrated experimentally.

Localized redox signaling within caveolar microdomains

Reactive oxygen species (ROS) are increasingly recognized as essential signaling mediators rather than

merely harmful metabolic by-products. During exercise, transient increases in ROS^[69] can contribute to mitochondrial biogenesis, antioxidant defense, glucose uptake, and adaptive gene expression. The biological effects of ROS depend largely on their spatial localization, concentration, and duration.

Several caveola-associated proteins, including endothelial nitric oxide synthase, Src-family kinases, and multiple receptor-associated signaling molecules, are sensitive to localized redox changes^[70-71]. This raises the possibility that caveolae may provide microdomains in which reactive oxygen and nitrogen species regulate signaling with high spatial precision in preventing widespread membrane damage. This function may be particularly relevant in exercise, where transient increases in ROS contribute to beneficial adaptations but require tight regulation, pointed by Sireno *et al*^[72]

Current evidence supporting this concept derives primarily from studies of endothelial biology and cellular stress responses rather than exercise interventions. Accordingly, although localized redox regulation represents a biologically plausible component of the proposed framework, direct evidence demonstrating exercise-specific caveolar redox remodeling remains limited.

Tissue Specificity of Caveolar Remodeling

An important limitation of current knowledge is the assumption that caveolae respond uniformly across tissues. In reality, caveolar abundance, molecular composition, and physiological function differ substantially among organs.

Endothelial cells possess abundant Caveolin-1-rich caveolae^[73] that respond rapidly to vascular shear stress, providing strong mechanistic support for exercise-induced caveolar adaptation. Adipocytes also contain numerous caveolae^[53] involved in lipid trafficking, membrane expansion, and insulin responsiveness, making adipose tissue another plausible target for exercise-induced remodeling.

By contrast, the liver contains comparatively fewer caveolae^[74] and available evidence suggests more specialized roles in receptor organization and lipid metabolism^[75]. Skeletal muscle expresses Caveolin-3-containing caveolae that contribute to sarcolemmal stability and mechanoprotection^[56], although direct links with exercise adaptation remain relatively limited. The nervous system is not the classic "caveolae-rich" tissue like muscle or adipose, yet caveolae and caveolin proteins play distinct, functionally important roles in neurons^[76], glia^[77], and neurovascular cells^[77]. Evidence supporting caveolae-

dependent regulation within the central nervous system is currently the weakest and should be regarded as largely hypothesis-generating.

Recognizing this tissue heterogeneity is essential for interpreting the proposed conceptual model. Rather than suggesting a universal mechanism operating identically in every organ, we propose that caveolae may contribute to exercise adaptation in a tissue-dependent manner, with the strongest evidence presently available for the vascular endothelium and adipose tissue.

Influence of exercise modality on caveolar adaptation

Exercise is frequently discussed as a single intervention despite substantial physiological differences among exercise modalities. Aerobic endurance exercise, resistance training, high-intensity interval exercise, and prolonged sedentary interruption generate distinct patterns of mechanical loading, vascular shear stress, substrate utilization, endocrine signaling, and inflammatory responses.

Aerobic exercise is likely to exert its greatest influence on endothelial caveolae through sustained increases in laminar shear stress and nitric oxide signaling^[78]. Resistance exercise may preferentially affect skeletal muscle caveolae by increasing sarcolemmal tension and cytoskeletal remodeling^[79]. High-intensity interval exercise combines large mechanical and metabolic perturbations and may therefore induce particularly dynamic caveolar responses, although direct evidence remains scarce.

Disease state is also likely to influence caveolar remodeling. Obesity, insulin resistance, aging, and metabolic dysfunction are associated with altered membrane lipid composition, impaired mechanotransduction, oxidative stress, and chronic inflammation, all of which may modify caveolar stability and responsiveness to exercise. Disruption of caveolae has been linked to key features of metabolic disease, including insulin resistance, impaired lipid handling, and endothelial dysfunction. These alterations may reflect a loss of the integrative capacity required to coordinate responses to metabolic and mechanical stimuli. From this perspective, caveolae dysfunction can be viewed as a breakdown in membrane-level signal processing, leading to dysregulated inter-organ communication and systemic metabolic imbalance. Understanding caveolae as integrative signaling platforms may provide a mechanistic bridge between systemic exercise physiology and cellular signaling. This perspective supports the emerging concept that effective metabolic

regulation depends not only on the generation of signals but also on the integrity of the membrane structures that interpret them^[9]. As such, caveolae may represent a critical interface through which exercise exerts its coordinated and multisystem effects. However, whether these pathological changes can alter the capacity for exercise-induced caveolar adaptation represents an important area for future investigation.

Current evidence is insufficient to identify the optimal exercise modality for promoting caveolar remodeling. Nevertheless, recognizing modality- and disease-specific differences provides a more realistic framework than assuming identical responses across all forms of physical activity.

Summary

Notably, caveolae are not static structures but dynamically remodel in response to environmental conditions. Changes in membrane lipid composition, mechanical stress, and metabolic state can alter caveolar number, morphology, and protein composition, thereby influencing their signaling capacity. This adaptability is central to the proposed model in which exercise reshapes membrane structural landscape to restore metabolic coordination.

Available evidence supports several established functions of caveolae, including mechanotransduction, membrane tension buffering, receptor compartmentalization, lipid organization, and endothelial signaling (reviewed by Lamaze *et al*^[37] and described in above sections). These independently validated functions provide a biologically plausible basis for proposing that caveolae participate in integrating multiple exercise-derived signals.

However, the central hypothesis advanced in this review, that exercise-induced caveolar remodeling contributes to collaborated systemic metabolic adaptation, remains incompletely tested. The strongest support currently derives from endothelial mechanobiology, whereas evidence linking caveolae to exercise-mediated endocrine communication, lipid remodeling, and inter-organ metabolic regulation remains indirect or tissue dependent.

Accordingly, caveolae should presently be viewed not as a proven master regulator of exercise adaptation but as a promising candidate integrative platform whose contribution can be evaluated through future mechanistic studies. The following section examines how this hypothesis may be tested experimentally and discusses its implications for the development of exercise-based therapeutic strategies.

Experimental validation of the caveolae-centered hypothesis

The caveolae-centered framework proposed in this review is intended as a testable biological hypothesis rather than an established mechanistic model. Although independent experimental evidence supports roles for caveolae in mechanotransduction, membrane organization, insulin signaling, lipid homeostasis, and endothelial biology, direct evidence demonstrating that exercise-induced caveolar remodeling causally mediates systemic metabolic adaptation remains limited. Consequently, future experimental studies should determine whether caveolae function as essential integrative platforms or represent one of several parallel mechanisms contributing to exercise-induced physiological adaptation.

A defining characteristic of a useful scientific hypothesis is that it generates predictions capable of being experimentally confirmed or refuted. Several experimental approaches could therefore be used to evaluate the present model.

Genetic models

Genetic manipulation of caveolar proteins provides one of the most direct methods for assessing the proposed framework.

Global or tissue-specific deletion of Caveolin-1, Caveolin-3, or members of the Cavin protein family allows investigators to determine whether disruption of caveolar architecture alters physiological adaptation to exercise. Exercise interventions performed in these genetically modified animals could evaluate changes in insulin sensitivity, endothelial function, mitochondrial adaptation, glucose tolerance, substrate utilization, vascular remodeling, and exercise performance.

Importantly, tissue-specific knockout models are likely to provide greater mechanistic insight than global deletion because caveolae perform distinct physiological functions in different organs. Endothelial-specific deletion may clarify roles in vascular adaptation, whereas skeletal muscle- or adipocyte-specific deletion could distinguish effects on metabolic flexibility from systemic endocrine regulation.

If exercise-induced improvements are substantially attenuated following disruption of caveolar proteins, this would provide strong support for the proposed integrative model. Conversely, preservation of normal exercise adaptation despite loss of caveolae would suggest that alternative membrane-signaling

mechanisms compensate for their absence.

Exercise intervention studies

Human and animal exercise studies should evaluate caveolar remodeling directly rather than inferring its involvement from downstream metabolic outcomes.

Future investigations should combine standardized exercise protocols with assessment of caveolar abundance, membrane ultrastructure, caveolin expression, cavin proteins, membrane lipid composition, and spatial receptor organization. Simultaneous measurements of insulin signaling, nitric oxide bioavailability, inflammatory mediators, mitochondrial function, and lipid metabolism would help establish temporal relationships between membrane remodeling and metabolic adaptation.

Comparisons among aerobic exercise, resistance training, high-intensity interval training, and combined exercise programs would further determine whether different patterns of mechanical loading generate distinct caveolar responses. Longitudinal designs are particularly important because acute exercise-induced membrane remodeling may differ substantially from chronic adaptations resulting from exercise training.

Spatial multi-omics and advanced imaging

Recent technological advances provide unprecedented opportunities to investigate membrane biology during exercise.

Recent technological advances, including super-resolution microscopy, single-molecule tracking, cryo-electron tomography, spatial transcriptomics, and integrated spatial multi-omics (proteomics, lipidomics, and metabolomics), now enable membrane organization to be characterized from the nanometer scale to intact tissues with unprecedented spatial and molecular resolution^[80-82]. These approaches permit simultaneous visualization of caveolar morphology, receptor localization, lipid composition, and intracellular signaling within individual cells.

Integration of spatial imaging with exercise physiology may determine whether caveolar remodeling occurs uniformly across tissues or whether responses differ according to organ function, exercise modality, age, or metabolic disease. Such studies are essential because the proposed framework predicts spatial reorganization of membrane-signaling rather than simply altered protein expression.

Human translational studies

Although animal models provide valuable mechanistic insight, translation to clinical practice

requires validation in humans.

Future clinical studies should investigate whether exercise modifies caveolar organization in skeletal muscle, adipose tissue, vascular endothelium, or circulating extracellular vesicles obtained before and after exercise interventions. These measurements should be correlated with improvements in insulin sensitivity, endothelial function, aerobic capacity, metabolic flexibility, and body composition.

Studies involving obesity, type 2 diabetes mellitus, MASLD, cardiovascular disease, and healthy aging will be particularly informative because these conditions exhibit abnormalities in membrane lipid metabolism, vascular function, and mechanotransduction. Determining whether restoration of caveolar integrity parallels clinical improvement would substantially strengthen the translational relevance of the proposed model.

Therapeutic implications

Exercise remains the most effective non-pharmacological intervention for improving metabolic health and providing cardioprotection^[83] because it simultaneously targets numerous physiological systems. The caveolae-centered framework proposed here suggests that future therapeutic strategies might benefit from preserving or enhancing membrane organization rather than targeting isolated "downstream" signaling pathways.

It is important to emphasize, however, that current evidence does not yet support direct therapeutic targeting of caveolae in routine clinical practice, despite it having been recently proposed by Zhang^[68]. Instead, caveolae are better understood as a mechanistic framework that can inform the development of complementary interventions aimed at enhancing exercise-induced adaptation. This perspective also raises several translational possibilities, including exercise mimetics, membrane-targeted interventions, precision exercise medicine, and biomarkers for monitoring exercise responsiveness.

Exercise as a systems-level therapy

Traditional pharmacological therapies often target individual receptors or signaling molecules. Although effective for specific pathways, such approaches rarely reproduce the broad physiological adaptations induced by regular exercise.

Exercise simultaneously modifies endocrine communication, vascular function, mitochondrial metabolism, immune regulation, extracellular matrix

remodeling, lipid metabolism, and neural signaling. If caveolae can contribute to integrating these diverse stimuli, preservation of membrane organization may represent an important determinant of exercise responsiveness.

This concept reinforces the view that exercise should be considered a multi-organ biological therapy rather than merely a means of increasing energy expenditure. It also provides a rationale for investigating whether pharmacological interventions can reproduce selected components of exercise-induced membrane and metabolic adaptation in individuals who are unable to undertake sufficient physical activity.

Exercise mimetics

The concept of exercise mimetics has emerged from efforts to reproduce selected molecular pathways activated by physical activity. Candidate approaches have targeted pathways involved in energy sensing, mitochondrial adaptation, glucose utilization, and fatty-acid oxidation. Such strategies may be particularly relevant for individuals who cannot achieve adequate exercise because of advanced age, severe obesity, cardiopulmonary disease, neurological disability, or other limitations.

From a caveolae-centered perspective, however, exercise mimetics should not be regarded as complete substitutes for physical activity. Exercise produces mechanical forces, changes membrane tension, alters membrane lipid organization, modifies blood flow and shear stress, and generates endocrine and inter-organ signals that cannot readily be reproduced by activation of a single intracellular pathway. An important future question is therefore whether exercise-mimetic interventions can reproduce selected membrane-level responses, including caveolar remodeling, receptor redistribution, and mechanotransduction.

Exercise mimetics may consequently be most useful as complementary therapies that augment rather than replace physical activity. Determining whether candidate exercise-mimetic approaches can influence caveolar structure or function will require direct experimental investigation.

Membrane lipid remodeling and membrane-targeted therapeutics

Because caveolae depend strongly upon membrane lipid composition, interventions that preserve membrane lipid homeostasis may theoretically enhance caveolar function.

Regular exercise improves membrane phospholipid composition, cholesterol handling, fatty acid

utilization, and mitochondrial lipid metabolism. Dietary modification may exert complementary effects by providing substrates necessary for membrane remodeling.

Although these observations suggest potential interactions between nutrition, membrane biology, and exercise adaptation, direct experimental evidence demonstrating that dietary interventions specifically can enhance caveolae-mediated exercise responses remains limited.

A related therapeutic possibility is the development of membrane-targeted interventions designed to preserve membrane organization or selectively modulate membrane-associated signaling. Rather than directly targeting caveolae, such approaches could potentially influence membrane cholesterol distribution, lipid composition, caveolin-cavin interactions, receptor clustering, or mechanosensitive signaling.

This approach requires caution because caveolae participate in multiple physiological processes, including mechanoprotection, endocytosis, lipid trafficking, vascular signaling, and receptor regulation. Excessive stabilization or disruption of caveolae could therefore have unintended consequences. Future membrane-targeted therapies may consequently need to restore appropriate membrane organization and adaptive plasticity rather than simply increase or decrease caveolae. At present, however, such approaches remain experimental and no caveolae-directed therapy has been established for routine clinical treatment of metabolic disease.

Precision exercise prescription

Exercise is increasingly recognized as a form of precision medicine^[84] in which optimal intervention depends upon age, disease status, genetic background, and baseline physiological function.

The caveolae-centered framework may further suggest that individuals with endothelial dysfunction, obesity, insulin resistance, or altered membrane lipid composition may exhibit different capacities for exercise-induced membrane remodeling. Consequently, future exercise prescription may eventually incorporate biomarkers reflecting membrane organization or mechanotransduction capacity.

This possibility may help explain part of the substantial inter-individual variability observed in responses to exercise. Differences in caveolin and cavin expression, membrane lipid composition, receptor organization, mechanosensitive signaling, and mitochondrial function could influence how cells

perceive and respond to mechanical and metabolic exercise stimuli.

Future precision exercise medicine may therefore combine conventional clinical characteristics with molecular measures of exercise responsiveness. Integrated physiological, metabolic, lipidomic, and membrane-associated biomarkers could eventually help identify the type, intensity, duration, and frequency of exercise most likely to produce beneficial adaptation in individual patients.

At present, however, these possibilities remain speculative and require validation in prospective clinical studies. In particular, it remains necessary to determine whether membrane-related phenotypes can reliably predict exercise responsiveness and whether biomarker-guided exercise prescription improves clinical outcomes compared with conventional exercise prescription.

Caveolae as potential biomarkers

Rather than serving as immediate therapeutic targets, caveolar proteins may prove valuable as biomarkers of exercise responsiveness.

Alterations in Caveolin-1 expression, caveolar density, membrane lipid composition, or caveola-associated extracellular vesicles could potentially reflect an individual's capacity for physiological adaptation. Combined with metabolomic and transcriptomic profiling, such biomarkers may assist in monitoring responses to lifestyle intervention.

Potential biomarker candidates include changes in Caveolin-1 and Caveolin-3 abundance, caveola-associated proteins, extracellular-vesicle-associated caveolar components, membrane lipid signatures, and circulating protein or metabolite profiles associated with membrane remodeling. Because exercise produces tissue-specific adaptations, circulating biomarkers should not automatically be interpreted as direct measures of caveolar abundance or function within individual organs.

A particularly promising strategy may be to combine caveola-associated measurements with lipidomics, proteomics, metabolomics, and transcriptomics. Integrated molecular profiling could identify signatures associated with favourable or impaired exercise responses and potentially distinguish individuals who respond strongly from those with limited adaptation. Serial measurements before and after exercise training could also provide a means of monitoring whether an intervention improves membrane-associated metabolic signaling.

Further research is required prior to these approaches becoming clinically applicable. Analytical

standardization, validation in independent populations, and demonstration of predictive or prognostic value will be necessary before caveola-associated biomarkers can be incorporated into routine clinical practice.

Integrated translational perspective

Taken together, these concepts suggest a translational continuum extending from exercise itself to exercise-inspired and membrane-oriented interventions. Exercise provides the most comprehensive physiological stimulus, whereas exercise mimetics may reproduce selected intracellular pathways, membrane-targeted approaches may modify the cellular environment in which signaling occurs, and biomarker-guided precision exercise medicine may help identify individuals most likely to benefit from particular interventions.

The caveolae-centered model therefore does not imply that caveolae should replace established therapeutic targets. Rather, it may provide a complementary framework linking mechanical stimulation, membrane remodeling, signal integration, and systemic metabolic adaptation. Future studies should determine which components of this pathway are causally responsible for beneficial exercise adaptation and which merely accompany it.

Ultimately, the translational objective should be to preserve the adaptive capacity of the membrane while integrating exercise, nutrition, pharmacological therapy, and individualized exercise prescription. Such an approach may move the field beyond treating isolated metabolic abnormalities toward restoring the integrated cellular systems that enable physiological adaptation.

Strengths and limitations

Strengths

The principal strength of this review is the integration of exercise physiology, inter-organ communication, membrane biology, mechanotransduction, and metabolic regulation into a unified conceptual framework. By considering exercise as a systems-level biological intervention, the review provides a broader perspective than traditional organ-specific models and identifies membrane spatial organization as a potentially important but underexplored determinant of metabolic adaptation. The framework integrates multiple established observations from diverse areas of exercise biology and cell biology, and uses these observations to

propose potential links between exercise-induced mechanical and metabolic stimuli, caveolar remodeling, cellular signaling, inter-organ communication, and systemic metabolic adaptation.

A second strength is the explicit distinction between established experimental observations and emerging mechanistic hypotheses. Rather than presenting caveolae as definitive regulators of exercise adaptation, this review evaluates the relative strength of evidence across different tissues and highlights important uncertainties requiring further investigation. The proposed model should therefore be regarded as a conceptual framework for integrating existing evidence and generating testable hypotheses, rather than as an established causal model.

Limitations

First, direct causal evidence linking exercise-induced caveolar remodeling with whole-body metabolic adaptation remains limited. Much of the proposed framework is based on the integration of independent findings from mechanotransduction, endothelial biology, membrane lipid metabolism, cellular signaling, and exercise physiology. Although these observations are biologically compatible with a caveolae-centered model, their integration does not by itself establish a causal relationship between caveolar remodeling and systemic metabolic outcomes.

Second, many of the relationships proposed within the framework remain associative rather than mechanistically demonstrated. Associations between exercise, caveolar organization, signaling pathways, metabolic adaptation, and inter-organ communication may not be necessary to establish that caveolar remodeling is the initiating or obligatory event. In several cases, caveolar changes may represent one component of a broader adaptive response or may occur in parallel with other membrane and cytoskeletal remodeling processes.

Third, evidence is not equally strong across tissues. Endothelial mechanotransduction currently provides relatively strong support for caveolae-dependent responses to mechanical stimuli, whereas evidence involving the liver, skeletal muscle, adipose tissue, and brain remains comparatively limited. Tissue-specific differences in caveolar abundance, caveolin and cavin expression, membrane composition, mechanical loading, and metabolic function may also influence the relevance of caveolar signaling in different organs.

Fourth, many available studies have been performed in cultured cells or genetically modified animal models. These experimental systems have been

essential for defining the molecular functions of caveolae, caveolins, cavins, and associated signaling proteins, but translation of these findings to human exercise physiology requires additional investigation. In particular, human studies combining exercise interventions with direct assessment of caveolar structure, membrane organization, signaling responses, and metabolic outcomes remain relatively scarce.

Fifth, relatively few studies have simultaneously examined exercise intervention, membrane remodeling, caveolar organization, and systemic metabolic outcomes within the same experimental design. Consequently, temporal relationships and causal direction remain difficult to establish. For example, it remains uncertain whether exercise-induced caveolar remodeling is an upstream driver of metabolic adaptation, a permissive structural response, or a consequence of other exercise-induced cellular changes. Future studies incorporating longitudinal interventions, tissue-specific manipulation of caveolar components, advanced imaging, lipidomic and proteomic approaches, and integrated metabolic phenotyping will be necessary to distinguish these possibilities.

Sixth, caveolae operate within a broader network of membrane and mechanosensitive systems that includes lipid rafts, integrins, focal adhesions, cytoskeletal complexes, primary cilia, ion channels, and other membrane-associated signaling platforms. The present framework does not suggest that caveolae function independently of these structures, nor does it imply that caveolae represent the sole mechanism underlying exercise adaptation. Instead, caveolae are proposed as one potentially important component of a larger membrane-centered signaling network.

Finally, future mechanistic studies are required to test the proposed relationships directly. Particularly important will be experiments that manipulate caveolar components specifically in relevant tissues while simultaneously measuring exercise-induced mechanical signaling, membrane remodeling, intracellular signaling, inter-organ communication, and whole-body metabolic outcomes. Such studies will help determine whether caveolar remodeling is causally required for particular aspects of exercise adaptation or instead represents one of several cooperated cellular responses.

Recognizing these strengths and limitations is essential for appropriate interpretation of the proposed framework. The available evidence provides a biologically plausible basis for considering caveolae as an integrative component of exercise-induced

Table 1 Strength of evidence linking caveolae to exercise-mediated inter-organ communication

Organ axis	Evidence	Caveolae involvement
Endothelium	Strong	Strong
Skeletal muscle	Moderate	Moderate
Adipose	Moderate	Moderate
Liver	Emerging	Limited
Brain	Speculative	Weak

metabolic adaptation, but the framework should not be interpreted as proof of a universal or causal role for caveolae. Its principal value at this stage is to integrate multiple established observations, identify areas in which evidence remains associative or incomplete, and provide a testable conceptual model that can guide future mechanistic and translational research.

Future perspectives

Several important questions remain unanswered. Future studies should determine whether exercise directly remodels caveolar architecture *in vivo*, establish the temporal relationship between membrane remodeling and metabolic adaptation, identify tissue-specific differences in caveolar responses, and determine how obesity, aging, diabetes, and metabolic dysfunction modify caveolar plasticity. Integration of exercise physiology with spatial lipidomics, proteomics, metabolomics, and advanced microscopy will likely provide important insights into membrane-signaling during exercise. Particular attention should be directed toward identifying whether caveolae can coordinate communication among skeletal muscle, adipose tissue, liver, vascular endothelium, and the central nervous system or whether multiple membrane-signaling platforms contribute cooperatively to these adaptive responses. Ultimately, resolving these questions may improve understanding of why exercise remains uniquely effective as a multisystem therapy and may identify new opportunities for enhancing exercise responsiveness in individuals with metabolic disease.

Conclusions

Exercise produces convergent endocrine, mechanical, metabolic, vascular, and inflammatory signals that collectively regulate whole-body metabolic homeostasis. Understanding how these diverse stimuli are processed collectively at the

cellular level remains a fundamental challenge in exercise biology.

This review proposes that caveolae may represent one important membrane platform capable of spatially organizing multiple exercise-derived signals. Current evidence strongly supports roles for caveolae in mechanotransduction, membrane tension buffering, receptor compartmentalization, lipid organization, and endothelial signaling. However, direct evidence demonstrating that exercise-induced caveolar remodeling causally mediates systemic metabolic adaptation remains limited.

Accordingly, the caveolae-centered model presented here should be regarded as a testable conceptual hypothesis rather than an established mechanistic paradigm. By distinguishing experimentally supported mechanisms from emerging concepts, evaluating tissue-specific evidence, and outlining falsifiable predictions, this framework provides a foundation for future investigations into membrane-level regulation of exercise adaptation.

As spatial biology, lipidomics, multi-omics, and advanced imaging technologies continue to evolve, the proposed model can be rigorously evaluated and refined. Whether caveolae ultimately prove to be central coordinators of exercise-induced metabolic adaptation or one component of a broader membrane-signaling network, investigating their contribution promises to advance understanding of exercise as a systems-level therapeutic intervention for metabolic disease.

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