

Review Article

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The impact of exercise on the role of lipid droplets in maintaining health: a narrative review

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Abstract

Introduction: Lipid droplets (LDs) are omnipresent intracellular organelles. Their number, size, and composition exhibit considerable heterogeneity within cells. Dysregulated lipid accumulation or depletion is not only a hallmark but also a potential contributor to various human pathologies. This

narrative review aims to elucidate the impact of excessive LDs on health in various tissues, summarize the potential mechanisms by which exercise-induced amelioration of related diseases through the regulation of LDs homeostasis, and provide important reference evidence for the prevention and treatment of related diseases.

Content: This review elucidates the life cycle, tissue specificity and functions of LDs. Furthermore, it examines the regulatory effects of exercise on LDs metabolism, focusing on mechanisms involving inflammatory factors, liposomes, LDs-associated proteins and immune function, glomerular filtration rate, and insulin sensitivity. Additionally, it highlights the activation of key signaling pathways, including IL-15, AMPK and CaMKII, as well as the enhancement of lysosomal activity in diseases characterized by excessive LDs accumulation and aberrant distribution.

Summary and outlook: LDs are formed in the endoplasmic reticulum and are primarily degraded through lipolysis and lipophagy, exhibiting distinct tissue specificity and multifunctionality. While moderate levels of lipid droplets can protect against lipotoxicity, excessive accumulation may trigger various diseases by promoting inflammation, viral infection, and tumor cell proliferation. Exercise has a significant ameliorative effect on these related diseases. Future research will focus on leveraging lipid droplets and their derivatives as signaling nodes to gain deeper insights into cellular signal transduction and the regulatory role of exercise in these processes.

Keywords: lipid droplets; exercise; tissue specificity; lipid droplet-associated disease; triacylglycerol

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Introduction

Lipid droplets (LDs) are ubiquitous organelles throughout evolutionary history. These organelles dynamically stockpile lipids and are primarily found within eukaryotic cells, as well as in certain prokaryotic organisms. While LDs are typically localized in the cytoplasm, specific cell types may as well contain them in the nucleus [1]. LDs share a common

monolayer, which is integrated with specific proteins and surrounds the neutral lipids (see Figure 2) [2, 3]. Structurally, LDs feature a central reservoir of neutral lipids, also referred to as the oil phase [3]. For decades, these organelles were considered merely inert cytoplasmic lipid inclusions. However, in the last decade, LDs have been recognized as dynamic organelles and biological macromolecules [4]. LDs exhibit significant fluctuations between periods of dynamic synthesis, growth, and breakdown, processes that closely reflect cellular needs and environmental signals [5]. Although the dynamic properties of LDs have been extensively investigated in the existing literature, the heterogeneity of LDs across different tissues and organs remains poorly characterized.

In the 5th century BC, Hippocrates, often referred to as the father of medicine in ancient Greece, stated: “The various parts of the body, if used moderately and through habitual bouts of exercise, become healthy, well-developed, and delay aging; however, if they are not used or remain idle, they become susceptible to disease, growth defects, and accelerated aging [6].” This statement not only laid the theoretical foundation for considering exercise as a therapeutic method (exercise is medicine), but also revealed the ancient wisdom that exercise maintains an organism’s homeostasis through mechanical biological effects. Physical activity involves complex biological processes, activating multigenic interactions among cells, tissues, organs, and systems, with significant cross-talk occurring among them. Given the systemic and health-promoting nature of exercise, the concept of “exercise as medicine” continues to be integrated into clinical practice. Conversely, physical inactivity is a significant contributor to chronic illness and mortality. But, by the 21st century, public belief in the value of exercise for health has diminished significantly, rendering physical inactivity a major public health challenge [7]. Exercise has garnered considerable research attention due to its multi-system responses [8]. However, the mechanisms by which exercise influences LDs in various tissues to promote health remain poorly understood. In this article, we summarize existing research findings and propose potential mechanisms of action.

The summary of this article is presented in Figure 1.

Study selection and search strategy

The current body of literature on LDs primarily focuses on their involvement in obesity, cardiovascular diseases, metabolic syndrome, and insulin resistance, as well as their regulatory dynamics in response to exercise. While studies consistently conclude that excessive ectopic lipid deposition

impacts health, findings on the impact of exercise on such lipid accumulation in different tissues, along with the properties of LDs in various tissue sites, are not universally consistent. Indeed, the effects of ectopic lipid deposition on health in diverse tissues remain contentious. Studies have reported that LDs as a buffering mechanism for lipids, mitigating lipotoxic cellular damage [2], whereas other studies indicate that excessive ectopic lipid deposition can lead to inflammation and the onset of various diseases [9, 10]. To clarify the confusion surrounding this significant subject, we performed a narrative review, incorporating studies of varying complexity and design across a broad range of topics. A literature search covered publications from 1894 to January 2025 in PubMed, Google Scholar, and Web of Science. The inclusion criteria comprised English-language empirical studies and review articles that: (I) Investigated LDs in different tissues/organs and elucidated the physiological mechanisms by which exercise influences LDs to prevent or treat lipid overload-induced diseases; or (II) Demonstrated that exercise significantly ameliorates disease phenotypes induced by excessive lipid accumulation, while suggesting that the protective effects may be mediated, at least in part, through exercise-induced modulation of LDs dynamics (e.g., turnover, lipolysis, lipid partitioning, or protein composition). Two investigators independently performed the initial screening of search results following the predefined eligibility criteria. The remaining articles were further examined by reviewing their titles and abstracts to identify and eliminate duplicate publications. Any disagreements regarding article were first discussed to reach consensus; unresolved discrepancies were then adjudicated by an independent third reviewer. We screened all available results, including studies related to LDs characteristics and the effects of exercise and LDs on health in different tissues (see Figure 3). Notably, we did not employ biased selection to exclude unfavorable data. This review explores and analyzes the effects of LDs on health across different tissues and evaluates exercise implications, and provides insights into potential future research directions.

Content

The origin and breakdown of LDs

The origin of LDs

In recent years, the origin of LDs has been gradually revealed. It is generally accepted that LDs biogenesis involves multiple steps, and is intimately related to the

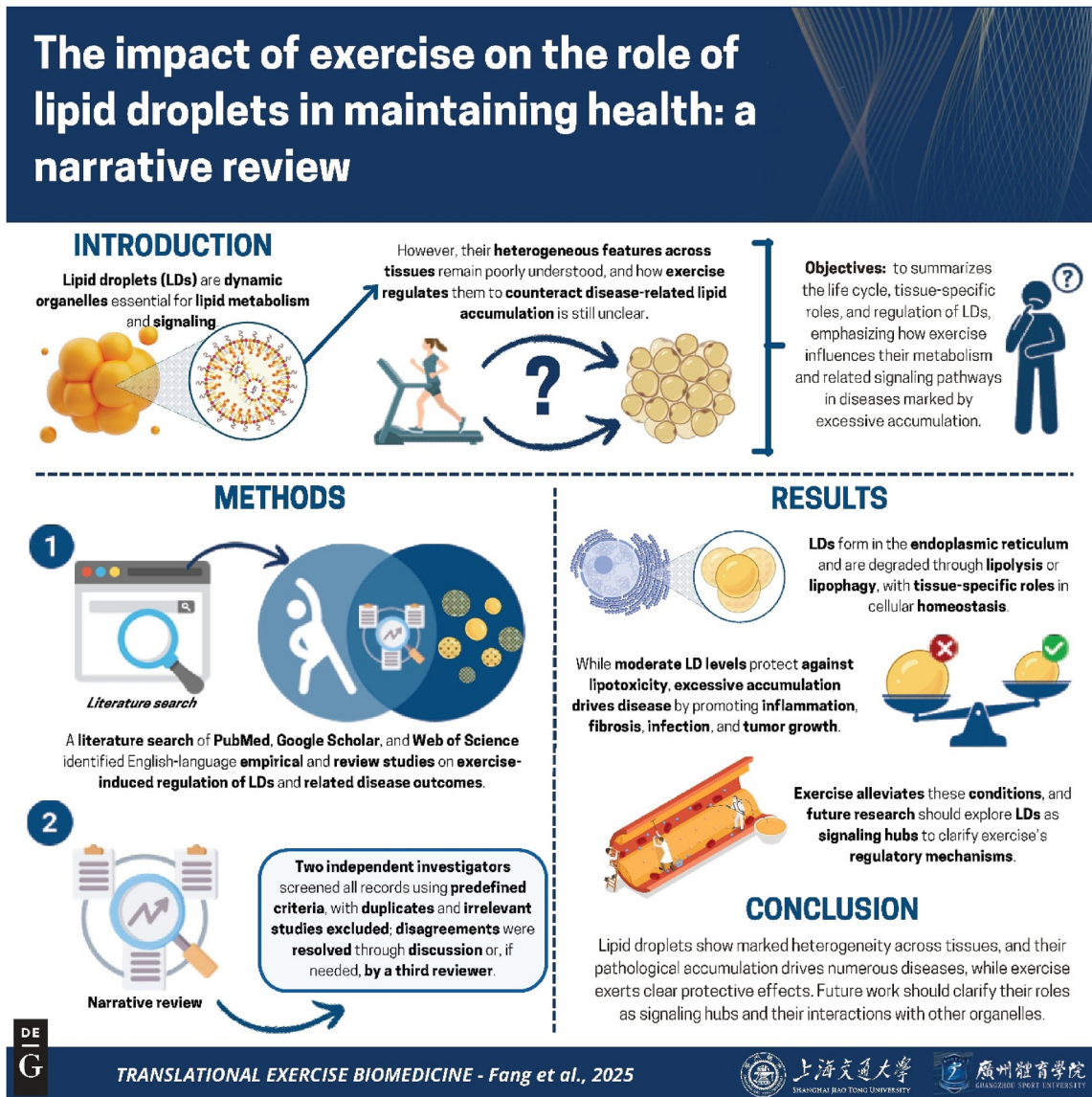


Figure 1: Graphical representation of this study. Key points: (1) lipid droplets (LDs), synthesized on the endoplasmic reticulum and degraded via lipolysis and lipophagy, display tissue-specific distributions and play key roles in cellular homeostasis. (2) while moderate lipid droplet (LD) levels confer protection against lipotoxicity, their aberrant accumulation promotes pathogenesis across tissues by exacerbating inflammation and fibrosis, facilitating viral infection, and fostering oncogenesis. Physical exercise constitutes an effective non-pharmacological intervention that mitigates these pathological processes through pleiotropic mechanisms. (3) future studies should prioritize lipid droplets and their derivatives as signaling hubs to decipher their role in cellular signal transduction and exercise-mediated regulation. Figure created with BioRender.

Endoplasmic Reticulum (ER). ER budding theory is a relatively mainstream theory.

First, the synthesis of triacylglycerol occurs in the endoplasmic reticulum.

Triacylglycerols (TAGs) were initially discovered in the early 1800s, with Richard Altmann's early observation of triglyceride storage in cells dating back to the 1890s [11]. Yet, it wasn't until around 1960 that Kennedy and his team clarified the biochemical mechanism responsible for the production of triglycerides [12]. This pathway utilizes glycerol phosphate

and fatty acyl-CoA to produce glycerol lipids, including glycerophospholipids and TAGs. Additionally, another pathway involving monoacylglycerol is utilized for synthesizing triglycerides in both intestinal enterocytes and adipocytes. This pathway is essential for the reclamation of monoacylglycerols and diacylglycerols produced during triglyceride hydrolysis, assisting in their transformation back into triglycerides through a reesterification mechanism [13]. It is important to highlight that sterol esters are also generated within the endoplasmic reticulum. The majority of LDs comprise a

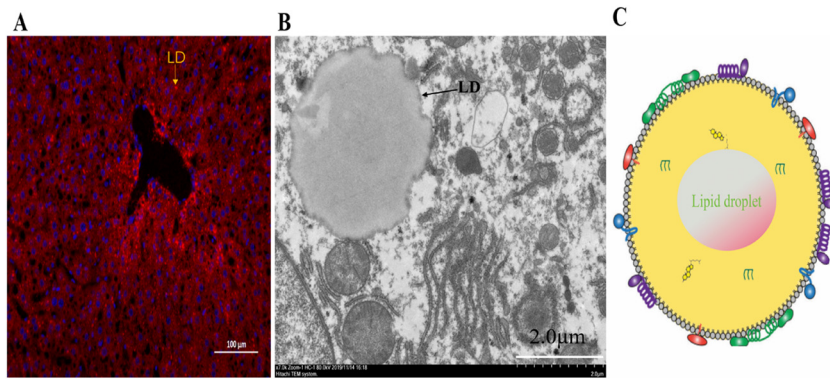


Figure 2: Lipid droplets (LDs). (A) Fluorescence microscopy image illustrates LDs stained red with Nile red inside the hepatic tissue of a C57BL/6 mouse (scale bar: 100 μm). (B) Transmission electron microscope showing a single LD inside the hepatic tissue of a C57BL/6 mouse (scale bar: 2.0 μm). Arrow heads: LDs (C) schematic diagram depicts the structural makeup of a LD, where the colored shapes denote proteins attached to the LD surface, situated within the phospholipid monolayer. The neutral lipid core comprises TAGs and SE.

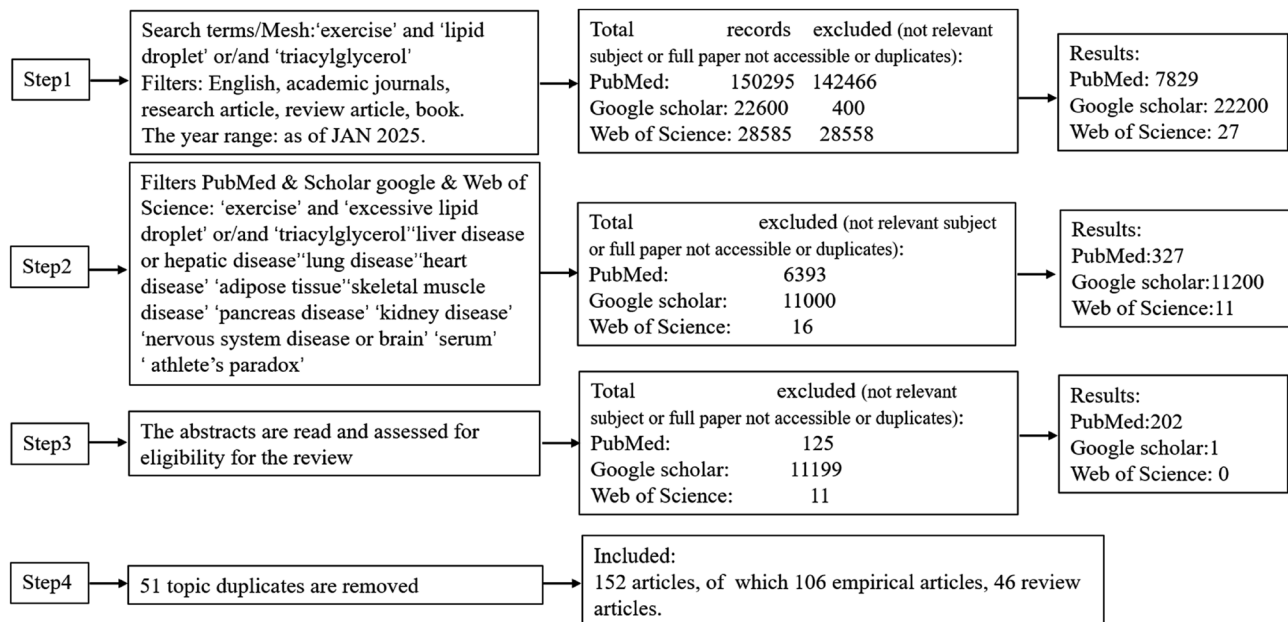


Figure 3: Flowchart of literature source selection.

combination of triglycerides and sterol esters. Nonetheless, genetic alterations in yeast facilitate the production of LDs that predominantly consist of either type of neutral lipid [14]. In comparison to research focused on TAG-rich LDs, there has been a relative paucity of exploration regarding the formation mechanisms of SE (sterol esters)-rich LDs.

Secondly, triacylglycerols phase separation and oil droplet biogenesis in the endoplasmic reticulum.

The biogenesis of LDs has been investigated through multiple experimental models, yielding several distinct mechanistic theories: (I) the membrane contacts site (MCS)-dependent formation theory [15]; (II) the *de novo* self-assembly hypothesis [16]; (III) the phospholipid remodeling-mediated mechanism [17]; (IV) the protein-nucleated assembly model [18]. Up to now, however, the mainstream theory posits that triglycerides could start an oil phase, thereby

decreasing the entropy penalties linked to the disruption of the endoplasmic reticulum bilayer leaflets [19]. The emergence of an oil lens in the endoplasmic reticulum enables the accommodation of newly synthesized triglyceride, which consequently results in a relative reduction of triglycerides in other regions of the bilayer leaflet [20]. This hypothesis was informed by early experimental observations that model bilayers can only hold a finite amount of triglyceride in a dispersed state before the formation of oil droplets [21].

Finally, this is followed by slow formation of budding and emerging LDs, and growth and expansion of LDs via the incorporation of particular proteins. Although the origin theory of LDs provides a compelling framework, its limitations in elucidating the physiological functions of LD-associated proteins underscore the necessity for further investigation. The effects of exercise on the biogenesis of

lipid droplets remain poorly characterized, highlighting a critical gap in current understanding.

The impact of exercise on LDs degradation

LDs can undergo degradation through two distinct pathways: (I) enzymatic lipolysis, mediated by enzymes like adipose triacylglycerol lipase and hormone-sensitive lipase, and (II) autophagic degradation, involving trafficking to autolysosomes and subsequent breakdown by lysosomal acid lipases [22]. During starvation, the hydrolysis of triacylglycerol is enhanced to provide sufficient free fatty acids for β -oxidation needed to satisfy the energy demands of cells. Moreover, lipophagy serves as an alternative energy source. PLIN2 (perilipin 2) is a critical regulator for lipophagy, and its expression is significantly downregulated by aerobic exercise via AMPK signaling pathway activation, this downregulation enhances lysosomal acid lipase (LAL) activity, promotes autophagosome biogenesis and autolysosome formation, and thereby augments lipophagic flux. Consequently, liberated free fatty acids are mobilized for β -oxidation to meet cellular energy demands [23]. Moreover, research has found that elevated levels of cellular triacylglycerol and cholesterol levels, alongside LDs accumulation, have been linked to the inhibition of lysosomal function [24]. While current research explores the effects of exercise on LD-associated proteins, autophagic lysosomes, and lipases, the impact on lipase substrates remains underexplored. Overall, exercise has been shown to facilitate LDs degradation, highlighting its potential role in lipid metabolism regulation. Exercise may further regulate the activity of lipolytic enzymes and the autophagosome-lysosome system through AMPK α -dependent PLIN2–LIPA axis, facilitating lipolytic processes [23].

The tissue specificity and functions of LDs

Recent research reveals that LDs are highly dynamic organelles with intricate functional interconnections, extending beyond their conventional role as mere fat reserves. Cells primarily defend against lipotoxicity by removing damaged or excess lipids. In this process, LDs play a crucial role as specialized organelles that regulate lipid uptake, storage, trafficking, and oxidation. Beyond their metabolic functions, LDs serve as dynamic signaling platforms that influence various cellular processes, including nuclear function and gene expression. Additionally, LDs facilitate intercellular communication by releasing bioactive lipid mediators. Furthermore, LDs serve as immune-responsive organelles that dynamically engage with the endoplasmic reticulum and mitochondria

through membrane contact sites. These interactions position LDs as pivotal regulators of immunometabolism and inflammatory signaling, enabling their modulation of immune cell activity [25]. Further physiological roles may yet to be uncovered through systematic investigation.

Structurally, LDs are closely associated with multiple organelles. Notably, a 10–15 nm neck connects LDs to the endoplasmic reticulum, enabling lipid exchange [26]. Proteins associated with LDs (LDAPs) are critical regulators of LDs turnover, significantly impacting lipid homeostasis [27]. An alternative possibility is that LDs may form intimate associations with other organelles, although such interactions remain to be identified.

Lipid intermediates, including diacylglycerol, ceramide, and fatty acyl-CoA, contribute to lipid-induced insulin resistance. Dysregulation of lipid storage, lipolysis, and fatty acid oxidation, along with alterations in LDAPs, may contribute to insulin resistance [28]. Even though our research found that exercise has an impact on ceramides, the molecular diversity and physiological roles of ceramides remain incompletely characterized.

In summary, these diverse functions underscore the versatility of LDs across different biological contexts. Notably, LDs exhibit distinct morphological and physiological properties depending on their tissue-specific localization (See Table 1), adipose tissue contains the largest LDs, with diameters exceeding 100 μ m. In contrast, other organ tissues demonstrate a broad distribution of LD diameters ranging from submicron scale ($<1 \mu$ m) to several tens of micrometers. Furthermore, LD abundance varies substantially across tissues, with some exhibiting high LD density while others contain relatively few. This size and distribution variation reflect specialized functional adaptations in lipid storage and metabolism across different tissues.

The role of exercise in LDs-associated diseases

LDs serve as reservoirs for various bioactive molecules, including vitamins, signaling precursors, and proteins, along with their role in membrane synthesis, is what LDs engage in. Additionally, LDs are key players in cellular signaling, protein management, and the response to cellular stress [42]. Despite these insights, the interplay between excessive LDs accumulation, exercise, and disease pathophysiology remains incompletely understood across different tissues.

Exercise training has been shown to reduce lipid intermediates, such as short-chain ceramides in liver, in obese mice [43], even without a concurrent reduction in ectopic lipid storage. Regular physical activity provides widespread health benefits, potentially by mitigating lipotoxicity through

Table 1: Tissue specificity of LDs.

Tissue	Morphological characteristics of LDs	Physicochemical properties of LDs
Adipose tissue	Nearing 100 μm , one or a few droplets filling almost the entire cell. As pre-adipocytes transition into mature adipocytes, gradually gather small LDs [29].	Early-stage adipocytes exhibit elevated <i>de novo</i> lipogenesis and LD formation, which decline at later differentiation stages [29]. Enhanced pyruvate oxidation in peridroplet mitochondria increases malonyl-CoA production, promoting lipid synthesis while inhibiting lipolysis and lipid oxidation [30].
Heart	Small LDs, the diameter ranges from 0.3 to 1.5 μm [31].	Obtain fatty acids through lipoprotein uptake or endogenous tri-glyceride hydrolysis [32]. Low TAG levels and rapid LDs turnover [33].
Skeletal muscle	In healthy individuals, LDs range from 0.3 to 1.5 μm , while genetic modifications increase the minimum size to 3 μm . Type 1 muscle fibers exhibit larger LDs than type 2 fibers [31].	Intramyocellular LDs exhibit heterogeneity in size, localization, lipid composition, and protein associations. They serve as energy reserves, complementing glycogen and supplying fuel via the bloodstream [31].
liver	LDs range from 1 μm to several tens of micrometers, with uneven distribution influenced by portal and hepatic vein blood flow. Peri-portal hepatocytes initially contain fewer LDs [34].	Excessive lipid accumulation in hepatocytes under pathological conditions [35] is driven by mitochondrial expansion and oxidative stress [36].
Kidney	LDs are scarce and primarily localized in proximal tubule cells, with minimal presence in glomeruli [37].	Total ceramide levels inversely correlate with triglyceride quantities. Moderate triglyceride storage in LDs protects cells from harmful metabolite accumulation [37].
Lung	Small LDs within cytoplasm in blood vessels and lung tissue, exhibiting a consistent structural composition in blood vessels [38].	LDs exhibit significant mechanical stability in lung cells, alveolar walls, and blood vessels [38].
Pancreas	Size of LDs ($\leq 3 \mu\text{m}$) and supersized LDs ($\geq 3 \mu\text{m}$) [39].	LDs influence beta-cell sensitivity to free fatty acids, while aberrant cholesteryl ester and LDs accumulation impact pancreatic cell function [39].
Nervous system	Small LDs form and accumulate in abundance within the glial cells of the cortex [40].	Hypoxia and metabolic disturbances enhance LD formation in astrocytes [36]. Blood-brain barrier permeability allows triglyceride-rich lipoproteins to enter the brain, further promoting LD accumulation [41].

enhanced lipid turnover and improved LD quality [44]. Additionally, exercise stimulates the secretion of myokines from skeletal muscle, which enter circulation and modulate LD dynamics in non-exercising organs. However, the tissue-specific effects of these adaptations remain insufficiently characterized, limiting their broader applicability. Moreover, the precise mechanisms underlying these effects have yet to be systematically summarized, leaving significant research gaps to be addressed. The review synthesizes the latest findings on the role of LDs in both health and disease, emphasizing their function in mitigating cellular stress. We present current knowledge on LD contact sites and their associations with genetic, metabolic, and infectious disorders (see Table 2). Furthermore, we discuss emerging therapeutic strategies targeting LD formation, expansion, and degradation, with potential applications in conditions such as steatosis, viral infections, inflammation, insulin resistance and cancer.

Excess LDs promote pathogen infection, while exercise mitigates the risk

Numerous intracellular pathogens, which encompass a range of viruses, bacteria, and parasites, exhibit a specific

affinity for host LDs throughout their life cycle. For instance, certain viruses, including the hepatitis C virus (HCV), dengue virus, and rotaviruses, exploit LDs as critical sites for assembling viral components. This strategic utilization allows these viruses to enhance their replication and viability within the host. In addition to viruses, various bacteria, such as mycobacteria and chlamydia, along with parasites like trypanosomes, also take advantage of host LDs, primarily for nutritional gain. By utilizing these lipid reserves, they can efficiently fulfill their metabolic needs, which aids in their survival and proliferation within the host organism. Furthermore, the engagement of LDs by these intracellular pathogens may signify a sophisticated anti-immunity strategy, enabling them to avoid the host's immune defenses and establish a successful infection [58].

HCV is the most recognized pathogen closely associated with LDs. LDs are believed to be potential sites for the assembly of the virus during the replication of HCV [59]. The process of assembling infectious HCV particles consists of multiple phases, such as the formation of the nucleocapsid, budding into the endoplasmic reticulum, and the maturation of virions. The capsid's core protein forms a robust association with LDs and attracts nonstructural proteins to their vicinity to facilitate virus production [59]. It is likely that the

Table 2: The contact site protein of LDs in diseases.

Organelles/organism	Contact site protein	Disease	Description	Refs
Endoplasmic reticulum	Seipin/SNX14/ VPS13A、VPS13C/ Rab18	Berardinelli-Seip congenital generalized lipodystrophy type 2, neurological seipinopathies, progressive encephalopathy with or without lipodystrophy, autosomal recessive spinocerebellar ataxia 20, Chorea acanthocytosis, McLeod syndrome, early onset Parkinson's disease, Warburg Micro syndrome, hereditary spastic paraplegia	Genetic diseases	[15, 45–47]
Peroxisome	Spastin/ABCD1	Hereditary spastic paraplegia, adrenoleukodystrophy	Infectious diseases	[48, 49]
Replication organelle	Poliovirus proteins 2B and 2C	Poliomyelitis	Infectious diseases	[50, 51]
Autophagosome	DENV protein NS4A	Dengue fever	Infectious diseases	[52]
The endoplasmic reticulum includes locations for viral replication and assembly.	NS5A	Hepatitis C	Infectious diseases	[53, 54]
Phagosome	LAM and PIM	Tuberculosis	Infectious diseases	[55]
Bacterial inclusions	Chlamydia protein Lda3	Chlamydia infection	Infectious diseases	[56]
Parasitophorous vacuole	Rab7	Toxoplasmosis	Infectious diseases	[56]
Mitochondria, plasma membrane, and endoplasmic reticulum, and fragmentation of the Golgi	Extended synaptotagmin 2, VPS13A, VPS13D	Non-alcoholic fatty liver disease	Metabolic liver disease	[57]

assembly of HCV occurs in locations that require the interaction of the endoplasmic reticulum with LDs [60]. Recent high-resolution imaging research conducted in cell culture systems reveals the targeted recruitment of endoplasmic reticulum membranes that encase LDs, consequently forming a membranous structure that connects the replication and assembly of the HCV [53]. Additionally, HCV infection can induce endoplasmic reticulum stress, resulting in the Ca^{2+} release, causing mitochondrial impairment. This sequence of occurrences initiates oxidative stress, enhances lipogenesis [61]. The Core protein of HCV can also be effectively directed to LDs, independent of virion assembly, resulting in a redistribution of LDs and the progress of hepatic steatosis [62]. This occurrence partially clarifies the reason metabolic dysfunction-associated fatty liver disease (MDAFLD) is a prominent feature in individuals suffering from chronic hepatitis C, and research has shown that antiviral therapy, which eliminates the HCV, results in a marked decrease in liver steatosis [63]. A key feature of hepatocellular carcinoma is their increased lipogenesis, alongside altered lipid metabolism [64]. Liver lesions that contain fat are frequently found in patients diagnosed with hepatocellular carcinoma [65], the lipogenesis pathway experiences heightened activation, while the process of fatty acid oxidation is concurrently reduced

[66]. Due to the rapid tumor growth associated with hepatocellular carcinoma, these cancer cells have an elevated demand for fatty acids to facilitate their proliferation [67]. When exposed to hypoxic environments, the catabolism of LDs is restricted by ATGL, which is the key lipase for lipolysis, resulting in the buildup of LDs and consequently altering cellular metabolism, thereby inducing resistance to apoptosis [68]. HCV patients generally receive biological therapy or antiviral treatment. However, the human studies have shown that aerobic exercise can reduce body fat and improve lipid metabolism in patients with Hepatitis C virus infection, and the clinical course of the disease demonstrated significant amelioration, accompanied by marked improvement in hepatic functional parameters [69]. Nevertheless, there are few studies investigating the impact of resistance exercise or forms of exercise in HCV infection. The exact molecular mechanisms that drive this effect require further empirical validation. Exercise-induced LDs degradation provides novel insight into reducing the risk of HCV infection.

Most pathogen research has focused on identifying specific species that may contribute to the development of human diseases. However, given that bacterial functionality is not only based on their own genetic information but also on interactions with other microorganisms, the use of

microbial consortia can be more effective in treating pathogen-induced infectious diseases. Existing studies have shown that exercise can regulate the structure and interactions of pathogens by improving host lipid metabolism, thereby reducing their pathogenicity [70]. This mechanism may partially explain the preventive effect of exercise intervention on infectious diseases. Additionally, existing literature indicates that the moderate intensity and duration of exercise, along with scientific and healthy diet, significantly inhibit both the onset and progression of pathogen infections. Notably, current studies endorse a “J” curve relationship that links the risk of pathogen infection with escalating levels of exercise workloads. The alterations in immune function triggered by exercise may offer a physiological explanation for the “J” curve phenomenon [71]. However, the molecular mechanisms by which exercise, including aerobic exercise and resistance training, prevents and combats pathogen infections through LDs degradation remain inadequately understood, highlighting a critical research gap that warrants further investigation.

Exercise regulates lipid metabolism to reduce LDs-related skeletal muscle disease risk

Previous studies employing transmission electron microscopy have identified two separate reservoirs of LDs within skeletal muscle cells: one situated beneath the sarcolemma and another found between the myofibrils. The skeletal muscle of chronically trained elite athletes demonstrates significant ectopic lipid accumulation, manifesting as a marked increase in intramyocellular lipid (IMCL) droplet content. The paradoxical coexistence of high IMCL accumulation and improved insulin sensitivity is referred to as the “athlete’s paradox.” Despite elevated IMCL accumulation, athletes demonstrate superior insulin sensitivity relative to two distinct groups: (I) insulin-resistant individuals with similar IMCL deposition, and (II) lean, sedentary individuals with reduced IMCL content [72]. In the past few years, significant research efforts have been directed toward elucidating the paradoxical metabolic effects associated with IMCL accumulation. The prevailing hypothesis posits that IMCL itself is not intrinsically lipotoxic. However, existing studies remain inconclusive. For instance, while one investigation reported significantly lower intramuscular saturated diacylglycerol (DAG) levels in athletes compared to a lean sedentary control group [73], another study observed elevated DAG concentrations in trained individuals [74]. These conflicting findings suggest that the athletes’ paradox

may involve differential regulation of specific lipid intermediates. As an alternative mechanistic explanation, it has been proposed that the dynamic turnover of intramuscular lipid stores, rather than their absolute content, serves as a critical determinant of lipotoxicity [75]. Furthermore, excessive IMCL deposition disrupts mitochondrial bioenergetics and activates pro-inflammatory signaling, collectively promoting the development and progression of skeletal muscle disease [25, 76].

Diseases linked to elevated intramyocellular lipids levels include age-related sarcopenia [77], spastic paraplegia [77], and related disorders. In these cases, the increase in LDs accumulation within skeletal muscle may primarily result from the associated muscle fiber atrophy involving diminished cross-sectional area and fiber quantity and insufficient mechanical stimuli. Variations in muscle mass are determined by the net balance of protein, organelle, and cytoplasmic constituent content. Dysferlinopathy, a variant of muscular dystrophy, is characterized by intramyocellular lipids accumulation and an early increase in the expression of the lipogenic transcription factor C/EBP- δ before related pathological symptoms [78], indicating a premature disturbance in lipid metabolism within this particular condition. Moreover, emerging evidence indicates that LDs dysfunction may contribute to hereditary spastic paraplegia. Research has demonstrated that spastin can interact with LDs and influence lipid metabolism in skeletal muscle tissues [79]. Despite limited research on the exercise-C/EBP- δ /spastin association, exercise is strongly rationalized as a potent modulator of skeletal muscle mass and function and a regulator of lipid metabolic pathways [80]. Current evidence substantiates that different types of exercise modalities effectively reduce IMCL accumulation in skeletal muscle, such as, endurance training significantly reduced the numerical density of LDs in both central and peripheral regions of type I and IIa muscle fibers, a process mediated through AMP-activated protein kinase (AMPK) and calcium/calmodulin-dependent protein kinase II (CaMKII) signaling pathways in skeletal muscle tissue [81]. While, aerobic exercise [82] and chronic high-intensity interval training (HIIT) [83] have been demonstrated to regulate the secretion of myokines (e.g., irisin) [82] and adipokines (e.g., leptin and adiponectin) [83], ameliorate myosteatosis and degenerative changes, and enhance muscle mass and functional capacity, thereby attenuating sarcopenia progression. Furthermore, acute exercise enhances LD-mitochondria contacts, facilitating lipid substrate channeling to augment lipid oxidative lipid metabolism and improve cellular function in skeletal muscle, and reducing the risk of skeletal muscle diseases [84].

Exercise attenuates LDs-associated kidney disease risk

Previous research has demonstrated ectopic lipid deposition in various renal diseases, underscoring the pivotal role of renal lipid metabolism in disease pathogenesis [85]. The primary avenue for decreasing lipid levels in the kidney is through fatty acid oxidation [86]. Ectopic lipid accumulation within renal compartments induces structural and functional alterations in mesangial cells, podocytes, and proximal tubular epithelium – key cell types governing nephron integrity. This lipid overload triggers ER stress, resulting in upregulation of TNF- α and IL-6, which potentiates reactive oxygen species overproduction, culminating in renal cytotoxicity, inflammatory cascades, and progressive fibrotic remodeling [86, 87]. An ever-growing body of clinical research highlights the positive impact of physical activity across all stages of chronic renal disease. A 12-week high-intensity interval training program (4 intervals of 4 min at 80–95 % of peak heart rate) has been proven to be a practical, safe choice and has shown positive effects on 14 individuals suffering from chronic kidney disease in stages 3 and 4 [88]. A meta-analysis of 11 randomized controlled trials included 362 individuals with stage 3 or 4 chronic kidney disease, Vanden Wyngaert et al. [89] demonstrated benefits for renal function that an 8-month aerobic exercise program, compared to standard therapy, improved estimated glomerular filtration rate by $+2.16 \text{ mL/min/1.73 m}^2$. Previous studies have demonstrated that both endurance exercise and resistance training can significantly reduce serum sphingolipids (e.g., ceramides) [43]. Evidence indicates that sphingolipid-mediated perturbations in podocyte function represent a key mechanism altering glomerular filtration barrier permeability [90]. Although this highlights the role of exercise in regulating lipid and enhancing kidney function, the signaling pathways through which exercise modulates renal LDs remain incompletely elucidated in kidney disease model, whether in animal models or human populations. Further investigation is needed to establish whether exercise-mediated reductions in cyclic and renal sphingolipids (e.g., ceramides, Sphingosine-1-phosphate) confer protective effects on podocyte function and glomerular filtration rate. Moreover, critical knowledge gaps remain regarding the temporal patterns of exercise-induced benefits, differential effects across exercise modalities, and the precise optimization of exercise load/intensity for renal protection.

Anti-inflammation serves as a potential mechanism by which exercise alleviates LDs-associated lung disease

Lipid depositions were initially characterized morphologically in pneumonia related to tuberculosis near the area of

caseous necrosis in the early 20th century, and later referenced in studies detailing unusual lung morphology [91]. In particular, within inflamed lung tissue, we observed small LDs situated in the cytoplasm of cells, as well as large, homogeneous LDs within blood vessels that lacked surrounding membranes. These latter droplets could potentially obstruct blood flow and disrupt gas exchange, which is critical to various forms of pneumonia [92], thereby playing a significant role in disease progression. Abnormalities in lipid metabolism might represent an early occurrence in lung inflammation, with tissue in the upper lung regions, while still appearing macroscopically normal, showing the initial morphological changes induced by pneumonia. This is supported by the morphological and physiological evidence indicating that abnormal lipid deposition could significantly influence the pathological processes associated with pneumonia [38].

LDs are essential for nutrient storage, but play a vital role in tumor growth and proliferation. The frequently elevated expression of the LDs shell protein PLIN3 within the lungs is linked to the pathological characteristics of lung cancer. This highlights the significance of LDs in relation to lung cancer. A more comprehensive understanding of lipid biology related to lung cancer could enhance the creation of novel therapeutic approaches, such insights can contribute to the formulation of new therapeutic approaches [93]. For patients with pneumonia or lung cancer, engaging in exercise serve as effective nonpharmacological approaches. Exercise may help mitigate pneumonia and other lung diseases by reducing LDs-driven inflammation, which is supported by empirical evidence. Aerobic exercise notably reduced the total cell count, including neutrophils and lymphocytes, in bronchoalveolar lavage fluid. Furthermore, aerobic exercise reduced inflammatory cell infiltration and significantly lowered pro-inflammatory cytokines (IL-1 β , IL-6, CXCL1, and TNF- α) while enhancing IL-10 (anti-inflammatory cytokine) expression [94]. Combining moderate intensity aerobic with resistance training partially restored the expression of interleukin-10 in airway epithelium of rats with pulmonary inflammation, suggesting an anti-inflammatory mechanism underlying the observed therapeutic effects [95]. The evidence suggests that investigating exercise-induced benefits will advance the development of exercise-based therapeutics for lipid disorder-associated pulmonary diseases, potentially stimulating broader scientific engagement in this field.

Exercise lowers MDAFLD risk by modulating LDs autophagy

The liver stands as one of the most critical and multifunctional metabolic organs within the human body. Lipid metabolism,

including lipid droplets, is a highly orchestrated process requiring coordinated interorganellar cross talk to maintain cellular homeostasis. Disruption of this equilibrium may induce organellar damage and promote the occurrence and development of diseases (e.g., MDAFLD, hepatitis, liver fibrosis, liver cancer). MDAFLD is characterized by hepatic steatosis accompanied by at least one of three factors: obesity/overweight, type 2 diabetes mellitus, or metabolic dysregulation [96]. As a newly defined condition, its precise epidemiology remains unclear, but it is estimated to affect about 25 % of the global population [97]. Wei Zhu identified exercise and dietary intervention as the most effective approaches to improving hepatic lipid metabolism [98]. Additionally, Chunlu Fang et al. revealed that 3-month aerobic exercise intervention reduced hepatic LDs accumulation and ameliorated non-alcoholic fatty liver disease (NAFLD was redefined as MDAFLD by international expert consensus) in a high-fat diet-induced mouse model. This beneficial effect was mediated through PLIN2-LIPA axis-regulated lipophagy) [23]. This article elucidated the mechanisms by which aerobic exercise promoted lipophagy but did not assess the effects of resistance training or compare the effectiveness of different exercise types. Future studies should explore the comparative effectiveness of various exercise modalities to better understand their effectiveness in improving MDAFLD.

Anti-inflammatory pathways or enhanced islet cell function: mechanisms underlying exercise-induced reduction of pancreatic cancer risk

Pancreatic cancer is a highly fatal malignancy and is expected to rank as the second leading cause of cancer-related mortality by 2030 [99]. LDs are pivotal in tumor cell metabolic reprogramming, promoting pancreatic cancer cell invasion and migration [100]. Although the precise mechanisms by which exercise reduces pancreatic cancer risk through modulation of pancreatic lipid droplets remain incompletely elucidated, it has been confirmed that exercise induces the alleviation of toxicity and apoptosis in pancreatic islet cells through transcriptional regulation in pancreatic islets, increases energy expenditure, thereby disrupting the carcinogenic process and reducing the incidence of pancreatic cancer [101]. Physical activity slows early obesity-related pancreatic ductal adenocarcinoma progression, highlighting its preventive potential. Its antitumor effects involve reduced tumor-associated inflammation and fibrosis, lower circulating inflammatory cytokines induced by a high-fat diet, and IL-15 pathway activation in white adipose tissue [102]. The findings provide evidence supporting the anti-carcinogenic potential of exercise, but the

underlying mechanistic pathways of different forms of exercise require systematic elucidation through rigorously designed *in vivo* studies and complementary *in vitro* experiments.

Exercise reduces the risk of LDs-associated brain diseases

LDs are closely associated with various diseases of the nervous system, such as Alzheimer's disease, hereditary spastic paraplegia, Parkinson's disease, Huntington's disease, multiple sclerosis, stroke and glioblastomas (see Table 3). The excessive accumulation of intracellular lipids induces an inflammatory phenotype, which ultimately impairs the repair processes within the central nervous system. This inflammatory condition can lead to prolonged damage and reduced efficacy in recovery and regeneration efforts following injury or disease. The LD-associated proteins PLIN2 is essential for protecting LDs from degradation via lipolysis, thereby maintaining the phagocytes' capacity to effectively process lipids derived from myelin. In the absence of PLIN2, there is an increase in LDs turnover within foamy phagocytes, facilitating a shift toward a less inflammatory phenotype. This transition back to a more anti-inflammatory state could enhance the functionality of phagocytes and their overall capacity to support central nervous system repair mechanisms. Consequently, modulating PLIN2 levels may offer a potentially effective treatment approach for alleviating inflammation and promoting recovery in central nervous system injuries [127]. Studies have indicated that PLIN2 is implicated in mediating the exercise-induced lipid metabolic improvements in the hypothalamus of Goto-Kakizaki rats [128]. While exercise-induced cognitive improvements are well-documented, including mechanisms such as APOEε4 modulation or LD-targeted therapies, the specific LD-related signaling pathways underlying exercise's neuroprotective effects in neurological disorders (e.g., Alzheimer's disease, Parkinson's disease) require further investigation (see Table 3), its intermediate pathway remains largely unexplored.

Summary: LDs in disease pathogenesis

In summary, excess LDs accumulation is implicated in the pathogenesis of multiple diseases, by facilitating viral infection, inflammation, and fibrosis. To date, although no specific exercise guidelines for patients with LDs-associated diseases are available, certain forms of exercise have been proven to have ameliorative effects. Even if certain molecular mechanisms have yet to be fully validated, extensive research has established the positive

Table 3: Exercise improves brain-related diseases closely associated with LDs.

Diseases	Lesion characteristics	The association with LDs	The association with exercise
Alzheimer's disease	Impacts cognitive functions that influenced by neurogenesis: Hippocampus-dependent learning and memory [103].	In the subventricular zone niche in the 3xTg mouse: a Significant reduction in subependymal cells and the accumulation of large LDs in the ependyma, alterations in metabolism [103].	Aerobic exercise and Apolipoprotein E (APOE) ϵ 4 interact to promote synaptic/neuronal health, thereby preventing Alzheimer's disease [104].
Hereditary spastic paraplegia	A range of inherited neurological conditions marked by significant lower-extremity spasticity, largely stemming from the degeneration of corticospinal neurons [105].	Endoplasmic reticulum-resident proteins promote LDs formation. Impaired fatty acid transport from LDs promotes hereditary spastic paraplegia [106].	Physical activity (squatting exercises, kneeling position exercises, movements involved in bathing) is beneficial in halting further deterioration of lower limb function, and in maintaining the individual's capacity to carry out daily living activities [106]. Yet, the intermediate pathway involved in this process requires further investigation.
Parkinson's disease	The second most prevalent neurodegenerative condition, motor symptoms: Tremors, stiffness, and slowness of movement. Non-motor symptoms: Sleep issues and a decline in cognitive functions [107].	A lipidopathy lipid dysfunction is a contributing factor [108]. drugs that target lipid-related mechanisms demonstrate significant potential for mitigating toxicity associated with Parkinson's disease [109].	Six months of aerobic exercise ($3 \times$ /week, 30–45 min) may slow corticostriatal network degeneration and enhance cognitive function, thereby improving Parkinson's disease [110]. However, whether the intermediate pathway modulates lipid metabolism and subsequently mitigates Parkinson's disease through this metabolic regulation remains to be elucidated.
Huntington's disease	A neurodegenerative disorder: Difficulties in exercise skills and cognitive functions. A dominant trinucleotide repeat expansion in the huntingtin gene leads to an excessive accumulation of polyglutamine residues in the huntingtin protein [111].	LDs accumulation in most cases of neuronal loss [112]. This disease driven by the LDs dysfunction [113].	A 12-week progressive exercise ($3 \times$ /week) has a therapeutic effect [114]. The specific molecular mechanisms require further investigation.
Multiple sclerosis	A persistent condition marked by neuro-inflammation and neurodegeneration, featuring the axonal demyelination and neuronal loss in the central nervous system [115].	Myelin consists of ~80 % lipids, with LDs enriched in active demyelination sites. During demyelination, LDs accumulate in infiltrating macrophages and microglia [116]. Elevated triglyceride and LD levels in motor neurons [117].	Exercise-induced brain adaptations: Connectivity, neuroprotection, and remyelination [118]. The mechanistic details of its intermediate pathway have not been fully elucidated.
Stroke	Ischemic stroke, caused by reduced blood and oxygen supply, leads to cell death primarily through glutamate-induced excitotoxicity [119].	Blood-brain barrier disruption during stroke increases lipoprotein influx, promoting LD formation [120]. Lipid accumulation in microglia worsens ischemic damage and impairs recovery [121].	High-intensity interval exercise promotes LD degradation in microglia, while lactate from aerobic exercise may aid in restoring inhibitory control post-stroke [122].
Glioblastomas	Highly aggressive glial-derived central nervous system tumors: Glioblastoma and oligodendroglioma [123].	LDs drive aggressive brain tumor progression [124]. Glioblastomas upregulate DGAT1, increasing neutral lipid production and tumor progression [125].	LD-targeted therapy and a 6-min walk exercise in glioblastoma treatment and support neural regeneration [126].

impact of exercise on inflammatory and fibrosis regulation, lipid metabolism, LD-associated proteins, immune function, glomerular filtration rate, insulin sensitivity, and the activation of key signaling pathways, including IL-15, interleukin-10, AMPK, and CaMKII. These findings underscore its therapeutic potential for disorders involving aberrant LD accumulation (see Figure 4).2

The response of lipid to exercise

Regular, suitable aerobic exercise can effectively limit the buildup of surplus lipids in different tissues and cells while ameliorating lipid metabolic disorders. The proposed mechanisms involve increased energy expenditure, enhanced lipid oxidation, reversal of lipid deposits, and

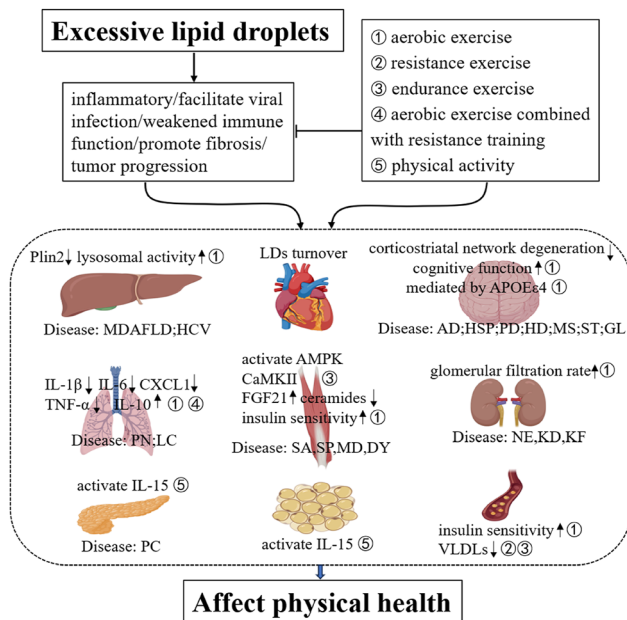


Figure 4: Postulated chronology of excessive LDs and exercise in health. (1) ①②③④⑤ corresponding to different exercise modalities; (2) diseases: (Liver) MDAFLD (metabolic dysfunction-associated fatty liver disease), HCV (hepatitis C virus); (lung) PN: pneumonia, LC: lung cancer; (skeletal muscle) SA: sarcopenia, SP: Spastic paraplegia, MD: muscular dystrophy, DY: dysferlinopathy; (kidney) NE: nephritis, KD: kidney disease, KF: Kidney failure; (pancreas) PC: Pancreatic cancer; (brain) AD: Alzheimer's disease, HSP: Hereditary spastic paraplegia, PD: Parkinson's disease, HD: Huntington's disease, MS: multiple sclerosis, ST: stroke, GL: glioblastomas.

improve insulin sensitivity [73, 129]. Empirical evidence includes: (I) a 12-week exercise intervention significantly remodeled skeletal muscle lipid partitioning, as evidenced by elevated IMCL content coinciding with reduced DAG and ceramide concentrations. Crucially, the morphology and spatial distribution of LDs serve as key determinants of skeletal muscle insulin sensitivity. Specifically, the characteristic storage pattern in untrained individuals – featuring fewer, larger subsarcolemmal LDs in type II fibers – is associated with insulin resistance. In contrast, the trained phenotype demonstrates a protective lipid distribution pattern, with numerous smaller LDs localized in the intra-myofibrillar region of type I fibers, which maintains insulin sensitivity [130]; (II) the benefits of exercise in improving lysosomal activity – particularly regarding the fusion of lysosomes and autophagosomes, acidification processes, and levels of acid lipase – thereby improving lipid degradation during the final phases of lipophagy [131]; (III) exercise stimulates the production of fibroblast growth factor 21 (FGF21) in muscle tissue, which in turn promotes hepatic lipophagy, and this process facilitates lipid clearance by activating the AMPK signaling pathway [132]; and (IV)

conversely, sustained elevated plasma insulin levels, lack of exercise promotes LDs accumulation in hepatocytes and striated muscle. This accumulation hinders the translocation of glucose transporters, leading to heightened insulin resistance linked to obesity, potentially further facilitating the buildup of LDs [133].

The intramyocellular neutral lipids and several proteins essential for developing the ability to undergo lipid remodeling are affected by acute training, resistance exercise, short-term sprint interval workouts, and moderate-intensity continuous training (see Table 4). Different types of exercise exhibit distinct physiological effects.

Table 4 is shown here. Table 4 Impact of various exercise modalities on intracellular lipid dynamics.

The lipid and lipoprotein dynamics in response to acute exercise

The acute effects of endurance exercise temporarily lower triglyceride levels while increasing HDL-C (high-density lipoprotein cholesterol) levels. These changes are likely associated with total energy expenditure; however, the existing evidence remains inadequate to establish whether these effects are primarily driven by caloric expenditure, exercise intensity, or a combination of both factors. Studies examining exercise cessation suggest that the elevated HDL levels seen in highly active individuals cannot be solely attributed to acute exercise effects. Conversely, fluctuations in triglyceride and HDL-C levels resulting from short-term exercise training may be predominantly, if not entirely, attributable to the immediate physiological response to acute exercise [140].

The highest rate of fat oxidation occurs during moderate-intensity endurance exercises (especially exceeds 1 h), peaking at approximately 65 % of a person's peak oxygen uptake [141]. Acute endurance exercise reduced LDs size and showed a trend toward decreasing total intramyocellular lipid content. Moreover, the density of smaller LDs in the peripheral sarcoplasmic region significantly increased, while larger LDs significantly declined [142]. Additionally, fat oxidation increases immediately following exercise [143]. The requirement for fatty acids is partially fulfilled by plasma lipids originating from adipose tissue, the intestine, and the liver. While both VLDLs (very-low-density lipoproteins) and chylomicrons contribute to supplying substrates for muscle metabolism [144], there is no indication that acute exercise enhances hepatic VLDL production [145], implying that acute exercise may instead facilitate the clearance of VLDLs and chylomicrons from circulation.

Table 4: Impact of various exercise modalities on intracellular lipid dynamics.

Subjects	Research design	Primary result	Refs
Acute exercise (AE) effects on IMCL			
Sixteen sedentary males	Muscle biopsies pre and post 60-min cycling at 65 % VO ₂ max both pre- and post- a 6-week intervention of either sprint interval training or endurance exercise.	(i) Resting IMTG increased post- 6-week training; (ii) pre-training AE reduced IMCL by 15–17 % in type 1 fibers; (iii) post-training AE further decreased IMCL by 27–43 % in type 1 fibers.	[134]
Ten individuals	Muscle biopsy (triceps brachii/vastus lateralis) pre- and post-training 20-km cross-country skiing (~57 min).	(i) AE reduced LD density but not size; (ii) IMCL decreased by 53 % in arms but remained unchanged in legs.	[135]
Twenty-one male participants	Muscle biopsies pre- and post-60-min cycling at 50 % VO ₂ max.	(i) AE decreased IMCL by 20–30 %; (ii) In older overweight individuals, exercise increased LD size by ~25 % in the sub-sarcolemma and by ~7 % in the intra-myofibrillar region.	[136]
44 individuals (n=14 obese, sedentary controls, n=15 type 2 diabetes mellitus (T2DM), n=15 endurance-trained)	Muscle biopsies pre- and post-90-min cycling at 50 % VO ₂ max.	(i) AE decreased IMCL exclusively in the trained participants (approximately 25 %). (ii) AE had no significant impact on IMCL in obese or T2DM groups. (iii) the fractional synthesis rate of IMCL increased during AE, but notably dropped in recovery for T2DM and obese individuals.	[137]
Short-term sprint interval training and moderate-intensity continuous training effect on IMCL (training adaptation)			
Sixteen sedentary obese males	Muscle biopsies pre- and post-4 weeks of either short-term sprint interval training exercise (4–7 × 30 s sprints, 3 × /week) or moderate-intensity continuous training (60 min ≥ time ≥ 40 cycling at <65 % VO ₂ peak, 5 × /week).	(i) PLIN2 and PLIN5 increased in type I fibers, PLIN3 increased in type I, II fibers. (ii) Unchanged total LDs, increased LD-mitochondria association. (iii) ceramide decreased, diacylglycerol levels remained stable.	[138]

Table 4: (continued)

Subjects	Research design	Primary result	Refs
Resistance training effect on IMCL (training adaptation)			
Thirteen sedentary males	Muscle biopsies pre- and post-6 weeks resistance training.	Post-resistance training: Increased LDs and PLIN2, PLIN5 in type I, II fibers.	[139]

The adaptations of lipid to chronic exercise

Long-term exercise training enhances lipid utilization for energy, promotes overall reductions in lipid levels, and induces adaptive changes in skeletal muscle lipid metabolism. These adaptations lead to increased lipid oxidation, as well as improved storage and metabolism of neutral lipids. Endurance training has been demonstrated to improve fat oxidation capacity [146], which is accompanied by an increased accumulation of intramyocellular lipids (IMCLs) [147]. Interestingly, lipid accumulation within skeletal muscle is paradoxically associated with insulin resistance [28]. A phenomenon known as the athlete's paradox [72, 148]. Despite their high sensitivity to insulin, endurance athletes exhibit higher amounts of intramyocellular lipids [149]. Moreover, exercise interventions designed to reduce IR in obese patients with type 2 diabetes have been observed to increase IMCL content instead [150]. The paradox faced by athletes arises from the distinct impacts of training and diabetes on muscle lipid turnover, lipid intermediate accumulation, and oxidative capacity [28]. Notably, research by Bergman et al. [73] indicated that the incorporation of palmitate into triacylglycerol within skeletal muscle is more pronounced in athletes who are endurance-trained than in sedentary individuals. This evidence indicates that long-term exercise enhances the diversion of fatty acids towards triacylglycerol synthesis, which may reduce the build-up of lipotoxic intermediates linked to insulin resistance. Consequently, this metabolic adaptation contributes to an improved lipid profile and enhanced metabolic efficiency in trained individuals.

Summary and outlook

LDs have garnered significant interest in recent years, leading to numerous important and exciting discoveries across various domains. Significant advancements have been achieved in clarifying the mechanisms governing LDs formation

and degradation. Furthermore, excess LDs are implicated in disease progression, including cancer, by facilitating viral infections, promoting inflammation and fibrosis. Importantly, exercise has been found to regulate inflammatory cytokines, lipid intermediates, and LD-associated proteins, as well as to activate the IL-15, AMPK, and CaMKII signaling pathways. Additionally, exercise enhances lysosomal activity, improves glomerular filtration rate, boosts insulin sensitivity, and strengthens immune function, mitigating these detrimental processes. Elucidating the characteristics of LD-associated diseases, and the dynamic regulation of exercise represents a significant advancement in this field of research. A key challenge lies in deciphering the signaling pathways associated with each disease, including the roles of relevant signaling cytokines and their regulation by cellular physiology. A detailed exploration of LDs tissue specificity, function, and exercise-induced modulation, may ultimately deepen our knowledge of the interplay between LDs and exercise in maintaining metabolic health. However, exercise has several limitations, such as, more prolonged exercise can cause lipid oxidation, and promote inflammation. Marathon runners are prone to developing myocarditis, minor hepatic injury and temporary decline in kidney function [151, 152].

Future research will focus on establishing lipid droplets (LDs) as central signaling hubs, with an emphasis on their interactions with other organelles and their roles in cellular signaling pathways. Elucidating the relationship between LDs and the epigenome may yield critical insights into the mechanisms underlying LD-nuclear signaling. A key research priority will be defining the role of fatty acids derived from LDs in nuclear signaling cascades. Currently, our understanding of the regulatory mechanisms governing LD-associated proteins, their interactions with organelles, and the influence of exercise remains limited. The crosstalk between exercise and LD-associated proteins represents another pivotal area of investigation. To date, few studies have examined the effects of exercise on the LD-mitochondria axis in the heart, a topic that warrants further exploration. Moreover, future empirical studies should investigate – in greater depth – the tissue-specific heterogeneity of LDs and their adaptive responses to exercise.

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