

Review

Impacts of exercise interventions on different diseases and organ functions in mice

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Abstract

Background: In recent years, much evidence has emerged to indicate that exercise can benefit people when performed properly. This review summarizes the exercise interventions used in studies involving mice as they are related to special diseases or physiological status. To further understand the effects of exercise interventions in treating or preventing diseases, it is important to establish a template for exercise interventions that can be used in future exercise-related studies.

Methods: PubMed was used as the data resource for articles. To identify studies related to the effectiveness of exercise interventions for treating various diseases and organ functions in mice, we used the following search language: (exercise [Title] OR training [Title] OR physical activity [Title]) AND (mice [title/abstract] OR mouse [title/abstract] OR mus [title/abstract]). To limit the range of search results, we included 2 filters: one that limited publication dates to “in 10 years” and one that sorted the results as “best match”. Then we grouped the commonly used exercise methods according to their similarities and differences. We then evaluated the effectiveness of the exercise interventions for their impact on diseases and organ functions in 8 different systems.

Results: A total of 331 articles were included in the analysis procedure. The articles were then segmented into 8 systems for which the exercise interventions were used in targeting and treating disorders: motor system (60 studies), metabolic system (45 studies), cardio-cerebral vascular system (58 studies), nervous system (74 studies), immune system (32 studies), respiratory system (7 studies), digestive system (1 study), and the system related to the development of cancer (54 studies). The methods of exercise interventions mainly involved the use of treadmills, voluntary wheel-running, forced wheel-running, swimming, and resistance training. It was found that regardless of the specific exercise method used, most of them demonstrated positive effects on various systemic diseases and organ functions. Most diseases were remitted with exercise regardless of the exercise method used, although some diseases showed the best remission effects when a specific method was used.

Conclusion: Our review strongly suggests that exercise intervention is a cornerstone in disease prevention and treatment in mice. Because exercise interventions in humans typically focus on chronic diseases, national fitness, and body weight loss, and typically have low intervention compliance rates, it is important to use mice models to investigate the molecular mechanisms underlying the health benefits from exercise interventions in humans.

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1. Introduction

Appropriate exercise can not only enhance body shape and physical fitness, but it can also prevent and treat diseases,

including cancers.^{1–7} Although numerous therapies and medications have been developed to treat the majority of diseases, exercise remains a natural alternative and convenient treatment method.^{8–10}

At present, there are many forms of exercise for people, such as quick walking, running, swimming, cycling, ball games, and weightlifting. Different exercise parameters, such as type, time, frequency, and intensity, can all influence the effects of exercise on the prevention or treatment of diseases.¹¹ For example,

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6-month vigorous jogging reduced body weight, waistline, body fat, and blood pressure in patients with obesity and nonalcoholic fatty liver disease (NAFLD), while moderate-intensity exercise has no such effect.¹ Recently, several reviewers summarized the benefits of various types of exercise on diseases, including Alzheimer's disease (AD), stroke, Parkinson's disease (PD), and Huntington's disease (HD).^{12–16} However, the illnesses and exercise types mentioned in those reviews were limited, and only a few of the reviews included the benefits that sports participation offers in the improvement of some physiological functions.^{17–20} Thus, the benefits that various exercise protocols have in treating diseases and improving physiological functions still need to be explored.

The animals used in most exercise studies are mice, partially because mice have many advantages compared with other animals. For instance, mice genes and human genes share a close homology, and mice can closely simulate the physiology and pathology of humans. Additionally, mice have relatively short reproductive cycles and low breeding costs, with well-developed experimental apparatus available for every researcher.

In this review, we summarize exercise information mentioned in mice experiments in different organ systems and their relation to special diseases or physiological status, including cancers, obesity, and aging.²¹ We sought to understand the differences among exercise interventions that contribute to effects in treating or preventing diseases, to establish a template for exercise intervention, and to provide a reference for additional exercise-related studies.

2. Methods

2.1. Data collection

PubMed was used as the data resource for articles reviewed in the present study. To identify studies related to the effectiveness of exercise interventions for treating various diseases and organ functions in mice, we used the following search language: (exercise [Title] OR training [Title] OR physical activity (PA) [Title]) AND (mice [title/abstract] OR mouse [title/abstract] OR mus [title/abstract]). To limit the range of search results, we included 2 filters: one that limited publication dates to “published within the past 10 years” and one that sorted the results as “best match”. In this way, we preliminarily found 1297 papers. Those studies that found benefits from exercise intervention were included in the review; those that were related to capacity assessment were excluded. As a result of this process, a total of 331 articles were included in our review. All articles were published before the end of June 2018.

2.2. Data analysis

We classified the 331 articles into 8 systems for which the exercise interventions were used in targeting and treating disorders: motor system (60 studies), metabolic system (45 studies), cardio-cerebral vascular system (58 studies), nervous system (74 studies), immune system (32 studies), respiratory system (7 studies), digestive system (1 study), and systems related to

the development of cancer (54 studies). Although cancer is not a conventional “system” in medical terms, we nevertheless included it as a system because studies on cancer and exercise interventions had many similarities to the other studies.

Within each system, the articles were subdivided into categories involving different types of diseases or organ functions. Tables were created to capture the details of the exercise interventions, and the articles were organized chronologically based on exercise methods and exercise durations.

We identified the following relatively common used exercise methods for mice: treadmill exercise, voluntary wheel-running, forced wheel-running, swimming, and resistance training. However, we identified a few uncommon methods as well, such as RotaRod or isometric contraction exercise. These uncommon training protocols are discussed as they relate to particular studies.

2.3. Classification of exercise types

2.3.1. Treadmill exercise

Treadmill exercise was the most common and effective way that researchers treated and prevented disease in mice. The most significant advantage for treadmill exercise is that the exercise intensity can be precisely controlled to better investigate the effects induced by different intensities. Usually, mice are willing to run at the speed set for the treadmill, but given individual differences, stimuli are sometimes used to keep mice running until exhausted. These stimuli include softly poking them on their hindquarters or shocking them with low levels of electric current.

Before the formal treadmill exercise begins, adaptive training is often administered to make mice familiar with the ambient environment. This process was used in about 40% of the studies using the treadmill exercise methods. Some researchers chose to use low-intensity running as an adaptation method, while other researchers simply put the mice in the vicinity of the equipment. In general, the familiarization starts 5–7 days before the formal training, and during the adaptation period, mice will run for 10–30 min/day at a speed of 8–15 m/min.

When formal exercise starts, it is crucial to maintain the intended exercise intensity and duration. Because we did not find any published standards for intensity, we defined intensity for treadmill exercise as follows: low intensity (<15 m/min at 0%–5% slope), moderate intensity (15–20 m/min at 0%–10% slope), and high intensity (>20 m/min at ≥0% slope). However, because both the sex and the strain of mice influence training performance, researchers should make adjustments based on these considerations. Likewise, individual variation among mice requires that an exhaustion test be conducted to determine each animal's exercise capacity before training. There are 4 parameters that should be measured during exhaustion testing to determine which levels of intensity should be used: maximal speed, maximal oxygen ($\text{VO}_{2\text{max}}$) uptake, maximal blood lactate steady state, and maximal heart rate.

As for exercise duration, although mice can run continuously for up to 2 h at a time,²² most studies use a training

protocol in which the mice run for 30–60 min/day, with a frequency of 5 or 7 days/week. In regard to the length of the intervention, short-term interventions are defined as lasting less than 6 weeks and long-term interventions last 6 weeks or more than 6 weeks. Acute exercise interventions are defined as using a bout of exercise that lasts 60–180 min or ends with exhaustion.

Another option is that running speed can be either fixed or incremental. Most studies using treadmill exercise interventions use incremental speed, because the body condition of mice improves with exposure to a fixed exercise intensity, thus weakening the effect of the exercise intervention. High-intensity interval training (HIIT) is also sometimes used in treadmill exercise. In general, this training typically involves 4–13 repetitions at 85%–100% $\text{VO}_{2\text{max}}$ at maximal running speed, separated by 2–3 min active recovery at 60% maximal running speed, with a 20°–25° incline.

2.3.2. Voluntary wheel-running

Compared with treadmill exercise, voluntary wheel-running enables mice to exercise at a lower intensity and to run freely. Although this practice may cause individual differences among mice in the amount of exercise they get, the mice do not experience as much stress, thus enabling us to obtain more accurate data. The duration of wheel-running is defined the same as treadmill exercise: short term (<6 weeks) and long term (≥ 6 weeks). To monitor activities of mice in cages, specific monitoring devices, such as mini-cameras and computers, are set up so to collect data on several mice at the same time.²³

Adaptive training is also used for voluntary wheel-running; researchers usually leave the mice in cages with a wheel for several days before the study begins.

2.3.3. Forced wheel-running

A relatively less used wheel-running pattern is forced wheel-running. In forced wheel-running, the wheel rotates automatically; if mice cannot maintain running speed, they will coast inside the wheel. Forced wheel-running can partly avoid the individual differences that happen in voluntary wheel-running, and it mostly uses a lower intensity (<10 m/min) and produces less physiological stress.²⁴ According to a previous report, if the wheel speed is greater than 10 m/min, mice spend more than 50% of their exercise time coasting in the rotating wheel, which largely impairs exercise effects.²⁵ The duration of forced wheel-running is the same as treadmill exercise: 30–60 min/day, with 6 weeks as the division point for short-term (<6 weeks) or long-period (≥ 6 weeks) duration.

2.3.4. Swimming

Swimming is less extensively used in mice exercise interventions, but it still has its advantages. Swimming is known to recruit whole body muscles and ligaments; thus, it is an effective form of aerobic endurance training.²⁶ However, a limitation is that the mice must be carefully attended to during the entire experiment to prevent them from drowning or floating. In addition, the water temperature should be kept at $30^{\circ}\text{C} \pm 1^{\circ}\text{C}$ during the swimming. Nevertheless, swimming is still used as a form of intervention for mice exercise.

It is important to let the mice acclimate to the swimming tank before training proceeds. Adaptive training consists of 3–7 days of swimming before the study commences, and mice are allowed to swim 15–180 min/day in the swimming tank.²⁷

For studies using swimming, intensity is defined by the amount of swimming that takes place each day: low intensity (20–59 min/day), moderate intensity (60–89 min/day), and high intensity (≥ 90 min/day). Depending on the training adaptation, either fixed or increased training time can be applied.

For duration, the same standard used for treadmill exercise is used: 6 weeks is the division point for short-term (<6 weeks) or long-period (≥ 6 weeks) duration.

2.3.5. Resistance training

Resistance training has long been proven to be helpful to athletes in improving performance.²⁸ However, resistance training is not common in mice exercise interventions, mainly because it requires complex manipulation. Procedures for resistance training in mice are typically much simplified, with ladder climbing with a load as the most commonly used procedure.

To achieve the desired results from resistance training, a ladder is often set nearly perpendicular to ground (80%–85% slope). Mice are familiarized with the ladder several days before training. Before ending the adaptive time, researchers should observe the mice successfully climbing the ladder from bottom to top.

The exercise intensity in ladder climbing is defined by how many climbing repetitions are completed and how much loading weight is attached to the mouse's tail. Most studies require 8–15 repetitions each day with 1–2 min rest between repetitions. Loading weight is increased in conjunction with the process of training and ranges from 50% to 100% of a mouse's body weight.

As with the other types of interventions, 6 weeks is the dividing point between short-term (<6 weeks) and long-term (≥ 6 weeks) duration.

3. Results

3.1. Effects of exercise on motor system

The motor system consists of 3 organs: bones, joints, and skeletal muscle. The primary function of the motor system is exercise; it also functions as structural support and protection, including maintaining body shape and posture, supporting weight, and protecting internal organs.

3.1.1. Skeletal muscle atrophy

Skeletal muscle atrophy is a common adaptation of the organism that results from chronic malnutrition, diseases, muscle disuse, and the use of some medications.^{29,30} Current treatments for skeletal muscle atrophy mainly involve physical therapy, pharmacotherapy, and nutrition intervention.³¹ Recent studies have proven that appropriate exercise plays an important role in the prevention and treatment of skeletal muscle atrophy because exercise increases brown adipose tissue, which can increase exercise capacity in muscle.³²

Supplementary Table 1 shows that in mice models of muscular atrophy, the main exercise treatment methods were treadmill exercise and voluntary wheel-running. Exercise training was usually performed on a treadmill at moderate or high intensity for short- or long-term duration. Only one of the treadmill exercise studies used adaptive training, in which mice were forced to run on the treadmill for 7 days for 10 min at a time with no inclination at a speed of 5 m/min before the formal exercise protocol began.³³ Some studies used voluntary wheel-running as an exercise method, in which wheel-running was performed for a long-term duration. Additionally, short-term, low-intensity swimming; resistance training using isometric contraction exercise; and short-term, low-intensity exercise using a rotating treadmill at a speed of 16 rotations/min were also used as intervention methods for treating muscular atrophy in mice. During the rotating treadmill exercise, all exercised mice underwent a period of acclimatization to the rotating treadmill, which turned at a very low speed of 16 rotations/min for 15 min during the first week and 30 min during the second week.³⁴ Mice models mainly used mice that had drug-induced or chronic disease-induced muscular atrophy, or used mdx mice that had Duchenne muscular dystrophy.

The exercise interventions usually showed positive effects on improving muscle mass and skeletal muscle function in mice with muscular atrophy. One study showed partially positive effects of exercise on mice with muscular atrophy induced through chronic kidney disease (Supplementary Table 1), indicating either that mice with chronic kidney disease may respond differently to treadmill exercise or that 2 weeks of exercise training is too brief to produce a notable positive effect.

3.1.2. Aging-related sarcopenia

The process of muscle mass loss and loss of function due to increasing age is known as “senile muscular atrophy” or “sarcopenia”,^{35,36} a special type of muscular atrophy. Supplementary Table 2 shows that the main exercise intervention methods for sarcopenia were treadmill exercise and voluntary wheel-running exercise. Treadmill exercise, including HIIT, was the most used exercise intervention and was performed for short- or long-term duration. Some studies used voluntary wheel-running with short- or long-term duration, or voluntary wheel-running combined with resistance training for long-term duration. Additionally, long-term resistance training alone was used for treating age senescence-accelerated mouse prone 1 mice. We noticed that, for sarcopenia treatment, the duration of the exercise intervention was always long term, probably because more time is required to create muscle function improvement in aged mice.

These exercise studies all showed positive effects on skeletal muscle regeneration, muscle metabolism, and motor function in mice with regard to sarcopenia.

3.1.3. Osteoporosis

Osteoporosis is a systemic bone disease resulting in an increasing propensity for bone fracture. It is estimated that in 2013 more than 200 million people suffered from osteoporosis worldwide, especially elderly people and postmenopausal

women.³⁷ Pharmacotherapy is the primary treatment for osteoporosis but cannot by itself efficiently improve muscle function or prevent fractures. Exercise is thus recognized as an important nonpharmacologic treatment, and is the first choice in preventing osteoporosis.^{38,39}

Only 2 articles discussed the therapeutic effects of exercise training on osteoporosis (Supplementary Table 3). The form of exercise used in these 2 research studies was treadmill exercise of long-term duration with an incremental speed. One of the studies used an adaptive training period in which mice performed consecutive treadmill running for 6 days at 8 m/min (0° slope) for 10 min/day during the first week.³⁹

The 2 exercise treatments showed positive effects for improving bone properties and alleviating osteopenia.

3.1.4. Skeletal muscle motor function

Studies on skeletal muscle mainly focused on its motor function, maintenance function, and metabolic function.^{40,41} In recent years, many studies have uncovered the mechanisms and gene expression patterns in exercise-induced skeletal muscle adaptations,⁴² which help us further understand how exercise improves skeletal muscle motor function.

Supplementary Table 4 shows that, in mice studies related to skeletal muscle motor function, the main exercise intervention methods were treadmill exercise, voluntary wheel-running, and swimming. Among all exercise protocols, treadmill exercise was performed at a low or moderate intensity. Most treadmill exercise training involved acute exercise, while others used long-term exercise duration with a stable speed. Mice were familiarized with the treadmill for 2–3 consecutive days at low-intensity speed before the beginning of formal exercise.⁴³ In studies using voluntary wheel-running, exercise was applied for short- or long-term durations. Additionally, short-term vibration training and long-term Rota-Rod treadmill methods were used in some studies. The main mice models used for studying skeletal muscle motor function involved wild-type C57BL/6J mice and proliferator-activated receptor gamma coactivator-1 (PGC1)- α /myostatin-deficient mice.

These exercise interventions showed positive effects on skeletal muscle adaptation and remodeling. These adaptive changes may be the basis for improvement in skeletal muscle motor function. However, for mice with diabetes induced by a high-fat diet (HFD), exercise alone only partially improved their mobility capacity, while only the combination of exercise and food restriction reversed the impaired mitochondrial function and oxidative dysfunction in the skeletal muscle.⁴⁴

3.1.5. Mitochondrial quality control

The mitochondrion is involved in the regulation of cellular metabolism, calcium homeostasis,⁴⁵ reactive oxygen species production,⁴⁶ and apoptosis.⁴⁷ Skeletal muscle function is closely related to mitochondrial quality, with numerous studies showing that exercise plays an important role in regulating mitochondrial quality.⁴⁸

Supplementary Table 5 shows that mitochondrial quality studies in mice used exercise interventions involving treadmill exercise and voluntary wheel-running. In treadmill exercise

protocols, training was performed at low-to-moderate intensity. Most treadmill training involved acute exercise, while other treadmill exercise was short- or long-term in duration. Exercise patterns similar to previous studies were applied and continued for at least 2 days before the actual treadmill exercise protocol began.^{49–51} Some studies used voluntary wheel-running at short-term duration as an exercise method. In 1 voluntary wheel-running study, animals were acclimatized to cages for several days before actual training.⁵² Wild-type C57BL/6J mice and PGC1- α /Parkin/Sirt1/IL-6 knockout mice were used in these studies.

The results of all these exercise interventions showed positive effects in that exercise maintained the function of the entire mitochondrial network in skeletal muscle and ensured that energy was supplied to muscle cells. Therefore, exercise can preserve the quality of skeletal muscle mitochondria.

3.1.6. Bone mineral density (BMD) and bone quality

BMD has always been an important index in evaluating the risk of osteoporosis and fracture. BMD, together with bone quality, define all characteristics related to bone strength.^{53,54} BMD and bone quality may decrease for a variety of reasons, including hormonal changes, aging, diet, and chronic diseases. Although there are many ways to improve BMD and bone quality, recent studies have shown that exercise therapy is among the better choices.⁵⁵

Supplementary Table 6 shows that the main exercise methods used for investigating bone properties were treadmill exercise and voluntary wheel-running. Treadmill exercise, at low-to-moderate intensity at stable or incremental speed for short- or long-term duration, was used in most exercise protocols. Other studies using voluntary wheel-running were of long-term duration. Additionally, voluntary climbing exercise was also used with short-term duration. The mice models used in these studies mainly used wild-type C57BL/6J mice and myostatin-deficient mice.

All exercise modes used in mice studies improved bone mass, bone strength, and BMD, which pointed to bone quality improvement.

3.1.7. Skeletal muscle angiogenesis

Angiogenesis involves multifactorial physiological processes with both proangiogenic and antiangiogenic factors, which interact with vascular endothelial cells and the vascular extracellular matrix.⁵⁶ Exercise is one of the physiological processes that activates angiogenic response in adults.^{56,57} Exercise can increase the expression of angiogenic growth factors and skeletal muscle capillaries, which are well-known beneficial alterations in healthy humans and animals.⁵⁷

Supplementary Table 7 shows that the main exercise training in studies related to skeletal muscle angiogenesis involved treadmill exercise and voluntary wheel-running. In the treadmill exercise protocols, the training was performed at high intensity either once or for a short term. The studies using voluntary wheel-running used acute exercise, or either short-term or long-term duration. In addition, a passive exercise called “whole-body periodic acceleration” was also used for

training.⁵⁸ NMRI mice, peroxisome PGC-1 knockout mice, adenosine 5'-monophosphate-activated protein kinase $\alpha 2$ over-expression mice, and C57BL/6J mice were all common choices in these mice models.

These exercise interventions showed positive effects on angiogenesis and induced the expression of angiogenic growth factors in skeletal muscles.

3.1.8. Switching of muscle fiber types

Skeletal muscles are composed of different types of fibers and use myosin heavy chain isoforms for basic classification. In mice, muscle fibers include myosin heavy chain isoforms of type I, type IIa, type IIb, and type IIx.⁵⁹ Muscle has high plasticity in that different fiber types can switch to each other under stimuli such as exercise.⁶⁰ Different exercise types modulate different switch directions,⁶¹ but the underlying pathways largely remain unknown.

Supplementary Table 8 illustrates that studies related to shifts in muscle fiber types used treadmill exercise and voluntary wheel-running as common exercise interventions. Both types of interventions were of short-term and long-term durations. In treadmill interventions, low-intensity exercise was sufficient to induce muscle fiber shift. Since most studies focused on molecular pathways, specific gene knockout mice or transgene mice were most commonly used.

Most studies indicated that specific genes or proteins are necessary in exercise-induced fiber shift, meaning that complex pathways are involved in exercise-modulated muscle fiber remodeling.

3.2. Effects of exercise on the metabolic system

The prevalence of metabolic diseases is increasing rapidly with the improvement of life expectancy.⁶² The most common metabolic diseases are obesity, diabetes, NAFLD, and metabolic syndrome (MS). Each has its unique characteristics, but are also associated with one another. Although many strategies have been developed to treat these metabolic diseases, conquering these diseases remains a challenge.⁶³ Nevertheless, we have learned from mice studies that exercise has beneficial effects on the treatment of these diseases.⁶⁴

3.2.1. Obesity

Obesity is caused by excessive fat accumulation in tissues. Presently, obesity is a globally prevalent health problem that affects many countries.⁶⁵ Obesity is closely associated with type 2 diabetes, NAFLD, cardiovascular disease (CVD), and cancers.^{66–69} Studies have shown that PA or exercise can reduce body weight, improve metabolic condition, and decrease the risks of other related diseases in humans, demonstrating the important role that PA and exercise can play in the prevention and treatment of obesity.²

Supplementary Table 9 shows that the main exercise methods used for mice experiments on obesity included treadmill exercise, voluntary wheel-running exercise, and swimming. In most protocols, exercise using the treadmill was performed on a motor treadmill at a low, moderate, or high intensity for

long-term duration, with a speed ranging from 3 to 22 m/min at a slope of 5°–25°. Mice were usually adapted to the exercise procedure for 3–4 consecutive days or 15 min before the exercise training protocol began. In those studies that used voluntary wheel-running, exercise was applied in a free style for short- or long-term duration. In studies involving swimming, exercise was usually performed at a low, moderate, or high intensity for short- or long-term duration, and mice were usually adapted to exercise for 3 days before the intervention. The most common mouse strain used in these studies was C57BL/6 mice, and the most common method used for establishing the obesity model was an HFD, suggesting that obese C57BL/6 mice fed an HFD may be an effective obesity model for studying the effects of exercise on obesity.

These exercise methods usually resulted in reduced body weight, improved lipid and glucose metabolism, and improved insulin sensitivity in obese mice.

3.2.2. Diabetes and prediabetes

Diabetes mellitus is a type of metabolic disease characterized by hyperglycemia and has in recent years become a serious public health issue.⁷⁰ In China, the prevalence of type 2 diabetes and prediabetes in adults has reached 10.9% and 35.7%, respectively.⁷¹ Diabetes and prediabetes are also associated with early nephropathy, small-fiber neuropathy, early retinopathy, CVD, and carcinoma.^{72–75} Recent studies have shown that exercise improved glucose metabolism and insulin sensitivity to a certain extent, suggesting that exercise has a potential role in the treatment of diabetes and prediabetes.³

As shown in Supplementary Table 10, exercise training in diabetic mice models was mostly performed on treadmills at moderate or high intensity for an acute or long-term duration, with a speed ranging from 6 to 21 m/min and a slope of 0°–10°. Some studies used voluntary wheel-running with a short-term duration. Additionally, a forced exercise walking wheel was used in some studies involving exercise training of diabetic mice. The major mouse strain used in diabetic mice studies was db/db mice, a type of spontaneous type 2 diabetic mouse with a deficient leptin receptor gene. Some studies also used HFD-induced type 2 diabetic C57BL/6 mice as a disease model.

In studies of mice with prediabetes (impaired glucose regulation), a treadmill was used in most exercise protocols. It was usually performed at a low, moderate, or high intensity for an acute, short-term, or long-term duration, with a speed ranging from 8 to 18 m/min and a slope of 0°–20°. In some studies, the mice were adapted to the exercise for 4–7 days before beginning the exercise training protocol. In addition, a motorized rotarod⁷⁶ and voluntary wheel-running exercise⁷⁷ were used in some studies. The mouse strains used in these studies were variable, but included C57BL/6 wild-type mice, Swiss wild-type mice, and other transgenic mice. The methods used for establishing disease models were also variable and included an HFD, chronic intermittent hypoxia-induced insulin resistance, and olanzapine-induced hyperglycemia.

These exercise protocols usually showed positive effects on glucose metabolism and insulin resistance in mice with diabetes and prediabetes.

3.2.3. NAFLD

The major symptom of NAFLD is excessive fat accumulation in the liver. The prevalence of NAFLD continues to increase each year. However, there is no approved drug available for treating NAFLD at present. Studies have shown that lifestyle interventions, including exercise and reduced the liver fat content of patients with NAFLD,⁷⁸ suggesting that exercise is a potential therapy for it.

As illustrated in Supplementary Table 11, treadmill exercise was the preferred method of exercise in mouse experiments. In the treadmill protocols, exercise was performed at low or moderate intensity for short- or long-term duration, with a speed from 8 to 18 m/min. Mice were adapted to exercise procedure for 1 week before beginning the exercise training protocol. C57BL/6 male mice were the most commonly used mouse strain in these studies, and an HFD was the most common method used for establishing the NAFLD model. A HFD-induced NAFLD model was frequently used for studying the effects of exercise on NAFLD.

The treadmill exercises decreased the liver fat content, improved liver steatosis and increased insulin sensitivity in HFD-induced NAFLD mice.

3.2.4. MS

MS is a group of clinical symptoms, including abnormal glucose metabolism, hypertension, dyslipidemia, and obesity. Results from a meta-analysis showed that exercise reduced body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, fasting blood glucose, and serum triglycerides level in patients with MS.^{79,80}

Supplementary Table 12 shows that the most commonly used exercise method in studies of mice with MS was voluntary wheel-running applied for short- and long-term duration. No adaptive training was used before beginning the exercise training protocol.

This exercise method usually reduced the weight, improved glycolipid metabolism, and promoted energy use in mice with MS.

3.2.5. Aging

Aging is an irresistible physiological or pathologic phenomenon. However, studies have shown that exercise delays aging by attenuating the aging phenotype and improving quality of life.⁸¹

Supplementary Table 13 shows that the major method used for aging-related mice experiments was voluntary wheel-running exercise of long-term duration. No adaptive training was used before formal training. Additionally, in 1 study, treadmill exercise was used at low intensity for long-term duration at speeds ranging from 5 to 13 m/min.

These studies showed that exercise prevented cellular senescence and improved arterial resilience and mitochondrial health in aging mice.

3.2.6. Metabolism-related signaling pathways

Supplementary Table 14 shows the studies that focused on the effects of exercise on metabolism-related signaling

pathways. Treadmill exercise and voluntary wheel-running exercise were the major methods used in these experiments. Treadmill exercise was performed at moderate or high intensity for short- or long-term duration, at speeds ranging from 12 to 28 m/min at a slope of 0°–4°. Voluntary wheel-running exercise was performed at short- or long-term duration. No adaptive training was used before exercise training in these studies.

These exercise protocols promoted biogenesis of cytochrome C oxidase, inhibited cholesterol and oxysterols accumulation in mitochondria, improved immune response, and reversed arterial inflammation.

3.2.7. Adipose tissue function

Adipose tissue is directly associated with obesity and type 2 diabetes. Studies have shown that exercise improves the function of adipose tissue, including promotion of browning of white adipocytes and induction of thermogenesis of brown adipocyte.^{82,83}

Supplementary Table 15 shows that studies focusing on adipose tissue function in mice used swimming as the primary exercise method. Swimming was usually performed at moderate or high intensity for short- or long-term duration. Adaptive training was used only in 1 study.⁸⁴

Swimming as an exercise intervention mostly showed positive effects on the function of adipose tissue and had beneficial effects on obesity and glucose metabolism.

3.3. Effects of exercise on the cardio-cerebral vascular system

Diseases of the cardiac and cerebral vessel systems relate to the ischemic or hemorrhagic effects of the heart, brain, and whole-body tissues. CVD, including heart failure and coronary artery disease, is the leading cause of death in the Western countries.⁸⁵ Notably, it has been reported that exercise training and PA can partially protect the cardiac and cerebral vessel systems from pathologic damage.⁸⁶

3.3.1. Myocardial infarction (MI)

Acute MI remains a leading cause of death worldwide. Increasing evidence confirms that endothelin induction after MI, if adequately prescribed and supervised, can prevent future complications and increase the lifespan and quality of life of infarcted patients.^{87–89} Exercise training can also benefit patients as an adjunct therapy of MI.^{90,91}

As shown in Supplementary Table 16, the exercise methods for MI treatment in mice were treadmill exercise, voluntary wheel-running, and swimming. In most protocols, exercise training performed on a treadmill was of short- or long-term duration, with only 1 study using acute exercise. Treadmill exercise was carried out using stable or incremental speeds at a low intensity, and the exercise frequency was 5–7 times/week. Usually, mice were adapted to the training process; a speed of 10 m/min was used at the beginning and it was increased by 1 m/min every day for 5 days.^{92,93} Another adaptive training method involved 10 repetitions of 4 min of running at 85%–90% of $\text{VO}_{2\text{max}}$ uptake ($\text{VO}_{2\text{peak}}$) speed separated by 2 min of active rest at 50% $\text{VO}_{2\text{peak}}$ speed during each interval,

followed by a cool-down period of 10 min.⁹⁴ Protocols for voluntary wheel-running included short-term or long-term duration. The swimming protocols were applied at low intensity of short- or long-term duration, with a swimming frequency of 2–5 times/week.

These exercise protocols showed positive effects for treating mice with MI. They also resulted in inhibited collagen hyperplasia after MI and protection of mice from MI. However, the specific mechanisms underlying these benefits remain unclear.

3.3.2. Atherosclerosis

Atherosclerosis is a progressive inflammatory artery disease that is responsible for 50% of mortality in the Western world.^{95,96} The risk factors associated with the development of atherosclerotic diseases include smoking, diabetes, hypertension, hyperlipidemia, and a lack of PA.⁹⁷ In recent studies, physical exercise was shown to be a therapeutic method for treating atherosclerosis.

Supplementary Table 17 shows that treadmill exercise and voluntary wheel-running were used in exercise interventions related to atherosclerosis in mice. Treadmill exercise was usually performed at low or moderate intensity with long-term duration at a speed ranging from 8 to 15 m/min with no incline. Exercise frequency was usually 5 days/week. As for voluntary wheel-running, it was applied in a free exercise style of short- or long-term duration. Exercise frequency was 7 times/week.

The results from these studies showed that both exercise patterns had the same positive effects in that they improved the symptoms of atherosclerosis and eased the progression of the disease.

3.3.3. Cardiac hypertrophy

Cardiomyocytes respond differently in response to various stimuli, resulting in physiological hypertrophy or pathologic hypertrophy.⁹⁸ Physiological hypertrophy usually occurs because of exercise or pregnancy; in this case, cardiomyocytes grow slightly in width and length to provide better cardiac function. But for pathologic hypertrophy, cardiomyocytes grow in thickness to compensate for cardiac disease until finally ending with cell death or even heart failure.⁹⁹ Exercise can significantly promote physiological hypertrophy for better cardiac output, but for pathologic hypertrophy, exercise is a double-edged sword: proper exercise can normalize myocardial metabolism¹⁰⁰ while high-intensity exercise aggravates it.¹⁰¹

In Supplementary Table 18, the exercise methods used in cardiac hypertrophy studies were treadmill exercise, voluntary wheel-running, and, most often, swimming. Treadmill exercise protocols were primarily performed in the short term but at various intensities. Wheel-running was applied in the short or long term. The protocols for swimming were almost the same: mice were forced to swim 2 sessions/day, and swimming time of each session increases from 10 to 90 min. The duration of whole swimming protocols was mostly short term. For physiological hypertrophy, all exercise interventions show positive effect in strengthen heart function while in pathologic hypertrophy-related exercise, proper exercise can partly reverse the

symptom caused by pathologic hypertrophy. To note, most studies use transgene (knockout or overexpression) mice.

3.3.4. Cardiac injury

Cardiac injury disrupts the balance between fibroblasts and cardiomyocytes and creates a state favoring inflammation and fibrosis.^{102,103} Studies have shown that exercise training is a key strategy for protecting the heart from injury.¹⁰⁴

Supplementary Table 19 shows that the methods most often used in treatment of cardiac injury were treadmill exercise, voluntary wheel-running, and swimming. In treadmill exercise, mice frequently performed for long-term duration at a high intensity for 30–45 min/day either 5 or 7 days/week. Training for voluntary wheel-running was of short-term duration. The protocols for swimming were of short- or long-term duration at moderate intensity 6 or 7 times/week.

C57BL/6J mice and db/db mice were the main types of mice used in studies related to this disease. All 3 exercise methods resulted in positive effects, indicating that proper exercise intervention can alleviate the deficits to the heart that cardiac injury causes.

3.3.5. Hypertension

Hypertension (a systolic blood pressure of ≥ 140 mm Hg, a diastolic blood pressure of ≥ 90 mm Hg) is associated with dysfunction of organs such as the heart, brain, and kidney. Fortunately, hypertension is a preventable CVD risk factor,^{105,106} and previous studies have shown that exercise can reduce resting blood pressure.¹⁰⁷

The only exercise study identified for treating hypertension used HIIT (Supplementary Table 20). The adaptive process included exercise at 15 m/min for 10 min/day for 5 days. Then mice were forced to run 4 min for 4 intervals at 90% peak running speed, separated by 3 min of recovery at 60% peak running speed at a 25° incline. The mice had 10-min warm-up and cool-down periods at 40% peak running speed before and after each session, respectively.¹⁰⁸

The results from this single study showed that induced hypertension in C57BL/6 male mice caused diaphragmatic contractile dysfunction through an oxidative-mediated mechanism, which might be prevented by HIIT.

3.3.6. Cardiac function

Normal cardiac function is an essential key in the well-being of a human life. It has been reported that left ventricular function and mechanical efficiency can be improved in patients with heart failure by participating in a 5-month endurance and strength training program.¹⁰⁹

As Supplementary Table 21 shows, the most commonly used exercise methods for studies on cardiac function in mice were treadmill exercise and swimming. In treadmill exercise, training was performed in short- or long-term duration for 5 days/week. The swimming protocol involved free access to swimming for short-term duration at moderate intensity 5 times/week.

These 2 exercise protocols showed positive effects in that regular exercise helped restore the signaling pathway and enzyme activities, leading to normalized cardiac functions.

3.3.7. Cerebrovascular function

Exercise can apparently enhance cerebrovascular function. For example, exercise can improve performance on cognitive tasks in aging people and delay the speed of brain trauma-caused bleeding injury.^{110,111} In addition, exercise can increase the bioavailability of nitric oxide, which is associated with vascular function,^{112,113} thus contributing to the formation of new blood vessels.^{114,115}

Supplementary Table 22 shows that the exercise methods applied for cerebrovascular function were treadmill exercise and voluntary wheel-running. In most protocols, exercise training was performed on a treadmill for short- or long-term duration with varied intensity for 5 or 7 days/week. Swimming protocols were applied for short- or long-term duration at moderate intensity for 7 days/week.

These exercise protocols demonstrated positive effects on mice and improved brain function by promoting the flow of blood in the brain's micro-vessels.

3.4. Effects of exercise on the nervous system

The nervous system functions to receive and integrate information from outside sources and then sends signals to other organs.¹¹⁶ It is the most complex and significant system among living organisms. Diseases occurring in the nervous system often lead to serious disorders.

3.4.1. HD

HD is caused by the Huntington (Htt) gene mutation.¹¹⁷ Patients with HD generally face mental disabilities, uncoordinated movements, and dementia until death.¹¹⁸ Presently, there is no cure for HD, and some medicines only alleviate particular symptoms.¹¹⁹ In addition to pharmacologic treatment, physical and psychological rehabilitations are necessary to improve the patient's quality of life.¹²⁰

Supplementary Table 23 shows that the most extensively used training methods for the study of HD in mice were treadmill exercise and voluntary wheel-running. Rotarod, a special training method, was also used in a short-term duration study.¹²¹ For treadmill exercise, all protocols were set at an incremental speed for 3 or 5 days/week at either low or high intensity. Before the training process began, the animals were adapted to the treadmill over several days (but for no more than 7 days) at a low intensity of exercise for about 30 min.^{122,123} For voluntary wheel-running, the wheel was accessible to mice 7 days/week, except for 1 training regimen that limited access to the wheel to 5 days/week.¹²⁴ Rotarod, which was used in conjunction with voluntary wheel-running, was performed at 15 rpm for 30 min/day for 5 days/week, lasting 5 weeks. To investigate HD, several transgenic mice models were used, of which the R6/1 mouse model was the most common.

As a treatment for HD, treadmill exercise showed a positive effect or no effect, while voluntary wheel-running showed both positive and negative effects. Rotarod also had a negative effect. These different effects in these exercises partly resulted from different training regimens: training showing positive

effects always had a much longer intervention time. Another reason for inconsistent results is that these research studies focused on different aspects of HD.

3.4.2. PD

The onset of PD is largely due to the death of neurons in the substantia nigra and the reduction of dopamine release, thus causing dementia or even death.¹²⁵ Thus far, there is no cure for PD; medications approved for treating PD mostly focus on improving motor symptoms.¹²⁶ Exercise and caffeine intake have been demonstrated to have a strong correlation with reduced risk of PD incidence.¹²⁷

Supplementary Table 24 shows that both treadmill exercise and voluntary wheel-running were used in the research. Some researchers also developed a more complex training protocol combining treadmill exercise with resistance climbing.¹²⁸ In treadmill exercise, all durations were short term, with either fixed or incremental speeds used. Training usually took place 5 or 7 days/week at either low or high intensity. Adaptive trainings took place before formal training commenced, usually for 5–7 days with 5–10 m/min of running for 5–30 min/day.^{129,130}

As for voluntary wheel-running, all training was short term in duration. However, the study combining training was of long-term duration. PD was most commonly induced in mice by using 1-methyl-4-phenyl-1,2,3,7-tetrahydropyridin.

All methods of exercise produced positive effects in terms of neurologic pathways, motor performance, and prevented PD progression. This result was consistent with human studies, and exercise should be recommended for disease improvement.

3.4.3. AD

Common symptoms of AD include cognitive dysfunctions, dementia, and other complications.¹³¹ Currently, there are a few medicines that temporarily improve cognition or psychological symptoms in AD patients.¹³² Exercise may benefit AD patients, but this needs further examination.¹³³

As shown in Supplementary Table 25, all exercise training included in AD studies in mice used treadmill exercise or voluntary wheel-running. Except for 1 voluntary wheel-running study,¹³⁴ all studies used protocols with long-term duration. As for the intensity of treadmill exercise, all but 1 training¹³⁵ used a low intensity with incremental velocities. The frequency of treadmill exercise in all the studies was 5 days/week. In 1 treadmill exercise protocol, adaptive training was performed at 10 m/min for 10 min/day over 5 days.¹³⁶ In regard to mouse model, 3 X Tg-AD mice were preferred. Almost all training protocols used long-term duration and low-intensity exercise, indicating that this may be an effective experimental pattern for treating mice with AD.

All results showed positive effects in inhibiting Amyloid β and Tau protein accumulation, treating AD symptoms, and protecting neurons, suggesting that exercise can play a significant role in treating AD.

3.4.4. Amyotrophic lateral sclerosis (ALS)

ALS specifically influences the motor neurons. Patients affected by ALS suffer from muscle stiffness and weakness,

leading to difficulty in swallowing and breathing.¹³⁷ The cause of ALS is unknown, and only a few patients with ALS inherit the disease from their parents.¹³⁸ For treatment, riluzole is the only approved medicine that delays the progress of ALS.¹³⁹ Apart from medicine, aerobic exercise and breathing assistance are widely used.¹⁴⁰

As Supplementary Table 26 shows, only 2 studies researching the effectiveness of exercise training in treating ALS were found, which was partly due to the unavailability of a suitable ALS mouse model. These 2 training protocols both used fixed-velocity and low-intensity treadmill exercise. The only difference was that 1 study trained the mice for only 2 weeks,¹⁴¹ while the other study trained mice for a long-term duration.¹⁴²

The results were positive for both exercise regimens. However, given that new mice models¹⁴³ and advanced technologies have only recently been developed, additional studies will be required to support any conclusions about exercise's positive effects.

3.4.5. Depression

Depression has severe consequences, but it can be cured with treatment. Medications, psychotherapy, and aerobic exercise are recommended for treatment of depression.¹⁴⁴

Supplementary Table 27 indicates that treadmill exercise, voluntary wheel-running, swimming, and sometimes forced wheel-running were used to treat depression in studies involving mice.²⁵ Treadmill exercise was short term in duration and was conducted at a stable velocity, with both low and moderate intensities being used. Before formal treadmill training, adaptive training was provided for 10–15 min every day at a speed of 5–10 m/min. Voluntary and forced wheel-running was of a short-term duration. Forced wheel-running included a 5-day adaptation in which mice ran at 9 m/min for 20 min/day. Swimming involved moderate-intensity training for 4 weeks.¹⁴⁵ In the adaptive training for swimming, the amount of exercise gradually increased from 15 min in the first week to 60 min in the last week.

Except for a no effect result in swimming training, the other exercise protocols all had beneficial effects. Because swimming is acknowledged to be an effective method for treating depression,¹⁴⁵ this no effect result might have been caused by a special knockout target, LepRb, because a leptin receptor may be required for the reversal of depressive symptoms among mice with induced depression.

3.4.6. Neuropathic pain

Neuropathic pain typically correlates with diseases such as cancer, multiple sclerosis,¹⁴⁶ and diabetes.¹⁴⁷ In recent years, some drug treatments have been approved for neuropathic pain, but more research is needed to provide other appropriate treatments for neuropathic pain.^{148,149} Exercise has proven to be beneficial in response to neuropathic pain in several animal models, but whether this positive effect can also be extended to humans remains unknown.

Supplementary Table 28 shows that treadmill exercise, voluntary wheel-running, and swimming were used in mice studies related to neuropathic pain. One study using treadmill exercise interestingly used a minus-degree slope with long-term

duration and low intensity.¹⁵⁰ The other studies using treadmill exercise were all performed with a short-term duration and at low intensity. Exercise frequency was 5 days/week, with a fixed speed during the training. Treadmill exercise studies all included adaptive training for 5–7 days at a speed of 10 m/min. Only 1 research study used voluntary wheel-running with a long-term duration.¹⁵¹ Swimming studies were conducted at low intensity with short-term duration, and adaptive training was administered before the formal swimming training. Partial sciatic ligation was used as a common method for developing neuropathic pain in the mouse model.

All studies showed positive effects in improving neuropathic pain in regard to neurotransmission pathways, neuroimmune response, and nerves in the mice models. Clinical trials should be conducted in the future to further assess the role of exercise in neuropathic treatment.

3.4.7. Nerve injury

In general, nerve injury is the cause of most neuropathic pain. Injuries occurring to the central nervous system are irreversible, while in peripheral nervous system, neuro-regeneration for damaged nerves is possible.¹⁵² Nowadays, surgery, nerve transfer, and other physical supports are recommended to treat peripheral nerve injury, but whether patients can experience a full recovery is still uncertain.

Supplementary Table 29 illustrates that treadmill exercise, voluntary wheel-running, swimming, and a combination method (resistance training with treadmill exercise) were used in research studies related to nerve injury, with treadmill exercise the most commonly used. In 1 treadmill exercise, the researcher designed a delicate experiment: mice with spinal cord injuries were supported with 80%–90% of their body weight on a treadmill and ran voluntarily at very low intensity for long-term duration after 1 week of adaptive training.¹⁵³ Other treadmill exercise studies used a short-term duration with fixed speed and mostly at a low intensity. Two studies using treadmill exercise included a 1-week adaptive training component.^{154,155} Voluntary wheel-running was used in training with short-term or long-term duration, while all swimming studies used short-term duration and moderate intensity. The single study using combined methods—resistance ladder climbing (summarized in the Methods section) combined with treadmill exercise¹⁵⁶—was of short-term duration and used incremental velocity. Before formal training commenced, the mice were adapted to the treadmill portion for 1 week at 10 m/min for 10 min/day.

All training effects were positive for nerve anti-inflammation and regrowth. Thus, the exercise interventions played promising roles in auxiliary therapy for nerve injury among mice. However, it is important to mention that most results pertain to peripheral nerve injuries, especially spinal cord injury. In short, further study is needed to confirm that improved changes to the central nervous system are possible when treated with exercise.

3.4.8. Cognition

Training can improve cognition, and many brain areas may contribute to this process. Many nerve-related diseases, especially

neurodegenerative diseases, severely impair cognition.¹⁵⁷ Therefore, ameliorating cognitive degeneration is important to maintaining nerve health.¹⁵⁸

Supplementary Table 30 indicates that voluntary wheel-running was primarily used in research on the relationship between exercise and cognitive improvements. The 1 study using treadmill exercise had a 5-day adaptation period, with exercise at the speed of 7 m/min performed at low intensity for short-term duration.¹⁵⁹ Voluntary wheel-running training was of short-term or long-term duration.

All but 2 studies showed a positive association between exercise training and cognitive performance. The 2 studies having a no effect result both focused on the effects of exercise on cognition impairment induced by an HFD, indicating that exercise failed to attenuate HFD-induced cognitive degeneration.

3.4.9. Neurogenesis

In mammals, neurogenesis occurs in embryonic development, but recent studies have suggested that neurogenesis can also occur in the adult brain, especially in the hippocampus and subventricular zone.¹⁶⁰ Because many nervous system diseases cause neurodegeneration, nerve formation in adult brains may be an important consideration for nerve therapy.

As shown in Supplementary Table 31, most mice-based studies in the field of neurogenesis reported using voluntary wheel-running as an exercise intervention. Two studies used different methods: one used treadmill exercise¹⁶¹ and the other used treadmill exercise combined with voluntary wheel-running.¹⁶² Treadmill exercise was conducted at low-to-moderate intensity for short-term duration, with either fixed or incrementally varied velocity. For the combined exercise protocol, the treadmill component was performed at a low intensity with short-term duration after a 1-week adaptation period. In the voluntary wheel-running protocols, most exercise was performed with short-term duration, while 3 studies used a long-term duration. Neurogenesis is often associated with cognitive formation, which may be the reason that neurogenesis studies and cognition studies used similar methods.

All but 1 study showed positive effects in neurogenesis, even when the exercise was of short-term duration at a low intensity. The 1 study showing a negative effect may be the result of the researchers' choice of the mouse model since a gene-overexpression model was used, which may have impaired neurogenesis stimulated by exercise.

3.4.10. Dopamine system-related mechanism

As part of the nervous system, the dopamine system is related to motivation and reward mechanisms. For example, obesity and drug addiction are related to dysfunction of the dopamine system.¹⁶³

As shown in Supplementary Table 32, three studies reported the influence of exercise on dopamine-related changes. One study used treadmill exercise with short-term duration, incremental velocity, and moderate intensity. The other 2 exercise interventions used voluntary wheel-running of short-term duration, with one of them having a 1-week adaptation period.¹⁶⁴

Although only 3 studies on the effects of exercise on dopamine-related changes were identified in our search, they nevertheless suggested that exercise can significantly change dopamine-related gene/receptor expression, and even short-term training duration yielded positive results.

3.5. Effects of exercise on the immune system

Dysfunction of the immune system can cause a variety of diseases. Modern medical approaches suggest that, in addition to medications, exercise may be a useful therapy for treating diseases caused by immune system dysfunction.¹⁶⁵

3.5.1. Immune diseases

In general, immune diseases can be categorized based on 2 sources of antigens: inflammation caused by external antigens¹⁶⁶ and autoimmune diseases attacking the body itself.¹⁶⁷ According to published reports, regular physical activities can strengthen the immune system and protect organs by suppressing the abnormal production of inflammatory cytokines and enhancing the development of anti-infective agents and antioxidants.¹⁶⁸ Supplementary Table 33 shows that in studies involving mice with immune diseases, the main exercise methods were treadmill exercise and voluntary wheel-running. Exercise training in these studies was mostly performed on a motor treadmill at a moderate intensity of short- or long-term duration, with either fixed or incremental speed. Treadmill exercise was conducted at a frequency of either 3 or 7 days/week. Mice were adapted to treadmill exercise procedures for 2–3 consecutive days for 10 min/day before the formal exercise training began. Some studies used voluntary wheel-running as an exercise method. Free access to wheel-running was given to mice, and the studies were of short- or long-term duration.^{169–171} In these studies, mice were adapted to the wheel procedure for 3 consecutive days.

All but 1 study yielded positive results, with improved immunity and T-cell function. The study that showed no improvement after exercise may have resulted from the mouse model chosen—mice used in this study were 23 months old, much older than mice used in other experiments. Older mice have different responses to anti-inflammatory cytokines, and this may be why exercise in this study had only limited regulatory effects.

3.5.2. Chronic-graft-versus host disease (GVHD)

GVHD is usually induced by hematopoietic stem cell transplantation, such as bone marrow transplantation.¹⁷² Exercise training can act as an adjunct therapy to a lower incidence of GVHD after hematopoietic stem cell transplantation, probably because exercise training can reconstitute the immune system and reduce activity of alloreactive T cells.¹⁷³

Supplementary Table 34 shows that 2 studies involving GVHD in mice used treadmill exercise as the training method. Both studies were of long-term duration and used moderate intensity exercise at a fixed speed for either 5 or 7 times/week. One study had mice exercise for 60 min at 70% $\text{VO}_{2\text{max}}$ and 25% slope. The other study reported 10 min of running as an

adaptation and in the formal running exercise the speed increased 3 cm/s every 2 min, with a 25% slope, until exhaustion.

Both protocols had positive effects on treating GVHD. In the clinical course of GVHD, conventional moderate-intensity aerobic exercise combined with standard immunotherapy has potential advantages in that it is a nonpharmacologic treatment that, to some extent, alleviates the debilitation of GVHD, along with improving quality of life and avoiding damage to the immune system.

3.5.3. Immune function

Some studies have reported that the immune function can be enhanced by exercise, thereby improving the body's immunity function.¹⁷⁴ In animal studies, exercise training has yielded good effects on improving immunity, including higher clearance efficiency, an improvement in phagocytosis and an increase in infective resistance.

Supplementary Table 35 shows that the main exercise methods used to explore connections between exercise and immune response were treadmill exercise and voluntary wheel-running. Treadmill exercise was of long-term duration and was performed at low or moderate intensity with a fixed or incremental speed. Voluntary wheel-running was much more commonly used than treadmill exercise, and it was usually performed at a moderate intensity with a long-term duration.

The studies showed that the effects of the exercise methods were positive and that suitable exercise enhanced immune functions.

3.6. Effects of exercise on respiratory diseases

Respiratory diseases have high incidence rates around the world. Different treatments are used for specific symptoms. Some studies have shown that regular exercise at moderate intensity can reduce the incidence of respiratory system diseases by modulating immune response.¹⁷⁵

3.6.1. Pulmonary impairment

An unbalanced inflammatory response to harmful microbes and air pollutants may promote tissue damage and ultimately lead to acute and chronic pulmonary impairment.¹⁷⁶ However, there is some evidence indicating that physical exercise has some positive effects on pulmonary impairment.

Supplementary Table 36 shows that the only exercise type used for studies of pulmonary impairment in mice was treadmill exercise performed at a low-to-high intensity, either 3 or 5 days/week, at fixed or incremental speed, with short-term or long-term duration. One study used an adaptation process consisting of exercise conducted at a speed of 0.2 km/h for 15 min/day lasting for 3 days.¹⁷⁷

The exercise protocols used for these studies showed protective effects on mice with pulmonary impairment in that they reduced pulmonary oxidative stress and pulmonary inflammation.¹⁷⁸

3.6.2. Chronic obstructive pulmonary disease (COPD)

COPD is the leading respiratory disease and the fourth most frequent cause of death.¹⁷⁹ Clinical studies have demonstrated

that aerobic exercise can improve COPD management and prevent the decline of lung function, thus improving the quality of life.¹⁷⁹

Supplementary Table 37 shows that mice with COPD were treated in 2 studies with treadmill exercise, which was performed at a moderate intensity for 5 days/week with either a short- or long-term duration. Adaptive training in both studies took place in advance for 3 days at a low speed of 0.2 km/h for 15 min/day with a 25% slope.^{179,180}

The exercise methods used in these 2 studies showed positive effects from exercise in the treatment of mice with COPD. These 2 findings suggested that regular exercise can reduce the decline of lung function and the risk of COPD among active smokers.¹⁷⁹

3.6.3. Chronic obstructive emphysema

Emphysema is a COPD notoriously unresponsive to medical treatment, and no current pharmacologic interventions have been shown to effectively halt disease progression. However, some researchers have found that moderate exercise can partially relieve emphysema.¹⁸¹

Supplementary Table 38 shows that 1 study involving mice with emphysema used treadmill exercise, which was performed at low intensity for 3 days/week with a short-term duration.

This study showed that regular aerobic training at low intensity can modulate lung inflammation and remodeling, thus improving pulmonary function.¹⁸¹ However, only 1 study provided insufficient data on the effects of exercise on emphysema; therefore, additional studies are needed.

3.6.4. Effects of exercise on the digestive system

As indicated in Supplementary Table 39, only 1 study was identified that related to exercise intervention for intestinal flora. The study, which was of short-term duration, allowed mice to perform voluntary wheel-running at any time.

This intervention had a positive effect on improving digestive system dysfunction among mice. It found that oral exposure to polychlorinated biphenyls can induce gut microbiome changes and systemic toxicity. However, the findings indicated that this toxicity could be attenuated by exercise.¹⁸²

3.7. Effects of exercise on cancer

Cancer is the leading cause of death in economically developed countries, and the second leading cause in developing countries.¹⁸³ Due to the increase in habits such as Westernized diets and smoking, the prevalence of cancer continues to increase.

The key methods of cancer treatment are chemotherapy, radiotherapy, surgery, adjuvant systemic therapy, and endocrine therapy.¹⁸⁴ PA is an adjuvant strategy used during and after conventional anticancer treatments to avoid complications and optimize recovery.¹⁸⁵ A body of evidence indicates that PA can reduce the risk of developing colon and breast cancer by about 25%, with reductions also possible for prostate, lung, and ovarian cancer. Interestingly, PA also seems to delay

disease recurrence, highlighting a possible role in the suppression of tumor growth.¹⁸⁵

3.7.1. Breast cancer

Breast cancer is the most commonly diagnosed cancer with the highest mortality among females worldwide.¹⁸⁴ Studies have shown that there is an association between PA and breast cancer incidence:¹⁸⁶ regular PA exerts beneficial effects on impeding the incidence and progression of the cancer.¹⁸⁷

Supplementary Table 40 shows that, in studies of mice with breast cancer, the main exercise protocols were treadmill exercise, voluntary wheel-running, swimming, and resistance training. In treadmill exercise protocols, exercise training, which was of either short- or long-term duration, was performed on a motorized treadmill at a low or moderate intensity with a fixed or incremental speed ranging from 5 to 20 m/min. In addition, the treadmill elevation ranged from 0% slope to 5% slope. Most treadmill training regimens used 10- to 60-min bouts/session. Usually, mice were familiarized with the treadmill procedure for 5 consecutive days before the formal exercise training protocol began, with the mice being allowed to walk or run slowly at 10–18 m/min.¹⁸⁸ Voluntary wheel-running was performed in a cage for a short- or long-term duration. Some studies used swimming as an exercise method. In these studies, which were of a short- or long-term duration, swimming exercise usually lasted 30–60 min/day. In general, for mice with breast cancer, exercise using a treadmill and voluntary wheel-running were the first and second choices, and these studies were of long-term duration, with exercise at moderate intensity. BALB/c mice were most commonly used as mice models for studies of mice with breast cancer.

Most of the studies on the effects of exercise on mice with breast cancer yielded positive results. Physical exercise typically targets different pathways for changing tumor metabolism and decreasing tumor growth and progression, indicating that exercise might be an effective strategy to reduce the risk of breast cancer. However, in some studies using special mouse strains, such as p53-deficient mice, exercise accelerated tumorigenesis.¹⁸⁹ Moreover, one of the studies using voluntary wheel-running seemed to impair endothelial function and promote metastasis in the murine orthotopic model of metastatic breast cancer.¹⁸⁷ These contradictory results call for more careful consideration of exercise methods and mouse strain choices when studying breast cancer in mice.

3.7.2. Colon cancer

Colon cancer is the third most commonly diagnosed cancer and the second leading cause of mortality among patients with cancer.¹⁹⁰ Worldwide, approximately 1.2 million people are diagnosed with colon cancer each year.¹⁸³ There is strong and consistent evidence that PA can reduce the risk of colon cancer.¹⁹¹

Supplementary Table 41 shows that, in mice with colon cancer, most training was performed using a treadmill or voluntary wheel-running. There were just a few studies using swimming and resistance training in colon cancer mice models. Treadmill exercise, which was of long-term duration, was

performed for either 3 or 6 days/week at a low-to-moderate intensity with a fixed or incremental speed ranging from 15 to 20 m/min and with a slope of either 0% or 5%. In some studies, voluntary wheel-running was of either short-term or long-term duration and was performed for either 5 or 7 days/week. There was only 1 study that combined voluntary wheel-running and resistance training, with an increasing loading weight and variable speed. This study had adaptive training for 1 week to familiarize mice with the 2 types of exercise.¹⁹² Another study, of long-term duration, used swimming as an exercise intervention, with intensity gradually increasing from low to moderate. The most common mouse strain used in these studies was Apc (Min⁺), and the most common exercise protocols used in studies of colon cancer in mice were treadmill and voluntary wheel-running. Most studies were of long-term duration, suggesting that long-term training can achieve better effect on alleviating colon cancer.

Physical exercise has been shown to be protective against colon carcinogenesis within different mice models. However, as shown in Supplementary Table 41, aerobic or resistance training was unable to prevent tumor-induced body weight loss in 12-month-old C26 female mice.¹⁹² When determining exercise intensity for older mice models, factors such as age, which might influence study outcomes, should be carefully considered.

3.7.3. Prostate cancer

Prostate cancer is the second most frequent cancer and the sixth-leading cause of cancer death in males worldwide.¹⁹¹ Evidence suggests that PA correlates with a 10% reduction in the development of prostate cancer, while case-control studies estimate a 14% reduction in the development of prostate cancer.¹⁹¹

Supplementary Table 42 shows that, in studies of mice with prostate cancer, the main exercise method used was voluntary wheel-running. The studies were typically of long-term duration. One study of long-term duration used forced exercise/walking wheel bed as an exercise method. In this study, forced exercise/walking was performed for 3 days/week at speeds ranging from 2 to 7 m/min.

PA has increasingly yielded positive results for treating prostate cancer. As shown in Supplementary Table 42, regular, long-term PA can play an important role in preventing prostate cancer, and it can also effectively slow the progression of prostate cancer by influencing the levels of some endogenous hormones.¹⁹³ However, forced exercise/walking wheel bed on 6-week-old male athymic nude mice had no effect (Supplementary Table 42), probably because their HFD counteracted the positive effect of exercise on prostate cancer.¹⁹⁴

3.7.4. Lung cancer

Lung cancer mainly happens in the bronchial mucosa epithelial cells or alveolar tissue. Worldwide, about 1.2 million people annually are diagnosed with lung cancer, and about 950,000 people die each year from lung cancer.¹⁹¹

Supplementary Table 43 shows that, in studies of mice with lung cancer, the main exercise methods used were treadmill exercise, voluntary wheel-running, and swimming. In most protocols, treadmill exercise was performed, for short-

term duration, for either 5 or 7 days/week at low-to-moderate speeds (10–20 m/min), lasting either 45 or 60 min. One study of short-term duration used voluntary wheel-running as an exercise method. Swimming for 3 or 4 days/week at a low intensity for 20 min/day was used in the remaining study, which was of long-term duration. Only 2 of the 4 studies incorporated adaptive training. The first adaptation process started gradually, beginning with a speed of 6 m/min for 15 min and increasing the speed and time daily until 60%–70% of maximum oxygen consumption (corresponding to 14 m/min for 45 min) was reached.¹⁹⁵ The other adaptation process was for the swimming intervention, which progressed in speed from 10 to 50 min/day over 5 days.

Most exercise interventions used in these studies had positive effects on the treatment of lung cancer. However, exercise training did not alter the survival rate or limit tumor growth in tumor-bearing mice with Lewis lung cancer.¹⁹⁶

3.7.5. Skin cancer

Skin cancer can be divided into 2 types—malignant melanoma and nonmalignant melanoma—and skin cancer rates seem to be increasing rapidly over time.¹⁹⁷ Melanoma is an aggressive malignancy associated with significant heterogeneity. Sunlight-induced nonmelanoma skin cancer is the most prevalent cancer in the United States, with more than 2 million cases per year.¹⁹⁸

Supplementary Table 44 demonstrates that, in studies of mice with skin cancer, the main exercise methods used were treadmill and voluntary wheel-running. Treadmill exercise of long-term duration was performed for either 5 or 7 days/week at low-to-moderate intensity. A 2-week adaptation training period, using a speed of 13.4 m/min, was used to adjust the mice to their new environment before the formal treadmill exercise.¹⁹⁹ Studies of short-term duration used voluntary wheel-running for exercise training.

All studies showed positive effects on the prevention or treatment of skin cancer. By regulating different pathways, exercise contributed to the prevention of skin cancer and to inhibiting tumor growth. However, there is inadequate evidence for definitive conclusion about the benefits of exercise in treating skin cancer. Thus, further study is urgently needed.

3.7.6. Other cancers and the dysfunction of cancer survivors

Liver cancer is the 5th most commonly diagnosed cancer in men throughout the world, but is the second-leading cause of cancer death; whereas in women, it is the 7th most commonly diagnosed cancer, and the 6th leading cause of cancer death.¹⁸³ Two types of exercise protocols, treadmill and swimming, were used in studies of mice with liver cancer. Treadmill exercise, of long-term duration, was performed at a speed of 12.5 m/min, while swimming, of short-term duration, was performed for 60 min/day. Swimming adaptation took place over 3 days, with mice swimming for 30, 40, and 50 min/day; the adaptive time period for the treadmill was 5 weeks.²⁰⁰ Both forms of exercise showed positive effects on the treatment of liver cancer.

Cachexia greatly associates with chronic illnesses. Cachexia accounts for 50%–80% of advanced stage malignancies in

patients with cancer and accounts for 20% of all cancer-related deaths. It has been demonstrated that during and after treatment, PA can reduce fatigue and counteract side effects of cancer therapy.²⁰¹ Three randomized clinical trials for different types and stages of malignancies in mice were identified, and 2 types of exercise—treadmill and voluntary wheel-running—were used. All protocols called for moderate intensity exercise. Treadmill exercise, of either short- or long-term duration, was performed for 45 min/day; voluntary wheel-running was of short-term duration. All forms of exercise showed positive effects on counteracting cachexia and improving muscle strength, indicating that PA may be a promising intervention strategy for the prevention and the treatment of cancer-related cachexia.

Intramuscular liposarcoma is the most frequent type of soft tissue sarcoma. As shown in Supplementary Table 45, voluntary wheel-running of long-term duration was used as an exercise intervention for male mice. Negative results from 2 studies suggest that no recommendation about the levels of PA can be made for patients with lower-extremity sarcomas.¹⁸⁵

The 1 study in Supplementary Table 45 involves research on tumor growth using an Ehrlich tumor mouse model. Swimming was used as the exercise method in this long-term duration study. A moderate exercise intensity of 60 min/day was used. The results showed that swimming can retard the development of Ehrlich tumors in mice.²⁰²

4. Discussion

Because more and more impressive evidence has shown a range of health benefits from exercise,²⁰³ researchers have increasingly become interested in conducting systematic exercise studies to further define those benefits.

4.1. Limitations of exercise intervention using mice models

In modern exercise science, mouse models are extensively used to explore the mechanism of exercise intervention on basic physiological changes and disease prevention. However, mice models still have limitations. First, mice models do not accurately reflect what actually occurs when humans experience a given disease. The biological system of mice, especially the immune system, is not completely consistent with the biological system of humans, which is demonstrated by many differences in innate immune molecules. Second, mice cannot simulate some forms of human exercise, and lifespan and exercise parameters for animals do not match well with those of humans. Therefore, more studies of the molecular mechanisms need to be conducted to better translate the data gathered in studies using animal models to human beings,²⁰⁴ and establishing an effective humanized mouse model will play an increasingly important role as a preclinical model for human research.²⁰⁵

4.2. The comparison of mouse and human exercise interventions

Researchers use mice models to mimic the progression of diseases in humans and to investigate the effects of exercise intervention. It is necessary to better understand how well

specific exercise interventions developed for mice translate to human conditions. Based on a survey of the literature on human exercise, the most frequent types of exercise used in humans are aerobic exercise (treadmill, cycling, yoga, and Tai Chi), resistance exercise (strength training and loaded training), and multimodal exercise.^{206–208}

4.2.1. Aerobic exercise

The most similar exercise type used by both mice and humans is aerobic exercise, which includes treadmill exercise and wheel-running in mice. Treadmill exercise has simple, easily modifiable parameters. Similar to human treadmill exercise, treadmill running in mice can be categorized as being of low to high intensity, and, as with humans, it can also be classified as a percentage of maximum heart rate or maximum oxygen uptake. However, this classification is sometimes confusing and lacks accepted standards, so most studies still use fixed speed for classification purposes.

Wheel-running for mice is similar to walking for humans. It is worth noting that it is difficult to define intensities in wheel-running because it is either self-controlled (voluntary wheel-running) or conducted at very low speeds (forced wheel-running).

Swimming is also commonly used for aerobic exercise in mice exercise interventions, especially for the cardiac system. However, swimming is seldom used in human exercise interventions, partly because of its inconvenience and its extreme demands in terms of facility needs.

4.2.2. Resistance training

In studies conducted with mice, resistance training is unusual because it requires complex manipulation design and precise muscle control. The only resistance training used in the studies we reviewed was ladder climbing. It is doubtful whether resistance training in mice can mimic resistance training in humans because the intensity of ladder climbing in mice can only be defined by climbing repetition and loading weight, which is much more simple to design for mice than it is for humans. Furthermore, studies have shown that there is a significant difference in fiber excursion and muscle biological function between mice and humans.²⁰⁹ Because resistance training is mainly dependent on muscle, it is better to be cautious when translating results from mice studies to humans.

4.2.3. Multimodal exercise

To achieve better exercise effects, combined training that consists of different training types is commonly used in studies involving humans. However, designing combined training interventions for mice is extremely difficult. Combining treadmill exercise and voluntary wheel-running is probably the best approach, but it is nevertheless unsatisfactory, given that mice have very few different exercise types. Moreover, it is very difficult to control for variance in mice when adding exercise types.

Developing exercise interventions for mice is much simpler than developing them for humans. Because of the limitations of their physiological structure, mice cannot complete the same complicated exercise sets that human can. Perhaps this factor

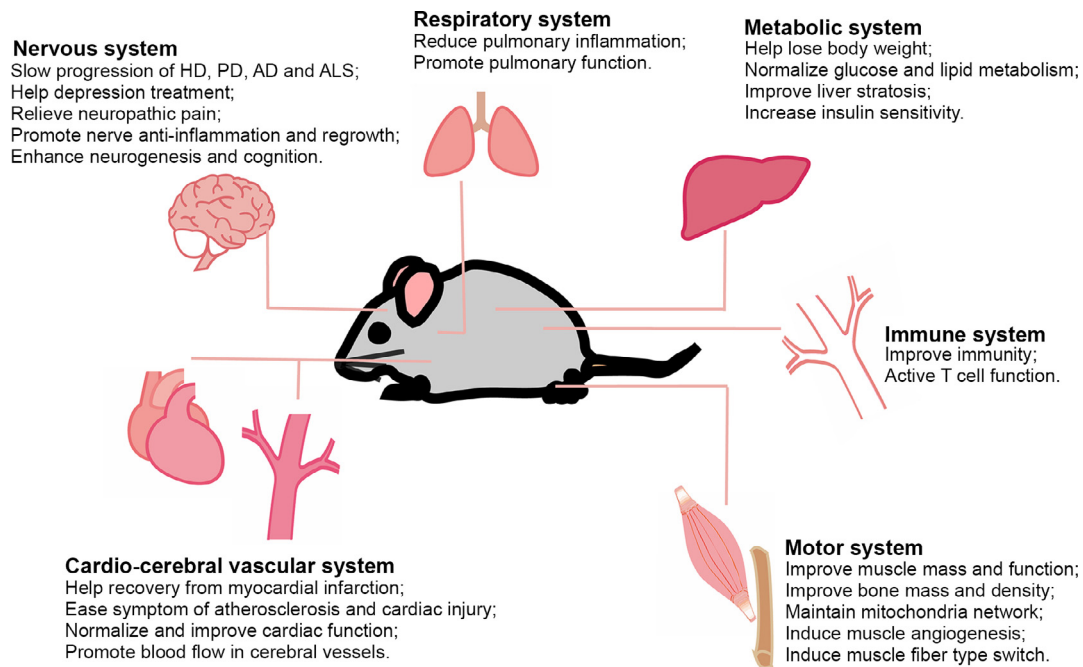


Fig. 1. Exercise-induced positive changes in different systems of mice. AD = Alzheimer's disease; ALS = Amyotrophic lateral sclerosis; HD = Huntington's disease; PD = Parkinson's disease.

explains why only treadmill exercise has been shown to provide useful comparisons. To address this problem, researchers may need to design devices that are suitable for improving resistance training effects on specific body parts of mice.

4.3. Additional considerations for mouse exercise interventions

The genetic background of mice has various influences on the efficacy of exercise. Some studies have demonstrated that many of the impacts of exercise intervention on the physiological processes of and diseases in mice depend on strain background, such as tumorigenesis,²¹⁰ hippocampal neurogenesis,²¹¹ diabetes,²¹² and adaption of chronic hypobaric hypoxia.²¹³ These results demonstrate that some of the experimental results obtained in studies of mice may not be applicable to humans considering the discrepancies between the 2 species. Finding more suitable animal models that more closely approximate humans in physiological structures and biological processes is a critical step in the study of exercise interventions.

In addition to genetic background, gender may also affect the impact of exercise interventions. Some effects are caused by differences in sex hormone secretion, which has been discussed in a previous review.²¹⁴ A recent study has suggested that treadmill exercise for female transgenic mice with early AD can more effectively delay the decline in spatial learning and memory abilities than for male transgenic mice. This is due to the sex-specific differences in the white matter and myelinated fibers of white matter in the AD mice.²¹⁵ Thus, it is important to conduct experiments using both genders when studying the influence of exercise interventions, even though the instability of hormone secretions of female mice presents

some difficulties in carrying out experimental operations and data analysis.

5. Conclusion

In this review, we identified recent studies related to the effects of exercise interventions in mice and summarized some of the practices used for different types of exercise being investigated in the studies. It was found that, regardless of the specific exercise method chosen, most studies demonstrated positive effects on various systemic diseases and organ functions, independent of the mouse model (Fig. 1). Most diseases can be remitted regardless of the exercise method used, although some diseases showed the best remission effects when specific exercise methods were used, which is consistent with the idea that exercise can be a form of medicine. Furthermore, to provide more information for those interested in metabolism related to exercise, we summarized the protocols used for treating different mouse systems with exercise interventions (Table 1). These summaries also have value for those interested in the effects of exercise interventions for humans. In conducting research on exercise training in humans, it is important to ensure that participants receive adaptive training and that a suitable exercise prescription is formulated with corresponding intensity levels assigned for specific situations.

Overall, our review strongly suggests that exercise intervention is a cornerstone in the prevention and treatment of diseases. Current research related to exercise interventions in humans focuses on chronic diseases, national fitness, and body weight loss. Unfortunately, compliance in studies of exercise among humans is extremely low. Therefore, because compliance in mice can be controlled, it is critical that mice models be used to investigate the molecular mechanisms underlying

Table 1
The suggested exercise interventions for different systems in mice.

System	Exercise method	Exercise protocols		
		Adaptive training	Frequency	Intensity
Motor system	Treadmill exercise	Mice were familiarized with the treadmill for 2–3 consecutive days at low intensity with a speed of about 5 m/min before the beginning of formal exercise.	6–8 weeks 5 days/week	60 min/day 10–15 m/min
Metabolic system	Treadmill exercise	Mice were usually adapted to exercise procedure for 3–4 consecutive days, or 15 min before the exercise training protocol began.	12–16 weeks 5–7 days/week	60 min/day 18–20 m/min (0%–5% grade)
Cardio-cerebral vascular system	Treadmill exercise	Mice were adapted to the training process with a speed of 10 m/min at the beginning, and the speed was increased 1 m/min every day for 5 days.	5–7 weeks 5–7 days/week	30–90 min/day 10–15 m/min
Nervous system	Voluntary wheel-running	Mice were usually adapted to wheels for consecutive 2–3 days.	12–16 weeks 7 days/week	Free to exercise
Immune system	Treadmill exercise	Mice were adapted to treadmill exercise procedures for consecutive 2–3 days, 10 min/ day before the formal exercise training began.	6–8 weeks 5–7 days/week	45–60 min 8–12 m/min, 5% grade
	Voluntary wheel-running	Mice were usually adapted to wheels for consecutive 2–3 days.	8–12 weeks 7 days/week	Free to exercise
Respiratory system	Treadmill exercise	—	6–8 weeks 3–5 days/week	60 min/day 8–12 m/min
Cancer	Treadmill exercise	Mice were familiarized with the treadmill procedure for consecutive 5 days before formal exercise training protocol, which allowed the mice to walk or run slowly at 10–18 m/min	8–10 weeks 5–7 days/week	60 min/day 16–18 m/min

the health benefits of exercise interventions. This is especially important if new and effective exercise pills are to be developed. Although there are currently no exercise pills available that fully simulate the beneficial effects of exercise, some of them partly simulate the many beneficial effects that exercise can have on organs and disease treatment. Thus, researchers urgently need to conduct further studies in this field.

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Authors' contributions

SG helped conceive the design of the study, performed the data collection, analyzed the data, and wrote the first draft of the manuscript; YH helped conceive the design of the study,

collected and analyzed data, and helped draft the manuscript; YZ and HH performed other data collection and edited the manuscript; and SH and TL helped conceive the design of the study, supervised data analyses, provided funding for the study, and helped draft the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.jshs.2019.07.004](https://doi.org/10.1016/j.jshs.2019.07.004).

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