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Article

Applications of physical exercise in frailty: Progress, mechanisms, and prospects

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Abstract: Frailty is a kind of clinical state or a kind of complex pathological syndromes characterized by impaired physiological functions, weakened physical and mental resistance to stress, and reduced ability to maintain homeostasis in multiple systems. Several types of risk factors can affect the occurrence and development of frailty either independently or in conjunction with one another, including age, gender, and exercise habits; and the multidimensional systemic treatment are often required to alleviate or improve frailty. Physical exercise is the various kinds of systematic and conscious activities, it has been demonstrated that regular exercise can promote the normal metabolism processes within the body, thereby preventing or alleviating the symptoms of various diseases. Physical exercise has the potential to regulate oxidative stress, immune response, and endocrine balance in the body of frail people by activating multiple signaling pathways including mitochondrial function, cytokine secretion, and regulation of inflammatory factors, its applications in frailty has been made the significant progress and the underlying mechanisms has been further elucidated. In this review, we have summarized the recent progress on the applications of physical exercise in frailty and the potential mechanisms, hoping that our reviews may provide some helpful guidance for the further research.

Keywords: physical exercise; frailty; oxidative stress; aging; biomechanics

1. Introduction

Frailty is a complex syndrome of multiphysiological decline, and frailty often results in the adverse health outcomes. These include reduced physiological function, reduced resistance to physical and mental stress, and reduced ability to maintain homeostasis. The occurrence of frailty is associated with several kind of diseases, including neurodegenerative diseases, cardiovascular diseases, and sarcopenia; Additionally, the prevalence of frailty exhibits particular characteristics. An epidemiological study conducted in Europe demonstrated that the prevalence of frailty in the community and in the non-community was 12% and 45%, respectively; there was the notable discrepancy between the two groups [1,2]; and in China, the prevalence of frailty among individuals aged 65 and above was 18.8%–50.9%; specifically, almost 10% individuals aged over 60 years old, 15% individuals aged between 75–84 years old, and approximately 25% of individuals aged over 85 years old were suffered from frailty, there is a significant correlation between the prevalence of frailty and age [3–5]. Statistical results of World Health Organization (WHO) demonstrated that there were 1 billion people aged 60 years old or older in 2019, this figure is projected to reach 2 billion by 2050. The significant increase in the elderly population is accompanied by a corresponding rise in the number of individuals experiencing frailty. This has the potential to place a considerable enormous economic and mental burden to frail people and their families [6–8].

Physical exercise is a kind of regular activities which could improve human body development and working ability, maintain the balance of mind and body, and reduce the occurrence of many kinds of metabolic diseases. The accumulating evidence demonstrated that physical exercise could improve the metabolism, reduce oxidative stress, enhance the immunoregulation and antioxidant effect, is emerging as a promising non-pharmacological intervention for reducing the incidence rate and mortality associated with various diseases. For example, Dempsey et al. [9] followed and studied the effect of physical activity (PA) volume and intensity on 88,412 middle-aged adults, and found that PA volume and physical activity intensity could decrease the risk of the cardiovascular disease; Wang et al. [10] provided the evidence that physical exercise could reduce the incidence rate of cancer and improve the prognosis of cancer patients, and had the better effects on various types of cancers at different stages by inhibiting the cancer cell proliferation and regulating the cancer mechanism. Similarly, frailty as a kind of complex multiphysiological decline syndrome, physical exercise is currently considered as the preferred solution for preventing or treating frailty at present, and the applications of physical exercise in frailty are manifold and include improvements in physical function, quality of life and mental health, which exhibit the irreplaceable advantages.

2. Clinical manifestations, risk factors and pathogenesis of frailty

The main clinical manifestations of frailty are the decline in the function of multiple organs in the body, including extreme fatigue, unexplained weight loss, and recurrent lung or urinary tract infections [11,12]. Exactly, frailty could result in a decrease of mitochondria in muscle cells and the functional muscles, further weakening the muscle strength and coordination [13]; lead to worsening of cardiovascular disease and poor prognosis [14]; affect the activity of nerve cells in patients, to reduce their cognitive function; decrease the number of T and B cells in the body, to further affect their immune function; even decrease the glomerular filtration rate of patients and to affect their renal function [15–17].

Frailty could increase the risk of disability, functional decline, hospitalization, and even death when the elderly under the stress, because the frail elderly people need the long-term care and treatment, usually bring the increasing medical expenses for the patients and their families [18]. The accumulative evidence demonstrated that many kinds of risk factors, including genetic factors, aging, economic conditions, education level, unhealthy lifestyle, and geriatric syndrome could result in the occurrence and deterioration of frailty, increasing difficulty of screening and identifying biomarkers of frailty [19,20]. Zheng et al. [21] recruited and analyzed the data of 500,000 middle-aged and older adults in the United Kingdom from 2006 to 2022, found that there was a statistical correlation between frailty and polygenic risk score on Parkinson’s disease; Zhou et al. [22] investigated and analyzed the data of 7471 older adults aged over 80 years from 2002 to 2014 from in China, results demonstrated that there were 2930 cases of frailty were identified, and the people with the polygenic risk score >2.47 × 10^{-4} suffered from frailty at the higher risk, this evidence suggested the correlation between genetic factors and frailty; Galluzzo et al. [23] provided the evidence that the prevalence and incidence of frailty in women was higher than that in men, and increased with the advancing age, demonstrated the relationship between aging and frailty; Sirven et al. [24] provided the data that the elderly people with the bad economic conditions can easily to withstand the frailty symptoms compared to people with better economic conditions in Europe, demonstrating that economic conditions also become the risk factor of frailty. To validate the relationship between unhealthy lifestyles and frailty, Li et al. [25] analyzed 3279 volunteers from Dongfeng-Tongji in China, the analysis results demonstrated that unhealthy lifestyles including smoking, drinking alcohol, and physical inactivity on cognitive impairment had the significant relationship with the frailty.

Brain deterioration, cardiovascular dysfunction, and deprivation of muscle function are the main manifestations of frailty, the evidences demonstrated that the high level of cerebral white matter, impaired cerebral perfusion, the occurrence of neuroinflammation [26,27], increased inflammation, reduced physical activity [28], and increased inflammatory inflammation [29] were highly associated with the process of frailty. Further evidences demonstrated physical inactivity could alter the brain structure, reduce neurogenesis, synaptic plasticity, and angiogenesis in frail people [30], and physical activity levels were the closely correlated with the total brain volume and cerebral white matter volume [31]; and reduced physical activity could decrease the synthesis of nitric oxide, which could result in arterial stiffness and cardiovascular dysfunction in frail people [32].

3. Exercise applications in frailty

3.1. Physical exercise and frailty

Physical exercise is a regular aerobic physical exercise which is used to improve the speed, strength, endurance, coordination, agility, and flexibility of body, there are numerous forms of physical exercise including jogging, push-ups, squats, sit-ups, single-leg pull-ups, and sitting forward bends, those different kinds of physical exercises could activate multiple physical functions and reduce the occurrence and development of multiple diseases [33]. These evidences demonstrated that physical exercise can also increase muscle density and mass, enhance cardiopulmonary function, accelerate metabolism in the body, regulate the excitability and inhibition processes of the central nervous system, improve immune regulatory function, and exhibit the superior therapeutic effects on frailty [34–36]. In particular, there are several kinds of physical exercises, including aerobic exercise, strength training, flexibility training, and balance training. Given that the specific methods of exercise, the desired outcomes and energy consumption expenditure involved vary from one exercise to another, these different physical exercises also have different advantages in alleviating the frailty.

3.2. Aerobic exercise and frailty

Aerobic exercise is a type of exercise that primarily provides the energy requirement for exercise through the process of aerobic metabolism [37]. In the human body, when the level of exercise is not high, the main source of energy supply for the body comes from the aerobic metabolism of sugar. During aerobic exercise, oxygen can fully decompose and consume sugars and fats in the body, enhancing and improving cardiovascular function, preventing osteoporosis, and regulating psychological and mental states [38,39]. Recent evidences have demonstrated that the efficacy of aerobic exercise applications in the treatment of frailty, with significant advancements being made in this field. For example, Bisset et al. [40] conducted an analysis of the effect of aerobic exercise on C57Bl/6 mice, comprising 12 male mice and 22 female mice, found that aerobic exercise could delay the development of frailty in both male and female mice, and extend the life expectancy of female mice; similarly, Lefferts et al. [41] compared the effect of total steps/day and faster aerobic steps/day (≥ 60 steps/min) on frailty in individuals with hypertension, demonstrated that aerobic steps/day could decrease the incidence of developing frailty compared with total steps/day; Zhang et al. [42] investigated the correlation between aerobic exercises and frailty from 2008 to 2011 in China, found that aerobic exercise could decrease the risk of aerobic exercise, it was determined that the NMJ pathway-related genetic risk was one of the key regulators of frailty, and aerobic exercise could partly decrease the effect of NMJ pathway-related genetic risk on frailty.

3.3. Strength exercise and frailty

Strength exercise is a form of exercises that has been demonstrated to enhance bone, muscle, and ligament strength, improve joint function, increase bone density and metabolism, and further control or slow down the progression of various chronic diseases, including osteoporosis and cardiovascular disease. Consequently, strength exercise also could retard the progression of frailty. For example, Weng et al. [43] collected and analyzed recent articles about the applications of strength exercise in frailty, the data demonstrated that strength exercise had a partial effect on alleviating the process of frailty; Similarly, Aas et al. [44] investigated the effect of strength training with protein supplementation on frailty, found that acute strength training could alleviating the symptoms of frailty by regulating the expressions of LC3-I and LC3-II, and by activating the ubiquitin-proteasome system and mitochondrial fission. Winters-Stone et al. [45] designed a single-blind, randomized controlled trial to study the effects of strength training or tai ji quan on frailty cancer people, the results demonstrated that both of strength training and tai ji quan could alleviate the symptoms of frailty, especially, strength training resulted in a three-fold reduction in inactivity, and had the better effects in women than that in men. Baltasar-Fernandez et al. [46] investigated the effect of a 6-week resistance training and fast walking interval training programme on frail older adults aged above 75 years old, found that this kind of 6-week training could effectively decrease the frailty index, alleviate the symptoms of frailty, offering a promising avenue for frailty treatment.

3.4. Balance exercise and frailty

As frailty progresses, the proliferation of muscle cells turns to slow, muscle tissue begins to atrophy, and muscle function begins to decline in individuals with frailty.

Impaired balance and lower limb muscle strength are one of the main symptoms of frailty, they also represent a significant risk factor to result for falls in older adults [47]. Many evidences demonstrated that exercise could increase the strength of muscle and reduce the risk of frailty. For example, Costa et al. [48] recruited 22 volunteers to investigate the effect of short-term balance exercise on frailty, the results demonstrated that this kind of balance exercise could alleviate the symptoms of frailty including muscle strength, psychological status, and postural balance; Similarly, Karagül et al. [49] designed a randomized prospective trial to assess the effectiveness of balance exercise, results demonstrated that the symptoms of frailty were improved in frail older adults after six weeks of balance exercise.

3.5. Traditional Chinese exercise on frailty

Traditional Chinese exercise is a form of exercise which formed under the guidance of traditional Chinese medicine and traditional Chinese martial arts. The Yellow Emperor's Inner Canon has recorded a variety of exercise and health preservation methods, including walking, guiding, and breathing [50], these methods have been further developed into traditional Chinese exercise, including Tai Chi, Baduanjin, and Yijinjing; these forms of exercise can be considered the inheritances and manifestations of traditional Chinese exercise [51–53]. It has been demonstrated that traditional Chinese exercise can prevent and alleviate the symptoms of diseases by smoothing the Qi and blood meridians, activating muscles and bones, and regulating and harmonizing the internal organs; furthermore, it also is proved to improve the muscle strength, cardiovascular function, and respiratory function [54,55]. The accumulative evidences demonstrated that traditional Chinese exercise also showed the effectiveness in frailty. For example, Xia et al. [56] compared the effect of the 24-week Baduanjin on the frailty people with cognitive functions, found that Baduanjin exercise could improve the cognitive and physical functions of frailty people; similarly, Wang et al. [57] evaluated the effect of Baduanjin exercise on frailty people, the results demonstrated that Baduanjin exercise could significantly improve the working memory and cognitive flexibility of frailty people after a 24-week treatment; Z et al. [58] provided the evidences that Tai Chi Chuan could alleviate the cognitive and physical function in frailty people; and Kasim et al. [59] demonstrated that Tai Chi could improve the antioxidant capacity and vascular function, thereby alleviating the symptoms of frailty including physical and mental fatigue.

A summary of the recent application progress of physical exercise on frailty from 2023 to 2024 is presented in **Table 1**. The data demonstrated that there were almost 20 countries in which clinical application research was conducted, including Thailand, Germany, Belgium, China, Canada, Singapore, Australia; and more than 70% of the trails occurred in developed countries; with a duration ranging from 4 weeks to 36 months; the exercise type included physical exercise combined with nutrition, exercise combined with nutritional interventions and psychological interventions. and traditional Chinese exercise; and there was no adverse effect have been reported (**Table 1**).

Table 1. The recent application progress of physical exercise on frailty.

The stage of trials	Country	Trials period	Exercise type	Therapeutic effect	Reference
randomized controlled trial	Thailand	24 weeks	multicomponent exercise	improve berg balance scale, timed up and go test, and frailty scores	[60]
randomized controlled trial	Thailand	24 weeks	multi-system physical exercise	increased muscle strength and improved proprioception	[61]
randomized controlled trial	Germany	32 weeks	multicomponent exercise	improve physical functioning, cognition, and psychosocial function	[62]
randomized controlled trial	USA	6 months	multidomain physical rehabilitation	improved physical function	[63]
randomized controlled trial	Belgium	12 weeks	physical exercise + nutrition	decreased the loss of skeletal muscle mass and function	[64]
HF-ACTION trial	USA	3 months	aerobic exercise training	decreased the risk of all-cause hospitalization	[65]
randomized controlled trial	China	12 weeks	resistance exercise	increased muscle strength, physical fitness, and metabolism	[66]
single-blind, parallel-arm, superiority randomized trial	Canada	4 weeks	Exercise + nutritional interventions + psychological interventions	did not affect postoperative outcomes	[67]
randomized controlled trial	China	24 weeks	Wu Qin Xi exercise + strength exercise + endurance exercise	improved the physical fitness and alleviating the symptoms of frailty	[68]
randomized controlled trial	Australia	6 months	home exercise prescription	frailty index was improved	[69]
double blind randomised trial	Canada	1 month	home-based total-body exercise training	improve postoperative recovery	[70]
randomized clinical trial	USA	8 weeks	qigong exercise	improve depression scores, fast gait speed, and standing balance	[71]
Cluster randomised control trial	Singapore	12 months	exercise and cognitive stimulation therapy	improve the cognition and depression	[72]
randomized clinical trial	China	12 weeks	physical exercise	improve frailty status and cognitive Function	[73]
cluster-randomized controlled trial	China	24 weeks	vitality acupunch exercise	improve the handgrip strength, upper-limb muscle endurance, and lung function	[74]
randomized clinical trial	Canada	24 months	physical exercise	decrease the major mobility disability	[75]
randomized clinical trial	New Zealand	25 months	nutrition-based intervention and physical activity intervention	decrease the symptom of frailty	[76]
randomized clinical trial	Japan	4 weeks	tablet-based exercise, paper-based exercise	improve body mass index and masticatory performance	[77]
randomized clinical trial	Spain	6 months	resistance training	improve respiratory function and health-related quality of life	[78]
randomized clinical trial	Zurich	36 months	vitamin D3+omega-3s+simple home exercise program	decrease the odds ratios for becoming pre-frail	[79]
randomized clinical trial	Ireland	3 months	home-based exercise + dietary protein intervention	improve grip strength and bone mass	[80]

Table 1. (*Continued*).

The stage of trials	Country	Trials period	Exercise type	Therapeutic effect	Reference
randomized clinical trial	Italy	24 months	physical activity	improve gait speed and muscle strength	[81]
three arms controlled trial	Portugal	28 weeks	Chair-based exercise	improve steroid hormone responses and functional disabilities	[82]
randomized clinical trial	Finland	24 months	home-based physical exercise	improve health-related quality-of-life	[83]
randomized clinical trial	Japan	12 weeks	oral and physical exercises	improve oral hypofunction	[84]
randomized clinical trial	Finland	12 months	home-based physical exercise	improve severity of frailty	[85]
randomized clinical trial	Brazil	12 weeks	exergaming and traditional multicomponent exercise	improve cognition	[86]
randomized clinical trial	Turkiye	6 weeks	aerobic, balance, and combined (aerobic-balance) exercise	improve cognitive and physical functions	[87]
randomized clinical trial	Finland	12 months	home-based exercise	improved physical performance	[88]
randomized clinical trial	Spain	12 months	Home exercise, branched-chain amino acids, and probiotics	decrease the probability of falls and emergency room visits	[89]
randomized clinical trial	Spain	6 months	multicomponent exercise	decrease risk of malnutrition	[90]
randomized clinical trial	Canada	28 weeks	MoveStrong exercises	improve gait speed, sit-to-stand functioning, dynamic balance	[91]
randomized clinical trial	South Korea	8 weeks	aerobic exercise and diet	improve physical fitness and vascular function	[92]
randomized clinical trial	Japan	12 weeks	home-based radio-taiso exercise	improve mobility and health-related quality of life	[93]
randomized clinical trial	/	12 months	exercise and protein supplementation	improve health-related quality of life	[94]
randomized clinical trial	Japan	12 weeks	moderate-intensity exercise	increase Muscle Strength	[95]
randomized clinical trial	Japan	6 months	physical exercise	improve muscle mass	[96]
randomized clinical trial	Spain	8 weeks	virtual running + physical gait exercise	improve gait, stand-up and sit-down	[97]
randomized clinical trial	Australia	6 months	exercise-nutrition	improve extremity physical+G43 function and handgrip strength	[98]
randomized clinical trial	China	6 months	aerobic exercise + muscle strength training + balance + coordination exercise	improve the frailty status and working memory	[99]
randomized clinical trial	United Kingdom	6 months	once weekly volunteer-led online group seated strength exercises	improve physical activity	[100]
randomized clinical trial	Turkey	6 weeks	aerobic, balance, and combined (aerobic-balance) exercise	improve the cognitive and physical deficits	[101]

Table 1. (*Continued*).

The stage of trials	Country	Trials period	Exercise type	Therapeutic effect	Reference
randomized clinical trial	Spain	12 months	home-based exercise, branched-chain amino acids, and a multistrain probiotic	decrease falls and emergency room visits	[102]
randomized clinical trial	Turkey	6 weeks	balance exercise	improve balance parameters and exercise performance	[103]
randomized clinical trial	Spain	10 months	multicomponent training	improve the physical fitness	[104]
randomized clinical trial	Thailand	12 weeks	resistance training	improve muscle strength	[105]
randomized clinical trial	China	12 weeks	multicomponent exercise	improve gait, balance, and muscle strength	[106]
randomized clinical trial	China	12 weeks	isolated resistance training	improve walking speed and hand grip strength	[107]
randomized clinical trial	Canada	26 weeks	physical exercises, cognitive training	improve cognition	[108]
randomized clinical trial	China	12 months	physical exercise	reduce fatigue	[109]
randomized clinical trial	Pakistan	/	resistance training	improve the clinical frailty score, strength, endurance	[110]
randomized clinical trial	Spain	12 weeks	power-oriented resistance training	improve physical function, and health-related quality of life	[111]
randomized clinical trial	Netherlands	13 weeks	hypocaloric diet and resistance exercise plus high-intensity interval training	decrease the expressions of circulating adipokines and anti-inflammatory cytokine	[112]
randomized clinical trial	Germany	16 months	high-intensity resistance training	increase lumbar spine bone mineral density	[113]
randomized clinical trial	Netherlands	16 weeks	dance interventions	improve frailty and depression	[114]
randomized clinical trial	Spain	12 months	multicomponent exercise	improve functional capacity and muscle strength	[115]
randomized clinical trial	Spain	6 months	multicomponent exercise	improve mobility, functional balance	[116]
randomized clinical trial	United Kingdom	6 weeks	resistance training	improve frailty	[117]
randomized clinical trial	China	12 weeks	resistance band use and tai chi	improve physical fitness, frailty conditions, self-care abilities	[118]

4. The underlying mechanisms of physical exercise application in frailty

4.1. Oxidative stress and frailty

Oxidative stress, as the negative effect caused by free radicals in the body, plays a crucial role in the process of aging and the development of age-related diseases. On one hand, normal physiological levels of oxidative stress are essential for cell signaling and immune defense. On the other hand, when oxidative stress is imbalanced, with excessive free radical production or a weakened antioxidant defense system, it can damage biomolecules such as proteins, lipids, and DNA within cells, triggering a series of pathological changes and becoming an important causative factor for many diseases, especially neurodegenerative diseases (such as Alzheimer's disease and Parkinson's disease) [119,120], cardiovascular diseases (such as coronary heart disease and heart failure), and chronic metabolic diseases (such as diabetes and obesity) [121,122].

In a healthy body, the antioxidant defense system within cells, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), can timely scavenge excessive reactive oxygen species (ROS) and maintain redox balance. However, with aging, disease invasion, or the influence of an unhealthy lifestyle (such as smoking, excessive alcohol consumption, and long-term lack of exercise), this balance is disrupted, and oxidative stress intensifies. Research has found that the level of oxidative stress in the brain significantly increases during the aging process, which is closely related to neurotransmitter synthesis disorders, increased neuronal apoptosis, and cognitive decline [123]. In addition, oxidative stress can also indirectly affect the occurrence and development of frailty by regulating the composition and function of the gut microbiota. The gut microbiota, as the "second genome" of the human body, is involved in many physiological processes, including nutrient metabolism, immune regulation, and neuroendocrine regulation. Oxidative stress can alter the ecological balance of the gut microbiota, leading to a decrease in beneficial bacteria and an increase in harmful bacteria, thereby triggering intestinal barrier dysfunction, endotoxemia, and a systemic inflammatory response, all of which are closely related to the aggravation of frailty symptoms. For example, Siyue Chen and other scholars found through animal experiments that oxidative stress can significantly change the diversity and structure of the gut microbiota in mice, increase intestinal permeability, and promote the release of inflammatory factors, ultimately leading to manifestations similar to frailty in mice, such as decreased muscle strength, reduced activity ability, and cognitive impairment [124].

Mounting evidence suggests that physical exercise is of great significance in regulating oxidative stress and alleviating frailty symptoms. Regular physical exercise can enhance the body's antioxidant defense capacity and reduce oxidative stress damage through various pathways. On one hand, exercise can activate the intracellular antioxidant enzyme system, increasing the expression and activity of antioxidant enzymes such as SOD, CAT, and GPx, thereby accelerating the clearance of ROS [125, 126]. For example, the activity of SOD and GPx in the blood of elderly people who engage in long-term aerobic exercise is significantly higher than that of sedentary peers, indicating stronger antioxidant capacity and lower oxidative stress levels [127].

4.2. Inflammation and frailty

The inflammatory response is a complex physiological defense mechanism of the body in response to external stimuli and internal damage, aiming to clear pathogens, repair damaged tissues, and maintain internal environmental stability. Under normal circumstances, the inflammatory response is short-lived and controllable, and once the stimulus is eliminated, the inflammatory response will quickly subside and the tissue will return to normal function. However, in certain pathological conditions, the inflammatory response may be continuously activated or dysregulated, leading to the occurrence of chronic inflammation and subsequently triggering a series of diseases. In the process of frailty development, the inflammatory response plays a crucial role and is closely related to all aspects of frailty.

In frail individuals, the inflammatory balance is often disrupted, manifested as an increase in pro-inflammatory cytokine levels and a relative deficiency of anti-inflammatory cytokines, resulting in a chronic systemic inflammatory state. For example, multiple clinical studies have found that the levels of pro-inflammatory cytokines such as IL-6 and TNF-αin the serum of frail elderly people are significantly higher than those of healthy elderly people and are positively correlated with the degree of frailty [128,129]. This chronic inflammatory state can promote the development of frailty through various pathways. Firstly, inflammatory cytokines can directly act on muscle tissue, inducing muscle protein degradation and inhibiting muscle protein synthesis, leading to a decrease in muscle mass and muscle strength, which is one of the important characteristics of frailty. Secondly, the inflammatory response can also affect the cardiovascular system, promoting the occurrence and development of atherosclerosis, reducing vascular elasticity, and increasing the risk of cardiovascular diseases, thereby aggravating frailty symptoms [130]. In addition, inflammatory factors can cross the blood-brain barrier, interfering with the normal function of nerve cells, triggering neuroinflammation, and leading to cognitive impairment, which is also a common manifestation of frail patients [131].

Physical exercise, as a non-pharmacological intervention, shows great potential in regulating the inflammatory response and improving frailty symptoms. Numerous studies have shown that different types and intensities of physical exercise have significant regulatory effects on the inflammatory response, and the mechanisms involve multiple levels. Moderate aerobic exercise can reduce the expression of pro-inflammatory cytokines and increase the level of anti-inflammatory cytokines, thereby improving the inflammatory balance. For example, the levels of inflammatory factors such as IL-6 and TNF-α in the serum of people who engage in long-term jogging are significantly reduced, while the levels of anti-inflammatory factors such as IL-10 are increased [40,132]. Diego Marcos-Pérez, et al. evaluated the effects of a three-month exercise on the 12 elder people and 12 aged C57BL/6 mice, found that pro-inflammatory biomarkers, including IL-6, CXCL-1, CXCL-10, IL-1β, IL-7, GM-CSF were decreased after exercise intervention, and CXCL-10 and IL-1β were identified as the potential biomarkers of functional improvement of frail people [133]. This may be because aerobic exercise can activate the body's immune system, prompting immune cells to produce anti-inflammatory mediators, while inhibiting the activation of inflammatory cells and the release of inflammatory factors.

4.3. Autophagy and frailty

Autophagy is a fundamental intracellular process that is highly conserved across eukaryotic organisms. It serves as a crucial quality control mechanism within cells, whereby damaged, aged, or dysfunctional cellular components, such as proteins, lipids, and organelles (including mitochondria and endoplasmic reticulum), are sequestered within double-membrane vesicles known as autophagosomes. However, in response to various stressors like nutrient deprivation, hypoxia, oxidative stress, and pathogen infection, autophagy is rapidly upregulated to enhance the cell's survival capabilities. By eliminating harmful or non-functional elements, autophagy helps cells to adapt and persevere under challenging circumstances, while also preventing the accumulation of potentially toxic substances that could otherwise lead to cellular damage and disease progression.

In the context of frailty, emerging evidence strongly implicates abnormal autophagy as a significant contributor to the pathophysiological processes underlying this complex syndrome. The natural aging process is accompanied by a progressive decline in autophagic activity, which impairs the cell's ability to efficiently clear damaged and obsolete components. As a consequence, these accumulated substances disrupt normal cellular metabolism and function, creating a permissive environment for the development and exacerbation of frailty-related conditions. For instance, Tsuyoshi Sasaki, et al. reported that IL-6 could regulate the expression of STAT3 and autophagy in myotubes via Fyn, Fyn could regulate the IL-6-STAT3-autophagy axis to affect the process of sarcopenia, exhibiting an autophagy-dependent signaling pathway in frailty [134]. Sebastián et al. [135] investigated the effect of TP53INP2 on sarcopenia, found that autophagy was increased in old transgenic mice, upregulation of autophagy improved the muscle atrophy in old mice, and re-expression of TRP53INP2 in aged mice improved muscle atrophy, enhanced mitophagy, and reduced ROS production. Wu et al. [136] provided the evidences that Artemisia leaf extract could activate TRPML1 and downregulate the autophagy/mitophagy to protect the neuron in Parkinson's disease. Physical exercise has emerged as a potent regulator of autophagy and holds great promise as an intervention strategy for frailty. Zeng et al. [137] provided the evidences that 12-week exercise training could regulate the expression of atrogin-1, MuRF1, and Beclin1, increase the LC3-II/LC3-I ratio, and improve the mitochondrial function in 21-month-old rats with sarcopenia;

The impact of exercise-induced autophagy on frailty is multi-faceted and far-reaching. In a Parkinson's disease mouse model, for example, exercise training was found to increase autophagy-mediated clearance of α-synuclein aggregates, which are toxic to neurons. This not only reduced neuroinflammation and oxidative stress but also protected dopaminergic neurons, leading to significant improvements in motor function and overall well-being [138]. Similarly, in aged skeletal muscle, exercise-induced autophagy helps to restore the balance between protein synthesis and degradation, attenuating muscle atrophy and enhancing muscle strength. By improving mitochondrial function and reducing oxidative damage, exercise-induced autophagy also contributes to enhanced energy metabolism and endurance, further alleviating frailty symptoms [139]. Notably, recent studies have identified novel regulators of exercise-induced autophagy, such as fibronectin (FN1), which is secreted by muscle in response to exercise and activates hepatic autophagy via the IKKα/β-JNK1-BECN1 pathway, driving metabolic benefits and highlighting the complexity and importance of this regulatory network in the context of frailty [140].

4.4. Biomechanics and frailty

Biomechanics is a quantitative discipline that employs principles and methods of mechanics to investigate mechanical problems in living organisms. And the primary characteristic of frailty is an imbalance of physiological reserves across multiple systems within the body and an increase in the vulnerability of the body. The evidence demonstrated that biomechanics also plays an important role in the development of frailty. For example, A Vallet, et al. investigated the relationship between the biomechanics of the CNS and frailty in older individuals, found that the biomechanical characterization of the CNS had a higher correlation with brain ageing [141]; Sophie Guillotin, et al. revealed a correlation between the homocysteine (Hcy) level and the frailty index and the CNS elastance coefficient, and the Hcy level was found to influence biomechanical response in the CNS and frailty [142]. Furthermore, Benoit Gobron, et al. developed a kind of dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-2 (GIP/GLP-2) analogue with the excellent biomechanical characteristics, and which was validated in the animal experiment experiments for its ability to improve the mineral-to-matrix ratio [143]. Jana Maria Hommen, et al. analyzed the impact of gait initiation on different stages of frailty individuals from a biomechanical perspective, found that the targeted exercise programs incorporating both the static and dynamic balance training may offer benefits for individuals experiencing frailty [144].

5. Conclusion and perspectives

The efficacy of physical exercise in mitigating frailty has been substantiated by empirical evidence. A multitude of clinical studies have demonstrated that diverse forms of physical exercises, including aerobic exercise, strength exercise, balance exercise and traditional Chinese exercise could alleviate the symptoms of frailty through the activation of distinct signaling pathways (**Figure 1**). However, there are still several issues require further investigation. (1) Types of physical exercise, exercise forms, exercise intensity and exercise duration are diverse, several clinical trials provided the evidences that physical exercise has the different therapeutic effects on frailty in different age people and in different sexes, some physical exercises have been shown to have the effect on female older people but not male people, It is therefore necessary to consider how to ensure the uniformity and standardization of clinical application of physical exercise; (2) the underlying mechanisms of physical exercise application in frailty was were insufficient and not sufficiently elucidated. Although there are the evidences that physical exercise can alleviate the frailty by regulating oxidative stress, inflammation, or autophagy, but there is a lack of direct evidence to prove the relationship among them, and the further mechanisms have not been explored; (3) the different frail people have the different medical histories, healthy statuses, endurance levels, and preferences, therefore, it is necessary to develop personalized or humanized exercise training.

Future research can approach this from several angles. For example, the rise of big data and artificial intelligence technologies offers possibilities for addressing individual differences. With the help of wearable devices that can monitor individual exercise data in real-time, combined with AI algorithms for analyzing massive datasets, it is possible to accurately depict the characteristics of each frail individual, thereby providing strong support for developing personalized exercise training programs. In exploring the potential mechanisms by which physical exercise alleviates frailty, the continuous development of advanced biotechnologies such as gene editing and proteomics provides more powerful tools for in-depth research into the relationships between oxidative stress, inflammation, and autophagy. These technologies facilitate comprehensive research at the molecular, cellular, tissue, and systemic levels and are expected to construct more precise network regulatory models, thereby revealing the deeper mechanisms by which physical exercise improves frailty.

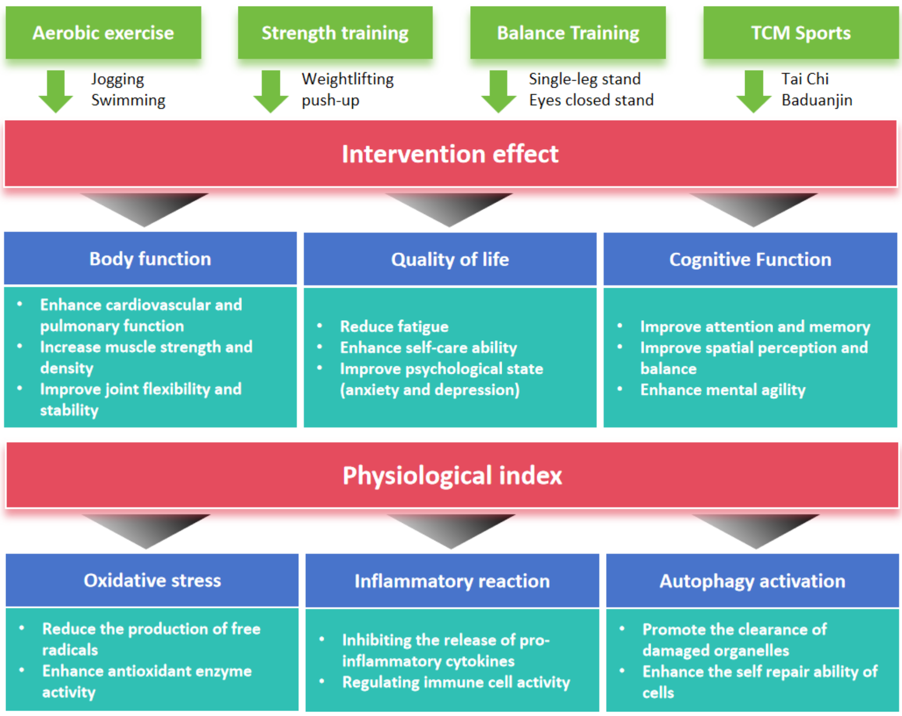

Figure 1. Overview of the intervention and physiological regulation mechanisms of physical exercise on frailty.

In conclusion, with the establishment of standardization of physical exercise application in frailty, the deepening of basic research, and the development of diversified personalized physical training will facilitate the resolution of numerous applications and result in significant advancements in the field of physical exercise applications in frailty.

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