Bairong Shen *Editor*

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Sports and Exercise Medicine

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About the Book

The book provides readers the informatics and data-driven models for the discovery of personalized excise prescriptions applied to different cases. Overdiagnosis or overtreatment often happened since the complex interaction among the lifestyle, genetic, and environmental factors. Sports and exercise are reported efficient to prevent or reduce the risk of diseases, but the interactions between sports/exercise and disease are personalized and complex. Translational informatics is a powerful paradigm, and it promotes the transfer of big data, knowledge, and models to the precision application of sports to prevent diseases. Sports and exercise may have different effects on diverse diseases, including cancers, neurodegenerative disease, and cardiovascular diseases. This book covers many modern informatics models such as ontologies, knowledge graphs, blockchain, participatory medicine, semantic artificial intelligence, and big data modeling. It also describes the challenges for the sports and exercise medical data sharing and standardization, the privacy protection of data, and the integration of data from genomic level to physiological phenotype level. This book will be helpful to the readers who are interesting in sports and exercise medicine, healthcare, big data modeling, and artificial intelligence in medicine and healthcare.

Contents

About the Editor

Bairong Shen is a professor and executive director general in Institutes for Systems Genetics, West China Hospital, Sichuan University. He received his Ph.D. in chemistry from Fudan University in 1997. Dr. Shen was appointed as associate professor of physical chemistry at Fudan University in 1999, for his accomplishments in theoretical and computational surface chemistry. In the early 2000s, Dr. Shen started his new exploration into biomedical informatics and related computational biology in his postdoctoral research in the University of Tampere, Finland. His success in the new paradigm of biological research won him a competitive faculty position in the European university as an assistant/associate professor of bioinformatics since 2004. He joined the Soochow University by founding the University's Center for Systems Biology in 2008. In Finland and China, Dr. Shen has taught more than ten different courses in biomedical informatics and systems biology and published more than 100 peer-reviewed articles in competitive journals which covered the medical genetic areas including cancer biomarker discovery, biomedical informatics, and the basic exploration in physics, chemistry, biology, and computational science. His recent researches focus on biomedical informatics and systems biology of complex diseases and healthcare.

Chapter 1
Ontologies and Knowledge Graphs for Exercise Medicine

Xingyun Liu and Bairong Shen

Abstract Informatics in exercise medicine is an emerging field. Ontologies and knowledge graphs are important in informatics, but they have not yet been developed in exercise medicine. In this chapter, I first explain what an ontology is, what a knowledge graph is, and what their relationship is. Then I focus on ontology by introducing related research and discussing what an exercise medicine ontology should include.

Keywords Ontology · Knowledge graph · Exercise medicine · Physical activity · Exercise prescription

1.1 Introduction

1.1.1 What Is an Ontology?

1.1.1.1 Ontology: From Philosophy to Informatics

In philosophy, ontology is a branch of metaphysics that studies the nature of existence. In the 1980s, the word "ontology" was first used in the field of artificial intelligence to refer to the "real world" or "robotic grounding" [1, 2]. In 1993, Gruber used "ontology" as a concept related to semantic networks and taxonomies [3]. In information science today, the term is more specific. According to Feilmayr and Wöß, "An ontology is a formal, explicit specification of a shared conceptualization that is characterized by high semantic expressiveness required for increased complexity." [4].

Ontology is used to designate concepts (or universals) and define classes, their attributes, and the relationships between them [5, 6]. An ontology is thus a sort of taxonomy of concepts, definitions, and synonyms. A class hierarchy constitutes the

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basic structure of an ontology and represents one of the most common relations: "is a" which means the relation of subclass and its parent class.

As a special kind of semantic network, an ontology can be represented as a graph and stored as a Resource Description Framework (RDF). To expand the storage of semantic information for ontologies, RDF Schema (RDFS) and the Web Ontology Language (OWL) were created and are widely used.

1.1.1.2 Classification of Ontologies

Domain ontologies (also known as domain-specific ontologies or material ontologies) focus on specific domains (such as biology, chemistry, or law) to represent the concepts and relationships in this domain [6]. The Gene Ontology (GO) is one of the most widely used domain ontologies. It describes the functions of genes at three levels: molecular functions, biological processes, and cellular components [7, 8].

A formal ontology (also known as an upper-ontology, top-level ontology, or foundational ontology) is an ontology that contains only the most common concepts, such as entities and processes, rather than those that are unique to specific domains. Formal ontologies provide a common structure for domain ontologies. Many formal ontologies have been developed, such as the Basic Formal Ontology (BFO), the Descriptive Ontology for Linguistic and Cognitive Engineering (DOLCE), and the Standard Upper Merged Ontology (SUMO) [6].

For the purpose and usage of ontology, there are application ontologies and reference ontologies. Application ontologies are built for a specific purpose. For example, an application ontology is used in Situational Awareness and Preparedness for Public Health Incidents Using Reasoning Engines (SAPPHIRE) to identify influenza-like illnesses [6, 9]. Reference ontologies serve as knowledge bases that contain the knowledge of a specific domain [6–8].

1.1.2 What Is a Knowledge Graph?

1.1.2.1 Graph-Structured Data Model

Combining the characteristics of a database, graph, and knowledge base, a knowledge graph is a data model or topology to store and represent entities and their relations [10, 11]. A knowledge graph is a special kind of semantic network, with a graph structure made up of triples (entity-relation-entity).

Figure 1.1 shows a simple example of a knowledge graph about pandas. It represents their habitat, food, and fur. "Panda"— "lives in"—"Sichuan" is a triple of "Panda", "Sichuan", and their relation "lives in".

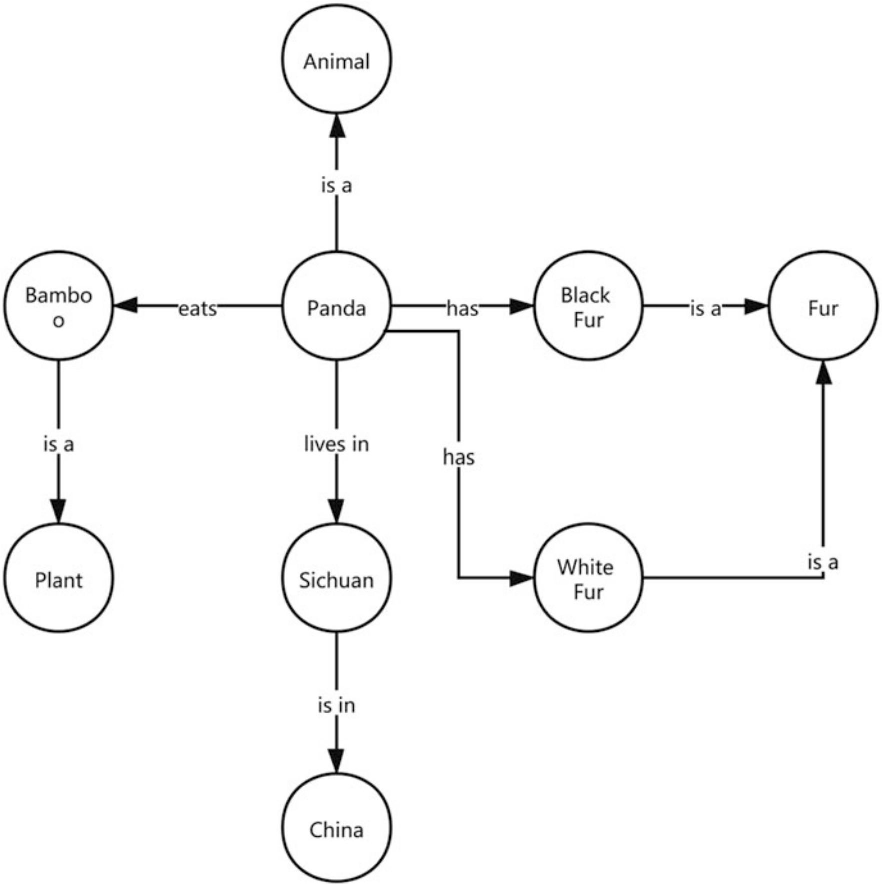

Fig. 1.1 Example of a knowledge graph

1.1.2.2 Applications of Knowledge Graphs

Google's Knowledge Graph was announced for their search engine in 2012. For example, using the knowledge graph, we can easily find the name of Donald Trump's wife and ex-wives by searching for "Trump's wife".

DBpedia is a project to extract structured content from Wikipedia, including knowledge graph linking resources from Wikipedia and other websites on the internet. Users can use SPARQL (SPARQL Protocol and RDF Query Language) queries to get the information they are interested in. For example, they can find other books written by the author of *Le Comte de Monte-Cristo*.

Wordnet is one of the largest English lexical databases. It includes nouns, verbs, adjectives, and adverbs, with their definitions, synonyms, and antonyms, thus constituting a large knowledge graph. Wordnet is mainly used for natural language processing [10].

1.1.3 Why We Need an Ontology for Exercise Medicine?

Nowadays, not only simple repetitive work but also complex work is done by computer programs and artificial intelligence. Knowledge in the form of natural language needs to be converted to a structured form for computers to read and use for specific processes. The structure of knowledge can be defined using ontologies that serve as a kind of protocol.

Exercise medicine is a new and interdisciplinary field, containing large amounts of data and publications to be investigated. A domain ontology is thus needed to structure and standardize this knowledge.

As seen in Fig. 1.2, an ontology includes the structure of knowledge without specific data. A knowledge graph contains this structured data. As a result, ontologies are often used as the schema for knowledge graphs [12]. Without an ontology, it is hard to get structured knowledge for artificial intelligence and other uses.

To my knowledge, there is no knowledge graph for exercise medicine, although several related ontologies have been built, as described in the next section.

1.2 Related Ontologies: Current Status

1.2.1 Physical Activity Ontology (PACO)

Kim et al. developed the Physical Activity Ontology (PACO) for physical activity structuration and standardization [13]. Generated from 1140 unique questions and sentences from questionnaires and other forms, PACO (version 0.2, https://bioportal.bioontology.org/ontologies/PACO) contains 224 classes to describe physical

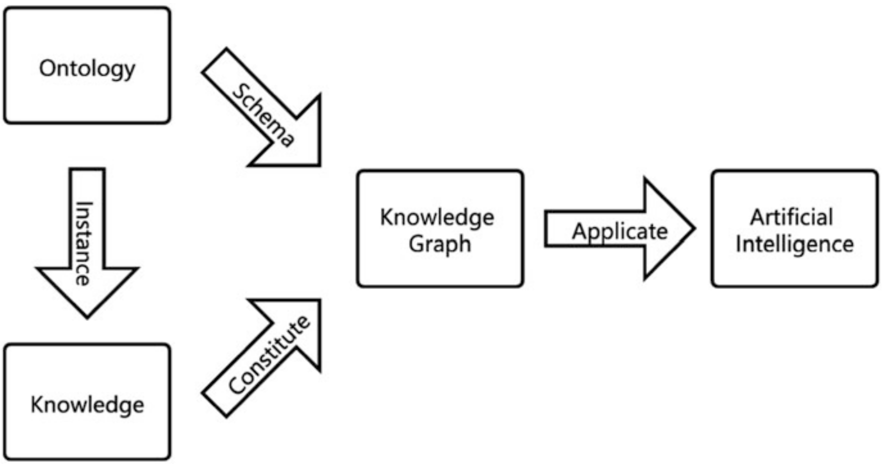

Fig. 1.2 Ontology as the schema for a knowledge graph

activities from several aspects: types, effects, equipment, and modifiers of physical activities and exercise. As an application ontology, PACO focuses exclusively on the things that concern developers, and the definitions of many classes are missing.

1.2.2 Ontology of Physical Exercises (OPE)

Another ontology, the Ontology of Physical Exercises (OPE), is similar to PACO in that it includes the classification, equipment, and outcomes of physical activities. OPE also includes ailments and musculoskeletal terms, which are more related to exercise medicine. Version 0.0.1 (https://bioportal.bioontology.org/ontologies/OPE) contains 634 classes, but OPE is still unfinished.

1.2.3 Ontology for Patient Adherence Modeling in Physical Activity Domain (OPTImAL)

The Ontology for Patient Adherence Modeling in Physical Activity Domain (OPTI-mAL, https://bioportal.bioontology.org/ontologies/OPTIMAL) is an application ontology that describes the factors of cardiovascular disease patients regarding their adherence to physical activity [14].

1.2.4 Human Disease Ontologies

In addition to ontologies about physical activity, disease ontologies are related to exercise medicine. Disease ontologies can be divided into two types: ontologies of all diseases, and specific disease ontologies. The Disease Ontology and ontologies of the ICD classification are examples of the first type. Specific disease ontologies are those that pertain to a specific disease.

1.2.4.1 Disease Ontology

The Disease Ontology (DO, https://disease-ontology.org/) is one of the best-known ontologies of human disease. It contains 10,791 disease terms (April 2021 release) divided into eight types: diseases by infectious agents, diseases of an anatomical entity, diseases of cellular proliferation, diseases of mental health, diseases of metabolism, genetic diseases, physical disorders, and syndromes. The attributes of each concept are annotated in detail. Definitions and relations are included, as well as synonyms and links to other databases (ICD-9, ICD-10, MeSH (Medical Subject Headings), NCI thesaurus, SNOMED CT (Systematized Nomenclature of Medicine - Clinical Terms), and UMLS (Unified Medical Language System)).

1.2.4.2 ICD-Based Ontologies

The International Classification of Diseases (ICD) was proposed by the World Health Organization (WHO) to popularize a global standard for disease classification. The first version of the ICD was established in 1893, and ICD-11 comes into effect in 2022. ICD ontologies are mainly based on ICD-9 and ICD-10 and aim to represent the ICD system as a formal ontology (Table 1.1).

1.2.4.3 Specific Disease Ontologies

Specific disease ontologies cover common diseases, including cardiovascular disease [15], cancer, and neurodegenerative disease (Table 1.2). These ontologies can help establish a standard for disease classification and assist with disease diagnosis and treatment. Specific disease ontologies are lower-level ontologies of disease, and some ontologies only focus on a specific domain of the disease. For example, the Prostate Cancer Lifestyle Ontology (PCALION) [16] is a lower-level ontology of the Prostate Ontology (PCAO).

Table 1.1 ICD-based ontologies

ICD version	Acronym	Term	URL
NA	International classification of diseases ontology		
	ICDO	1254	http://bioportal.bioontology.org/ontologies/ICDO
ICD-9	International classification of diseases ontology		
	ICD9CM	22,533	http://bioportal.bioontology.org/ontologies/ICD9CM
ICD-10	International classification of diseases, version 10		
	ICD10	12,445	http://bioportal.bioontology.org/ontologies/ICD10
	International classification of diseases, version 10—clinical modification		
	ICD10CM	95,798	http://bioportal.bioontology.org/ontologies/ICD10CM
	International classification of diseases, version 10—procedure coding system		
	ICD10PCS	190,800	http://bioportal.bioontology.org/ontologies/ICD10PCS

The data are based on the latest versions (June 2021).

Table 1.2 Specific disease ontologies

Ontology	Acronym	Term	URL
Alzheimer's disease ontology	ADO	1565	http://bioportal.bioontology.org/ontologies/ADO
Bilingual ontology of Alzheimer's disease and related diseases	ONTOAD	5899	http://bioportal.bioontology.org/ontologies/ONTOAD
Cardiovascular disease ontology	CVDO	518	http://bioportal.bioontology.org/ontologies/CVDO
Chinese diabetes mellitus ontology	CDO	1484	https://bioportal.bioontology.org/ontologies/CDO
Coronavirus infectious disease ontology	CIDO	7564	https://bioportal.bioontology.org/ontologies/CIDO
Chronic kidney disease ontology	CKDO	280	http://bioportal.bioontology.org/ontologies/CKDO
Coronavirus infectious disease ontology	CIDO	7564	http://bioportal.bioontology.org/ontologies/CIDO
Human dermatological disease ontology	DERMO	3521	http://bioportal.bioontology.org/ontologies/DERMO
Melanoma ontology	MELO	528	https://bioportal.bioontology.org/ontologies/MELO
Prostate cancer ontology	PCAO	636	http://bioportal.bioontology.org/ontologies/PCAO
Sickle cell disease ontology	SCDO	2072	https://bioportal.bioontology.org/ontologies/SCDO
Thyroid cancer ontology	TCO	578	http://bioportal.bioontology.org/ontologies/TCO

The data are based on the latest versions (June 2021).

1.3 Exercise Medicine Ontology: Future Directions

As there is no ideal ontology for exercise medicine, I suggest that the ontology should follow the Open Biological and Biomedical Ontologies (OBO) Foundry and cover related domains such as personal health status, physical activity, benefits, and outcomes.

1.3.1 Open Biological and Biomedical Ontologies (OBO) Foundry

1.3.1.1 Introduction to the OBO Foundry

The OBO Foundry is a community for biological and biomedical ontologies, whose purpose is to develop logically well-formed and scientifically accurate ontologies. For this mission, the OBO Foundry proposed several principles, and developers who want their ontology to participate in the OBO library must follow the principles.

Fig. 1.3 Characteristics of the OBO foundry

Popular biological and biomedical ontologies, such as the Gene Ontology, the Disease Ontology, and the Human Phenotype Ontology are collected in the OBO Library.

All ontologies that follow the OBO Foundry use the Basic Formal Ontology (BFO) as their upper-level ontology. Other principles, such as 'Common Format', 'URI/Identifier Space', and 'Relations' (reused from the Relation Ontology (RO)) make the ontology general. Treating the ontology as software engineering with version control is beneficial for the development of the ontology, especially when the ontology is very large. The ontology should be open-access and the developments should be communicated to the community. (Fig. 1.3)

1.3.1.2 Structure of BFO

The OBO Foundry uses BFO as the upper-level ontology for their ontologies. BFO divides entities into those that are continuant and occurrent. Continuant entities are those that can persist, endure, and continue (e.g., cells, persons, the Earth, etc.), and they include independent continuants, generically dependent continuants, and specially dependent continuants. Occurrent entities are those that happen or appear (e.g., meiosis, operation, and orbital revolution), and they include processes, process boundaries, temporal regions, and spatiotemporal regions (Fig. 1.4) [6].

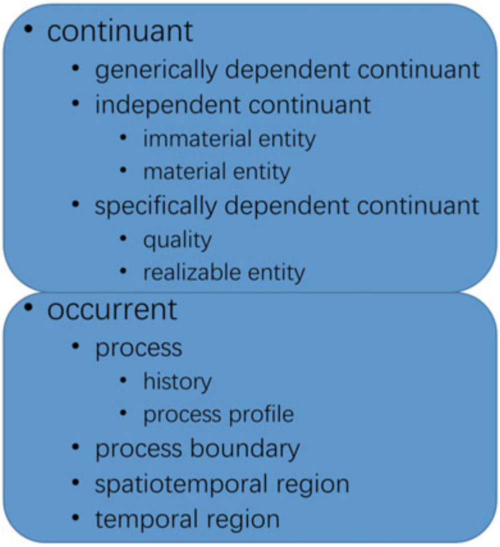

Fig. 1.4 Structure of BFO 2.0

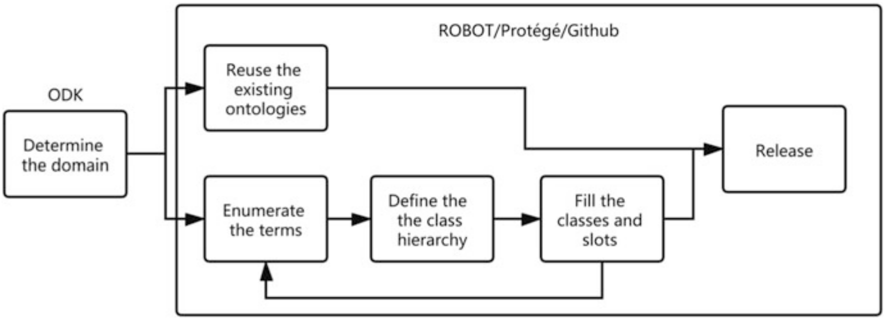

Fig. 1.5 OBO workflow

1.3.1.3 Workflow Suggested by OBO

Traditionally, an ontology workflow is designed by editing the file in IDE, saving it locally, and sharing it using an FTP server. The OBO Foundry suggests treating the building of ontologies more like software engineering, for example by using hosted version control for backup and teamwork. The OBO Foundry also suggests separating the source and release files and managing dependencies that can be finished by the Ontology Development Kit (ODK) and ROBOT (Fig. 1.5).

1.3.2 Evaluating Ontologies

After building the ontology, evaluation is essential. Expert-based evaluations, application tests, and automatic methods are common ontology evaluation methods [17].

Experts evaluate the ontology manually to ensure that the concepts, their attributes, and their comments are correct. Also, experts can view and search the ontology using browser tools to check for correctness [17].

Application tests are also a common way to evaluate ontologies. Questions can be asked using SPARQL and DL to test the expressivity of the ontology. Gomez-Valades et al. adapted an ontology to a new project and updated the ontology using a new ontology for evaluation [18].

Automatic evaluation refers to using a program to evaluate the ontology automatically. So-called reasoners are often used to infer logical consequences from a set of facts in an ontology [17]. Reasoners for OWL include Pellet, FaCT++, and the HermiT OWL Reasoner.

1.3.3 Domains of an Exercise Medicine Ontology

To develop an ontology, the first step is to determine the purpose and the domains of the ontology. An exercise medicine ontology must declare a relationship between exercise (or physical activity) and health or disease for exercise prescriptions and advice for patients and healthy people. The domains of the ontology should include personal health status, physical activities, and health outcomes. These should establish with some regularity which people need what kind of physical activity and which people cannot do certain activities (Fig. 1.6).

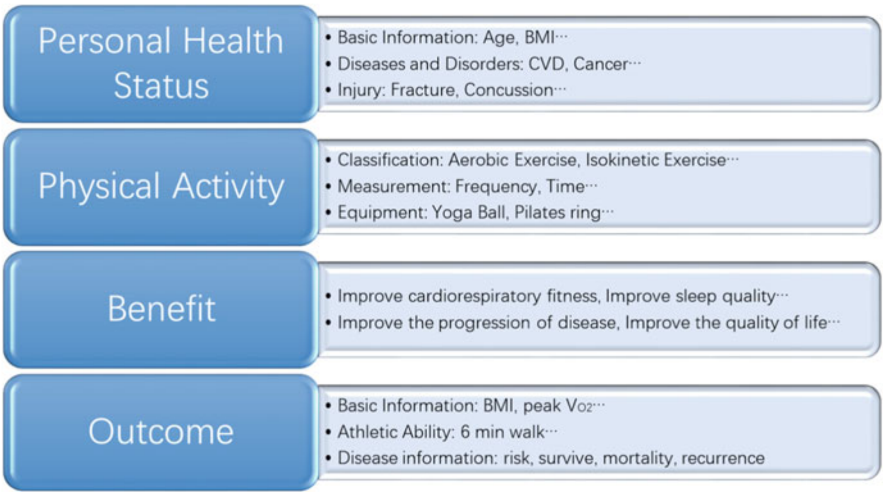

Fig. 1.6 Suggested domains for an exercise medicine ontology

1.3.4 Personal Health Status

Any prescription should be based on personal information, and the more information, the more precise the prescription will be. So the first related domain of exercise medicine ontology is personal health status. We can divide this domain into three parts: basic information, diseases and disorders, and injuries.

1.3.4.1 Basic Information

We define basic information as personal information related to health and physical activities, except for diseases, disorders, and injury.

Age is one of the most important factors of diseases and health. People of all ages (except babies) should perform physical activity every week. As a result of growth, children and adolescents will benefit a lot from physical activity, so it is recommended that they get at least 60 min of physical activities every day (Fig. 1.7) [19].

Gender is also an important factor, as males are usually stronger than females. For females who are menstruating, pregnant, or have recently given birth, exercise prescriptions or advice will differ.

Height, *weight*, and *body mass index (BMI)* are important as well. The BMI measures whether a person is underweight, normal weight, overweight, or obese. This helps when giving exercise prescriptions. For example, obese people should exercise more to lose weight.

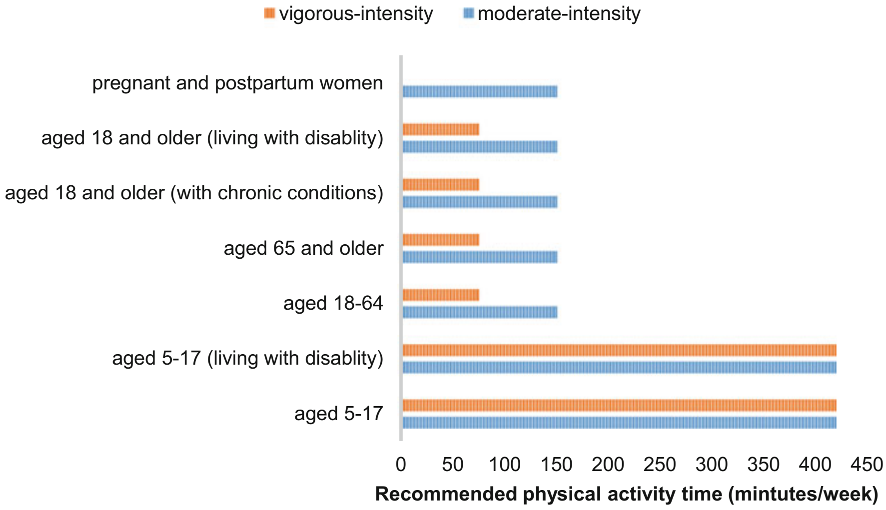

Fig. 1.7 Recommended minimum physical activity by the WHO

Other signatures related to health status and exercise capacities, such as *blood pressure, vital capacity*, and *pulse rate* are important for doctors to make personal exercise prescriptions according to a person's situation—namely, how much and how often that person should exercise.

Accord to the WHO, people of all the ages can choose vigorous- or moderate-intensity physical activity, except pregnant and postpartum women who should not engage in vigorous physical activity.

1.3.4.2 Disease and Disorder

For exercise prescriptions for patients, disease information is vital, especially if the patient suffers from chronic diseases.

Regular physical activity is an important component of most *cardiovascular disease* therapy and can reduce the risk [20]. However, physical activity can also cause CVDs, i.e., sudden cardiac death, especially in athletes [20].

Physical activity also benefits patients with *diabetes mellitus* [21], *cancer* [22–24], and *neurodegenerative diseases* [25–27], but not all of these diseases have strong relations with physical activity [28–30].

Of course, not all exercise and sports are suitable for all people. For example, patients with aortic valve stenosis should not take part in vigorous or even moderate physical activity, although low-intensity activity is recommended [20]. Meanwhile, an operation or some other treatment can limit the physical activity of patients while they recover.

1.3.4.3 Injury and Disability

Injury and disability limit the choices of physical activity. For example, swimming is not recommended if one has an open wound.

Another problem is that physical activity can lead to athletic injuries, disability, or even death in some dangerous sports. Ligament injuries, ankle sprains, finger injuries, and muscle ruptures are common injuries when playing basketball, for example.

1.3.5 Exercise

The WHO defines physical activity as "any bodily movement produced by skeletal muscles that requires energy expenditure" [19]. The term "exercise" refers to physical activity used to maintain or enhance health and fitness, whereas "sport" refers to competitive physical activity. Since the focus here is on maintaining health and preventing and treating diseases, the term "exercise" is used in this chapter.

1.3.5.1 Classification

To classify exercise, the distinction between aerobic and anaerobic exercise is apt. This distinction is relatively objective and indicates the purpose of exercise: i.e., aerobic exercises are for health and losing weight, whereas anaerobic exercises are for muscle gain and body shape.

Aerobic exercises are exercises that mainly depend on the aerobic energy-generating process. The most common sports are aerobic, such as running, basketball, football, and tennis. People can pursue aerobic exercises to maintain health and reduce the risk of some diseases, such as diabetes and heart diseases.

Anaerobic exercises break down glucose in the body into ATP without oxygen [31]. As a result, anaerobic exercises are shorter and more intense than aerobic exercises. Explosive exercises such as dashes in running or swimming, high-intensity interval training (HIIT), and strength training are anaerobic exercises. Anaerobic exercises can build endurance and muscle gain but they are riskier than aerobic exercises.

1.3.5.2 Measurement

Exercises can be described using the concept of FITT (frequency, intensity, time, and type) [20].

Frequency refers to the number of times spent exercising over a period (usually a week). For example, children should exercise at least 3 days each week, and adults should exercise at least twice a week, according to the WHO [19].

Intensity can be described as endurance and strength or power, both of which can be measured by %peak HR or %HRR (heart rate reserve). Endurance can also be measured by %VO_{2peak} (peak oxygen consumption), and strength can be measured by %1RM (repetition maximum) or %5RM [20].

Time refers to the duration of exercise. Figure 1.7 lists the recommended minimum time spent exercising every week, according to the WHO.

Type refers to what the exercise mainly trains: (a) endurance, (b) strength or resistance, (c) speed and speed endurance, (d) flexibility, or (e) coordination and balance [20].

1.3.5.3 Equipment

There are two types of equipment: exercise equipment and wearable devices. The former include equipment like basketballs and dumbbells. Wearable devices or sensors are used to measure heart rate, temperature, and even electrocardiogram (ECG). Also, some equipment can be used to measure the exercise condition, such as distance and the maximum running speed.

1.3.6 Benefits

Exercising regularly will bring many benefits to healthy people and those with chronic diseases.

First, healthy people can improve physical fitness such as cardiorespiratory fitness and muscular fitness. Meanwhile, improved sleep quality and mental health are among the benefits of exercise. All-cause mortality and risk of some chronic diseases (including hypertension and diabetes) can also be reduced through regular and appropriate exercise.

In addition to the above benefits, people with chronic diseases or disabilities benefit more from exercise. Cancer survivors can reduce the chance of recurrence and second primary cancer [19]. Patients with hypertension can improve the progression of the disease and their quality of life. Type-2 diabetes patients can also improve the disease progression [19].

1.3.7 Outcomes

Most studies of exercise-fitness and exercise-disease relationships have an outcome, although the outcomes differ from each other due to the different study objects. The outcomes can be classified into three categories: basic information, athletic ability, and disease information.

Basic information is similar to that in Sect. 1.3.3 BMI, peak V_{O2}, and other values are often used to measure the fitness status of healthy people.

Athletic ability is another important outcome that can be used in exercise-fitness and exercise-disease studies to compare the impact of exercise. Six-minute walks are one of the common measurements for cardiovascular diseases [32].

Disease information depends on which disease is studied. Specific disease indicators, risk, survival, mortality, and recurrence are common measurements.

1.4 Conclusion

Ontologies and knowledge graphs for exercise medicine are emerging fields. Although there are several related ontologies, they do not meet the demands of exercise medicine. To our knowledge, there is no knowledge graph for exercise medicine. Yet to normalize and formalize big data on exercise medicine, an ontology is needed, along with a knowledge graph for processing and storage.

Based on the related ontologies above, we describe an exercise medicine ontology workflow and its related domains: personal health status, exercise, benefits, and outcomes.

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Chapter 2
Participatory Exercise Medicine and Personalized Healthcare

Shumin Ren and Bairong Shen

Abstract The proposal of P4 medicine has brought about a change in the current medical model. Patients pay greater attention to their participation in the medical process, and personalized medicine also plays an important role in the treatment process. The sedentary lifestyle of modern people has brought about an overall decline in their health condition. The promotion of exercise medicine can not only provide effects that medical treatment cannot bring, but can also prevent diseases and relieve symptoms of chronic diseases. This chapter first introduces the concept of participatory medicine and personalized medicine, as well as their current related applications, such as the Internet of Things, sensors and smartphone-based devices and applications (SBDAs), mHealth, social media platforms, gene sequencing applications, personalized medical solutions and frameworks, etc. It then introduces the development of exercise medicine in combination with these concepts, such as exercise prescriptions and related applications, and finally, proposes future development directions.

Keywords Exercise medicine · Participatory medicine · Personalized medicine · Exercise prescription · Wearable devices

2.1 Introduction

The current healthcare model is supposed to transform from being traditional, passive, disease-centered, to being more personalized, predictable, preventive, and patient-centered. The greater economic spending brought about by the advancement of medicine and the increase in population has prompted patients to pay greater attention to their role in healthcare [1]. At the same time, significant changes are taking place in the medical field, including the use of systems medicine, big data, and cloud computing, and the combination of engineering science with clinical research.

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This trend has promoted the emergence of P4 medicine, which stands for predictive, preventive, personalized, and participatory medicine [2]. Among them, personalization and participation will be the focus of this chapter in relation to exercise medicine.

Insufficient physical activity is a common problem in modern people, which has led to a marked increase in lifestyle-related chronic diseases [3] and medical costs. Many studies have shown that correct exercise has an active effect on improving health and preventing chronic diseases in all ages. For example, a non-exercise lifestyle is related to seven types of cancer [4], depression [5], and Alzheimer's disease and related dementia [6]. Personal lifestyle and behavior is one of the most important factors affecting health. Unhealthy lifestyles (including smoking, inappropriate drinking, bad sleep, and stress) can induce chronic diseases. Among cancer patients, lifestyle compliance with physical activities guidelines has been shown to reduce the relative risk of mortality by nearly 40–50% [7]. Manini and Todd [8] pointed out that no drug treatment can have such a positive effect on so many organ systems as physical activity does. Physical activities (PA) improve daily life quality, health conditions and reduce medical costs [9].

This chapter will discuss the current development and related applications of exercise medicine combined with participatory medicine and personalized medicine, and puts forward suggestions for the future.

2.2 Participatory Medicine and Related Applications

As for the definition of participatory medicine, it's usually explained as involving individuals in their health by strengthening patients' empowerment and autonomy, promoting communication among patients and HCPs (healthcare professionals) or other stakeholders [10]. In modern medicine, the model of doing things to patients plays a leading role [11]. However, although this approach is useful for acute diseases, it has a limitation in the treatment of chronic diseases. In recent decades, the shared decision-making model has been proven practicable in clinical decision-making [12], especially in the area of evidence-based medicine [13] and patient-centered care [14], which shows the importance of participatory medicine. Meanwhile, patients nowadays are easy to acquire their laboratory data online, which helps them in being informed and managing their health. Current research shows that active participation from patients significantly improves treatment efficiency, reduces drug use, and makes people feel greater happiness in being part of the medical care process [15].

Participatory health is an evolving field, with an increasing number of applications and practices. Currently, emphasis is placed on the use of health social networks and applications for self-management, health research data collection with public participation, crowdsourced research [16], and building health collaboration communities with multi-stakeholder participation.

Accompanying the concept of participatory medicine are the terms e-patients and e-health. E-patients have been described as "patients who are equipped, enabled, empowered, and engaged in their health and health care decisions, and use the Internet to collect information about interesting medical conditions" [17]. In the meantime, lots of technologies are being developed to promote healthcare services. The emergence of e-health enables healthcare stakeholders to share digital medical information in order to efficiently collect information and provide patients with healthcare services of high quality. eHealth includes information and technologies as follows: wearable sensors, medical recordings, smartphone applications, cloud-sharing, etc. [18, 19]. The popularity of e-patients and eHealth is accelerating the transformation of the medical care model from a traditional, passive model to an interactive relationship between patients and HCPs [20].

The implementation of P4 medicine must rely on the development of the technology in order to collect and analyze big data so as to track the physical conditions of patients and make predictions. With the large increase of personalized big data generated by the medical Internet of Things and sensors attached to patients [21], P4 medicine has a foundation of technology and data. In addition, artificial intelligence (AI)-driven analysis can be applied to these data [22], which will have a profound effect on the change of the medical model.

The use of digital technology is rapidly developing in the fields of monitoring, prevention, prediction, treatment, and maintenance of health. Advances in sensors, computing architecture, and transmission technology will gradually make the medical Internet of Things mainstream.

As the basic component of the Internet of Things, the development of sensors is crucial. First of all, there are various types of sensors, which can be implanted in the body, attached around the body (e.g., wearable sensors), or be placed on a wall or floor at home, etc. By integrating different sensor devices, patients' health can be monitored in a non-intrusive way, and related data can be input into the analysis system continuously. Therefore, it can intervene in a patient's health early on, especially for people with chronic diseases. At present, there are many commercial sensor services that can monitor the user's health data. Because these sensor devices can transmit data to smartphones or other portable equipment, related smartphone-based devices and applications have been developed.

As the above participatory concepts and technologies are being incorporated, more and more platforms and applications are being developed. For example, Sagar and Broadbent [23] proposed an avatar model to participate in personal healthcare, with a virtual nervous system and the ability to convey emotions, which is also regarded as a virtual physiological person (VPH). By participating in their own daily health care and interacting with VPH, patients can gain information and prediction from the VPH [24] so as to improve their health management motivation. Kodric [25] proposed creating a data cloud for patients. To study a disease and its underlying mechanism, a panel of genes, transcripts, and other biomarkers could be constructed through the methods of systems biology. Patients can predict the risk of a certain disease through the biomarkers in the cloud so as to prevent the disease as much as they can. For example, there is currently a large number of genetic testing applications accessible for the public. Users can submit their DNA-carrying tissues, such as their saliva, to learn about their genetic information. 23andMe is a well-known genetic testing agency in the United States. It makes original genetic information available for all users, including on related diseases and drug metabolism. Meanwhile, they also guide customers to complete questionnaires about their phenotypes and lifestyles, and encourage them to propose new research questions [26]. Riveir et al. [27] developed a series of apps to monitor the physical conditions of the elderly, especially in terms of common dangers, such as falls, urinary incontinence, and insomnia. On a unified platform, patients, their families, and their HCPs are allowed to share and manage the elderly's health information. Barrett et al. [28] proposed a virtual doctor system named Abby, which combined artificial intelligence-driven digital therapies (e.g., decision support systems, interactive virtual interfaces, gamification, etc.). Abby can contribute to the self-care of patients with comorbidities through safe prescription and drug management. Schleimer [29] created a digital tool called the Open MS BioScreen, which is for multiple sclerosis screening. Through this platform, patients can input basic MS-related parameters, making their treatment process more visual. Meanwhile, they can access the research tools operated by HCPs to acquire their determinations.

These platforms and applications use sensors, advanced data analysis and processing technology, virtual models, and interactive models between HCPs and patients and combine systems biology and clinical knowledge to develop innovative applications that increase patient participation. These tools can track patients' conditions and communicate with patients in real-time, ultimately improving the life quality of patients with chronic diseases and functional impairments. Furthermore, it provides a reference for the future development of participatory exercise medicine applications.

2.3 Personalized Medicine and Related Applications

Generally speaking, personalized medicine is a medical model that customizes the most suitable treatment plan for the patient based on personal genome information, proteome, metabolome, and other relevant internal environment information. It divides people into different groups and determines the best medical decisions and practices based on patients' unique clinical, genetic, and environmental characteristics [30]. With the increase and utilization of big data, as well as the improvement of disease management and computing capabilities, personalized medicine has gradually made achievements in various fields.

Personalized medicine was first proposed due to the application of genomics (e.g., human genome sequencing), which is expected to lead to powerful predictive functions and tailor-made treatments, thereby changing medical practice [30]. With the development of science and technology, gene sequencing is already affordable for most users, such as the aforementioned 23andME. Molecular diagnosis and biomarker results based on genetic testing can provide information about the patients' health, while HCPs and patients can use the test results to determine disease prevention and treatment plans. As richer genetic information can be obtained from gene sequencing technology, there will be more innovations in the application of genome sequencing in the future.

Personalized medicine is also widely used in drug development, 3D printing technology, digital implant design, and so on. The relationship between genetic variation, susceptibility to specific diseases, and responses to specific drugs are considered in the drug development and use. In addition, personalized implants include personalized bone and plate implants, personalized navigation locators, personalized invisible tooth braces, personalized dental implants, personalized prosthetic sockets, and other internal implants. Furthermore, personalized treatment also extends to therapeutics based on proteomics [31], imaging analysis [32], nanoparticles [33], etc.

Nowadays, big data technology is able to manage the whole life cycle of individuals since personal information can be accessed continuously. Health analysts can analyze personal health conditions according to the information they receive so as to provide a patient with effective and timely intervention when the patient is found to be unhealthy. During the health management progress, the most important aspect is to detect physical abnormalities and early warning of disease risks quickly and precisely, while wearable devices can realize real-time detection of physical abnormalities regardless of regions and help users monitor their health activities, and subsequently propose personalized suggestions for sleep, diet, exercise, etc. On this basis, SBDAs have allowed for cost-effective and personalized mHealth (mobile healthcare) [34], which is very useful for managing chronic health conditions, such as diabetes, obesity, etc., by measuring a person's weight, activity, sleep, and so on.

New clinical decision-making tools have emerged in recent years, contributing to disease prevention, prediction, diagnosis, treatment, risk identification, and drug safety improvement. It also promotes the change of the health care model [35]. Some personalized medical frameworks have been developed for specific medical practices. For example, Chawla [36] proposed the Collaborative Assessment and Recommendation Engine (CARE) framework, whose core is a novel collaborative filtering method. It can compute the similarities of patients and create personalized disease risk profiles for individuals. The framework demonstrates its patient-centric features and reduces the readmission rate.

2.4 Exercise Medicine

Exercise medicine is a branch of medicine that deals with physical fitness and the treatment and prevention of injuries related to sports and exercise. At present, an increasing amount of attention has been paid to the influence of exercise on health and disease treatment. There is evidence demonstrating that regular physical activity (PA) has an inverse association with premature mortality, CVD/CAD, hypertension, stroke, cancers, depression, and cognitive function [9, 37, 38]. In general, the appropriate kind of exercise can improve cardiovascular fitness, reduce cardiovascular disease risk factors, and decrease morbidity and mortality, which could be seen as a prevention of coronary artery disease and secondary myocardial infarction for patients with hypertension. Meanwhile, PA also has a positive effect on reducing anxiety and depression, preventing cognitive competence decline, enhancing the ability to live independently for older people, increasing happiness, etc. [39]. At the same time, studies have shown that appropriate PA plays a key role in physical therapy for common diseases, such as chronic low back pain [40]. As a treatment method, exercise has a much wider range of effects and potential than any single medicine and prescription. However, exercise also brings related risks. For example, PA is associated with an increased risk of musculoskeletal injury (MSI) and cardiovascular complications [37]. Adverse cardiovascular events, such as sudden cardiac death (SCD) and acute myocardial infarction (AMI), are usually associated with strenuous exercise [41].

Therefore, in order to ensure the positive effect of exercise and prevent the occurrence of adverse events, pre-exercise screening is necessary. For example, potential cardiovascular disease risk factors and related signs or symptoms are important assessment areas before engaging in exercise. According to the risk classification and the exercise intensity, patients are supposed to participate in a physical examination and exercise screening. In addition, the informed consent procedure, medical history, laboratory testing, and exercise guidance are necessary preparations before exercise.

2.4.1 Exercise Prescription and Personalized Healthcare

The World Health Organization (WHO) defines exercise prescription as follows: healthcare professionals make the exercise plan based on patients' medical data (including exercise and physical examination) and a patient's specific health, physical strength, and cardiovascular function [42]. In order to generate a personalized exercise treatment plan, healthcare professionals need to make a comprehensive judgment based on the individual's specific condition. First, the exercise prescription is different for various age groups. For example, the bones of prepubertal children are immature, so young children should not participate in excessive high-intensity exercise. In addition, environmental factors should also be considered in the design of exercise programs, especially for high-altitude areas, low-temperature areas, and high-temperature areas. In high latitudes, the atmospheric pressure decreases, and the partial pressure of oxygen in the inhaled air decreases, resulting in a decrease in arterial oxygen levels, as well as a decline in physical performance with a longer recovery time. For patients with cardiovascular disease, physicians need to consider their medical and surgical history, including recent cardiovascular events and comorbidities. Cardiopulmonary and musculoskeletal system examinations, recent cardiovascular tests, electrocardiogram (ECG), etc. should also be reviewed. These procedures also apply to patients with peripheral, cerebrovascular, and pulmonary disease. In addition, for special conditions, such as low back pain, arthritis, pregnancy, and even cancer, cerebral palsy, and so on, exercise prescriptions need to be formulated according to the patients' different conditions [39].

Theory-based interventions are useful for increasing the participation rate in PA [43]; therefore, the behavior change techniques (BCTs) theory was proposed. BCTs are the active ingredients within an intervention [44]. This theory is applied to exercise medicine, achieving the expected behavior change through goal-setting and self-monitoring of behavior.

Clinical reasoning is the process that leads to clinical decision-making. First, HPs collect and evaluate data, and then they determine the diagnosis and management of patients' situations. The process of clinical reasoning includes the interaction between the HP and the patient, collecting information, proposing and verifying hypotheses, and determining the most appropriate diagnosis and treatment [45]. The patient's clinical status, relevant research evidence, and patient preferences should be integrated into this process.

One of the most cost-effective ways to increase the patient's physical activity is for physicians to give exercise prescriptions. Personalized exercise medicine is based on exercise prescriptions, which need to meet the individual's physical condition and exercise environment, and ultimately achieve their personal exercise goals. The American College of Sports Medicine (ACSM) introduced exercise prescription guidelines in 1990 to guide the design of exercise prescriptions for members of the public and patients with chronic diseases [46]. In these guidelines, the ACSM proposed FITT principles based on the existing scientific evidence, which are currently important and widely used exercise prescription principles.

According to the above theories, HPs should design reasonable exercise prescriptions according to patients' various factors, as shown in the Fig. 2.1. The following factors should be considered: (1) Basic individual information, including physical indicators, relevant exercise test and physical examination results, drug use, disease situation, related medical history, risk factors, etc. (2) Exercise habits and living habits, personal preferences, and exercise environment. Finally, a reasonable exercise plan is determined in compliance with the FITT principles.

2.4.2 Participatory Exercise Medicine and Related Applications

In the past few years, life expectancy in many developed countries has increased to over 80 years, mainly due to reduced mortality related to infectious diseases, childbirth, and malnutrition [47, 48]. At the same time, insufficient physical activity has led to a rapid increase in lifestyle-related chronic diseases [3]. Nearly 70% of Americans are overweight and 35% are obese. PA plays a key role in improving health conditions, daily life quality, and reducing medical costs. Therefore,

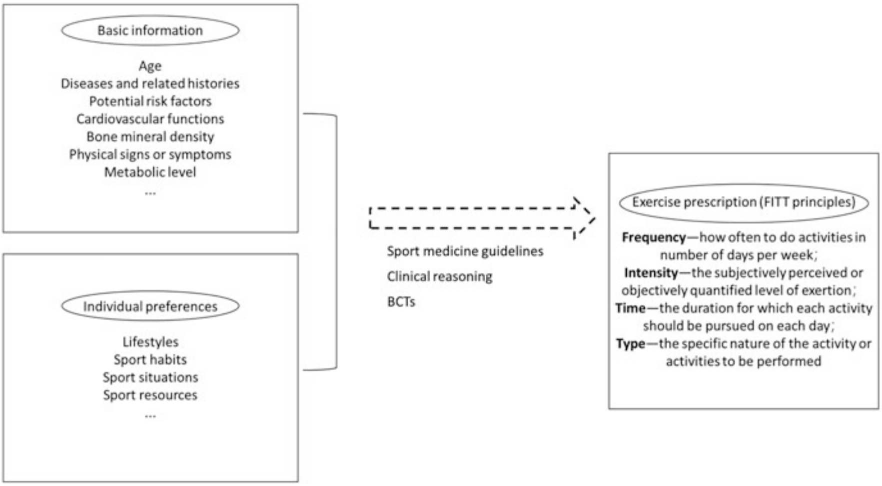

Fig. 2.1 Exercise medicine reasoning model

improving PA has been identified as the best choice for public health. Lack of exercise is an important factor in chronic diseases, weight imbalance, and mortality. Although other determinants of health (genetics, environment, and medical care) affect health outcomes, the most important factors related to health are by far personal lifestyles and behaviors [6]. Studies have shown that appropriate intervention can promote people's willingness to exercise. Especially with the popularization of mobile devices and applications, scientific exercise intervention for people is an important pathway of participatory medicine. In the next stage of participatory exercise medicine, it is expected that we can use smartphones for exercise prescriptions and wearable devices for monitoring and intervention. In addition, it is likely that there will be a participatory exercise medicine information-sharing platform to generate more personalized big data, provide evidence for scientific research and promote communication among users.

2.4.2.1 Wearable Devices

Due to the demand for monitoring one's body status during exercise, various wearable device systems have been developed to offer an in-depth analysis of human physical activities. Recently, portable wearable sports devices incorporating sensor technology, such as smartphones, smartwatches, fitness trackers, etc., have become effective tools for evaluating physical activities. This trend is driven by the availability, non-invasiveness, and lower cost of these devices. Seshadri defines a wearable sensor as a wireless device that can detect and monitor physical activities in real-time and continuously, and then transmit physiological data to the users or researchers through the analysis platform [49]. These wearable devices are equipped

Table 2.1 The categories of sensors

The categories of sensors	Definition
Movement sensors	position, accelerometers, gyroscopes, pedometer, magnetometers, GPS, or combined integrated technologies (IT)
Biochemical sensors	Sensors to analyze bodily fluids such as sweat, or saliva
Lmpact sensors	Sensors to quantify and mitigate for head trauma
Biomechanical-based sensors	Sensors to measure impact forces or kinematics on various joints

with sensors, such as cameras, gyroscopes, accelerometers, and optical sensors. Wearable sensors monitor both physical and chemical signals. According to measurement standards, sensors are divided into four categories (Table 2.1) [49]. Currently, wearable devices can apply the collected data into clinical areas and exercise medicine for the formulation of exercise prescriptions [50].

2.4.2.2 mHealth in Participatory Exercise Medicine

mHealth is a concept that has been put forward in recent years. In order to adapt to the popularization trend of smartphones and other mobile devices, much attention is being paid to telemedicine and mobile healthcare. mHealth programs use mobile and wireless technologies to improve health and medical outcomes. These programs have been proven to be effective in helping people increase their physical activity, keep fit, and cope with other secondary risk factors for non-communicable diseases, such as increased blood pressure. Using motion detection applications allows for a quantitative analysis of physical activity and increasing the user's health. The e-health system architecture proposed by Vidavo SA, a Greek e-Health company, consists of four parts (Fig. 2.2 [51]: (1) Sensors installed on the user to transmit biomedical data, (2) a smartphone with GPS and Bluetooth connections, managing real-time data transmission through the receiver and GSM for real-time data transmission to the server, (3) a receiver on the smartphone, preprocessing the acquired sensor data through embedded software, and (4) a data server to store, process, and manage the data.

Based on the popularization of mHealth, some applications have been developed to promote PA, improve health, prevent obesity, and so on. For example, Mhurchu [52] designed a mobile health program called OL@-OR@. By collecting the demands of users for health with a sense of control and participation, it could increase uses' usage intention, and ultimately change their health-related behaviors. Subasinghe et al. [53] proposed a mobile health intervention application called Tap4Bone, which encourages certain health behaviors related to the risk of osteoporosis among young women through the use of mobile phone applications, short message services, and e-mail. Sousa et al. [54] created a mobile health intervention program called TeenPower to promote healthy behaviors and prevent obesity in adolescents, including multimedia education (e.g., through videos, infographics,

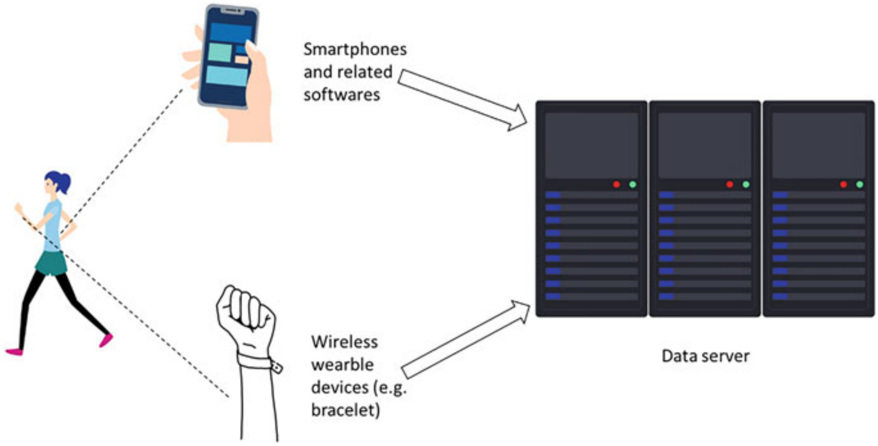

Fig. 2.2 The e-health system architecture

etc.), self-monitoring of behavior (e.g., through a step counter and physical activity records, such as sit-ups and push-ups), social support (e.g., from forums), and interactive motivational modules (health behavior and biometric data share). Through the game-based behavior change process, the application aims to create an attractive virtual environment for young people, thereby mobilizing their enthusiasm for engaging in healthy behaviors. The applications mentioned above actively intervene in people's health behaviors through evidence-based exercise medicine, BCTs theory, and incentive interactive models.

At the same time, incorrect exercise can cause injury. Timely monitoring of one's exercise status can effectively improve exercise effects. In order to exercise correctly, supervision from experts is necessary for exercisers. Nowadays, through the input of large amounts of data, mobile devices can perform automatic machine learning on these data. For example, the mHealth self-report monitoring (mHSM) enables users to detect overuse syndromes early on during exercise by observing indicators from the sensors, such as heart rate, oxygen saturation, etc. According to the continuous recording of external body loads, the efficiency decline of exercisers can be identified, e.g., during running [55] or cycling competitions [51], which help exercisers detect health disorders at an early stage and avoid dangerous incidents. In addition, there are currently some software frameworks on mobile devices, such as Apple ARKit and Google's Tensorflow Pose Estimation, etc., which can automatically detect the position of joints through image recognition. They support a variety of new applications, such as mobile health care applications, mobile exercise games, and so on. These frameworks and applications use advanced sensors and algorithms to help users engage in exercise in a more scientific way and avoid possible dangers related to exercise.

In recent years, the smartphone market and the demand for physical exercise and fitness applications have grown rapidly. However, it is not clear whether the current exercise apps follow sound fitness principles and scientific evidence, whether they are suitable for various fitness levels, and whether these apps use BCTs that have previously been proven to be effective in promoting physical activity [56]. Therefore, regarding the numerous exercise apps that exist nowadays, based on ACSM's FITT principles, Modave et al. [57] selected 30 popular mobile exercise apps to assess the app quality for aerobics (level 0–6), resistance (level 0–6), and flexibility (level 0–2), and ultimately obtain a comprehensive score. Similarly, Guo et al. [58] also developed a tool based on the ACSM guidelines for scoring the content quality of exercise apps, so that the users are able to obtain apps that can provide safe, evidence-based exercise programs. Dallinga et al. [59] also evaluated various leisure exercise apps based on an expert panel, such as running, cycling, and walking. In their assessment process, they found that experts in different fields believe that multiple features, such as the design, technology, and behavior change model, are key factors for the effectiveness of exercise-related applications.

2.4.2.3 "Exercise Is Medicine" Framework

Promoting participatory health behaviors is emphasized by the "Exercise as Medicine" initiative, which is essential for improving peoples' current lifestyles as chronic diseases are becoming more widespread. Exercise as Medicine (EIM) is an initiative launched by the American College of Sports Medicine (ACSM) and the American Medical Association in 2007 to encourage primary care physicians to incorporate exercise into their therapeutic regimen. Its ultimate goal is to make evidence-based PA intervention (e.g., PA assessment, consultation, and prescription/referral [60]) part of the standard care for each patient [61], especially for patients with chronic diseases. EIM allows patients to be more active in managing their health. EIM can prevent and manage chronic diseases and adapt to the health needs of an aging society. Based on this, in various disease fields, researchers are trying to use this framework to improve the treatment outcomes of patients. For example, Jagannathan et al. [62] described a clinical exercise intervention EIM framework developed for patients with advanced chronic kidney disease (CKD), who are transitioning to dialysis, including exercise activities assessment during the treatment, brief consultations pre-dialysis, use of wearable devices, and group exercise programs led by EIM practitioners. Through these strategies, the framework is supposed to help CKD patients recover through physical activity. Krops et al. [63] introduced a project called Physicians Implement Exercise = Medicine (PIE = M). First, it investigates the exercise situation of patients and healthy people in the cohort, the implementation status of EIM by clinicians, and the needs of clinicians and department managers for an EIM tool to develop a demand-based EIM tool that provides tailored PA prescriptions, referrals, and effect assessment using an RE-AIM framework. Linke et al. [64] described an embedded quality improvement (QI) project, which integrates EIM into routine clinical practice. It combines IS (implementation science) and QI (quality improvement) methods to identify patients with insufficient PA in primary care so as to improve their exercise intensity.

McCormack et al. [65] designed an exercise intervention program called pulmonary hypertension and home-based (PHAHB) as an adjuvant treatment for PH patients. Through a family-based exercise mode, the program can relieve patients of a lot of burdens, such as traffic problems and medical resource accessibility. It has been shown to have a positive impact on patients' exercise capacities, functional abilities, and quality of life. In addition, Tuka and Linhart [66] proposed the FITT-EE on the basis of FITT. The first "E" represents "enjoy" because, if the patients enjoy the prescribed exercise and the effect of these exercises can meet their expectations, they will stick to it. So, it's important to find the most suitable exercise for different patients according to their characteristics. The second "E" in FITT-EE represents "effective," which means HPs need to accurately match the patient's physical condition with achievable goals so as to improve patient compliance.

However, because the EIM-based treatment framework requires a lot of personalization, which, in turn, needs expertise, time and energy, clinicians are not inclined to use PA treatment when treating patients. Regarding this situation, Bowen et al. [67] suggested that EIM can be used in electronic medical records (EMRs) in routine clinical care, which could assess the patient's current PA capacity, cardiometabolic risk, etc., and then determine a PA prescription for each patient through a clinical decision-making algorithm. By automatically tailor-making PA prescriptions, clinicians' excessive time investment in PA could be avoided.

2.4.2.4 Practical Application of Exercise Prescription

As the main method of exercise medicine, practices and applications of exercise prescription have been developed. The Royal National Orthopaedic Hospital (RNOH) NHS Trust runs the first exercise prescription clinic in the UK as a supplement for medical treatment [68]. In this clinic, patients undergo consultation based on physical activity, nutrition, sleep, etc. The goals set for individuals are determined by the SMART (specific, measurable, achievable, realistic, and time-limited) principle. Patients are then followed up with every few weeks. Some key quantitative indicators, such as blood pressure and weight, and qualitative indicators, such as pain and mental health scores, are measured to quantify how the patients' health can be changed through health interventions. Advice on physical activity is provided at each stage of the treatment path. In addition, some researchers have developed digital decision support systems for exercise prescriptions. In Dominique Hansen's research [69], the computerized decision support (CDS) system is a web-based interactive system that provides personalized exercise prescriptions for CVD patients after providing the following information to the system: age, weight, cardiovascular function, rehabilitation goals, exercise test parameters, etc. The exercise prescription results include exercise frequency, duration, intensity, and evaluation tools. The exercise program could be divided into several stages based on the patient's rehabilitation goals. Pescatello [70] designed an evidence-based clinical decision support system called P3-EX for patients with multiple cardiovascular disease risk factors. The system is combined with the ACSM guidelines and the

AHA Life's Simple 7 cardiovascular health (AHA7CVH) scoring system (including five risk factors for CVD, physical inactivity, dyslipidemia, hypertension (HTN), diabetes mellitus, and obesity). According to the principles of FITT, it provides HPs with guidance for exercise prescriptions for patients. Similarly, Sun et al. [71] designed an exercise prescription decision system, which can analyze the patient's complex physical condition combined with the patient's preferences for exercise, providing an effective, safe, and intelligent exercise scheme for patients, especially for people with multiple comorbidities. The program includes (1) an assessment of personal needs, motivations, preferences, and obstacles, (2) effective behavior change paths, and (3) regular follow-up, self-monitoring, and social support. Physitrack (https://www.physitrack.com) is a web-based online exercise prescription tool that collects real-time patient data [72]. The site provides exercise counseling education and manages the patient's entire exercise session. It (1) increases patient participation through exercise videos sent to a patient's smartphone or computer and (2) analyzes the data through real-time monitoring to provide patient-centered exercise healthcare. Both HPs and patients can log on to the website, leading to positive doctor-patient interaction.

2.5 Discussion and Suggestions

With the advent of an aging society and the continuous extension of life expectancy, the number of elderly and chronically ill patients is increasing, while medical resources are increasingly scarce. In order to reduce the burden on hospitals, improve medical efficiency, and realize the transformation of disease management, it is necessary to promote the concept of self-care. Exercise is one of the most important ways of engaging in self-care. Different from traditional medical treatment, exercise medicine is patient-centered. However, this field has not yet fully developed, including the practice of participatory medicine, personalized medical technology, and the promotion of exercise prescriptions. In order to achieve a more intelligent and personalized participatory exercise medicine management, the following suggestions are proposed.

Participatory medicine and personalized medicine need greater engagement with exercise medicine. Participatory medicine is a new medical care model, in which patients are able to discuss their treatment options to a large extent with their HCP. The development of exercise medicine should incorporate the concept of participatory medicine. HCPs need to treat patients as part of the healthcare team, while patients should move from their traditionally passive role to an active role of self-management. In addition, the popularization of the concept of personalized medicine has promoted the development of exercise prescriptions. Exercise prescriptions should be based on the patient's personal characteristics and unique circumstances to formulate different exercise content and exercise goals to improve exercise effects. For example, in addition to the regular basic personal information and disease conditions, HCPs also need to be aware of the patient's exercise preferences and exercise conditions to adapt to their needs so as to maximize the therapeutic effect of the exercise prescription. Besides, biological factors, such as genes, intestinal flora, and family genetic information can also be considered in the exercise prescription decision. Then, a scaled sport medicine database needs to be built. The establishment of a comprehensive and multi-dimensional exercise medicine database is the basis for exercise prescriptions. Therefore, upholding structured data collection standards and relationships between databases is necessary. After that, intelligent decision support systems could be established and improved to help HCPs make exercise prescriptions with sufficient flexibility so as to adapt the treatment to the patients' specific conditions. During the follow-up to the exercise prescription, HCPs should also closely monitor the patient's exercise and recovery status and continue their interactions with the patient. Patients should be allowed to monitor their development and make decisions on their own. Through the interaction with other individuals, the process of acquiring medical knowledge, and the control of disease conditions, the decision-making process and individual behavior could be improved [73].

From the perspective of technology, participatory exercise medicine and personalized medicine are inseparable from the development of technology, which is reflected in the development of eHealth and mHealth. In order to integrate participatory medicine and personalization into individual medical care, the advancement of wearable devices will be an important aspect. The portability of wearable devices needs to be improved (e.g., combining physiological data sets of multiple organ systems simultaneously and monitoring blood metabolism analytes using non-invasive methods such as interstitial fluid [74]) to achieve a better real-time, continuous collection of individual data. The application of the Internet of Things is one of the important challenges in future healthcare. In addition to wearable devices, advanced communication technologies and cloud-based data analysis methods should also be focused on. Current healthcare applications need to merge existing technologies to provide end-to-end solutions to adapt to transmission characteristics in heterogeneous scenarios. Therefore, we need ultra-low latency communication protocols and more efficient computing architectures [75]. In addition, the development of streaming-learning models, semantic networks, and so on, will also be of great concern in the future. Meanwhile, the investment in infrastructure should be increased, and the personalized medicine chain and technology chain at the central and local levels should be integrated to promote greater cooperation [76]. The industry should accelerate the conversion of scientific research results to speed up the development and dissemination of related technologies to promote exercise medicine.

With the widespread use of mobile phones and other communication devices, participatory medical apps will be one of the important means for promoting patients' participation in exercise. More theory-based and evidence-based mobile exercise medicine apps should be developed according to ACSM's guidelines. At the same time, these apps should increase the patient's sense of participation, and even add gamification aspects to attract patients to continue using them, thereby improving patient compliance. There are already methods and criteria for evaluating such apps. Characteristics including design, technology, and the behavioral change model, are considered to be important factors of the quality assessment of PA-related applications. The Mobile App Rating Scale (MARS) is a recognized standard for evaluating the quality of medical applications. Its scoring standards include subjective and objective measures. The objective quality scoring part is divided into four subscales, which are participation, function, aesthetics, and information quality. These standards can be used for reference in the evaluation and improvement of current exercise medicine apps.

In addition, the information-sharing platform for participatory exercise medicine should be promoted. With the development of the Internet, more and more people rely on the Internet to obtain health information. 72% of Internet users state that they have used the Internet for searching for health information online, while HCPs are no longer the only source for patients to obtain information and instructions. At the same time, an increasing number of HCPs are using social media for peer communication and clinical practice, but also for the purpose of informing and helping patients [77]. Social media have also promoted the rise of online health communities. The Internet and social media make it easier for patients to acquire high-quality health information. Patients can share experiences with other patients in the same situation to obtain more suitable healthcare suggestions. By establishing an online information platform or community for patients and connecting them with related medical institutions, both patients and HCPs can participate in the acquisition of disease information and research progress. As one of the most accessible resources, social media have a positive effect on promoting healthy lifestyles and health management. Under this trend, e-patients are on the rise; that is, individuals with the right to be informed can make the decision on their treatment course and actively manage their own healthcare, moving patients away from the passive role they held in traditional medicine. Based on the background of diversified data integration, a participatory exercise medicine interactive platform that supports users in sharing their disease data, exercise statuses, and other personal data should be established.

However, in the process of applying participatory exercise medicine to clinical practice, there are still many difficulties, such as the insufficient PA knowledge of HCPs, low acceptance of exercise prescriptions, time constraints, and insufficient resources, preventing doctors from providing physical activity consultations and prescription exercises for their patients. To provide exercise therapy for patients with complex health conditions, specific knowledge and skills are a prerequisite. HCPs should be educated on the interaction of pathology and exercise physiology, chronic disease management principles, and so on [78]. In addition, HCPs' awareness of exercise medicine should be increased, and a scientific exercise medicine knowledge base and decision support systems could be introduced to help HCPs provide patients with exercise prescriptions. For example, Exercise is Medicine Canada (EIMC) is a national initiative of Canada that promotes the idea that physical activity and exercise assessment, consultation, and prescription should be part of routine healthcare practices. Therefore, the institute organized a nationwide education seminar, which increases the proportion of HCPs providing physical activity consultation and exercise prescriptions [79]. In addition, for HCPs with insufficient PA knowledge, Public Health England and the Faculty of Sport and Exercise Medicine have also launched educational initiatives to help clinicians improve their professional PA knowledge, such as Moving Medicine (https://movingmedicine.ac.uk/) [68], a website that provides HPs with accessible, evidence-based information to help patients in different conditions.

2.6 Conclusion

Patients' participation in their own medical processes will become the mainstream direction in the future, and exercise medicine, as a part of holistic medicine, will have unique advantages in the treatment process, contributing to achieving the low-cost management of chronic diseases and public health. With the development of science and technology, the continuous emergence of wearable devices, and the popularization of mobile devices, combined with advanced algorithms and big data, full coverage of the medical Internet of Things could be achieved so that the entire process of patient recovery can be professionally monitored. Meanwhile, patient feedback will also be submitted to HCPs or related research institutions to improve the interactional aspect of the medical process. The concept of personalized medicine reminds us that exercise medicine should not only be based on routine information collection, but that it should also learn from the ideas of systems medicine, combining personal biological factors, preferences, exercise conditions, etc., to establish a more personalized exercise medicine knowledge base and decision-making system.

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Chapter 3
Integration of Genetic and Phenotyping Data for Sports Medicine

Tong Tang and Bairong Shen

Abstract Sports medicine has had considerable success in different domains, including injury prevention, disease treatment, and patient recovery. By integrating genetic and phenotype data, this research is primarily utilized to promote the development of sports medicine. Recently, studies have begun to focus on the genetic basis of sports phenotypes, and they have discovered genetic variation underlying these traits. The relationships between genetic variation and phenotype changes in sports medicine, as well as genetic models and databases connected to sports medicine, are examined in detail in this chapter. Furthermore, in the future, exercise prescriptions could be based on this comprehensive analysis and contribute to the creation of personalized healthcare, based on individual differences in genotypes and phenotypes of different populations.

Keywords Genotype-phenotype associations · Sports medicine · Genetic models · Exercise therapy · Precision medicine

3.1 Introduction

Experts in the field of sports medicine have been concerned about how to improve people's physical and mental health through suitable exercise [1]. Due to the diversity of physical abilities, recommending a sport to the general public is challenging. Swimming, for example, can reduce joint pain, boost lung capacity, and enhance respiratory function, but swimming is not suitable for all people. For instance, people with heart difficulties are more prone to lose consciousness while swimming, and those with hearing impairments lose their ability to adjust their balance in the water [2].

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Sports medicine has focused on the relationship between disease and exercise but neglected the influence of genetic factors on human health. Recent studies have shown that a large number of single nucleotide polymorphisms (SNPs) are strongly associated with athletic ability [3–6]. Genetic factors have a strong influence on the performance of exercise, such as endurance, strength, explosive power, flexibility, neuromuscular coordination, psychological characteristics, and other phenotypes [7]. Exercise prescription is a main function of sports medicine and can be customized according to the patient's age, sex, health state, physical fitness, cardiovascular disease status, and the function of different forms of sports, as well as subjective and objective circumstances. Sports medicine consultants make plans to help patients to improve their health status, including the recommendation of specific exercises, exercise intensity, exercise time, and the frequency suitable for patients or athletes, and they point out matters needing attention in exercise. Traditional exercise prescriptions only focus on the relationship between phenotype and exercise, while ignoring the fact that genes also affect exercise.

There are many forms of exercise, and endurance and explosive sports are two extremes of sports. Sports medicine tends to identify people most suited to one type or the other by physical traits but neglects using genetic association analyses to screen for their suitability for endurance or explosive sports. Evidence suggests that genetic markers can partly explain individual differences in physical performance characteristics in response to endurance or strength training [8]. For example, a study found 77 genetic markers associated with endurance and 43 genetic markers associated with strength. The benefits of exercise are influenced by genetic differences between individuals as well as physical traits. A great deal of research has examined the impact of sports medicine on population health. In the era of precision medicine, understanding the connection between genetics, phenotypes, and exercise may enable personalized approaches for disease therapy and patient rehabilitation. It is challenging to develop a universal sports medicine program that is beneficial for all populations and individuals. Understanding the differences in genotypes and phenotypes between individuals allows for the effective prescription of diverse exercise programs. Exploring the mechanism of gene-phenotype-exercise interaction may contribute to the prevention of diseases, as well as inhibit and eliminate chronic diseases by increasing the implementation of precision medicine.

3.2 Sports Genes and Sports Phenotypes

3.2.1 Sports Genes

Sports genes refer to genes that can affect people's athletic abilities. Common exercise genes mainly include endurance genes and strength genes, and general endurance genes include angiotensin converting enzyme (*ACE*) [9], adenosine monophosphate deaminase I (*AMPD1*) [10], transcription factor A mitochondrial (*TFAM*) [11], and ATP-sensitive inward rectifier potassium channel 11 (*KCNJ11*), while general strength genes include actinin alpha 3 (*ACTN3*) [12], nitric oxide synthase 3 (*NOS3*) [13], and vitamin D receptor (VDR) [14]. How these endurance and strength-related genes affect exercise ability will be introduced in detail.

The *ACE1* gene was first reported by Montgomery in 1988 [9]. Variation in *ACE* is associated with the elite endurance performance of high-altitude climbers. The encoded ACE protein degrades vasodilator kinins that convert angiotensin I to the vasoconstrictor angiotensin II. Angiotensin II is an effective vasopressor and aldosterone stimulating peptide that controls blood pressure and fluid-electrolyte balance. ACE also inactivates the vasodilator bradykinin [15]. An insertion/deletion (indel) polymorphism of the *ACE* gene has been associated with cardiovascular diseases [16], hemorrhagic stroke [17], and type 1 diabetes [18]. For instance, the ACE includes insertion homozygous (II), deletion homozygous (DD), and insertion/deletion heterozygous (I/D). The ACE DD phenotype is a risk factor for acute myocardial infarction [19], and exercise prescriptions for people with this genotype should try to avoid exercises related to endurance.

AMDP1 is an enzyme that catalyzes the deamination of adenosine monophosphate (AMP) to inosine monophosphate (IMP) in skeletal muscle and is involved in the purine nucleotide cycle [20]. Rico-Sanz discovered that those with the AMPD1 XX genotype had lower sedentary exercise capacity and cardiorespiratory response [21]. In a study by Thomaes et al., 935 individuals with coronary artery disease who responded to endurance training had a relative rise in peak VO_2 after 3 months of aerobic exercise. The exercise effect of AMPD1 X allele carriers, on the other hand, was much lower than those who did not carry the X allele [22]. In summary, people with the AMPD1 XX allele should limit or avoid endurance exercise.

Mitochondrial Transcription factor A (TFAM) encodes a key transcription factor for mitochondrial DNA replication and repair [23]. The *TFAM* Ser2Thr polymorphism (rs1937_G/C) is closely related to endurance sports. After comparing 588 Russian endurance athletes with 1113 controls in the general population, Ahmetov et al. found that athletes have a higher frequency of the *TFAM* 12Thr polymorphisms [24]. Therefore, the *TFAM* 12Thr polymorphism of the *TFAM* gene is also linked to the physical performance of athletes.

The *KCNJ11* gene encodes a component of the ATP-sensitive potassium (K-ATP) channel. Two independent case-control studies showed that *KCNJ11* Glu23 is significantly more frequent in endurance athletes than in controls in Caucasians. Furthermore, *KCNJ11* Glu23 was more frequent in endurance athletes in a Spanish cohort [25].

In addition to these genes closely related to endurance sports, sports genes are also closely linked to strength. The *ACTN3* gene encodes a member of the alpha-actin binding protein that is only expressed in type-II muscle fibers [26]. The *ACTN3* RR genotype (the Arg577 allele) is over-represented among strength athletes or sprinters compared to the *ACTN3* XX genotype [12]. Studies have shown a highly significant correlation between *ACTN3* genotype and sports performance. The frequency of the Arg577 allele in sprinters was significantly higher than that of the control group. This indicates that the presence of α-actin-3 has a beneficial effect on

Table 3.1 Exercise-related gene polymorphisms and suitable exercise

Gene	Sports type	Exercise-associated polymorphisms
ACE	Endurance Sports	DD
AMPD1	Endurance Sports	XX
TFAM	Endurance Sports	Ser2Thr
KCNJ11	Endurance Sports	Glu23
ACTN3	Strength Sports	XX
NOS3	Strength Sports	Glu298
VDR	Strength Sports	Fokl

the function of skeletal muscle to produce powerful contraction at high speeds, thereby improving sprint performance.

NOS3 is involved in the modulation of oxygen consumption in muscle. Sessa et al. showed that the Glu298 allele in 28 Italian power athletes has a higher mutation frequency than the control group. Analysis of performance-associated genetic polymorphisms helps to rationally plan the strength training of athletes and achieve a personalized exercise program [27].

Vitamin D maintains sufficient serum calcium and phosphate concentrations to prevent convulsion. A study showed that vitamin D supplementation has a positive effect on athletes' lower limb muscle strength. Different muscle groups and functions may respond differently to vitamin D supplementation [28]. Diogenes et al. evaluated the influence of polymorphisms in the *VDR* gene, and they found that the *VDR* Fokl genotype was greatly linked to strength-related exercise. Carriers of that genotype may be more amenable to strength-related exercises [29]. Genes related to endurance and strength sports are listed in Table 3.1.

3.2.2 Sports Phenotypes

The observable traits of individuals, like height, weight, and hair color, are known as phenotypes. An organism's phenotype is determined by two main variables: the expression of the organism's genetic makeup and the influence of environmental conditions. These two elements interact to influence the phenotype [30]. Physical performance qualities associated with exercise, such as strength, endurance, flexibility, and muscle coordination, as well as other phenotypes, are known as sports phenotypes.

The essential exercise phenotype is physical fitness. There are two types of physical fitness: competitive physical fitness and healthy physical fitness. Competitive physical fitness refers to the physical fitness required by athletes to achieve good athletic performance in competitive tournaments. Healthy physical fitness is the physical fitness required to promote health, prevent disease, and increase daily work efficiency, which includes cardiopulmonary endurance, muscle endurance, flexibility, and an appropriate body fat percentage [31]. Physical fitness also refers to the status of one's physical health. The most fundamental stage of physical fitness is adaptation to basic activities and productive labor. Adapting to sports training and competition is a more advanced adaptation to physical fitness [32].

Sports phenotypes mainly include endurance, strength, and flexibility. Endurance is the body's ability to perform continuous muscle work for a long time without fatigue. According to the physiological systems of the human body, endurance can be divided into muscle endurance and cardiovascular endurance [33]. Muscle endurance is also called strength endurance, or the ability to contract the muscles continuously without using maximum force. Cardiovascular endurance is the ability of the heart, blood vessels, and lungs to supply oxygen to the working muscles and is divided into aerobic endurance and anaerobic endurance [34]. Regular endurance training can strengthen the regulation of muscles, organs, heart and lungs, blood, the immune system, and metabolism.

Strength is also known as muscular strength and is the ability to exert force by the muscles. Muscular strength refers to the amount of force you can exert or the weight you can lift [35]. During strength training, metabolism is mostly based on the glycolytic system, which mainly consumes glycogen. The consumption of sugar is fast and cannot be replenished and fully recovered in time, so the body will experience fatigue because of the lack of this essential energy source [36]. It is necessary to rest and replenish energy to ensure strength training quality and strength training results.

Flexibility refers to the inherent characteristics of body tissues, which determine the maximum range of joint motion without causing injury [37]. The quality of flexibility has a direct impact on sports performance [38]. An increase in flexibility can help reduce the possibility of sports injuries. Meanwhile, different sports have different requirements for flexibility to avoid injuries. For instance, swimming athletes focus on the flexibility of the shoulder and ankle joints, while track and field [39] athletes and football players focus on the range of motion of the hip and ankle joints [40]. Additionally, different sports have various requirements for flexibility. Basketball, volleyball, and table tennis do not have high requirements for flexibility, while gymnastics, diving, and martial arts have strict requirements for flexibility. Doing flexibility exercises is especially crucial for activities that involve explosive force, as they can help prevent sports injuries [41].

3.3 Sports Medicine and Disease Prevention

3.3.1 Sports Medicine

Sports medicine is a multidisciplinary field that combines sports and medicine. It investigates medical issues in sports, employs medical technology and knowledge to supervise and guide sports training, prevents injuries, and conducts medical and preventative research to achieve the goals of improving people's physiques, protecting athletes' health, and boosting sports performance [42]. Sports medicine consists of sports injury recovery and medical sports. Sports injury recovery focuses on injury prevention and treatment, as well as post-injury rehabilitation exercise. Medical sports are a type of sports therapy in which diverse sports methods are used to prevent and treat injuries, particularly prevalent diseases [43].

Sports medicine plays an important role in preventing diseases. For instance, the mechanism of obesity is complicated, but endocrine disorders are the main underlying etiology. Regular exercise can improve the body's metabolism, regulate the function of the neuroendocrine system, and maintain better coordination and steady-state [44]. Exercise can essentially eliminate the pathways that cause fat storage and control weight when combined with food regulation. Exercise can widen the blood vessels, enhance capillary density, improve blood circulation and metabolism, lower blood pressure, and reduce total peripheral resistance [45]. Simultaneously, during exercise, blood flow increases, minimizing the formation of thrombus [46].

3.3.2 Scientific Sports and Disease Prevention

Scientific and appropriate exercise is critical for improving physical fitness, alleviating stress, preventing diseases, and enhancing patient recovery. Providing appropriate exercise plans for diverse individuals is one of the aims of sports medicine. Different people might choose appropriate sports based on their condition when it comes to sports choices. Mental labor should exercise outside and choose activities such as walking, jogging, and mountain climbing. Overweight persons could choose aerobic endurance exercises such as long-distance running, swimming, or cycling. The elderly should avoid high-intensity exercise. Meanwhile, low-intensity activities such as walking, running, and Tai Chi are recommended [47–49].

Aside from the type of exercise, the amount of time spent training is the most concerning issue among athletes. Athletes can achieve higher exercise results in a reasonable time. Excessive exercise is severely damaging to both physical and mental health. On the contrary, the exercise goals will not be met if the activity is insufficient [50]. Most healthy adults need at least 150 min per week of moderate-intensity aerobic activity, 75 min per week of vigorous aerobic exercise, or a combination of moderate-intensity and strenuous exercise. It is beneficial not just to improve muscle performance but also to maintain physical strength [51]. Every day, older individuals should engage in some form of physical activity that suits them to increase their strength, balance, and flexibility. It is advised that seniors engage in at least 150 min of moderate-intensity training every week [52].

Disease sufferers can engage in scientific exercise to prevent or mitigate the effects of the disease. Aerobic exercises with low intensity and gradual movements, such as Tai Chi, are appropriate for hypertensive patients [53, 54]. Lower limb strength exercises can enhance the pressure of the blood returning to the heart in patients with coronary heart disease [55, 56]. Swimming is the most helpful activity for people with asthma, helps to keep the respiratory tract wet, and reduces the burden on the respiratory tract [57, 58].

3.3.3 Personalized Prescription for Exercise Based on Genetics

Exercise prescription is a particular schedule of health-related activities, usually developed for clients or patients by fitness professionals or rehabilitation experts. Customers or patients often have specific and distinct needs and interests. Therefore, exercise prescriptions typically focus on motivation, personal abilities, and hobbies, making the person's goals more likely to be achieved [59–62].

The primary focus of genetically-related exercise prescription is how genes affect the response to exercise training. Personalized fitness activities can improve patients' exercise prescriptions by assessing different genetic data [63]. Furthermore, risk variables associated with sports participation can be identified, allowing participants to prevent and avoid these risk factors.

Patients and the general public can benefit from scientific exercise recommendations that help them achieve better fitness and rehabilitative benefits in less time. Individuals with different genotypes, on the other hand, will respond differently to identical exercise prescriptions. For instance, the I/D polymorphism of the *ACE* gene has a significant influence on exercise intensity. The *ACE* I/I genotype is associated with endurance performance and is responsible for the body's aerobic endurance. It can influence endurance quality by modulating the body's cardiopulmonary function. Due to variations in exercise genes, people with the I/I genotype may benefit more from endurance training in exercise prescriptions. Endurance activities can assist them in improving their health more efficiently.

3.4 Sports Genetic Models and Clinical Databases

3.4.1 Sports Genetic Models

Researchers often utilize the rat as a model animal to investigate the relationship between sports and genetics and have developed a genetically-related rat exercise model [64–67]. Differences exist between rats and humans, and animal motion genetic models are not generally used in humans. As more exercise-related genes have been identified and confirmed, researchers have begun to construct human exercise genetic models to evaluate exercise performance based on genetic variation.

Polymorphisms in 23 endurance exercise-related genes were used to examine the distribution of a polygenic score in the population for endurance exercise. They assigned ratings to specific polymorphisms for each genotype. The identified variant is usually biallelic and can result in one of three genotypes. Genotypes linked to the endurance trait receive a score of two, heterozygotes a score of one, and other homozygotes a score of zero [68]. The summed effects of all 23 polymorphisms linked with endurance were estimated. The results of all 23 genotypes for people were then entered into a model. Finally, the entire score was converted to a 0–100 scale as the total genotype score (TGS). A TGS of 100 suggests a "perfect" polygenic score for endurance, while a TGS of 0 indicates the "worst" possible polygenic score for endurance [68]. The TGS formula was calculated as:

$$\mathrm{TGS} = (100/46) \times (\mathrm{GS1} + \mathrm{GS2} + \ldots + \mathrm{GS23})$$

Ruiz et al. used Williams and Folland's methodology to look for polymorphisms in seven endurance genes (*ACE* I/D, *ACTN3* Arg577Ter, *AMPD1* Gln12Ter, *CKMM* 1170 bp/985 + 185 bp, *HFE* His63Asp, *GDF-8* Lys153Arg, and *PPARGC1A* Gly482Ser). The average TGS of athletes was higher than that of the control group, indicating that athletes have a higher polygenic load of exercise-associated genetic variants. The study also revealed that three Spanish endurance athletes had the highest scores for up to six genes, indicating that this approach can aid in the identification of people who have the potential to become talented endurance athletes [69].

Massidda and colleagues attempted to refine and optimize Williams and Folland's model to investigate the influence of genes related to acceleration and jumping in sports performed by Italian male football players. The total genotype score was calculated by modeling polymorphisms in *ACTN-3*, *ACE*, *BDKRB2*, *VDR*-FokI, *VDR*-ApaI, and *VDR*-BsmI. The total weighted genotype score (TWGS) was then produced by assigning a weight to each polymorphism to study the association between individual differences in sports performance variables and genotypes. Athletes' genetic variants can assist sports trainers in developing personalized training plans and doing specialized training to improve their activity efficiency [70].

3.4.2 Sports-Related Databases

In 2014, the United Kingdom's National Institute for Health and Care Excellence collected exercise-related data for the future development of exercise referral programs. The National ReferAll Database: An Open Dataset of Exercise Referral Schemes Across the United Kingdom contains information on 24,086 people from 19 ERS. Physical activity, blood pressure, body mass index (BMI), resting heart rate, the short Warwick-Edinburgh mental well-being scale score, the exercise self-efficacy scale score, the World Health Organization-five well-being index score, and the Health-related Quality of Life score are all indications of pre-recommendation and post-recommendation data. The database can contribute to the ongoing assessment of ERS, as well as scientific studies and evidence generation linked to healthcare procedures [71].

The Fitness Registry and the Importance of Exercise National Database is a cardiorespiratory fitness database based in the United States. It comprises test data from different geographic areas and includes baseline information such as age, sex, height and weight (BMI), cardiovascular disease risk factors, comorbidities/diagnoses, resting heart rate and blood pressure, geographic location, race/ethnicity, and socioeconomic level. VO_2 at ventilatory threshold allows for the characterization of long-term aerobic endurance related to functional activities. Peak at respiratory exchange ratio is the confirmation of sufficient exercise intensity during cardiopulmonary exercise, measured by heart rate and blood pressure response during exercise and recovery. These data may be utilized to improve patients' cardiorespiratory health and physical condition. Furthermore, it could help the development of more appropriate exercise regimens [72].

3.5 Genotype-Phenotype-Sports Interactions

Genotype refers to the two alleles inherited from a genetic locus, while phenotype refers to any observable physical feature from the molecular to the whole-organism scale [73]. The relationship between genotype and phenotype is often not clear in biology. The advancement of next-generation sequencing technology and quantitative trait locus (QTL) analysis made it possible to analyze the particular phenotype of each genetic variation [74, 75]. For instance, muscles are composed of slow-twitch and fast-twitch fibers. Slow-twitch fibers are related to endurance, and fast-twitch fibers determine explosive power. As an example, the *ACTN3* RR genotype allows the body to produce a protein that exists in fast-twitch fibers [26]. However, a growing number of studies have revealed that phenotypic differences are also caused by factors other than genetics such as genetic epigenetics and environmental factors [76].

Phenotype is not completely determined by genotype. Phenotypic plasticity refers to phenotypic changes in an organism's behavior, morphology, and physiology that result from environment and lifestyle. These variations include appearance, physiology, behavior, and other environmental variables [77]. When the human body is engaged in physical work or sports, the sports phenotype refers to the various functional capabilities of different organ systems. Sports phenotypes include speed, strength, endurance, agility, and flexibility, among others [7, 78].

Eating habits as a lifestyle factor, as well as the geographical environment, have a significant impact on sports phenotype [79, 80]. The intensity of sports events and physical conditions impact athletes' nutritional requirements. Athletes can increase their physical fitness by following scientifically validated and appropriate eating habits [81]. One of the most important aspects affecting an athlete's athletic abilities is the quality of protein required. Protein is the major component of muscles, and it is essential for sustaining regular muscular movement [82]. Maintaining basal metabolic rate and energy balance requires sufficient muscle mass and quantity. Exercise-induced anemia can be caused by a lack of protein in the diet [83]. A well-balanced protein-rich diet is essential for increasing motor function [84]. Vitamins are essential elements for survival and metabolic regulation. There is no need to supplement with vitamins if the supply of fruits and vegetables is sufficient. In general, endurance training requires a high intake of vitamin B1, vitamin C, and other vitamins [85]. The secretion of growth hormones and other growth factors in the body

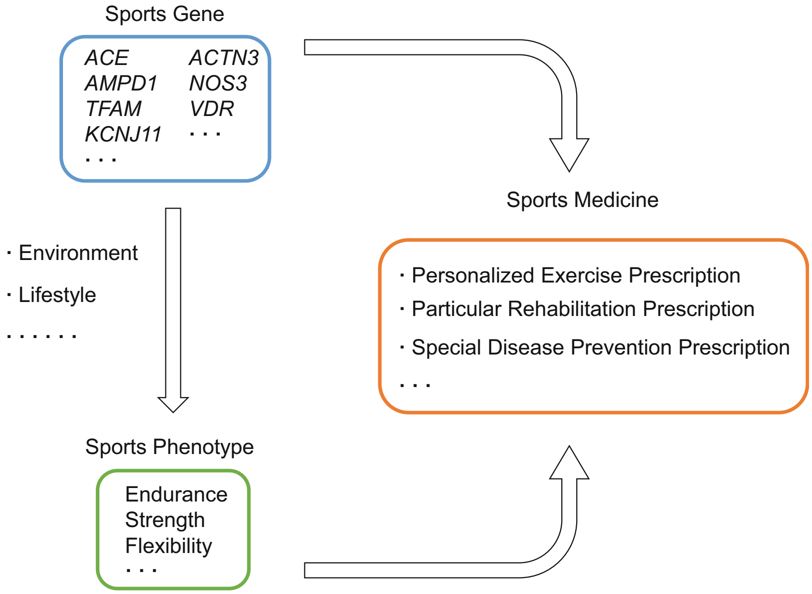

Fig. 3.1 A diagram of how genetics and phenotype can guide sports medicine

increases when athletes conduct weight-bearing activities. Appropriate levels of various amino acids in the muscles and blood are necessary to meet the needs of muscle growth. Strength athletes need 1.4–1.8 g of protein per kilogram of body weight per day to achieve the amino acid content essential for muscle building [86].

Environmental factors, in addition to eating habits, influence exercise phenotypes. Low air pressure at high altitudes impairs the body's ability to absorb oxygen and transmit it to the lungs as well as blood circulation [87]. Hemoglobin is responsible for binding oxygen, and the oxygen-carrying capacity of the blood is affected by the number of red blood cells in the blood, which carry hemoglobin. Oxygen is then transferred to all regions of the body via the blood [88]. The body rapidly adapts, with greater oxygenation after 3 weeks of high-altitude training. The red blood cells' ability to carry oxygen and the body's ability to transport oxygen remain increased when returning to low-altitude regions [89]. As shown in Fig. 3.1, sports medicine can be guided through genetics and phenotype.

Precision medicine considers a patient's genetic, molecular, and cellular analyses, as well as clinical symptoms and indicators, to find the most appropriate and effective drug and create a scientific-based medical plan [90]. Precision medicine aims to use the human genome and other similar technologies to investigate the molecular biological foundation of diseases, integrate clinical electronic medical records, and personalize disease prevention and therapy to each patient's unique characteristics. Sports medicine pays more attention to the scientific guidance of athletes, including effective treatment and rehabilitation of bone, joint, and surrounding tissue injuries caused by sports [91, 92].

The future development of precision medicine in the sports field is combining sports genotypes and phenotypes in sports medicine. The endothelial PAS domain-containing protein 1 (*EPAS1*) gene plays a crucial role in the hypoxia-induced regulatory pathway, which is one reason why altitude training can improve endurance athletes' performance [93–95]. Due to the low oxygen content in the air, the oxygen content in the blood decreases in high-altitude areas. The *EPAS1* gene is then activated, resulting in more red blood cells and increased oxygen transport by hemoglobin [95], meeting the needs of the body's many tissues and organs to maintain physiological activity.

Furthermore, the Egl nine homolog 1 (*EGLN1*) and Heme oxygenase 2 (*HMOX2*) genes can reduce hemoglobin in the blood and maintain a relatively low hemoglobin level at high altitude conditions, allowing humans to adapt to low oxygen environments and improve endurance exercise abilities [96–99]. On the other hand, altitude training is not suited to everyone. Some individuals with specific genotypes have a difficult time adjusting to high altitudes. Athletes who lack or have mutations in the *EPAS1*, *EGLN1*, or *HMOX2* genes are unable to adapt to the high altitude environment. High altitude environmental variables, which generate additional stress and boost cortisol levels, influence human exercise phenotypes [100]. Muscle performance suffers as a result of decreased renal hormone output. If an athlete's muscular capacity living in the plateau area has diminished over time, this indicates that the athlete is not fit for altitude training [101]. In summary, it is feasible to create individualized exercise prescriptions for athletes by combining information on their genotype and phenotype.

Patients with diseases can aid the body's recovery to health by engaging in scientific or targeted exercises. Sports medicine can help patients remain stable or as close to normal as possible when they are ill or have injuries. Patients with the same illness, on the other hand, do not respond to the same sports rehabilitation program. Acute myocardial infarction, for example, is commonly treated with moderate-intensity aerobic activity such as walking, running, or yoga. However, the *ACE* DD genotype is linked to exercise risk polymorphisms as well as acute myocardial infarction [19]. For these people, rehabilitation methods based on endurance training are ineffective. Resistance exercises should be advised to these patients to assist their recovery [102, 103]. Simultaneously, the patient's sports phenotype is a significant factor in the evaluation of rehabilitation in developing sports rehabilitation programs. People with shortness of breath, chest pain, a heart rate of more than 80 beats per minute, and severe arrhythmia must stop training. Sports medicine, which integrates genotypes and phenotypes to create individualized exercise prescriptions, is a discipline of rehabilitative medicine [104, 105].

3.6 Conclusion

Currently, there is evidence that an athlete's genotype influences their sports phenotype. Using this genetic information to assist athletes in selecting the appropriate professional sports activities and providing the optimum training conditions would undoubtedly release their innate genetic potential. Simultaneously, this genetic information can aid ill patients in developing individualized disease rehabilitation exercise regimens, accelerating their recovery time, and avoiding subsequent injuries caused by ineffective exercise programs. In addition, they can also construct more acceptable rehabilitative exercise plans. Sports genetic features and phenotypes play an essential part in the advancement of sports medicine. They can encourage the discovery of exceptional athletes, the individualization of illness care, and the dawn of the precision medicine era in sports medicine.

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Chapter 4
Microbiota, Sports and Exercise Medicine

Ke Shen and Bairong Shen

Abstract The impact of the gut microbiota and physical activity (PA) on human health is well documented. Extensive research has indicated that the microbiota and PA work interactively to improve human health. However, deciphering a pathway to personal health through the vast ocean of biomedical multi-omics data is not straightforward. Therefore, in this chapter, we summarize evidence and underlying biological mechanisms shared between the microbiota and PA, and review data resources and bioinformatics approaches exploring the relationship of PA and the microbiome on human health. Furthermore, we analyze the impact of PA and the human microbiome on disease prevention, prediction, treatment, and health management within the context of personalized medicine.

Keywords Microbiota · Exercise · Disease · Database · Bioinformatics methods

4.1 Introduction

Physical exercise is an effective way to prevent disease, improve disease prognoses, and augment disease therapy [1]. Moderate physical activity (PA) enhances body vitality, accelerates metabolism, and promotes personal health. In contrast, physical inactivity is a major cause of up to 35 diseases [2]. Booth et al. summarized the repercussions from a lack of exercise, and identified accelerated cardiovascular loss, reduced age of chronic disease onset, a shortened duration of health, and an accelerated risk of death [3]. A global investigation on the impact of PA on non-infectious diseases reported that PA increased the global life expectancy by 0.68 years [4]. With a global escalation in age expectancy, inadequate PA levels could lead to age-related functional decline; therefore, it is imperative to expand PA awareness for all [5]. However, unhealthy exercise, excessive exercising or the impertinence of sports may also lead to somatic damage and even lethiferous.

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According to the Registre des Accidents Cardiaques lors des courses d' Endurance à Paris (RACE PARIS) registry, 18 sudden cardiac arrest cases were recorded during marathons in the Paris area between 2006 and 2016 [6]. Therefore, research on the customization of personalized sports in terms of type and quantity are necessary.

In the human body, the ratio of bacteria to human cells is nearly 1:1 [7], with microbial genomes having more than 10 times the number of human genes [8]. Microorganisms are widely distributed in the human gut, reproductive tract, oral and upper respiratory tract, and skin [9–11], however, more than 70% are gut based [12]. As the reported 'second human genome', the microbiota is highly significant to our bodies at all life stages. Once born, gut microbes colonize the gastrointestinal tract, promote the development and maturation of our immune systems, and endure a lifelong relationship with the host [13]. Humans cannot synthesize most vitamins; they are accumulated via food intake and biosynthesis via the gut-microbiota, e.g., folate and riboflavin are produced by *Bifidobacteria* [14]. Gastrointestinal microbiota are also involved in host metabolism and circadian rhythms [15]. Intestinal bacteria also convert liver-produced primary bile acids (BAs) to secondary BAs, which are involved in natural killer (NK) cell-mediated anti-tumor immune mechanisms [16, 17]. However, an unhealthy microbiota is hazardous to our health. Inflammatory bowel disease (IBD) is driven by symbiotic bacterial dysbiosis [18]. Some *Escherichia coli* strains produce the toxin, colibactin, which is a key driver of colorectal cancer in humans [19]. Since the National Institutes of Health Human Microbiome Project (HMP) was launched in 2007, the co-development of sequencing technologies and computational methods have provided an in-depth understanding of relationships between microorganisms, human health, and underlying biological mechanisms [20, 21]. In general, the microbiome is a highly dynamic, complex, and heterogeneous ecosystem that varies between humans. However, and more importantly, personalized microbial health and the clinical application of the microbiota to host health warrant increased investigations.

The human microbiota and PA have synergistic roles in promoting human health. As a secretory organ of the human body, the microbiota controls hypothalamus-pituitary-adrenal (HPA) axes which affect the competitive ability and health levels of athletes, both physically and psychologically [22]. Furthermore, an evidence-based study recently confirmed that PA modulated the structure and function of the microbiota, promoted microbial health, and a fit body [23]. A recent study reported that the relative abundance of *Veillonella* increased in runners after a marathon, and that these bacteria metabolized lactic acid produced during exercise, to produce short chain fatty acids (SCFAs) which provided energy and reduced discomfort [24]. However, even in the era of big data, there are no comprehensive data supports and reliable models to apply microbiome knowledge to PA and personal health.

In this chapter, we summarize evidence outlining the interrelationship between the microbiota and PA. We also propose a research paradigm where the microbiome and PA contribute to health, based on big data and computational methods. Finally, we put forward ideas for the application of microorganisms and exercise health in clinical settings. An overview of this study is shown (Fig. 4.1).

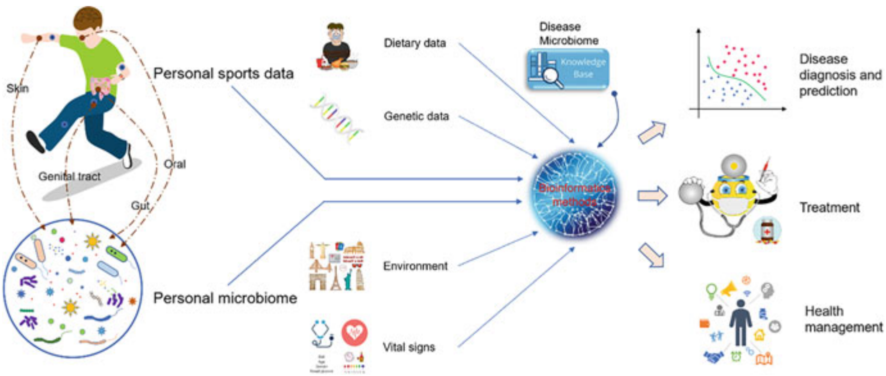

Fig. 4.1 Overview of how sports and the microbiota contribute to human health

4.2 The Microbiome and PA Interactions

4.2.1 The Human Microbiome

The human microbiome represents a collection of genes and genomes of all microbiota in the human body [25]. Since the development of HMP and the Metagenomics of the Human Intestinal Tract (METAHIT) project [26], the study of human microorganisms has been extensive. Studies outlining correlations between the gut, oral, urogenital, and skin microbiomes have been considerable. In some intestinal diseases such as IBD [27], oral diseases such as oral squamous cell carcinoma (OSCC) [8], metabolic diseases such as diabetes mellitus [28, 29], some complex cancers such as colorectal [19], liver [17], breast [30], and many other diseases [31], the microbiota has been implicated in the occurrence, development, treatment, and drug action of these diseases. From birth to death, microbes are involved in metabolism, immunity, diet, absorption, nutrient production, and many more health aspects [32–35]. To fully comprehend this complexity, computational biology, or bioinformatics, provides us with practical methods and tools to gain information on the human microbiome and its hosts, humans.

4.2.2 Sports and Exercise Improves Gut Microbiota Health

Differences in microbial community composition and structures exist in individuals with different athletic abilities. These differences are reflected in microbial community diversities and particularly functional microbial species. Clarke et al. analyzed the intestinal microbiota from professional sportsmen and sedentary individuals, and found that microbial diversity in athletes was higher than sedentary individuals; 22 distinct phyla were mainly related to creatine kinase and protein consumption [36], and fungal diversity was higher in those who exercised more [37]. Gut microbiota analyses of females who regularly exercised indicated they had more bacterial species that promoted health, including *Akkermansia Muciniphila*, *Roseburia hominis,* and *Prausnitzii Faecalibacterium* [38]. Exercise not only improved an individual's microbial health, but also microbial changes induced by exercising pregnant mothers during pregnancy induced microbial changes in their infants [39]. However, more studies are required to confirm the pathways between exercise and change of microbiota composition.

Associations between the human microbiota and PA are listed (Table 4.1). The effects of improving intestinal microbiota through exercise are obvious; after 6 weeks of endurance exercise, the microbiota of a previously thin person considerably increased butyrate levels (a type of SCFA). Once an individual returns to his/her everyday lifestyle, the gut microbiota rapidly enters a washout period [51]. Endurance exercise leads to increased *Akkermansia* levels and decreased *Proteobacteria* levels in over-weight females [47]. Long-term exercise has a significant impact on shaping the gut microbiota, while short-term exercise also leads to changes in microbes. Two hours after a marathon, runners finish their workouts, *Veillonella* gut levels were increased 140-fold [44]. Long-term exercise not only increased microbial diversity, but also enhanced human metabolic health and improved microbial community health [43].

PA is a dynamic process that shapes gut microbial communities. Regular exercise over a long period time renders the gut microbiome a stable and healthy system. Equally, short-term exercise exerts significant changes in some species over a short period, but for a long-term, stable lifestyle, intestinal microorganism will also have a corresponding stable state.

4.2.3 Microbiome Mechanisms and Exercise

Figure 4.2 shows how the gut microbiota interacts with physical activity through its connections to the human brain, muscles, bones and joints. The gut microbiota is one of factor that contributes to age-related muscle decline [52]. *Lactobacillus rhamnosus GG* increased *Clostridia* abundance in the intestine, and produced more butyric acid, which in turn increased regulatory T cells (Tregs) in the gut and bone marrow of mice, thereby activating signaling pathways associated with osteoblasts, to ultimately stimulate bone formation [53]. In childhood, the gut microbe, *Akkermansia muciniphila* mediate anti-osteoporosis effects, which increased bone strength [54]. *Bifidobacterium longum* OLP-01 isolated from an Olympic athlete was administered to mice who then showed a higher endurance and grip strength, with improved fatigue-related indicators [55]. In individuals who have exercised regularly for a long time, withdrawal from exercise led to increased negative emotions and feelings of fatigue [56]. Studies reported a two-way interaction between intestinal microbiota and the mitochondria. Intestinal microbiota regulated mitochondria by interacting with *PGC-1α*, *SIRT1*, and *AMPK*, and provided energy for mitochondria via metabolite production. In turn, genetic variations in mitochondria were also

Table 4.1 The impact of different sport on the microbiota

Subjects	Methods and participants	Microbiota
Cyclists [40]	11 females, 22 males, aged 19–49; 22 professional levels, 11 amateurs	High *Prevotella and* high *Bacteroides* abundance; A mix of *Bacteroides*, *Prevotella*, *Eubacterium*, *Ruminococcus*, and *Akkermansia*; *Methanobrevibacter smithii* transcripts increased in professional cyclists
Endurance exercise [41]	33 elderly Japanese men, 5 weeks	*Clostridium difficile* decreased, *Oscillospira* increased
Rugby players [42]	40 male elite professional rugby players, mean age 29; 46 controls, mean age 29	Amino acid, antibiotic biosynthesis and carbohydrate metabolism pathways increased. Microbes increased short-chain fatty acid (SCFA) levels; acetate, propionate, and butyrate
Rugby players [36]	40 male elite professional rugby players, mean age 29; 46 controls, mean age 29	Higher diversity, 22 distinct phyla correlated with protein consumption and creatine kinase
Rowers [43]	Four well-trained male rowers, 33 days, 5000 km transoceanic rowing race	Microbial diversity increased; butyrate-producing species increased; improved metabolic health and insulin sensitivity
Marathon runners [44]	A 32-year-old world class ultra-marathon runner, 2 h post-race	*Veillonella* (+14.229%) and *streptococcus* (+438%) increased, *Alloprevotella* (−79%) and *Subdolingranulum* (−50%) decreased
Bodybuilders, and distance runners [45]	15 bodybuilders of average age 25 years, 15 distance runners average 20 years and 15 healthy men controls	Athlete type associated with an abundance of gut microbiota; *Faecalibacterium*, *Sutterella*, *clostridium*, *Haemophilus*, and *Eisenbergiella* were highest in bodybuilders; *Bifidobacterium adolescentis* group, *Bifidobacterium longum* group, *lactobacillus sakei* group and *Blautia wexlerae*, *Eubacterium hallii* were lowest in bodybuilders, but highest in controls
Martial arts athletes [46]	12 higher-level athletes and 16 lower-level athletes	*Parabacteroides*, *Phascolarctobacterium*, *Oscillibacter* and *Bilophila* were enriched in higher-level athletes. *Megasphaera* was abundant in lower-level athletes
Endurance exercise [47]	19 over-weight women in a 6-week endurance exercise regime	*Akkermansia* increased and *Proteobacteria* decreased

(continued)

Table 4.1 (continued)

Subjects	Methods and participants	Microbiota
Polish endurance athletes [48]	14 marathon runners, 11 cross-country skiers, and 46 sedentary healthy controls	Lower *Bacteroidetes* and higher abundance of *Prevotella* in athletes; more diverse in skiers compared to controls
Irish Olympic athletes [49]	37 international level athletes, 14 female, 23 male	Composition and function of gut microbiome different in sports groups
Rowers [50]	19 females classified as adult elite athletes, youth elite athletes, and youth non-elite athletes	Diversities in elite athletes were higher than youth non-elite athletes. Microbiome taxonomy and functions were different across groups

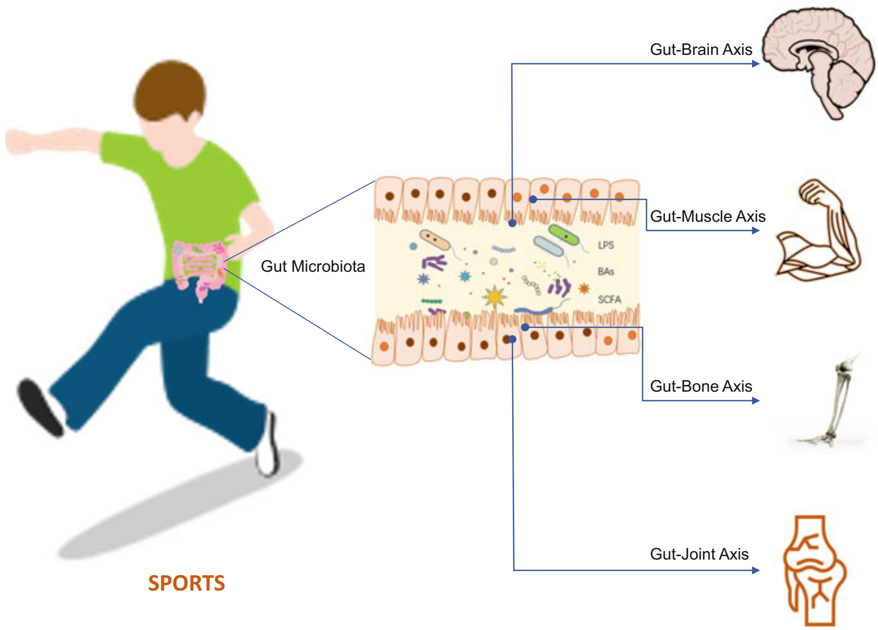

Fig. 4.2 Microbiota and PA interactions

shown to affect the gut microbiota [57]. Metabolites, immune regulation, and the nervous system are the main modes of action of the gut-brain axis [58]. *Lactobacillus casei* inhibited joint deterioration and bone destruction in arthritic mice, while upregulating probiotic abundance, and downregulating pro-inflammatory cytokine expression [59]. Santisteban et al. proposed the brain-gut-bone marrow axis where the gut microbiota connected with the brain and bone marrow via the nervous system [60]. *Pseudomonas* species in the gut was shown to rely on caffeine as its sole source of carbon and nitrogen [61]. Appropriate PA has positive effects on health, PA at the college level can change the composition of oral microbiota, reduce anxiety, and enhance oral immunity [62].

4.3 Disease Studies

4.3.1 Alzheimer's Disease

Alzheimer's disease (AD) is a common degenerative disease of old age, with no known cure [63]. The condition seriously affects an individual's ability to master language, memory, and daily activities. In 2020, an estimated 5.8 million Americans aged 65 years or older reportedly had AD [64], and 121,499 deaths were associated with AD in 2019 [65]. Medical management and maintenance improved the quality of life of patients with AD, but was associated with high costs of medical treatment and care. Such medical costs impose a heavy burden on patients and families.

PA may help reduce the risk of AD [66]. In their literature review, Piotr et al. reported that PA and exercise could be used to prevent and alleviate AD [67]. Interestingly, these researchers reported that most patients with AD had a distinct gut microbiome, but similar populations were not identified in control groups [68]. The gut microbiota also regulates mood and maintains the health of the brain via the microbiota-gut-brain axis, probiotics may improve cognition in AD patients [69]. Furthermore, mice with AD who received oral probiotics displayed delayed disease progression. Moreover, researchers also identified gut microbiota impaired glucose metabolism in AD patients [70].

In addition, the synergism of PA and the microbiome may be effective in preventing and treating AD. Thus, the muscle-gut-brain axis is worthy of future research [71]. However, going forward, more experimental models are required to prove axis regulatory mechanisms, and similarly, more artificial intelligence (AI) models should be identified that can cope with multi-dimensional and complex data.

4.3.2 Diabetes

China has the highest number of diabetics in the world, it is estimated the country has 113.9 million adults with diabetes, accounting for approximately a quarter of the world's diabetic population. Also, more than 95% of these patients have type 2 diabetes mellitus (T2DM) [72].

Genetic variations, unhealthy diets, and a lack of exercise have contributed to the development and progression of T2DM. A disequilibrium of gut microbiota can also lead to T2DM, which could be the root cause of disease in some instances [73]. A cohort study reported that long-term antibiotic-use destroyed healthy gastrointestinal microbiota, and increased the risk of T2DM in women [74]. PA is not only effective in preventing T2DM, but also helpful for T2DM treatment. In a cohort of more than 3000 individuals over an average of 12 years, PA reduced approximately 12% of the T2DM incidence [75].

Due to genetic, lifestyle, microbiota, and physiological complexity in T2DM, more efficient computational models and methods must be developed to prevent and manage the disease. Paola et al. developed a machine learning model which used vital signs, PA, lifestyles, and other data to predict the risk of T2DM [76].

4.3.3 Cardiovascular Disease

Globally, cardiovascular disease (CVD) is the leading cause of death [77]. CVD complexity is not only reflected in its genetic diversity, but is also related to the intestinal microbiota, everyday environments, and lifestyles [78–81].

PA, the immune system, and the microbiome have a complex relationship with CVD [82]. PA is associated with a reduction in CVD in both high- and low-income countries where it is used for recreation and non-recreation purposes [83]. For patients with CVD, the European Society of Cardiology implemented guidelines on sports and PA, and detailed the risks and benefits of the exercise type and duration for patients of different ages and genders [84]. The guidelines provided a scientific basis to effectively guide patients on how to exercise to improve their condition. However, individuals have different genetics, microbes, lifestyles, and living environments, therefore, it is difficult to achieve a perfect fit from guidelines alone. For example, increasing PA in high air pollution environments increases the risk of CVD in young people [85].

Combined, gut microbiota and genetic factors account for up to 76.6% of the variation in CVD-related proteins at the individual level [86]. The gut microbiota is associated with the occurrence and development of CVD via the trimethylamine/trimethylamine N-oxide pathway [87]. Aryal et al. developed a machine learning model for CVD diagnostics using the gut microbiota [88]. In the future, it will be challenging to use machine learning models to integrate multiple omics data, including gut microbiota and PA.

4.4 Bioinformatics Methods and Datasets

In this section, we explore the data science and computational methods underpinning PA and microbiota in health (Table 4.2).

Table 4.2 Bioinformatics databases and datasets

Classification	Name	Description	Website	PMID
Microbial reference genomes	Silva	High quality rRNA databases	http://www.arb-silva.de	23193283
	RDP	rRNA databases with bacterial and archaeal 16S and fungal 28S data	http://rdp.cme.msu.edu/	24288368
	MG-RAST	Metagenomic server for submitting, analyzing, and sharing	http://metagenomics.anl.gov	26656948
	NCBI-RefSeq	RefSeq microbial genomes database	http://www.ncbi.nlm.nih.gov/genome	24316578
	UHGG	Reference genomes from the human gut microbiome	http://ftp.ebi.ac.uk/pub/databases/metagenomics/mgnify_genomes/	32,690,973
	HPMCD	Human pan-microbe communities database	http://www.hpmcd.org/	26,578,596
	GMrepo	Database of human gut metagenomes	https://gmrepo.humangut.info	31,504,765
	HumanMetagenomeDB	Repository of standardized metagenomes for humans	https://webapp.ufz.de/hmgdb/	33,221,926
	gutMEGA	Database of the human gut MEtaGenome atlas	http://gutmega.omicsbio.info	32,496,513
	VIRGO	Human vaginal non-redundant gene catalog	https://github.com/ravel-lab/VIRGO	32,103,005
	eHOMD	Human Oral microbiome database	http://www.ehomd.org	20,624,719
Microbial and disease relationships	HMDAD	Datasets on microbe and human disease associations	http://www.cuilab.cn/hmdad	26,883,326
	Disbiome	Database for microbiota-disease information	https://disbiome.ugent.be/home	29,866,037
	gutMDisorder	Database for gut microbiota in disorders and interventions	http://bio-annotation.cn/gutMDisorder	31,584,099

(continued)

Table 4.2 (continued)

Classification	Name	Description	Website	PMID
	Peryton	Experimentally supported microbe-disease associations database	https://dianalab.e-ce.uth.gr/peryton/	33,080,028
	EviMass	A literature evidence-based miner for human microbial associations	https://web.rniapps.net/evimass	31,616,466
	MDAD	Resource for microbe-drug associations	http://chengroup.cumt.edu.cn/MDAD	30,581,775
Sports and health-related data resources	The national ReferAll database	Exercise referral schemes database	https://osf.io/uzbw9/	33,946,537
	HERITAGE	The cohort datasets to explore the relationship between genetics, exercise and health	https://clinicaltrials.gov/ct2/show/NCT00005137	
	PASS	A multimodal database of physical activity and StresS	http://musaelab.ca/pass-database/	33,363,449
	Sport database	Cardiopulmonary data collected through wearable devices during different exercise	https://ars.els-cdn.com/content/image/1-s2.0-S2352340919311485-mmc1.zip	31,788,519

4.4.1 Data Resources

The data-information-knowledge-wisdom model is one of the most fundamental and effective paradigms in information science, especially, in the big data era [89]. Began the HMP and with the proliferation of next-generation sequencing, 16S rRNA data, metagenomes, metaproteomes, metabolome and other data about human microbiota have been generated. In addition, with more comprehensive research, host genes, living environments, lifestyles, physical signs, and other signals have been associated with the microbiome. Thus, we have entered a new age of big data for biology and health.

4.4.1.1 Microbial Reference Databases

Mapping sequencing reads to reference sequences is fundamental to understanding and classifying microbial data. The SILVA and RDP databases are commonly used as microbial amplicon reference sequence resources [90, 91]. The Metagenome Rapid Annotation using Subsystem Technology (MG-RAST) server contains 464,441 metagenomes and 1970 billion sequenced data items in the 4.0.3 version [92]. The National Center for Biotechnology Information database, NCBI-RefSeq, is the default reference for many metagenomic analysis tools and pipelines [93]. The Unified Human Gastrointestinal Genome (UHGG) catalog was designed by EMBL-EBI and contains 204,938 human gut microbiota reference genomes [94]. HPMCD (The Human Pan-Microbe Communities Database), GMrepo (data repository for Gut Microbiota), HumanMetagenomeDB, gutMEGA database (database of the human gut MEtaGenome Atlas) has also aggregated huge microbiome data resources related to human beings [95–98]. To understand the characteristics of the microbiome distributed in the vagina of the human bod, Ma et al. established the VIRGO (the human vaginal non-redundant gene catalog), which now includes 0.95 million genes from human vaginal microbiota [99].

The Human Oral Microbiome Database (HOMD) and expanded HOMD (eHOMD) collated comprehensive information on human oral and respiratory bacteria [100, 101]. Thus, these databases provide convenient data resources for scientists to study the human microbiome. However, from simple data collation to a fully integrated knowledge system, more efforts are required by data scientists.

4.4.1.2 Databases and Datasets for Human Microbe-Disease Associations

Many human diseases are associated with microbiota dysbiosis. Ma et al. was the first to manually construct a literature-based human microbe-disease network, identifying relationships and mechanisms among genes, diseases, microbiota, and drugs from network analytical methods [102]. The gutMDisorder database covers intestinal microbiota-related diseases and interventions, of which 579 microbes and 123 diseases or 77 interventions were identified in humans [103]. The Disbiome database collates microbiota compositional changes in disease from more than 1000 published papers [104]. An experimentally proven microbe-disease association database, Peryton (version 1), includes 43 diseases linked to 1396 microbes [105]. EviMass is a web-based database that provides evidence of human microbial associations from the literature [106]. Similarly, interactions between gut microbes and drugs also deserve our attention. To gain insights into this, a microbe-drug association database (MDAD) was developed, and included 180 microbe interactions with 1388 drugs [107].

4.4.1.3 PA-Related Data Resources

With the improvement of people's health awareness, health-related smart wearable devices are increased considerably. However, content and data standards of various equipment records are different. The HERITAGE (HEalth, RIsk factors, exercise Training And GEnetics) Family Study project is a 13-year cohort study exploring relationships between health, risk factors, PAs, and genetics [108], and provides data support to unravel complexities between PA, genes, and disease. The National Referral database collated 123 exercise referral schemes data from 39,283 patients across the UK, with accessibility for researchers [109]. The relationship between physical activity and vital signs is more like a complex system, with varying degrees of influence among each variable. Based on this, Parent et al. generated a database of PA and stress, named PASS, which measured correlations between PA and electroencephalography signals [110]. The Sports Database collected 126 cardiopulmonary data items from 81 subjects who wore sensors while performing ten different exercise [111]. However, not all sports work for everyone. Future research should include not only investigate sports genomics [112, 113], but also the sports related microbiome and disease state (i.e., whether or not an individual is sick, type of disease, and disease progress).

4.4.2 Bioinformatics Models and Tools

Bioinformatics tools and models in microbiome and sports health are outlined (Table 4.3).

4.4.2.1 Bioinformatics Methods to Reconstruct Microbial Communities

To fully understand and comprehend raw sequence reads from high-throughput sequencing platforms of microbiome data, scientists require microbial sequence analytical tools or models. Qiime 2 is the most popular open-source pipeline for 16 s sequencing data [114]. The relatively old software package, Mothur is also used to analyze amplicon sequences [115]. Kraken 2 greatly increases the speed of metagenomic analyses, while maintaining high accuracy [116]. MetaPhlAn2 accurately reconstructs microbial communities from whole-metagenome shotgun samples [117]. Thanks to developments in single-molecule sequencing technologies, we can now investigate complete microbial genomes, which provide highly accurate representations of microbial communities inside our bodies. Lathe and metaFlye are examples of bioinformatics tools that assemble long-read metagenomes [118, 119].

Table 4.3 Bioinformatics methods related to the microbiome and physical activity

Classification	Name	Description	Website	PMID
Microbial bio-informatics tools	Qiime 2	Microbiome bioinformatics platform	https://qiime2.org/	31341288
	Mother	Microbial amplicon sequence analysis tool	https://mothur.org/	31704678
	Kraken 2	Metagenomic analysis tool	https://github.com/DerrickWood/kraken2	31779668
	MetaPhlAn2	Metagenomic taxonomic profiling tool	http://segatalab.cibio.unitn.it/tools/metaphlan2/	26418763
	Lathe	Long-read sequencing assembly from microbiomes using nanopore sequencing	https://github.com/bhattlab/lathe	32042169
	metaFlye	Long-read metagenome assembly	https://github.com/fenderglass/Flye	33020656
Human microbe-drug associations prediction	KATZHMDA	Predict associations of human microbiota with non-infectious diseases	http://dwz.cn/4oX5mS	28025197
	EviMass	A literature evidence-based miner for human microbial associations	https://web.rniapps.net/evimass	31616466
	MicroPro	Metagenomic analysis pipe-line provide microbiota and disease associations	https://github.com/zifanzhu/MicroPro	31387630
	DisBalance	Disease prediction and microbial biomarker discov-ery platform	http://lab.malab.cn/soft/DisBalance	33834198
	RapidAIM	Methods of individual microbiome responses to drugs	NA	32160905
	GCNMDA	Graph convolution network based tool to predict microbe-drug associations	https://github.com/longyahui/GCNMDA	32597948
Sports recogni-tion and calculation	ExerSense	Physical exercise recogni-tion and counting algorithm from wearables	NA	33375683
	NA	Energy expenditure estima-tion system for physical activity	NA	34205472

4.4.2.2 Microbial Disease and Microbial Drug Association Predictions

The influence of microbes on disease is highly complex. Thanks to differences in human lifestyles, genetics, and physiology, huge differences inevitably exist in individual microbiota [120]. Chen et al. [121] proposed a microbe-disease prediction tool based on the social network KATZ measure method while using data from HMDAD. MicroPro uses unmapped metagenomic reads associated with human disease [122]. Due to the unique characteristics of microorganisms, studying the microbiota as markers of disease is quite effective. DisBalance is a microbial biomarker discovery platform and provides computer aided information on the microbiome and disease [123]. The gut microbiota also metabolizes many drugs, which impacts drug efficacy. Long et al. constructed a convolutional network based tool to predict microbe-drug relations, GCNMDA [124]. A metaproteomic-based method for drug screening was also developed to facilitate rapid personalized medicine selection [125].

4.4.2.3 Sports Type Recognition and Quantification

The key difficulty in applying PA to the clinic is the vague quantification of its outcomes. In particular, different sports and exercise times can exert different effects on multiple indicators in the body. For CVD, a large Danish population study showed that increasing PA during leisure time was associated with a lower risk of CVD, while higher occupational sports increased risk [126]. ExerSense accurately identifies movement types via sensors on wearable devices [127], and similarly, Lin et al. designed a machine learning model to estimate the energy expenditure of different sports [128].

Athletes often acquire injury due to long and intense training sessions, or from competitions. Professional footballers are reported to have between 2.5 and 9.4 injuries per 1000 h. Thus, while it is important to predict these injuries in athletes [129], designing appropriate exercise programs for different populations is a significant challenge for computational scientists.

4.5 The Application of Microbiota and Exercise Medicine in Human Health

4.5.1 Disease Diagnosis

Correct PA facilitates a balanced lifestyle and benefits human health. In terms of genetic risk, the relative risk of developing coronary artery disease was nearly 50% lower for those with a good lifestyle when compared with a poor lifestyle [79]. Low PA was associated with an increased risk of fracture in patients with CVD [130]. Levels of daily PA were associated with insulin sensitivity in T2DM patients [131]. In their study, de Souza-Teixeira et al. reported that *PGC-1α* could function as a biomarker to indicate the protective effects of PA on colon cancer patients [132]. For women diagnosed with breast cancer, if they were physically active before diagnosis, their risk of death was reduced [133]. PA is also a biomarker of CVD and prostate cancer [134, 135], but exercise is a long-term lifestyle that affects health and diet [136].

Microbial data reflects human health status, and can be used as a disease diagnostic biomarker to reflect sub-health/good health status in individuals. Biomarkers are measurable entities that predict disease occurrence and progression; both qualitative and quantitative biomarker indices can predict current health status/future disease progression. Lin et al. proposed a computational-aided biomarker paradigm using data, models, and applications, and established a theory of computational discovery of biomarkers [137]. Microorganisms impact both positively and negatively on the human body and correlate well with host phenotypic characteristics, therefore, they are good biomarkers [138]. A recent study identified ovarian cancer from benign ovarian tumors using metagenomic data from serum-derived extracellular vesicles [139]. The risk and prodrome of Parkinson's disease, such as PA, smoking and others are correlated to biodiversity and composition of gut microbiota [140]. Intestinal microbiome analyses can be us as tools to target non-invasive biomarkers for early hepatocellular carcinoma detection [141]. Based on ten abnormal metabolic pathways, we developed a novel microbiome-derived risk factor model for prostate cancer [142]. Similarly, quantitative metagenomics revealed a unique intestinal microbiome biomarker associated with ankylosing spondylitis [143].

4.5.2 *Disease Treatments*

Unequivocally, microbes and exercise complement each other, and exercising can improve microbial composition or supplement unique elements, such as probiotics. Increasing PA has a positive effect by preventing and ameliorating some diseases, especially chronic diseases and geriatric degenerative diseases [144]. PA is also associated with decreased breast cancer and colon cancer mortality [145]. Similarly, PA as a lifestyle change, is a highly effective intervention for non-alcoholic fatty liver disease [146]. Exercise has unique benefits in improving mood, providing active therapy, and augmenting patients' health-related quality of life (HRQoL), in particular moderate or vigorous-intensity sports [147]. However, it may not work for individuals with depression; exercise does not significantly improve depression or reduce medication-use when compared with conventional care [148]. Exercise therapy for some individual diseases requires more extensive studies and adequate data validation.

The most direct means of microbial treatment is to eliminate pathogens using antibiotics, but this has the potential to destroy some of the host's microbial communities. Fecal microbiota transplantation (FMT) is highly beneficial in treating *Clostridium difficile* infection and other intestinal diseases [149]. Babies with disturbed bowels during cesarean sections were administered oral FMT from their mothers to generate healthy gastrointestinal tracts [150]. Bacteriophages can also be used to specifically eliminate single intestinal pathogens [151]. Equally, metabolism outputs between the gut microbiota and drugs must be considered during therapy [152, 153]. A computational approach was developed that uses a gene-microbiota interaction-based framework to screen potential target drugs for IBD [154].

4.5.3 Personalized Health Management

Microbial data, especially intestinal composition and structural data, reflects particular characteristics and changes in the human body, with structural changes often related to host health [155]. For example, based on deep learning, gut microbe data can reveal a person's age, and the error range is within 4 years [156]. Prevotella and Bacteroidetes are interpreted as biomarkers of diet and lifestyle then "enterotypes" [157]. Even identical twins responded differently to blood sugar and lipids after eating the same food, suggesting that gut microbiota may play an important role in precise nutrition [158]. Bar et al. measured 1251 serum metabolites from 491 healthy individuals and constructed a model based on genetics, intestinal flora, clinical parameters, diet, lifestyle, and anthropometric data, via machine learning [159]. Hood et al. found that plasma metabolites more accurately reflect the α-diversity of intestinal microbes than plasma proteins, it's a big step forward for microbial health management [160]. Longitudinal cohort analysis revealed a dynamic association between intestinal microbiota and changes in serum metabolites [161]. Data from microorganisms and associated metabolites can accurately provide real-time health information on the body. In particular, human microbiological data can reflect more personalized health related information. By integrating other data, such as electrocardiograms, blood pressure, and blood lipids, we can comprehensively monitor how the microbiota effects human health.

4.6 Conclusions

PA and the human microbiome exert a vital impact on health. Current studies have shown that exercise and human microbiota had synergistic effects in promoting human health. In this chapter, the sports microbiome in human health was proposed, and was based on evidence and interactions between sports (PA) and microorganisms. Recent studies reported that exercise increased beneficial microbial species, enriched microbial community diversity, and promoted the development of symbiotic relationships [36, 38]. Unequivocally, these effects benefit the host and improve general health. In terms of data science development, we reviewed current data resources and bioinformatics methods related to PA and the microbiome. Lastly, we explored the potential application of microbes and sports in real-life situations.

Personalized, Predictive, Participatory, Precision, and Preventive mottos are topical in contemporary medical research; therefore, we must not only analyze genotypes and phenotypes, but also consider personal habits, diets, and microbial communities as crucial effectors of health [162–164]. In terms of high medical costs and scarce medical resources, O4 (overtesting, overdiagnosis, overtreatment, overcharging) medicine provides a novel opposite view for P4 medicine, these challenges provided by O4 are what precision personalized medicine needs to solve in the future [165]. From the large-scale biomedical big data to the small-scale personalized privacy application of individuals, from the big data-driven scientific discovery to the specific clinical intelligent prevention and treatment of patients, it is worth our thinking [166].

Further research is required in exercises medicine and the personalized health microbiome. Athlete selection should be based not only on physical signs, genes, athletic ability, and skills, but also on microbial community structures and function. Equally, it is also important to improve athletic performances by improving their microbiomes. The intelligent toilet designed by Park et al. detects fecal indicators. If the function of detecting fecal microbiome can be added on this basis, it will provide more information related to personal health [167]. In conclusion, when smart-wearable devices and co-analysis methods are combined with data sharing, the real-time monitoring of human health is an inevitability.

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Chapter 5
Human Immune System and Exercise Medicine: Current Process and Future Directions

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Abstract The emerging research field of exercise immunology is becoming an essential sub-discipline of exercise medicine. Many studies have revealed a strong association between physical exercise and human immune system function. Moderate daily exercise can enhance general immunity whereas individuals deficient in exercise or engaged in heavy training tend to be more liable to infection. This review summarizes the effects of long-term moderate and heavy exercise on the immune system, and the general mechanisms of the immune response to physical activity and the biomedical changes of the exercise–immune relationship are illustrated in detail. Nutritional influences on exercise and exercise-induced immune dysfunction are also summarized. Together with advanced informatics technologies, the challenges and future directions of exercise immunology are also discussed.

Keywords Exercise medicine · Immune system · Translational medicine · Medical informatics · Systems health

5.1 Introduction

The increasing number of studies on exercise and immunity is resulting in the development of a specific research field, exercise immunology, which is attracting increasing attention. A well-known concept that has been widely accepted is that physical activity is positively correlated with the promotion of human health, protecting us from pathogenic infections or organ lesions [1]. However, the association between exercise and the human immune system is complicated, and relevant research was initiated over a century ago [2]. In 1902, Larrabee [3] observed an increased number of white blood cells (WBCs) in marathon runners; based on this observation he proposed that such exertion may lead to inflammation-like overload of WBCs. Since then, a number of researchers, clinicians and physiotherapists have

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devoted themselves to investigating the dynamic balance between exercise and immunity, and the fundamentals of exercise immunology have been generally established.

The human immune system plays a key role in maintaining the inner microenvironment to a stable degree, as well as in monitoring and resisting outer pathogens. Relevant studies have revealed that this system is highly responsive to physical activity [4]. On one hand, considerable clues have proved huge benefits to health from exercise. For example, a comprehensive review from Fairey et al. [5] reported that a significant improvement in the immune system was observed in cancer survivors after long-term and continuous exercise. Moderate exercise has demonstrated its role in the reduction of monocyte-platelet aggregates, decreasing the risk of cardiovascular clinical events [6]. On the other hand, immune responses induced by exercise, usually over-exercise, may also have negative influences and even worsen patients' disease states. Researchers have demonstrated heavy training may do harm to immune system, including upper regulation of pro-inflammatory cytokines and biomarkers, suppression of certain immune cells and decrease of metabolism activity [7–11]. Thus, providing appropriate training suggestions, especially to athletes under rehabilitative care, is an emerging challenge in the precision medicine era.

Advanced informatics technology provides major support to the development of body monitoring equipment and in the provision of exercise and medication advice, via artificial intelligence approaches [12], and minimizes personal heterogeneities to a great extent. In the respective fields of immunology and exercise medicine, a cumulative number of tools and databases are now available for basic research, such as IMGT [13], ImmPort [14], and JARD [15]. However, wide clinical application remains far off. From the user's perspective, application scenarios and the simplicity of the developed tools are the primary consideration. From the perspective of developers, data normalization standards, the efficiency of the embedded algorithms, the explainability of the process, and the accuracy of the results are several challenges that need to be overcome.

This chapter will summarize current research discoveries in exercise immunology in three parts. In the first part, we will discuss the roles of different types of immune cell in response to physical activity. The biomedical changes will be illustrated at four different levels, including inflammation, chronic disease, and the gut microbiota. The influence of nutrition on exercise-induced immune dysfunction will be summarized, and a future direction based on big data will be proposed in the final part, as the next step for exercise immunology research and clinical application.

5.2 The Effects of Physical Activity on the Immune System

The mechanisms of the effects of physical activity on adaptive and innate immune functions are complex, owing to dynamic changes in components such as immune cells, proteins, and cytokines between different workloads, lengths of exercise interval, and exercise types. Figure 5.1 illustrates general trends in immunity for moderate exercise and heavy training over time.

5.2.1 Cytokines

Cytokines are types of glycoproteins that play critical roles in cell-cell communication and regulation of the immune system. Typically, cytokines can be classified into two groups according to their main role: pro-inflammatory and anti-inflammatory. In the general immune system, these two groups of cytokines are in a state of dynamic balance and any dysregulation of each group may cause dysfunction of immune system, then causing damage to tissues and organs. The effects of exercise on the immune system begin from changes in cytokine production. Considerable evidence exists showing that cytokine production changes in people under conditions of moderate exercise [16, 17]. For example, studies have observed that the production of pro-inflammatory cytokines such as TNF-α will be suppressed through increased IL-6 in circulation after a short bout of exercise [18]. At the same time, the expression of IL-10 may be elevated, which can counteract the effect of pro-inflammatory cytokines and reduce the infiltration activity of immune cells,

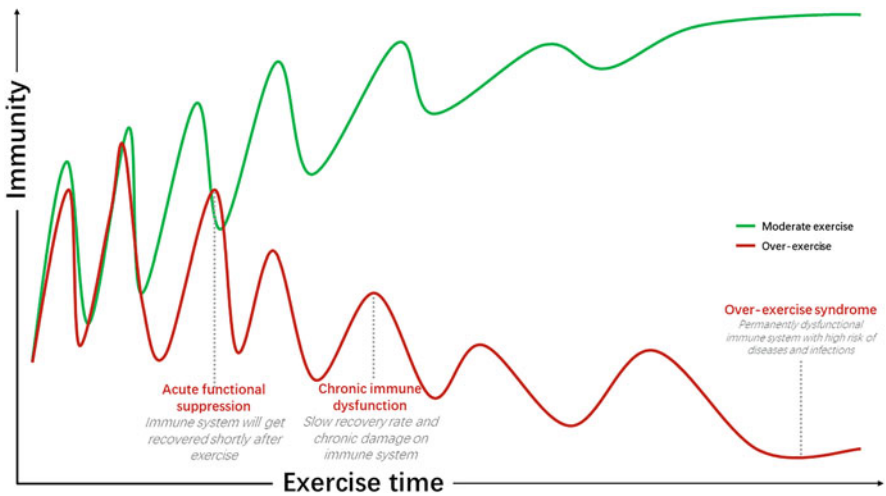

Fig. 5.1 A comparison of the dynamic changes in the human immune system between constant moderate exercise and constant heavy exercise

thus creating an anti-inflammatory environment for several hours after exercise [19–21]. The source of these IL-6 cytokines is considered to be skeletal muscle, whereas IL-6 from other sources such as hepatocytes or adipose tissue is associated with increases in pro-inflammatory TNF-α and C-reactive protein (CRP) [22, 23]. The production of IL-6 in the brain is also increased by exercise, although slightly more slowly than circulating IL-6. The elevation of IL-6 in the brain is considered to have effects on the regulation of neuronal excitability, signal propagation within glial networks, and synaptic transmission [24]. Exhausting exercise, however, may remarkably increase both pro- and anti-inflammatory cytokines and result in a pronounced anti-inflammatory response, which may, in contrast, suppress several immune components and increase the risk of infection [25].

5.2.2 T Cells

Investigation of the influence of exercise on T cells has mainly focused on phenotype and functional changes. Some studies have demonstrated apparent changes in the activity of T cells during constant moderate exercise [26, 27]. For example, Steensberg et al. [28] observed a significant decrease in Th1 cells, but that Th2 cells remained stable [28], and considered this the response to exercise as the hormonal level is increased. Potential mechanisms of the decrease of Th1 cells involve two components, cortisol and epinephrine. Cortisol plays a role in inhibiting the production of IL-12 from antigen-presenting cells (APC) and IL-12 is the factor that promotes the development of Th1 cells [29]. Epinephrine is also elevated during exercise, and it inhibits the activity of Th1 cells via the suppression of APC and direct T-cell receptor blockage [30]. Other studies have focused on immunosenescence, which describes the dysfunctional progress of the immune system due to aging that is reported to be related to increased mortality risk [31–33]. Some investigations have found clues that moderate exercise may slow down this progress and improve immune system function, especially in the elderly. For instance, previous studies have demonstrated the widely accepted concept that aerobic exercises such as running can increase the CD4+/CD8+ ratio in older adults [4]. During an investigation of older pre-diabetic subjects, Philippe et al. [34] found that daily moderate exercise increased the proportion of naive and central memory T cells but decreased the proportions of CD8+ TEMRA cells [34]. Spielmann et al. [35] noticed that aerobic fitness reduced dysfunctional senescent T cells (KLRG1+/CD57+/CD28–), maintaining a relatively active immune system in older people [35]. Duggal et al. [36] claimed that maintained physical activity prevents the reduction of thymic output, which is strongly associated with high mortality risk [36, 37]. There is also evidence that moderate training may improve vaccine response [38].

However, immune balance will be damaged in those who are training heavily, and will include a decreased number of T cells in circulation and increased mobilization in muscle [28, 39]. This series of phenomena is called the "open window"

[40]. Evidence has shown that T cell activity is significantly suppressed after strenuous exercise [41]. The gene expression patterns from marathon runners also indicate that the Th1/Th2 balance is shifted to a Th2 cell predominance, which increases susceptibility to infections and allergies, including upper respiratory tract infection (URTI) [42, 43]. The detailed mechanisms of this alteration and how it induces and influences immune-related diseases require further research.

5.2.3 Natural Killer Cells

Natural killer cells (NK cells), originating in bone marrow from CD34+ hematopoietic precursor cells, are cytotoxic lymphocytes that can rapidly recognize and kill virus-infected or tumor cells. Typically, NK cells account for around 5%–15% of all circulating lymphocytes in healthy individuals [44]. However, exercise may change this ratio due to the remarkable sensitivity of NK cells to exercise-induced stress. Studies have demonstrated alteration in their composition in the blood during aerobic exercise, shortly after which these cells revert to their pre-exercise status [45–48]. The mechanism of mobilization from the tissue into the blood during exercise and return after exercise is probably due to catecholamine, which is induced by physical training [49, 50]. When exercise time is prolonged, usually over 3 h, NK cells revert to their pre-exercise levels, or reduce even further. An explanation for this phenomenon is that lengthy heavy training will induce tissue injury that will recruit more NK cells to injured sites, which at the same time will induce inflammation [51]. Two subgroups of NK cell, CD56bright and CD56dim, increase during physical activity, but the mobilization of them differs. Investigations have pointed out that the CD56bright/CD56dim ratio tends to be lower during rest and during exercise, but becomes higher during the recovery period when CD56bright is elevated. This observation suggests that CD56bright has an important role in recovery from homeostasis and tissue adaption [52–54]. CD56bright cells are also found around tissue inflammation sites induced by heavy training, as they are one of the main producers of relevant cytokines, adhesion molecules that target them at injury sites, and growth factors that contribute to angiogenesis [55–57]. This information taken together indicates that regular exercise may activate NK cells and, from a long-term perspective, enhances their effects and functions. Too much training will lower the proportion of NK cells in circulation and induce chronic inflammation at injury sites.

5.2.4 Macrophages

Macrophages are a type of white blood cell that play an essential role in the initiation, maintenance, and resolution of inflammation. Moderate exercise is proven to improve macrophage functions. For example, studies have found that physical training may inhibit the expression of β_2-adrenergic receptor (β_2AR) in macrophages [58, 59]. β_2AR is a family of G protein-coupled receptors that can support the sympathetic nervous system to regulate the immune system. The stimulation by its agonist can inhibit pro-inflammatory cytokine production, lymphocyte traffic and proliferation, and antibody secretion through the generation of cAMP and the activation of protein kinase A (PKA) [60, 61]. The loss of β_2AR induced by physical exercise may increase the production of catecholamine, indicating the adaption of macrophages to long-term exercise. Compared with groups engaged in daily exercise, visceral fat accumulates in the bodies of those individuals who are overweight or who do not exercise. This accumulation increases immune activity and adipose tissue infiltration by pro-inflammatory immune cells such as macrophages. This process induces a low-grade systemic inflammatory state [62]. Despite these discoveries, whether and how macrophages are involved in regular exercise-induced anti-inflammatory effects are still under debate. More studies, such as investigation of the systematic interaction between networks of macrophages and other immune cells during and after exercise, are required.

5.2.5 Neutrophils

Neutrophils are the most abundant type of white blood cell and are involved in many inflammatory events. The main functions of these cell types include chemotaxis, phagocytosis, and pathogen elimination [63]. Like the other immune cells mentioned above, evidence indicates a tight linkage between exercise and neutrophils. Over 30 years ago researchers observed that functions such as phagocytosis and adherence could be dynamically changed based on different types and workloads of exercise [64, 65], and the factors involved in the response of neutrophils to exercise are still being discovered now. For example, Brickson et al. [66] revealed that the increased release of calcium induced by the activation of muscle fiber may elevate the levels of pro-inflammatory cytokines such as TNF-α and IL-1β, further influencing gene regulatory patterns and recruiting circulating neutrophils to inflammation sites. A study of 15 amateur dancers showed similar change patterns, with the production of IL-8, TNF-α, and IL-1β, as well as neutrophil counts, increasing after dance classes [67]. Kawanishi et al. [68] found that neutrophils can also exacerbate muscle injury via inflammatory regulation, through the induction of macrophage infiltration after exhaustive exercise. These roles of neutrophils suggest they may be a potential biomarker for exercise-induced innate immune response monitoring [69, 70].

5.3 Exercise-Induced Biomedical Mechanism Changes

5.3.1 Support for the Prevention and Recovery from Chronic Diseases

It is frequently heard that positive mood and persistent exercise are of enormous benefit to patients with chronic diseases such as cancer, neurodegenerative disorders, obesity, and cardiovascular disease, for which one of the commonalities is that inflammation occurs during their development. The general countermeasure of exercise is to balance the expression of pro- and anti-inflammatory factors, avoiding a heightened immune response and enhancing the activity of immune cells in a stable manner.

Randomized clinical trials and epidemiologic studies are consistent in the conclusion that participants who engage in moderate exercise are less likely to experience URTI [71–73]. Statistics from those studies have shown that, for example, the incidence of URTI in subjects participating in weekly aerobic exercise (20 min or longer per session) is 43% lower than in inactive subjects [74]. An interesting phenomenon demonstrated in recent studies is that in high-workload elite athletes, the risk of URTI is highly decreased, instead of increased [75]. One of the possible reasons for this is that the interactions between pathogens and host may change genome or transcriptome patterns and the host immune system state may be slightly affected. The consequences of these small changes on URTI susceptibility are still under debate and more clues are required for further explanation.

According to World Health Organization statistics, the prevalence of obesity in children and teenagers aged 5–19 years has increased from 4% to 18% globally in the last four decades [76]. The main risk factors include high-calorie diets and sedentary lifestyles, which are also the main causes of type II diabetes and cardiovascular disease. Recent research showed that one of the main features of obesity-induced insulin resistance (IR) is existing chronic, low-level inflammation, which indicates a strong association between obesity and immune system activation [77, 78]. Evidence indicates that the activation of the innate immune system is mediated by components involved in metabolic and inflammatory signaling, such as free fatty acids (FFA), IκBα kinase, nuclear factor-κB (NF-κB), unfolded protein response (UPR), and NOD-like receptor P3 (NLRP3) [79, 80]. Exercise has been demonstrated as one of the most efficient approaches for obesity management in improvement of insulin sensitivity and suppression of obesity-induced chronic inflammation. Medeiros et al. [81] have proven that the NF-κB pathway is inhibited after 12 weeks of exercise training, alongside an increase in activity of the mTOR/p70S6k pathway, which promotes the synthesis of insulin-dependent proteins. The IR induced by high-calorie diets in cardiac tissues was finally reduced [81]. Also, moderate exercise can limit the level of FFAs and their production of free fatty acid receptors (FFARs), after which endoplasmic reticulum stress and UPR will be further reduced and, finally, the inflammation weakened via the downregulation of inflammasomes such as NLRP3 [80].

There is a considerable overlap of factors and signaling pathways between obesity and cardiovascular disease. Inflammation is the key mediator in the development of both. However, the mechanisms partially differ in detail. For example, the first step for atherosclerosis development is endothelial dysfunction and increase of endothelial permeability, which gives support for the accumulation of low-density lipoprotein and further sedimentation into the intima layer, forming barriers in the vascular system. Cytokines and chemokines produced from immune cells are key regulators and induce inflammation during this process [82, 83]. Frodermann et al. [84] claimed that exercise can modulate the microenvironment of hematopoietic stem and progenitor cells and change the signaling features, limiting the production of inflammation-related immune cells. Other investigations have shown negative correlations between cardiovascular functions and the expression levels of IL-6, CRP, and IL-18 [85].

In summary, the linkage between exercise and chronic disease follows a typical route: exercise—inflammation—immune system—disease. Exercise boosts the expression of cytokines and chemokines and promotes the circulation of immune cells, and it mediates anti-inflammatory and antioxidant states through multiple mechanisms. Although the ambiguity of the mechanisms remain, exploring them could provide excellent references for chronic disease prevention and recovery.

5.3.2 Linkages Between Exercise, Gut Microbiota, and Immune Functions

Trillions of microbes colonize the gastrointestinal tract and their genomes are hundreds of times larger and more complex than the human genome. The gut microbiota has very strong associations with physiological and mental health. Behaviors such as diet, sleep, disease, and exercise, and the environments surrounding humans can also variously influence their diversity. In recent decades, the results of investigations into these associations have emerged, and several mechanisms of the interactions between the microbiota and immune system have been identified. For example, Dodd et al. [86] found that *Clostridium sporogenes* produces indolepropionic acid (IPA) that can not only enhance intestinal absorption capacity, but also maintain immune cell balance [86]. Microbial metabolites, especially butyrate, can directly enhance the immune response of CD8+ T cells and promote anti-tumor therapeutic efficacy [87]. In addition, *Akkermansia muciniphila* and *Enterococcus hirae* were inferred to mediate the liberation of pro-inflammatory cytokines such as IL-12 from dendritic cells, recruiting more CD4+ T cells to the tumor site [88].

How exercise affects the gut microbiota and further changes immune system dynamics is still being explored. Some studies have reported that exercise contributes to the enhancement of microbiota diversity and increases benign microbial community counts [89]. However, the gut microbiota is also involved in post-exercise inflammation. Jeukendrup et al. [90] investigated lipopolysaccharide (LPS) levels in blood taken from long-distance triathlon athletes at different time points, and noticed a sharp increase immediately after the event that peaked 1 h later. This investigation indicated an increase in intestinal permeability induced by heavy exercise [90]. Research from Marycz et al. [91] also pointed out that extended training can lead to an elevation of developmentally early stem cells in bone marrow, which may be partially mediated by LPS from the gut microbiota. It seems that different exercise types, workloads, and health status may lead to various changes in gut microbiota and different immune responses to these changes. Therefore, it is still too early to determine the exact role of exercise in the regulation of microbiota and their effect on the immune system. Larger scale and more detailed explorations are required.

5.4 Nutrition Effects on Exercise-Induced Immune Changes

The anti-pathogen function of the immune system is closely associated with daily nutrition intake. Inadequate intake of either macronutrients (fats, carbohydrates, proteins) or micronutrients (vitamins, minerals, water) will lead to suppression of the immune system and further negatively affect immune function. Nutrients in the human body are also in a state of balance, as different nutrients have different roles in supporting the immune system. The most important and efficient nutrients for athletes include carbohydrates, glutamine, and vitamins. Table 5.1 shows the roles and recommended intake of some key nutrients.

5.4.1 Carbohydrates

From the middle 1980s to the early 2000s, a series of studies revealed that the intake of carbohydrate supplements (30–60 g/h) after extended and high-intensity exercise could reduce the levels of inflammatory factors in plasma, including decreasing neutrophil and monocyte counts, attenuation of granulocyte phagocytosis, and the downregulation of stress hormones and inflammatory cytokines [92–95]. The general influence chain of daily carbohydrate intake is shown in Fig. 5.2.

To date, a number of studies have revealed the mechanisms by which carbohydrates act on the immune system. For example, researchers found that the ingestion of carbohydrates may result in the increase of blood glucose and tissue glucose intake, leading to the diminished activation of the central nervous system and a decrease in stress hormone output [96]. Another investigation noticed a suppression of inflammatory cytokines and a reduction of inflammation after carbohydrate intake [97]. Exercise taken under higher blood glucose levels may decrease the activation

Table 5.1 The main functions and recommendations of nutrients for exercise and immune enhancement

Nutrients	Roles	Recommendations
Carbohydrates	1. Glucose maintenance 2. Limitation of stress hormones 3. Suppression of pro-inflammatory cytokines	30–70 g/h of heavy training
Glutamine	1. Balance of cytokine production 2. Substrates for immune cell consumption	More detailed information should be provided in future investigations; however, athletes should increase intake in winter
Vitamin C	1. Antioxidant (suppression of reactive oxygen species [ROS]) 2. Assistance in boosting immunity	Precise data are needed. It can boost the immune system but some indications of a decrease in athletic performance have been seen
Vitamin E	1. Antioxidant (suppression of ROS) 2. Assistance in boosting immunity 3. Adjuvant to vitamin C	Not recommended for single use as no significant changes. Possibly a useful adjuvant to vitamin C
Vitamin D	1. Regulation of the antibody secretions of T and B cells	Precise data are needed
Amino acids	1. Energy supplementation 2. Protein and lipid synthesis 3. Nitrogen and carbon donation	The consumption of amino acids is still under debate

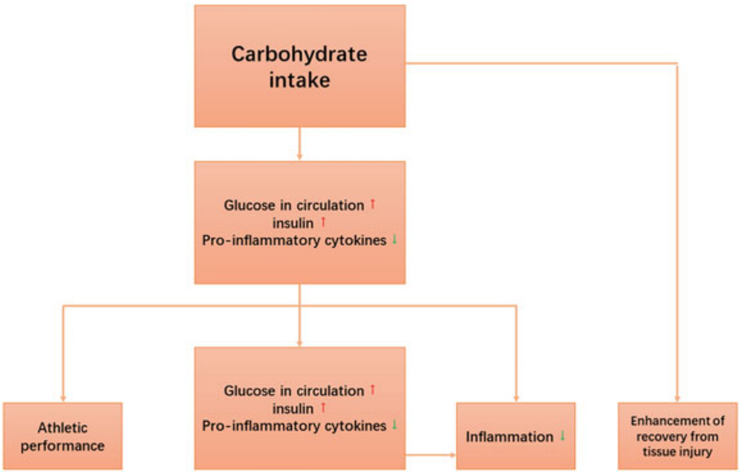

Fig. 5.2 The general influence cascades of daily consumption of carbohydrates

of the hypothalamic-pituitary-adrenal axis, which can result in moderate release of adrenocorticotrophic hormone, cortisol, growth hormone, and epinephrine. This release control is strongly linked to cytokine production and may influence immune cell functions. From a systematic perspective, the interactions between exercise and carbohydrates also have regulatory powers over the whole signal transduction cascades that influence protein regulatory systems [98–100]. However, insufficient carbohydrate supplementation after exercise, especially after heavy training, could result in high risk of exercise-induced inflammation in athletes. This information taken together suggests that the intake of carbohydrates might be an efficient strategy for heavy exercise-induced immune dysfunction recovery [96, 97].

5.4.2 *Glutamine*

Glutamine is the most abundant free amino acid in human blood and muscle and plays roles in protein and lipid synthesis, nitrogen and carbon donation, and ammonia transportation, as an energy source for cellular activities, and in the regulation of the immune system. Evidence suggests that extended exercise may lead to a decrease in plasma glutamine, which will further suppress immune function [101, 102]. The mechanisms of glutamine-induced immune suppression have been investigated extensively. Studies of marathon runners revealed that timely glutamine supplements after extended running can reduce the risk of URTI [103]. It seems that daily glutamine ingestion can maintain cytokine production balance and avoid immune suppression. In addition, according to a meta-analysis by Ahmadi et al. [104], influences on immune functions induced by glutamine also include changes to CD4+/CD8+ ratio [105], increases in T cell and leukocyte percentages [106, 107], elevation of NK cell activity [105], changes in neutrophil counts [108], and lower plasma TNF-α levels [109]. However, some studies debate that the immune suppression role of glutamine may be non-existent, as moderate doses of glutamine can also enhance immune functions such as promoting the proliferation of T cells and maintaining the balance between M1 and M2 macrophages [110, 111]. Thus, although glutamine may have positive effects on exercise performance, there remains conflicting evidence about its response to exercise and its role in immune functions, and more research is required.

5.4.3 *Vitamins*

Vitamins such as C, D, E, B6, and B12 are requisites for the proper operation of the immune system. The roles that vitamins play in assisting immune functions are varied. Oxidative stress may lead to a decrease in leukocyte counts in circulation via apoptosis, which further weakens immunity, and this mechanism is considered associated with exercise-induced immune suppression. Several anti-oxidative vitamins such as vitamins C and E are reported to have an effect on banishing reactive oxygen in both intracellular and extracellular fluids [112]. The functions of vitamin C include promoting of T cell proliferation, increasing neutrophil activity, suppressing virus replication, and, ultimately, enhancing anti-infection capacity [113]. Some clinicians and researchers have noticed that athletes under heavy exertion who take high doses of vitamin C daily lower their risk of URTI [114, 115]. Combined with vitamin E, the elevation in cortisol concentration induced by extended exercise is significantly suppressed [116]. Vitamin E itself, however, shows no obvious impact on immune dynamic changes. Prolonged ingestion of vitamins C and E can avoid the accumulation of oxidation products in injured tissues and suppress the overexpression of cytokines [117, 118]. In summary, anti-oxidative vitamins may prevent the damage induced by muscle contraction and can be considered a key nutritional supplement for athletes in recovery.

5.5 Future Perspectives: What Are the Next Steps for Exercise Immunology?

Research into exercise immunology continues to accumulate. These discoveries provide crucial evidence that has already been applied to clinical diagnosis and treatment. The continuous development of computational science and informatics technology is also widely applied in biomedical research and has become indispensable. Over 15 years ago, IBM started their trial of the IBM Watson computer system in clinical decision support [119]. Despite difficult processes and reported failure in its use in health care, Watson still provided numerous potential strategies and computational methods as reference for later study. With lessons from Watson and the help of state-of-the-art methods such as deep neuro networks, many tools and algorithms have been developed for clinical diagnosis and treatment support. For example, He et al. [120] developed a natural language processing system based on BERT for medical question answering and disease information recognition [120]. The Tencent AI lab developed a series of medical image analysis algorithms that cover classification, color normalization, disease site detection, and semantic segmentation [121–125]. The exercise-immunology-informatics combination may be a vital direction for future study and application development. Accordingly, we propose two potential opportunities below, the roles and relationships of which are shown in Fig. 5.3.

5.5.1 Integrated Systems for Immune System Monitoring

Prevention is always difficult, as health status is affected by many factors. Many current health management policies and suggestions lag, only being provided when

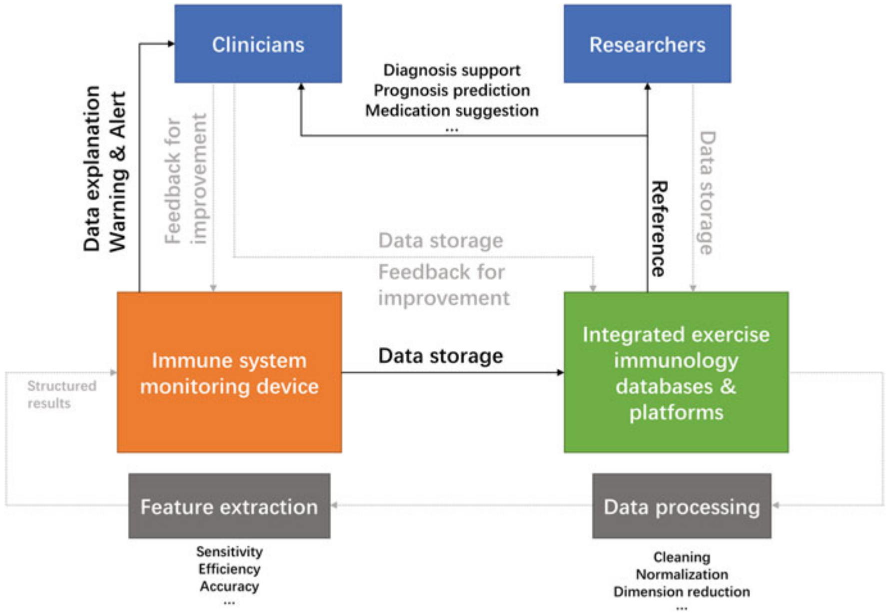

Fig. 5.3 The functional relationships between immune system monitoring and exercise immunology databases

physical abnormality or disease emerges. This may cause significantly negative impact on the body's physical function and shorten the athlete's career [126]. As the immune system acts as the sensor for changes in the human body, monitoring the whole immune system of athletes will be extremely beneficial to injury and disease prevention and assist in prolonging their careers. Thus, a multi-point, integrated, and explainable system for observing the immune system and analyzing data is demanded. Although efforts have been made in other fields such as cancer health management [127], exercise immunology has a long way to go as many new factors need to be considered.

5.5.2 Databases for Exercise Immunology

Databases are very useful tools for both biological investigation and clinical application; the stored data are well-structured and can provide an enormous amount of information that is especially useful for retrospective studies and healthcare references. Databases such as the TCGA and ICGC currently used in cancer research are not only containers for data storage but also functional platforms for users to perform complex data analysis. Although there are already some excellent databases and platforms for the immunology and exercise medicine fields, these tools need integrating urgently so that integrated data analysis can be conducted. Like the monitoring system mentioned above, many difficulties need to be overcome during the development progress, such as data cleaning; the integration and normalization of biological, clinical, and exercise data; and data evaluation [128]. Also, if the platforms embed algorithms for data mapping and analysis, efficiency and explainability should be the primary consideration [129]. Once such databases or platforms are constructed, they will not only provide support for future basic research and clinical reference, but also serve as the fundamental modules for AI-assisted immune monitoring systems.

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Chapter 6
Circadian Rhythm and Personalized Exercise

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Abstract Almost all physiological and biochemical processes in the human body follow a circadian rhythm. Studies have found that the biological rhythms of the human body, especially circadian rhythms, affect the capacity for and performance of exercise. Exercise also affects circadian rhythms. The circadian rhythm influences core body temperature, muscle strength, aerobic and anaerobic exercise capacity, and flexibility. Exercise also causes a phase shift that remodels circadian rhythms. Research has shown that exercise can improve fitness if it is timed to coincide with peak performance. In addition to considering diurnal variations, preferences regarding the time of exercise (day or night) are important for studying the effects of circadian rhythms on exercise performance. Furthermore, there are differences in circadian rhythms among different exercise types. Therefore, arranging exercise time and intensity according to the characteristics of the human circadian rhythm is of great significance for improving training efficiency, reducing the occurrence of exercise injuries, and overcoming biological clock disorders.

Keywords Circadian rhythm · Exercise performance · Synchronizer · Chronotype · Circadian disruption

6.1 Introduction

The rhythm in which life activities repeatedly change in a certain time sequence is called biological rhythm. Biological rhythms affect the body's normal physiological functions, mental activities, mood swings, body temperature, and pulse. Biological rhythm is preserved as part of genes, so rhythm is a special property of organisms. The 2017 Nobel Prize in Physiology or Medicine was awarded to three American scientists (Drs. Michael W. Young, Jeffrey C. Hall, and Michael Rosbash) in recognition of their contributions to the discovery of biological clock genes and

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regulatory mechanisms [1]. Sustained research on biological rhythms has given rise to a new discipline—chronobiology, the study of biological rhythm phenomena, regulatory mechanisms, and applications. Since the 1970s, chronobiology has carried out interdisciplinary research, with some attention to applications in the field of sports. For example, the impact of jetlag on athletic performance has been widely valued by sports teams [2].

To date, it is widely accepted that people perform best when they exercise in the late afternoon or early evening, during which the somatic function peaks. Accumulating evidence has revealed the crucial role of circadian rhythms in sport performance. Circadian rhythms are physical, mental, and behavioral changes that follow a 24-h cycle. Circadian rhythms are endogenous characteristics, and they are influenced by exogenous factors such as light and ambient temperature. In this chapter, the molecular mechanisms and interfering factors of circadian rhythms are summarized, the effects of which on sport performance and feedback from exercise are also addressed. The concept of chronotypes and the relationships among exercise, health, and circadian rhythms are discussed.

6.2 Mammalian Circadian Clock System

Circadian rhythms are oscillating phenomena with a cycle of roughly 24 h that affect physiological, biochemical, behavioral, and other life activities of the body. They are periodically driven by clock genes and clock-controlled genes [3]. All living things face environmental challenges from alternating days and nights. To adapt to these changes, algae, bacteria, plants, animals, and other organisms have evolved a special system called a circadian clock. Circadian rhythms help the organism's physiology and behavior synchronize with the light–dark cycle and participate in and adapt to the physiological functions of the human body at different phases of the day. They also help regulate body temperature, blood pressure, sleep, and hormones. Circadian rhythms are important for maintaining the body's homeostasis and normal physiological activities. They are related to many physiological indicators, such as diet, sleep, metabolism, and exercise. Specifically, circadian rhythms affect the body by coupling downstream signals and outputting signals to organs. Internal homeostasis is related to whether the organism can maintain the coordination and order of various organs and parts, and adapt to changes in the external environment.

Generally, the circadian rhythm system of mammals is composed of three main components: input pathways, the central clock, and output pathways. Organisms rely on the input system for environmental information and integrate this information through the circadian rhythm center. The output system synchronizes the cells and organs in the body with the external environment [4]. The mammalian circadian rhythm system is mainly composed of the pineal gland and the suprachiasmatic nucleus (SCN) in the front of the hypothalamus. The SCN is a small cluster of pacing neurons located in the anterior part of the hypothalamus. It is the pace point of circadian rhythm in the human body and the source for generating and transmitting circadian rhythm signals. The SCN is located above the intersection of the optic nerves of the two eyes. This area contains many types of neurons. Neuronal chemical phenotypes and neural inputs and outputs play different roles in the circadian rhythm function [5]. Under the control of the SCN, the pineal gland transmits time information to other parts of the body by secreting melatonin. Circadian clock genes exist not only in the SCN (called the central clock) but also in peripheral tissue (called the peripheral clock), such as the brain, heart, kidneys, lungs, liver, skeletal muscles, and saliva [6]. The peripheral clock plays an important and unique function in tissue, driving the rhythmic expression of specific genes involved in physiological functions [7]. Rhythmic activity of the peripheral clock is autonomous and depends on the regulation of the signal output by the SCN [8].

6.2.1 Synchronizers

The circadian rhythm responds to timing signals. These signals are called zeitgebers (literally "time giver" in German) and they harmonize the circadian rhythm in the organism with the external 24-h pace. As shown in Fig. 6.1, light is the most important zeitgeber to synchronize external time and the body's clock. Other external factors such as food and exercise, along with intracellular factors (e.g., temperature) and various social and psychological factors, can cause the body to reset the settings of circadian rhythms.

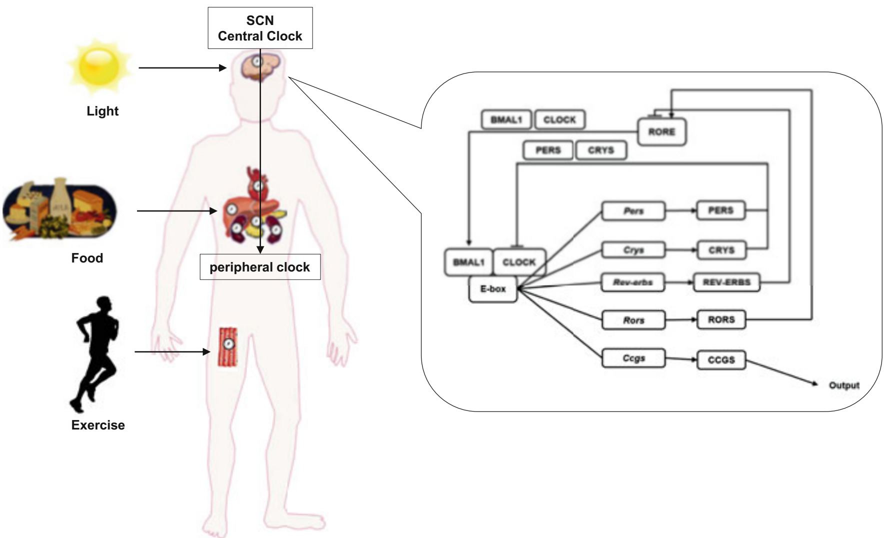

Fig. 6.1 Circadian clock system in mammals

6.2.1.1 Light

Light is an important factor affecting the body's circadian rhythm, neuroendocrine, and neurobehavior, and has a major impact on the health of all mammals. Three aspects of light are pertinent: light cycle, light intensity, and light wavelength. The light cycle is the most important environmental signal for conveying information about the surrounding environment to organisms. The light cycle can adjust the phase of clock genes, the relationship between the waveform, and the amplitude of the expression. Karatsoreos [9] disrupted the circadian rhythms of mice by artificially shortening the cycle time 20-h day (10 h dark/10 h night). Under this condition, the body temperature, weight, heart rate, metabolism, and cognition of mice changed, leading to the atrophy of neurons in the front of the temporal lobe and the reconstruction of sleep patterns. Mariana G. Figueiro [10] designed an experiment whereby adult men were exposed to a high-pressure pump lamp and a series of blue-light-emitting diodes at night. Exposure to the lamp inhibited melatonin and increased pupil contraction, indicating that the subjects' circadian rhythms were altered. The guiding mechanism changes in the spectral sensitivity of two different light sources at night. In addition, the color of light has an obvious regulatory effect on circadian rhythms. Rats receive red-green-blue lights during the day, and their rhythm is normal under a combined red-green light cycle at night. But a red, green, and purple light cycle at night becomes arrhythmic [11].

Light-mediated changes in circadian rhythms are closely related to diseases such as diabetes, obesity, heart disease, and cancer [12]. Short-wavelength-enriched light emitted by electronic devices at night affects sleep, decreases the secretion of melatonin, shifts the biological clock, and reduces alertness the next morning, disrupting the circadian rhythm [13]. But light can also mitigate sleep disorders, jetlag, shiftwork problems, and aviation flight problems. In cancer research, circadian rhythm disorder, one of the risk factors for cancer, has received widespread attention. An important risk factor that affects circadian rhythm disorders is nocturnal light exposure. Long-term exposure to light at night causes hormone secretion disorders, DNA damage, and increased probability of tissue canceration [14]. A survey showed that [15], compared with those who work day shifts, the ratio of the incidence of prostate cancer among people working night shifts is as high as 1.79, and the risk will be higher as the duration increases. In 2007, the WHO International Cancer Institute confirmed that shift work can cause circadian rhythm disorders and is a possible human cancer risk factor (level 2A) [16].

6.2.1.2 Temperature

The synchronization effect of temperature on body rhythms is another powerful traction factor for circadian rhythms. The circadian rhythm has a temperature compensation mechanism. Through transcription, post-transcription, and post-translational mechanisms, the circadian rhythm system buffers the cycle changes of the circadian rhythm caused by temperature changes within a certain range. The gears of the circadian rhythm—that is, the periodic activity of genes and the concentration of proteins—will not change with temperature changes, so the cycle of the biological clock remains unchanged. At the same time, the core mechanism of the biological clock is related to external and temperature-sensitive factors, and this external coupling leads to the advance and retreat of the circadian rhythm [17].

6.2.1.3 Food

Circadian rhythms can be synchronized by light, so the light-responsive central clock SCN is an oscillator that can carry light. Food is a non-light stimulus that can reset the circadian rhythm. Japanese scientist Dr. Makoto Akashi [18] found that insulin mediates the phase adjustment of the circadian rhythm of the tissues related to food in mice. This affects tissue function, thereby helping with digestion and absorption and synchronizing the stomach's circadian rhythm with meal times. For jetlag, dinner should include ingredients that can promote insulin secretion to advance the circadian rhythm, while breakfast is the opposite.

6.2.1.4 Others

Other zeitgebers, including exercise, hormones and other non-light stimulation, can also synchronize the circadian rhythm. Exercise helps to promote the circadian rhythm to adapt to the sleep–wake cycle. Barger [19] reported that exercise accelerates the phase delay of the human circadian rhythm caused by forced sleep. The daily rhythm of melatonin in plasma is used as the circadian rhythm. Compared with a non-exercise control group, the start, offset, and midpoint of melatonin in an exercise group showed greater changes, and there was a significant phase shift. Exercise at different times of the day can be used to measure changes in the circadian rhythm. Night exercise causes a phase delay of the onset of dim-light melatonin, but there are few reports on the phase advancement of melatonin caused by exercise. Nevertheless, the influence of exercise on the circadian rhythm may depend on the time of day.

The SCN interacts with the peripheral clock by controlling the secretion of endocrine factors (such as glucocorticoids and insulin), thereby synchronizing with each other in time [20]. Glucocorticoid is an anti-inflammatory hormone released by the adrenal cortex and a powerful synchronizer of the peripheral clock. Glucocorticoids bind to the glucocorticoid receptor (GR), which acts as a transcription factor and regulates the transcription of multiple genes as a result of these transcriptional changes. It does so by binding to specific glucocorticoid response elements or interacting with other transcription factors. They regulate various physiological processes, such as glucose homeostasis, immune response, and water–ion balance [21]. By comparing the circadian rhythms of wild zebrafish and GR-mutant zebrafish, it was found that the mutant zebrafish has weaker activity, more unstable activity paths, and weaker circadian rhythms for melatonin secretion [22].

6.2.2 The Molecular Mechanism of Circadian Rhythm

The 2017 Nobel Prize in Physiology and Medicine was awarded to research results in the molecular mechanisms of circadian clock. At the molecular level, the core circadian clock genes follow an autonomous transcription-translation feedback loop. The transcription factors Clock and Bmal1 form a heterodimer and bind to the upstream and downstream of the E-box to drive the transcription and translation of the cryptochrome gene *Crys* (*Cry1* or *Cry2*) and the core circadian clock repressor gene *Pers* (*Per1*, *Per2* or *Per3*) in the cytoplasm. When the expression of Crys and Pers proteins in the cytoplasm is too high, they will partially enter the nucleus, thereby inhibiting the binding of the circadian clock protein Bmal1 and Clock [23]. Because the above-mentioned gene transcription and protein nucleus reactions take a certain time to complete, the changes in the up- and down-regulation of the expression of these core biological rhythm-regulating genes are maintained at the oscillation period of about 24 h. In addition, Rev-erbα and Rev-erbβ negatively regulate the circadian clock gene *Bmal1*, while RORα and RORβ can positively activate the transcription of *Bmal1* [24]. The schematic diagram of its molecular mechanism is shown in Fig. 6.1. In addition, these circadian clock genes can regulate downstream transcription factors through rhythmic expression. For example, the heterodimer formed by Bmal1 and Clock can bind to histone deacetylase 3 to regulate the deacetylation of Bmal1 [25]; Cry interacts with Rev-erbβ protein to affect the transcriptional activity of glucocorticoids; Cry protein can also inhibit the downstream glucagon receptors. This regulation method helps the body to fluctuate according to a certain rhythm within a day [26]; Clock and Bmal1 can also be combined with Sirt1 to affect the transcription of liver [27]. In summary, circadian clock genes regulate many intracellular functions, such as maintaining redox balance, metabolism and cell proliferation.

6.3 Contribution of the Circadian Rhythm to Exercise Performance

6.3.1 Circadian Rhythm Affects Exercise Performance

The tight association between circadian rhythms and exercise performance has been demonstrated by numerous studies (list in Table 6.1). These studies suggest that the rhythmicity of physiological processes is related to peak exercise performance time points. For example, Guette et al. [28] noticed that soccer players tend to achieve

Table 6.1 Summary of circadian rhythm influence on exercise performance

Reference	Sample	Exercise	Objectives	Results
Masmoudi et al. [47], PMID: 34572225	32 males (age: 11 ± 0.7 years; height: 1.45 ± 0.07 m; body-mass: 38.9 ± 7.8 kg)	Soccer	Assess the effect of time of day on kicking performance	The shooting quality of soccer is not affected by the time of day, but is related to time pressure ($p < 0.05$)
Jang et al. [48], PMID: 33457389	12 soccer players (age, 23 ± 2 years; height, 175 ± 6 cm; body mass, 71 ± 5 kg)	Soccer	Determine the influence of indoor temperature of summer rest space on soccer players', physical fitness and health condition	There were no significant differences in physical fitness, fatigue and sleep quality between groups at 20 °C, 26 °C and 30 °C, but negative psychological effect at 30 °C was significant
Silveira et al. [49], PMID: 32899823	16 male athletes: Age 34.81 ± 5.76 years, body mass 70.2 ± 5.4 kg	Mountain bike (MTB)	Analyze the effects of morning and afternoon exercise on physiological variables and mechanical in mountain bike time trial	The afternoon temperature was significantly higher than the morning ($p < 0.001$), 26.67 °C and 33.33 °C, respectively. The afternoon stroke rate was significantly lower than the morning ($p < 0.05$)
Chtourouet al. [50], PMID: 30416454	14 male elite judo athletes (age: 21 ± 1 years, height:172 ± 7 cm, body-mass: 70.0 ± 8.1 kg)	Elite judo	Examine the effect of time of day on performance and psychological variables of elite judo athletes	The afternoon countermovement jump was higher than the morning jump ($p < 0.05$), but the pressure was lower ($p < 0.05$). Psychological variables and fatigue index didn't differ between morning and afternoon
Aloui et al. [51], PMID: 28361573	11 healthy volunteers: Age, 21.00 ± 0.48 years; height,	Level-1 Yo-Yo	Investigate the effects of time of day on muscle damage,	Hormone, metabolic and oxidative responses are higher in the

(continued)

Table 6.1 (continued)

Reference	Sample	Exercise	Objectives	Results
	181.36 ± 2.28 cm; body weight, 72.75 ± 1.79 kg; body mass index (BMI), 22.15 ± 0.54 kg/m^2		cardiovascular parameters and hormonal responses to the level-1 Yo-Yo intermittent recovery test (YYIRT)	evening (17:00 h) than in the morning (07:00 h). Cortisol and testosterone levels are higher after a morning YYIRT
Chtourou et al. [52], PMID: 23012632	20 male soccer players (age: 17.6 ± 0.6 yr.; weight: 71.3 ± 4.8 kg; height: 181.3 ± 5.4 cm)	Soccer	Determine the effects of time of day on aerobic and anaerobic performance of soccer players on Yo-Yo, repeated sprint ability (RSA) and Wingate tests	On the Wingate test, the RSA test and the Yo-Yo test, performance at 17:00 h was higher than that at 07:00 h
Knaier et al. [53], PMID: 31476879	19 males (age: 24.1 ± 2.5 years)	Isometric and isokinetic strength assessments	Assess diurnal and daily changes in leg, arm, and trunk strength at different times of day	There was no difference in isometric leg strength at different times of the day, and diurnal variations in leg and arm strength were almost three times greater than daily variations

better performance in the evening (16:00–20:00) compared to in the morning (07:00–10:00). Tests on the quadriceps and semi-tendinosus muscles of football players' legs showed that the maximal levels of muscles would be reached at 18:00. Similar results were found in studies of biceps brachii and triceps brachii, the peak torque of which was also at 18:00 [29]. Further, the aerobic contribution of high-intensive exercise is significantly increased in the afternoon compared to in the morning, indicating better aerobic participation in energy production during exercise in the afternoon than in the morning [30]. Zadow et al. and Fernandes et al. found higher levels of heart rates, VO_2max, and performance after physical activity in the afternoon [31, 32]. Other athletic abilities, including stamina, strength, agility, vigilance, anaerobic exercise capacity, and reaction time, are dynamically influenced by the time of the day [33–35].

Most previous research considered core body temperature (Tc) as a major index for evaluating biorhythm in physiological processes and physical activities. The best time for exercise ranges from later afternoon (16:00) to early evening (18:00), during which Tc peaks [36]. Exercise performance will be apparently weakened at the minimal Tc, which is at the beginning of the day (03:00) [37]. There is evidence of a strong correlation between Tc and short-duration maximal exercise performance.

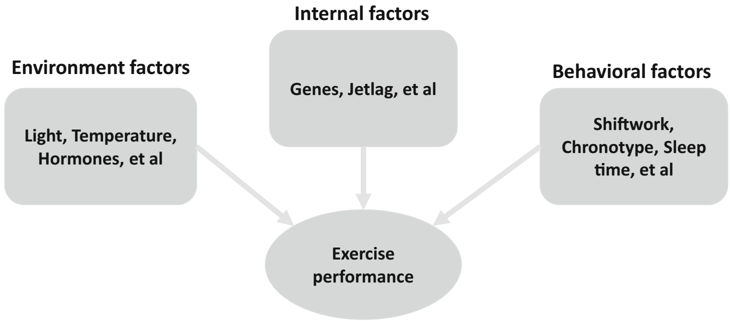

Fig. 6.2 The influence of external factors on circadian rhythm

The increase of Tc may warm up the body, enhance metabolism, increase the extensibility of connective tissue, lower muscle viscosity, strengthen nerve impulse propagation, and promote the interaction between actin and myosin [38–40]. Bergh et al. [41] noticed that power output weakened by 5% when muscle temperature decreased by 1 °C. Hidenori et al. [42] found that the increased body temperature and heart rates of baseball players in the heat gives more pressure to inner temperature adjustments in the morning, suggesting a lower risk of exertional heat-related illness among those involved in exercises in the afternoon. Besides an increase in body temperature, high ambient temperature is considered a major contributor to the enhancement of muscle contractility [43].

Unlike physiological factors, the dynamic changes of cognitive performance are still under debate. For example, due to the higher body temperature and increased grip strength in early afternoon, the serve speed of tennis players is apparently faster than in the morning. The accuracy of tennis serves, however, is much lower [44]. Exercising in the afternoon might be more effective for improving cognitive function and the mood than in the morning [45]. Meanwhile, there are also some studies holding different opinions. For instance, Elise et al. [46] claimed that ‘morning larks’ may have higher psychomotor vigilance in the morning, whereas ‘night owls’ may exhibit the same in the evening. This suggests that cognitive performance for exercise might be influenced by multiple factors. A complex dynamic model is needed to better describe these effects.

Due to the complexity and ambiguity, it remains challenging to determine the effect of circadian rhythms on sport performance. As shown in Fig. 6.2, the factors involved can be divided into three parts: environmental factors, including light, temperature, and hormones; behavior factors, including shiftwork and sleeping time; and internal factors, such as circadian genes and jetlag. Individual changes and the dynamic interactions of these factors contribute to the formation and development of personal circadian rhythms.

6.3.2 Effects of Circadian Characteristics on Exercise Performance

6.3.2.1 Core Temperature

Core temperature (Tc) has a circadian rhythm that peaks in the late afternoon and is lowest in the early morning, typically 2 h before waking up [54–56]. Tc plays a crucial role in all circadian rhythm-related events, the dynamic changes of which may be one of the major driven regulators for circadian rhythm. For example, the elevation of Tc speeds up nerve conduction and increases the catalytic activities of relevant enzymes. The flexibility and contraction of muscles and tendons enhance as Tc increases [37, 57]. However, increased Tc can have negative effects on endurance exercises. Therefore, it seems that morning is the most suitable time for these exercises, as Tc is lower [49]. The afternoon, especially late afternoon or early evening, is better for anaerobic exercises such as sprints and high-jumping. Besides circadian rhythms, ambient temperature also plays vital roles in Tc regulation. How the environmental factors contribute to the Tc circadian rhythms remain to be further investigated.

6.3.2.2 Skeletal Muscle

The main regulators for the circadian rhythm of skeletal muscle are clock genes. Those genes influence the control of muscle density, strength, myofiber types, and mitochondria functions [58]. Muscle strength varies following diurnal variation. Evidence suggests that the peak of muscle strength appears in the early evening (around 17:00–19:00), which is consistent with that of Tc [59]. Although different muscle types may have slightly different peak times, strength in the afternoon and evening is always higher than that in the morning on average. For example, the average strength of back muscles is obviously higher in the afternoon. The time for peak isometric strength ranges from 16:00 to 19:00, whereas quadriceps femoris strength peaks around 19:00. In general, athletes will get a better boost in their muscle strength if they set their daily training in the afternoon [60].

6.3.2.3 Body Flexibility

Body flexibility is one of the most important contributors to exercise performance and has attracted increasing attention in recent studies. It varies in a wide range throughout the day, by around 20% on average. Although the time of peak body flexibility is heterogeneous, it usually appears in the afternoon or night [61]. A study of 26 young volunteers (around 25 years old) found that the scores of sit-and-reach tests were significantly better at night compared to in the daytime [62]. Therefore, when making exercise plans, the circadian rhythm of body flexibility should be considered to reduce the risk of muscle strain.

6.3.3 Effects of Chronotype on Exercise Performance

The time preferences of exercise participants can also affect exercise performance. Time preferences are divided into so-called chronotypes. A chronotype is the propensity for the individual to sleep at a particular time during a 24-h period [63]. Eveningness and morningness are two extremes, with most individuals having some flexibility in the timing of their sleep period. People with different chronotypes may have different physiological circadian rhythms [64–66]. Days can be divided into various time ranges that are suitable for people with different chronotypes, to maximize their exercise performance.

Measurements of individual chronotypes are mainly based on self-evaluation questionnaires. The most widely used one is the Morningness-Eveningness Questionnaire (MEQ), which is developed by James A. Horne and Olov Östberg [67]. The MEQ identifies three chronotypes: morning types, evening types, and intermediate types. Chronotypes are not only subjective preferences. They are also reflections of different peak times [68, 69]. Compared to morning groups, for example, peak oral temperature and serum cortisol levels are about 3 h later in evening types [64, 70]. Melatonin in the saliva and blood of intermediate-type people peaks about 3 h earlier than in evening-type people, indicating that intermediate groups tend to sleep and wake up earlier [68]. Chronotypes are also influenced by age and gender. Women and the elderly tend to wake up earlier than men and younger people [68].

In recent years, studies (list in Table 6.2) have focused on the impact of morning and evening chronotypes on exercise performance. For instance, Rae et al. [76] noticed that the swimming athletes with an intermediate chronotype swam faster in the morning, whereas those in the evening-type groups performed better in the early evening. Also, Henst et al. [77] explored the effect of chronotypes on marathon performance. They found that South African runners are more morning-type-like compared to Dutch athletes. There was a negative correlation between MEQ scores and exercise performance in the South African group but not in the Dutch group. The researchers suggested that, for better performance, African athletes should participate in track and field sports in the morning. Such results emphasize the significance of chronotypes in daily exercise.

Table 6.2 Summary of chronotype influence on exercise performance

Reference	Sample	Chronotype	Exercise	Objectives	Results
Lim et al. [71], PMID: 33413572	340 athletes (males = 261, females = 79)	No definitely morning type, moderately morning type, neither type, moderately evening type, definitely evening type	Basketball, rugby, wrestling, boxing, short track, swimming, squash, baseball, weight lifting, judo, soft tennis, rowing, canoe, tennis, fencing, field hockey, handball	Investigate the sleep quality and athletes' performance according to chronotype of athletes	The athletic performance and sleep quality of the early chronotype were higher than in the late chronotype
Hill et al. [72], PMID: 32924652	14 volunteers	"Morning types" (M-types), "evening types" (E-types)	Extreme intensity cycling	Determine the effect of time of day and chronotypes on mood state and performance of extreme intensity cycling exercise	Wingate test was higher in the afternoon than in the morning, higher in the evening, regardless of chronotype. However, time of day and chronotype interaction exist in all the three variables of Wingate test
Roveda et al. [73], PMID: 32093513	141 male players (mean age 14.9 ± 1.79 years)	Morning-types, evening-types, neither-types	Soccer	Study the effects of chronotype and time of day on soccer skills including agility, aerobic endurance and explosive power	M-types performed better in the morning than in the afternoon ($p < 0.05$), E-types performed better in the evening than in the morning ($p < 0.05$), and type N showed no difference
Anderson et al. [74], PMID: 30210568	27 swimmers (age range 18–22 years; 8 males, weight 78 kg, height range 1.75–1.93 m; 19 females, weight	Morning type, evening type	Swimming	Evaluate the effects of time of day, diurnal preference, chronotype and *PER3* genotype on swimmer effort and performance	E-type swimmers were 6% slower in the morning than in the evening, and the diurnal preference and *PER3* genotype

	62 kg, height range 1.55–1.83 m)				significantly affected swimming effort and performance
Küüsmaa et al. [75], PMID: 26361893	72 male volunteers (mean age 32±6 years; height 1.8 ± 0.1 m; weight 80.9 ± 10.8 kg)	Neutral types, slight late types, moderate late types, slight early types, moderate early types	Maximal isometric force	The circadian rhythm of the participants' maximum isometric force and the effect of chronotype on the maximum isometric force were tested	Maximal bilateral isometric leg press force and maximal unilateral isometric knee extension force were 4.4 ± 12.9% ($p < 0.01$) and 4.3 ± 10.6% ($p < 0.01$) higher in the evening compared to the morning. Maximal unilateral isometric knee extension force and maximal voluntary activation level did not show significant diurnal variation
Rae et al. [76], PMID: 25631930	26 swimmers (18 males, 8 females; age 32.6 ± 5.7 years)	Morning type, evening type	Swimming	Examined the effects of swimmers' morning and evening performance, ratings of perceived exertion and emotional states	Morning chronotype swimmers were faster and had lower RPE scores. Evening chronotypes swimmers had higher vitality and lower RPE scores at night

6.3.4 Contribution of Different Types of Exercise to Circadian Rhythm

6.3.4.1 Aerobic Exercise

The use of oxygen is critical for aerobic exercise. Oxygen uptake (VO_2) at rest has obvious circadian rhythm characteristics. The level at 4:00 in the morning is the lowest, and it peaks in the evening, which coincides with the time when core temperature peaks. Oxygen uptake levels during resting states, submaximal exercise, and lactic acid training have circadian rhythms, while maximal oxygen uptake (VO_2max) does not [78]. The circadian rhythm of oxygen uptake for submaximal exercise depends on the selected exercise mode. Aerobic exercise is the main form of exercise to improve cardiorespiratory endurance. Cardiovascular function and lung function are also affected by the circadian rhythm [79]. Performing aerobic exercises when the functional status of the cardiopulmonary system is at a better level during the day is conducive to long-term exercise, thereby improving cardiopulmonary function.

6.3.4.2 Anaerobic Exercise

Studies [80] have found circadian rhythms in short-term high-intensity exercise, especially anaerobic exercise, such as the 30 s full-strength Wingate bicycle exercise. Similar circadian rhythms were also found in step tests and stair running and jumping. A more systematic study used force-velocity tests to study anaerobic exercise capacity. The results found that maximum strength appeared at 17:10 $\pm$ 00:52, with maximum amplitude of 7%, and that peak strength appeared at 17:24 $\pm$ 00:36, with amplitude of 7.6%. Moreover, body temperature is positively correlated with anaerobic exercise capacity [81]. Body temperature can be used as an indicator for predicting anaerobic exercise capacity. Exercise training in accordance with the circadian rhythm of anaerobic exercise often has better results.

6.4 Influence of Exercise on Circadian Rhythm

As mentioned above, circadian rhythms are affected by light–dark cycles and non-light signals (such as exercise). Exercise can cause a phase shift in circadian rhythms, and it can change the body's main rhythm initiator and reshape other biological rhythms. Table 6.3 summarizes some of the effects of exercise on the circadian rhythm. Studies have found that exercise in the morning and at night causes phase delays. The melatonin phase shift in a group that exercised at night increased their heart rate during sleep, while those exercising in the morning showed enhanced activity of the parasympathetic nerve [85]. Regular exercise during the day

Table 6.3 Summary of exercise influence on circadian rhythm

Reference	Sample	Exercise	Objectives	Results
Jahrami et al. [82], PMID: 34046817	82 depression patients (32 males, 50 females)	High-intensity interval training (HIIT)	To study the effects of high-intensity interval training (HIIT) on sleep and cardiopulmonary health in patients with	After HIIT training, the scores of Beck depression inventory-II (diff $= -1.57$ [95% CI –2.40 to –0.73], $P = 0.001$), Pittsburgh sleep quality index (diff $= -1.20$ [95% CI -2.10 to -0.32], $P = 0.008$) and cardiopulmonary exercise testing VO_2 (diff $= 0.95$ [95% CI 0.62–1.28], $P = 0.001$) were significantly improved, and the sleep quality was improved
Weitzer et al. [83], PMID: 32976649	5365 participants (breast cases: 1438, female controls: 1593; prostate cases: 1004, male controls: 1330)	Lifetime recreational, household physical activity	To investigate whether the time of day physical activity affects the risk of prostate and breast cancer in a case-control study (MCC-Spain)	Physical activity in the morning (8–10 am) had a protective effect on breast (OR $= 0.74$, 95% CI $= 0.48$–1.15) and prostate cancer (OR $= 0.73$, 95% CI $= 0.44$–1.20), physical activity in the evening had a moderate protective effect on prostate cancer (OR $= 0.75$, 95% CI $= 0.45$–1.24)
Lavin et al. [84], PMID: 31751180	21 old lifelong exercisers (LLE), 10 old healthy nonexercisers (OH), 10 young exercisers (YE)	Acute resistance exercise	To examine the inflammatory responses of exercisers and nonexercisers to acute resistance exercise challenges	LLE had predominantly anti-inflammatory muscle profile [higher IL-10 ($P \leq 0.05$ vs. YE), TNF-α, TGF-β, and EP4 levels ($P \leq 0.05$ vs. OH)], acute exercise in OH only increased expression of proinflammatory factors TNF-α,

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Table 6.3 (continued)

Reference	Sample	Exercise	Objectives	Results
				TGF-β, and IL-8 ($P \leq 0.05$)
Yamanaka et al. [85], PMID: 26333783	22 male participates (age 22.0 ± 1.8 years; body mass index 20.9 ± 2.2 kg/m^2)	Bicycle ergometer	Study the effects of physical exercise each morning or evening on the circadian rhythm of melatonin and the core body temperature of young men exposed to dim light for 7 days	Melatonin phase delay was detected in both morning and evening exercise, and the decline in rectal temperature at night was attenuated by night exercise, not by morning exercise

can strongly promote the stability and amplitude of the circadian rhythm, and exercise can be used as a tool to restore bad circadian rhythms [86]. In a randomized controlled trial, sleep quality improved significantly after 12 weeks of moderate-intensity exercise training compared with mere stretching exercises [87]. However, vigorous exercise at night within an hour of going to bed increased the time before falling asleep and impaired sleep quality [88]. Till Ronneberg [89] at the University of Munich coined the term "social jetlag" in 2006, to describe the difference between work and free days. The switch between going to bed early and getting up early on workdays and going to bed late and getting up late on free days leads to the body rhythm being out of sync with the outside time. Proper exercise on free days can alleviate social jetlag on workdays [90].

Insufficient sleep and circadian disruption (such as jetlag and shift work) have become new modifiable risk factors for obesity, disrupting the metabolic function of specific tissues. They are risk factors for lifelong obesity in children and young people [91–93]. Obesity is associated with an increased prevalence of cardiovascular disease, and exercise is associated with reducing cardiovascular risk, improving cardiometabolic risk factors, and promoting weight loss by creating a negative energy balance [94]. In a randomized controlled trial, the body weight of obese participants was significantly reduced after different intensity exercise interventions, and the effect of high-intensity exercise on weight loss was significantly better than with low-intensity exercise [95]. As a regulator of circadian rhythm, lifelong regular physical exercise can delay the aging process, improve life quality, and prolong life [96].

6.5 Physical Activity, Circadian Rhythm, Health

Physical inactivity is a global health problem and is listed as the fourth-largest behavioral risk factor for global mortality [97]. Physical inactivity is a variable factor for cardiovascular and other chronic diseases, including cancer, obesity, hypertension, diabetes, depression, and joint diseases [98]. The WHO recommends that adults do at least 150 min of moderate-intensity exercise or 75 min of vigorous exercise per week [99]. Adults should also perform muscle-strengthening activities twice a week and minimize sedentary time. Similar guidelines are also suitable for those under 18 years of age. Routine physical activity promotes the growth of human bones and muscles. By improving the nervous system's ability to control muscles, the speed of muscle response to nerve stimulation and the ability of various muscle groups to cooperate with each other are improved, thereby achieving an ideal exercise effect [100]. Moreover, physical activity can also increase lung capacity, improve the function of the respiratory system, and protect lung function in smokers [101]. Aerobic exercise reduces the risk of myocardial infarction and stroke by lowering blood pressure, lowering cholesterol levels, and improving weight control [102]. In a meta-analysis of the effects of physical activity intervention on mental health in children and adolescents, researchers found that moderate physical activity significantly lowered psychological discomfort, such as depression, stress, negative effects, and psychological distress. Physical activity intervention can improve the mental health of young people [103].

There are mutual influences between circadian disruption and health. Circadian disruption increases the severity of disease, and disease disrupts circadian rhythms. Circadian disruption increases the risk of cancer, diabetes, hypertension, and other diseases [104–107]. Circadian disruption leads to increased arterial blood pressure, decreased sleep efficiency, and increased risk of cardiovascular disease [108]. Physical activity can improve heart metabolism and reduce the risk of cardiovascular disease. The regulation of circadian rhythms by physical activity is achieved partly through the regulation of skeletal muscle [109]. Disrupting the circadian rhythms of skeletal muscles increases the risk of chronic diseases in the human body. Studies have shown that skeletal muscle disorders lead to reduced glucose tolerance, and increased risk of cardiovascular disease, cancer, and diabetes [110, 111]. Cancer patients generally suffer from poor sleep quality, circadian rhythm disruption, and poor quality of life. Weekly walking exercises can significantly improve sleep time and quality in lung cancer patients. Exercise for lung cancer patients is an important factor in patient recovery [112]. As one of the external factors that regulate the circadian rhythm, physical activity is inferior to light, but its regulation of human body functions (such as skeletal muscle and cardiopulmonary function) will affect human health.

6.6 Concluding Remarks and Future Perspectives

Routine physical activity or sports exercise should be based on scientific circadian rhythms and be synchronized as much as possible. Doing so will lead to better results while avoiding injuries during exercise and fitness. Most sports exercise is better performed in the afternoon than in the morning, because in the afternoon the core body temperature, heart rate, strength, and flexibility of the human body are higher than in the morning. In general, exercise performance and exercise-induced physical fitness will be better if the exercise is performed at a certain time of the day. In addition, the influence of the circadian clock on sports performance varies with the individual's chronotype. There are differences in sleep–wake patterns, core temperature, and hormone secretion in the early and late chronotypes of people in different physiological and behavioral rhythms. People working shiftwork and those with jetlag or sleep disorders can have circadian rhythm disorders, which are detrimental to human health and sports performance. Exercise can regulate circadian disruptions and reshape circadian rhythms. Exercise can improve sleep quality, alleviate social jetlag, reduce the risk of chronic diseases, and delay aging.

Core temperature, skeletal muscles, and flexibility are guided by their own rhythms, but research on circadian rhythms has not been combined with efforts to improve sports performance. The following are avenues for future research. First, a rhythmic model of sports performance can be designed using algorithms to find the appropriate time and exercises to improve sports performance based on circadian rhythms. At present, there is extensive research on the circadian clock and sports performance, but there is no database or knowledgebase that summarizes and organizes relevant publications on the circadian rhythm and sports performance. Such a database or knowledgebase would facilitate research. Second, specific exercises are often prescribed for patients. If the theory of circadian rhythms is added to exercise prescriptions, they will be more scientific and provide unique opportunities for personalized precision medicine and overall social well-being.

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Chapter 7
Data-Driven Exercise Medicine for Cardiovascular Disease

Ke Zhang and Bairong Shen

Abstract According to the Global Burden of Disease Study, in the past 20 years, cardiovascular disease (CVD) has consistently ranked as the leading cause of human death and loss of healthy life. Regular and systematic physical exercise is a crucial treatment strategy for CVDs, and many evidence-based medical studies support its safety and effectiveness. Therefore, most CVD patients are encouraged to take long-term physical exercise. Although there are many exercise guidelines for patients with CVD, most of them are at population level rather than individualized, and thus overlook individual differences such as disease severity, drug intake, and common risk factors. In addition, when prescribing exercise for individuals, knowing how to combine different exercise training guidelines properly is a major challenge in the clinical practice of traditional exercise medicine. Data-driven exercise medicine, based on objective data and computer technology, improves the efficiency and safety of exercise intervention and offers an excellent solution to these issues by fully considering the individual differences of patients and dynamically generating optimally customized exercise prescription. This article takes CVDs as an example to review the concept, data integration, and modeling methods of data-driven exercise medicine, discussing specific application cases and summarizing challenges and future development trends.

Keywords Exercise medicine · Cardiovascular disease · Exercise prescription · Data integration · Clinical decision support system

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7.1 Introduction

7.1.1 Traditional and Data-Driven Exercise Medicine

Exercise medicine is a comprehensive applied science that combines medicine and exercise. It involves the study of medical problems related to exercise and the use of medical knowledge and technology to provide supervision and guidance, prevent diseases, and enhance physical fitness. According to the European Standards of Postgraduate Medical Specialist Training, a professional sports and exercise medicine doctor needs 4 years of specialist training including in internal medicine (cardiology, emergency medicine, and clinical nutrition), orthopedics and traumatology, physical therapy, and rehabilitation medicine [1].

The practice of traditional exercise medicine is mainly based on the professional knowledge and clinical experience of practitioners. Therefore, the professional ability of practitioners largely determines the quality of diagnosis and treatment. Unfortunately, many regions lack professional exercise medicine specialists due to financial or other constraints. Although exercise training is regarded as an important measure in the prevention and treatment of cardiovascular diseases (CVDs), clinicians and other health care professionals rarely provide safe and effective personalized exercise guidance [2–4]. In addition, in diagnosis and treatment in traditional exercise medicine, patients seldom participate in the decision-making of their health care and disease management; the formulation of the therapeutic regimen mainly relies on the subjective decisions of the doctor, which may cause unnecessary differences in exercise prescription [5–11]. Furthermore, exercise prescriptions based solely on clinical guidelines cannot adequately account for patient heterogeneity. Many studies have shown that when prescribing exercise training for cardiovascular patients, it is necessary to fully consider related risk factors according to the severity and type of disease, especially for CVDs [12].

With technological innovation, health care has gradually turned to digitization, and data-driven exercise medicine provides solutions for traditional exercise medicine's issues. Based on objective data rather than solely on personal experience or intuition, data can be collected through electronic information technologies (mobile applications, wearable devices, and sensors), and analyzed and processed through models. Feedback can then be given according to the analysis results, providing decision support for clinicians (Table 7.1). In this way, data-driven exercise medicine effectively solves the above problems faced by traditional exercise medicine.

Table 7.1 The difference between traditional and data-driven exercise medicine

Traditional exercise medicine	Data-driven exercise medicine
Based on individual experience and intuition	Based on data analysis
Oriented to population	Oriented to individuals
Slow iteration of knowledge	Fast iteration of knowledge
Static prescription	Dynamic prescription

7.1.2 Cardiovascular Disease and Physical Activity

CVDs are a class of circulatory system disorders related to the heart and blood vessels [13]. Common CVDs include coronary heart disease, stroke, peripheral arterial disease, hypertensive heart disease, rheumatic heart disease, and congenital heart disease, as well as deep vein thrombosis and pulmonary embolism [14].

Generally, CVDs occur because fat accumulates in blood vessels and forms deposits, resulting in hardening, narrowing, blockage, and damage of blood vessels, so that blood cannot flow into the heart or brain. The occurrence of CVDs is related to multiple risk factors, among which smoking, hypertension, hyperlipidemia, diabetes, lack of exercise, obesity, poor diet, and excessive drinking are the main behavioral risk factors [13]. Many studies have shown that by breaking bad habits and taking moderate exercise, eating healthily, quitting smoking and drinking, and controlling weight, CVDs can be effectively prevented [15]. Furthermore, adequate exercise can reduce not only the occurrence but also the adverse effects of CVDs. Aside from medicine and surgery, exercise training is also considered an effective treatment and rehabilitation measure for those who have already suffered CVD [16]. Taylor et al. [17] discovered that exercise-based rehabilitation treatment can significantly reduce all-cause hospitalization rates by 30% and CVD hospitalization rates by 41% [17]. Not only that, exercise training can significantly improve prognosis markers for patients with CVDs. According to the systematic review of Cipriano et al. [18], aerobic exercise has a favorable impact on N-terminal pro–B-type natriuretic peptide (NT-proBNP) and minute ventilation/carbon dioxide production (VE/VCO_2) slope, two typical prognosis markers of heart failure that improved by −817.75 pg/mL and −6.55, respectively in the study [18].

Many exercise training guidelines are accessible presently for CVD patients and the general public with a high risk of CVD, such as the *2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease*, the *sixth Edition of the Guidelines for Cardiac Rehabilitation Programs by American Association of Cardiovascular and Pulmonary Rehabilitation*, and the *2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease* (referred to as the 2020 ESC guidelines). According to the 2020 ESC guidelines, regular exercise helps prevent CVD and lowers the risk of early death in patients. Patients are diverse and have varying exercise risks, and cardiovascular doctors should analyze each patient's exercise risks before recommending exercise training. In addition, the 2020 ESC guidelines give specific exercise recommendations for different CVDs and describe exercises according to five characteristics: frequency, intensity, time, type (FITT principle), and mode of exercise training [19]. The exercise training mode is classified as aerobic or anaerobic based on the type of metabolism, isometric or isotonic based on the condition of muscle work, continuous or intermittent, targeting large or small muscle groups, etc. [19].

Undoubtedly, prescribing exercise is a complex task, especially for patients. Only after many factors are examined can an effective exercise prescription be given. For CVD, data-driven exercise medicine first integrates the latest guidelines, evidence,

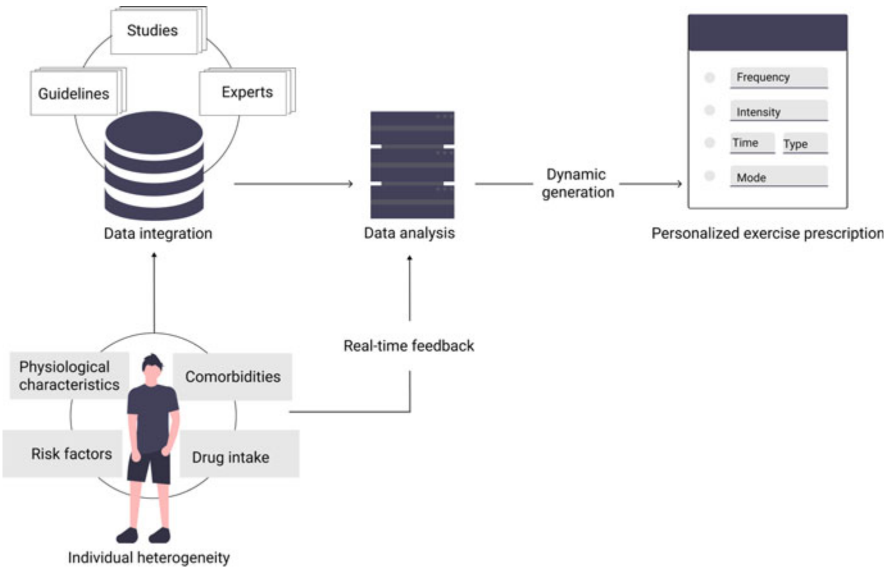

Fig. 7.1 Data-driven exercise medicine

and multiple expert opinions, using interactive digital information technology. Then, it works hand in hand with patients to consider fully the individual's heterogeneity (physiological characteristics, drug intake, adverse events in exercise tests, CVDs, and risk factors). Next, it generates a highly personalized and standardized exercise intervention program and provides a tailor-made solution for each patient, providing answers that traditional methods cannot offer (Fig. 7.1).

7.2 Data Integration

Data-driven science is inseparable from the support of big data. However, existing exercise medicine data varies widely, has a complex structure and scattered distribution, and cannot be directly utilized. Data integration is the prerequisite for data-driven science. By logically or physically integrating data from different sources, formats, and characteristics into a unified data set, comprehensive data sharing is realized [20]. Conventionally, data integration has three categories: data warehouses, federated databases, and middleware-based methods (Tables 7.2) [21]. Data integration based on a data warehouse is the physical integration of heterogeneous data sources. It physically integrates data distributed across multiple data sources into a central database through continuous extraction, transformation, and loading (ETL) [22]. Data integration based on the federated data system is based on the interoperability of multiple autonomous databases. Multiple heterogeneous databases are interconnected through a computer network to realize data sharing between disparate

Table 7.2 A summary of data integration

	Data warehouse	Federated database system	Middleware
Resource	Database Semi-structured data Unstructured data	Database	Database Semi-structured data Unstructured data
Operation	Extract Transform Load	Schema mapping	Mediated schema mapping
Storage	Local control	Leaving data at the source	Leaving data at the source

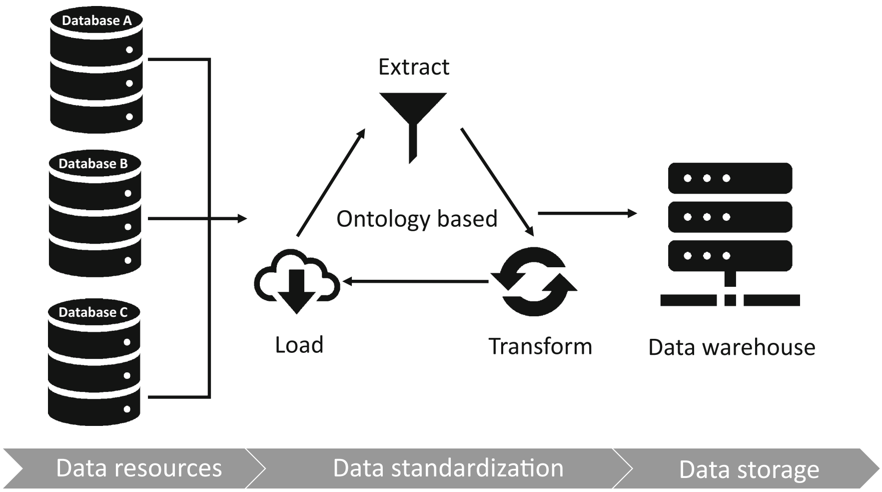

Fig. 7.2 Ontology-based data warehouse diagram

databases. Data integration based on middleware is a data integration method at the model layer by which middleware is added to the federated data system for data requests and heterogeneous data sources are accessed through the global data model.

Compared with the latter two methods, the data warehouse is more suitable for exercise medicine data integration. Integration based on the federal database is an integration of existing autonomous databases, whereas there is no such database for exercise medicine currently. Although integration based on middleware can integrate non-database data sources, such integrated data is usually read only, whereas a data integration system based on a data warehouse is both readable and writable. In addition, a data warehouse is usually local storage, and the data is preprocessed by data cleaning, so the quality, accessibility, and privacy of the data are better, and it is suitable for highly proprietary data integration, such as UCSC Genome Browser [23] and BioMolQuest [24]. However, the complexity and heterogeneity of exercise medicine data are still a big challenge to the traditional ETL process. Ontology, as a conceptual specification, can accurately describe data semantics, relationships, and functions [25]. Combined with ontology, the data warehouse system (Fig. 7.2) can effectively solve this problem.

7.2.1 Data Resources

The core of data-driven exercise medicine is the big data created by a plethora of new biological science technology. With the continuous innovation of technology and the increasing clarification of the benefits of exercise on CVDs, more and more studies have focused on data-driven CVD exercise medicine. There is still a lack of public open-source databases or data sets for CVDs and exercise medicine. As a result, data from CVD exercise medicine is primarily obtained in three indirect ways: integrating from existing CVD or exercise data sources, extracting from unstructured information (literature, guidelines, and expert opinions), and collecting from clinic cohorts (Fig. 7.1). Public databases such as PubMed, Ovid, and MEDLINE provide access to CVD and exercise medicine research and guidelines. Search terms commonly used include "exercise, ""physical activity," and "cardiovascular disease," among others.

Exercise databases were introduced in Chap. 4 and this information is not repeated herein. Table 7.3 displays the databases for CVDs. The National Cardiovascular Disease (NCVD) database combines various current CVD databases in Malaysia, and gathers and analyzes domestic CVD-related data, which is helpful for CVD prevention, treatment, and management. Among the four databases, NCVD is the only one that is still available. Although the remaining three databases have been rendered inoperable, their methodologies for building CVD databases can still be taken as a reference.

C/VDdb collected 13,945 molecular entities related to CVD from 92 studies and described the study design, sample size, and significantly different molecular expression changes. The database provides users with retrieval and data browsing functions through the interactive web [26]. CVDHD has collected 3518 natural herbs, 35,230 natural products, 2395 target proteins, 302 diseases, and 260 clinical markers related to CVD [27]. It builds a database of CVD-related natural products, providing users with data screening and browsing tools [27]. The Cardio is also a web-based database, including CVD-related genes, proteins, drugs, interrelationships, and reference information, supporting studies about the pathological mechanism of specific CVDs [28].

7.2.2 Data Standardization

The essence of data integration is to transform data from different sources into unified standard data sets. Data standardization is the key to data integration—it largely determines the quality of data integration. The following points are typical in good data: accessibility, accuracy, comparability, completeness, reliability, flexibility, plausibility, relevance, timeliness, uniqueness, and validity [29–33]. In addition to these features, as the number of data sources grows, data consistency becomes an essential factor for evaluating data quality. Various data sources are heterogeneous

Table 7.3 The cardiovascular disease databases

Name	Description	PMID	URL
The National Cardiovascular Disease Database (NCVD)	The NCVD is a service supported by the Ministry of Health to collect information about cardiovascular disease (CVD) in Malaysia, enable calculation of incidence of CVD and evaluation of its risk factors and treatment in the country	N/A	http://www.acrm.org.my/ncvd/index.php
C/VDdb	The cardiovascular disease (C/VD) database is an integrated and clustered information resource that covers multi-omic studies (microRNA, genomics, proteomics, and metabolomics) of cardiovascular-related traits with special emphasis on coronary artery disease [26]	30419069	www.padb.org/cvd
CVDHD	The cardiovascular disease herbal database (CVDHD) was designed to be a comprehensive resource for virtual screening and drug discovery from natural products isolated from medicinal herbs for cardiovascular-related diseases [27]	24344970	http://pkuxxj.pku.edu.cn/CVDHD
Cardio	Cardio is a web-based system built to provide a knowledge environment with a visual interface to integrate information about major CVDs in relation to genes and proteins [28]	15458691	http://www.cardio.bjmu.edu.cn/

and complex, with different structures or descriptions. Therefore, data standardization is indispensable to assure data quality [34].

Ontology is a vital method of data standardization that can effectively identify and classify entities from numerous perspectives. Ontology for Biomedical Investigations (OBI) [35], for example, which is extensively used in the integration and analysis of biomedical big data, provides a standard for the investigation and research of life science and clinical data, enabling the interchange and reuse of various data. Furthermore, Ontology for BioBanking (OBIB) [36] and Informed Consent Ontology (ICO) [37] provide a uniform standard for the informed consent procedure as well as the collection, storage, and utilization of biological samples from research subjects. The Human Phenotype Ontology (HPO) [38] and Illness Ontology (DOID) [39] provide a universal standard for disease symptoms and diagnosis, whereas Drug Ontology (DrON) [40] provides a unified standard for therapeutic medications.

Although ontology is critical for data-driven exercise medicine research, it is still in its early stages, without well-established exercise medicine ontology, particularly for CVD. Kostopoulos et al. [41] proposed an ontology framework to support tailored exercise prescriptions for CVD rehabilitation that encompasses the concepts

Table 7.4 Ontologies of exercise medicine for CVD

Name	Description	PMID
An ontology-based framework aiming to support personalized exercise prescription	The framework encapsulates the necessary domain knowledge and the appropriate inference logic, to generate exercise plan suggestions based on patient's profile. It also supports readjustments of a prescribed plan according to the patient's response with respect to goal achievement and changes in physical-medical status [41]	22254621
OPTImAL	OPTImAL describes relations of 320 factors originated from 60 multi-dimensional aspects (e.g., social, clinical, psychological) affecting CVD patient adherence to physical activity and exercise [42]	31023322

and linkages of relevant medical knowledge and exercise prescriptions. This ontology framework divided exercise prescription into three stages: initial, improvement, and maintenance. Furthermore, to achieve personalized exercise training, it stipulated the logical process of exercise prescription formulation, ensuring that the exercise prescription at each stage is tailored to the patient's situation [41]. However, the research only stayed at the theoretical level and was not put into clinical practice. Later, Livitckaia et al. [42] proposed an ontology for standardizing exercise compliance in CVD patients: OPTImAL (an ontology for patient adherence modeling in the physical activity domain). Different from the former (Table 7.4), OPTImAL focuses on describing the relationship between CVD patient characteristics and exercise compliance. It contains 142 categories, 10 object attributes, 371 individuals, and 2637 logical axioms, describing the relationship between 320 factors in 60 multi-dimensional aspects (for example, social, clinical, psychological) [42].

Apart from these, only a small number of exercise or CVD-related ontologies can be used as a reference for standardization of exercise medicine data for CVD. Exercise-related ontology, covered in Chap. 1, will not be discussed here. The CVDO (CVD ontology, https://bioportal.bioontology.org/ontologies/CVDO) is an ontology library established jointly by Sherbrooke University (Canada) and the INSERM research institute and provides integrated omics data linked to cardiovascular illnesses, building a systemic model for investigating the pathogenic process [43].

7.2.3 Data Storage

As biomedical data enters the era of multi-dimensional big data [44], data warehouse systems can better meet the management needs of the rapidly growing massive data and ever-changing data structure than traditional databases (Oracle, Mysql, PostgreSQL). A data warehouse (DW or DWH), as defined by Bill Inmon, is "a subject-oriented, integrated, non-updateable collection of data that changes over time to support management's decision-making analysis process." Although the essence of both a DW and a traditional database is a collection of data, the database's data source is single, the amount of data is small, and it is primarily used for online transaction processing (OLTP). The DW is a central warehouse that houses integrated data from various data sources. It is capable not only of storing data, but also of performing online analytical processing (OLAP), reporting data, and providing decision support (Tables 7.5) [45].

In the field of medical care, there are many data resource platforms based on data DWs, such as the Maternal and Infant Data Hub (MIDH) [46] built by Cincinnati Children's Hospital Medical Center, a perinatal DW that integrates data from multiple institutions, including data on 42,000 postpartum examinations and 70,000 newborns. In addition, BioVU [47] and the Synthetic Derivative [48] constructed by Vanderbilt University Medical Center store more than 50,000 biological samples and associated genotype and phenotype information, and automatically associate biological samples with the clinical information of patients, which makes big data. A large number of cohort studies become possible.

7.2.4 Challenges

Challenge 1: Public and Open-Source CVD Exercise Medicine Data

Because of the sheer scarcity of specialized public data resources, the acquisition of CVD exercise medicine data sources is essentially the data integration of unstructured or semi-structured data. Unlike structured data integration, unstructured data integration needs to be complex. For structured databases, the primary goal of data integration is to integrate distributed heterogeneous resources and provide users with a unified view, which can be accomplished by ETL or extract-load-transform (ELT) systems, such as IBM InfoSphere DataStage, Oracle Data Integrator, and Microsoft SQL Server Integration Services [49]. As for unstructured data such as CVD exercise medicine data, because there is no fixed data format and the data source is complex, unstructured data integration requires more labor.

Currently, CVD exercise medicine data can only be obtained indirectly through the extraction and integration of existing information, including manual extraction, automatic algorithm mining, or a combination of both methods. Purely artificial extraction ensures data quality but is inefficient, so the latter two computer-assisted

Table 7.5 Differences between data warehouse and database

Characteristics	Data warehouse	Database
Essence	Data collection	Data collection
Data source	Multiple	Single
Suitable workloads	OLAP	OLTP
Data scale	Large	Limited
Subject areas	Multiple	Single

strategies are more widely employed. Generally, computer-aided text mining needs the usage of a corpus for model training, which also relies on a database or data set. Consequently, the absence of a public open-source CVD exercise medicine-specific database or data set is an unavoidable issue and a challenge in the growth of data-driven exercise medicine.

Challenge 2: Ontology of Exercise Medicine for CVD
Ontology is the cornerstone of data standardization, and data standardization is the foundation of data-driven exercise medicine. Standardized data based on a robust ontology could effectively implement knowledge integration, reuse, and sharing. For CVD exercise medicine data in particular, which is complex and heterogeneous biomedical data, the ontology can accurately define related entities and their relationships from part to whole and clarify the relationship between exercise interventions and individual differences. Undoubtedly, a well-established CVD exercise medicine ontology could promote the high-quality development of data-driven exercise medicine for CVD.

Challenge 3: Big Data Storage and Management for Cardiovascular Exercise Medicine
With the continuous increase of data scale, traditional small-scale database storage methods can no longer meet the storage requirements of the big data era. How to effectively store and manage cardiovascular exercise medical data is also a major challenge. Adopting the DW storage mode, a shift from OLTP to OLAP is necessary, with full integration of the underlying data, improvements to data quality and utilization, and support for clinical decision-making.

7.3 Modeling and Applications

At present, the main application of data-driven exercise medicine is to provide decision support for relevant practitioners. Based on data integration, a clinical decision support system (CDSS) is developed to provide clinicians and related health care providers with professional knowledge and patient personal information, to improve the quality of doctors' health decisions (Fig. 7.3) [50].

"Exercise is medicine" has been proven by a growing number of studies in recent years. For CVD especially, exercise training is considered a Class 1A intervention in prevention [51, 52]. According to the ESC guidelines, patients with CVD or at high risk are encouraged to engage in moderate-intensity endurance exercise training 3–5 days per week, with a total exercise duration of more than 150 minutes and energy consumption of 1000–2000 kcal [51, 52].

Unfortunately, owing to a lack of adequate exercise prescription skills education and training, few clinicians are confident in prescribing exercise for patients. In addition, in clinical practice, patients have varied baseline features; therefore, when prescribing exercise, evaluating the patient's conditions and training goals is necessary in order to provide appropriate exercise guidance. However, traditional exercise

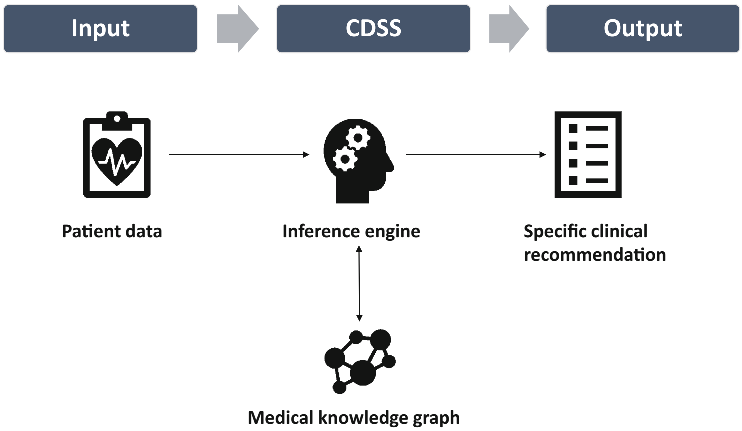

Fig. 7.3 Clinical decision support system (CDSS) diagram

prescriptions based on guidelines and experience cannot fully consider individual heterogeneity [53]. The CDSS converts data into knowledge, making clinical decision-making more objective, intelligent, and personalized, and can effectively solve the problems faced by exercise medicine. This section will focus on this issue, taking CVD as an example and introducing commonly used data-driven exercise medicine modeling methods and specific cases: data-driven exercise medicine CDSS-personalized exercise prescription tools.

7.3.1 Modeling: Medical Knowledge Graph

Most CDSSs are composed mainly of medical knowledge graphs and reasoning engines (Fig. 7.3) [54]. The medical knowledge graph is the core of the CDSS, which stores the collection of all the knowledge needed for problem-solving, including basic facts, rules, and related information. The reasoning engine applies logical rules to the medical knowledge graph to infer new information, combines knowledge with patient information, and provides personalized decision support [55].

A medical knowledge graph is a kind of knowledge base that uses graph or topological structure to integrate medical data. It stores the entities and relations between entities in a triple (head entity, relationship, and tail entity), including the association of multi-granularity and multi-level semantic units [56]. A medical knowledge graph is constructed with four parts: ontology construction, knowledge acquisition, knowledge fusion, and knowledge storage (Fig. 7.4).

The crucial process of constructing a medical knowledge graph is similar to that of data integration, although with differences in storage data structures. The essence of both is the integration of knowledge from different sources. Unlike relation-based

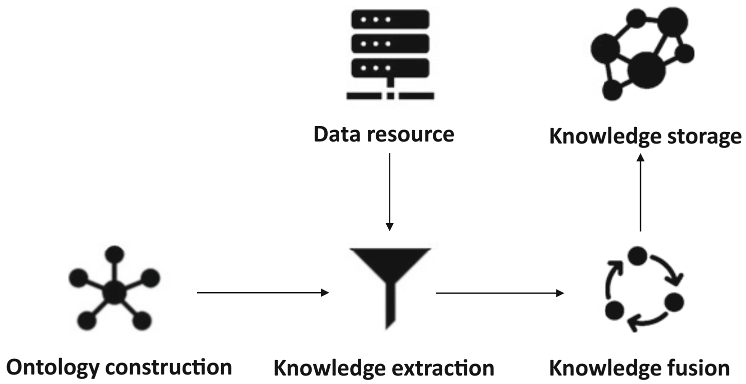

Fig. 7.4 Knowledge graph diagram

storage in DWs, the storage of existing knowledge graphs is based mainly on graph models. Compared with storage based on relational models, graph models are more suitable for dealing with complex relational issues and can effectively use relation-centric data expression. Large-scale knowledge graphs based on graph models such as DBpedia [57] and Freebase [58] integrate massive entities and relationships across domains, providing a rich source of knowledge for many systems and for software development.

How to transform from relational model storage to graph model storage is the focus of data-driven exercise medicine modeling. Graph databases (GDBs) are the primary tool for knowledge graph storage [59]. At present, mainstream GDBs are Neo4j, Microsoft Azure Cosmos DB, ArangoDB, OrientDB, Virtuoso, GraphDB, and HugeGraph. (Table 7.6). Neo4j is the most commonly used GDB, especially in the field of biomedical research. Balaur et al. [60] built EpiGeNet based on Neo4j, a knowledge map of the relationship between genetic and epigenetic molecular events in colorectal cancer. It enhances the ability to query molecular events at different stages of colorectal cancer. Lose et al. [61] built COMBAT-TB-NeoDB based on Neo4j, an omics knowledge base integrated with Mycobacterium tuberculosis. COMBAT-TB-NeoDB provides researchers with a joint query solution across tuberculosis data through graph model algorithms.

7.3.2 Application: Personalized Exercise Prescription Tool

7.3.2.1 The Everyday Practice and Rehabilitative Training Tool

The Everyday Practice and Rehabilitative Training (EXERT) tool is the first exercise prescription optimization tool. It was developed by the European Association of Preventive Cardiology (EAPC) and Hasselt University (Belgium) over 3 years [62].

Table 7.6 Popular graph databases

Name	Languages	Operating systems	Description	Website
Neo4j	.Net Clojure Elixir Go Groovy Haskell Java JavaScript Perl PHP Python Ruby Scala	Linux OS X Solaris Windows	Scalable, ACID-compliant graph database designed with a high-performance distributed cluster architecture, available in self-hosted and cloud offerings	neo4j.com
Microsoft azure cosmos DB	.Net C# Java JavaScript JavaScript (node.Js) MongoDB client drivers written for various programming languages Python	Hosted	Globally distributed, horizontally scalable, multi-model database service	azure.microsoft.com/services/cosmos-db
ArangoDB	C# C++ Clojure Elixir Go Java JavaScript (node.Js) PHP Python R Rust	Linux OS X Windows	Native multi-model database management system (DBMS) for graph, document, key/value and search. All in one engine and accessible with one query language	www.arangodb.com
OrientDB	.Net C C# C++ Clojure Java JavaScript JavaScript (node.Js) PHP Python Ruby Scala	All OS with a Java JDK (> = JDK 6)	Multi-model DBMS (document, graph, key/value)	orientdb.org

(continued)

Table 7.6 (continued)

Name	Languages	Operating systems	Description	Website
Virtuoso	.Net C C# C++ Java JavaScript Perl PHP Python Ruby Visual basic	AIX FreeBSD HP-UX Linux OS X Solaris Windows	Virtuoso is a multi-model hybrid-RDBMS that supports management of data represented as relational tables and/or property graphs	virtuoso.openlinksw.com
GraphDB	.Net C# Clojure Java JavaScript (node.Js) PHP Python Ruby Scala	All OS with Java VM Linux OS X Windows	Enterprise-ready resource description framework (RDF) and graph database with efficient reasoning, cluster and external index synchronization support. It also supports SQL JDBC access to knowledge graph and GraphQL over SPARQL	www.ontotext.com
HugeGraph	Groovy Java Python	Linux MacOS Unix	A fast-speed and highly-scalable graph DBMS	github.com/hugegraph

First, the latest CVD-related exercise training guidelines and evidence were consulted, according to medical experts from different European countries. These were used to formulate exercise training and safety recommendations considering various CVDs, relevant risk factors, common chronic non-CVDs, patients' baseline exercise tolerance, commonly used cardiovascular drugs, and adverse events in exercise tests. Based on the above data, computer science experts from Hasselt University constructed the core algorithm of the interactive digital decision support system [62].

The system has three main functions: an exercise training recommendation center, an exercise prescription training center, and exercise prescription history visualization. The exercise prescription recommendation center can automatically generate personalized exercise prescriptions and safety recommendations according to the input, and optimize exercise prescriptions for cardiologists, physical therapists, clinical exercise physiologists, and/or medical workers engaged in cardiovascular rehabilitation. The exercise prescription training center provides 64 cases of CVD in different situations to help practitioners train their exercise prescription skills. Exercise prescription history visualization can be used to view exercise prescription recommendation records to help users compare different exercise prescriptions [62].

As the first interactive electronic exercise prescription CDSS, the EXPERT tool comprehensively considers various types of CVD, multiple risk factors, different medications, and other clinical conditions to automatically generate detailed exercise training recommendations. It effectively improves the efficacy and safety of exercise prescriptions. However, the EXPERT tool has limitations. First of all, it does not consider the difference between in-hospital and out-of-hospital exercise training. All exercise training needs to be under the guidance of professionals. Second, although the recommended exercise prescription of the EXPERT tool has been tested, it has not been fully verified in clinical practice.

7.3.2.2 The Prioritize, Personalize, Prescribe Exercise

The Prioritize, Personalize, Prescribe Exercise (P3-EX) was developed by Pescatello et al. [63], based on the evidence-based recommendations of the American College of Sports Medicine (ACSM) and the American Heart Association (AHA). It comprehensively considers multiple CVD risk factors (diabetes, dyslipidemia, hypertension, obesity, etc.) to formulate personalized exercise prescriptions for patients [63].

The P3-EX includes four steps when giving exercise suggestions. The first step is to complete the ACSM health screening to identify people with a high risk of sudden death from exercise. The second step is to identify the types and numbers of risk factors for CVD. The third step is to give priority to heart diseases such as hypertension, diabetes, dyslipidemia, and obesity, then formulate exercise prescriptions based on risk factors of vascular disease. The last step is to design exercise prescriptions and recommend them [63].

P3-EX is the first CDSS to formulate exercise prescriptions for patients with multiple CVD risk factors. Based on the industry guidelines and consensus of the AHA and ACSM, it provides clinicians with evidence-based and time-sensitive references. However, the P3-EX tool is still in the testing stage, and further evaluation is needed to verify its feasibility before it can be promoted to clinical applications.

7.3.3 Challenges

Challenge 1: Data Security

The use and storage of exercise medicine data involves patient privacy. Sharing data without infringing on patients' sensitive information is the main challenge faced by exercise medicine data drivers. In 2020, Saranya et al. [64] proposed a graph-based data encryption method, which can effectively protect the privacy of medical data. Encryption is a commonly used data security measure at present. How to further effectively combine data encryption with GDBs and realize secure data sharing will be a major research direction for exercise medicine data applications in the future.

Challenge 2: A Truly Personalized Exercise Prescription Tool

Both EXPERT and P3-EX are data-based decision support systems (Table 7.7), which fully consider the heterogeneity of patients. However, they cannot consider

Table 7.7 Current data-driven exercise prescription tools

System	Methodology	Function	Target audience	URL
EXPERT	Decision support system based on expert opinions, guidelines, clinical trials, reviews	Exercise training recommendation, exercise prescription training, exercise prescription history visualization	Cardiologists, physiotherapists, clinical exercise physiologists, nurses specifically involved in CVD rehabilitation	https://expert-tool.edm.uhasselt.be
P3-EX	Decision support system based on guidelines	Exercise training recommendation, risk factors for CVD identification	Physicians, health care professionals	Not reported

the timeliness of various input indicators and adjust exercise prescriptions in time. Combining the use of wearable devices and the generation of dynamic exercise prescriptions based on the patient's real-time physiological conditions will be one of the development directions of data-driven exercise medicine in CVD.

Furthermore, the current target audience for EXPERT and P3-EX is restricted to relevant doctors and healthcare practitioners, aiming to help them optimize exercise prescriptions and provide more personalized exercise programs. To ensure safety and effectiveness, patients must still exercise under the observation and instruction of specialists. With the advancement of technology and a better understanding of the relationship between exercise and disease, the targeted use of data-driven exercise prescription tools, used in combination with mobile applications, can be expanded to the general public in the future to achieve unsupervised, efficient, and safe exercise anytime, anywhere [63].

7.4 Conclusion

With CVD as an example, this chapter briefly reviews the concept, data integration, and application of data-driven exercise medicine, an emerging interdisciplinary specialty that is both diverse and complex. Although it provides novel solutions to the problems faced by traditional exercise medicine, it also faces new challenges.

The establishment of public databases or data sources is the primary challenge faced by data-driven exercise medicine. Because of the lack of public exercise medicine databases, data sources can only be obtained through data integration. Data integration comprises three parts: data extraction, data standardization, and data storage. Data extraction methods can be either manual or computer assisted. Although pure manual extraction has high accuracy, it is inefficient, whereas computer-assisted methods, for example, automatic mining through artificial intelligence technologies such as natural language processing, are fast but cannot guarantee data quality. Only by establishing a high-quality public data source can this problem be solved.

Establishing a robust exercise medicine ontology is the second challenge faced in data-driven exercise medicine. Data standardization is an important method for ensuring data quality. As the cornerstone of data standardization, an effective ontology can achieve efficient data integration and sharing. Ontology is not only the cornerstone of data standardization, but also a key technology for constructing medical knowledge graphs. Owing to the complexity and diversity of medical knowledge, designing a unified and comprehensive logical model to ensure the validity and availability of data storage is difficult in the construction of knowledge graphs. A knowledge graph constructed based on effective ontology can represent knowledge in a more accurate and meaningful way.

Efficient storage and management of exercise medicine data is the third challenge faced by data-driven exercise medicine. With the development of big data and the explosive growth of biomedical data, traditional database storage has been unable to meet the storage and management needs of medical data. Finding and establishing a new DW storage model is one of the future development directions of data-driven exercise medicine. Different from traditional database storage modes, DW-based storage is more suitable for the storage and analysis requirements of medical big data and provides powerful data support for data-driven application development.

Data security and privacy protection are also unavoidable issues in medical data sharing and application. The use and storage of medical data usually involves the sensitive personal data of patients, and protecting patient privacy is a significant prerequisite for the sharing and application of exercise medicine data. Encryption is the current mainstream data security protection measure. How to effectively combine data storage and encryption to protect patient data from the source is an important part of the development of data-driven exercise medicine.

The practical applications of data-driven exercise medicine, such as EXPERT and P3-EX, still have limitations. First, the current applications, which are mainly based on a data-driven decision support system, consider individual needs but not timeliness. This can be integrated through the use of wearable devices to obtain real-time changes in the patient's physiological condition, achieving personalized precision medicine. Second, the intended audience of most existing data-driven exercise medicine products are only relevant practitioners in the field, which means professional advice is still required for the general public to conduct safe and effective exercise training. The use of mobile devices will expand data-driven exercise medicine to the public, realizing unsupervised training for the entire population anytime and anywhere, a key development direction in this field.

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Chapter 8
Physical Activities and Prevention of Neurodegenerative Diseases

Shikha Joon, Rajeev K. Singla, and Bairong Shen

Abstract Physical activity (PA) boosts mental health and well-being in both healthy and diseased populations. As regards to the latter, its therapeutic effects have been noted in patients diagnosed with various neurodegenerative disorders, and in this chapter we summarize these effects. The neuroprotective effects of PA are conferred via improved neuronal hormones, neurotransmitters, and neurotrophic factor production. These changes are effected through several cellular and molecular mechanisms. PA also leads to enhanced neuroplasticity and neuronal survival, as well as the optimization of physiological and neuroendocrine responses to physical and psychosocial stressors. PA also contributes to the sensitization of the autonomic nervous system, central nervous system, and parasympathetic nervous system. This is done via the promotion of angiogenesis, autophagy, neurogenesis, and synaptic plasticity, amongst other neurological processes. Altogether, PA confers neuroprotective and neuropreventive effects, including improved cognition, memory, sleep, and angiogenesis in the nervous system, and reduced anxiety, insulin resistance, neuro-inflammation, and stress.

Keywords Physical activity (PA) · Neurodegenerative diseases · Neuroprotective and neuropreventive effects · Neuronal hormones · Neurotransmitters · Neurotrophic factors

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8.1 Introduction

Neuroprotection is the process of interfering with the processes responsible for cellular dysfunction and death. This is done to avert neuronal cell death. The notion of neuroprotection has piqued the scientific community's interest in the search for new medicines that can assist maintenance of brain tissue while also improving overall outcomes [1]. In the elderly, the most prominent risk factor for neurological illnesses is aging [2]. Physical activity reduces the risk of Alzheimer's disease (AD) and dementia by 45% and 28%, respectively, according to epidemiological research [3, 4].

Physical activity (PA) has garnered much attention as a potential neurological disease-modifying therapeutic method, based on prior studies [5–7]. PA has appropriately been described as a non-drug therapy for a variety of disorders. These include cardiovascular, metabolic, neurological and psychiatric diseases [8]. For example, a study by Lu et al. investigated the effect of treadmill-mediated physical activity on cognitive function in a rat model of AD caused by streptozotocin. They found a significant inhibition of neuronal apoptosis in the rat hippocampal Cornu ammonis (CA1) [9]. Furthermore, Lu et al. showed that the induction of angiogenesis probably occurred due to the upregulation of MT1-MMP expression caused by the treadmill exercise. This, in turn, conferred neuroprotection to the rat models of AD against cerebral ischemia [10]. Also, there are considerable data from various *in vivo* studies on neurological disorders and physical activity that indicate the therapeutic potential of exercise for improving cognition [11, 12].

Various PA-induced molecules involved in neurological processes have been discovered, due to considerable breakthroughs in molecular methods [13]. The identified neurological molecules include brain-derived neurotrophic factor (BDNF), endothelial nitric oxide synthase), insulin-like growth factor (IGF), nerve growth factor, superoxide dismutase (SOD), and vascular endothelial growth factor (VEGF), whose levels are increased in the brain hippocampus. In contrast, there occurs a decline in the production of free radicals that are detrimental to neurological functions. Together, these are involved in memory [14]. Figure 8.1 illustrates the neuroprotective and neuropreventive effects of PA for various neurodegenerative disorders.

PA has been shown to slow the progression of neurodegeneration and is known to help reduce the risk of dementia and other neurodegenerative disorders such as Parkinson's disease (PD), AD, and others [15]. In a meta-analysis, PA was found to be a safe and efficient additional therapy for improving attention, cognition, and memory, impairment of which is associated with various neurological disorders such as AD, PD, Huntington's disease, multiple sclerosis, schizophrenia, and unipolar depression. PA also improves psychomotor speed, and quality of life, with no complications [16]. Authors of another study reported that PA in midlife maintains functions associated with cognition and minimizes or postpones the risk of dementia in later life [17]. Furthermore, PA and diet modulate the substrates involved in brain neuroplasticity, including antioxidant defense, inflammation, neurogenesis,

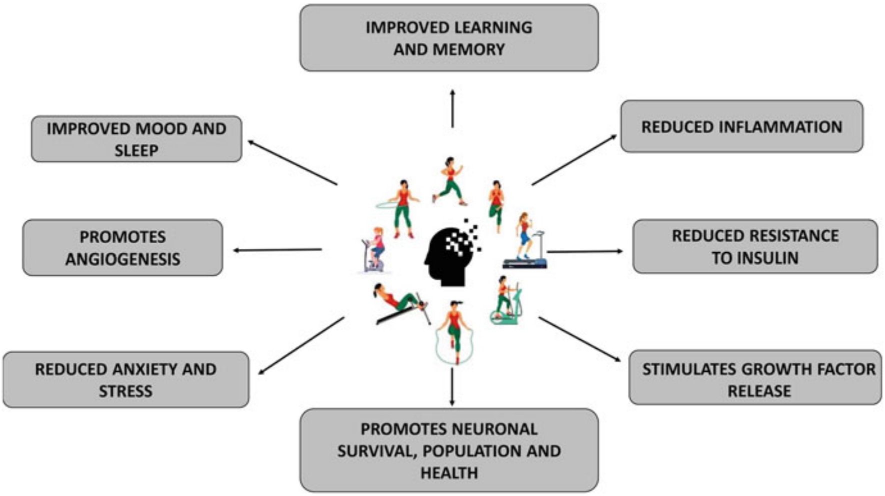

Fig. 8.1 The neuroprotective and neuropreventive effects of PA for various neurodegenerative disorders

neurotropic signaling, and stress response. As a result, these are regarded as crucial therapeutic alternatives for age-related disorders, including dementia [18]. Furthermore, Bass et al. found that PA was positively correlated to the academic performance of schoolchildren [19]. In addition, individuals who exercise aerobically improve their attention, executive function, memory, and processing speed, according to a meta-analysis of randomized controlled studies [20]. Exercise also causes an increased blood flow to the hippocampus and reduced neuro-inflammation [21, 22]. Moreover, numerous biological pathways are affected by PA. In particular, it optimizes the physiological and neuroendocrine responses to physical and psychosocial stressors, acts as an armor against stress in general or stress associated with chronic diseases, promotes a state of anti-inflammation, and enhances the expression of growth factor and neuroplasticity [23]. PA affects brain functioning and causes structural alteration as reported in a neuroanatomical study. Here, there was a significant improvement in the cortical tissue density of the frontal, temporal, and parietal cortices, which are otherwise known to be reduced with age (55 to 79 years). This could be attributed to the cardiovascular fitness levels associated with the PA in the study group [24]. Similar findings were reported in an *in vivo* study, wherein arborization, spine density, and spine morphology were altered among rats that performed voluntary long-term running on the wheel [25]. Interestingly, neuropathology related to AD was attenuated and cognitive functions (hippocampus-mediated) were improved with PA, particularly in the early stages of disease progression. However, specific PA guidelines are yet to be reported [26].

PA, when performed regularly, alleviates the symptoms of AD, as evidenced from animal studies and human clinical trials [23]. PA is also advantageous to PD patients, leading to improved balance, gait, physical functioning, strength, and quality of life, and reduction in the occurrence of PD [27, 28]. In this chapter, we have summarized the neuroprotective and neuropreventive effects of PA for neurodegenerative diseases to aid researchers and medical professionals interested in this area (Table 8.1).

8.2 Role of PA in Neurodegenerative Disease

A sedentary lifestyle with insufficient exercise may increase the risk of AD, PD, and stroke [133]. Aerobic exercise improves cognitive function in elderly people [134]. This could be attributed to decreased chronic oxidative stress while increasing mitochondrial biogenesis and autophagy upregulation, and the neurotransmitters and trophic factors that are stimulated by PA. These include BDNF, fibroblast growth factor 2, glial-derived neurotrophic factor (GDNF), and IGF-1 [28].

Autophagy, anti-oxidant defense mechanisms, neurogenesis, neural plasticity, and other neurophysiological features and pathways are all affected by PA, along with a reduction in neurodegeneration and neural apoptosis. Neuro-plastic changes in the brain are induced by PA, although there is a lot of variation across people [15]. Regular PA enhances neurological function and promotes autophagy [10, 135]. Also, it stimulates mitochondrial biogenesis and lowers chronic oxidative stress. In the hippocampus, there occurs an enhanced expression of neurotrophic factors (BDNF and GDNF) and neurotransmitters (irisin and dopamine [DA]), while BAX and neuro-inflammatory cytokines are suppressed [136]. PA regulates BDNF, which performs crucial functions that include neuronal stress resistance, synaptic transmission and plasticity, neuronal plasticity, activation of DA and NFκB in the neurons, and neuronal differentiation and maturation [13, 137].

AD is perhaps the most common form of dementia and a major healthcare concern [138]. AD patients are often treated with a combination of pharmacological drugs and counselling to retard disease progression [7, 139]. PA prevents cognitive decline and lowers AD risk [140]. It aids in the stabilization and improvement of cognitive functions as well as the prevention and delay of severe neuropsychological symptoms such as apathy, disorientation, and depression in AD patients [141]. Anti-inflammatory and neurotrophic factors have also been found to be induced by PA [142, 143]. *In vivo* studies have shown that PA can avert damage to white matter (induced by obesity) via suppression of vascular dysfunction and neuro-inflammation. These effects were evident even when there was weight gain in the study animals [144]. Aerobic exercise, in particular, enhances *ABCA1* mRNA expression, which in turn may cause improved cognition via alleviating and avoiding symptoms of AD [145]. The above reports provide strong evidence for the therapeutic utility of PA for age-related neurodegenerative disorders such as AD.

PD is the second most common age-related neurodegenerative disease [146]. PD is characterized by α-synuclein accumulation (cytosolic protein) and dopaminergic degeneration at the cellular level [27]. Many efforts have been undertaken to utilize various ways to address its therapeutic element. However, despite numerous

Table 8.1 Physical activities and prevention of neurodegenerative diseases

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Systematic review	Effect of PA on the PD-associated depression in patients	28749970	[29]
PD	Review	Effect of physical activity on PD	30532351	[30]
PD	Review	Effects of PA on the functional and physical capacities of the PD patients	27567884	[31]
PD	Systematic review	Investigation of effects and molecular mechanisms of PA on PD patients	32215173	[32]
PD	Systematic review	Definition and summary of the concepts and evidences on PA, physiotherapy, and exercise on PD	31970204	[33]
PD	Patient-based epidemiological study	Examination of self-reported activity scores and their associations with clinical attributes (Parkinson progression markers initiative; PPMI) in subjects with early PD	29480222	[34]
PD	Systematic review	Assessment of the efficacy of PA, occupational and physiotherapy therapy on motor and non-motor symptoms in PD	27583249	[35]
PD	Clinical study	Investigation of the relationship between PA-related prodromal attributes and PA	31719136	[36]
PD	Systematic review and meta-analysis	Quantification of association (dose-response) between PA and PD-risk	30646166	[37]
Dementia	Systematic review	Prospective evidence on the risk of developing neurodegenerative disease and PA	18570697	[38]
PD	Review	Role of BDNF in increased PA-induced neurodegenerative processes and neuro-regeneration mechanisms	30901514	[39]
PD	Randomized controlled trial	Examination of the relationship between PA and cognition in PD (YOPD)	32353174	[40]
PD	Cohort implementation study	Promotion of PA by telehealth (engage-PD) in PD patients (newly diagnosed) in response to coronavirus pandemic	32734298	[41]

(continued)

Table 8.1 (continued)

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Observational study	Effects of the coronavirus pandemic on PA, psychosocial distress and severity of symptoms in PD patients	32925108	[42]
PD	Review	The impact of PA and inactivity in PD patients	27477046	[43]
Dementia	Clinical study	Impact of PA on subjects diagnosed with the neurodegenerative disease	33467309	[44]
PD	Clinical study	Changes in PA and its correlation with the effects seen in PD patients during coronavirus pandemic	32837960	[45]
PD	Review	Impact of PA on PD	30245949	[46]
PD	Observational study	Using an activity monitor to quantify PA in PD (early)	31420310	[47]
PD	Multi-center clinical study	Intervention of PA in association between cognition in PD and availability of striatal dopamine transporter	30722964	[48]
PD	Prospective and longitudinal clinical study	Self-reported PA levels and PD progression (early)	30554993	[49]
PD	Clinical study	Investigation of the effect of postural stability of the PD-patients on their PA	31688224	[50]
PD	Feasibility study	Technology intervention in assessing PA levels in PD patients (older adults)	1069250	[51]
PD	Clinical study	A gender-based analysis of the factors associated with PA levels in PD patients	31387476	[52]
PD	Cross-sectional study	Investigation of the predictors of PA levels in PD patients	32870459	[53]
PD	Qualitative systematic review	Collective experiences of PD patients and their opinion on PA interventions	30973527	[54]
PD	Clinical study	Identification of potential factors of PA (spontaneous) in PD patients	32369962	[55]
PD	Clinical study	Examination and comparison of self-reported PA, its objective monitoring and PD with respect to its clinical features	31621608	[56]

(continued)

Table 8.1 (continued)

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Clinical study	Promotion of PA in PD patients (older adults) via the *ReadySteady* intervention	32211555	[57]
PD	Clinical study	Correlation of total regular PA, pathologies in brain and PD (older adults)	32348372	[58]
PD	Literature review	Behavioural epidemiologic framework for the scrutiny of PA and PD literature	27777097	[59]
PD	Patient-based study	Mixed-methods approach for unraveling PA in PD patients and veteran	31036158	[60]
PD	Clinical study	Association of mood disorders and cognition with PA (daily) in PD (early-stage, treatment-naive patients)	31571008	[61]
PD	Clinical study	Fall frequency is reduced with increased PA training in PD patients	31648204	[62]
PD	Patient-based study	PD and prolonged impacts of balance-training (HiBalance program) based PA in PD patients (older adults)	31485305	[63]
Dementia and PD	Cross-sectional study	PA's association with dementia risk factors in PD patients	30746564	[64]
PD	Cohort study and meta-analysis	Association of PA with PD risk in the Swedish national march cohort	25410713	[65]
Neurodegenerative diseases	Review	Role of the Chinese nutraceuticals and PA in neurodegenerative tauopathy	33407732	[66]
PD	Observational cross-sectional study	Association of pain in PD patients with PA, mood and sleep	32333551	[67]
PD	Randomized study	Mendelian randomization study (two-sample) for PD and PA	33093192	[68]
PD	Clinical study	Investigation of the role of motor subtypes in PD patients and evaluation of PA by sensor- and patient-based methods	33302434	[69]

(continued)

Table 8.1 (continued)

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Clinical study	Effect of falls on PA in PD patients	26639446	[70]
PD	Clinical study	ICF-based holistic approach for evaluating PA in PD patients	32781376	[71]
PD	Clinical study	Association of PA and PD risk	15728289	[72]
PD	Observational study	Quantification of PA and determinants in PD patients (sedentary lifestyle)	23769178	[73]
PD	Review	Benefits of PA in PD patients	21750523	[74]
PD	In vivo study (C57BL/6 male mice)	Impacts of NAC in neuroinflammation in PD (sub chronic parkinsonism) and utility of PA	30477535	[75]
PD	Clinical study	Determination of the step-rate threshold for PA intensity in PD patients	32255504	[76]
PD	Clinical study	Impact of subthalamic stimulation on motor symptom improvement and PA in PD patients (advanced)	25361545	[77]
PD	Clinical study	Parkinsonism risk and PA in older adults dwelling in community	31046115	[78]
PD	Cross-sectional study	Impact of lower back pain-associated disability in PD patients on PA, functional mobility and QoL	31343700	[79]
PD	Clinical study	Frailty phenotypes in PD female patients and PA	22919489	[80]
PD	Clinical intervention trial	Secondary per protocol analysis of sleep, fatigue, and PA, and PD patients	30258564	[81]
PD	Randomized controlled trial	Objective assessment of PA and its association with physical function, balance and dyskinesia in PD patients	27589536	[82]
PD	Prospective cohort study	Risk of PD and PA	16926235	[83]
PD	Cohort study	Parkinsonism (mild) and PA in PD patients (older adults)	29931236	[84]

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Table 8.1 (continued)

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Clinical trial	Impacts of a group protocol on PA and changes associated with health locus of control and mood in PD patients with impaired mobility	30624196	[85]
PD	Cross-sectional study	Chair rising ability and its relation to PA and daily activities in PD patients	33292833	[86]
PD	Case control study	Risk of PD and leisure time as well as lifetime occupational PA	27177695	[87]
PD	Patient-based study	PD and falls and their association with PA (daily-living) and motor severity (laboratory-based evaluation) in PD patients	30718220	[88]
PD	Patient-based feasibility study	mHealth-based peer coaching for PA in PD patients	29449201	[89]
PD	Patient-based feasibility study	PA tracking in PD patients via wearables and their accuracy	29729611	[90]
PD	Patient-based study	PA (recreational) and PD risk	17960818	[91]
PD	Cross-sectional study	Attenuation of motor symptoms (nigrostriatal degeneration-independent) in PD patients by PA (non-exercise based)	26330028	[92]
PD	Pilot study	PA relationships with motor symptoms in PD patients as measured by a three-axis accelerometer	32912171	[93]
PD	Large population-based case-control study	PA (recreational and occupational) and PD in Denmark	28319247	[94]
PD and MS	Review	PA-associated behavioral alterations in PD and multiple sclerotic patients	23632452	[95]
PD	Review	PA-induced neuroprotection in PD and role of inflammatory processes and trophic factors	28894046	[96]
	Patient-based study	Neuropsychiatric symptoms of PD and PA	22914597	[97]

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Table 8.1 (continued)

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Randomised controlled trial	Encouraging PA and fitness in PD patients with sedentary lifestyle	23457213	[98]
DA, PSP, and PD	Pilot study	Fall risk in neurodegenerative patients in relation to PA	30617629	[99]
PD	Narrative review	Amelioration of PD as induced by PA	33532136	[100]
PD	Patient-based study	Association between depression, PA, cognition, and health-related QoL (objectively measured) in PD	29307560	[101]
PD	Multifactorial clinical study	PA, binge eating and nutritional status as determinants of body weight in PD patients	28649617	[102]
PD	Patient-based study	Evaluation of PA (ambulatory) in PD patients	27164042	[103]
PD	Clinical trial	Effects of fatigue on function and PA in PD patients	12682317	[104]
PD	Patient-based study	Evaluation of the factor structure and reliability of PASIPD in PD patients	25184403	[105]
PD	Patient-based study	PA level determinants in PD patients	26982987	[106]
AD, ALS and PD	Mendelian randomization study	Evaluation of PA effects on AD, ALS and PD (neurodegenerative disorders)	33515719	[107]
PD	Case-control study	Wearable devices for PA monitoring in PD patients	28660562	[108]
PD	Review	PA as a rehabilitation tool for PD	25332912	[109]
PD	Pilot study	Evaluation of PA and cognitive association with PD	28596093	[110]
PD	Clinical trial	Cognitive changes (longitudinal) in PD (early) patients and their association with *APOE* genotype and PA	33790041	[111]
PD	Pilot study	PA and its association with BDNF and cognitive function in PD patients	28338380	[112]
PD	Randomized controlled trial	Impact of fatigue on PD patients (idiopathic) and its association with PA	19514069	[113]

(continued)

Table 8.1 (continued)

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Clinical study	Impact of leg muscle fatigue on gait in PD and controls groups based on their PA (high and low)	27264409	[114]
PD	Clinical study	Profiles of PA in PD patients	33581724	[115]
PD	Patient-based study	Social opinion on PD control (early) via PA	19479519	[116]
PD	Clinical trial	Effect of cueing training on PA improvement in PD patients	20179328	[117]
PD	Clinical study	Determination of PA accelerometer cut points for PA evaluation in PD patients (older adults)	26332765	[118]
PD	*In vivo* study (A53T mice models of PD)	Elevated PA and energy expenditure is ameliorated by orexin/hypocretin neuronal inhibition in mouse models of PD	33466831	[119]
PD	Randomized controlled trial	Multifaceted behavioral program (ParkFit study) for the evaluating the efficacy of PA in PD patients	20723221	[120]
PD	Systematic review	A qualitative analysis of the PD patients' experiences and opinions on PA interventions	29135743	[54]
PD	Clinical study	Monitoring (3 months) the association between gait patterns in PD patients and PA (objectively measured)	30416704	[121]
PD	Longitudinal follow-up study	Improved anxiety and apathy with PA in PD (early) patients	33519706	[122]
PD	Patient-based study	Association of PA, daily energy expenditure and loss in weight in PD patients	19117356	[123]
PD	Cohort study	Association of reduced PD risk with PA (heavy and leisurely) and lower BMI	24633681	[124]
PD	Randomized controlled-trial	Assessment of ParkFit program (multifaceted intervention) for promoting PA in PD patients	23972329	[125]
PD	Patient-based study	Investigation of the effects of kinesiophobia and fatigue on PA, functional capacity and QoL in PD patients	33290306	[126]

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Table 8.1 (continued)

Neurological disorder	Study type	Theme of the study	PMID	References
PD	Comparative study	Investigation of proxy reports (QoL self-reports and caregiver reports) in PD and PA	16028212	[127]
PD	Randomized controlled-trial	Effects of PA (patterns and levels) and sedentary life-style in PD (mild to moderate) patients (elderly)	25655884	[128]
PD	Patient-based study	Non-association of reduced PA with fatigue in PD patients	18591055	[129]
PD	Patient-based study	Investigation of PA (adapted program) on motor and non-motor functions, and QoL in PD patients	25318771	[130]
PD	Patient-based study	Role of PA against neuro-muscular deterioration in PD patients	33595917	[131]
PD	Patient-based study	Effect of the coronavirus pandemic on PA, depression, and anxiety in the PD patients	33653991	[132]

Abbreviations: *AD* Alzheimer's disease, *ALS* amyotrophic lateral sclerosis, *APOE* apolipoprotein E, *DA* degenerative ataxia, *ICF* International Classification of Functioning, Disability and Health (ICF), *MS* multiple sclerosis, *NAC* N-acetyl-L-cysteine, *PD* Parkinson's disease, *PSP* progressive supranuclear palsy, *PASIPD* Physical Activity Scale for Individuals With Physical Disabilities, *QoL* quality of life; mHealth, mobile health.

advancements in treatment that have slowed the disease's development and reduced locomotor impairment, clinical management remains a problem [147]. Only high-intensity PA has been shown to be beneficial in alleviating the motor symptoms in PD patients [148]. Furthermore, mood, fatigue, aerobic fitness, motor function, and quality of life have been improved in PD patients [149]. In PD patients, 8 weeks of multi-component PA have improved functional status and gait speed [150]. Another study showed an increase in the concentrations of BDNF, DJ-1, and Hsp70, while aggregation of α-synuclein decreased, in the brains of mice who performed voluntary activity on a running wheel, in contrast to a control group. This provides compelling evidence that the PA can reduce the progression of PD by preventing aberrant protein aggregation in the brain [151]. According to a recent simulation study, PA such as horseback riding improves balance and cognitive impairment in PD-affected elderly [152]. Numerous studies have shown that PA can improve brain function while also reducing the risk of neurodegeneration [153]. PA is also known to improve neuroplasticity through synaptic structural alterations and functional changes in different brain regions. Multiple systems concerning the regulation of neuroinflammation and glial activation are also modulated [153]. Furthermore, using food additives (for example, carvacrol) in combination with PA has led to a reduction in both rotational behavior and aversive memory deficit when observed in rat models of PD. This study also demonstrated a decline in the levels of lipid peroxidation together with an increase in the hippocampus concentration of total thiol in rat models of PD [154]. These observations strengthen the notion that a combined PA-carvacrol therapy may be a promising therapeutic approach for PA patients suffering from impaired neurobehavioral characteristics [154]. PA is also known to benefit benefits PD patients' health by improving the patient's ability to adjust to impediments encountered during gait [155].

In a pilot study, coordination and manipulation therapy led to improved cardiac function and balance, and reduced mobility disorder, in PD patients over the control group [156]. In another study, the changes in lifestyle concerning PA and including natural anti-oxidants in the diet alleviates dopaminergic neuronal deterioration. However, this requires strategizing PA and dietary incorporation of oxygen radical scavengers as well as iron-binding agents [157]. PAs such as running on a treadmill improve stability in posture and gait activity, and promote α-synuclein and dopaminergic homeostasis *in vivo* However, in the same study PA did not significantly induce cerebral alkaline phosphatase [158].

8.3 Neurological Diseases and the Underlying Mechanisms of PA Intervention

8.3.1 PA-Mediated Regulation of the Neuroendocrine System

If the activity is of sufficient intensity and/or duration, PA serves as a stressor for the human body and acts as a neuroendocrine system activator. Chronic exercise training causes neuroendocrine system modifications, such as a reduction in the hormone stress response to submaximal activity [159]. Many substantial alterations in hormone concentrations (β-endorphin, cortisol, vasopressin, adreno-corticotropic hormone) are induced by PA as compared to resting levels. The higher the PA duration and intensity, the larger is the neuroendocrine response [160]. PA triggers various physiological responses, including stimulation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis, which causes optimal metabolic substrate selection and use. The stimulation of the hypothalamus-pituitary-adrenal axis by PA relies upon myriad attributes, including activity type, when it is performed, dietary intake, and characteristics of the individual [161].

8.3.2 PA and Regulation of Neurotransmitters

The central serotonergic, dopaminergic, and noradrenergic systems are all affected by PA [162]. PA gives rise to peripheral physiological adaptations to compensate for the activity-stimulated disruption in homeostasis in the resting state. Alterations in neurotransmitters and monoamine synthesis and metabolism take place during PA, as documented in various studies that used homogenized tissues to evaluate the levels of the neurotransmitters [162]. The use of voltammetry and microdialysis has revealed that PA influences the release of most of the neurotransmitters *in vivo* [162]. DA, noradrenaline, and serotonin or hydroxytryptamine (5-HT) are altered by PA, causing an increase in their release, and also affecting their extracellular levels along with γ-aminobutyric acid (GABA), and glutamate (GLU) [163]. Brain DA upregulation has been reported to be associated with PA-induced elevated serum calcium levels. Consequently, calcium/calmodulin-dependent DA production is influenced via tyrosine hydroxylase enzyme activation [164]. Furthermore, PA improves DA-receptor binding affinity [165, 166]. Also, in response to unpredictable stress, PA causes neural adaptation [167]. The galanin expression in the locus coeruleus is responsible for the PA-mediated anti-stress protective mechanism [168]. The expressed galanin, in turn, causes hyperpolarization of noradrenergic neurons, leading to neuronal firing inhibition by the locus coeruleus. This ultimately suppresses norepinephrine (NE) release [169]. It is well-documented that memory consolidation and retrieval are also aided by NE [170]. In comparison to sedentary controls, elevated levels of NE in the pons and medulla of the spinal cord were observed in chronic treadmill running and wheel running-based activities [171]. PA also elevates the endogenous NE activity levels, indicating an association between PA-mediated improved cognition and NE [163]. PA affects the HT system, however it depends on the region of the brain and is influenced by the intensity and duration of the activity. For example, moderate treadmill activity (4 weeks) caused a decline in the hippocampus levels of 5-HT while its metabolism remained unaffected [172]. In contrast, a high-intensity treadmill activity (1 week) led to a significant elevation of hippocampus levels of 5-HT [173].

8.3.3 PA and Neural Insulin Signaling

Insulin signaling in the brain is necessary for the survival of neurons and restoration of critical brain functions. Also, it causes aversion and reversal of BDNF transport abnormalities [174]. Abnormalities in the pathways associated with neural insulin signaling are associated with learning, memory impairment and neurodegenerative disorders, while its deregulation is related to cardiovascular diseases, diabetes, hypertension, and obesity [175]. The pyramidal cell axons of the hippocampal-CAl and other brain regions associated with cognition, memory, and learning have overexpressed insulin receptors [176].

The concentration of IRs is comparatively higher in the cerebral cortex, hippocampus, and hypothalamus regions of the brain [177, 178]. BDNF, insulin, IGF-1, IGF-2, and VEGF are actively involved in intracellular hippocampal neuronal signal transmission under normal physiological conditions. This maintains hippocampal neuronal integrity and functionality [179]. The risk of AD development becomes higher when these are suppressed [179]. A decline in aversive memory, elevation in inflammatory markers (interleukin-1(IL1-β), tissue necrosis factor-alpha (TNFα), and NF-kβ), and decline in anti-inflammatory markers (IL-4) have been observed in the rat models with aging. In the same study, histone H4 acetylation levels were found to have decreased. However, PA caused a reversal in the observed levels [180]. Improved hippocampal neuronal insulin signaling and anti-inflammatory effects have been shown to be exerted by PA, along with the elicitation of insulin-sensitizing effects in the peripheral nervous system (PNS) [179, 181]. Researchers have therefore speculated that PA confers neuroprotection and induces similar effects in the central nervous system (CNS) [182]. Many more investigational pieces of evidence suggest that PA assists in neuroprotection by acting on both CNS and PNS. Insulin-independent glucose uptake in the peripheral tissues is promoted by PA through activation of protein kinase. This is achieved by mammalian targets of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) - mediated activation. By contrast, in the CNS, cognition, synaptic plasticity, angiogenesis, and neurogenesis are improved by PA [183–186]. Furthermore, neurotransmitter synthesis and degradation are also regulated by PA [187, 188].

8.3.4 BDNF-Signaling and PA

BDNF is a hippocampal neurotrophin and critical regulator of neuronal and synaptic plasticity, and neuronal stress resistance. It is involved in learning and memory-related processes, and may be a key player in depression [189, 190]. It is well known for stimulating the differentiation and maturation of developing neurons [191]. However, positive regulation of the synaptic transmission and plasticity is undertaken in the mature neurons [192]. As a result, BDNF helps with memory and learning [193]. Brain size in humans and PA endurance are positively correlated, which is suggestive of cognition and locomotion co-evolution [194]. Furthermore, brain BDNF expression is elevated by endurance-based PA, and brain growth (of the hippocampus, in particular) is enhanced by improved PA capacity [195]. PA such as running on the treadmill has been found to ameliorate peri-neuronal net disorganization (specifically on the axotomized motoneurons) and synaptic stripping in peripheral nerve injury. Although this is credited to PA-mediated BDNF increases, the underlying molecular mechanisms remain unclear [196]. The hippocampal- and amygdala-associated neuronal functions are enhanced with PA. AD onset could also be delayed with PA as studied in double transgenic mouse models of (aged 1.5–-4 months) AD. In this study, 10 weeks of treadmill training elevated the memory associated with the hippocampus while the amygdala-associated memory was restored. Also, the dendritic arbor of amygdala basolateral neurons was restored while those of CA1 and CA3 neurons increased *in vivo*. The amygdala and hippocampal phosphorylated- protein kinase B, phosphorylated-protein kinase C, and p-TrkB (phosphorylated-tropomyosin receptor kinase B) levels (all signaling molecules of BDNF/TrkB) increased due to PA while the soluble amyloid-β levels declined *in vivo* [197]. Treadmill and running wheel exercises *in vivo* (in mouse models aged approximately 4 weeks) significantly elevated the mRNA and protein levels of BDNF and synaptic load in the dentate gyrus. Also, the exercises caused alterations in astrocyte morphology and the orientation of their projections. These could be due to astrocytic TrkB receptor level elevation [198]. The DA content in the neurons and their release are pivotal for neuronal survival as well as learning and memory. All these were modulated by BDNF [199].

8.3.5 Production and Secretion of Irisin and PA

PA induces the muscle protein FNDC5 (fibronectin type III domain containing 5), which in turn is cleaved and secreted as a myokine called irisin [200, 201]. Irisin is known to promote thermogenesis while improving glucose homeostasis and related obesity. There occurred an enhanced BDNF expression due to a forced neuronal FNDC5 expression [200]. Additionally, elevated blood irisin-induced BDNF and hippocampal neuroprotective gene expression were observed upon adenovirus-mediated peripheral FNDC5 delivery to the liver. It has been suggested that the brain's BDNF expression, endurance-based PA, and metabolic mediators are all linked [200]. It has been further suggested that irisin may serve as a link between motivation and reward mechanisms, and PA. These are, in turn, associated with DA that is activated via BDNF [199]. The neuronal injury induced by ischemia has also been ameliorated by irisin. This was achieved via Akt and ERK1/2 signaling pathway activation. Therefore, it appears that irisin aids the PA-induced neuroprotection against cerebral ischemia. There could be a possible irisin-mediated association between cardio-cerebrovascular disorders and metabolism [202]. Further, irisin has been shown to ameliorate neuronal injury induced by deprivation of oxygen and glucose. This is achieved via inhibition of the ROS-NLRP-3 (reactive oxygen species-Nod-like receptor pyrin-3) signaling pathway (involved in inflammation), which indicates therapeutic effects of irisin in the case of ischemic stroke [203]. Other therapeutic PA effects include neuropathic pain reduction as observed in rat models (male) of chronic constriction injury. In this study, it was observed that the pain threshold increased upon acute administration of irisin while the neuronal number was still reduced [204]. *In vitro* studies reported that a 12-hour irisin pretreatment conferred neuroprotection against amyloid-β toxicity. Here, IL-6 and IL-1β release was also attenuated along with the reduction in COX-2 expression, and AKT phosphorylation in cultured astrocytes. There occurred a reduction in the activation of NFκB in amyloid-β exposed astrocytes due to abrogation of IκBα phosphorylation and loss. These convincing findings suggest irisin as a potential therapeutic candidate for AD and memory dysfunction associated with diabetes mellitus [205].

8.3.6 PA-Mediated Neuronal Responses: Anti-Inflammatory and Oxidative Responses

To maintain homeostasis, the hypothalamic-pituitary-adrenal axis and the autonomic nervous system are activated in response to PA. Consequently, the plasma levels of catecholamine and cortisol increase. There occurs a stimulation of prolactin and growth hormone secretion. This, in turn, stimulates the TH_2 (T-helper cells) response profile and might impact the immune response generated [206]. Attempts have been made to discover novel biomarkers for characterizing PA-induced responses and unraveling the molecular mechanisms underlying neurodegenerative disorders. This would also be beneficial in assessing the effects of PA in these conditions. Kurgan et al. performed proteomic analysis (liquid chromatography-tandem mass spectroscopy) post-2D-gel electrophoresis on the samples obtained from six patients. A significant alteration was observed in the serum levels of 20 proteoforms post high-intensity PA at durations of 5 and 60 min, respectively. These proteoforms included apolipoproteins, protease inhibitors (serpins), and immune system proteins with known anti-inflammatory and antioxidant effects. These are also documented to have important roles in neuro- and cardio-protection, and lipid clearance [207].

Numerous studies have been performed to determine the synergistic and neuroprotective effects of anti-oxidants and PA on neurons in neurological disorders, such as PD. A combination neuroprotection strategy that involved NAC (N-Acetyl-L-cysteine, an anti-oxidant) and PA revealed its neuroprotective effects on mouse models of PD. Later, it was found that only NAC was responsible for conferring this neuroprotection *in vivo* [75]. PA is also known to induce the production of heat shock proteins (iHSP70, intracellular and eHSP70, extracellular). The iHSP70 activation is essential for anti-inflammatory mechanisms, cellular protection, and promotion of tissue repair while eHSP70 participates in immune system activation. In general, the internalization of eHSP70 (chaperones) by the motor neurons occurs as a stress response to attain cellular protection against oxidative damage and protein denaturation. Furthermore, neurodegenerative disorders (Amyotrophic lateral sclerosis, AD, PD, and Huntington's disease) are often characterized by lower expression levels of iHSP70. Therefore, it is important to elucidate their functional attributes and the neuroprotective effects of PA [208]. In response to PA, the anti-oxidant enzyme SOD is also released [28]. Together, these delay the onset of neurodegenerative disorders such as PD by retarding neural apoptosis, promoting neuroplasticity, and delaying neurodegenerative processes [133].

8.3.7 *Effects of PA on Survival and Apoptosis of Neurons*

PA is known to effectuate brain cell activity, survival, and apoptosis. PA, when performed voluntarily under favorable conditions, has caused cognition improvement, brain microvasculature, and neurogenesis promotion in hypobaric hypoxia exposed rat models. These effects were observed to be mediated via VEGF signaling [209]. PA, in the early stages of life, has been observed to induce prolonged neuronal (cortical) and hippocampal morphological changes in rat models. These *in vivo* effects were noticeable in a subsequent sedentary period. This study's authors speculated that neuronal growth promotion and neurotrophic factor expression are enhanced by PA, which replenishes the neuronal reservoir for later use in life. Also, there occurred PA-induced elevation in the neuronal (cortical) and hippocampal cellular population along with dendritic arborization [210]. Additionally, survival protein expression increased. These included hippocampal BDNF and cortical mTOR [210]. Reportedly, BDNF promotes PA-induced neuroprotective effects against type-II diabetes and dementia [211]. PA training type determined alterations in brain cell survival and inflammatory protein levels and their expression in rat models (aged rats). In particular, PA such as aerobics enhanced brain (cortex) Akt, p38, p70S6k, and ERK protein expression levels [212]. PA such as running improved spatial learning and memory in APP/PS1 transgenic mouse models (middle-aged) of AD. This was attributed to the neurogenesis and neuroprotection conferred by the PA in the dentate gyrus of these mouse models [213].

Further, PA such as treadmill exercise retarded Aβ-42 deposition via β-secretase (BACE-1) and C-99 inhibition and checked memory impairment (PS2 mutation-induced) in the cortex and the hippocampal region of PS2 mutant mouse models (aged). Also, there occurred a downregulation of protein disulfide (PDI) and glucose-related protein/binding immunoglobulin protein (GRP78/Bip) expression and abrogation of activating transcription factor-alpha (ATF6α), eukaryotic initiation factor-2α (eIF2α), Jun N-terminal kinases-p38- mitogen-activated protein kinases (JNK-p38 MAPK), protein kinase R-like endoplasmic reticulum kinase (PERK), and spliced X-box binding protein 1 (sXBP1). PA also led to Bcl-2 upregulation, CHOP, caspase-3, and caspase-12 activation, and BAX downregulation in PS2 mutant mouse models (aged) [214]. PA with varied intensities was observed to produce distinct effects on the nervous system. For instance, moderate intensity PA (treadmill) conferred neuroprotection in rat models of ischemia over a high-intensity workout, which causes downregulation of the neurotrophic factors influencing cell cycle-related protein expression levels [215]. PA that involved voluntary running stimulated progenitor cell proliferation in the dentate gyrus, and neurogenesis [216]. Reportedly, PA confers protection to the injury-susceptible retinal ganglion cells. This could be due to neuronal functional restoration and survival via thwarting of synaptic elimination (complement-mediated), and abrogation of retinal BDNF loss by the PA [217]. Finally, PA was observed to positively affect BDNF resting serum levels and cognition in adolescent mouse models (male) that were exposed to aerobics-based PA (moderate to high intensity) [218].

8.3.8 PA and Its Effects on Neural Autophagy

Under conditions of stress, such as restricted food supplies, evolution favored species with greater cognitive and physical abilities. This is suggestive of the fact that brain function can be improved by PA and dietary restrictions. Autophagy, DNA-repair proteins, mitochondrial biogenesis, neurotrophic factors, and protein chaperones are all involved in the neuronal signaling pathways for stress-response under energy limitations. The risk of neurodegenerative disorders, such as AD, PD, depression, and stroke might increase due to dietary malpractices, suppressed cellular adaptive stress responses, and lack of PA [133]. Furthermore, brain functions have been shown to improve *in vivo* with PA and dietary regulations, which checked the neurodegenerative processes. PA along with dietary regulations stimulate the signaling pathways for cellular adaptive stress responses, which, in turn, promote proteostasis, DNA repair, mitochondrial biogenesis, and neurotrophic signaling [219]. Aerobics-based PA and food deprivation have been observed to activate the neuronal signaling pathways involving PGC-1α, NFκB, CREB, and Ca^{2+}. These, in turn, induce mitochondrial biogenesis and cellular stress responses [220].

Autophagy is the cell's natural, conserved breakdown process, which removes unwanted or malfunctioning components via a lysosome-dependent, controlled mechanism. It enables the breakdown and recycling of cellular components in a controlled manner. Autophagic dysfunction leads to an increased sensitivity to stress conditions such as oxidative damage or starvation, loss of stem cells, neurodegeneration, and a rapid deterioration in neuromuscular function *in vivo* [221]. Autophagy plays a pivotal role in the production of β-amyloid and therefore its dysfunction can cause AD progression. Under genetically hyper-activated autophagic conditions, there occurs a significant decline in the accumulation of β-amyloid in knock-in mouse models of AD ($Becn1^{F121A}$). A restoration in the cognitive decline and survival was also observed in this study. This could be due to the mutated Becn 1 ($Becn1^{F121A}$), which led to a significant decline in the BECN 1 and BCL2 (inhibitor) interaction. Consequently, there occurred a constitutive autophagy activation. The amyloid-β-oligomers were found to be segregated inside the brain autophagosomes *in vivo*. Finally, PA was observed to be a physiological inducer of autophagy, which confers neuroprotective effects similar to those of Becn1. These included the removal of amyloid-β and improved memory *in vivo* [222].

8.4 Conclusion

Physical activities have been shown to improve people's overall health and well-being when they participate in them regularly. Regular exercisers reap the benefits in every part of the body in some way. When it comes to the effects on neuronal cells and brain function, numerous studies show that the PA has neuroprotective effects. The neuroprotective effects of physical activity are elicited by signaling processes that have yet to be fully understood. However, hormones such as irisin, neurotransmitters such as DA, and neurotrophins such as BDNF are known to directly participate in these signaling mechanisms. Furthermore, PA improves balance, cognition, and gait in PD patients, and retards disease progression by preventing brain aggregation of the protein. Furthermore, disease progression is retarded and the onset of neuropsychological symptoms is delayed in AD patients, along with improved cognition and memory. PA affects different neurophysiological aspects in afflicted patients. These include anti-inflammatory and anti-oxidant responses, autophagy, cell survival, apoptotic pathways, and hippocampal insulin signaling. PA is also known to upregulate BDNF expression that contributes to its neuroprotective effects. These neuroprotective mechanisms also involve Akt are DA, GABA, and irisin. In conclusion, PA is an excellent therapy for patients diagnosed with various neurological disorders when used in combination with other well-established treatment regimens.

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Chapter 9
Exercise Guidelines for Cancer Patients

Min Jiang, Yalan Chen, and Bairong Shen

Abstract Cancer remains the main cause of death, and the burden of cancer incidence and mortality continues to grow rapidly, seriously affecting the quality of life (QoL) and life expectancy of cancer patients and survivors. In recent years, an increasing number of people are engaging in exercise with increased awareness of the safety and benefits of exercise and the strong national promotion of comprehensive fitness. Although general exercise guidelines for the public are not completely suitable for this heterogeneous group because of their weakened physical and psychological conditions, it is generally recommended that they avoid inactivity and participate in exercise as much as possible if their physical conditions permit it. Therefore, this chapter provides information for cancer patients by discussing the relationship between physical exercise and cancer control, the safety of exercise programs, exercise guidelines for specific cancer groups, and the role of healthcare practitioners and physical activity specialists. The chapter also introduces several bioinformatics platforms and models.

Keywords Exercise guidelines · Exercise prescription · Cancer prevention · Cancer control · Cancer patients · Cancer survivors

9.1 Introduction

Global Cancer Statistics estimated that there were 19.3 million new cancer cases in 2020 (18.1 million, excluding non-melanoma skin cancer) and nearly ten million cancer deaths (9.9 million, excluding non-melanoma skin cancer) [1]. Among the new cases, female breast cancer (11.7%) was the most commonly diagnosed cancer,

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followed by lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach cancers (5.6%). Lung cancer (18%) was the primary cause of cancer death, followed by colorectal (9.4%), liver (8.3%), stomach, (7.7%), and female breast cancers (6.9%) [1]. By 2040, the global cancer burden will reach 28.4 billion cases, a 47% increase from 2020 [1].

Physical activity is defined as any bodily movement using skeletal muscles that increases energy expenditure. It refers to all movement, including leisure activity, transport to and from places, and activity at work [2]. By contrast, exercise is a specific type of physical activity that is repetitive and planned, with the aim of improving or maintaining physical fitness [2]. The main purpose of this chapter is to introduce the effects and corresponding mechanisms of physical activity and exercise on cancer control, and to introduce exercise guidelines for cancer patients.

Physical activity is a key factor in physical and psychological wellbeing and QoL in cancer patients [3]. Cancer treatment disturbs daily activities and increases sedentary behavior and physical inactivity [3, 4]. Over time, insufficient physical activity leads to the loss of muscular strength and a decrease in physical fitness, along with increased difficulty carrying out the basic activities of daily life [4, 5]. Sedentary behavior and a lack of physical activity are known risk factors for cancers and may account for nearly one-third of the poor physical conditions of cancer patients [4, 6–8].

Physical exercise benefits the whole spectrum of cancer. It is safe and effective during pharmacological treatment, and it has been proposed as a promising and effective intervention for cancer patients and survivors during and after treatment [2, 6, 7, 9]. Exercise helps prevent at least seven common cancers (namely, bladder, breast, colon, endometrial, esophageal, kidney, and stomach cancers) and it has positive effects on the survival rates of three common cancers (namely, breast, colon, and prostate cancers). Active exercise decreases cancer morbidity by 48% and cancer mortality by 27% [6, 10]. Participating in exercise improves surgical outcomes, reduces disease symptoms and treatment-related side-effects (e.g., fatigue, pulmonary and immune system dysfunctions, lymphedema, and cardiotoxicity), and improves physical and psychological health. It has compliance and survival benefits for particular cancers, helps cancer survivors deal with and recover from treatment, improves their long-term health, and prolongs survival [2, 6, 7, 9–11]. Exercise may also significantly save both short- and long-term costs by preventing disability, mitigating symptom severity, and reducing common treatment-related sequelae (e.g., fatigue, lymphedema, and pain) [12].

Although the American College of Sports Medicine (ACSM) provides exercise guidelines for cancer patients and treats cancer as a chronic disease, 53%–70% of patients do not engage in exercise programs [6]. A retrospective cohort study indicated that only 14.2%–20.5% of endometrial cancer patients perform community or home-based unsupervised exercise at the dose recommended by the ACSM [13]. At the same time, the lack of attention to exercise training principles and prescriptions leads to insufficient exercise stimulation [14].

9.2 Physical Exercise and Cancer Control

In 2007, Courneya et al. proposed a physical exercise and cancer control framework. In this framework, the authors proposed six cancer-related periods and eight corresponding cancer control categories. Based on this framework, we can determine when and how exercise may work in cancer control [9, 15–18]. In Fig. 9.1, we use prostate cancer for an example. There is level 1 evidence that exercise interventions are efficacious in improving cancer-specific quality of life, fatigue, and exercise capacity in men with prostate cancer.

Since prostate cancer is the most common malignant tumor diagnosed in the male population, there is a clear interest in determining the possible impact of physical exercise on disease prevention and improvement of disease-related outcomes. So far, the data has been contradictory and there is no clear identification of the prevention of prostate cancer through physical exercise. However, due to the many potentially annoying and health-threatening side effects of prostate cancer treatment, researchers have studied the impact of exercise training on reducing treatment-related complications and improving outcomes and QoL.

Physical exercise plays a corresponding role in the prevention, pre-treatment, treatment, and prognosis of prostate cancer [19–25]. Structured, supervised, and moderate-intensity physical exercise can slow down the occurrence and development of prostate cancer.

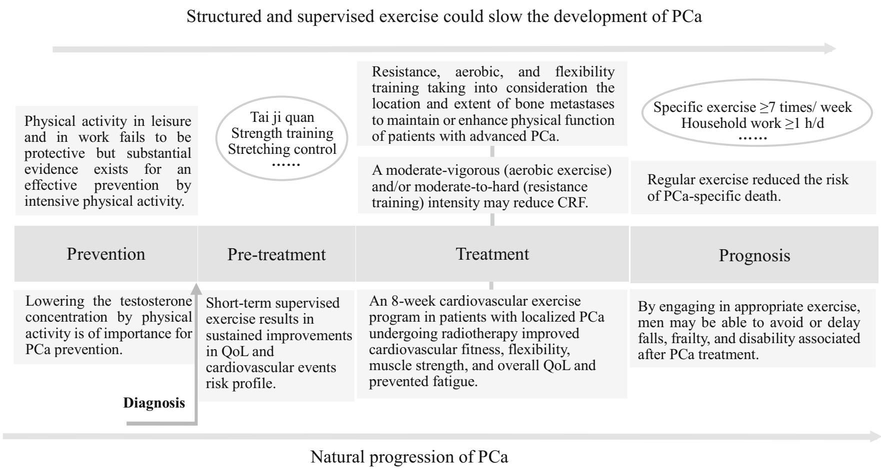

Fig. 9.1 The framework for physical exercise and prostate cancer cycle. *PCa-Prostate cancer, CRF-Cancer-related fatigue, QoL-Quality of life

9.2.1 When: Six Cancer-Related Periods

The six cancer-related periods include two pre-diagnosis periods (pre-screening and screening) and four post-diagnosis periods (pre-treatment, treatment, survivorship, and end of life). The pre-screening period refers to the entire period before cancer screening (i.e., lifetime). The screening period is the time from a given screening test until the results of the test are known (usually several weeks or months). The pre-treatment period consists of the period from a definitive cancer diagnosis to the initiation of treatment (from several weeks to years). The treatment period mainly focuses on "primary" cancer treatment, such as surgery, radiotherapy, chemotherapy, and biologic therapies (usually months or years). And survivorship is the period before cancer recurrence or death after the first cancer diagnosis and treatment [17]. In prostate cancer (Fig. 9.1), we adjust it to four periods: prevention, pre-treatment, treatment, and prognosis.

9.2.2 How: Eight Cancer Control Categories

Based on the six cancer-related periods, Courneya et al. proposed eight cancer control categories: two pre-diagnosis cancer control categories (prevention and detection), treatment preparation/coping, treatment effectiveness/coping, recovery/rehabilitation, disease prevention/health promotion, and two end-of-life cancer control categories (palliation and survival) [17]. Physical activity interventions during these six cancer-related periods influence any of the eight cancer control categories. For instance, physical activity during the pre-treatment period may have an impact on treatment preparation/coping, treatment effectiveness/coping, and recovery/rehabilitation [17].

9.2.2.1 Physical Activity and Cancer Prevention

Physical activity levels are considered contributory and modifiable lifestyle factors for some cancers, and moderate exercise may reduce the risk of developing primary and secondary cancers [7, 17]. Moreover, there is a dose-response relationship between physical activity levels and several specific cancers (such as colorectal, breast, and prostate cancers), and cancer risk declines as the result of increased physical activity levels. The US Department of Health and Human Services 2018 Physical Activity Guidelines Advisory Committee determined that individuals with the highest category of physical activity showed reduced risks of bladder, breast, colon, endometrial, esophageal adenocarcinoma, renal, gastric, and lung cancers, when compared with the lowest category of physical activity-with relative risk reductions ranging from approximately 10% to 25% [18]. Therefore, healthy populations should avoid sedentary behavior and inactivity: some physical activity is better than none, more is generally better than less, and at the very least exercise should meet the recommended levels set by national guidelines [7].

9.2.2.2 Physical Activity and Cancer Detection

Physical activity may affect cancer detection in the following two ways [17]:

1. directly affecting the sensitivity and/or specificity of screening tests (e.g., mammography, prostate-specific antigen, and fecal occult blood), and
2. indirectly influencing cancer detection by motivating patients to stick to cancer screening behavior, thus leading to earlier detection.

9.2.2.3 Physical Activity and Cancer Treatment Preparation/Coping

Physical activity has a positive impact on cancer treatment preparation/coping in the following ways [17]:

1. improving physical and psychological conditions while waiting for treatment,
2. improving health and fitness and increasing the feasibility of certain treatments (e.g., lung surgery and cardiotoxic drugs), and
3. controlling the development of the disease and its symptoms to delay treatment needs.

For example, home-based preoperative interventions for breast cancer patients indicated that physical activity and functional capacity improved after health behavior changed among this group [16].

9.2.2.4 Physical Activity and Cancer Treatment Effectiveness/Coping

Physical activity may positively influence the therapeutic effects of traditional radiotherapy and chemotherapy in the following ways [11, 17, 26]:

1. increasing tolerance and reducing treatment-related toxicities and side effects (e.g., fatigue),
2. maintaining and improving physical function, lowering the risk of chronic diseases, preventing muscle loss and fat gain, and improving psychological conditions and QoL, and
3. promoting the success of some difficult treatments and the effect of cancer treatments.

9.2.2.5 Physical Activity and Cancer Recovery/Rehabilitation

Whether the treatment intention is curative or palliative, cancer treatment may have late-appearing and long-term effects on multiple body systems related to exercise training, such as the cardiovascular, musculoskeletal, nervous, endocrine, and immune systems [7, 27]. Exercise programs serve an important role in cancer rehabilitation after diagnosis, and patients should start exercising as early as possible [28]. Physical activity can help cancer survivors expedite recovery from the acute effects of treatments [17]. The effects of exercise on promoting postoperative recovery during and after treatment relate to improved QoL, reduced sarcopenia and cardiac arrhythmia by maintaining heart function, reduced central adiposity, and improved physical activity levels and functional capacity. Exercise also mitigates drug-related negative effects on the cardiovascular system and treatment-related side effects, and helps to avoid excessive medicalization by preventing the need for additional drug therapy [6, 15, 16].

9.2.2.6 Physical Activity and Disease Prevention/Health Promotion

The benefits of physical activity for cancer survivors include the following [7, 9, 17]:

1. improving QoL and physical function,
2. improving chronic and late-appearing effects of cancer treatments (e.g., fatigue, lymphedema, fat gain, and bone loss),
3. improving long-term health by optimizing physical function and preventing cancer recurrence and other chronic diseases (e.g., osteoporosis, heart disease, and diabetes), and
4. improving physical and psychological health by preventing or mitigating depression, anxiety, rigor, and anger, with improved self-esteem, satisfaction with life, and overall QoL.

9.2.2.7 Physical Activity and Palliation

Physical activity supports cancer survivors in controlling their disease symptoms, improving mobility, alleviating functional decline, and maintaining QoL at the end of life [17].

9.2.2.8 Physical Activity and Survival

Physical activity prolongs the survival time of cancer survivors in the following two ways [17]:

1. reducing the risk of cancer recurrence or slow cancer progression, and
2. decreasing the risk of other life-threatening diseases, including second primary cancers.

Pre- and post-diagnosis physical activity benefits the survival outcomes of breast, colorectal, and prostate cancers, and post-diagnosis physical activity has a better impact on cancer survival [29]. In addition, there is a significant dose-response relationship between physical activity levels and the risk of cancer recurrence, cancer-specific death, and all-cause mortality in breast cancer and colon cancer

[9, 30]. In a group of 847 Swedish breast cancer patients aged 34–84 years, mortality in the most active group was significantly lower than in the least active group, and subgroup analysis results showed the group aged 55 years or over when diagnosed experienced lower all-cause mortality. Thus, physical activity should be encouraged in women diagnosed with breast cancer, particularly post-menopausal women [30]. Resistance and aerobic exercise training improved cancer cachexia and increased survival by mitigating systemic disruptions, such as inflammation, anemia, and hypogonadism [31].

9.2.3 Potential Mechanisms

The potential mechanisms for exercise-based improvements in the physical and psychological health of cancer patients are related to changes in cardiovascular and pulmonary function [11, 32–40], skeletal muscle [4, 11, 32, 38, 41, 42], psychosocial well-being [4, 11, 40, 43–45], QoL [4, 11, 40, 44, 46], tumor micro-environment [4, 11, 47, 48], and others [32, 44, 46, 49] (Fig. 9.2).

Fig. 9.2 Potential mechanisms for exercise-related improvements in physical and psychological health of cancer patients

9.3 Safety of Exercise Programs

9.3.1 Safety

Safety is always a priority for elderly patients with chronic diseases, and likewise for cancer patients and survivors [50]. Generally, exercise is safe for most cancer survivors. Cancer patients and survivors with specific cancer types and those with doubts about the safety of exercise can consult with professionals and perform the corresponding medical clearance and exercise testing before starting an exercise program. In particular, head and neck cancer survivors are considered a special group because of their greater impairments in mobility and dysfunction of the shoulder and neck [51]. To ensure the safety of exercise programs, medical evaluations and assessments are recommended for individuals with peripheral neuropathy, musculoskeletal morbidities or bone metastases, or known cardiac conditions [49]. Several shorter exercise sessions per day seem to be better tolerated and safer for patients in poor physical condition [9]. Appropriate exercise prescriptions for prostate cancer patients are accepted, and androgen-deprivation therapy is safe and may mitigate the side effects of treatment [52]. Specificity, overload, progression, initial values, reversibility, and diminishing returns are the main principles of exercise training and should be strictly applied to prescribe the most appropriate and safe exercise type and dose. Doing so will help achieve the desired outcomes and maximize the potential benefits [2, 53]. Furthermore, to ensure the safety of exercise and to reduce the risk of injuries and other side effects, the following guidelines should be noted during exercise [54]:

1. patients should understand and pay attention to the potential risk,
2. patients should choose appropriate types and intensities of exercise according to their fitness level and health goals,
3. patients should increase exercise intensity and duration gradually over time to meet key guidelines or health goals,
4. patients should use appropriate safety gear and sports equipment and choose a safe environment, and
5. patients should communicate with healthcare providers or physical activity specialists about exercising.

Exercise progression is also an important factor affecting the safety of exercise. Exercise progression may depend on individual health goals, exercise tolerance, and age. Therefore, it is recommended that the frequency and duration should be increased before increasing the intensity, and that exercise progression should be slower and more progressive for patients with disease remission and those who are experiencing severe treatment side effects [9]. In sum, exercise can be performed safely during and after cancer treatments, but individualized exercise prescriptions are recommended to prevent increases in cancer treatment toxicities according to cancer type, treatment history, personal limitations, specific side effects, and other physical and medical conditions [5, 37, 39].

9.3.2 Medical Evaluation and Exercise Testing Before Exercise

The diagnosis and treatment of cancer may influence the safety and effectiveness of exercise training for cancer survivors, so performing a corresponding medical evaluation and exercise testing beforehand may help healthcare professionals better understand their patients' potential physical and psychosocial limitations towards exercise. Such testing can also help survivors better adapt to exercise programs, while ensuring and improving the safety and effectiveness of exercise prescriptions [44, 55]. Generally, for most cancer survivors, low-intensity aerobic exercise (e.g., walking and cycling), progressive resistance training, and flexibility training do not need assessments [44]. Individuals with high-risk factors (e.g., known cardiovascular disease, new or changing cardiovascular disease symptoms, and specific lung diseases) require a medical evaluation and exercise testing before starting exercise programs of moderate or vigorous intensity [6, 49]. The exercise testing process involves assessing the physical activity and functional capacity of cancer patients or survivors based on their past exercise history and current physical conditions, and can be divided into low, moderate, and high capacity. Low capacity is defined as follows: unable to participate in 30 min of brisk walking, limited self-care, and has participated in little or no physical activity in the past 6 months. Moderate capacity is defined as follows: able to participate in 30 min of brisk walking and take care of themselves, and has participated in some physical activity in the past 6 months. High capacity is defined as follows: able to participate in more than 30 min of brisk walking, able to do basic and light work (such as housework and office work), able to restore exercise levels before cancer diagnosis, and has participated in regular physical activity in the past 6 months [44]. Cancer patients and survivors with exercise contraindications after cancer diagnosis should conduct medical screening before taking part in exercise programs and may benefit from an individualized and supervised exercise program [9, 50]. Table 9.1 introduces some recommendations for medical evaluation and exercise testing corresponding to exercise contraindications [4, 9, 44, 49, 50].

9.3.3 Contraindications to Exercise

Cancer patients are considered a special group when provided with exercise prescriptions [7]. Acute or chronic physical impairments should be taken into consideration when prescribing exercise programs for cancer patients, such as ataxia, anemia, or a limited range of exercise resulting from surgery, chemotherapy, radiotherapy, or hormone therapy [50]. Given the potential immunosuppressive effects, vigorous exercise should be avoided by cancer patients during cancer treatment [50]. Table 9.1 introduces some contraindications to exercise.

Table 9.1 Contraindications and recommendations of exercise programs

	Contraindications	Recommendations	PMID	Ref.
Surgery	Lung or abdominal surgery; Ostomy; Continent urinary diversions; Ureterostomies; Colostomies	Adequate recovery (up to 8 weeks); Pre-exercise medical evaluation and clearance; Avoid open-ended pouch appliances	31626055 29395306	[44] [49]
Hematological disease	Anemia (hemoglobin <8 g/dL)	Not exercise until hemoglobin >10 g/dL	20596305	[9]
	Neutropenia; Complete blood counts; Absolute neutrophil count $\leq 0.5 \times 10^9/\mu L$; Platelet count $< 50 \times 10^9/\mu L$; Leukocyte count $\leq 0.5 \times 10^9/\mu L$; Thrombocyte count $< 20 \times 10^9/L$	Avoid high-intensity activities; Avoid swimming and activities with risk of bacterial infection; Avoid contact sports, high-impact exercises, and activities with risk of bleeding; Pre-exercise medical evaluation or consultation	31587570 19428291 20596305 20086640	[6] [7] [9] [50]
Peripheral neuropathy	Ataxia; Dizziness; Peripheral sensory neuropathy	Avoid activities that require balance and coordination; Pre-exercise medical evaluation and clearance	19428291 20596305 31626055 20086640	[7] [9] [44] [50]
Musculoskeletal issues	Bone marrow transplanted therapy	Avoid public places at least 1 year after transplantation	20596305	[9]
	Bone pain	Avoid activities with risk of fracture; Pre-exercise medical evaluation or consultation	29395306 20086640	[49, 50]
	Arthritis; Osteoporosis/osteopenia; Extreme muscle weakness	Pre-exercise medical evaluation or consultation; Exercise to tolerance	31626055	[44]
Metastatic disease	Known or suspected bone metastases	Avoid resistance training; Pre-exercise medical evaluation or consultation	19428291	[7]
Infection	Acute infectious diseases (regardless of etiology)	Avoid exercise *OR* exercise is at least one day apart and slowly resumes training after asymptomatic exercise; Pre-exercise medical evaluation or consultation	29395306	[49]

(continued)

Table 9.1 (continued)

	Contraindications	Recommendations	PMID	Ref.
Cardiovascular	Uncontrolled symptomatic heart failure; Acute myocarditis/myocardial infarction; Recent myocarditis/myocardial infarction; Aortic aneurysm (dissecting); Aortic stenosis (severe); Congestive heart failure; Crescendo angina Pulmonary or systemic embolism (acute); Thrombophlebitis; Ventricular tachycardia and other dangerous dysrhythmias (e.g., multifocal ventricular activity)	Avoid exercise	20596305	[9]
	Dyspnea	Exercise to tolerance	20086640	[50]
	Unstable cardiovascular disease history	Pre-exercise medical evaluation or consultation	31626055	[44]
Others	Cardiac medication; Pulmonary symptoms; Unstable gastrointestinal symptoms; Extreme fatigue; Unstable renal disease; Severe nutritional deficiencies; Worsening or changing condition; Lymphedema	Pre-exercise medical evaluation or consultation	31626055	[44]
	Severe nausea; Vomiting within 24-36 h; Unusual fatigability; Disorientation; Blurred vision; Faintness; Pallor; Night pain or pain not associated with injury	Exercise to tolerance	20596305 20086640	[9] [50]
	Mental or physical impairment	Avoid exercise	20596305	[9]
	Severe cachexia	Recommend mild-intensity exercise	20086640	[50]

(continued)

Table 9.1 (continued)

	Contraindications	Recommendations	PMID	Ref.
	Immunosuppressants	Avoid public places, not exercise until white blood cell count >500/ mm^3	20596305	[9]
	Indwelling catheter	Avoid resistance exercise	20596305	[9]
	Fever >38 °C(100.4 °F)	Avoid high-intensity exercises or not exercise	20086640	[50]

9.4 Exercise Guidelines

9.4.1 General Exercise Guidelines for Cancer Prevention

The general exercise guidelines for individuals who want to prevent cancer are the same as the physical activity guidelines for Americans: 150–300 min of moderate exercise or 75–150 min of vigorous aerobic training each week and two or more days of moderate to vigorous resistance training that involves all major muscle groups each week (bit.ly/cancer_exercise_guidelines) [54].

9.4.2 General Exercise Guidelines for Most Cancer Patients and Survivors

The primary health-related types of exercise are aerobic, resistance, and flexibility training. Ideally, an exercise prescription should consist of aerobic training, resistance training, and flexibility training, and individuals should gradually increase the duration and intensity of their exercise programs. It is generally recommended that cancer patients and survivors who have no significant limitations and contraindications perform appropriate exercises based on their physical conditions. And the best exercise guidelines for cancer survivors depend on the individual characteristics, health goals, physical condition, medicine usage, cancer type, cancer-related symptoms, previous exercise history, and attitudes, reactions, and preferences towards exercise training [6, 9, 49, 56]. To my knowledge, there are no specific exercise prescriptions published for cancer patients and survivors, although the ACSM proposed general exercise recommendations for this group [28]. The physical activity guidelines for Americans, proposed by the US Department of Health and Human Services (US DHHS) in 2008 and updated in 2018, indicated that patients with chronic diseases such as cancer should avoid inactivity and be as physically active as possible depending on their abilities and conditions. They were recommended to gradually meet the current physical activity guidelines for health (150 min of aerobic exercise each week and strength training twice a week) [27, 31, 54]. Generally, an exercise program of 150 min of moderate to vigorous exercise each week is deemed feasible and acceptable for cancer patients and survivors [57]. And for older adults, additional varied multicomponent physical activities focusing on functional balance and strength training are recommended, with three or more days per week of moderate or greater intensity to enhance functional capacity and prevent falls. Table 9.2 lists the recommended amount of aerobic and resistance training for most cancer patients and survivors [11].

Any type or mode of exercise program is beneficial for cancer patients because some physical activity is always better than none. Individually prescribed home-based exercise programs are cost-effective and safe, have little to no adverse effects on cardiac function, and can moderately improve body composition, muscle strength, and total body water distribution [15]. There is growing evidence that the combination of both aerobic and resistance training is beneficial for cancer survivors of breast, lung, prostate, and pancreatic cancers. Targeted resistance training may improve cytokine response and the musculoskeletal function and structure of cancer survivors [32, 56]. Zeng et al. conducted a one-year personalized exercise intervention combining aerobic and resistance training to investigate the impact of exercise on the health outcomes of Chinese breast cancer survivors. At the end of the intervention, significant changes were found in blood glucose levels and functional fitness (consisting of agility and balance, aerobic endurance, and lower-body flexibility) in 33 participants who had completed the exercise program [58]. The guidelines of the ACSM indicate that two to three days each week of combinational training, consisting of moderate-intensity aerobic training and resistance training, may improve the fatigue and QoL of lung cancer survivors. And a systematic review indicated that at least two sessions per week of combinational training, including high-intensity aerobic interval exercise and resistance training, may improve the symptoms and QoL of lung survivors, especially for those undergoing lung resection [59]. For prostate cancer patients, exercise programs that combine aerobic and resistance training improve physical function and muscle strength [32, 36]. In pancreatic cancer patients, the combination of aerobic and resistance training improves physical fitness and body composition [36, 60]. In addition, flexibility training for major muscle groups and tendons is recommended [11, 27]. Flexibility training helps ease tired muscles and prevent the formation of scars in joints caused by radiation and chemotherapy, thus allowing cancer patients and survivors to obtain a normal range of motion [9]. High-intensity anaerobic training is also safe for cancer patients but needs to be carefully applied in personalized exercise prescriptions [61].

9.4.3 Exercise Guidelines on Health-Related Outcomes

Fatigue is a common and distressing symptom in cancer patients, and one of the challenges to performing exercise programs [5, 7]. Evidence has indicated that aerobic exercise, resistance training, and the combination of aerobic and resistance training can mitigate fatigue and help cancer survivors avoid becoming trapped in a

Table 9.2 Guidelines for cancer patients and survivors

Goals	Aerobic only	Resistance only	Combination (Aerobic + Resistance)	PMID	Ref.
Cancer prevention	150–300 min/week, moderate-intensity, or 75–150 min/week, vigorous-intensity, or an equivalent combination of moderate- and vigorous-intensity	≥2 times/week, moderate- to vigorous-intensity	–	–	[54]
Most cancer patients and survivors	3–5 times/week, 20-60 min/session, moderate- to vigorous-intensity	1–3 times/week, 1–4 sets of 6–12 repetitions, moderate- to vigorous-intensity	–	18704691	[11]
Fatigue	3 times/week, 30 min/session, moderate-intensity	2 times/week, 2 sets of 12–15 repetitions, moderate-intensity	Aerobic: 3 times/week, 30 min/session, moderate- intensity Resistance: 2 times/week, 2 sets of 12–15 repetitions, moderate-intensity	–	bit.ly/cancer_exercise_guidelines
QoL	2–3 times/week, 30–60 min/session, moderate- to vigorous-intensity	2 times/week, 2 sets of 8–15 repetitions, moderate- to vigorous-intensity	Aerobic: 2–3 times/week, 20–30 min/session, moderate-intensity Resistance: 2 times/week, 2 sets of 8–15 repetitions, moderate- to vigorous- intensity	–	bit.ly/cancer_exercise_guidelines
Physical function	3 times/week, 30–60 min/session, moderate-intensity	2-3x/week, 2 sets of 8–12 repetitions, moderate- to vigorous-intensity	Aerobic: 3 times/week, 20–40 min/session, moderate- to vigorous-intensity Resistance: 2–3 times/week, 2 sets of 8–12 repetitions, moderate- to vigorous- intensity	–	bit.ly/cancer_exercise_guidelines

(continued)

Table 9.2 (continued)

Goals	Aerobic only	Resistance only	Combination (Aerobic + Resistance)	PMID	Ref.
Anxiety	3 times/ week, 30–60 min/session, moderate- to vigorous-intensity	–	Aerobic: 2-3 times/ week, 20–40 min/session, moderate- to vigorous- intensity Resistance: 2 times/ week, 2 sets of 8–12 repetitions, moderate- to vigorous- intensity	–	bit.ly/cancer_exercise_guidelines
Depression	3 times/ week, 30–60 min/session, moderate- to vigorous-intensity	–	Aerobic: 2–3 times/ week, 20-40 min/session, moderate- to vigorous-intensity Resistance: 2 times/ week, 2 sets of 8–12 repetitions, moderate- to vigorous- intensity	–	bit.ly/cancer_exercise_guidelines
Lymphedema	–	2–3 times/ week, progressive intensity, supervision	–	–	bit.ly/cancer_exercise_guidelines
Bone health	–	2–3 times/ week, moderate- to vigorous-intensity	–	–	bit.ly/cancer_exercise_guidelines
Sleep	3–4 times/ week, 30–40 min/session, moderate-intensity	–	–	–	bit.ly/cancer_exercise_guidelines

Moderate-intensity: 40%–59% heart rate reserve or VO_2R.
Vigorous-intensity: 60%–89% heart rate reserve or VO_2R.

negative cycle of deteriorating physical function and increasing fatigue, particularly for breast and prostate cancer survivors, and older cancer survivors [5, 26, 39, 56, 62–64]. Pre-habilitative exercise may somewhat improve the psychosocial health of cancer patients with several different types of cancer, including colorectal, esophageal, gastric, prostate, and bladder cancer [36]. The exploratory secondary analysis of a randomized control trial found that six weeks of home-based structured exercise programs that combined aerobic and resistance training of low to moderate intensity improved anxiety and the mood of older cancer patients undergoing chemotherapy, especially those with worse baseline symptoms [45]. A randomized controlled trial for breast cancer-related lymphedema indicated that there was no deterioration in arm swelling or symptom severity in both low-load (15–20-repetition maximum, 55%–65% single-repetition maximum [1RM]) and high-load groups (6–10-repetition maximum, 75%–85% single-repetition maximum [1RM]), and resistance training of moderate to vigorous intensity showed significant improvements in muscle strength and tolerance, and QoL [65].

In 2018, the ACSM introduced evidence-based exercise recommendations for cancer prevention, and prevention and treatment for health-related outcomes (i.e. fatigue, QoL, physical function, anxiety, depression, lymphedema, bone health, and sleep) (Table 9.2) (bit.ly/cancer_exercise_guidelines).

9.4.4 Supervision

Generally, supervised and individually tailored patient-centered exercise interventions may lead to better adherence [66–68]. The results of an unsupervised exercise program conducted among 42 breast cancer survivors suggested that exercise resulted in moderate improvements in the physical composition, physical fitness, and health-related QoL in breast cancer survivors [69]. A meta-analysis of the effects of exercise on cancer-related fatigue among both breast and heterogeneous cancer patients found that exercise interventions in supervised settings provided a more significant reduction in fatigue when compared with no exercise or no supervision [64, 67, 70]. Tailored and supervised resistance training is safe and effective for prostate cancer patients with bone metastases as has positive effects on physical function, skeletal muscles, comorbidities, and disease burden [32]. About 80% of patients with endometrial cancer benefit from referral to medical-based supervised exercise programs [13].

9.5 The Role of Healthcare Practitioners and Physical Activity Specialists

However, the current reality is not ideal. Common barriers to implementing exercise programs among cancer patients include limited resources, limited exercise-related expertise, and a lack of awareness of the benefits of exercise among patients, healthcare practitioners, and physical activity specialists. The side effects of cancer and its treatment may lead individuals diagnosed with cancer to lose trust and confidence in their physical knowledge and physical abilities, as well as to reduce persistence in exercise [50, 62]. Cancer patients are generally more reluctant to engage in physical activity than adults without cancer, and 53%–70% of cancer survivors do not follow the recommended physical activity guidelines [6]. Poor physical activity participation by cancer survivors during and after cancer treatment is not only associated with medical, demographic (e.g., age), and behavioral factors, but also with social cognitive factors such as self-efficacy, attitude, and intention [17, 71, 72]. Further, unawareness of the health benefits of exercise and not knowing who to ask for help are problems that cancer survivors commonly complain about, resulting in a poor attitude towards exercise [73]. Healthcare professionals and physical activity specialists can provide cancer survivors with useful and personalized exercise advice and prescriptions, and they can help avoid the risk of injuries [54]. Therefore, cancer patients can turn to healthcare practitioners or physical activity specialists for guidance regarding an appropriate type and amount of physical activity, as well as precautions, contraindications, and support throughout their exercise period [54, 73]. A certain degree of coaching or interpersonal interaction can also increase patient satisfaction with exercise [74]. Written information resources on exercise are the most common exercise services provided by healthcare professionals and physical activity specialists [75]. Yet adequate time to heal after surgery and gradually increased exercise time and intensity should be taken into consideration when professionals recommend an exercise prescription, given the weakened physical and psychological condition of patients and their inability or unwillingness to start and tolerate exercise training during this process. For patients undergoing surgery, the recovery period may take up to eight weeks [27, 50]. Huang et al. conducted a 12-week home-based walking-exercise program among 78 women with breast cancer and found that participant exercise adherence, time, and intensity decreased as the exercise prescription dose increased. Thus, they indicated that exercise time and intensity in exercise prescriptions for breast cancer patients undergoing chemotherapy may be increased during the initial stage and decreased during the final stage [76]. Motivation and persistence are significant factors affecting the effectiveness of exercise training strategies and are regarded as the main challenges facing healthcare professionals [50]. Moreover, clinicians and fitness professionals need to pay attention to and embrace individual preferences and the interests of cancer survivors when instructing and helping cancer survivors, to better motivate and encourage cancer survivors to adopt and adhere to positive lifestyle changes [3].

9.5.1 Physicians, Oncologists, and Clinicians

Evidence has indicated that exercise prescriptions provided by physicians can improve the enthusiasm and persistence of patients regarding exercise programs [50]. However, to reduce potential risks, many oncologists are reluctant to provide their patients with exercise prescriptions, citing that the risk–benefit ratio of exercise prescriptions is not as clear as with drug prescriptions [73]. Clinicians with limited prescription knowledge will be less likely to recommend that cancer survivors exercise. An investigation among 123 oncologists surveyed their knowledge, attitudes, confidence, and behavior towards physical activity in cancer survivors, and the outcomes indicated that only 46% of oncologists regularly recommended physical activity to their patients, and only 20% and 23% of oncologists provided written information and referrals, respectively. Furthermore, oncologists themselves reported poor participation in physical activity, with only 26% of them reporting that they were physical active [77].

Cancer treatment-related adverse effects are major exercise barriers facing patients and account for about 54% of all barriers [78]. Consequently, clinicians should inform their cancer patients that exercise is safe during and after multiple types of cancer treatment, and they should educate them about the negative effects of sedentary behavior and inactivity, and about the benefits of moving [8, 27]. They should also acknowledge that their perceived behavioral control, confidence, and recommendations about physical activity may influence themselves and their patients' physical activity behavior and outcomes, and therefore, they should start with themselves first [77]. Further, clinicians should be aware of the diagnosis and treatment details of cancer survivors to better access the physical capacity of cancer survivors and prescribe an achievable, enjoyable, safe, and effective exercise program [27]. Understanding the exercise behavior and behavioral determination factors of cancer survivors may help clinicians identify specific intervention strategies to facilitate this population to adopt and maintain existing exercise programs [56]. And, if possible, clinicians should directly participate in uniting and leading multidisciplinary clinical teams to individually tailor supportive interventions for cancer patients, such as exercise prescriptions and referrals [68, 79].

9.5.2 Physiotherapists

Physiotherapists play an important subsidiary role in exercise planning and intervention for cancer patients by providing healthcare, confidence, and emotional support. The results of the UK Prevention of Shoulder Problems (PROSPER) trial indicated that exercise intervention with the support of physiotherapists may help women undergoing breast cancer treatment to address the sense of powerless and enhance their confidence towards mobilizing their arms after surgery [62]. An investigation carried out among 35 physiotherapists in Ireland reported that they still need further graduate education, although three-quarters of them offered suggestions or prescriptions to more than 81% of their cancer patients [75].

9.5.3 Oncology Nurses

An investigation carried out among 170 oncology nurses in Ireland reported that the response rate was only 34% (58/170), and only 33% (18/54) of oncology nurses believed that they had sufficient exercise knowledge, owing to a lack of undergraduate education and training opportunities about cancer care [75]. Adding relevant knowledge about physical activity and exercise to the nursing education curriculum can help this group better address and manage topics such as treatment-related side effects, as well as better perform their cancer care work [80].

9.5.4 Fitness Professionals

Fitness professionals play an important role in promoting public health, supporting the medical management of cancer, and optimizing cancer recovery for cancer patients and survivors [7]. To evaluate patient tolerance and provide a safe and effective exercise program for cancer survivors, fitness professionals should know as many details of their patients as possible, such as cancer diagnosis, cancer treatment, side effects, physical function, exercise contraindications, exercise preferences, and daily life priorities [27, 44].

9.6 Bioinformatics Platforms and Models for Cancer Care

An increasing amount of evidence has demonstrated that exercise is good for cancer survivors during and after treatment, and exercise training should be provided for more cancer survivors. Hirschey et al. proposed meta-analytic path modeling of longitudinal studies to analyze the relationship of psychosocial predictors and physical activity, and to improve physical activity engagement and adherence among cancer survivors [81]. Rammant et al. proposed an intervention mapping based on the evidence and theory of bladder cancer to promote the physical activity of cancer patients before and after radical cystectomy [82]. Trekstock, a UK-based cancer charity, delivered a 12-week exercise referral program on physical function and health for young-adult cancer survivors [83]. Mina et al. designed an exercise care-plan model that can be used to help healthcare practitioners participate and assist in providing healthcare, and to promote and support exercise for cancer patients. This model is also suitable for patients diagnosed with cancer and their subsequent cancer healthcare process to improve the accessibility and participation of exercise guidelines and programs, and to promote the health and well-being of cancer patients [84]. Serrano et al. introduced an *in silico* modeling platform of anti-tumor immune responses and early-stage solid tumor growth to incorporate exercise oncology into immunotherapy, analyze the tumor microenvironment during the anti-tumor immune response, and prescribe personalized immune checkpoint inhibitors for aerobically training patients to reduce the risk of side effects [85]. The analysis and report of receptiveness and readiness for e-Health utilization in exercise-based cancer rehabilitation may help improve the receptiveness and readiness of cancer survivors in rehabilitation contexts and narrow the gap in the distribution of healthcare resources and technology [86]. Further, project cooperation between hospitals and communities may help cancer patients develop exercise programs and gradually transition to independent home-based exercise. Hospitals can provide patients with a cancer diagnosis, exercise consultation, health and exercise capacity assessment, and personalized exercise prescriptions, and then refer patients to the community. Communities can then provide cancer patients with risk management, psychosocial support services, exercise guidance, and supervision from exercise experts, before patients ultimately transition to home-based exercise [87, 88].

9.7 Discussion and Perspective

Physical activity is a safe, economical, and effective strategy for cancer prevention and intervention. It can reduce the incidence and mortality of several cancer types, improve long-term health conditions, and prolong survival, thus providing patients with a longer and more enjoyable life [4, 8, 9]. Yet the attitudes and behavior of cancer patients and survivors towards exercise are sometimes negatively influenced by a lack of knowledge or by the advice of family and friends. Moreover, cancer patients are often unwilling to exercise owing to several other factors: higher BMI, increased sedentary behavior, advanced age, gender differences, physical ability, and the side effects of cancer treatment [73, 75, 89]. Furthermore, attendance barriers can influence adherence to exercise programs. The most common such barriers are cancer-related during cancer treatment (e.g., symptoms and appointments) and life-related after treatment (e.g., vacations and work) [90]. Future platforms for cancer care service should integrate onsite training with investments in clinical services, infrastructure development, community services, internet resources, and web-based tools. These may improve the exercise environment, accessibility, and adherence, while disrupting the barriers of cancer diagnosis and treatment [4, 49, 74, 77, 91–98]. Furthermore, multidisciplinary approaches based on physical training and therapeutic optimization, dietary and lifestyle advice, control of risk factors and psychological support, and web-based intervention may promote comprehensive rehabilitation and narrow the gap between inpatient and outpatient rehabilitation and home treatment. Such approaches can also promote communication and timely responses between professionals and patients to facilitate patient exercise programs [6, 99, 100].

In short, cancer patients and survivors should avoid sedentary behavior and inactivity. They should develop exercise programs with help from medical professionals and physical specialists based on their health conditions, type of cancer treatment, target health outcomes, and trajectory of disease development.

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Chapter 10
Diabetes as a Metabolic Disease and Translational Exercise Medicine Informatics

Ting Bao and Bairong Shen

Abstract For decades, the rapid increase in metabolic diseases has posed a global health challenge. Diabetes is one such critical metabolic disease. The active control of body weight, blood sugars, and the treatment of multiple risk factors (including lifestyle intervention and drug treatment) for impaired glucose tolerance and early diabetes stages, can delay diabetes. Abnormal fat metabolism damages tissues and organs, thereby increasing diabetes complications and cardiovascular and cerebrovascular end-point events. The adoption and maintenance of physical activity is key to good blood glucose management and the overall health of patients with diabetes and pre-diabetes, but its implementation remains poor. Personalized exercise prescriptions can help patients derive considerable benefits from exercise-based intervention therapies. However, how to transform existing paradigms, guidelines, and translate the latest clinical research to provide patients and doctors with truly personalized exercise prescriptions remains a vexing issue. In this chapter, the classification of diabetes and pre-diabetes types is outlined. Also outlined are the goals of an exercise intervention for diabetes, the benefits of exercise and physical activity, exercise intervention goals and recommendations, the adverse events caused by exercise intervention and its prevention strategies, personalized exercise prescriptions and how translational exercise-medicine informatics can help.

Keywords Metabolic disease · Diabetes and pre-diabetes · Personalized exercise prescriptions · Translational exercise medicine informatics

10.1 Introduction

Energy intake, utilization, and storage are collectively referred to as the metabolism, which is highly complex. Under the influence of genetic and environmental factors, metabolism may lead to under-nutrition, over-nutrition, abnormalities in certain

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metabolic pathways, and ultimately metabolic-related diseases [1, 2]. For decades, the rapid increase in metabolic diseases has posed a global health challenge [3–5]. Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia. In 2017, approximately 425 million people were affected by diabetes, equivalent to 8.8% of the world's population. By 2045, this number is expected to increase to 628 million, equivalent to 9.9% of the world's population [5–10]. Many studies have shown that exercise intervention is comparable with drug therapy, and that exercise intervention therapy plays an increasingly important role in the secondary prevention and treatment of most chronic diseases [11–13]. Particularly for pre-diabetes and diabetes patients, exercise is often a good treatment prescription [14, 15]. However, the prescription and effective implementation of physical activity interventions to treat diabetes are not routinely used [16, 17]. Imperfect and impaired blood glucose regulation leads to a higher risk of adverse events of hypoglycemia after exercise intervention compared with healthy people [18–24]. Thus, for diabetic patients, the psychological fears induced by exercise therapy, insufficient knowledge of exercise intervention management strategies, and insufficient control of exercise dose responses, will hinder the real and appropriate implementation of exercise therapy [23, 25–30].

Limited by existing research and knowledge, health care workers and clinicians cannot accurately provide effective and personalized exercise prescriptions for patients, thereby promoting often ineffective exercise intervention therapies. Currently, many consensus and guideline documents have proposed exercise intervention programs for patients with different types of diabetes [31–41], but these programs cannot be quickly translated to individual practice, and cannot truly mediate the "drug effect" of exercise therapy for diabetes. In fact, kinesitherapy, which is an alternative therapeutic approach, is not widely used in clinical settings when compared with traditional drug therapy.

Currently, two issues must be addressed. First, how to approach clinical decision-making to personalize the prescription of physical activities using an evidence-based clinical decision support tool. Second, how to translate and incorporate effective and safe exercise therapies into clinical practice, and patients' lives. Personalized exercise prescriptions may reduce the risk of adverse events, and heterogeneous responses to exercise therapy [42–44]. More well-designed randomized clinical trials must be conducted to confirm the effectiveness of exercise prescriptions, and security within different combinations of different risk factors of diabetes.

Translational informatics is extremely important in exercise medicine, especially for the application and practice of personalized exercise prescriptions [11, 45–49]. To achieve high quality therapy outcomes, the constant flow of new research, guidelines, and other evidence-based recommendations requires sophisticated and timely decision support [50, 51]. Medical informatics methods have major roles in the dissemination of new research and clinical decision support [46, 52, 53]. In this chapter, we use diabetes as an example: we briefly outline the classification of diabetes and pre-diabetes types, the goals of exercise intervention for diabetes, the benefits of exercise and physical activity exercise intervention goals and recommendations. Next, we also summarized the possible adverse events of diabetic patients during exercise intervention and the prevention strategies for these adverse events. Finally, we elaborated on the role and future prospects of translational exercise medicine informatics in formulating exercise prescriptions for diabetic patients.

10.2 Classification of Diabetes and Pre-Diabetes Types

DM comprises a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [54]. Chronic hyperglycemia in diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. The American Diabetes Association (ADA) [54] classified diabetes into the following general categories: (1) type 1 diabetes mellitus (T1DM): due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency), (2) type 2 diabetes mellitus (T2DM): due to a progressive loss of β-cell insulin secretion, frequently in the background of insulin resistance), (3) gestational diabetes mellitus (GDM): diabetes diagnosed in the second or third trimester of pregnancy, but clearly not overt diabetes prior to gestation), and (4) specific diabetes types due to other causes, e.g., monogenic diabetes syndromes (neonatal diabetes and maturity-onset diabetes of the young (MODY), diseases of the exocrine pancreas (cystic fibrosis and pancreatitis), and drug or chemical induced diabetes (resulting from glucocorticoid use, human immunodificiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) treatments, or post organ transplantation).

The Expert Committee on Diagnosis and Classification of Diabetes Mellitus [55, 56] recognized an intermediate group of individuals whose glucose levels did not meet the criteria for diabetes, yet whose levels were higher than normal. These individuals were categorized as two conditions, (1) impaired fasting glucose (IFG): fasting plasma glucose (FPG) levels 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L), or (2) impaired glucose tolerance (IGT): 2 h values in the oral glucose tolerance test (OGTT) of 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L). Individuals with IFG and/or IGT were classified with pre-diabetes, indicating a relatively high risk of developing diabetes in the future.

10.3 Benefits of Exercise and Physical Activity

In 2015, the global economic cost burden of diabetes was US$1.31 trillion or 1.8% of global gross domestic product. Notably, indirect costs accounted for 34.7% of the total burden [57]. The global cost of diabetes and its consequences are huge, and will substantially increase by 2030 [58]. With increasing evidence supporting exercise intervention to reduce diabetes [59–63], opportunities exist to improve population interventions based on cost-benefit analyses of exercise intervention programs [64, 65]. Exercise intervention therapy effectively improves the medical cost burden of diabetes [66–68]. In addition, there are many physiological benefits to improving health. In this section, we systematically summarize the benefits of exercise intervention for patients with pre-diabetes and diabetes.

10.3.1 Improving Blood Glucose Levels, Insulin Sensitivity, and Insulin Resistance

Physical activity improves blood glucose levels in pre-diabetes and diabetes [69, 70]. The most meaningful index is the prevalence of hyperglycemia within 24 h [71–76] (other blood glucose control indicators include postprandial blood glucose levels [73, 74], 24 h average glucose concentrations [72, 75, 77, 78], and 3 or 4 h glucose area under the curve (AUC) [75, 77, 78] estimations). In line with this view, some studies suggest a single bout of moderate- to high intensity exercise substantially improved glycemic control in the subsequent 24 h period in patients with T2DM [71–76]. A Dutch randomized controlled clinical trial showed a single resistance or endurance exercise significantly reduced the incidence of hyperglycemia during the subsequent 24 h in IGT patients, insulin-treated, and non-insulin-treated T2DM patients [75]. However, evidence for reductions in fasting blood glucose is insufficient [79]. Different exercises, patterns, and different time points exert different blood glucose improvement effects, but on average, they all reduce postprandial hyperglycemia [71, 73, 75–79]. Long-term regular exercise not only improves blood sugar levels, but also improves insulin sensitivity [80–86] and reduces insulin resistance [87–89]. Studies have shown that regular training increases and improves mitochondrial function recovery, and improves muscle insulin sensitivity [83, 90].

10.3.2 Reducing Cardiovascular Risk Factors

Another important goal of preventing and controlling diabetes occurrence and development is the reduction of cardiovascular disease (CVD) risk factors. The Italian Diabetes and Exercise Study assessed the efficacy of an intensive exercise intervention strategy in promoting physical activity and improving hemoglobin A1c (HbA1c) levels, systolic and diastolic blood pressure, high-density and low-density lipoprotein cholesterol levels, waist circumference, body mass index, and other modifiable CVD risk factors in patients with T2DM [91–93]. There is evidence that regular physical activity is associated with a substantial decrease in CVD and all-cause mortality [94]. During a mean 18.7 year follow-up in an adult Finnish cohort with diabetes, scientists identified that moderate or high level physical activity was associated with a reduced risk of total CVD mortality among patients with T2DM [95]. A meta-analysis revealed the effects of exercise on CVD risk factors in T2DM; all aerobic exercise training types impacted positively on some traditional and non-traditional risk factors for CVD [96, 97].

10.3.3 Preventing or Delaying Diabetes and Diabetes Complication Development

Diabetes is a preventable and controllable chronic disease, especially in patients with IGT, IFG, and T2DM [60, 98–100]. Principal investigator, William Knowler (the US National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Phoenix, AZ, USA) stated "The most important message is that type 2 diabetes is not inevitable, the process is reversible, at least in some people for some period of time" [100]. A systematic meta-analysis showed that a higher level of physical activity was positively correlated with a significantly lower incidence of T2DM [60]. A cohort study of 44,828 Chinese adults aged 20–80 years with newly detected IFG but free from CVD and cerebrovascular disease, participants who participated in the leisure time physical activity level (LTPA) recommended by WHO can avoid at least 19.2% of diabetes events [98]. In addition to delaying disease progress and development, the effects of physical activity on controlling diabetes complications should not be underestimated. Studies have reported that appropriate physical activity can reduce the risk of severe diabetic retinopathy in T1DM [101–103] and control diabetic nephropathy [104–106]. The Finnish Diabetic Nephropathy Study showed that low-intensity physical activity was closely related to impaired renal function, proteinuria, retinopathy, and CVD [104, 105]. The study was cross-sectional in nature, compared with the general diabetic population, individuals with diabetic complications are restricted in physical exercise and physical activity to varying degrees. This may have been due to the absence of complications at early stages. At the early stage of diagnosis of diabetes, no physical activity intervention measures were taken. These conclusions must be confirmed by more prospective, randomized controlled trials and cohort studies.

10.3.4 Improving Weight Loss and Blood Lipid Levels

One of the direct effects of exercise is weight and fat loss [1, 3, 4]. Considerable evidence suggests that individuals at high risk for T2DM (or GDM) can prevent or delay the disease via lifestyle modifications or weight loss [1, 3, 4, 34, 35, 43, 44, 107–112]. Current guidelines for pre-diabetes and T2DM recommend losing 7% body weight and increasing physical activity to at least 150 min/week [34, 35, 43, 44]. The Diabetes Prevention Program randomized clinical trial showed that the lifestyle group still had the lowest cumulative incidence of diabetes after a 10-year follow-up, when compared with placebo and metformin groups [110–112]. Evidence has also suggested that increased triglycerides, cholesterol, and low density lipoprotein (LDL)/high density lipoprotein (HDL) ratios are risk factors for atherosclerosis and CVD [113]. Recently, the Japan Diabetes Complications Study confirmed that serum triglyceride levels were a leading predictor of cardiovascular heart disease (CHD), comparable with LDL cholesterol, in Japanese patients with T2DM [114]. upervised and high-intensity physical activity intervention can effectively improve the blood lipid levels of diabetic patients, such as lowering LDL levels and increasing HDL levels [115–118].

10.3.5 Improve Other Health Well-Beings

The benefits of exercise intervention are far more than these. A prospective cohort of 1948 adults with T2DM who met weekly moderate-to-vigorous physical activity recommendations, reported better physical functioning, and were more likely to maintain their physical and overall health-related quality of life (HRQL) over time [119]. A randomized controlled trial confirmed that combined aerobic-resistance exercises were highly effective for HRQL in patients with T2DM [120–122]. Regular aerobic exercise training and yoga were effective in improving mental health among diabetic patients [123–127]. In addition to improved HRQL and mental health, other well-being effects were observed, such as improved sleep quality [128–130], prolonged life expectancy [131], dementia and Alzheimer's disease (AD) prevention [132, 133], and improved cardiorespiratory fitness [134–137].

10.4 Goals and Recommendations of Exercise Intervention for Diabetes

The main goal of an exercise intervention for diabetic patients is to control and improve blood sugar levels.

Going forward, an exercise intervention has two major goals; (1) to prevent the occurrence of CVD in diabetic patients and (2) to prevent the occurrence of diabetic complications. In this section, we systematically organized and analyzed existing guidelines, consensus documents, and position papers on diabetic intervention goals (Table 10.1). HbA1c was the most popular assessment tool for long-term glycemic control in several studies [138–147]. Depending on the target population, HbA1c control levels ranged from 6.5%–8.0% or less. Blood glucose targets, formulated by different guidelines and consensuses, emphasized the importance of setting individualized targets for patients based on factors such as the years of diagnosed of diabetes, acute and chronic complications, and life expectancy. We emphasize here that physical activity is one of the main lifestyle choices that controls blood sugar levels. In reality, diabetic patients will combine multiple treatment methods.

Table 10.1 Summary of glycemic goals for diabetes

Individuals		Index	Control goals	Reference
Non-pregnant adults with diabetes		HbA1c	<7.0% (53 mmol/mol)	ADA [138]
		Preprandial capillary plasma glucose	80–130 mg/dL (4.4–7.2 mmol/L)	
		Peak post-prandial capillary plasma glucose	<180 mg/dL (10.0 mmol/L)	
GDM and preexisting diabetes in pregnancy		Fasting plasma glucose	<95 mg/dL (5.3 mmol/L)	ADA [139]
		1-h post-prandial glucose	<140 mg/dL (7.8 mmol/L)	
		Or 2-h post-prandial glucose	<120 mg/dL (6.7 mmol/L)	
Women with T1DM or T2DM		Fasting glucose	70–95 mg/dL (3.9–5.3 mmol/L)	
		1-h post-prandial glucose	110–140 mg/dL (6.1–7.8 mmol/L)	
		Or 2-h post-prandial glucose	100–120 mg/dL (5.6–6.7 mmol/L)	
Glycemia, blood pressure, and dyslipidemia in older adults with diabetes	Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	HbA1c	<7.0–7.5% (53–58 mmol/Mol)	ADA [140]
		Fasting or preprandial glucose	80–130 mg/dL (4.4–7.2 mmol/L)	
		Bedtime glucose	80–180 mg/dL (4.4–10.0 mmol/L)	
	Complex/intermediate (multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	HbA1c	<8.0% (64 mmol/Mol)	
		Fasting or preprandial glucose	90–150 mg/dL (5.0–8.3 mmol/L)	
		Bedtime glucose	100–180 mg/dL (5.6–10.0 mmol/L)	
	Very complex/poor health (LTC or end-stage chronic illnesses or moderate-to-severe cognitive	HbA1c	Avoid reliance on HBA1C; glucose control decisions should be based on avoiding hypoglycemia and symptomatic	

(continued)

Table 10.1 (continued)

Individuals		Index	Control goals	Reference
	impairment or 2+ ADL impairments)	Fasting or preprandial glucose	100–180 mg/dL (5.6–10.0 mmol/L)	
		Bedtime glucose	110–200 mg/dL (6.1–11.1 mmol/L)	
Children and adolescents with T1DM	Selected individual patients if they can be achieved without significant hypoglycemia, negative impacts on Well-being, or undue burden of care, or in those who have non-glycemic factors that decrease HbA1c (e.g., lower erythrocyte life span)	HbA1c	<6.5% [48 mmol/Mol]	ADA [141]
	Appropriate for many children	HbA1c	<7% (53 mmol/Mol)	
	Appropriate for patients who cannot articulate symptoms of hypoglycemia; have hypoglycemia unawareness; lack access to analog insulin, advanced insulin delivery technology, and/or continuous glucose monitoring; cannot check blood glucose regularly; or have non-glycemic factors that increase HbA1c (e.g., high glycators)	HbA1c	<7.5% [58 mmol/Mol]	
	Appropriate for patients with a history of severe hypoglycemia, limited life expectancy, or where the harm of treatment is greater than the benefits	HbA1c	<8% [64 mmol/Mol]	
Patients with T2DM	Present CVD	HbA1c	<6.5% [48 mmol/Mol]	KDA [142]
	Absent CVD	HbA1c	<6.5% [48 mmol/Mol]	

(continued)

Table 10.1 (continued)

Individuals		Index	Control goals	Reference
Adults except for pregnant women patients with DM	Intended for individuals capable of achieving glycemic control with appropriate diet therapy (MNT) or exercise therapy or those capable of achieving glycemic control while on pharmacotherapy without developing hypoglycemia.	HbA1c	<6.0%	JCPGD [143]
	Defined as HbA1c <7.0% for the prevention of diabetic complications, which is assumed to correspond to fasting glucose <130 mg/dL and postprandial 2-h glucose <180 mg/dL as measured glucose values.	HbA1c	<7.0%	
	Intended for individuals deemed less amenable to treatment intensification due to associated hypoglycemia or for some other reason.	HbA1c	<8.0%	
Children and adolescents with T2DM		HbA1c	≤6.5% [48 mmol/Mol]	APEG [144]
Patients with DM		HbA1c	<7.0% [53 mmol/Mol]	ESC and EASD [145]
Patients with T2DM		HbA1c	<7.0% [53 mmol/Mol]	JAMA [146]
Children, adolescents, and young adults who have access to comprehensive care with DM		HbA1c	<7.0% [53 mmol/Mol]	ISPAD [147]

HbA1c glycosylated hemoglobin, *ADA* American Diabetes Association, *GDM* gestational diabetes mellitus, *DM* diabetes mellitus, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus, *LTC* long-term care, *ADL* activities of daily living, *CVD* cardiovascular disease, *KDA* Korean Diabetes Association, *MNT* medical nutrition therapy, *JCPGD* Japanese Clinical Practice Guideline for Diabetes, *APEG* The Australasian Pediatric Endocrine Group, *ESC* the European Society of Cardiology, *EASD* the European Association for the Study of Diabetes, *JAMA* Journal of the American Medical Association, *ISPAD* the International Society for Pediatric and Adolescent Diabetes.

At the same time, consider that patients may have different complications and different baseline levels. Especially for patients with type 1 diabetes, whether the left-leaning HBA1C control level is more beneficial, we cannot rashly conclude.

In terms of exercise program recommendations, different guides have slightly different recommendations (Table 10.2). These guidelines vary in terms of exercise training methods, but most institutions recommend that diabetics perform at least 150 min of moderate to vigorous aerobic exercise/week, under favorable conditions. Although improvements in glucose metabolism have been observed in moderate-intensity structured exercise programs, recent studies confirmed that for patients with T2DM, more pronounced effects were observed during more vigorous exercises. Also, intermittent exercises may have exert the most beneficial effects [148, 149]. For patients with T1DM, the greatest difficulty in designing an exercise program is reducing hypoglycemic response, and how to achieve the maximum benefit while exercising. When using diabetes management strategies, such as reducing the night basal insulin dose or using continuous glucose monitoring (CGM) technology, exercise-related hypoglycemia did not increase after high-intensity intermittent exercise [150, 151]. For patients with GDM, all guidelines recommend 60–150 min of aerobic training/week, with an upper limit of 30 minutes per day. Exercise has been proven to be safe and effective [151]. For children and adolescents, under the premise of the basic goals, exercise programs have stricter requirements in terms of intensity and time for exercise. Generally, it is recommended this group exercise for at least 60 min/exercise, three times/week or more intensity exercise, and they should pay attention to bone and muscle training [37].

10.5 The Adverse Effects of Exercise Intervention and Prevention Strategies

Regular physical activity benefits patients with pre-diabetes or diabetes. However, due to the adverse side effects of some exercise medications, many patients eschew exercise therapy, especially those with T1DM who are not up to the standard weight when compared with healthy individuals [152]. For diabetic patients, the most common adverse reaction of exercise intervention is hypoglycemia, which may occur during exercise or within 24 h post exercise (delayed hypoglycemia) [153, 154]. The mechanisms leading to these responses in T1DM have been attributed to relative or absolute increases in insulin levels or incomplete glycogen repletion after exercise [155–157]. Studies indicate that an episode of hypoglycemia or exercise in a T1DM patient can feed forward to downregulate the neuroendocrine and autonomic nervous system, thereby creating further hypoglycemia (reciprocal vicious cycles) [158–160]. Conversely, with more comprehensive research and the digitization of diabetes care technologies, more strategies are available to prevent and manage hypoglycemia during exercise interventions. In this section, we

Table 10.2 Summary of exercise intervention recommendations for diabetes

Population	Recommendations	Reference	Country/ region	Institute	Year
Pre-diabetes/T1DM/ T2DM/ GDM/ MODY	• 150 min or more of moderate-to-vigorous intensity activity/week, spread over at least 3 days/week, with no more than two consecutive days without activity. Shorter durations (minimum 75 min/ week) of vigorous-intensity or interval training may be sufficient for younger and more physically fit individuals • Children and adolescents with T1DM or T2DM should engage in 60 min/day or more of moderate or vigorous intensity aerobic activity, with vigorous, muscle-strengthening, and bone-strengthening activities included at least 3 days/week • Adults with diabetes should engage in 2–3 sessions/week of resistance exercise on nonconsecutive days • Flexibility training and balance training are recommended 2–3 times/week for older adults with diabetes. Yoga and tai-chi may be included based on individual preferences to increase flexibility, muscular strength, and balance • Individuals with diabetes or pre-diabetes are encouraged to increase their total daily incidental (non-exercise) physical activity to gain additional health	Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association [34]	USA	ADA	2016

(continued)

Table 10.2 (continued)

Population	Recommendations	Reference	Country/ region	Institute	Year
	benefits • To gain more health benefits from physical activity programs, participation in supervised training is recommended over non-supervised programs • Women with preexisting diabetes of any type should be advised to engage in regular physical activity prior to and during pregnancy • Pregnant women with or at risk of GDM should be advised to engage in 20–30 min of moderate-intensity exercise on most or all days of the week				
Pre-diabetes/T2DM	• A minimum of 210 min of moderate intensity or 125 min of vigorous intensity exercise each week • A combination of aerobic and resistance training • Resistance training (2–4 sets of 8–10 repetitions) should make up two or more sessions each week • Aerobic and resistance training can be combined in one session • Exercise should be performed on at least 3 days each week with no more than two consecutive days without training • At least 60 min of resistance exercise be completed per week	Exercise prescription for patients with type 2 diabetes and pre-diabetes: a position statement from Exercise and Sport Science Australia [43]	Australia	ESSA	2012

(continued)

Table 10.2 (continued)

Population	Recommendations	Reference	Country/ region	Institute	Year
	(e.g. two 30 min sessions)				
GDM	• Aerobic (large muscle activities in a rhythmic manner) e.g., walking, running, swimming, and cycling Intensity: Moderate 60%–90% of age predicted heart rate maximum, rate of perceived exertion 12–14 previously sedentary overweight/obese should begin training at 20%–30% of age predicted VO2 reserve rate of perceived exertion 12–14 vigorous rate of perceived exertion 14–16 Duration: ≤ 30 min continuously (up to 45 min if self-paced) Frequency: No more than two consecutive days without exercising • Resistance (multi joint exercises, large muscle groups) e.g., dumbbells, resistance band, and pregnancy pilates Intensity: Moderate 50% 1 repetition maximum 5–10 exercises 8–15 repetitions 1–2 sets Duration: 60 min Frequency: At least two but ideally three times a week	Exercise guidelines for GDM [38]	Australia	–	2015
T1DM	• No exercise plan mentioned • Blood glucose concentrations before exercise commencement and	Exercise management in T1DM: a consensus statement [32]	Europe	–	2017

(continued)

Table 10.2 (continued)

Population	Recommendations	Reference	Country/ region	Institute	Year
	recommended glucose management strategies • Carbohydrate requirements for endurance (aerobic) exercise performance and hypoglycemia prevention • Suggested reduction in bolus insulin dose before exercise, based on intensity of exercise, for exercise started within 90 min of consumption of the meal				
Children and adolescents with DM	• All children and adolescents between 6 and 18 years should engage in 60 min or more of physical activity/day • Two of which should include (1) moderate to vigorous aerobic exercise, (2) muscle strengthening. And (3) bone strengthening activities • Aerobic exercise should constitute the main part of 60 min. It is recommended to do more intense (vigorous) exercise at least three times a week • At least three times a week should include muscle and bone strengthening exercises	ISPAD Clinical Practice Consensus Guidelines 2018: Exercise in children and adolescents with diabetes [37]	Sweden	ISPAD	2018

DM diabetes mellitus, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus, *GDM* gestational diabetes mellitus, *MODY* maturity-onset diabetes of the young, *ADA* American Diabetes Association, *ESSA* Exercise and Sport Science Australia, *ISPAD* the International Society for Pediatric and Adolescent Diabetes.

systematically summarize exercise prevention and control strategies that may limit hypoglycemia events (Table 10.3). The section includes the following six aspects; (1) endogenous insulin regulation which reduces the occurrence of hypoglycemic events by adjusting intake doses and insulin schedules; (2) exogenous insulin regulation pre-, mid- and post-exercises diet control; (3) personalized exercise

Table 10.3 Summary of adverse effects of exercise intervention and prevention strategies

S. no.	Classification of intervention and prevention strategies	Specific plans
1.	Endogenous insulin regulation	• Continuous subcutaneous insulin infusion pumps [21, 161–163] • Continuous glucose monitoring (CGM) [161, 162, 164]
2.	Exogenous insulin regulation	• Fasting high-intensity interval exercise (HIIE) [165] • Pre-exercise intake of fructose [166] • Rapid acting carbohydrates to effectively resolve hypoglycemia in children during aerobic prolonged physical activity [167, 168].
3.	Personalized exercise prescriptions	• HIIE combined reduction of night basal insulin doses [19, 150, 165, 169, 170]
4.	Digital assistive technology	• Novel artificial pancreas system [171] • Personalized exercise carbohydrate requirement estimation system [172] • The development of an exercise advisor app. For T1DM [173, 174] • Machine learning techniques for hypoglycemia prediction [175]
5.	Strengthening acquisition and training for diabetes blood glucose management	• Diabetes self-management education [176]
6.	Conduct positive psychological motivation interviews	• Positive psychology-motivational interviewing [177]

prescriptions based on minimizing hypoglycemia events, and recommended personalized exercise programs that generate the greatest benefits; (4) exploration of advanced digital assistive technologies, such as new artificial pancreas systems, digital personalized guidance exercise consultant applications, the personalized Exercise Carbohydrate Requirement Estimation System, and modern computer information methods and machine learning approaches to develop hypoglycemic event prediction models; (5) strengthening acquisition and training for diabetes blood glucose management; and (6) conducting positive psychological motivation interviews.

10.6 Personalized Exercise Prescriptions and How Translational Exercise-Medicine Informatics Can Help

Whether for diabetic patients or health care workers, identifying the best exercise program is a major issue. The "best exercise program" not only achieves the best blood sugar control effects, but minimizes the adverse effects of exercise

[43]. Therefore, in this section, we explore how translational exercise-medicine informatics contribute to the generation of personalized exercise prescriptions, and relative research progress.

10.6.1 The Requirement for Personalized Exercise Prescriptions

Multiple and complex variations exist between individuals with diabetes. Risk factors for different diabetes stages are different, suggesting personalized exercise prescriptions for individuals with different basal glycemic status could be beneficial. Exercise prescriptions were originally derived from exercise therapies for CVD [47, 48]. Kottke et al. first proposed an "exercise prescription" during cardiac rehabilitation, where exercises were used as a treatment method to treat and rehabilitate heart disease [178]. Wilmore et al. [179] advocated four factors that should be considered when formulating individualized exercise prescriptions: (1) activity type, (2) frequency of participation, (3) duration of the exercise period, and (4) effort intensity. Between the late 1990s and the early twenty-first century, personalized exercise prescriptions were mainly prescribed by doctors and primary care medical workers. Generally, after individual pre-exercise screening tests, medical workers requiring a comprehensive assessment of an individual's health status, illness condition, medical need goals, and personal interests, manually prescribed an individualized exercise prescription. But in reality, this kind of exercise prescription was not very effective for both medical workers and individual patients. A cluster randomized trial study revealed that the effectiveness of physical activity advice and prescription by physicians in routine primary care was generally unsatisfactory [180]. A cross-section survey of 254 general practitioners in southern France showed that relying on general practitioners to issue exercise prescriptions was very effective in controlling chronic diseases, but there is still a big problem in the practice of general practitioners' exercise prescriptions, it is urgent to use network-based auxiliary tool development [181]. In 2013, it was reported that physical activity (exercise) guidelines differed in some training methods, but most institutions recommended patients with diabetes performed 150 minutes of moderate to vigorous aerobic exercise a week, but there remained an urgent need to use personalized prescriptions to maximize the health benefits of training [44, 182]. In contrast, other studies reported that some middle-aged and elderly individuals with pre-diabetes had limited physical functions, suggesting exercise prescriptions may not be suitable for everyone [183].

10.6.2 How Can Translational Exercise-Medicine Informatics Help?

Medical informatics involve a set of methodologies that cross "translational barriers" with translational medicine [184]. The transformation of exercise medicine informatics, using informatics technology and methods, may transform basic research results or current evidence-based research evidence and guidelines into clinical practice applications. Here, we provide a brief outline of the status of some informatics technologies for personalized exercise prescriptions. In 2011, Maglaveras et al. proposed an ontology-based framework to promote personalized exercise prescriptions [46]. The framework encapsulated key cardiac rehabilitation domain knowledge and appropriate reasoning logic to generate exercise plan recommendations based on a patient's personal data [46]. In 2017, the European Association of Preventive Cardiology developed a digital training and decision support system for optimized exercise prescriptions in CVD (The European Association of Preventive Cardiology Exercise Prescription in Everyday Practice and Rehabilitative Training (EXPERT) tool), this set of digital training and decision support system formulates exercise training recommendations and safety recommendations for different combinations of cardiovascular diseases and cardiovascular disease risk factors. Doctors can automatically provide exercise prescriptions based on provided variables [47, 48]. In 2021, the American College of Exercise medicine developed the "P3-EX" tool, a clinical decision support system for exercise prescription, to provide physicians and other health care professionals with evidenced-based and time-efficient guidance on how to design personalized exercise prescriptions for patients with multiple CVD-risk factors, who may have other chronic diseases and health conditions [49]. Currently, artificial intelligence-based clinical decision support tools provide personalized exercise prescriptions for patients with CVDs, although current modalities incorporate diabetes as a CVD risk factor in decision-making for diabetes patients (especially type 1 diabetes patients). Thus, going forward, artificial intelligence technologies and other information methods may be used to generate personalized exercise prescriptions.

10.6.3 The Role of Digital Therapy and Computer Decision Support Systems for Personalized Exercise Prescriptions

With the rapid development of diabetes technologies and digital therapies, diabetes-related medical equipment technologies (e.g., insulin pumps, automatic insulin delivery systems, and CGM equipment) and wireless/mobile applications may be used to generate lifestyle guidance and management for diabetic patients. Thus, controlling blood glucose levels via technical means in the digital domain has become a significant trend. Also, with the advent of artificial intelligence, a clinical decision support system based on computer information technology has emerged. For diabetic patients, the rapid development of such technologies has provided a unique environment for the generation of personalized exercise prescriptions. First, existing diabetes technologies and digital therapies can be largely used to avoid hypoglycemic events caused by exercise prescriptions. Second, computer information technology can be similarly used to build a personalized exercise prescription clinical decision support system for diabetic patients. A closed-loop personalized exercise prescription for patients of different genders, ages, health status, different risk factor combinations, and different diseases and diabetes complications, will ultimately improve the quality of life for diabetic patients, and limit CVD occurrence and development. As shown (Fig. 10.1), for diabetic patients, we propose a conceptual framework for personalized exercise prescriptions and the prediction of hypoglycemia events based on digital therapy assistance and computer decision support systems.

10.7 Conclusions and Perspectives

Diabetes is a key metabolic disease. Lifestyle interventions for diabetic patients are essential treatment modalities, and the effects of physical activity interventions on blood sugar control should not be underestimated. However, due to fears from adverse side effects of exercise medication, many patients eschew exercise therapy, particularly T1DM patients. Personalized exercise prescriptions could help solve these issues. In the future, artificial intelligence and other information technologies will facilitate personalized exercise prescription decision support systems for diabetic patients. Undoubtedly, this will accelerate the translation of current evidence-based information and guidelines into clinical practice.

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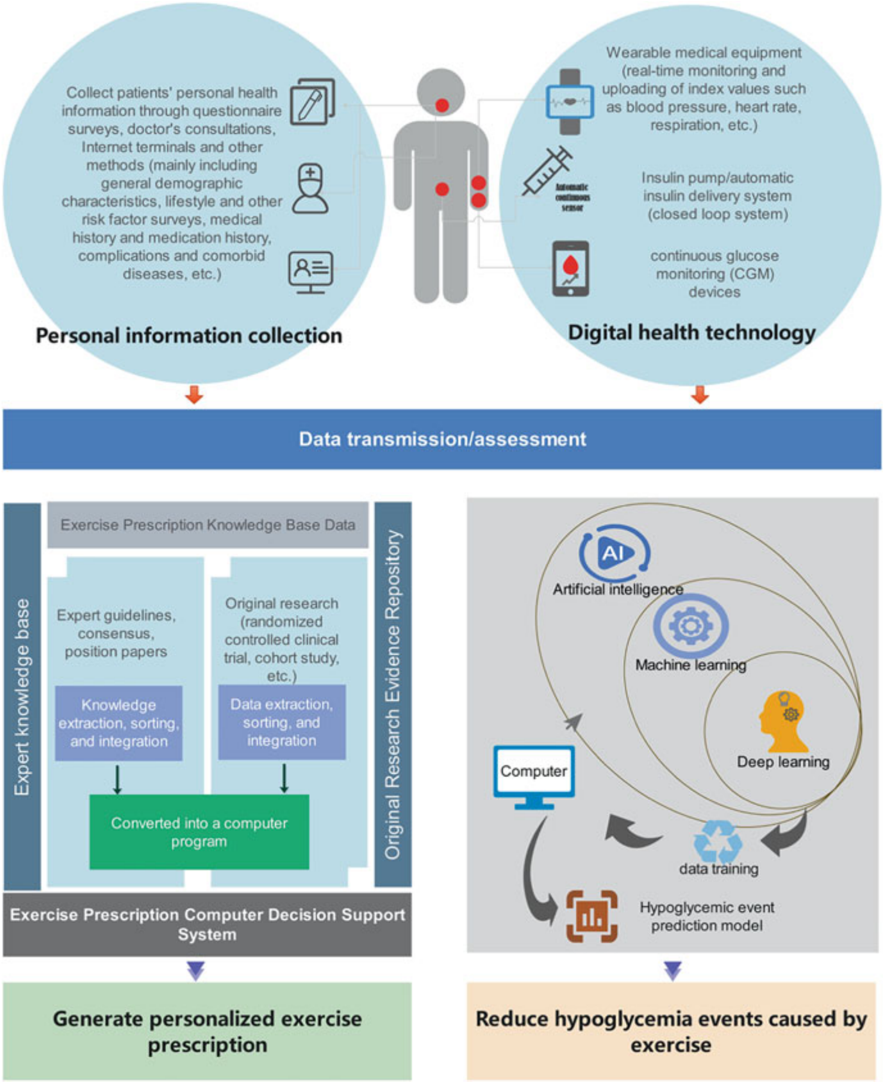

Fig. 10.1 A conceptual framework of personalized exercise prescriptions and the prediction of hypoglycemia events for diabetic patients, based on digital therapy assistance and a computer decision support system

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