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JUNTENDO MEDICAL JOURNAL

順天堂醫事雜誌

February 2024

Reviews

51th Health Topics for Tokyoites

"To survive the 100-year life -What we can do now for healthy longevity-" [1]

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Publication List

Publications from Juntendo University Graduate School of Medicine, 2021 [5/6]

Instructions to Authors

Juntendo Medical Journal Vol. 70 No. 1 p.2-96 Tokyo 2024. 2

70-1
(948th issue)

JUNTENDO MEDICAL JOURNAL

順天堂醫事雑誌

The History of *Juntendo Medical Journal*

This *Juntendo Medical Journal* has been published under the Japanese name *Juntendo Igaku* (順天堂医学) from 1964 to 2012. However, the origin of *Juntendo Medical Journal* dates back to the oldest medical journal in Japan, *Juntendo Iji Zasshi* (順天堂醫事雑誌), which had been published between 1875 and 1877 (total of 8 issues). Between 1885 and 1886, Juntendo issued a limited release of a research journal titled *Houkoku* [*Juntendo Iji Kenkyukai*] (報告) for a total of 39 issues.

In 1887, *Juntendo Iji Kenkyukai Houkoku* (順天堂醫事研究會報告) was published with the government's approval and we used to regard this as the first issue of *Juntendo Medical Journal*. Since then, *Juntendo Medical Journal* has undergone a series of name changes: *Juntendo Iji Kenkyukai Zasshi* (順天堂醫事研究会雑誌), *Juntendo Igaku Zasshi* (順天堂医学雑誌), and *Juntendo Igaku* (順天堂医学).

Now in commemoration of the 175th anniversary of Juntendo University, starting with the first volume issued in 2013 (Volume 59 Number 1), we return to *Juntendo Medical Journal*'s original Japanese title in 1875-*Juntendo Iji Zasshi* (順天堂醫事雑誌). We also reconsidered the numbering of the journal and set the first issue in 1875 as the initial publication of *Juntendo Medical Journal*. The Volume-Number counting system and the English name *Juntendo Medical Journal* started in 1955 from the January 10 issue. Although this is not our intension, we will retain the Volume-Number counting system to avoid confusion. However, Volume 59 Number 1 will be the 882nd issue, reflecting the sum of all issues to date: 8 issues of *Juntendo Iji Zasshi* (順天堂醫事雑誌), 39 issues of *Houkoku* [*Juntendo Iji Kenkyukai*] (報告) (47 issues combined), and 834 issues from *Juntendo Iji Kenkyukai Houkoku* (順天堂醫事研究會報告) in 1887 to the present.

出典：小川秀興（OGAWA Hideoki, M.D., Ph.D.）：順天堂醫事雑誌（Juntendo Medical Journal）2013；59：6-10.

本誌は昭和39年（1964年）から平成24年（2012年）末まで『順天堂医学』として刊行されてきた．しかし，その起源は明治8年（1875年）から10年（1877年）にかけて発刊された日本最古の医学誌『順天堂醫事雑誌』（計8巻）にある．さらに明治18年（1885年）から19年（1886年）まで，会員限定配本として順天堂醫事研究會の雑誌『報告』（計39集）が発行されている．

その後『順天堂醫事研究會報告』が明治20年（1887年）に官許を受けて公刊されたので，順天堂ではこれを通刊1号としてきた．以来，『順天堂醫事研究会雑誌』，『順天堂医学雑誌』，『順天堂医学』と名称を変更して刊行されてきた．

今般，順天堂が創立175周年を迎える平成25年（2013年）の59巻1号を期して，本来の名称である『順天堂醫事雑誌』と復刻し，その起源である明治8年（1875年）第1巻をもって創刊号（通刊第1号）とすることとした．従来の巻号と欧文誌名は，昭和30年（1955年）1月10日発行のものを1巻1号としており，欧文誌名もこれより付け始めたもので不本意であるが，混乱を避けるためにこれらを継承する．ただし，通刊数は明治8年（1875年）から19年（1886年）にかけて刊行された『順天堂醫事雑誌』8巻分と順天堂醫事研究會の雑誌『報告』39集，計47巻分を通巻834号に加え，59巻1号を通刊882号とした．

出典：小川鼎三，酒井シヅ：順天堂医学　1980；26：414-418.
小川秀興：順天堂醫事雑誌　2013；59：6-10.

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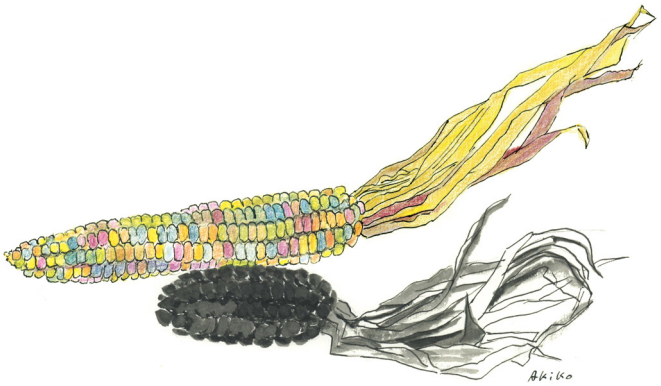

Contents

Reviews

51th Health Topics for Tokyoites

"To survive the 100-year life -What we can do now for healthy longevity-" [1]

Home Based Exercise Rehabilitation Programs to Prevent Physical Frailty and Hospitalization-Associated Disability ..... Tetsuya Takahashi, *et al.* 2

Nutrition, Exercise, and Cognitive Rehabilitation for Dementia Prevention ..... Tomokazu Takakura 9

Perspectives

Endothelial Glycocalyx Protection in Sepsis ..... Jerrold H. Levy, Toshiaki Iba 23

Organ Dysfunction in Sepsis-associated Intravascular Coagulation ..... Marcel Levi, Toshiaki Iba 26

Original Articles

Effectiveness of Nutritional Guidance Focusing on Leucine Intake During Cardiac Rehabilitation Maintenance ..... Saki Kawakubo, *et al.* 29

The Impact of Exercise and Health Management on Workplace Creativity ..... Yasuyuki Hochi, Motoki Mizuno 44

Health and Productivity Management in Hospital Organizations and Work Engagement of Nurses ..... Yumi Arai, *et al.* 54

Publication List

Publications from Juntendo University Graduate School of Medicine, 2021 [5/6] 65

Instructions to Authors 86

The Juntendo Medical Society

From the illustrator: One student in my art class brought me two corns as the motif for paintings. The corns were very distinctive in shape and color. So, I thought it would be interesting to draw them separately with Indian ink and colored pencil. I decided to try drawing them, and the painting turned out to be unexpectedly unique.

Reviews

Juntendo Medical Journal
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Home Based Exercise Rehabilitation Programs to Prevent Physical Frailty and Hospitalization-Associated Disability

TETSUYA TAKAHASHI[1, 2], TOMOYUKI MORISAWA[1, 2], MASAKAZU SAITOH[1, 2], KOTARO IWATSU[1], TOSHIYUKI FUJIWARA[1-3], HIROYUKI DAIDA[4]

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Daily health management and exercise are important for staying healthy and avoiding the need for long-term care. However, it is not easy to maintain regular exercise. Therefore, exercise needs to be done efficiently. In recent years, due to the aging population and increasing severity of illness, older patients often experience a significant decline in physical function, even with minimal rest, which often interferes with their daily life after discharge from the hospital. Frailty not only affects ADLs, but also strongly influences prognosis, including the development of atherosclerotic disease and rehospitalization. This perspective is a summary of the 51st Metropolitan Public Lecture held on June 17, 2023, and discusses exercise-based rehabilitation programs that can be delivered at home to prevent physical frailty and avoid hospitalization-related disability.

Key words: home exercise, prevention, physical frailty, hospitalization-associated disability

Introduction

Without going back to Marcus Tullius Cicero's (BC106~BC43) "Essay on Old Age", it is obvious that moderate exercise is essential for the prevention of age-related muscle wasting and weakness. In 1990, when the author had just become a physical therapist, the New England Journal of Medicine published a paper entitled "Exercise training and nutritional supplementation for physical frailty in very elderly people[1]", which was deeply etched in my inexperienced mind. The content of the study was that resistance training (80% of maximum repetitions per session) targeting muscles important for activities of daily living (ADL) was performed three times a week for 10 weeks on older residents of a nursing home with an average age of 87.1 years, resulting in an increase in muscle strength of 113 ± 8% and an increase in walking speed of 11.8 ± 3.8%. I remember being surprised to learn that muscle mass could be increased by resistance training even in the older population. In addition, it has been reported that resistance training causes a shift from type IIb fibers to type IIa fibers in the older population, along with an increase in muscle strength and muscle mass[2], and the fact that the muscle adaptation of the older populations by resistance training is similar to that of younger people has even become a cornerstone of the author's thinking when conducting physical therapy.

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Since Rosenberg[3] defined sarcopenia in 1989, frailty and sarcopenia associated with loss (wasting) and reduction of skeletal muscle have been of great interest in rehabilitation medicine, coupled with an aging patient population. In addition to sarcopenia, "dynapenia", derived from the Greek words dyna (strength) and penia (decrease), has recently gained attention[4]. Sarcopenia is diagnosed by age-related muscle loss, muscle weakness, and decreased walking speed, but muscle strength is not originally a function dependent solely on muscle mass (muscle wasting). In addition to muscle cross-sectional area (muscle mass), muscle strength is affected by an increase in the type and total number of motor units mobilized (recruitment), an increase in the frequency of alpha motor nerve firing (rate coding), and the involvement of the nervous system in the regulation of motor unit activity phases (synchronization). Dynapenia is described as "the age-related loss of muscle strength and power", but since muscle strength and muscle power (strength x speed) are different to begin with, further research is expected in the future.

Originally, in the field of rehabilitation medicine, in addition to comprehensive assessment of physical function, it is necessary to explore possible life-related problems through comprehensive geriatric assessment by a multidisciplinary team for life functions and activities, and develop a personalized rehabilitation program that integrates the environment.

Preventing frailty at home

Frailty is a comprehensive health concept that includes not only the decline in physical and mental function associated with aging, but also cognitive decline, depression, loneliness, and poor nutrition. Among them, physical frailty is the most common and has a significant impact on healthy life expectancy[5].

To understand "physical frailty", Fried's diagram of the frailty cycle is very helpful[5]. First, "loss of independence" means "need for long-term care". To avoid the state of needing long-term care, we must prevent the upstream disability. Disability is related to abilities such as "walking speed (ability to walk fast)", "muscle strength and power", and "VO2max (endurance)". To maintain this "ability to walk fast," "muscle strength," and "endurance," training that focuses on ankle and hip flexibility (stretching), especially leg strength (muscle training), and endurance (aerobic exercise) is necessary.

In addition, changes in physical condition due to aging, various diseases, and loss of appetite can cause loss of muscle mass, or "weight loss". One of the causes of this loss of muscle mass is "decreased physical activity". Furthermore, "decreased physical activity" is affected by "decreased walking speed" and as mentioned above, "decreased walking speed" is affected by muscle strength and endurance. So these are interrelated in a cycle, and the vicious cycle needs to be broken somewhere. To achieve this, 1) muscle training and 2) aerobic exercise are necessary.

Muscle training to increase muscle strength

Muscle strength is essential for human daily physical activities. By increasing muscle strength, people can perform a single movement with less effort. So-called "muscle training" is important for increasing muscle strength. Professionally, it is sometimes referred to as "resistance training"[6].

Resistance training uses resistance and load on the muscles through the use of weight machines, rubber tubing, or own body weight to increase muscle size, activate nerves that facilitate muscle strength, and improve overall muscle function.

To perform muscle training safely and effectively, it is important to follow the rules[6].

1) Muscle training precautions

The following precautions should also be taken[6].

- Perform preparatory exercises and avoid overexertion from the start.
- Exercise large muscles first.
- Do not fully extend elbows and knees.
- Exercise with proper form and be aware of the muscles.
- Hold the grip lightly as it may cause an excessive increase in blood pressure.
- Do not hold breath.
- Exhale when lifting the weight and inhale lowering the weight.
- Lift and lower the weight slowly for about 4 seconds.
- Rest between exercises.
- Stop exercising immediately if experience dizzi-

ness, irregular pulse, unusual shortness of breath, or angina-like discomfort.

2) Intensity and amount of muscle training (Number of repetitions x sets x frequency)[6]

To strengthen muscles, it is necessary to place a load on the muscles that is greater than the muscle strength used in everyday life. To set the specific load, find the weight that can be lifted only once (called 1 repetition maximum: 1RM) and calculate and set the load to 30-40% for the upper body and 50-60% for the lower body.

In practice, however, it is often difficult to measure the exact 1RM, so a method is used in which an approximate load is determined and the load is gradually increased while checking to see if 10 repetitions can be performed. This is called the titration method.

It is best to use a load that feels "a little hard" after 10 repetitions. On the other hand, if it doesn't feel "a little hard," it won't be very effective.

Repeat the same type of exercise for two or three sets. If you start to feel lighter, you can gradually increase the weight. It is said that 2-3 days a week is quite effective.

3) Specific methods

This section describes the most important lower body exercise (squatting) that can be done at home. Do it without jumping and without stopping to breathe. As lowering the hips, it is best to consciously exhale (Figure 1).

Aerobic exercise to improve endurance[7]

Endurance is "the ability to move the body for an extended period of time. An energy source is needed to move muscles. Oxygen and nutrients are needed to produce this energy in the body. The more oxygen the body can take in, the more energy it can sustainably produce for muscle contraction. In other words, it is important for the body to be able to take in a lot of oxygen in order to move for a long period of time. Therefore, to use a more technical term, "endurance" can be defined as "the ability of the body to take in oxygen through exercise".

Aerobic exercise is exercise that can be performed continuously for long periods of time, such as walking or cycling. Because individual has a different level

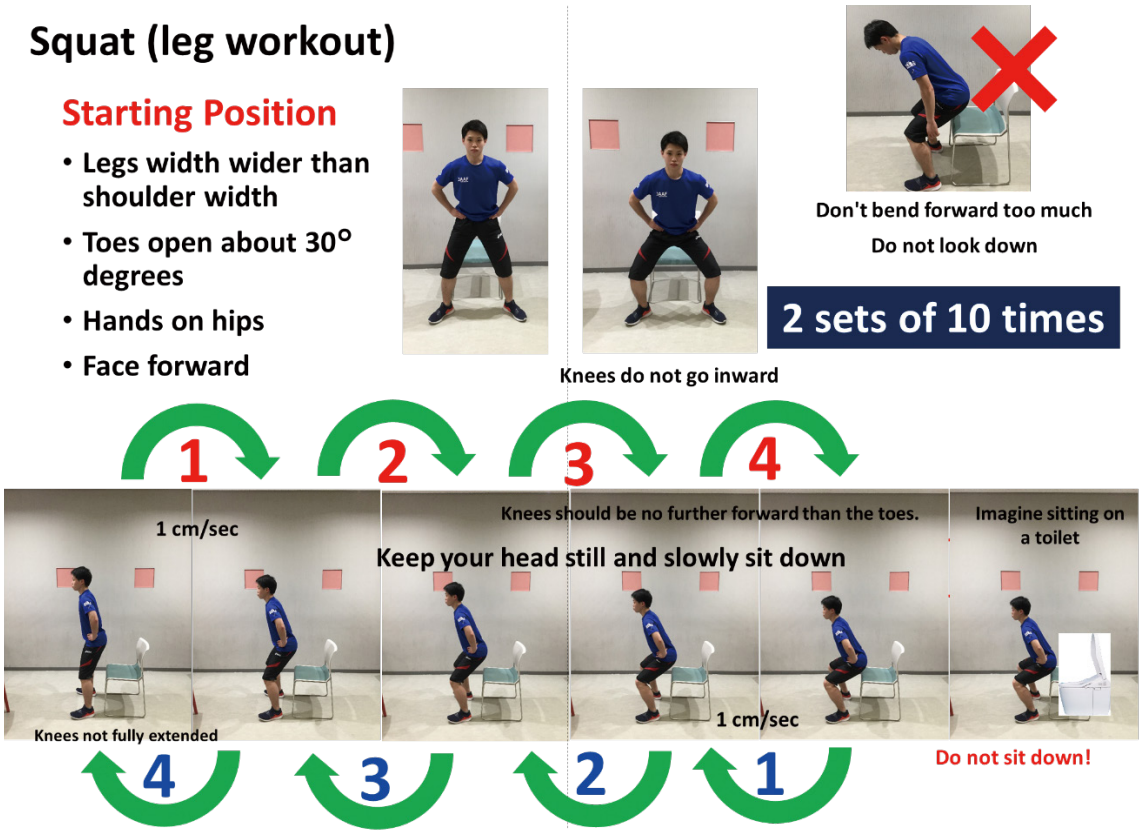

Figure 1 How to perform appropriate squatting exercise

of fitness, it is important to determine the frequency, intensity, duration, and type of exercise according to the individual's fitness level. People with a pre-existing heart condition or those who have been hospitalized for a medical condition should consult their physician before exercising.

When walking as an aerobic exercise to improve endurance, take a slightly larger stride and walk to maintain an effective walking posture and walking speed (Figure 2).

Frequency (F), intensity (I), duration (T) and type of exercise (T) are referred to by the acronym "FITT".

Four key points of aerobic exercise[7]

- Frequency: 3 to 5 times a week. If possible, do it every day.
- Intensity: The intensity should be easy to moderately strenuous, and should be able to exercise while talking.
- Time: 20 to 30 minutes. If it is difficult to exercise continuously, it is said that the effect is the same if the exercise is divided into several sessions so that the amount of exercise per day is 20 to 30 minutes.
- Type: Walking, cycling, aerobic exercise, etc. are suitable.

Muscle training for older patients with frailty

In Japan, there has been a trend toward shortening the length of stay in acute care hospitals. In recent years, due to the aging of the target patient population and the increasing severity of illness, frail and older patients often experience a marked decline in physical function even with short time bed rest, which often interferes with their daily lives after discharge from the hospital. Frailty and physical functional decline not only affects ADLs, but also strongly influences prognosis, including the development of atherosclerotic disease and rehospitalization.

More recently, due to the aging of patients, there is a significant number of patients whose exercise function cannot be fully restored within a short hospital stay and who are unable to return to their pre-hospital exercise function[8]. These patients have become known as "Hospitalization-Associated Disability" or "Hospitalization-Acquired Disability" (HAD)[9]. To ensure a more efficient recovery with a shorter hospital stay, optimal exercise programs need to be further investigated.

The usual rehabilitation program is a step-by-step program that gradually increases gravity loads and movement, such as lifting, sitting, standing, and walking, after absolute rest is lifted, but in older patients with frailty, in addition to increasing walking distance, a rehabilitation program to improve ADL functions, such as the ability to stand up safely and stand stably with good balance. Knee extension exercises are often performed with the patient in a bed-sitting position to strengthen lower extremity muscles. However, it is easier to achieve the specificity of the desired training effect by repeating ADL activities such as standing and sitting than by simply repeating knee extension.

The Japanese Geriatrics Society defined frailty in

Figure 2 How to keep walking speed

Table 1 Short Physical Performance Battery (SPPB) and Juntendo original scale

SPPB	BASE	Balance (10-s balance tests)	Ambulation (a timed 4-m walk)	Sit-ups (a timed 5 times-repeated chair sit-to-stand test)	Endurance (maximum walking distance)
4	5	One leg 10s	Less than 4s	< 9.2 s	340 m (6 min)
	4	Full-tandem 10s	Less than 4.82s	< 11.19 s	180 m
3	3	Full-tandem 3 ~ 9.99s	4.82 ≤ 6.20s	11.2 ≤ 13.69 s	80-179 m
2	2	Semi-tandem 10s	6.21 ≤ 8.70s	13.7 ≤ 16.69 s	40 m
1	1	Side-by-side, 10s	More than 8.70s	> 16.70 s	15 m
0	0.8	Side-by-side, 3 ~ 9.99s	4m with light assistance	> 60 s or stand up 2-5 times	4 m
	0.6	Broad base 10s (without support)	4m with moderate assistance	Stand up once without support	Wheelchair 30 min
	0.4	Able to stand with support	4m with heavy assistance	Stand up with arm support	Wheelchair 10 min
	0.2	Able to stand with assistance	2.3 steps with heavy assistance	Stand up with assistance	Able to sit on the edge of bed
	0	Unable to stand	Unable to walk	Unable to stand up	Bed rest

SPPB 0-6: low function, 7-9: moderate function, 10-12: high function.

2014 as follows[10]: Frailty is a state of increased vulnerability to stress due to a decline in physiological reserve capacity in old age, which may lead to lifestyle dysfunction, need for care, and death. The concept includes not only physical problems such as loss of mobility due to muscle weakness and increased susceptibility to falls, but also mental and psychological problems such as cognitive dysfunction and depression, and social problems such as living alone and economic deprivation.

Focusing on physical frailty, the following three points are important for an exercise program for older patients with frailty.

- Overcoming muscle weakness
- Preventing loss of mobility
- Preventing falls

Currently, the Short Physical Performance Battery (SPPB)[11] is widely used worldwide in the assessment of physical frailty, and each domain of the SPPB has three components: standing balance, walking speed, and leg strength (power). These three components of the SPPB are precisely what characterize the assessment of physical frailty. Therefore, at Juntendo University Hospital, these three SPPB components plus the walking distance (endurance) component are evaluated regularly on a daily basis to standardize the training menu (Table 1)[12]. For example, if the patient can perform semi-tandem standing for 10 seconds in the balance test, but tandem standing is difficult, the 4-meter walking time is slow at 9.2 seconds, and the patient cannot stand without upper limb support (can stand using a handrail) in the standing test. The patient can walk 30 meters down a corridor in the ward. In such a case, the performance level of muscle strength, balance, movement and endurance is as shown in Table 1, and it will be easy to see where the patient's physical function is most impaired.

By visually presenting the results of such an assessment, patients themselves can easily understand the decline in their abilities, leading to adherence to exercise therapy. With the current trend to reduce the length of stay in acute care hospitals, this system will be used as a standard HAD prevention training program to be implemented immediately after hospitalization with a view to discharge. Then, at the time of discharge, physical therapists provide discharge guidance with awareness of these four components to prevent progression of frailty (Figure 3).

The five-chair rise test is important for overcoming the dynapenia described at the beginning of this article and is one of the exercises that should be consciously performed in addition to regular muscle training, especially in patients with frailty.

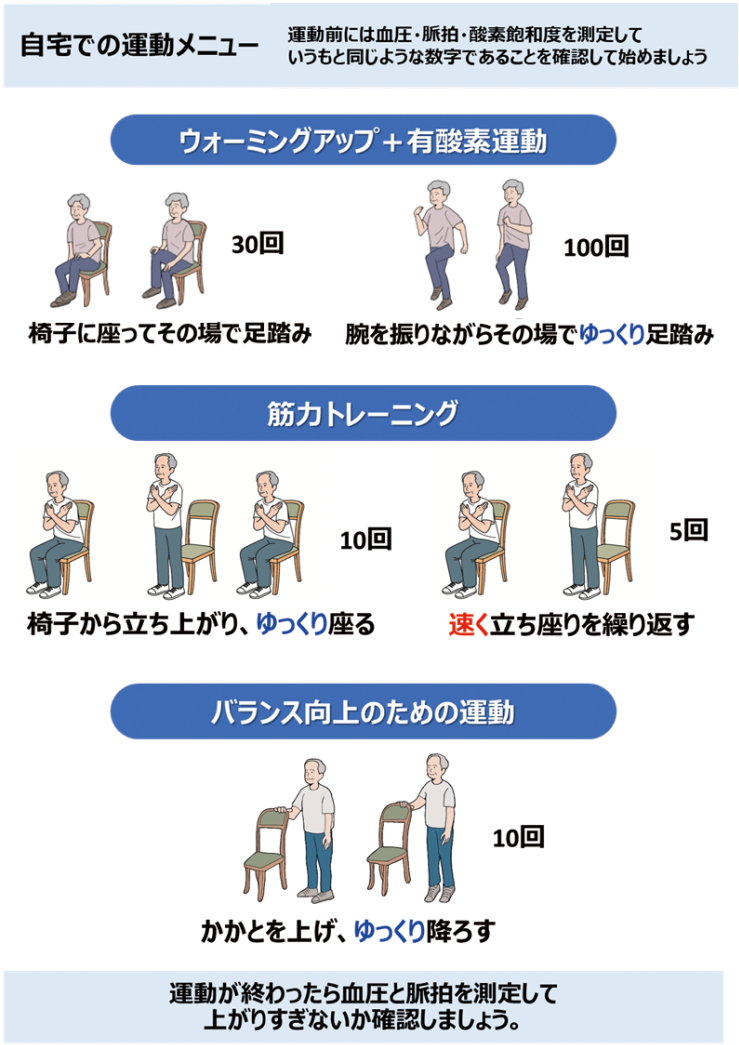

Figure 3 Home exercise program for frailty prevention

Tele-cardiac rehabilitation

Currently, access to medical facilities for the older people is a problem due to geographical and time constraints, economic issues, lack of caregivers and carers, and uneven distribution of medical resources. In addition, many people are reluctant to go out due to recent new coronavirus infections, and the problem of difficulties in visiting hospitals is a major issue for all generations[13]. These difficulties are not limited to general outpatient visits, but also extend to rehabilitation for the recovery of functional disabilities caused by various diseases, traumas, and pathological conditions[14].

In Japan, "tele-cardiac rehabilitation" conjures up images of so-called "real-time online exercise" using the Internet, but in reality, "tele-cardiac rehabilitation" devices and systems are used in a variety of ways, and there is no clear definition. In general, "telemedicine" is based on an infrastructure using computer and communication technology, but by distinguishing between "asynchronous (store-and-forward, asynchronous)" and "synchronous (real-time, synchronous)" telerehabilitation[15].

In Japan, the synchronous model is interpreted as a model that provides comprehensive exercise program, patient education, and psychological support similar to those provided in outpatient program, while monitoring real-time biometric data such as electrocardiogram and blood pressure, in addition to video communication over the Internet[16,17]. Tele-cardiac rehabilitation does not require an exercise bike for exercise. Many older patients require more basic exercise than cycling on an exercise bike. Especially in the immediate post-discharge period after cardiac surgery, patients are

often forced to rest longer than necessary or leave the hospital without a better understanding of their disease or current condition during their short hospital stay. For such patients, we use home-hospital videoconferencing to monitor their physical condition, subjective symptoms, daily blood pressure, steps, weight change, facial expression, lower extremity edema, and median incision site while monitoring their ECG, blood pressure, and oxygen saturation in real time. In addition to thorough pre-orientation, limiting the tablet's functions, minimizing the use of apps, and keeping the procedure simple, even elderly patients are able to complete the procedure without major operational problems.

Conclusion

This perspective paper has described the importance of preventing physical frailty and specific approaches, particularly exercise-based rehabilitation programs, that can be implemented to minimize hospitalization-related disability in frail older patients, as well as the current state of telerehabilitation.

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Author contributions

TT gave a lecture at the 51st Metropolitan Public Lecture, which was summarized in the manuscript. MT, SM, and IK collected relevant information and provided relevant content advice on the manuscript; FT and DH provided clinical and research advice on the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of interest statement

The authors declare that they have no competing interests related to this manuscript.

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Reviews

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Nutrition, Exercise, and Cognitive Rehabilitation for Dementia Prevention

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Dementia is one of the most significant global challenges in medical and social care in the 21st century. It affects not only the patients themselves, but also their families, caregivers, and society in general, causing physical, psychological, and socioeconomic effects. As of 2020, there are approximately 6 million people in Japan aged 65 or older with dementia, and this number is expected to increase to around 7 million by 2025, meaning that one out of every five elderly people will have dementia. To prevent the onset and progression of dementia, it is crucial to have a proper understanding of its risks and adopt a healthy lifestyle. Leading an active life from an early stage can also aid in delaying or preventing the onset of dementia. Livingston has identified 12 risks that can lead to dementia, including physical inactivity, smoking, excessive alcohol consumption, air pollution, head injury, social isolation, poor educational history, obesity, hypertension, diabetes, depression, and hearing loss. Modifying one's lifestyle and leading an active life can be crucial in reducing these risks. The Mediterranean diet is gaining attention as a good practice for dementia prevention due to its diversity, richness in omega-3 fatty acids and vitamins. Exercise has been shown to prevent dementia on biological, behavioral, and socio-psychological levels. Repetitive transcranial magnetic stimulation is a non-invasive brain stimulation method that can alter brain plasticity and is being studied for clinical applications as a non-drug therapy for preventing dementia progression.

Key words: dementia, nutrition, physical exercise, cognitive rehabilitation, repetitive transcranial magnetic stimulation

Introduction

A super-aging society is one in which the elderly population aged 65 and over accounts for 21% or more of the total population. In Japan, due to the rapid aging of the population, the country has already entered a super-aging society in 2007. According to recent data from the Statistics Bureau of the Ministry of Internal Affairs and Communications, Japan's elderly population aged 65 and over is projected to reach 36.27 million by October 2022. This translates to 29.1% of the total population, representing a 0.3 percentage point increase from the previous year's figure of 28.8%. These figures mark the highest ever recorded for this demographic group. Furthermore, according to the same report, as of October 2022, there will be 19.37 million people aged 75 or older in the late stages of life, accounting for 15.5% of the total population. In comparison with other countries, Japan (29.1%) has the highest percentage of elderly in the total population, followed by Italy (24.1%), Finland (23.3%) Puerto Rico (22.9%), and Portugal (22.9%)[1)]. By 2025, the number of the elderly aged 75 and over is expected to reach 21.8 million, and the number of the elderly aged 65-74 is expected to reach 14.97 million, totaling about 37 million people aged 65 and over. On the other hand, Japan's total

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population peaked in 2008 and has been declining since then. Therefore, as a result of the relative increase in the elderly and relative decrease in the number of young people due to demographic changes, about one in three of the nation's population will be 65 years of age or older, and about one in five will be 75 years of age or older. The baby boomer generation born between 1947 and 1949 will enter late-elderly status in 2025, marking a significant milestone[2]. This will have a major impact on society as a whole in terms of social security, medical care, long-term care, and pensions to support the growing number of late-elderly citizens, and it has been likened to the "2025 problem," and the problem is expected to become even more apparent. To maintain the social security system in the future, it is becoming increasingly important to extend the healthy life expectancy of every citizen.

Dementia is generally defined as a decline in cognitive function beyond what is normally expected with aging. Cognitive decline and psychiatric symptoms of dementia are commonly divided into higher brain dysfunctions such as memory impairment, aphasia, and apraxia, which are considered core symptoms, and behavioral and psychological symptoms of dementia (BPSD) such as delirium, hallucinations, and decreased vitality. Dementia is one of the greatest global challenges in health and social care in the 21st century[3]. It is estimated that there are currently more than 55 million patients worldwide, with an additional 10 million new cases each year[4]. According to the Ministry of Health, Labour and Welfare's survey on long-term care insurance certification in Japan, dementia is the leading factor in the need for long-term care[5]. Dementia has physical, psychological, and socioeconomic effects not only on the patients themselves, but also on their families, caregivers, and society. Taking active steps towards dementia prevention is crucial to maintain not only the health of the patient but also of their family and social circle. This approach can also help in reducing the demand for medical care in society as a whole. As of 2020, there will be approximately 6 million people in Japan aged 65 or older with dementia, and this number is expected to increase to approximately 7 million by 2025, meaning that one out of every five elderly people will have dementia[6]. With such a rapidly aging population, there is no doubt that the prevention of the onset and progression of dementia is one of the most important and urgent issues in Japan. On a global scale, efforts to understand and prevent dementia are gradually being made, and the number of dementia patients is decreasing in developed countries. To prevent the onset and progression of dementia, it is crucial to have a proper understanding of its risks and adopt a healthy lifestyle. Leading an active life from an early stage can also aid in delaying or preventing the onset of dementia. This article outlines the risks of developing dementia and the non-pharmacologic therapies, such as diet, nutrition, exercise, and cognitive rehabilitation, that are necessary to prevent dementia.

Causal diseases of dementia

Alzheimer's disease (AD) is the most common causative disease of dementia in Japan at 67.4%, followed by cerebrovascular dementia (CVD) at 18.9%, dementia with Lewy bodies (DLB) at 4.6%, mixed dementia at 4.2%, and frontotemporal dementia (FTLD) at 1.1%[7, 8]. These dementias are fatal diseases and have a prognosis of 10 years or less, depending on the age of onset[9, 10].

On the other hand, there is a type of dementia that can be treated, which is referred to as "treatable dementia"[11]. Treatable dementia can occur at a young age and often has a more acute course than AD and other degenerative diseases. It is important to note that there are several types of dementia that can be treated effectively. These include endocrine disorders such as hypothyroidism, essential vitamin deficiencies such as vitamin B1, vitamin B12, and folate deficiencies, neurosyphilis, fungal infections, central nervous system infections such as encephalitis and meningitis, chronic subdural hematoma, normal pressure hydrocephalus, and nonconvulsive status epilepticus. These treatable dementias can occur even in patients already diagnosed with AD, CVD, DLB, etc. However, if these diagnoses have already been made, any exacerbation of symptoms tends to be dismissed as a symptom progression of this disease, and then cognitive declines to be overlooked without an opportunity to be re-examined.

Physicians and healthcare professionals who treat patients with dementia must always take into account the impact of multiple factors. Rather than attributing fluctuations in mental symptoms to a

single disease, they should approach diagnosis and treatment flexibly. This should be done considering both progressive dementia and treatable dementia, and adapting to changes in the patient's condition. Furthermore, the human "mind" and "body" are closely linked, and cognitive functions, mental states, and physical functions interact with each other. In particular, as represented by the term "brain-gut correlation", gastrointestinal tract functions, autonomic nervous system functions, and brain functions interact with each other. Therefore, it must be recognized that in patients with dementia, cognitive and mental status fluctuate due to various physical complications such as infections, pain from intra-abdominal organ diseases, falls, and fractures, and that dementia can easily become severe. It is important to avoid polypharmacy and cognitive decline when treating individual diseases. When different specialists focus on treating specific organs, they may overlook the effects of drug administration, resulting in a vicious cycle of treating physical diseases and cognitive decline. Many patients who develop dementia are elderly and are prone to unanticipated side effects from drugs. As dementia is a progressive systemic disease that starts with cognitive decline, it is important to conduct a thorough assessment of the entire body, including cognitive function, internal organs, and the musculoskeletal system, and to administer the minimal drug therapy required. Therefore, it is important to select treatment and care options from a bird's-eye viewpoint based on a thorough understanding of the characteristics and limitations of both pharmacological and non-pharmacological therapies.

Global trends in the increase and decrease of dementia patients

The world population is getting older, which is resulting in a rise in the number of people diagnosed with dementia. As per the estimates of 2019, the number of dementia patients is around 57.4 million[12]. It is expected to increase to 152.8 million, almost triple the current number, by 2050[4]. The number of dementia patients is expected to increase in line with population growth, particularly in sub-Saharan Eastern Africa, North Africa, and the Middle East. In East Asia, on the other hand, the aging of the population is expected to be a major factor in the increase in the number of dementia patients[12]. However, it has been reported that in high-income countries in the United States and Europe, the prevalence of dementia has been declining in recent years[13–15], the incidence of dementia has also been reported to be declining in recent years[16–18]. In a study conducted by Langa et al. from the University of Michigan, USA, the prevalence of dementia was compared between the years 2000 and 2012 in the US. The study revealed that there was a significant decrease in the prevalence of dementia during this period, and that this reduction was partly attributed to an increase in the number of years of education[14].

However, the number of dementia patients in Japan has been increasing in recent years, and the situation differs from that in other developed countries[19]. The increase in the number of elderly people in Japan has outpaced that of other developed countries[20] then the aging of the population in Japan is much higher than in other Western countries. From the well-known Hisayama Town study, a cohort study of lifestyle-related diseases, the prevalence of dementia patients is on the rise[21], and reports show that cerebrovascular dementia is decreasing, while tauopathies like AD and SD-NFT are increasing with society's aging[22, 23].

Current status of pharmacotherapy for dementia diseases

AD is the most common form of dementia, but as of August 2023, no drug can cure AD. In Japan, four drugs have been approved for the treatment of dementia: three cholinesterase inhibitors (ChEIs) and one NMDA receptor antagonist, but these are all symptomatic therapies[24]. The choline hypothesis has been proposed to explain cognitive dysfunction in AD, which is thought to be caused by a decline in the function of the acetylcholine (ACh) system in the central nervous system[25–27]. Three drugs currently approved for the treatment of AD, donepezil, galantamine, and rivastigmine, are cholinesterase inhibitors (ChEI) that were developed to inhibit the degradation of ACh[28]. In AD, the NMDA receptor (N-methyl-D-aspartate receptor: NMDAR), one of the glutamate receptors, is activated excessively, which causes neurotoxicity and cognitive dysfunction[29]. Memantine was developed for the treatment of AD based on the hypothesis of glutamate-induced neurotoxicity and is thought to antag-

onize NMDAR, inhibit excessive glutamate stimulation, improve synaptic transmission, and inhibit neuronal cell loss[30]. ChEI affects both peripheral and central cholinesterase, causing side effects such as gastrointestinal and cardiovascular symptoms, frequent urination, muscle spasms, nightmares, and insomnia due to excess Ach[24]. It is important to note that while ChEI may improve motivation and activity, it also increases irritability and can be challenging to differentiate from delirium. It is important to note that while ChEI may improve motivation and activity, it also increases irritability and can be challenging to differentiate from delirium. Memantine also causes side effects such as somnolence, dizziness, confusion, headache, constipation, and incontinence.

A survey conducted between 2015 and 2016 in Japan found that almost half of those prescribed antidementia drugs were 85 years or older. This is surprising because 17% of the elderly aged 85 years or older were prescribed some of these anti-dementia drugs[31]. The target population for these anti-dementia drugs in the clinical trial phase was 85 years of age or younger, and the current situation in prescribing is becoming divergent from the subjects targeted in the clinical trials. The prescribing of anti-dementia drugs to super-aged patients must be approached with greater caution due to insufficient efficacy and safety, and potential adverse events. These drugs are only intended to alleviate the psychiatric symptoms of dementia, not to treat the disease itself. Because the effects of these dementia medications are difficult to understand and side effects are difficult to detect, behavioral and psychological changes due to side effects can easily be misinterpreted as worsening BPSD symptoms or dementia symptoms. In France, as of August 2018, the four dementia drugs mentioned above have been excluded from insurance coverage due to their potentially serious side effects, while their effects on patients' behavioral disturbances, quality of life, and mortality have not been established. The government is shifting its policy to focus on long-term care and comprehensive community care rather than these drugs whose usefulness is not yet certain.

Disease-modifying drugs have long been under development as therapeutics for the fundamental treatment of dementia, but many of them have failed in the clinical trial stage.

The U.S. FDA approved the use of lecanemab in July 2023. Lecanemab is an antibody drug that is based on the amyloid hypothesis. It is designed to remove amyloid-β accumulation in the brains of patients with Alzheimer's disease. Lecanemab is the first drug that is expected to modify the disease course of Alzheimer's disease. It is expected that lecanemab will be approved in Japan shortly. However, before administration of lecanemab, a positron emission tomography (PET) scan or spinal fluid analysis must be performed to confirm the presence of amyloid-β[32]. This creates a hurdle for patients to choose whether they can afford an expensive PET scan or an invasive CSF test before they start receiving lecanemab. In addition, cerebral edema and microhemorrhages, known as amyloid-related imaging abnormalities (ARIA)[33, 34], have been reported as serious side effects of this drug. Regular MRI scans are required to monitor these side effects[32]. In addition, testing for APOE4 gene carriage is necessary for some APOE4 gene carriers who are at an increased risk of developing ARIA[33]. Individuals who are prescribed anticoagulants for the prevention of cardiac disease or stroke are at a greater risk of experiencing cerebral hemorrhage[32]. The administration of lecanemab concurrently with anticoagulants may intensify the likelihood of adverse effects, posing a challenge when considering this medication for patients who have a history of stroke or ischemic heart disease. The price of lecanemab in the U.S. is set at $26,500 per year[35], making it currently a very expensive treatment. Although the improvement of dementia symptoms by this treatment is expected to have an economic benefit by reducing the burden of caregiving and financial burden on those around the patient, there are concerns about the increased burden on medical resources, such as twice-monthly intravenous infusions and periodic MRI scans. It remains uncertain whether the benefits of disease-modifying drugs outweigh the risks of side effects and the expenses associated with medical resources. Additionally, it may take some time before these drugs become readily accessible and commonly used as a treatment option worldwide. Although there are high expectations for the emergence of disease-modifying drugs, their indication is currently limited to MCI or mild AD, and they are expected

to be effective as secondary or tertiary prevention after such a diagnosis has been made. In the current situation where we have to deal with the increasing number of dementia patients on a global scale, efforts for primary and secondary prevention, particularly through non-pharmacologic interventions like lifestyle modifications, are critical.

Stages of progression from normal to dementia

The process of progression from normal to dementia is classified into four stages. The first stage is called subjective cognitive decline (SCD)[36, 37], in which the patient has only subjective symptoms of forgetfulness, followed by mild cognitive impairment (MCI)[38, 39], in which the patient has objectively mild cognitive impairment but is still independent in daily living, and finally dementia when the symptoms progress further and daily living becomes difficult to be independent. It is estimated that 5–20% of MCI patients will develop dementia in a year[39]. MCI has also been reported to revert to normal cognitive function[40, 41], early diagnosis and prevention of dementia in the MCI stage is extremely important.

Dementia symptoms and stages of progression

Dementia is commonly associated with cognitive function and mental symptoms. However, it is a degenerative brain disease that progressively causes a variety of brain dysfunctions. It can lead to a decline in motor abilities such as walking, standing, and balance[42, 43]. Additionally, it can also worsen swallowing and eating functions[44–46]. Mental functions gradually deteriorate, leading to delirium and psychomotor agitation, eventual loss of facial expressions, communication difficulty, inaction, self-enclosure, immobility, and muteness. As the disease progresses, patients may experience complications such as malnutrition, aspiration pneumonia, pyelonephritis, sepsis, injuries from falls, and ultimately death.

In the case of AD, the main initial symptom is memory impairment, such as the inability to remember the names of people one knows well. After experiencing memory impairment, individuals may develop symptoms such as executive dysfunction, disorientation, apraxia, and unconsciousness which can hinder their ability to perform instrumental activities of daily living. In the middle and later stages, basic ADLs are impaired and the patient requires nursing care. During the course of the disease, individuals may develop symptoms such as anxiety, depression, insomnia, agitation, irritability, paranoia, wandering, hallucinations, and delusions that may require pharmacotherapy. The progression of AD is assessed by the Functional Assessment Staging of Alzheimer's Disease (FAST) developed by Reisberg in 1984 and is used worldwide to assess the progression of AD[47, 48]. FAST is composed of 7 stages, 5 sub-stages for Stage 6 and 6 stages for Stage 7, and a total of 16 stages. Reisberg emphasizes the need to watch for the worsening of disease due to treatable factors, including electrolyte abnormalities and stroke complications, when symptoms progress more rapidly than the typical course shown in FAST. (Table 1)

Three phases in dementia prevention

There are three phases in dementia prevention[49]. Primary prevention is to prevent the onset of dementia from a healthy and asymptomatic state. Secondary prevention is to delay the onset of dementia through early detection and treatment. Tertiary prevention is to delay the progression of symptoms after the onset of dementia. In the primary and secondary prevention stages, non-drug therapy and lifestyle modification are most important. In the tertiary prevention stage, pharmacotherapy may be necessary for BPSD symptoms such as hypoactivity, apathy, and psychomotor agitation; however, it should only be used as part of an overall treatment plan that also includes non-pharmacological interventions.

Even if a patient has already been diagnosed with a dementia disease such as AD or DLB, complications of "treatable dementia" such as hydrocephalus, chronic subdural hematoma, endocrine abnormalities, and essential vitamin deficiencies may exacerbate dementia symptoms. In addition, as patients age, they are more likely to suffer head trauma from easy falls due to the progression of frailty, and polypharmacy due to the increased use of medications to treat increased medical complications also contributes to the progression of frailty. For these various reasons, the overlap of various diseases and conditions can lead to further cognitive decline. Older people suffering from dementia are at increased risk of malnutrition due to various

Table 1 The Functional Assessment Staging of Alzheimer's Disease (FAST)

Stage	Clinical diagnosis	Characteristics
1	Normal adult	No difficulty either subjectively or objectively
2	Normal aged adult	Complains of forgetting the location of objects—subjective word-finding difficulties
3	Compatible with incipient AD	Decreased job functioning evident to co-workers. Difficulty in traveling to new locations. Decreased organizational capacity
4	Mild AD	Decreased ability to perform complex tasks (e.g., planning dinner for guests, handling. personal finances, difficulty marketing, etc.)
5	Moderate AD	Requires assistance in choosing proper clothing to wear for the day, season, or occasion (e.g., a patient may wear the same clothing repeatedly unless supervised)
6a	Moderately severe AD	Improperly putting on clothes without assistance or prompting (e.g., may put street clothes on overnight clothes, put shoes on wrong feet, or have difficulty buttoning clothing) occasionally or more frequently over the past weeks
6b		Unable to bathe properly (e.g., difficulty adjusting bathwater temp.) occasionally or more frequently over the past weeks
6c		Inability to handle mechanics of toileting (e.g., forgets to flush the toilet, does not wipe properly or properly dispose of toilet tissue) occasionally or more frequently over the past weeks
6d		Urinary incontinence occasionally or more frequently over the past weeks
6e		Fecal incontinence occasionally or more frequently over the past weeks
7a	Severe AD	Ability to speak limited to approximately a half-dozen different intelligible words or fewer in an average day or the course of an intensive interview
7b		Speech ability is limited to using a single intelligible word on an average day or in an intensive interview (the person may repeat the word over and over)
7c		Ambulatory ability is lost (cannot walk without personal assistance)
7d		Cannot sit up without assistance
7e		Loss of ability to smile
7f		Loss of ability to hold head up independently

Adapted from Reisberg B (1986) Geriatrics, 41: 30-46.

nutritional problems[50]. In particular, after the onset of dementia, it is not uncommon for nutritional disorders to develop as a result of decreased food intake due to decreased food recognition and interest, impaired chewing and eating function, and other complications such as vitamin B1 deficiency (Wernicke-Korsakoff encephalopathy), vitamin B12 deficiency, folate deficiency, and hypoglycemic encephalopathy associated with decreased food intake. Complications associated with low dietary intake can worsen symptoms of dementia. Poor nutritional status increased BPSD, especially verbal aggressiveness/emotional disinhibition, in those with MCI and early-stage AD. Patients with MCI and early-stage AD need to be assessed for nutritional status from early on, at the onset of mild cognitive decline, and require intervention to prevent worsening of BPSD[51].

Therefore, even after the diagnosis of dementia is confirmed, it is important to continue periodic imaging with head CT, MRI, and periodic blood sampling for evaluation of thyroid hormone abnormalities and vitamin deficiency as tertiary prevention after the onset of dementia.

Risk factors related to the development of dementia

Sixty percent of the risks for dementia are difficult to modify, while 40% are considered modifiable. The "12 modifiable risks" proposed by Livingston, University of London, include physical inactivity, smoking, excessive alcohol consumption, air pollution, head trauma, social isolation, poor educational history, obesity, hypertension, diabetes, depression, and hearing loss (Figure 1). Maintaining an active and social lifestyle is crucial in preventing dementia. It is recommended to focus on dementia prevention from an early age, but it's never too late to take steps to prevent it. As the saying goes, "It is never too early or too late to be greedy in preventing

Figure 1 Twelve potentially modifiable risk factors presented as infographic by Alzheimer's Disease International (ADI), based on Livingston's report: Dementia prevention, intervention, and care: 2020 report of the Lancet Commission
https://www.alzint.org/about/risk-factors-risk-reduction/

dementia." The report highlights the importance of engaging in activities that prevent dementia, regardless of age[52].

Diabetes increases risk of dementia

Several epidemiologic studies have shown that type 2 diabetes decreases cognitive function and increases the incidence of dementia; the Rotterdam Study reported that type 2 diabetes increases the risk of developing dementia and AD, especially during insulin therapy[53]. The Hisayama study also reported that type 2 diabetes significantly increased both AD and VaD[54]. The pathogenesis of cognitive dysfunction due to type 2 diabetes includes tau phosphorylation due to increased insulin resistance, neuronal and synaptic damage via amyloid-β accumulation, and vascular damage. Other postulated mechanisms of cognitive dysfunction due to type 2 diabetes include neuropathy and vascular damage mediated by increased amyloid-β accumulation, advanced glycation end-products (AGEs) accumulation due to hyperglycemia, inflammation, and increased reactive oxygen species (ROS) production[55].

Postprandial hyperglycemia and diurnal fluctuations in blood glucose are risks for developing dementia. In diabetes mellitus, the hazard ratio for developing dementia was 1.40 times higher for postprandial blood glucose levels of 190 mg/dL compared to 160 mg/dL[56]. Therefore, it is important to limit carbohydrate intake, consume foods with a low glycemic index (GI) (brown rice and other unrefined grains rather than white rice), increase the number of chews and eat as slowly as possible, and consume vegetables before carbohydrates to reduce the rise in blood glucose levels (meal order). It is important to maintain a diet that does not cause hyperinsulinemia. Hypoglycemia tends to cause irreversible changes in the brain, and it has been reported that the hazard ratio for developing dementia increases from 1.26 for a single hypoglycemic attack to 1.80 for two attacks and 1.94 for three or more attacks[57]. The frequency of hypoglycemic attacks is also high in patients after the onset of dementia and is related to the fact that hypoglycemic attack symptoms are not easily recognized,

meals are more likely to be irregular, and patients are more likely to be undernourished. Especially in elderly patients with frailty, hypoglycemia can easily lead to falls and fractures, creating a vicious cycle.

Diet and nutritional management for dementia prevention

In recent years, the Mediterranean diet has been attracting attention as a good dietary practice for dementia prevention[52, 58–62]. The Mediterranean diet is a dietary habit of Mediterranean countries such as Italy, Spain, and Greece, characterized by abundant use of fresh fruits and vegetables, more fish than dairy products and meat, olive oil, nuts, legumes, and often unrefined grains such as whole grains. It is also characterized by the use of whole grains and other unrefined cereals. They also drink moderate amounts of red wine with their meals and can be characterized as having a very diverse eating style. (Figure 2) Adherence to the Mediterranean diet was associated with a 20% lower risk of dementia overall in a Mediterranean study involving over 16,000 middle-aged and elderly participants followed up for over 20 years. Associations were stronger for non-AD dementia in women and for AD in men, and among participants with lower education[63]. There are significant geographical and historical differences between Japan and the Mediterranean countries in Europe, which result in unique food cultures. As a result, it may be challenging to replicate the Mediterranean diet entirely. However, there are still some valuable points that we can learn from it. Compared to the Mediterranean diet, the traditional Japanese diet has a higher carbohydrate intake due to the consumption of rice. Therefore, to build a highly diversified diet based on the Japanese diet, it is recommended that a balanced diet be maintained by actively consuming fish, shellfish, vegetables, fruits, nuts, and legumes, and by moderating the intake of white rice as a carbohydrate and including millet and unrefined grains with low GI values.

Consuming fish is a great way to get protein and omega-3 fatty acids, which are crucial for preventing

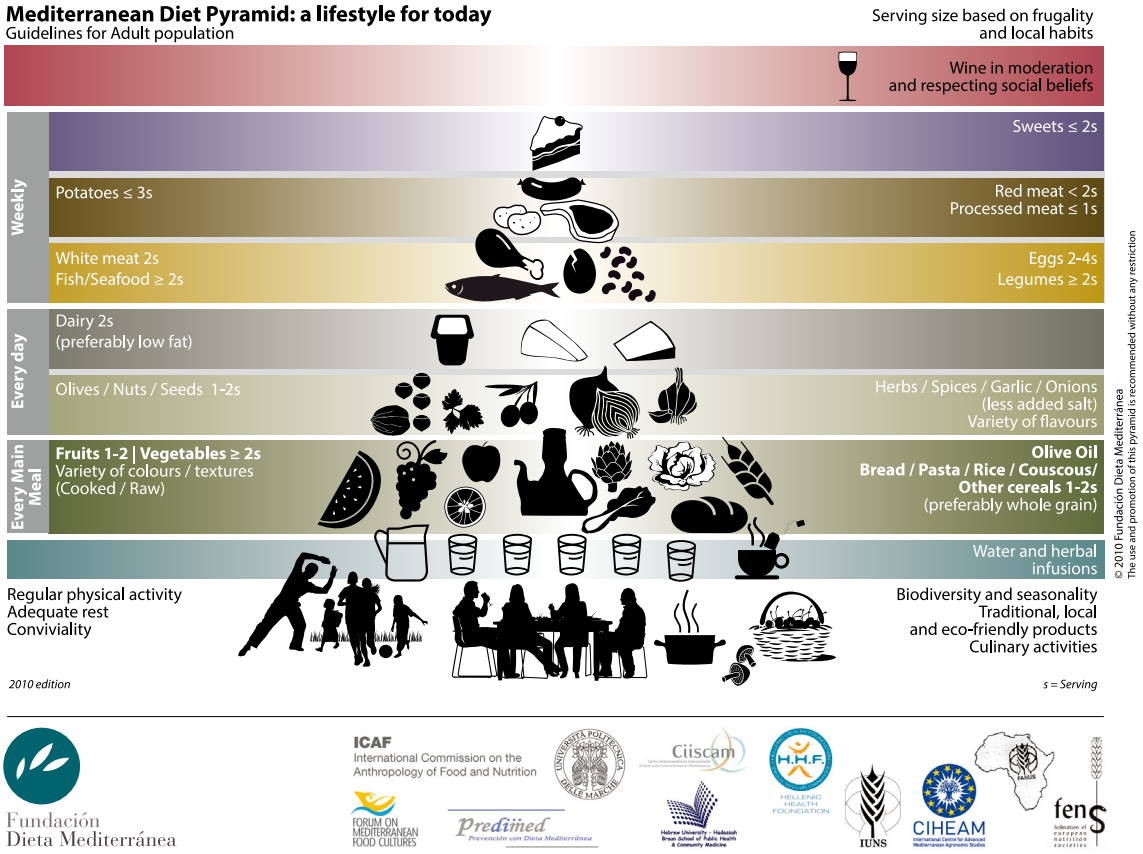


Figure 2 Mediterranean diet pyramid
Retrieved from FUNDACIÓN DIETA MEDITERRÁNEA website: https://dietamediterranea.com/nutricion-saludable-ejercicio-fisico/#piramide

dementia. Shellfish is a great source of essential minerals such as calcium, iron, zinc, magnesium, and potassium, as well as vitamin B12. Vegetables and fruits are packed with vitamins C, carotene, vitamin E, and folic acid. Nuts are also an excellent source of calcium, magnesium, and dietary fiber. Beans provide protein and vitamin B1, while unrefined grains offer carbohydrates, vitamin B1, minerals, and dietary fiber. Additionally, olive oil is rich in oleic acid, and red wine contains polyphenols. Consuming a diverse range of nutrient-rich foods is essential in preventing dementia. Nutritional management is important for preventing dementia progression, even after onset.

Patients with dementia often experience various eating behavior abnormalities[64], such as undernutrition due to anorexia, and overnutrition due to overeating. Furthermore, dementia patients have a reduced sense of taste and tend to prefer sweet and strong-tasting foods[65], leading to a diet that is high in carbohydrates and deficient in essential vitamins, minerals, and proteins. This can further exacerbate the disease condition and its symptoms.

Adequate fatty acid intake for dementia prevention

Fatty acids are divided into four general categories: saturated, monounsaturated, polyunsaturated, and trans fatty acids[66]. Saturated and trans fatty acids increase the risk of coronary heart disease. Monounsaturated and polyunsaturated fatty acids decrease the risk of coronary heart disease[66]. The brain is a lipid-rich organ, then the intake of good fats is crucial for the brain. Omega-3 (n-3) fatty acids have been linked to healthy aging throughout life[67]. The omega-3 fatty acids from fish, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are associated with fetal development, improved cardiovascular function, and Alzheimer's disease prevention. EPA reduces neutral fat, preventing arteriosclerosis and heart disease[68,69]. DHA is a component of nerve cell membranes in the brain[70] and is believed to dilate blood vessels[71], improve immunity and suppress inflammation[72], and aid insulin function[73]. DHA and EPA are derived mainly from bluefish. Alpha-linolenic acid (ALA), which is also a representative of ω-3 fatty acids, is contained in plant-derived oils such as linseed oil, perilla oil, perilla sesame oil, and walnut oil[74]. People who are not fond of fish should actively try to consume such plant-derived ω-3 fatty acids. Since trans fatty acids are contained in foods containing margarine and shortening (cakes, French fries, potato chips, doughnuts, etc.), one should be careful not to eat too much fast food and sweets.

Vitamin intake and dementia prevention

Insufficient intake of vitamin B1, B12, and folic acid may lead to dementia[75]. In particular, vitamin B1 deficiency, known as beriberi, has long been a feared national disease, particularly among the Japanese whose staple food is white rice. Even today, vitamin B1 deficiency is potentially quite common, especially among the elderly, and unfortunately, it is still a condition that has a high risk of going undiagnosed and leading to death[76]. As vitamin B1 deficiency is a potential risk, it is imperative to conduct serum vitamin B1 measurements and administer vitamin B1 supplementation in infusions for patients with impaired consciousness or nutritional disorders. One of the "treatable dementias" caused by vitamin B1 deficiency is Wernicke's encephalopathy, an acute hemorrhagic upper gray matter inflammation described by Carl Wernicke in 1881, classically known as a triad of impaired consciousness, eye movement disorder, and ataxia. However, the triad is rather infrequent, with only about 16% of patients presenting with all three signs[76]. The sad reality is that during their initial medical examination, more than 80% of patients remain undiagnosed. It's important to note that despite the prevalence of rich diets, vitamin B1 deficiency remains a common issue that can arise due to various factors. These factors include prolonged periods of unbalanced carbohydrate-heavy diets, excessive alcohol consumption, reduced food intake due to loss of appetite, and strenuous exercise. In addition, long-term diuretic therapy for heart failure and leg edema can cause vitamin B1 deficiency[77] due to the water-soluble nature of the vitamin B1; however, vitamin B1 measurements are rarely taken during heart failure treatment. Therefore, it is important to educate clinicians involved in emergency room care and heart failure treatment to prevent treatable dementia. To prevent vitamin B1 deficiency, it is advisable to include familiar foods rich in vitamin B1, such as rice bran, pork fillet, seaweed, eel, soybeans, sesame seeds,

peanuts, brown rice, and rye bread in the daily diet.

Vitamin B12 deficiency and folate deficiency are known causes of megaloblastic anemia[78, 79] and subacute association spinal cord degeneration[80], but even without these conditions, they are known to cause cognitive decline[81]. Folic acid deficiency and associated elevated homocysteine levels are also thought to cause dementia and affective disorders such as depression[82]. A study on the association between hyperhomocysteinemia and Alzheimer's disease was conducted to investigate the correlation between blood homocysteine levels and Alzheimer's disease over 8 years in 1,092 dementia-free men and women in the United States with an average age of 76 years. 5 μmol per liter of homocysteine in the blood per liter increased the risk of Alzheimer's disease by 40%. The risk of developing dementia or Alzheimer's disease is doubled in the group with the highest blood homocysteine levels compared to the group with the lowest levels, and subjects with persistently elevated blood homocysteine levels are reported to be at the highest risk of dementia[83]. It has been suggested that folic acid and vitamin B12 supplementation may help prevent mood disorders, Alzheimer's disease, and vascular dementia[84]. In postgastrectomy/gastrectomy patients, vitamin B12 deficiency occurs due to insufficient secretion of internal factors secreted by the stomach, which is necessary for vitamin B12 absorption. In addition, long-term administration of proton pump inhibitors (PPIs) is known to impair vitamin B12 absorption and cause dementia[85]. A study examining long-term PPI administration and the development of dementia reported that long-term users who had used PPIs for a cumulative total of more than 4.4 years had a significantly increased risk of developing dementia by 33% compared to those who had never used PPIs. In contrast, the researchers found no significant increased risk among short- to medium-term users of 4.4 years or less[86]. From the perspective of dementia prevention, it is advisable to include foods containing vitamin B12 and folic acid in the menu daily. Foods rich in vitamin B12 include shellfish such as clams, and laver, anchovies, sweetfish, pork liver, and chicken liver. However, the liver is high in purines, so care should be taken not to consume too much if you have hyperuricemia or gout. Foods rich in folic acid include seaweed, wakame seaweed, chicken liver, pork liver, green tea, soybeans, parsley, kale, and broccoli.

Exercise to prevent dementia

It has been calculated that about 3% of all dementia cases could be prevented by increasing levels of physical activity[3]. Both aerobic exercise and resistance training are important for dementia prevention[87, 88]. The effects of exercise on dementia prevention are estimated to be at the biological level: increased cerebral blood flow due to exercise, increased BDNF and IFG-1, increased brain capacity such as the hippocampus due to improved insulin resistance, behavioral level: improved sleep, decreased fatigue, improved physical activity and physical function, and social psychological level: improved depression, increased self-efficacy, more friends, improved social networks[89]. A study examining the correlation between physical activity measured with a physical activity meter and brain volume by MRI imaging reported a correlation between prolonged light-intensity physical activity and increased brain volume[90].

For aerobic exercise, daily walking is as important as a low-intensity exercise load. It is recommended to use a pedometer, smartphone, or smartwatch to record the number of steps taken and the amount of activity, as this will help maintain motivation. The recommended aerobic exercise for psychiatric symptoms such as cognitive dysfunction and depression is 5,000 steps or more than 3 METs of moderate-intensity activity for at least 7.5 minutes per day[91].

In addition to squats, calf raises, and other bodyweight training, dumbbell exercises with dumbbells are recommended for resistance training. Among various types of physical activities including calisthenics, walking, strength exercise, dancing, yoga, aqua exercise, ball games, bicycling, hiking, tai chi, golf, quoits, Japanese croquet, ten-pin bowling, jogging, martial arts, participation in calisthenics significantly reduced the risk of cognitive decline in community-dwelling older Japanese women, indicating that calisthenics may be a useful type of exercise for promoting dementia prevention[92].

Good sleep for dementia prevention

Good sleep, in addition to diet and exercise, has

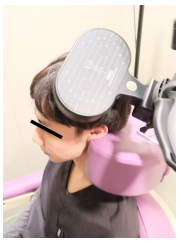
been highlighted as a modifiable factor in dementia prevention[59, 62]. Accumulating evidence indicates that sleep disturbances contribute to cognitive decline and increase the risk of Alzheimer's dementia by increasing the beta-amyloid burden. Although sleep disturbances are easily thought of as a consequence of Alzheimer's disease, sleep disturbances are a candidate risk factor for Alzheimer's disease. There is a bidirectional relationship between sleep and Alzheimer's disease, and the systemic hyperinflammation induced by sleep disturbances is thought to increase the beta-amyloid burden and promote the etiology of Alzheimer's disease[93].

To achieve good sleep, studies have been reported using a variety of sleep interventions for patients with MCI and Alzheimer's disease. Psychotherapeutic approaches such as cognitive behavioral therapy (CBT), melatonin, suvorexant, and continuous positive airway pressure (CPAP) for obstructive sleep apnea (OSA) have shown promise. Acoustic and transcranial stimulation are also assumed to have significant effects on non-REM sleep, but their long-term cognitive and disease-modifying effects are not yet known[94].

NIBS and cognitive rehabilitation for dementia prevention

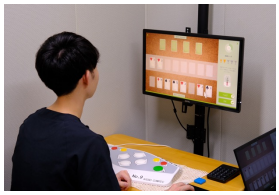
We believe that cognitive training is also necessary to treat memory impairment (forgetfulness), which is called the core symptom of dementia. Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation (NIBS), is expected to be a non-drug therapy for the prevention of dementia progression. Repetitive transcranial magnetic stimulation (rTMS), a non-pharmacological therapy for the prevention of dementia progression, is being studied for clinical application in Japan and abroad. Although there is no unified consensus on the stimulation site and method, there are many reports using high-frequency stimulation (HF-rTMS) of the left dorsolateral prefrontal cortex (Lt. DLPFC) as in the treatment of depression, and more recently, intermittent theta burst stimulation (iTBS) has been used in some studies. Lazzaro et al. conducted a systematic review of RCTs conducted up to 2020 in AD, MCI, MCI due to Parkinson's disease (PD-MCI), and others[95]. According to this report, the left dorsolateral prefrontal cortex (DLPFC) was the most frequently stimulated area, followed by bilateral DLPFC, right DLPFC, right DLPFC, low-frequency stimulation of right DLPFC, bilateral DLPFC, and multiple areas such as Broca's area, Wernicke's area, bilateral inferior parietal lobes, and precuneus (Figure 3). This review also concluded that rTMS-Cog therapy with high-frequency stimulation of the left dorsolateral prefrontal cortex (DLPFC) alone and with high-frequency stimulation of multiple regions may improve cognitive function, apathy, memory, and language function in patients with mild (early) AD (Level of Evidence C and B, respectively).

Combined cognitive training (rTMS-Cog therapy)



HF-rTMS of the left DLPFC

iTBS to left DLPFC (approx. 3 min) induces plastic changes within the stimulus site/memory-related network.



Computer assisted cognitive rehabilitation (CACR)

Computer-based cognitive rehabilitation training (40 min)
(working memory, attention, word memory, image memory, and mental rotation tasks are performed)

Figure 3 Expectations for rTMS-Cog therapy
We are currently implementing a 2-week intensive short-term cognitive rehabilitation treatment program with iTBS to the left DLPFC and CACR for patients with MCI.

may also be useful to improve cognitive and memory functions in daily life. Computer-assisted cognitive rehabilitation (CACR) is a fun, game-like, repetitive task. Currently, our department is working on cognitive rehabilitation using a combination of rTMS and CACR to improve cognitive and memory functions.

Summary

In this paper, the key strategies for preventing dementia, which include proper nutrition, exercise, and cognitive rehabilitation were discussed. Dementia prevention is increasingly important as Japan is expected to have around 7 million elderly people with dementia by 2025, which is approximately 1 in 5 elderly people. There are 12 risks identified by Livingston, which include physical inactivity, smoking, excessive alcohol consumption, air pollution, head injury, social isolation, poor educational history, obesity, hypertension, diabetes, depression, and hearing loss. Lifestyle modifications and an active lifestyle are important to reduce these risks. The Mediterranean diet, with its diverse range of foods, has gained attention as a dietary practice for preventing dementia. Exercise has been shown to prevent dementia on biological, behavioral, and socio-psychological levels. rTMS, a noninvasive brain stimulation method, can alter brain plasticity and is being studied for clinical application as a non-drug therapy for preventing dementia progression.

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Author contributions

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Conflicts of interest statement

The author declares that there are no conflicts of interest.

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Perspectives

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Endothelial Glycocalyx Protection in Sepsis

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The glycocalyx serves as the covering layer of the luminal surface of vascular endothelial cells, comprising proteoglycans, glycosaminoglycans, and adherent plasma proteins. This intricate structure is crucial in promoting antithrombogenicity, controlling vascular permeability, regulating vascular tone, and managing leukocyte/platelet adhesion. However, during sepsis, the glycocalyx undergoes significant degradation through inflammatory mechanisms; this process can be further facilitated by treatment for sepsis and septic shock. Therefore, it is crucial to exercise careful management to avoid damage to the glycocalyx during sepsis treatment.

Key words: glycocalyx, endothelial cell, sepsis, shock, anticoagulation, syndecan

The vascular endothelial surface is covered by a gel-like layer, namely glycocalyx. The glycocalyx is composed of membrane-binding proteoglycans (syndecan and glypican), glycosaminoglycan side-chains (heparan sulfate and chondroitin sulfate) conjugated with the core protein of the proteoglycans, and high-molecular-weight polysaccharide hyaluronan that interacts to transmembrane receptor CD44. The hydrophilic polysaccharides bind functional proteins such as albumin and antithrombin[1)] (Figure 1). The vascular glycocalyx exhibits important roles that include attenuating flow resistance, controlling vascular tone, maintaining antithrombogenicity, and regulating vascular permeability. However, since the glycocalyx is highly fragile and easily damaged via upregulated inflammatory reactions, increased shedders such as metalloproteinases, heparanase, and hyaluronidase are needed. Intravascular inflammation is closely associated with glycocalyx degradation, leading to vascular permeability, edema formation, thrombotic shift, and neutrophil and platelet adhesion[1)]. Consequently, the circulating glycocalyx components, such as syndecan and hyaluronic acid, are degraded and serve as biomarkers of endothelial damage[2)]. The derangement of glycocalyx is tightly connected with the presence of organ dysfunction and high mortality in sepsis[3)]. Therefore, protection and maintenance of glycocalyx are critical in sepsis management. The following part introduces the potential pragmatic approach for glycocalyx protection.

Hypervolemia is thought to be associated with increased glycocalyx degradation. Previous studies suggested that hypervolemia induces atrial natriuretic peptide release, leading to glycocalyx degradation[4)]. A randomized controlled trial (RCT) examined the efficacy of restricted resuscitation fluid protocol, which could successfully reduce resuscitation fluid volumes in adult patients with septic shock[5)]. In this study, the standard care group received fluid boluses as long as circulation continued to show improvement, whereas the fluid restriction

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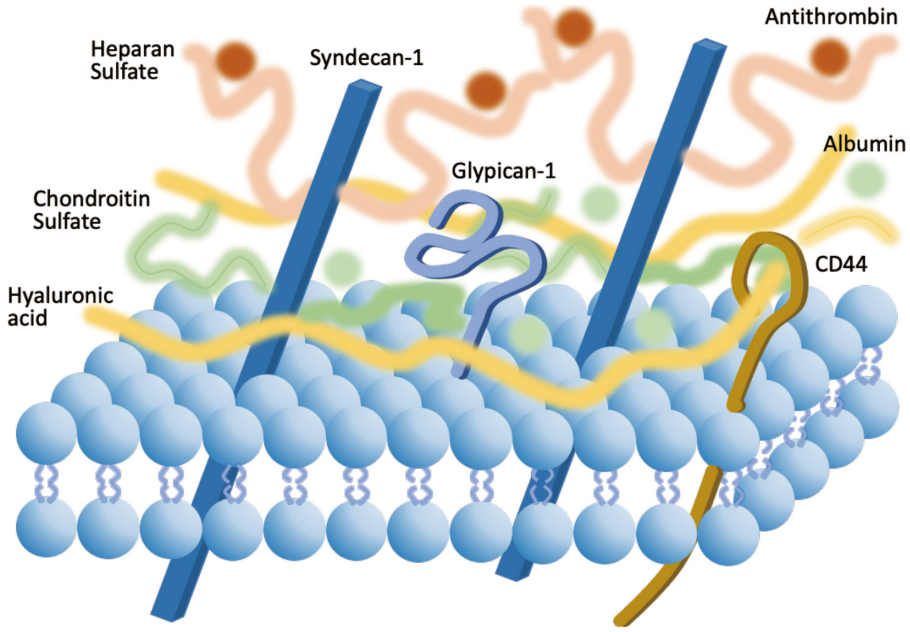

Figure 1 The structure of the endothelial glycocalyx
The major components of the glycocalyx are transmembrane glycoprotein i.e., syndecans, membrane-attached glypicans, and hydrophilic polysaccharides, including heparan sulfate, chondroitin sulfate, and hyaluronan. Physiological plasma proteins, including albumin and antithrombin, are maintained in this structure.

group received fluid boluses only when severe hypoperfusion appeared. However, the following larger RCT examining restricted intravenous fluid failed to show a better outcome[6]. Thus, the effect of restricted fluid therapy is still unclear, but we think avoiding volume overload by regularly reassessing the patient's response to fluid resuscitation is necessary.

Excess catecholamine use is toxic to the glycocalyx. The glycocalyx shedding is known to be markedly increased in Takotsubo disease, where the surge of catecholamine occurs[7]. In cases of septic shock, when adequate fluid resuscitation fails to restore perfusion, the dose of vasopressors (norepinephrine) will be increased, and that can damage the vascular integrity. Therefore, Surviving Sepsis Campaign Guidelines 2021 state, "For adults with septic shock on norepinephrine with inadequate mean arterial pressure levels, we suggest adding vasopressin instead of escalating the dose of norepinephrine[8]." The effect of the restriction of catecholamine should be examined in the future study.

Hyperglycemia is also known to be related to glycocalyx injury. Nieuwdorp et al. reported that hyperglycemia increased plasma hyaluronan levels, endothelial dysfunction, and activation in coagulation[9]. The mechanism can be explained by the increased reactive oxygen species and receptor activation for advanced glycation end-products (RAGE), but we demonstrated that neutrophil activation and neutrophil extracellular trap formation are also involved in the mechanisms of glycocalyx injury[10]. Since hypoglycemia is harmful to septic patients, glycemic control by intensive insulin therapy is not the current trend in sepsis management[8]. However, the toxic effect of hyperglycemia on the glycocalyx should be kept in mind.

Colloid therapy using fresh frozen plasma (FFP) and albumin has been proposed to protect glycocalyx. FFP contains physiological oxidase, protease, and matrix metalloproteinase inhibitors that help maintain the glycocalyx. Furthermore, FFP can suppress the fluid volume for resuscitation compared to crystalloids[11]. Meanwhile, albumin is expected to protect glycocalyx via carrying erythrocyte-derived sphingosine-1-phosphate (S1P) to the endothelium, where it can mediate glycocalyx recovery by suppressing metalloproteinase activity[12]. However, the result of the clinical trial was disappointing. A phase 2, multicenter randomized trial was conducted among the patients who underwent abdominal surgery. Dexamethasone and 20% albumin (100

mL) were followed by 200 mL of 20% albumin with subsequent 1000 mL of crystalloid administered to the study group, while crystalloid fluid was only given to the control group. The damage of the glycocalyx was compared by the levels of circulating syndecan-1, and the levels did not differ between the groups[13]. However, the effects of colloid therapy should be reexamined in larger trials.

One of the pivotal functions of the glycocalyx is antithrombotic. Heparan sulfate is an essential glycosaminoglycan side-chain of the glycocalyx and is a cofactor of physiological anticoagulant antithrombin. Since antithrombin activity significantly decreases in sepsis, antithrombin supplementation is a rational approach for the management of sepsis-induced coagulopathy. It is of interest that antithrombin not only balances the hypercoagulation but can stabilize the glycocalyx by binding to the heparan sulfate[14].

Given the critical role the glycocalyx plays in maintaining vascular integrity, it is imperative to protect this component during sepsis management.

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Perspectives

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Organ Dysfunction in Sepsis-associated Intravascular Coagulation

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Sepsis is frequently associated with disseminated intravascular coagulation (DIC) and multiple organ damage. It is widely accepted that DIC is not merely a complication but also plays a role in the development of organ dysfunction. Thrombus formation in the microvasculature leads to impaired tissue perfusion and organ damage. Activated neutrophils interacting with platelets, endothelial injury, and an imbalance of coagulation and fibrinolysis are the essence of thromboinflammation induced in sepsis-associated DIC. The above mechanisms are typically seen in sepsis-associated acute kidney injury (AKI), and the development of AKI is known to be strongly associated with the severity of sepsis. It is important to recognize the pathway of this mechanism in the context of sepsis management.

Key words: sepsis, disseminated intravascular coagulation, acute kidney injury, thrombus, neutrophil

Disseminated intravascular coagulation (DIC) is defined as "an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction" in 2001[1]. As time has passed, we now understand that intravascular inflammation and subsequent immunothrombus formation, along with endothelial damage, are the principal mechanisms of organ dysfunction in sepsis-associated DIC, and this process is termed "thromboinflammation"[2]. Thromboinflammation is a fundamental host response to severe and/or systemic infection and is recognized not only in sepsis but also in various diseases such as trauma, heat stress, and virus infection, including coronavirus disease 2019. Although major players, coagulation/fibrinolytic systems, monocytes, neutrophils, platelets, and vascular endothelial cells, are the same, the detail of the mechanisms differs slightly between the underlying diseases, with immunothrombus-induced tissue malcirculation being the primary mechanism of organ dysfunction in sepsis[3].

Among various targets, the kidney is one of the most frequently affected organs in sepsis, but the incidence is significantly different between various reports. White et al.[4] performed a retrospective cohort study in 12 intensive care units from 2015 to 2021 and reported that approximately 16% of septic patients met the acute kidney injury (AKI) criteria (13,451 out of 84,528), and about half of them were stage 1. Meanwhile, cases with stage 3 and required renal replacement therapy were only 21% and approximately 3% of total septic patients. However, it is also known that the incidence of severe AKI increases dramatically when DIC is present, and Helms et al.[5] reported that 47.3% of patients with

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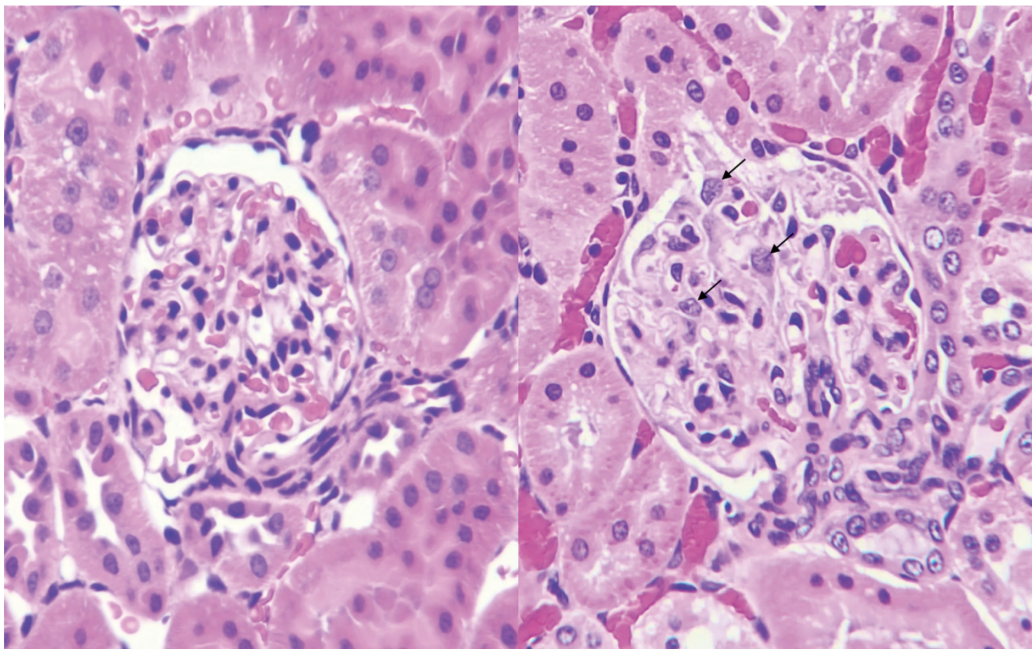

Figure 1 Pathologic findings of the kidney
Sepsis-associated disseminated intravascular coagulation (DIC) was induced by intravenous infusion of *E. coli*. Rats were sacrificed 2.5 hours after the infusion, and kidney specimens were stained with hematoxylin and eosin. In the normal kidney (left), red cells and the capillary lumen were observed. In contrast, in the kidney of a septic DIC rat, the glomerular capillary was occupied by leukocytes (arrows), and the capillary lumen was hardly visible (right). Mild renal tubular cell injury was observed in the septic DIC rat.

sepsis-associated DIC and shock required renal replacement therapy, compared to 21.3% of patients without DIC ($P < 0.001$). Furthermore, the complication of AKI considerably enhances the severity of sepsis. Seymour et al.[6] analyzed data from over 60,000 septic patients by using machine learning techniques and subdivided them into four sepsis phenotypes. Among phenotypes, the α phenotype was the most frequent (33%), although less severe and requiring less vasopressor support. Patients in the β phenotype (27%) were older and had more chronic illnesses. Those in the γ phenotype (27%) exhibited more inflammation and pulmonary dysfunction. The δ phenotype (13%) represented the most severe cases with a higher incidence of AKI development, hepatic dysfunction, and endothelial dysfunction, and a greater risk of death at 32% was reported. Of note, the coagulation markers were significantly greater in the δ phenotype compared to the others. These findings suggest a tight connection between DIC and AKI, and their association with poorer outcomes in sepsis.

Regarding the etiology of sepsis-associated AKI, Peerapornratana et al.[7] described three major factors: microvascular dysfunction, inflammation, and metabolic reprogramming. In addition to those mechanisms, we think the microclots formed by the neutrophils and platelets (immunothrombus) play a pivotal role. Microclot-mediated tissue malcirculation is a common scenario in other organ dysfunctions[8]; however, the kidney can be more significantly affected due to its anatomical nature during DIC. The renal tubular cell is generally considered the primary target of injury in sepsis. It is known that tubular cell-specific biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1) elevate as the increased damage to the kidney[9]. However, Kidney Disease Improving Global Outcomes (KDIGO) is recognized to be a standard scale for evaluating AKI in sepsis, and the urine output and serum creatinine level, which consists KDIGO scale, were primarily determined by the volume of glomerular filtration. In a rat model of sepsis-associated DIC, we observed that the glomerular capillaries are filled with adhered neutrophils, and the blood flow was significantly reduced (Figure 1). The unique structure of the renal circulation is characterized

by the presence of a glomerular capillary between the afferent and efferent arterioles, ultimately supplying the blood flow to the renal tubular system. When microthrombi are formed in the glomerular capillary, not only the glomerular filtration but the renal tubular system is also disturbed [10,11]. AKI in sepsis encompasses two subtypes i.e., glomerular damage-predominant type and tubular cell damage-predominant type, and DIC is more likely to be associated with the former type. We assume dividing AKI into subtypes may help in planning therapeutic strategy.

In summary, AKI is a common complication in sepsis, and severe AKI frequently appears when the patients are complicated by DIC. Since severe AKI is tightly associated with high mortality, it is crucial to understand the pathomechanism. The development of AKI is owing to its unique vascular structure, and immunothrombus plays a major role in the pathogenesis.

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Author contributions

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Conflicts of interest statement

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Original Articles

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Effectiveness of Nutritional Guidance Focusing on Leucine Intake During Cardiac Rehabilitation Maintenance

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Objective: Due to the lack of information on the effects of nutritional guidance focused on leucine intake in patients undergoing maintenance cardiac rehabilitation, this study investigated on plasma leucine concentrations, lean body mass, and muscle strength.
Methods: Nutritional guidance, focused on leucine (intervention group) or general nutritional guidance (control group), was provided for six months to patients participating in cardiac rehabilitation. Body composition, grip strength, hematological test results, and diet of both groups were compared before and after the intervention.
Results: Seven patients in the intervention group (53.2 ± 18.2 years) and 7 patients in the control group (58.6 ± 15.3 years) were included. Dietary survey results showed that the six-month intervention significantly ($p < 0.05$) increased protein intake and estimated leucine intake only in the intervention group. There was no significant difference in the rate of change in plasma leucine concentration between the two groups. The rate of change in lean body mass was significantly higher in the intervention group compared to the control group ($p = 0.035$). The rate of change in plasma leucine concentration and that in lean body mass was positively correlated only in the intervention group ($r = 0.777$, $p = 0.040$), and the rate of change in plasma leucine concentration was also positively correlated with the rate of change in grip strength ($\rho = 0.857$, $p = 0.014$).
Conclusions: In the patients undergoing maintenance cardiac rehabilitation, increased plasma leucine concentration by nutritional guidance focused on leucine increased lean body mass without any increasing the training load.

Key words: leucine, amino acid, nutrition guidance, lean body mass, grip strength

Introduction

Patients with cardiac disease tend to have a low lean body mass and reduced muscle strength[1)]. Loss of lean body mass and muscle strength can reduce the quality of life of patients with heart disease[2)], and can worsen heart failure[3)] and cardiac cachexia[4)] particularly in older patients. For this reason, it has recently been recommended that exercise therapy in cardiac rehabilitation includes not only aerobic exercise to increase exercise tolerance, but also strength training to maintain and increase lean body mass[2)]. Studies have reported that adding strength training to aerobic exercise in patients with cardiac disease improves muscle strength and cardiorespiratory fitness more than aerobic exercise alone[5, 6)].

However, for patients with heart disease, it's difficult to set an exercise load produced sufficient exercise effects. Therefore, blood pressure rises

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and falls at excessively increased the exercise load, acute coronary syndromes and fatal arrhythmias might be develop during exercise, even in patients with preserved left ventricular ejection fraction[7].

On the other hands, it has been reported that nutritional intervention in addition to exercise increased lean body mass more than exercise alone[8]. Therefore, it is considered that nutritional intervention combined with exercise is effective in increasing lean body mass.

Nutritional guidance is the conventional concept of limiting intake such as salt reduction and fat restriction has recently been replaced by the recommendation of nutritional guidance that adjusts the overall diet by adding appropriate nutrients[9, 10]. For example, nutritional guidance that promotes protein intake may be effective in preventing the loss of lean body mass[11]. In particular, leucine, an amino acid found in proteins, is the only amino acids that stimulates muscle synthetic pathways[12, 13]. Therefore, leucine intake is expected to enhance the effects of exercise therapy, especially in patients at risk for sarcopenia. In fact, a study of leucine supplements reported an increase in lean body mass in participants over 50 years of age when they were given leucine supplements in addition to resistance training[14]. Moreover, older patients undergoing cardiac rehabilitation who consumed a leucine-containing beverage were founded to have increased grip strength, a measure of muscle strength[15].

However, no studies have been reported to date examining the effects of nutritional guidance aimed at increasing leucine intake in the daily diet in cardiac rehabilitation patients without relying on dietary supplements. In this study, patients with cardiac disease who participated in maintenance cardiac rehabilitation were provided nutritional guidance focusing on leucine intake over a six-month period, and the effects of this guidance on intake, plasma leucine concentration, lean body mass, and muscle strength.

Materials and Methods

Study design

This study was a parallel group comparison trial. Patients were stratified by sex, age, and ability to take pictures and operate machines for a long time and assigned to two groups: one receiving leucine-focused nutritional guidance (intervention group), and the other receiving general nutritional guidance that did not focus on leucine (control group). We also assessed the body composition, grip strength, blood test, and diet of all participants before and six months after the intervention.

Subjects

Nineteen patients who participated in maintenance cardiac rehabilitation at Juntendo University Hospital between February 2021 and January 2022 were included in the study. The selection criteria were patients (1) at least 20 years old, (2) whose medical condition was stable, and (3) who could obtain permission from their primary physician. We excluded patients with (1) hemodialysis or peritoneal dialysis, (2) decompensated liver dysfunction such as the liver cirrhosis, (3) dysphagia, (4) those taking amino acid supplements, and (5) those unable to regularly attend outpatient cardiac rehabilitation. This study was conducted in compliance with the ethical principles of the Declaration of Helsinki and with the approval of the Ethics Committee of the Juntendo University Hospital (20-078). Written informed consent was obtained from each participant before the study began. This study has been registered in the Japanese Clinical Trials Registry (UMIN000044069).

Body composition

Height (cm), weight (kg), and lean body mass (kg) were measured using a height meter and bioelectrical impedance method body composition analyzer (780A, TANITA, Tokyo, Japan).

Grip strength

Long-term decline in grip strength is associated with worse survival and QOL in patients with heart failure[16], and grip strength has also been reported to stratify cardiovascular mortality and cardiovascular disease risk in patients with heart disease[17]. Furthermore, grip strength is said to reflect the muscle strength of the whole body[7], and is also used to diagnose frailty[18]. Therefore, grip strength was measured using a grip dynamometer (T.K.K. 5001: Takei Scientific Instruments Co., Ltd., Kamo, Japan). Measurements were performed alternately twice on the left and right sides, and the maximum value of each side was evaluated using an average of these values.

Dietary survey

Due to the proven validity of the three-day dietary survey[19, 20], nutrient intakes were assessed using pictures and food records over a three-day period, including holidays. In addition, based on previous study[21], participants took pictures of their meals together with a predetermined index (9.0 cm x 5.5 cm paper in this study), and noted the amount and type of drinks consumed excluding water. Moreover, participants were instructed by us not to change their diet from their routine diet for three days and the researchers also confirmed this by interviewing the subjects about their diet. Nutritional value calculation was performed by a registered dietitian other than the researchers using a nutritional value calculation software (Excel Add-in Eiyo-plus, KENPAKUSHA Co., Ltd., Tokyo, Japan). A nutritional value calculation software is in line with the Standard Tables of Food Composition in Japan 2020 (Eighth Revised Edition)[22] and Standard Tables of Food Composition in Japan 2020 (Eighth Revised Edition)-Amino Acids[23].

Hematological tests

Hematological tests were performed by fasting blood collection. Blood counts and general biochemical tests (hemoglobin (Hb), hemoglobin A1c (HbA1c), uric acid (UA), gamma glutamyl transpeptidase (γ-GTP), total cholesterol (TC), triglycerides (TG), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), total protein (TP), albumin (Alb), serum iron, ferritin, C-reactive protein (CRP), cystatin C, estimated glomerular filtration rate (e-GFRcys), N-terminal fragment of human brain natriuretic peptide precursor (NT-pro BNP), and amino acid levels were evaluated. Thirty-nine amino acid results were obtained. Nine essential amino acids (leucine, isoleucine, valine, histidine, lysine, methionine, phenylalanine, threonine, and tryptophan) and eleven non-essential amino acids (serine, asparagine, aspartic acid, glutamine, glutamic acid, glycine, alanine, tyrosine, arginine, cysteine, and proline) were evaluated in the results. The values for branched-chain amino acids (BCAA: leucine, isoleucine, and valine) and essential amino acids (EAA) were also calculated.

Blood counts and general biochemical tests other than amino acid analysis were performed in an in-house clinical laboratory, and amino acid analysis was performed in a clinical laboratory (SRL, Inc., Tokyo, Japan) using liquid chromatography-mass spectrometry.

Nutritional guidance

The intervention group received nutritional guidance at least twice a month, using materials prepared by the researcher, a registered dietitian, with reference to the Standard Tables of Food Composition in Japan 2020 (Eighth Revised Edition) - Amino Acids[23]. In addition, the frequency of nutritional guidance was set in consideration previous study[24] and insurance coverage of nutritional guidance in Japan. In the first nutritional guidance session, we explained the proper intake of EAA (especially leucine) and presented the recommended foods (meat, fish, eggs, soy, and dairy products)[25] for the intake of EAA using materials, while instructing the participants to actively consume them. Specifically, we encouraged the consumption of meat with low fat content and fish with high leucine content per gram of protein, including salmon, mackerel, and tuna. In addition, soy and dairy product consumption was encouraged according to dietary balance and renal function. Before the intervention and six months after the intervention, a questionnaire was used to evaluate the frequency and quantity of meat, fish, eggs, soy, and dairy products consumed and to enable participants to reflect on their diet. During the intervention period, the participants were instructed to take pictures of their meals daily during the first three months and at least three days per week after three months, and to report their diet to the registered dietitian.

The control group received standard nutritional guidance based on the Guidelines for Rehabilitation in Cardiovascular Disease[2, 26].

Cardiac rehabilitation

During the intervention period, both groups participated in weekly cardiac rehabilitation (an exercise program) at a specialized cardiac rehabilitation facility. Prior to implementing the exercise program, vital signs were checked, and the program was implemented only if the patient was deemed able to exercise. The exercise program consisted of a warm-up, including stretching, followed by 15 to 20 minutes of aerobic exercise (including various

combinations of walking, bicycling, and jogging) and approximately 10 to 15 minutes of light isotonic exercise (including arm curls, shoulder presses and push-ups) and moderate rest, followed by stretching and exercises as a cool-down, for a total of 60 minutes. Aerobic exercise was performed at an intensity equivalent to the anaerobic threshold (AT) measured in the cardiopulmonary exercise stress test or subjective exercise intensity.

Statistical analysis

After testing for normality using the Shapiro-Wilk test, comparisons were made between groups using Fisher's exact test for sex, disease, and medication status before intervention, and using an unpaired t-test or Mann-Whitney U test for age, body composition, blood pressure, and left heart ejection fraction, and the participation rate of cardiac rehabilitation, depending on whether the date were normally distributed. The participation rate of cardiac rehabilitation was calculated as 100 × the number of sessions actually participated / the number of rehabilitation sessions held. Within-group comparisons between pre-intervention and six months post-intervention were calculated using a paired t-test. In addition, comparisons of each group before and six months after the intervention were analyzed using a two-way repeated-measures ANOVA to identify interactions with and without intervention (group) and before and after intervention (period). In addition, we calculated the percentage change from baseline (pre) in order to variation of change between individuals. The difference between the two groups in the percentage change (⊿) was subjected to an unpaired t-test. Furthermore, the association between the rate of change in plasma leucine concentration, lean body mass, and grip strength was confirmed using Pearson's correlation coefficient or Spearman's rank correlation coefficient, depending on whether the data were normally distributed. Descriptive statistics are presented as mean ± standard deviation, and the significance level was set at $p < 0.05$. Statistical analyses were performed using SPSS version 28 (IBM Corp., Armonk, NY, USA).

Results

A total of 14 patients in both groups (7 in the intervention group: 53.2 ± 18.2 years, 7 in the control group: 58.6 ± 15.3 years) were included (Figure 1), excluding the patient who was hospitalized due to dehydration without exacerbating heart failure, 2 patients who participated significantly less in nutritional guidance and exercise therapy, and 2 patients who were unable to measure multiple items.

The characteristics of all the analyzed subjects are shown in Table 1. There were no significant differences in the physical characteristics between the two groups. There was also no significant difference in diseases subject to cardiac rehabilitation between the two groups, nor was there a significant difference in left ventricular ejection fraction, a measure of cardiac function. Regarding medication status, two patients in the intervention group were taking diuretics before the intervention, but one of them finished one month after the intervention, and the other reduced the dose immediately after the start of this study. There was no difference between the two groups in β-blocker use or other medications.

Participation rate of cardiac rehabilitation

The average participation rate for cardiac rehabilitation was 83.9 % in the intervention group and 90.5 % in the control group, with no significant differences between the two groups.

Nutrient intake

The weight-adjusted nutrient intakes before and six months after the intervention are shown in Table 2. Only in the intervention group, protein intake increased significantly from 1.00 ± 0.16 g/kg to 1.32 ± 0.31 g/kg after six months compared to pre-intervention ($p = 0.003$), and confirmed the interaction effect ($p = 0.002$). Estimated leucine intake also increased significantly from 70.58 ± 16.83 mg/kg to 94.85 ± 26.78 mg/kg after six months compared to pre-intervention ($p = 0.004$), indicated an interaction effect ($p = 0.005$). Regarding lipid content, only the intervention group showed a significant increase after six months compared to pre-intervention ($p = 0.045$), but there was no interaction between the two groups. In the control group, there were no changes in protein, estimated leucine intake, or lipid intake. Energy and carbohydrate content did not change significantly between the two groups. In terms of food intake, meat intake increased significantly in the intervention group

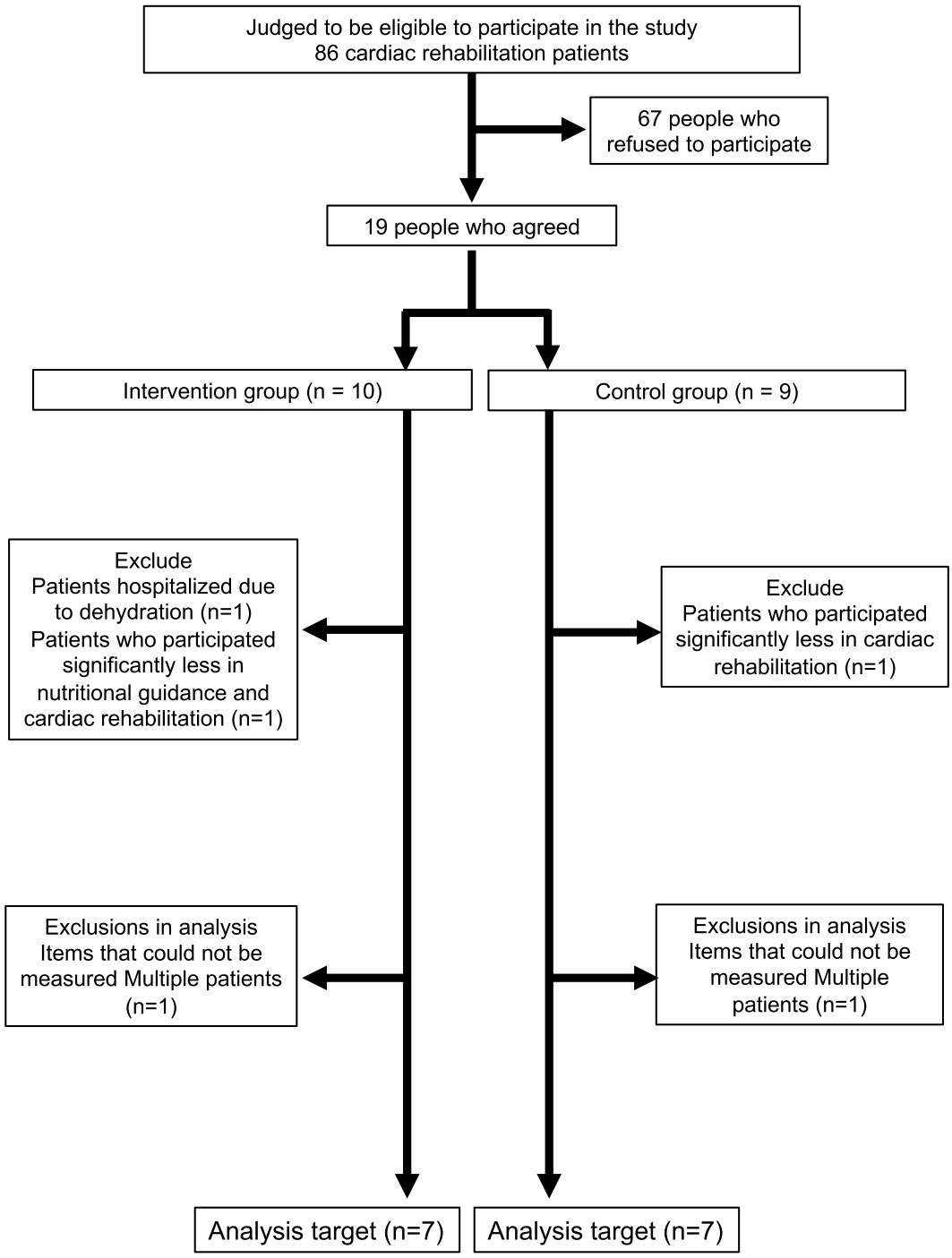

Figure 1 Flowchart of this study

after six months compared to pre-intervention ($p = 0.033$). The intakes of fish, eggs, soy, and dairy products did not change during the intervention period in either group, and no interaction effects were observed.

Hematological tests

There were no significant differences in the plasma amino acid concentrations between the two groups prior to the intervention. No significant differences were found between the two groups in other blood collection parameters before the intervention. Six months after the intervention, the plasma concentrations of amino acids (EAA, BCAA, and leucine) were not statistically different, and there was no interaction effect, although the values of EAA, BCAA, and leucine were higher in the intervention group (Supplement 1). The rate of

Table 1 Characteristics of the subject

	Control group (n=7)	Intervention group (n=7)	*P*
Age: Years	58.6 ± 15.3	53.0 ± 18.2	0.559
Height: cm	165.7 ± 7.4	162.3 ± 6.4	0.374
Weight: kg	74.2 ± 14.0	66.9 ± 13.1	0.334
BMI: kg/m^2	27.0 ± 4.6	25.5 ± 5.2	0.576
Systolic blood pressure: mmHg	122.3 ± 15.0	116.3 ± 19.6	0.532
Diastolic pressure: mmHg	78.7 ± 20.3	76.6 ± 10.3	0.565
left ventricular ejection fraction: %	64.6 ± 6.1	64.4 ± 11.3	0.388
Disease			
Angina pectoris	2	2	1.000
Myocardial infarction	1	2	1.000
Chronic heart failure	1	1	1.000
Auricular fibrillation	1	0	1.000
Postoperative valvular heart disease	2	1	1.000
Postoperative ascending aorta replacement	0	1	1.000
Postoperative congenital heart disease	0	1	1.000
Medication			
Antihypertensive drugs	7	6	1.000
Diuretics	0	2	0.462
Antithrombotic drugs	7	4	0.192
Cardiotonic drugs	1	0	1.000
Drugs for dyslipidemia	6	5	1.000
Diabetes medications	2	0	0.462
Hyperuricemia drugs	1	1	1.000
Amino acid concentration in the plasma			
EAA: nmol / mL	1070.3 ± 127.6	1020.6 ± 123.8	0.474
BCAA: nmol / mL	494.4 ± 70.2	462.3 ± 80.7	0.443
Leucine: nmol/mL	148.2 ± 22.3	138.2 ± 26.7	0.464

Mean ± standard deviation or Number of cases (the number of people)
The p-value was calculated using Fisher's exact test for categorical variables for and t-test or Mann-Whitney U test for continuous variables.
Diseases were included for all applicable diseases.
BMI; Body Mass Index, BCAA; Branched-chain amino acids, EAA; essential amino acids.

change in EAA, BCAA, and leucine levels (100 × results after 6 months/results before intervention-100) also increased in the intervention group, but no significant difference was observed (Figure 2). On the other hand, histidine showed only significant change among intervention duration (p = 0.002, Supplement 1). However, only in the intervention group, histidine concentration significantly increased from 31.40 ± 39.18 nmol/mL to 79.50 ± 12.66 nmol/mL after 6 months compared to before intervention (p = 0.008). There were no significant differences between the two groups before and after intervention for cystatin C and estimated glomerular filtration rate (e-GFRcys), human brain natriuretic peptide precursor N-terminal fragment (NT-pro BNP), and lifestyle-related parameters (HbA1c, UA, LDL-C, HDL-C, and TG) (Supplement 2).

Body composition and grip strength

Body weight changed from 73.3 ± 7.3 kg to 72.9 ± 7.0 kg and grip strength changed from 28.7 ± 6.8 kg to 30.5 ± 7.3 kg in the intervention group, but there was no significant change in either group before and after the intervention. However, only in the

Table 2 Results of dietary survey

	Control group (n=7)			Intervention group (n=7)			Intervention Duration	Group	Interaction
	Before the intervention	After 6 months	p^*	Before the intervention	After 6 months	p^*	$p^\#$	$p^\#$	$p^\#$
Energy/ Weight (kcal/kg)	25.12 ± 4.96	25.17 ± 4.05	0.970	23.72 ± 4.47	26.10 ± 5.39	0.143	0.278	0.919	0.301
Carbohydrate content/ Weight (g/kg)	2.97 ± 0.77	2.98 ± 0.53	0.941	3.14 ± 0.95	3.14 ± 0.81	0.984	0.947	0.648	0.970
Fat content/Weight (g/kg)	0.95 ± 0.29	0.91 ± 0.23	0.667	0.84 ± 0.18	1.03 ± 0.22	0.045	0.229	0.982	0.083
Protein content/ Weight (g/kg)	1.10 ± 0.18	0.94 ± 0.18	0.097	1.00 ± 0.16	1.32 ± 0.31	0.003	0.186	0.169	0.002
Estimated leucine content/ Weight (mg/kg)	78.24 ± 21.89	70.09 ± 14.07	0.251	70.58 ± 16.83	94.85 ± 26.78	0.004	0.117	0.402	0.005
Protein mass by food group									
Seafood intake/ Weight (g/kg)	1.20 ± 0.45	1.08 ± 0.62	0.525	0.80 ± 0.48	1.20 ± 0.10	0.050	0.304	0.531	0.069
Meat intake/ Weight (g/kg)	1.10 ± 0.46	0.95 ± 0.32	0.633	1.24 ± 0.60	1.97 ± 1.22	0.033	0.201	0.102	0.063
Egg intake/Weight (g/kg)	0.64 ± 0.50	0.72 ± 0.30	0.627	0.63 ± 0.32	0.94 ± 0.47	0.071	0.105	0.591	0.316
Soy product intake/ Weight(g/kg)	1.83 ± 1.30	0.57 ± 0.66	0.117	0.60 ± 0.45	1.81 ± 2.30	0.718	0.964	0.994	0.032
Dairy product intake/ Weight(g/kg)	1.70 ± 1.62	1.69 ± 0.73	0.972	1.80 ± 1.05	2.34 ± 1.90	0.321	0.493	0.579	0.464

Mean ± standard deviation
*The p-value for within-group comparison was calculated using a paired t-test.
#The p-value between groups was calculated using a two-way repeated-measures ANOVA.
Interactions were assessed by the duration of intervention × groups.

intervention group, lean body mass increased significantly from 47.3 ± 8.5 kg to 48.0 ± 8.6 kg after six months compared to pre-intervention ($p = 0.033$) and confirmed an interaction effect ($p = 0.033$). In the control group, there were no changes in lean body mass (Supplement 3). In addition, the rate of change in lean body mass was significantly higher in the intervention group compared to the control group ($p = 0.035$, Figure 3).

Plasma leucine concentration, lean body mass, and rate of change in grip strength

The rate of change in plasma leucine concentration and the that in lean body mass were positively correlated only in the intervention group ($r = 0.777$, $p = 0.040$, Figure 4). In the intervention group, the rate of change in plasma leucine concentration was also positively correlated with the rate of change in grip strength ($\rho = 0.857$, $p = 0.014$, Figure 4).

Discussion

This is the first study to show that nutritional guidance focused on leucine over a six-month period in patients undergoing maintenance cardiac rehabilitation may increase lean body mass. In addition, these results are also considered important in that they are the first research findings in nutritional guidance.

A previous study reported that skeletal muscle index and grip strength improved after eight weeks of intervention in a group of older post-stroke patients who received a high leucine-containing amino acid supplement in addition to rehabilitation, compared to a group that received only rehabilitation[27]. Furthermore, it has been reported that in older patients with sarcopenia, 13 weeks of supplementation with leucine, vitamin D, and other nutrients resulted in a significant increase in lean body mass compared with placebo intake[28]. While

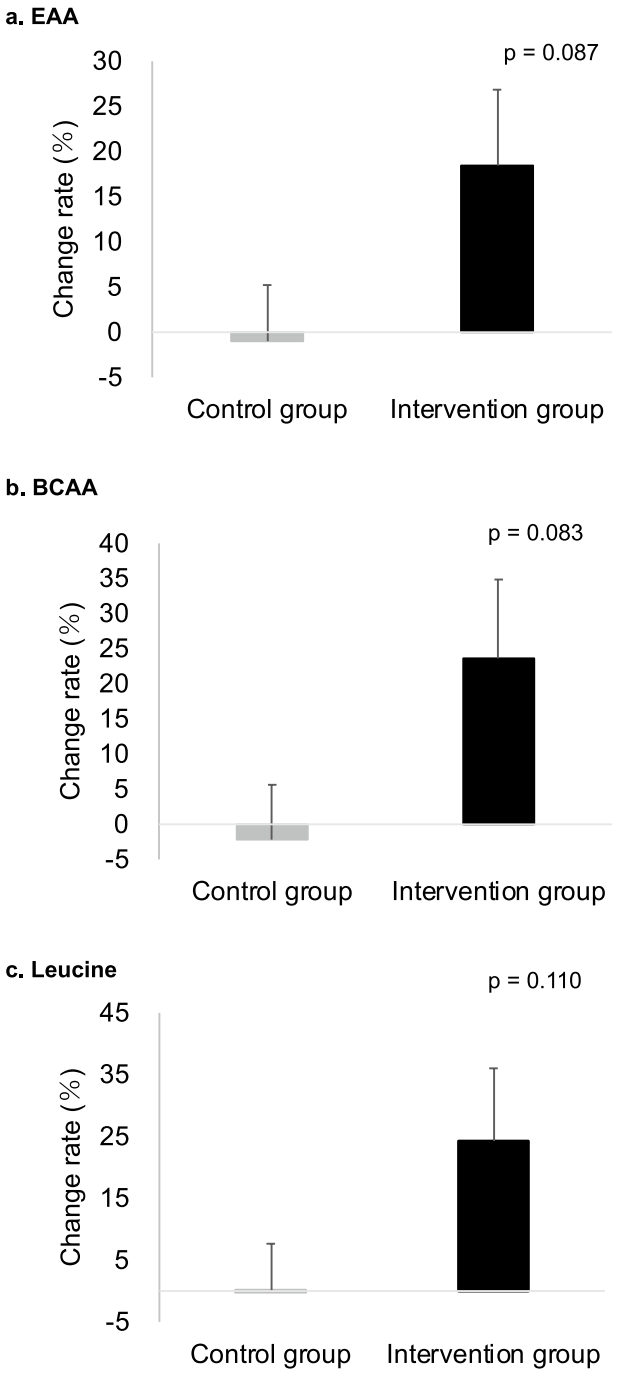

Figure 2 Rate of change in plasma concentrations of EAA, BCAA, leucine
The rate of change was calculated as 100 × results after six months/results before intervention−100.
BCAA; Branched-chain amino acids, EAA; essential amino acids.
The p-value was calculated using an unpaired t-test.

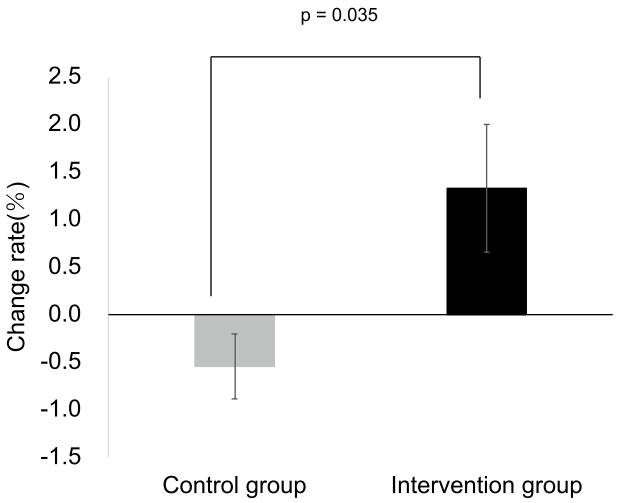

Figure 3 Rate of change in lean body mass
The rate of change was calculated as 100 × results after six months/results before intervention−100.
The p-value was calculated using an unpaired t-test.

previous studies have suggested the potential for increased lean body mass and improved muscle strength with leucine supplementation, this study revealed that similar effects may occur with nutritional guidance focused on leucine when it comes to increasing lean body mass.

On the other hands, no significant changes in grip strength observed as a result of the intervention. However, grip strength increased by approximately 6.3% in the intervention group and 2.6% in the control group after the intervention compared to before the intervention, with the difference being greater in the intervention group. This study had a small number of subjects. Therefore, it is likely that grip strength in the intervention group increased numerically after the intervention compared to the control group, but no difference in the overall average value. Furthermore, it is possible that there were individual differences in results, as some subjects in the intervention group showed a significant improvement in grip strength results after the intervention, while others showed a slight decrease. This may also be relevant to the results of this study.

The results of this study showed that nutritional guidance focusing on leucine increased plasma leucine concentrations in 5 of the 7 patients. Among them, those with the largest increases not only increased lean body mass, but also improved grip strength (Figure 4, Supplement 4). Three patients were able to significantly increase plasma leucine concentrations: case A: Before the intervention, a 22-year-old male's diet consisted of bread and yogurt for breakfast, single dishes such as rice balls and sandwiches for lunch, and an assortment of staples, main dishes, and side dishes for dinner,

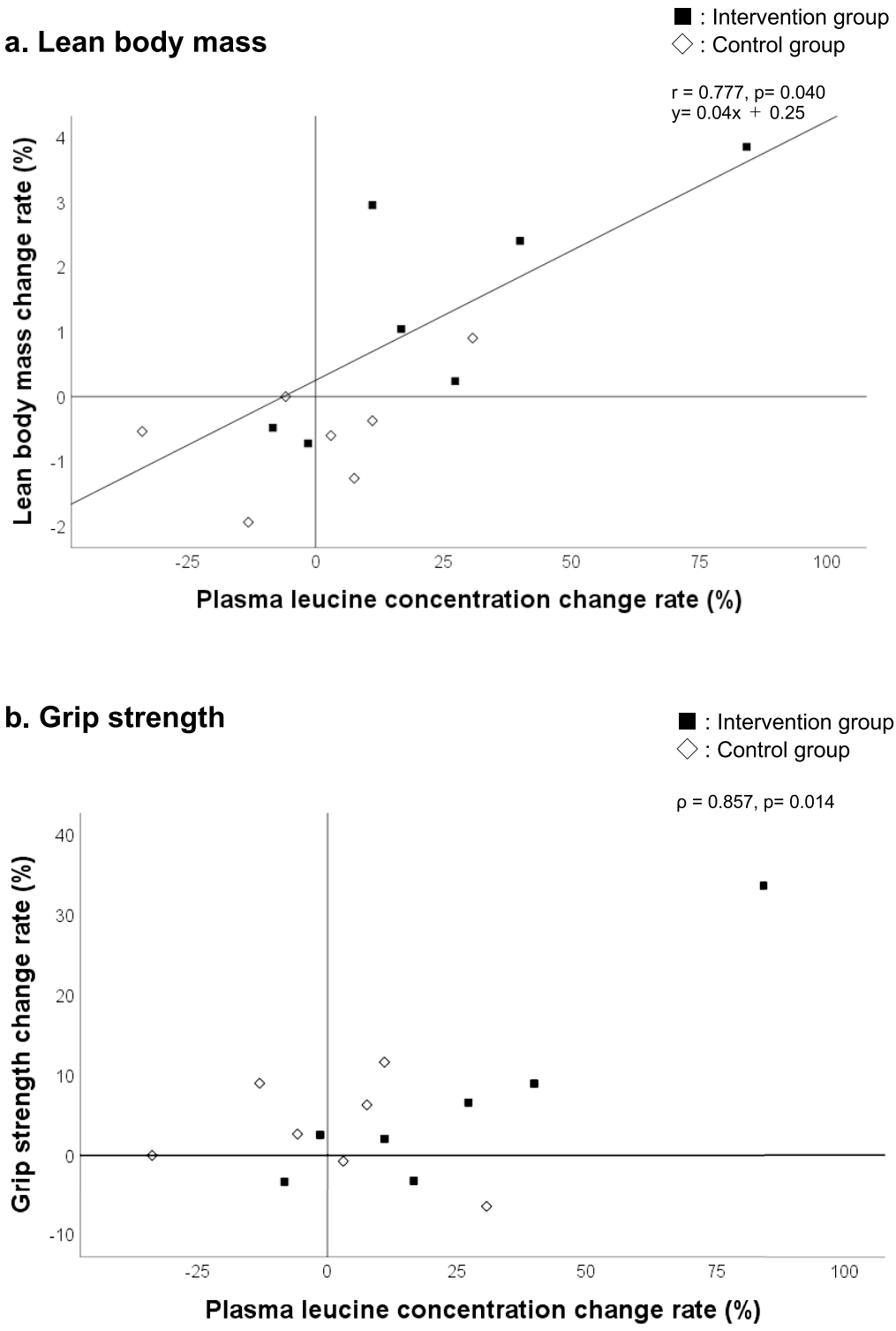

Figure 4 Plasma leucine concentration, lean body mass, and rate of change in grip strength

The rate of change was calculated as 100 × results after six months/results before intervention−100.

The p-value was calculated using the Pearson product-moment correlation coefficient or Spearman's rank correlation coefficient.

a: Five of 7 participants in the intervention group had elevated plasma leucine concentrations and increased lean body mass after the intervention. Conversely, one out of seven control patients had elevated plasma leucine concentrations and lean body mass after the intervention. In addition, only the intervention group showed a significant positive correlation between plasma leucine concentration and rate of change in lean body mass.

b: Four of 7 patients in the intervention group had elevated plasma leucine concentrations and increased grip strength after the intervention. Conversely, in the control group, two out of seven patients had increased plasma leucine levels and lean body after the intervention. In addition, there was a significant positive correlation between the plasma leucine concentration and the rate of change in grip strength only in the intervention group.

with lunch being particularly simple. After the intervention, he began to consume more meat and fish at lunch and added soy products to dinner in addition to increasing meat and fish intake. The person in the upper right corner of the intervention group in Figures 4a and 4b is case A. Case B: Before the intervention, a 38-year-old man often ate granola with milk for breakfast, products such as commercial curry and vegetable dishes such as salads for lunch, and staple foods, main dishes, and side dishes for dinner. After the intervention, he added chicken tender and yogurt to breakfast, began consuming meat and fish at lunch, and increased meat and fish intake at dinner. Case C: Before the intervention, a 66-year-old woman consumed a well-balanced diet of staple foods, main dishes, and side dishes at home, but the amount was small overall, and she ate whatever she liked when eating out. After the intervention, she was able to regulate the amount of food eaten at home and choose when eating out. Three patients had been particularly concerned about eating meat and fish before this study. It has also been reported that animal protein is an efficient source of leucine[25]. In fact, two of three patients listed above increased their meat and fish intake after the intervention, while the other one did not increase after the intervention as fish intake was already secure to begin with, but meat intake did increase. Moreover, the increase in intake of protein-sourced foods in the three participants was greater than in the others, and their diets remained stable throughout the study period. Therefore, establishing a diet that increases intake of protein-sourced foods, especially animal protein, may contribute to increased lean body mass and improved grip strength.

However, despite these changes, increasing dietary leucine intake did not significantly increase plasma leucine concentrations in the intervention group. Plasma leucine concentrations have been reported to be maintained longer with higher leucine intake[29]. On the other hands, relationships with lipids in the diet[30], relationships with dietary fiber[31], relationships with dietary forms[32], and relationships with lean body mass have also been reported[32]. Therefore, it is expected that an increase in leucine intake would lead to an increase in plasma leucine concentrations, but there may be variability.

Furthermore, another reason why the plasma leucine concentration did not rise much after the intervention may be that the plasma leucine concentration before the intervention was not low in the intervention group. Although few studies have examined blood amino acid concentrations in Japanese patients with heart disease, it has been reported that the mean blood leucine concentration was 119.6 nmol/L in older patients with heart disease (mean age: 73.1 ± 9.4 years, mean BMI: 22.9 ± 3.2 kg/m2)[33] and 125.8 ± 22.7 nmol/L in patients with heart failure with frailty (mean age: 68 ± 12 years, mean BMI: 22.4 ± 4.7 kg/m2)[34]. In patients without cardiac disease, blood leucine levels were reported to be 140.1 nmol/L in patients with hypertension and other diseases (mean age: 69.1 ± 9.4 years, mean BMI: 24.4 ± 3.4 kg/m2)[33], and in persons of similar age and body size as in this study (mean age: 57.0 ± 0.6 years, mean BMI: 27.6 kg/m2) reported 135.5 ± 1.2 nmol/L[35]. Although there are differences in blood leucine concentration to previous studies, the mean pre-intervention blood leucine concentration of the patients in this study (mean age 53.0 ± 18.2 years, mean BMI: 25.5 ± 5.2 kg/m2), was 138.2 ± 26.7 nmol/L in the intervention group, suggesting that their blood leucine concentrations were not low. The participants in this study had a high BMI and a tendency to overeat before this study, which also likely ensured that they had some leucine intake on a daily basis. This may also have been influenced by the fact that the patients received nutritional guidance during their hospitalization (either during acute or convalescent cardiac rehabilitation) and were less likely to have extreme bias in their diets. Therefore, post-intervention increases in plasma leucine concentrations may have been limited. On the other hand, in these patients, plasma leucine concentrations not only did not increase but also did not decrease after the intervention. Nutritional guidance focusing on leucine intake may have improved the efficiency of leucine intake. Therefore, even if there was a tendency to overeat before the intervention, the efficient intake of leucine would not have led to a reduction, if not an increase, in plasma leucine concentrations after the intervention.

In addition, although no change was observed in plasma leucine concentration, plasma histidine concentrations increased over time in the intervention group. Participants in the intervention group

were increased their intake of soy products, which are said to contain antioxidants[36], after the intervention compared to before the intervention. The previous studies have reported a negative correlation between the amount of oxygen peroxide, a type of oxidative stress, and blood concentrations of histidine, which is also thought to inhibit oxidation[37]. Therefore, it is possible that the intake increasing soya products affected increasing plasma histidine concentrations.

This study has several limitations. First, owing to the small number of examinees, it is necessary to consider generalization. However, by providing careful nutritional guidance to the intervention group, we were able to reduce the number of dropouts during the six-month intervention trial. Second, the measurement conditions in this study were not unified. In the future, it will be necessary to standardize the amount of physical activity and meal intake time during rehabilitation at hospitals. Third, participants were provided nutritional guidance using pictures of meals three days, not a daily, a week. Moreover, nutritional guidance in this study was provided at least twice a month, not daily. Although these aspects are generally practiced within the Japanese insurance coverage which effectiveness is well known, in clinical setting, it would be usually discussed about whether the patient complies about meals on other days and whether more frequency of nutritional guidance is more effective. On the other hand, the fact that some patients could change their behavior with nutritional guidance only focusing on content of diet despite such restriction of Japanese insurance system is clinically very important in aspect of patient's behavioral change. Therefore, we would like to consider increasing the number of days for dietary surveys and frequency of nutrition guidance in the future. Finally, in this study, all participants were outpatients and some of them had normal fitness and muscle strength. Therefore, it may have been difficult to generate differences in strength result in leucine intake alone in all participants in this study. The effects of leucine supplementation on muscle strength have been reported, but much of the research has focused on people with low muscle strength[27,38]. In the future, approaches to leucine intake should be considered for patients with a maintained ejection fraction who have some fitness and muscle strength, while considering rehabilitation menus.

Conclusions

In the patients undergoing maintenance cardiac rehabilitation, increased plasma leucine concentration by nutritional guidance focused on leucine increased lean body mass without any increasing the training load.

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Author contribution

FK provided their knowledge of sports medicine and revising it critically for important intellectual content. YS provided knowledge of statistical analysis. JN, MD and YS provided cardiac rehabilitation and obtained data acquisition. MY, MT and TM provided knowledge of cardiology. HN provided revising it critically for important intellectual content. KS conceived the original research idea and drafted the manuscript, and provided nutrition guidance and data acquisition and statistical analysis. All authors read and approved the final manuscript.

Conflicts of interest statement

The authors declare that there is no conflict of interest.

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Supplement 1 Plasma amino acid profile

	Control group (n=7)		Intervention group (n=7)		Intervention Duration *P*	Group *P*	Interaction *P*
	Before the intervention	After 6 months	Before the intervention	After 6 months			
EAA							
Leucine (nmol/mL)	148.19 ± 22.33	146.07 ± 26.88	138.24 ± 26.68	170.04 ± 45.34	0.147	0.623	0.102
Isoleucine (nmol/mL)	82.34 ± 17.36	75.59 ± 16.76	76.04± 17.71	94.17 ± 28.11	0.341	0.524	0.051
Valine (nmol/mL)	263.86 ± 39.60	254.50 ± 47.50	249.03 ± 38.21	303.54 ± 71.00	0.190	0.459	0.074
Histidine (nmol/mL)	46.06 ± 43.11	85.29 ± 10.08	31.40 ± 39.18	79.50 ± 12.66	0.002	0.395	0.701
Lysine (nmol/mL)	194.16 ± 22.43	193.50 ± 39.40	201.63 ± 43.80	229.26 ± 50.50	0.112	0.304	0.097
Methionine (nmol/mL)	29.51 ± 5.56	28.44 ± 9.26	26.27 ± 3.47	35.07 ± 12.45	0.153	0.657	0.075
Phenylalanine(nmol/mL)	72.91 ± 12.93	71.74 ± 15.25	66.91 ± 15.83	80.96 ± 21.42	0.099	0.847	0.056
Threonine (nmol/mL)	137.51± 35.70	134.34 ± 27.96	128.70 ± 18.77	145.43 ± 23.73	0.419	0.927	0.243
Tryptophan (nmol/mL)	60.57 ± 11.10	60.83 ± 13.40	58.89 ± 10.50	69.11 ± 15.25	0.064	0.609	0.076
NEAA							
Serine (nmol/mL)	108.71 ± 19.90	115.66 ± 29.78	112.04 ± 22.48	123.26 ± 30.41	0.075	0.684	0.654
Asparagine (nmol/mL)	50.11 ± 6.35	50.79 ± 10.99	45.66 ± 5.02	59.73 ± 21.55	0.117	0.625	0.154
Aspartic acid (nmol/mL)	4.87 ± 1.15	4.73 ± 0.86	5.06 ± 1.17	5.50 ± 1.94	0.662	0.465	0.399
Glutamine (nmol/mL)	535.14 ± 61.5	549.01 ± 74.00	581.46 ± 68.23	568.69 ± 101.72	0.956	0.431	0.193
Glutamate (nmol/mL)	63.40 ± 12.52	63.07 ± 16.85	64.29 ± 15.37	64.44 ± 17.70	0.973	0.891	0.922
Alanine (nmol/mL)	431.76 ± 93.52	426.67 ± 105.28	423.90 ± 106.67	447.56 ± 88.61	0.636	0.897	0.467
Tyrosine (nmol/mL)	73.59 ± 11.97	73.31 ± 9.08	69.37 ± 11.45	87.01 ± 27.02	0.104	0.596	0.174
Arginine (nmol/mL)	83.49 ± 18.38	75.93 ± 23.89	88.76 ± 14.08	98.96 ± 21.46	0.853	0.101	0.226
Cysteine (nmol/mL)	31.87 ± 4.52	31.36 ± 6.99	24.66 ± 6.54	24.43 ± 9.27	0.936	0.055	0.835
Glycine (nmol/mL)	203.06 ± 42.92	219.11 ± 50.87	206.61 ± 53.39	204.24 ± 57.15	0.35	0.839	0.215
Proline (nmol/mL)	239.74 ± 90.22	235.09 ± 57.52	194.26 ± 35.08	213.50 ± 51.92	0.614	0.285	0.413
Total BCAA (nmol/mL)	494.39 ± 70.21	476.16 ± 83.21	462.31 ± 80.67	567.76 ± 143.72	0.175	0.505	0.063
Total EAA (nmol/mL)	1070.29 ± 127.63	1050.30 ± 152.01	1020.60 ± 123.83	1207.09 ± 246.86	0.134	0.487	0.069

Mean ± standard deviation
The p-value was calculated using a two-way repeated-measures ANOVA.
Interactions were assessed by the duration of intervention × groups.
EAA; essential amino acids, NEAA; non-essential amino acids, BCAA; branched-chain amino acids.

Supplement 2 Blood test values other than amino acids

	Control group (n=7)		Intervention group (n=7)		Intervention Duration *P*	Group *P*	Interaction *P*
	Before the intervention	After 6 months	Before the intervention	After 6 months			
Hb (g/dL)	14.56 ± 1.83	14.69 ± 1.28	14.70 ± 1.34	14.29 ± 1.07	0.490	0.862	0.201
Cystatin C (mg/L)	0.96 ± 0.18	0.96 ± 0.14	0.94 ± 0.08	0.90 ± 0.12	0.293	0.550	0.214
e-GFRcys (ml/min)	80.06 ± 20.11	78.09 ± 15.45	79.63 ± 14.50	85.57 ± 20.73	0.131	0.737	0.760
HbA1c (%)	6.01 ± 0.67	6.01 ± 0.53	5.61 ± 0.29	5.69 ± 0.34	0.394	0.180	0.394
UA (mg/dL)	5.54 ± 1.07	5.04 ± 0.60	5.10 ± 1.38	4.84 ± 1.15	0.097	0.563	0.574
γ-GTP (U/L)	35.29 ± 23.31	35.57 ± 18.35	76.29 ± 90.42	67.14 ± 69.71	0.436	0.265	0.408
TC (mg/dL)	176.71 ± 37.36	175.29 ± 41.77	174.57 ± 47.95	163.00 ± 33.81	0.188	0.739	0.297
TG (mg/dL)	132.86 ± 74.93	159.29 ± 74.47	134.29 ± 38.11	141.29 ± 60.75	0.219	0.798	0.465
HDL-C (mg/dL)	58.00 ± 19.06	57.43 ± 16.34	53.86 ± 9.39	52.29 ± 8.12	0.584	0.533	0.797
LDL-C (mg/dL)	89.57 ± 41.47	87.86 ± 38.55	94.43 ± 46.52	84.71 ± 37.83	0.186	0.969	0.345
TP (g/dL)	6.81 ± 0.28	6.93 ± 0.39	7.04 ± 0.42	6.90 ± 0.13	0.878	0.515	0.182
Alb (g/dL)	4.20 ± 0.26	4.26 ± 0.27	4.41 ± 0.30	4.34 ± 0.14	0.885	0.249	0.208
NT-pro BNP (pg/mL)	213.30 ± 275.72	175.21 ± 200.51	69.08 ± 65.05	80.42 ± 66.48	0.463	0.260	0.188
Serum iron (μg/dL)	97.86 ± 43.20	114.43 ± 64.54	82.86 ± 18.09	93.57 ± 30.65	0.051	0.430	0.650
Ferritin (ng/mL)	175.00 ± 141.50	175.14 ± 150.61	220.29 ± 94.27	217.14 ± 87.50	0.900	0.508	0.891
CRP (mg/dL)	0.10 ± 0.09	0.15 ± 0.21	0.40 ± 0.71	0.10 ± 0.13	0.313	0.461	0.190

Mean ± standard deviation
The p-value was calculated using a two-way repeated-measures ANOVA.
Interactions were assessed by the duration of intervention × groups.

Alb; albumin, CRP; C-reactive protein, e-GFRcys; Estimated glomerular filtration rate (cystatin C), Hb; hemoglobin, HbA1c; hemoglobin A1c, HDL-C; HDL cholesterol, LDL-C; LDL cholesterol, NT-pro BNP; Human cerebral natriuretic peptide precursor N-end fragment, TC; Total cholesterol, TG; triglycerides, TP; Total protein, UA; uric acid, γ-GTP; γ glutamyl transpeptidase.

Supplement 3 Results of lean body mass and grip strength

	Control group (n=7)			Intervention group (n=7)			Intervention Duration $p^{\#}$	Group $p^{\#}$	Interaction $p^{\#}$
	Before the intervention	After 6 months	p^{*}	Before the intervention	After 6 months	p^{*}			
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD				
Lean body mass (kg)	53.5 ± 6.9	53.3 ± 7.2	0.334	47.3 ± 8.5	48.0 ± 8.6	0.033	0.343	0.195	0.033
Grip strength (kg)	34.4 ± 7.7	35.3 ± 6.4	0.442	28.7 ± 6.8	30.5 ± 7.3	0.111	0.101	0.185	0.526

Mean ± standard deviation
*The p-value for within-group comparison was calculated using a paired t-test.
#The p-value between groups was calculated using a two-way repeated-measures ANOVA.
Interactions were assessed by the duration of intervention × groups.

Supplement 4 Results of plasma leucine concentration, lean body mass, and grip strength in the intervention group (Cases A, B, C, subjects with significantly elevated plasma leucine concentration) and other subjects (Cases D, E, F, G)

	Gender	Age	BMI	Rate of change in plasma leucine concentration (%)	Lean body mass (kg)	Grip strength (kg)
Case A	man	22	17.3	84.3	41.5 → 43.3	24.5 → 32.8
Case B	man	38	29.2	40	62.4 → 63.9	36.3 → 39.5
Case C	woman	66	31.2	27.3	42.0 →42.8	22.8 → 24.3
Case D	man	45	22.3	16.8	47.9 → 48.4	31.5 → 30.5
Case E	man	68	24.8	−1.5	55.4 → 55.0	39.0 → 40.0
Case F	woman	66	22.4	11.1	40.6 → 41.8	24.3 → 24.8
Case G	woman	66	31.1	−8.3	41.6 → 41.4	22.8 → 22.0

The rate of change was calculated as 100 × results after six months/results before intervention−100.
BMI; Body Mass Index.

Original Articles

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The Impact of Exercise and Health Management on Workplace Creativity

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Objectives: This study aimed to investigate Japan's service sector employees to determine whether employee creativity is associated with the provision of a fitness program (that encourages employees to perform physical exercise) or a health and productivity management (H&PM) program at the workplace.
Design: This was a cross-sectional study.
Methods: A nationwide online survey was conducted using stratified sampling. Data were obtained for respondents' demographic characteristics, subjective health, exercise frequency, and organizational wellness support. Workplace creativity, psychological safety, and leadership were evaluated using standardized scales. A binary logistic regression was performed to examine the relationship between organizational wellness support programs and workplace creativity.
Results: Respondents were 1,955 full-time employees in private-sector organizations (979 men and 976 women; mean age 40.30 ± 10.85). Workplace creativity was significantly more likely respondents whose employers provided a fitness program (*adjusted OR* = 1.86, *95% CI* = 1.39–2.48, $p<.001$) or an H&PM program (*adjusted OR* = 2.07, *95% CI* = 1.53–2.80, $p<.001$). Furthermore, workplace creativity was significantly more likely in employees who perceived themselves as rather healthy or healthy. Employees who exercised frequently over the past year were more likely to display creativity than those never exercised.
Conclusions: Workplace creativity was associated with good subjective health, high exercise frequency, and organizational wellness support programs offered by employers. Human resource management for employees' fitness and health is crucial for cultivating the productivity and innovation necessary for business success.

Key words: employee health, workplace creativity, exercise, health and productivity management

Introduction

In Japan, the Third Sport Basic Plan was formulated on March 25, 2022. The new plan outlines the specific policies and targets to be advanced by the government and other organizations over the next five years (2022/4 to 2027/3)[1]. The plan has been designed to ensure the legacy of the Tokyo 2020 Olympic and Paralympic Games and to facilitate the growth of the sports industry among others. However, for Japan to achieve economic growth, a major hurdle must be overcome: low productivity amid a lack of innovation[2]. This is a particularly important issue in Japan's industry (the service sector)[2], which employs around 70% of the country's working population and encompasses the sports and health sectors[3]. Moreover, as an impediment to innovation, around half of the companies in a government survey revealed that they lacked talented workers[2]. While there is a growing focus on using digital technology in the workplace, Furukawa et al. notes that human knowledge and human skills are all the more important in a volatile business environment[4]. Amabile et al. defined creativity

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as the production of novel and useful ideas in any domain, and innovation as the successful implementation of creative ideas within an organization[5]. In this light, individual and team creativity is a starting point for innovation. Considerable evidence suggests that employee creativity can substantially contribute to organizational innovation, effectiveness, and survival[5–7]. When employees exhibit creativity at work, they produce novel, and potentially useful, ideas about organizational products, practices, services, or procedures[5, 8]. Thus, in the workplace, both individual and team creativity is essential for addressing all manner of workplace problems; as such, it will become an increasingly important priority for all organizational layers in the service sector[9]. Therefore, there is an increasing need for a greater understanding of the contextual factors that may enhance or diminish employees' creativity as well as the interaction between personal characteristics and work environment[8–10]. Further, it is important to identify the role of leadership in encouraging employee creativity[9, 10]. Another concept gaining increasing attention in the corporate sector is psychological safety (as defined by Edmondson, 1999)[11]. Studies have shown that psychological safety correlates positively with creativity, and that effective leadership facilitates both psychological safety and employee creativity in the workplace[12–16].

Japan has shown interest in organizational support for employee wellness, inspired by the ideas in The Healthy Company (Rosen, 1992)[17]. In this context, Japan sports agency (MEXT) led a wellness program named the Sports Yell Company program[18]. Alongside this, there are company-level "health and productivity management" (H&PM) programs, which align with a model of employee wellness promoted by the Ministry of Economy, Trade and Industry (METI)[19]. Previous studies have revealed that, companies with an effective H&PM program tend to have better stock performance[20, 21]. Given the well-demonstrated association between employee health (as measured by absenteeism, for instance) and productivity (as measured by presenteeism, for instance), greater corporate interest in employee health will lead to more positive outcomes. However, thus far, the literature has focused on outcomes such as return on (or loss on) investment in health, productivity measures, and health problems[22–31]; few studies have measured creativity in a workplace context or changes in employee attitudes and behaviors. Some reports suggest that physical exercise positively affects creative thinking, creative idea generation, and cognitive processing[32, 33]. However, systematic reviews concluded that further research is necessary to obtain clear evidence of the association between exercise and creativity[34, 35]. The present study was motivated by the following idea: if it was demonstrated that employee creativity is greater in workplaces with wellness programs, this would offer the corporate sector a greater incentive to invest in human resource management for employee health, ultimately leading to greater innovation.

To this end, we conducted a cross-sectional study on employees in the service sector to determine whether employee creativity is associated with the provision of either one or both of the following types of organizational wellness support: a fitness program (a program encouraging employees to engage in physical exercise) and an H&PM program.

Method

Sample and procedure

A nationwide online survey was conducted using stratified sampling, including individuals who were aged 20–59 and employed full time in private-sector organizations, classified as tertiary industry (service sector) employers by the Ministry of Internal Affairs and Communications. The study sample comprised participants selected from the panel registered with Cross Marketing, Inc., a leading marketing research agency in Japan. The survey was conducted between October and November 2022. Before starting the online survey, the participants were presented with a webpage detailing the rationale, objective of the survey, ethical considerations and stating that their anonymity would be safeguarded. The participants were then invited to click on an "agree" button to indicate their informed consent to participate in the survey.

Survey data cleaning was performed to eliminate data from respondents whose responses could bias the results. Specifically, we identified and removed straight liners (respondents who chose the same answer option repeatedly) and set a trick question (a question designed to "trap" respondents who were not paying attention).

Measures

Participant characteristics

The following participant attributes were obtained: gender, age, education (highest level of education), marital status, parental status (whether the person has any children), age of the youngest (or only) child (if any), managerial status (whether the person has a management title), work hours, occupation, subjective health, exercise frequency, and whether wellness support was provided in the workplace. Subjective health was rated on a 4-point scale, with the following answer options: unhealthy, rather unhealthy, rather healthy, and healthy. For exercise frequency, respondents described how frequently they had engaged in an exercise session lasting at least 30 minutes, over the past year; the answer options were: never, one to three days a year, four to eleven days a year, one to three days a month, one to two days a week, and at least three days a week. To determine whether organizational wellness support was provided, the following questions were presented: "Does your workplace provide a fitness program?" and "Does your workplace provide a H&PM program?" In both cases, respondents could answer "yes," "no," or "unsure."

Workplace creativity

Creativity in the workplace was measured using a six-item scale by Maruyama and Fuji (2022)[36], based on the original scale by Carmeli and Schaubroeck (2007) that measures creative involvement at work[10]. Each item contained a statement rated on a 7-point scale to indicate level of agreement (absolutely disagree to strongly agree). The items (as translated from Japanese) were as follows: "I exhibit originality at work," "I take risks to generate new ideas needed in my work," "I'm prepared to change existing work procedures and methods and I look for new ways to use equipment," "I resolve the issues that entail difficulties," "I try out new ideas when approaching problems," and "I generate ideas that are unprecedented but useful for work." Based on their total scores for the six items, the respondents were divided into quartiles, with the top 25% categorized as the high creativity group and the remaining 75% as the non-high creativity group.

Workplace culture and leadership

The previous study suggests that employees' creativity is moderated by contextual factors such as workplace culture and leadership, as well as by intra-individual factors[8, 9]. To evaluate workplace culture, we used Edmondson's (1999) Team Psychological Safety Scale[11]. To assess leadership, we used Walumbwa et al.'s (2008) Authentic Leadership Questionnaire[37]. The Team Psychological Safety Scale consists of seven items, each rated on a 7-point scale (from "completely disagree" to "absolutely agree"). The items were prefaced with the following statement: "We will ask you about your team (workplace, department, store members) with which you usually work." The Authentic Leadership Questionnaire consists of 16 items, each rated on a 5-point scale (from "not at all" to "frequently, if not always") and prefaced with the following statement: "The following survey items refer to your leader's style, as you perceive it. Judge how frequently each statement fits his or her leadership style using the following scale."

Ethical considerations

This study was approved by the research ethics committee of the Japan Women's College of Physical Education (Application Number: 2022-20).

Statistical analysis

A binomial logistic regression was performed, with the explanatory variables being subjective health, exercise frequency, and organizational wellness support, and the objective variable being workplace creativity. We also set several moderator variables (confounders) on the premise that the variables in question could affect workplace creativity directly or indirectly. These moderator variables included: gender, age, education, marital status, parental status, managerial status, work hours, occupation, psychological safety, and authentic leadership. Using the adjusted odds ratios for these items, we could control the confounding factors. IBM SPSS version 28 for Windows was used for statistical analysis.

Results

Participant attributes

Table 1 shows the attributes of participants. The cleaned survey data comprised 1,955 respondents

employed full-time in private-sector organizations classified as tertiary industry companies. In total, there were 979 men (50.1%) and 976 women (49.9%); 958 (48.0%) respondents were married. Furthermore, 673 (34.4%) respondents had children; the youngest (or only) child was aged below 6 in 206 (10.5%) cases, 6–11 in 118 (6.0%) cases, 12–17 in 140 (7.2%) cases, and 18 or above in 209 (10.7%) cases. The respondents' mean age was 40.30 ± 10.85; 485 (24.8%) were in their 20s, 486 (24.9%) in their 30s, 488 (25.0%) in their 40s, and 496 (25.4%) in their 50s. Regarding education level, 384 (19.6%) had completed high school, 226 (11.6%) technical/vocational college, 169 (8.6%) junior college (or vocational high school), 1,077 (55.1%) university (four-year undergraduate program), 66 (3.4%) a master's program, 11 (0.6%) a doctoral program, and 22 (1.1%) other. Regarding managerial status, 598 (30.6%) participants had a management title, while 1,357 (69.4%) were general employees with no management title. Regarding work hours per week, 1,349 (69.0%) participants worked for less than 45 hours, 462 (23.6%) worked between 45 and 54 hours, 103 (5.3%) worked between 55 and 64 hours, and 41 (2.1%) worked for 65 hours or longer. Regarding occupation, 301 (15.4%) participants worked in sales, 549 (28.1%) in admin/accounts, 44 (2.3%) in HR, 57 (2.9%) in planning/marketing, 60 (3.1%) in senior or middle management, 269 (13.8%) in customer services, 286 (14.6%) in specialized services, 184 (9.4%) in technical services, and 205 (10.5%) in others.

Exercise frequency and organizational wellness support

Table 2 shows the exercise frequency and organizational wellness support of participants. Regarding subjective health, 140 (7.2%) respondents answered "unhealthy," 330 (16.9%) "rather unhealthy," 966 (49.4%) "rather healthy," and 519 (26.5%) "healthy." When asked how frequently they had engaged in an exercise session lasting at least 30 minutes over the past year, 879 (45.0%) answered never, 175 (9.0%) answered one to three days a year, 66 (3.4%) answered four to 11 days a year, 154 (7.9%) answered one to three days a month, 415 (21.2%) answered one to two days a week, and 266 (13.6%) answered at least three days a week. When asked whether their workplace provided a fitness program, 1,393 (71.3%) participants said no, 294 (15.0%) said yes, and 268 (13.7%) were unsure. When asked whether their workplace provided a H&PM program, 1,030 (52.7%) participants answered no, 280 (14.3%) answered yes, and 645 (33.0%) were unsure.

Creativity at the workplace

A total of 502 respondents were classed as creative, their total scores falling in the top quartile of scores ($M = 30.48 \pm 3.27$), while 1,453 were classed as uncreative ($M = 17.53 \pm 6.39$). The two groups were compared regarding their basic attributes using a chi-squared test. The analysis revealed significant inter-group differences for gender, age, education, marital status, parental status, whether the respondent had a managerial status, work hours, and occupation (Table 1).

The two groups also differed significantly on all items of subjective health, exercise frequency, whether a fitness activity was promoted, whether an H&PM program was promoted, Team Psychological Safety Scores, and Authentic Leadership Questionnaire scores (Table 2). For the team psychological safety scale and the Authentic Leadership Questionnaire, following the precedent set in the literature, using Welch's t-test.

Factors related to employee creativity in the workplace.

Table 3 shows the results of the binomial logistic regression analysis. Employee creativity in the workplace was significantly more likely in respondents who perceived themselves as rather healthy (*adjusted OR* = 2.14, *95% CI* = 1.23–3.71, $p<.01$) or healthy (*adjusted OR* = 2.09, *95% CI* = 1.18–3.70, $p<.05$) than those who perceived themselves as unhealthy. Furthermore, workplace creativity was significantly more likely in respondents who engaged in an exercise session lasting at least 30 minutes for one to three days a month (*adjusted OR* = 1.90, *95% CI* = 1.26–2.86, $p<.01$), one to two days a week (*adjusted OR* = 1.69, *95% CI* = 1.26–2.27, $p<.001$), or at least three days a week (*adjusted OR* = 1.76, *95% CI* = 1.27–2.46, $p<.001$), than by those who had never exercised in the past year. Of the exercise frequency categories, "at least three days a week" was associated with the greatest increase in adjusted odds ratio. In addition, workplace creativity was

Table 1 Differences in workplace creativity according to the participants' attributes

		Non-high Creativity (n=1,453)		High Creativity (n=502)		
		n	%	n	%	χ^2
Gender	Male	688	47.4%	291	58.0%	16.83**
	Female	765	52.6%	211	42.0%	
Marital status	Unmarried	769	52.9%	228	45.4%	8.41*
	Married	684	47.1%	274	54.6%	
Parental status	No children	978	67.3%	304	60.6%	15.65*
	< 6 years old	156	10.7%	50	10.0%	
	6–11 years old	84	5.8%	34	6.8%	
	12–17 years old	87	6.0%	53	10.6%	
	≥ 18 years old	148	10.2%	61	12.2%	
Age	20s	383	26.4%	102	20.3%	8.90*
	30s	362	24.9%	124	24.7%	
	40s	356	24.5%	132	26.3%	
	50s	352	24.2%	144	28.7%	
Education	High school	307	21.1%	77	15.3%	40.36**
	Technical/vocational college	176	12.1%	50	10.0%	
	Junior college (or vocational high school)	140	9.6%	29	5.8%	
	University (four-year undergraduate program)	765	52.6%	312	62.2%	
	Master's program	40	2.8%	26	5.2%	
	Doctoral program	4	0.3%	7	1.4%	
	Other	21	1.4%	1	0.2%	
Managerial status	Yes	378	26.0%	220	43.8%	55.74**
	No (general employee)	1,075	74.0%	282	56.2%	
Working hours (per week)	< 45 h	1,023	70.4%	326	64.9%	9.27*
	45 h–54 h	337	23.2%	125	24.9%	
	55 h–64 h	67	4.6%	36	7.2%	
	≥ 65 h	26	1.8%	15	3.0%	
Occupation	Sales	212	14.6%	89	17.7%	62.14**
	Admin/accounts	445	30.6%	104	20.7%	
	Human resources	26	1.8%	18	3.6%	
	Planning/marketing	29	2.0%	28	5.6%	
	Senior/middle management	30	2.1%	30	6.0%	
	Customer services	211	14.5%	58	11.6%	
	Specialized services	202	13.9%	84	16.7%	
	Technical services	137	9.4%	47	9.4%	
	Other	161	11.1%	44	8.8%	

**p<.01, *p<.05.

significantly more likely in respondents whose employers promoted fitness activities (*adjusted OR* = 1.86, *95% CI* = 1.39–2.48, p<.001) and those whose employers provided an H&PM program (*adjusted OR* = 2.07, *95% CI* = 1.53–2.80, p<.001) than in respondents whose employers did not provide either.

Discussion

This study examined survey data from employees in the service sector to reveal how employee

Table 2 Differences in workplace creativity according to exercise frequency and health management

		Non-high Creativity (n=1,453)		High Creativity (n=502)		
		n	%	n	%	χ^2
Subjective health	Unhealthy	122	8.4%	18	3.6%	18.92**
	Rather unhealthy	256	17.6%	74	14.7%	
	Rather healthy	711	48.9%	255	50.8%	
	Healthy	364	25.1%	155	30.9%	
Exercise frequency	Never	717	49.3%	162	32.3%	50.39**
	1–3 days/year	131	9.0%	44	8.8%	
	4–11 days/year	45	3.1%	21	4.2%	
	1–3 days/month	103	7.1%	51	10.2%	
	1–2 days/week	286	19.7%	129	25.7%	
	≥ 3 days/week	171	11.8%	95	18.9%	
Promote fitness activities	No	1,082	74.5%	311	62.0%	60.14**
	Yes	165	11.4%	129	25.7%	
	Unsure	206	14.2%	62	12.4%	
Health and productivity management program	No	813	56.0%	217	43.2%	70.97**
	Yes	152	10.5%	128	25.5%	
	Unsure	488	33.6%	157	31.3%	
Psychological safety	M (±SD)	4.52	(±.689)	5.03	(±.790)	**
Authentic leadership	M (±SD)	2.90	(±.754)	3.26	(±.849)	**

[a] **p<.01, *p<.05.
[b] The psychological safety and the Authentic Leadership were using Welch's t-test.

creativity is associated with exercise and organizational wellness support. Having controlled for certain respondent attributes that could affect employee creativity (gender, age, education, marital status, parental status, managerial status, work hours, occupation, psychological safety, and authentic leadership), we found that employees' creativity in the workplace is associated with their subjective health and whether the employer provides a fitness program or an H&PM program. To the best of our knowledge, this finding constitutes the first scientific evidence of such an association.

Exercise and workplace creativity

Our survey revealed that, over the past year, 45% (879) of the respondents had never engaged in an exercise session lasting at least 30 minutes, while 34.7% (681) had done so at least one day a week. In a 2022 survey on engagement in sport, the Japan Sports Agency found that 47% of Japanese men and women aged 20–59 engage in exercise at least one day a week. However, the agency's exercise data pertained to general members of the public, who may or may not have been employed and who could have been employed in any kind of job; the value of our data lies in the fact that it specifically highlights exercise frequency among people employed full-time in Japan's private sector. Our analysis revealed that workplace creativity was significantly more likely to be exhibited by employees who perceived themselves as rather than by those who perceived themselves as unhealthy. The literature on the relationship between employee health and workplace productivity has shown that effective organizational support for employee wellness, as measured by a decline in presenteeism among other things, leads to higher workplace creativity. Creativity was also significantly more likely to be exhibited by employees engaged in an exercise session lasting at least 30 minutes on one to three days a month (*adjusted OR* = 1.90, *95% CI* = 1.26–2.86, p<.01), one to two days a week (*adjusted OR* = 1.69, *95% CI* = 1.26–2.27, p<.001), or at least three days a week (*adjusted OR* = 1.76, *95% CI* = 1.27–2.46, p<.001) over the past year, than by those who had never exercised in the past year; further-

Table 3 Results of the binomial logistic regression analysis

		Crude OR	(*95%CI*)	*P*-value	Adjusted *OR*	(*95%CI*)	*P*-value
Subjective health	Unhealthy	1.00	(*Reference*)		1.00	(*Reference*)	
	Rather unhealthy	1.96	(*1.12–3.42*)	*	1.80	(*0.99–3.27*)	*n.s.*
	Rather healthy	2.43	(*1.45–4.07*)	**	2.14	(*1.23–3.71*)	**
	Healthy	2.89	(*1.70–4.90*)	**	2.09	(*1.18–3.70*)	*
Exercise frequency	Never	1.00	(*Reference*)		1.00	(*Reference*)	
	1–3 days/year	1.49	(*1.01–2.18*)	*	1.39	(*0.93–2.09*)	*n.s.*
	4–11 days/year	2.07	(*1.20–3.56*)	**	1.54	(*0.86–2.75*)	*n.s.*
	1–3 days/month	2.19	(*1.50–3.19*)	**	1.90	(*1.26–2.86*)	**
	1–2 days/week	2.00	(*1.53–2.61*)	**	1.69	(*1.26–2.27*)	**
	≥ 3 days/week	2.46	(*1.82–3.33*)	**	1.76	(*1.27–2.46*)	**
Promote fitness activities	No	1.00	(*Reference*)		1.00	(*Reference*)	
	Yes	0.96	(*0.70–1.30*)	*n.s.*	1.86	(*1.39–2.48*)	**
	Unsure	2.60	(*1.80–3.74*)	**	1.03	(*0.74–1.43*)	*n.s.*
Health and productivity management program	No	1.00	(*Reference*)		1.00	(*Reference*)	
	Yes	3.15	(*2.39–4.17*)	**	2.07	(*1.53–2.80*)	**
	Unsure	1.21	(*0.95–1.52*)	*n.s.*	1.03	(*0.80–1.33*)	*n.s.*

[a] $^{**}p<.01$, $^{*}p<.05$; *n.s.*=non-significant; *OR* = Odds ratio; *95% CI* = 95% confidence interval.
[b] Objective variable: workplace creativity (0 = non-high creativity, 1 = high creativity).
[c] The adjusted OR were intended to control for the following: gender, marital status, parental status, age, education, managerial status, work hours, occupation, psychological safety, and authentic leadership.

more, the highest adjusted odds ratio was found for those exercised "at least three days a month. The Government of Japan is committed to the goal of having 70% of the adult population engage in exercise at least one day a week and having 50% engage in exercise at least three days a week. In this regard, our findings offer important insights for employees in the service sector; exercising one to three days a month is more effective for facilitating creativity in the workplace than not exercising at all. Other studies suggest that exercise can facilitate workplace creativity even at a low frequency, provided that the physical activity is regular. Specifically, one report suggested that even a single exercise session can facilitate creative thinking[32]; other studies showed that habitual physical activity has a moderate effect on creative ideation, and that chronic physical activity interventions enhance creativity[33–35].

Organizational wellness support and creativity

Our second main finding concerns the role of organizational wellness support in employees' creativity. We found that workplace creativity was significantly more likely to occur among respondents whose employers promoted fitness activity (*adjusted OR* = 1.86, *95% CI* = 1.39–2.48, $p<.001$) than among those whose employers did not. Furthermore, creativity was significantly more likely to occur among respondents whose employers provided an H&PM program (*adjusted OR* = 2.07, *95% CI* = 1.53–2.80, $p<.001$) than among those whose employers did not. Admittedly, these results offer no precise insights into how such programs contribute to individual employees' behaviors and health condition. Nonetheless, they do corroborate the claim made in "The Healthy Company" that companies with healthier workforces are more profitable; that is, individual and team creativity constitutes both the starting point for innovation and a process for resolving problems. There is extensive evidence showing that employee creativity facilitates organizational innovation and organizational effectiveness[6, 7].

Finally, we discuss the results in Table 2. Japan has shown increasing interest in having the corporate sector execute integrated strategies for encouraging employees to engage in physical and health-supporting activities, as evidenced by government-led programs such as the Sports Yell Company

program[18] and the H&PM program[19]. However, our results suggest that the government's employee wellness agenda is yet to gain traction; in our survey, few companies provided a fitness or H&PM program for employees. As stated in the Introduction section, a report suggested that the greatest impediment to innovation is a lack of talented workers within the company[2]. In today's volatile, uncertain, complex, and ambiguous business environment, it is all the more essential to provide a workplace and talent management strategy that unleashes employees' creativity. While it is true that profit growth will always be paramount to business survival, and that employers are sometimes unable to invest enough in talent development and employee welfare, sacrificing employee wellness for the sake of immediate profit is the wrong approach. Although investing in employee wellness yields no instant or immediately apparent return on investment, organizational support for employees' fitness and health plays a crucial role in cultivating the productivity and innovation necessary for business success in a volatile, uncertain, complex, and ambiguous environment.

Conclusions

Using survey data pertaining to 1,955 full-time employees in Japan's service sector, we conducted a cross-sectional study to examine the relationship between organizational wellness support at the workplace, exercise frequency, and workplace creativity. Based on the results, three conclusions can be drawn. First, creativity in the workplace is associated with subjective health: compared with those who perceived themselves as unhealthy, respondents who perceived themselves as healthy had increased adjusted odds ratios from 2.09 to 2.14 for demonstrating workplace creativity. Second, workplace creativity is associated with habitual exercise: compared with those who had never exercised in the past year, respondents who performed exercise showed increased workplace creativity, with adjusted odds ratios of 1.90 for those who exercised for one to three days a month, 1.69 for those who exercised for one to two days a week, and 1.76 for those who exercised at least three days a week. Third, workplace creativity is associated with organizational wellness support: provision of a fitness program and an H&PM program by employers was associated with increased adjusted odds ratios of 1.86 and 2.07, respectively, for workplace creativity. Thus, human resource management for employees' fitness and health is crucial for cultivating the productivity and innovation necessary for business success.

Limitations and future research

This study adopted a cross-sectional approach and analyzed survey data pertaining to a single time-point. As such, the findings warrant no conclusions about any direct causal relationship that exercise and organizational wellness support may have with workplace creativity (the interaction mechanism). Furthermore, we believe that the impact of company size, such as number of employees and capitalization, should also be taken into consideration. When interpreting the results, the following precautions should be observed. First, as respondents rated their own creativity, we cannot rule out the possibility that their self-reports were affected by cognitive bias (such as the Dunning-Kruger effect). Thus, workplace creativity as measured in our study may not accurately reflect actual behaviors and outcomes in everyday workplace activities. Second, as respondents were asked about their exercise frequency over the past year, there is a possibility that their responses were influenced by recall bias, too. Many complex and latent factors moderate employee behavior in the workplace. By combining survey data with objective data from wearable devices or physiological measures, it is possible to deliver more reliable evidence for the effects of exercise and organizational wellness support on employees. Rigorously conducted randomized controlled intervention studies and more cross-sectional studies are needed to broaden the evidence in this nascent field of research.

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Author contributions

YH and MM conceived the idea of the study. YH developed the statistical analysis plan and conducted statistical analyses. YH and MM contributed to the interpretation of the results. YH drafted the original manuscript. MM supervised the conduct of this study. All authors reviewed the manuscript draft and revised it critically on intellectual content. All authors approved the final version of the manuscript to be published.

Conflicts of interest statement

The authors declare that they have no conflicts of interest.

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Original Articles

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Health and Productivity Management in Hospital Organizations and Work Engagement of Nurses

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Objective: In Japan, there is an urgent need to strengthen efforts to retain nurses and prevent high turnover. The Japan Nurses Association has set the goal of creating a supportive work environment for nurses to work with peace of mind and improve outcomes throughout their lives. Against this background, we examined the relationship between nurses' health and productivity management and their work engagement (WE) in Japanese hospital organizations.
Design: A cross-sectional design was used.
Methods: A web-based survey was administered to full-time employed nurses working in Japanese hospitals with 100 or more beds.
Results: Total WE scores were analyzed as the objective variable; WE crude odds ratios (ORs) were significantly higher in the high group than in the low group for all indicator items related to a healthy workplace culture. For adjusted ORs, propensity scores were calculated from gender, age, years of service, years of experience, job title, marital status, work shift, frequency of exercise per week, and hours worked per week and used as moderator variables. The results showed that the adjusted ORs for the high group were significantly higher than the adjusted ORs for the low group for all items except "participation of the person in charge from the planning stage of the initiative" and "reflection of the person in charge's opinion in the planning of the initiative."
Conclusions: This study suggests that health and productivity management initiatives in hospital organizations may positively impact nurses' WE. Furthermore, it suggests that these initiatives may contribute to improving nurse retention and preventing turnover.

Key words: health, productivity management, hospital organization, nurses, work engagement

Introduction

Nurses (excluding assistant nurses) working in hospitals, clinics, and as care workers exceed 1.33 million in Japan[1)]. Since 2008, Japan's average nursing attrition rate has remained at 10–11%[2)]; therefore, there is an urgent need to strengthen efforts to retain and prevent high turnover among Japanese nurses. The Japanese Nursing Association has developed an occupational safety and health guideline[3)] to ensure healthy and safe workplaces, as well as promote environments that enable nursing staff to engage in health promotion. In 2021, as a work style reform, the Japanese government set the goal of creating work environments that support nurses in working at ease and improve outcomes throughout their working lives[4)]. In this new policy effort, the turnover problem is approached from

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the perspective of health promotion, and the aim is to maintain nurses' morale so that they continue to work in their current position. It also aims to ensure that nurses' workplaces support them in maintaining their physical and mental well-being.

The concept of health and productivity management, proposed by Rosen[5], has been attracting considerable attention. This is because, from a managerial perspective, placing focus on employee health management is expected to have multiple positive outcomes[6].

Previous studies identifying the relationship between employee health status and productivity have shown that health risks are increasingly associated with lower productivity[7,8]. A particularly notable finding was that, "Physical activity may have a direct and indirect relationship to quality resident care and long-term care organizational success through impacts on employee absenteeism, job performance and employee satisfaction"[9–12]. Another study found that, "Physical activity level may also indirectly impact resident care through employee job satisfaction. A small increase in physical activity has been shown to increase healthcare employee job satisfaction"[10]. Given these trends, medical organizations and social medical corporations are making efforts to promote health and productivity management[13].

The concept of work engagement (WE) has been defined as individuals' "positive, fulfilling, work-related state of mind that is characterized by vigor, dedication, and absorption"[14]. Thus, WE can be used as an index of an individual's positive and energized state of mind toward work. It is characterized by "vigor, dedication, and absorption"[14] toward work and higher WE reportedly has positive outcomes, such as increased happiness, job satisfaction, and organizational commitment[15,16]. Higher WE among nurses reduces their risk of impaired physical and mental health, enabling them to contribute more to their work[17–19]. One prior study also emphasized the importance of further analyzing the current state of nurses' WE and its driving factors[20].

Despite the emphasis on the Japanese context above, concerns related to the shortage and turnover of nurses are not unique to Japan[21]. For example, the American Nurses Association[22] works to prevent high turnover by advocating safe and ethical work environments, staffing levels, and the physical and emotional well-being of nurses. The Healthy Nurse, Healthy Nation™[23] program of the American Nurses Association Enterprise encompasses six domains (mental health, physical activity, nutrition, rest, quality of life, and safety) and serves as an action plan to improve nurses' health. These efforts related to health and productivity management are similar to those in Japan. In the latter case, the certification system for health and productivity management is a mechanism for evaluating systems, programs, and management that promote health maintenance at the corporate level, and this system evaluates some aspects of corporate health climate and culture[24]. WE has been suggested to be associated with factors of corporate health culture. Furthermore, WE research has demonstrated the positive correlation among support from supervisors and colleagues, coaching by supervisors, innovative environment, and congruence between organizational and individual values[25].

Furthermore, previous studies suggest a close association between Japanese nurses' exercise habits and job satisfaction/intention to continue working[26]. Therefore, efforts made by hospital organizations to improve health and productivity management by encouraging health activities such as exercise and sports are expected to improve nurses' WE and retention and prevent turnover. We examine the relationship between nurses' perceptions of health and productivity management in hospital organizations and their WE. Particular attention will be paid to identifying health culture that contributes to nurses having high WE.

Materials and Methods

Procedure and sample

Sampling

A web-based survey was conducted among full-time employed nurses, midwives, and public health nurses working in Japanese hospitals with more than 100 beds. The sample comprised 500 respondents selected from the panel registered with Cross Marketing, Inc., a leading marketing research agency in Japan. The survey period was from March 1 to April 18, 2022, and 518 responses were initially included in the study. After excluding those with extremely short response times (under four minutes) and samples with the same response to a single

question (straight line cut), 377 answers were selected for the final analysis (valid response rate: 72.8%).

Attributes of participants

The participants' attributes are shown in Table 1. There were 65 men (17.2%) and 312 women (82.8%). The mean age was 43.1 (± 9.6) years, consistent with the volume zone of nurses' age, 40–44 years (14.2%), as reported by the Ministry of Health, Labor and Welfare[1]. The number of years of nursing experience was 18.6 (± 9.5), and the number of years of service in the current position was 12.6 (± 8.7). Furthermore, 268 (71.1%) participants were in the staff class, 81 (21.5%) were in the supervisor class, 16 (4.2%) were in the head nurse class, and 12 (3.2%) were in the director class. The percentage of positions was also consistent with the Japanese Nursing Association survey[4], with 73.0% of the respondents in non-managerial positions (staff class) and 22.8% in middle-managerial positions (chiefs and division chiefs).

Measures

Basic attributes

The respondents were asked to answer questions regarding the following demographic variables: gender, age, years of service at the current workplace, years of experience, position, marital status, work shifts, frequency of exercise per week, and working hours per week.

Nurses' perceptions of health and productivity management

To assess hospital organizations' efforts toward maintaining nurses' health and productivity management, a questionnaire with 20 items was developed based on the indicators developed by Takahashi et al.[27]. This served as an evaluation index of a healthy workplace culture. As our focus was on hospital organizations, the original term "company" was replaced with "hospital" or "the current workplace"; further, "employee" was replaced with "personnel." These adjustments served to retain the original intended meanings while ensuring the questionnaire's suitability for our sample. The response method was the same as the original[27], with a three-point scale comprising the options of "I don't know," "I'm not sure," and "I know." Similarly, a four-point scale was used to measure "Strongly disagree" to "Strongly agree."

Work engagement

The Japanese version of the Utrecht Work Engagement Scale[28] was used. Responses were given on a seven-point scale ranging from "Not at all" to "Every day (feel it all the time)." For the analysis, the total scale scores and scores of the three sub-factors (vigor, dedication, and absorption) were used.

Statistical analysis

First, for the question on healthy workplace culture, one group of positive answers (e.g., "I know," "Strongly agree," "Agree") was designated as Recognizing Healthy Culture (RHC) and the group of negative answers (e.g., "I don't know," "I'm not sure," "Strongly disagree," "Disagree") was designated as Not Recognizing Healthy Culture (NRHC). Further, a quartile was used for WE, with the 75th percentile as the cutoff point. The group with the highest scores was designated "high work engagement" (HWE) and the group with the lowest scores was designated "low work engagement" (LWE).

Next, binomial logistic regression analysis was conducted with RHC/NRHC as the explanatory variables and HWE/LWE as the objective variable to calculate crude odds ratios (CORs) and adjusted odds ratios (AORs). For AORs, propensity scores were calculated for gender, age, years of service at the current workplace, years of experience, position, marital status, work shifts, frequency of exercise per week, and working hours per week and used as moderator variables. SPSS version 28 for Windows (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Ethical considerations

This study was approved by the ethics committee at the Graduate School of Sports and Health Science, Juntendo University (Application Number: 2021-115). The start screen of the survey clearly stated its purpose and informed respondents that clicking the answer button implied consent to participate.

Results

Logistic regression analysis of nurses' perceptions of health and productivity management and work engagement

The results of the analysis are presented in Tables 2, 3-1 and 3-2. First, in the analysis using total WE scores as the objective variable, the CORs for WE tended to be higher in the RHC group than in the NRHC group for all indicator items related to healthy workplace climate. Similarly, the AORs for WE tended to be higher in the RHC group than in the NRHC group for all items except "Participation of personnel from the planning stage of the efforts" and "Reflection of personnel's opinions in the planning of the efforts." Items with particularly high AORs were as follows: "Hospital's interest in its personnel's health" (AOR=3.25, 95% confidence interval (CI) [1.97, 5.37]); "Supervisors' support for participating in health promotion efforts during work hours" (AOR=2.69, 95% CI [1.60, 4.49]); "Active participation of the management team in these efforts" (AOR=2.68, 95% CI [1.61, 4.45]); "Colleagues' interest in health" (AOR=2.59, 95% CI [1.54, 4.33]); and "Colleagues' support for taking sick leave" (AOR=2.53, 95% CI [1.30, 4.94]).

Second, analysis was conducted using vigor as the objective variable. The COR for vigor tended to be higher in the RHC group than in the NRHC group for all indicator items related to healthy workplace climate. The AORs of WE tended to be higher in the RHC group than in the NRHC group for all items except "Hospital policy on maintaining and promoting health."

Third, analysis was conducted using the dedication sub-factor as the objective variable. The CORs for dedication tended to be higher in the RHC group than in the NRHC group for all indicator items related to healthy workplace climate. The AORs for WE tended to be higher in the RHC group than in the NRHC group for all items except "Participation of personnel from the planning stage of the efforts," "Reflection of personnel's opinions in the planning of the efforts" and "Conversations with colleagues about health promotion efforts."

Finally, analysis was conducted using the absorption sub-factor as the objective variable. The CORs for absorption tended to be higher in the RHC group than in the NRHC group for all items except "Reflection of personnel's opinions in the planning of the efforts." The AORs for WE tended to be higher in the RHC group than in NRHC group for "Program and support for returning to work after a long absence," "Feedback on physical condition from supervisors to personnel," "Provision of useful information about health promotion," "Communication about the importance of promoting a healthy workplace from supervisors to personnel," "Participation of personnel from the planning stage of the efforts," "Hospital's interest in its personnel's health," "Supervisors' support for participating in health promotion efforts during work hours," "Active participation of the management team in these efforts," "Colleagues' support for taking sick leave," "Colleagues' interest in health promotion," and "Participating with colleagues to promote a healthy workplace."

Discussion

In this study, we examined the relationship between nurses' positive attitude toward WE and the efforts made by hospitals (employers), supervisors (e.g., nursing departments, managers, and chiefs), colleagues, and other individuals in hospital organizations to promote health and productivity management. This section examines the relationship between WE and four items that showed high overall AOR scores in our findings: "Hospital's interest in its personnel's health," "Supervisors' support for participation in health promotion efforts during work hours," "Active participation of the management team in these efforts," and "Colleagues' interest in health."

Hospital's interest in its personnel's health

To promote new measures in health and productivity management, the need for a corporate culture that accepts new programs and a workplace environment where supervisors and colleagues can use the programs is suggested[29]. In other words, to achieve organizational results, employees must participate in health promotion efforts. Employees' thoughts and feelings cannot be controlled directly[26], but can be addressed indirectly through changes in the workplace environment. In our study, the item "Hospital's interest in its personnel's health" had the highest AOR (2.67). The process of measuring WE involves the evaluation of the values employees

Table 1 Participants' attribute scores

	n	%	Mean	SD
Gender				
Men	65	17.2		
Women	312	82.8		
Age			43.1	8.7
Years of nursing experience			18.6	9.5
Years of service at the current workplace			12.6	8.7
Position				
Staff class	268	71.1		
Chief class	81	21.5		
Manager class	16	4.2		
Director class	12	3.2		
Marital status				
Unmarried	120	31.8		
Married (including separated and widowed)	257	68.7		
Work shifts				
Day shift only	88	23.3		
Two-shift system	216	57.3		
Three-shift system	68	18.0		
Night shift only	5	1.3		
Frequency of exercise				
Less than 1 day/month	233	61.8		
More than 1 day/month	46	12.2		
More than 1 day/week	78	20.7		
More than 3 days/week	20	5.3		
Working hours per week				
1–34	12	3.2		
35–39	70	18.6		
40–49	204	54.1		
More than 50	91	24.1		

Table 2 Participants' work engagement scores

	Total (n=377)				HWE (n=279)				LWE (n=98)			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Total	20.8	13.7	0	54	38.8	7.4	29	54	14.5	8.9	0	28
Vigor	6.3	4.8	0	18	11.9	2.8	9	18	3.7	2.9	0	8
Dedication	7.9	4.9	0	18	14.4	2.0	12	18	5.7	3.4	0	11
Absorption	6.6	4.7	0	18	12.9	2.5	10	18	4.3	3.0	0	9

Notes: HWE; High work engagement. LWE; Low work engagement. Cut-off point; Total = 29.0, Vigor = 9.0, Dedication = 12.0 Absorption = 10.0

perceive in an organization's actions against its espoused values to determine sincerity and against personal values to determine congruence[30]. The results suggest that hospitals' concern for the health of their employees contributes effectively to the improvement of their WE. Based on these results, we believe that hospitals need to create a work environment that affirms health manage-

Table 3-1 Association between health and productivity management and work engagement (logistic regression analysis)

#	Index items for healthy workplace culture	n*	Total						Vigor					
			Crude OR	95% CI		Adjusted OR	95% CI		Crude OR	95% CI		Adjusted OR	95% CI	
1	Hospital policy on maintaining and promoting health	46	3.08	1.63	5.80	2.26	1.12	4.55	2.71	1.44	5.07	1.65	0.82	3.32
2	Procedures for handling health issues	120	2.45	1.52	3.96	1.83	1.09	3.06	3.01	1.89	4.76	2.20	1.35	3.60
3	Program and support for returning to work after a long absence	167	2.40	1.49	3.84	2.12	1.31	3.43	2.37	1.52	3.70	2.04	1.28	3.23
4	Programs and menus for improving health	77	2.18	1.27	3.71	2.00	1.15	3.48	2.46	1.47	4.12	2.19	1.28	3.73
5	Program and support for improving mental health	194	2.29	1.41	3.71	2.07	1.26	3.40	2.74	1.73	4.33	2.41	1.50	3.86
6	Feedback on physical condition from supervisors to personnel	193	2.79	1.71	4.56	2.50	1.51	4.13	3.28	2.06	5.23	2.91	1.81	4.69
7	Provision of useful information about health promotion	108	2.91	1.78	4.74	2.50	1.51	4.13	3.32	2.07	5.32	2.77	1.70	4.51
8	Communication about the importance of promoting a healthy workplace from supervisors to personnel	117	2.75	1.70	4.45	2.36	1.44	3.88	3.39	2.13	5.39	2.93	1.81	4.72
9	Participation of personnel from the planning stage of the efforts	83	1.88	1.11	3.18	1.58	0.90	2.77	3.29	1.98	5.46	2.66	1.56	4.53
10	Reflection of personnel's opinions in the planning of the efforts	98	1.67	1.01	2.77	1.40	0.83	2.36	2.22	1.37	3.58	1.83	1.10	3.02
11	Places to consult with others about health and safety issues	72	2.90	1.69	4.97	2.25	1.27	3.97	3.32	1.95	5.65	2.48	1.41	4.33
12	Hospital's interest in its personnel's health	154	3.72	2.29	6.03	3.25	1.97	5.37	4.56	2.86	7.25	3.88	2.40	6.25
13	Hospital's interest in creating a healthy work environment	157	2.64	1.64	4.23	2.18	1.33	3.56	3.66	2.32	5.77	3.03	1.89	4.86
14	Supervisors' support for participating in health promotion efforts during work hours	193	3.17	1.92	5.22	2.69	1.60	4.49	3.10	1.95	4.93	2.54	1.57	4.11
15	Active participation of the management team in these efforts	183	3.23	1.97	5.29	2.68	1.61	4.45	3.64	2.28	5.80	2.99	1.85	4.85
16	Colleagues' support for taking sick leave	285	2.88	1.49	5.56	2.53	1.30	4.94	2.26	1.27	3.99	1.94	1.08	3.48
17	Colleagues' interest in health promotion	201	3.01	1.82	4.98	2.59	1.54	4.33	3.06	1.91	4.89	2.67	1.65	4.32
18	Conversations with colleagues about health promotion efforts	114	2.43	1.50	3.94	1.77	1.05	2.98	3.43	2.15	5.47	2.43	1.47	4.00
19	Encouraging colleagues about these efforts	117	2.44	1.51	3.95	1.79	1.07	3.00	3.03	1.91	4.82	2.22	1.36	3.63
20	Participating with colleagues to promote a healthy workplace	97	2.86	1.74	4.71	2.41	1.43	4.03	3.46	2.13	5.61	2.88	1.74	4.75

Notes: For the adjusted odds ratios, propensity scores were calculated for the moderator variables of gender, age, years of service at the current workplace, years of experience, position, marital status, work shifts, frequency of exercise per week, and working hours per week. Crude OR/Adjusted OR: Odds ratio of RHC with NRHC as the reference. 95% CI: 95% confidence interval.
* Number of those in the RHC group.

ment, explains resource use, communicates a clear vision, and makes health goals known[31] throughout the organization. We believe that this will increase trust in the hospital as a workplace where employees' health is protected.

Thus, the results suggest that acceptance by the hospital organization of health and productivity management and the creation of a work environment where the use of resources is explained—as well as a clear vision and health goals are commu-

Table 3-2 Association between health and productivity management and work engagement (logistic regression analysis) continued

#	Index items for healthy workplace culture	n*	Dedication						Absorption					
			Crude OR	95% CI		Adjusted OR	95% CI		Crude OR	95% CI		Adjusted OR	95% CI	
1	Hospital policy on maintaining and promoting health	46	4.36	2.30	8.25	2.96	1.47	5.96	2.72	1.44	5.14	1.84	0.91	3.73
2	Procedures for handling health issues	120	3.28	2.02	5.32	2.33	1.39	3.91	2.00	1.24	3.23	1.47	0.87	2.45
3	Program and support for returning to work after a long absence	167	2.71	1.68	4.38	2.35	1.43	3.84	1.96	1.23	3.12	1.65	1.02	2.67
4	Programs and menus for improving health	77	2.26	1.32	3.86	2.11	1.21	3.67	1.99	1.16	3.39	1.71	0.98	2.99
5	Program and support for improving mental health	194	2.99	1.81	4.93	2.53	1.51	4.24	1.85	1.15	2.97	1.52	0.93	2.49
6	Feedback on physical condition from supervisors to personnel	193	2.84	1.73	4.67	2.57	1.54	4.27	2.11	1.31	3.40	1.76	1.07	2.88
7	Provision of useful information about health promotion	108	3.25	1.99	5.31	2.70	1.62	4.48	2.37	1.45	3.85	1.92	1.16	3.19
8	Communication about the importance of promoting a healthy workplace from supervisors to personnel	117	2.72	1.67	4.41	2.31	1.40	3.81	2.25	1.39	3.63	1.83	1.11	3.02
9	Participation of personnel from the planning stage of the efforts	83	1.82	1.07	3.09	1.60	0.91	2.80	2.13	1.26	3.58	1.76	1.01	3.06
10	Reflection of personnel's opinions in the planning of the efforts	98	1.99	1.20	3.28	1.65	0.98	2.79	1.64	0.99	2.71	1.35	0.80	2.29
11	Places to consult with others about health and safety issues	72	2.59	1.50	4.45	1.84	1.03	3.28	2.26	1.31	3.90	1.63	0.91	2.91
12	Hospital's interest in its personnel's health	154	3.32	2.04	5.37	2.84	1.72	4.69	3.19	1.98	5.14	2.67	1.63	4.38
13	Hospital's interest in creating a healthy work environment	157	2.98	1.84	4.81	2.39	1.45	3.94	2.04	1.28	3.25	1.56	0.95	2.55
14	Supervisors' support for participating in health promotion efforts during work hours	193	3.03	1.84	5.00	2.51	1.50	4.21	3.04	1.85	4.99	2.45	1.46	4.10
15	Active participation of the management team in these efforts	183	3.29	2.00	5.40	2.64	1.58	4.43	3.11	1.91	5.07	2.49	1.50	4.14
16	Colleagues' support for taking sick leave	285	3.54	1.75	7.17	3.11	1.52	6.35	2.37	1.27	4.42	2.01	1.06	3.80
17	Colleagues' interest in health promotion	201	2.53	1.54	4.16	2.02	1.21	3.39	2.25	1.38	3.65	1.84	1.11	3.03
18	Conversations with colleagues about health promotion efforts	114	2.12	1.30	3.45	1.38	0.81	2.36	2.11	1.30	3.41	1.44	0.85	2.44
19	Encouraging colleagues about these efforts	117	3.27	2.01	5.31	2.35	1.40	3.95	1.88	1.16	3.04	1.30	0.77	2.19
20	Participating with colleagues to promote a healthy workplace	97	2.31	1.40	3.81	1.89	1.11	3.18	2.31	1.40	3.80	1.86	1.10	3.13

Notes: For the adjusted odds ratios, propensity scores were calculated for the moderator variables of gender, age, years of service at the current workplace, years of experience, position, marital status, work shifts, frequency of exercise per week, and working hours per week. Crude OR/Adjusted OR: Odds ratio of RHC with NRHC as the reference. 95% CI: 95% confidence interval.
* Number of those in the RHC group.

nicated[31]—across the organization lead to a good evaluation of the hospital and contribute toward improving nursing personnel's WE.

Supervisors' support for health promotion efforts during work hours

Studies comparing employees' participation rates in health programs have shown higher participation rates among employees of small- and medium-sized

companies compared to among employees of large companies[32]. The suggested reason for these findings is the rapid communication of knowledge and motivation because of a smaller staff in small- and medium-sized companies' networks. Nursing organizations tend to be organized into nursing units, such as hospital wards[33, 34], where nurses are assigned under the supervision of a nurse manager. The staffing levels (organizational design) of these organizations are similar to those of small businesses with fewer than 50 employees. Higher levels of engagement have been observed when supervisors exhibit relationship-related behaviors[35]. The current study also showed a significant difference for the item related to supervisors' support for health promotion efforts during work hours (AOR, 2.69), suggesting that supervisors' support for such efforts increases nurses' WE. In the organizational design of nursing organizations, we believe that the actions of the supervisor—the head nurse—build the organizational climate. We infer that in an organization where the supervisor's support for health activities is demonstrated without discomfort, employees feel secure and form a sense of belonging. We believe that the formation of such a sense of belonging will enhance WE.

Active participation of management team in health promotion efforts

A good work environment is essential for workplace health promotion efforts to be effective[36], and the outcomes of such health promotion programs depend on organizational factors such as the top management's leadership[24]. Berry et al.[37], in their discussion on "engaged leadership at multiple levels," suggested that if chief executive officers find time for exercise, employees would be less reluctant to take a fitness leave. In other words, creating a work environment that allows people to participate willingly in organizational efforts, explaining the use of resources, communicating a clear vision and health goals, and demonstrating exemplary behavioral changes by the top management will likely lead to successful health and productivity management[38]. In this study, the item related to the active participation of the top management team in the health promotion efforts of the organization showed significant results regarding WE (AOR, 2.68), followed by the AOR of the item on supervisors' support for these efforts. As an intervention process to improve WE, Bakker and Leiter[30] reported that, "In the initial phases of a new initiative to enhance WE, this role could be effectively served by the CEO," which is consistent with our results. Thus, it is suggested that WE is associated with specific behaviors (e.g., expression of concern about personnel's health) by physicians in management and leadership roles, heads of nursing organizations, and nurse directors. Creating a safe environment for engaging in health activities will lead to a positive attitude toward the workplace. We believe that this sense of being protected by the workplace will increase nurses' WE.

Colleagues' interest in health promotion

Interactions with social networks of friends and colleagues[38, 39] and communicating about health[40] are believed to contribute to behavioral changes. Thus, a growing interest in health among colleagues seems to create a positive work environment, including helping promote support for each other's physical condition. In our findings, colleagues' interest in health was significantly associated with WE (AOR, 2.59), corroborating the findings of the cited research and indicating an association between colleagues' interest in health and individual WE. In another study, an increase in WE due to individual health efforts seemed to influence nurses[41] and lead to the creation of a vibrant and rewarding work environment. The nature of nurses' work tends to hinder their ability to focus on their own health during working hours. However, crossover effects[42-45] can be expected by building a support system that provides opportunities to discuss club activities in hospitals and encourages efforts to improve an individual's health. Thus, although it can be extremely difficult[46] to change established lifestyles and exercise habits, if energetic colleagues can inspire other nurses and help the latter imagine themselves as energetic, this process can improve the awareness and importance of physical exercise and health, and eventually of WE.

The effects of improving WE in health management

Regarding the effects of health management initiatives, organizations with higher rates of

employee participation have a positive impact on presenteeism[32]. Furthermore, presenteeism is negatively correlated with WE and satisfaction[47].

We believe that if presenteeism can be reduced through health management, it may positively change the attitude toward work and contribute to an improvement in WE. Active participation of management was significant in the hospital organization that we studied. Previous studies that have examined the relationship between presenteeism, climate, and organizational support for nurses have also linked organizational support to the risk of presenteeism[42]. Until now, the retention and prevention of turnover of nurses has required the development of a work environment that allows nurses to continue working, including improvements in working hour management, night shift systems, and occupational health and safety[48]. However, the Ministry of Health, Labour and Welfare's recent survey of reasons for leaving the workforce[49] shows that the top reason for turnover is physical and mental health. These findings suggest that efforts to engage in health activities through health management may lead to improved effects on physical and mental health and WE, and may contribute to the prevention of nurse turnover and retention.

Conclusion

Reducing the high nurse turnover rate in Japan is an important concern. The impact of the nursing shortage, due to a declining workforce and falling birth rate, on patient care is multifaceted[50]. We argue that health and productivity management initiatives in hospital organizations may have a positive impact on nurse WE. Other major implications of the survey results are that the enhancement of health promotion support systems[51] and the development of a highly energetic and enthusiastic work environment in the field may contribute to promoting a rewarding workplace, improving retention rates, and preventing turnover.

Limitations

As this study is based on an online questionnaire survey, it does not reveal the specific health activity initiatives required for health management. We believe that future qualitative surveys, such as interviews, will reveal a more detailed relationship between the perception of health management initiatives and WE. Analyzing the relationship between specific initiatives and WE will lead to expectations for further development of future research on health management. Furthermore, we believe that the activation of health activities in hospital organizations, not only among nurses, will enhance WE among all healthcare workers, leading to their retention in the workplace and prevention of their intention to leave the workforce. We believe that this will lead to new insights into future work styles in the medical field.

Scope for further research

Although the number of medical corporations certified for health management is increasing, a measurement scale for health activity initiatives in hospital organizations has not yet been developed. Therefore, we employed health culture indicators in corporate organizations to measure perceived health efforts. In the future, it is necessary to develop a scale to measure health activity efforts in highly specialized organizations such as medical corporations and social medical corporations. In addition, this study revealed that the relationship between awareness (perception) of health activity efforts and WE is highly significant. In the future, it will be necessary to further explore the factors necessary to continue working by focusing on the relationship between vitality, enthusiasm, and immersion, which are sub-factors of WE.

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Author contributions

IK performed the data analysis; IT, HY, MY, and MM interpreted the analysis results and contributed significantly to the writing of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest statement

The authors declare that they have no conflicts of interest.

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Publication List

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Ophthalmology

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Neuroradiology section, Dept. of Radiology

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JMJ undertakes single-anonymized peer review. When a manuscript is submitted to the journal, it is assigned to the Editor-in-Chief, who performs initial screening. Manuscripts that do not fit the journal's scope or are not deemed suitable for publication are rejected without review. For peer reviewing, the manuscripts that pass through the initial screening are assigned to two external reviewers by the Editor-in- Chief. Reviewers are selected based on their expertise, reputation and previous experience as peer reviewers. The deadline for submission of the reviewers' reports is basically 3 weeks.
Upon receipt of the two reviewers' reports, the Editor-in-Chief makes the first decision on the manuscript. If the decision is to request revision of the manuscript, authors are requested to re-submit their revised manuscript within one to six months, depending on the comments of the reviewers. Revised manuscripts submitted after this deadline may be treated as new submissions. The Editor-in- Chief may send the revised manuscripts to peer reviewers for their feedback or may use his or her own judgment to assess how closely the authors have followed the Editor-in-Chief's and the reviewers' comments on the original manuscript. The Editor-in-Chief is responsible for making the final decision on each manuscript.
If a manuscript satisfies the journal's requirements and represents a significant contribution to the published literature, the Editor-in-Chief may recommend acceptance for publication in JMJ. If a manuscript does not meet the journal's requirements for acceptance, but it has a high probability of acceptance after minor or major revision, the Editor-in-Chief may ask the authors to revise it accordingly. Revised manuscripts must be submitted within one to six months, depending on the comments of the reviewers; otherwise they will be treated as new submissions. If a manuscript does not meet the journal's requirements for acceptance or revision, the Editor-in-Chief may recommend rejection.

Reviewer selection, timing and suggestions

Reviewers are selected without regard to geography and need not belong to the journal's Editorial Board. Reviewers are selected based on their expertise in the field, reputation, recommendation by others, and/or previous experience as peer reviewers for the journal.

Reviewers are invited within 2 weeks of an article being submitted. Reviewers are asked to review the manuscript based on the Acceptance criteria, described below, and submit their first review reports within 3 weeks of accepting the invitation to review. Reviewers who anticipate any delays should inform the Editorial Office as soon as possible.

When submitting a manuscript to the journal, authors may suggest reviewers that they would like included in the peer review process. The Editor may consider these suggestions but is under no obligation to follow them. The selection, invitation and assignment of peer reviewers is at the Editor's sole discretion.

Reviewer reports

It is the journal's policy to transmit reviewers' comments to the authors in their original form. However, the journal reserves the right to edit reviewers' comments, without consulting the reviewers, if they contain offensive language, confidential information or recommendations for publication.

Acceptance criteria

If a manuscript satisfies the journal's requirements and represents a valuable contribution to the published literature, the Editor-in-Chief may recommend the acceptance for publication in JMJ. The questions addressed when considering a manuscript for publication in JMJ are as follows: Relevance:

- Is the work within the journal's Aims and Scope?

Reproducibility:

- Do authors show sufficient information to reproduce their experiments or data?

Written quality:

- Is the manuscript clearly presented?

Title:

- Does the Title accurately reflect the contents of the manuscript?

Abstract:

- Does the Abstract adequately describe the background or context of the work, the objectives of the research project and the methods used?

Introduction:

- Does the Introduction provide adequate background and context for the work?

Materials and Methods:

- Have the authors described the methods in enough detail to allow others to replicate them?
- Have the authors adhered to established codes of practice and ethics if human/animal experimentation has been undertaken?
- Did the authors use appropriate methods?

Results:

- Have the authors explained their results clearly and adequately?

Discussion:

- Is the Discussion supported by the results?
- Have the authors considered any alternative explanations for their results?
- Have the authors made unsupported claims or inappropriate speculations?

General:

- Are all cited references relevant and necessary?
- Has any relevant literature been omitted?
- Have the authors cited the data described in the manuscript adequately?
- Is each table and figure necessary?
- Are any potentially useful figures or tables missing?
- Are the tables and figures complete and interpretable?
- Is the manuscript clearly written in English?
- Have the authors adhered to established codes of publication ethics?
- Are there any errors in fact, methodology, or analyses?
- Has the manuscript been published previously, in part or in whole, in any language?

If a manuscript does not meet the journal's requirements for acceptance or revision, the Editor-in-Chief may recommend rejection.

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As the journal owner, the Juntendo Medical Society (JMS) has granted the journal's Editorial Board complete and sole responsibility for all editorial decisions. The JMS will not become involved in editorial decisions, except in cases of a fundamental breakdown of process.

Editorial decisions are based only on a manuscript's scientific merit and are kept completely separate from the journal's other interests. The authors' ability to pay any publication charges has no bearing on whether a manuscript is accepted for publication in the journal.

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Authors who believe that an editorial decision has been made in error may lodge an appeal with the Editorial Office. Appeals are only considered if the authors provide detailed evidence of a misunderstanding or mistake by a reviewer or editor. Appeals are considered carefully by the Editor-in-Chief, whose decision is final. The guidelines of the Committee on Publication Ethics (https://publicationethics.org/appeals) (COPE) are followed where and when relevant.

Confidentiality in peer review

The journal maintains the confidentiality of all unpublished manuscripts. Editors will not:

1. disclose a reviewer's identity unless the reviewer makes a reasonable request for such disclosure
2. discuss the manuscript or its contents with anyone not directly involved with the manuscript or its peer review
3. use any data or information from the manuscript in their own work or publications
4. use information obtained from the peer review process to provide an advantage to themselves or anyone else, or to disadvantage any individual or organization.

Conflicts of interest in peer review

A conflict of interest exists when there are actual, perceived or potential circumstances that could influence an editor's ability to act impartially when assessing a manuscript. Such circumstances might include having a personal or professional relationship with an author, working on the same topic or in direct competition with an author, having a financial stake in the work or its publication, or having seen previous versions of the manuscript.

Members of the journal's Editorial Board undertake to declare any conflicts of interest when handling manuscripts. An editor who declares a conflict of interest is unassigned from the manuscript in question and is replaced by a new editor.

Editors try to avoid conflicts of interest when inviting reviewers, but it is not always possible to identify potential bias. Reviewers are asked to declare any conflicts of interest to the Editor, who will determine the best course of action.

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The journal recognizes the importance of maintaining the integrity of published literature.

A published article that contains an error may be corrected through the publication of an Erratum. Errata describe errors that significantly affect the scientific integrity of a publication, the reputation of the authors, or the journal itself. Authors who wish to correct a published article should contact the editor who handled their manuscript or the Editorial Office with full details of the error(s) and their requested changes. In cases where co-authors disagree over a correction, the Editor-in-Chief may consult the Editorial Board or external peer reviewers for advice. If a Correction is published, any dissenting authors will be noted in the text.

A published article that contains invalid or unreliable results or conclusions, has been published elsewhere, or has infringed codes of conduct (covering research or publication ethics) may be retracted. Individuals who believe that a published article should be retracted are encouraged to contact the journal's Editorial Office with full details of their concerns. The Editor-in-Chief will investigate further and contact the authors of the published article for their response. In cases where co-authors disagree over a retraction, the Editor- in-Chief may consult the Editorial Board or external peer reviewers for advice. If a Retraction is published, any dissenting authors will be noted in the text.

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Any member of the journal's Editorial Board, including the Editor-in-Chief, who is an author on a submitted manuscript is excluded from the peer review process and from viewing details about their manuscript.

A manuscript authored by an editor of JMJ is subject to the same high standards of peer review and editorial decision making as any manuscript considered by the journal.

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As part of their responsibilities, reviewers agree to maintain the confidentiality of unpublished manuscripts at all times. By accepting the invitation to review a manuscript, reviewers agree not to:

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3. discuss the manuscript or its contents with anyone not directly involved in the review process
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Color printing charges: 30,000 JPY per page

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Manuscript Preparation

Style

Manuscripts should be prepared in Microsoft Word or other appropriate software using double line spacing throughout, page numbers on the lower right, and with margins of at least 2.5 cm.

English standards

Manuscripts should be written in clear, grammatically correct English. Authors whose native language is not English are strongly encouraged to have their manuscript checked by a native English speaker or by an editing service prior to submission; a certificate of English editing that accompanies submissions can be useful in many circumstances. If a manuscript is not clear due to poor English, it may be rejected without undergoing peer review.

Format

The first page of each manuscript should contain: Title, Authors' full names, Affiliations, Key words, Running Title, and the name and full address (including telephone number, facsimile number, and e-mail address) of the corresponding author. Manuscripts should be divided into the following sections and presented in this order: Introduction; Materials and Methods; Results; Discussion; Acknowledgements; Funding; Authors' contributions; Conflicting interest statement; and References.
Manuscripts should be arranged in the following order: 1. Title page; 2. Abstract and keywords; 3. main text; 4. Acknowledgements, Funding, Author Contributions, Conflict of interest statements; 5. tables together with any accompanying legends; 6. figure legends; 7. other as required. Each of the numbered items should begin on a separate page.

Title page

The first page should include:

1. The title of the manuscript in sentence case. No abbreviations other than gene names or in common use
2. Full names of all authors and ORCID ID (https://orcid.org/) if desired
3. Affiliations of the authors; use numbers not symbols
4. If authors make an equal contribution, indicated with an asterisk (up to 2 authors, including the first author) and a note indicating this under the author names
5. Name, full postal address, including street number and name, and e-mail address of the corresponding author(s)
6. Key words (no more than five key words). Refer to Medical Subject Headings in MeSH or Index Medicus
7. Running title preceded by the first author's name (maximum 120 characters with spaces, including the author's name).

Title

The title should describe the content of the article briefly but clearly and is important for search purposes by third-party services. Do not use the same main title with numbered minor titles, even for a series of papers by the same authors. Do not use abbreviations in the title, except those used generally in related fields.

Footnotes

Footnotes, if any, should be typed in a separate sheet (the second page of the manuscript). Abbreviations should also be listed on this page.

Abbreviations

Each abbreviation should be defined in parentheses together with its non-abbreviated term when it first appears in the text (except in the Title and Abstract).

Units

SI or SI-derived units should be used. More information on SI units is available at the Bureau International des Poids et Mesures (BIPM) website (https://www.bipm.org/en/home).

Abstract

The second (and, if necessary, the third) page of the manuscript should contain only the abstract (maximum 250 words). The abstract must be fully comprehensible without reference to the text. Abstracts should be divided into sections as follows:

1. Objectives
2. Materials (or "Design")
3. Methods (or "Interventions")
4. Results
5. Conclusions

Introduction

The Introduction should provide sufficient background information to allow the reader to understand the purpose of the investigation and its relationship with other research in related fields, although it should not include an extensive review of the literature.

Materials and Methods

The description of the methods should be brief, but it must include sufficient details to allow the experiments to be repeated. The sources of unusual chemicals, animals, microbial strains or equipment should be described, and the location (city, country) of the company should be provided in parentheses. If hazardous materials or dangerous procedures are used in the experiments and the precautions related to their handling are not widely recognized, it is recommended that the authors provide the necessary details.

Results

This section includes the results of the experiments. The Results and Discussion sections may be combined if this helps readers to understand and evaluate the study. Tables and figures, including photographs, can be used to present the experimental results (see below). Excessive explanations of the data presented in tables and figures should be avoided.

Discussion

The Conclusion or Discussion should be concise and should deal with the interpretation of the results. Novel models or hypotheses may be proposed in this section only if they are suggested by the results obtained in the experiments. Do not repeat the description of the experimental results in this section.

Acknowledgments

Contributors who do not meet the criteria for authorship should be listed in the Acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, or a department chair who provided only general support. If you do not have anyone to acknowledge, please write "Not applicable" in this section.

Funding

All articles should have a funding acknowledgement statement included in the manuscript in the form of a sentence under a separate heading entitled "Funding" directly after Acknowledgements section, if applicable. The funding agency should be written out in full, followed by the grant number in brackets. Multiple grant numbers should be separated by commas and spaces. Where the research was supported by more than one agency, the different agencies

should be separated by semicolon, with "and" before the final funder. If the research is not funded by a specific project grant, please state in the manuscript as follows: "The author(s) received no financial support for the research" or "No funding was received".

Author contributions

The individual contributions of authors to the manuscript should be specified in this section after Funding section. Please use initials to refer to each author's contribution in this section, for example: "AU analyzed and interpreted the patient data regarding the hematological disease. KT performed the histological examination of the liver, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

Conflicts of interest statement

All manuscripts must include a "Conflicts of Interest statement" in line with the 'Author competing interests and conflicts of interest' section above. If no conflicts exist, please state that "The Author(s) declare(s) that there are no conflicts of interest". If the Editorial Board member(s) of JMJ is (are) included as author(s) of the manuscript, please state that "AUTHOR (the name of the member), one of the Editorial Board members of JMJ was not involved in the peer review or decision-making process for this paper.

References

References, including those given in tables and figure legends, should be numbered sequentially in the order they appear in the text and listed in numerical order at the end of the manuscript under the heading "References". Including AI-generated material as the primary source in the reference is not allowed. In the text, citations should be indicated as superscript numbers with an end parenthesis character following each citation number. Three or more consecutive citations should be indicated as a range using a hyphen, e.g. "3-5)". Journal titles should be abbreviated as shown in Index Medicus and List of Journals Indexed. When there are six or fewer authors, all should be listed; when there are seven or more, include only the first three and add "et al." Please note the following examples.

Example citation list entries:

Journal article

1) You WC, Blot WJ, Li JY, et al: Precancerous gastric lesions in a population at high risk of stomach cancer. Cancer Res, 1993; 53: 1317- 1321.

Book

2) Matsumoto A, Arai Y: Hypothalamus. In: Matsumoto A, Ishii S, eds. Atlas of Endocrine Organs. Berlin: Springer-Verlag, 1992: 25-38.

Tables

Tables with suitable titles and numbered with Arabic numerals should be placed at the end of the text on separate sheets (one table per page). They should be understandable without referring to the text. Column headings should be kept as brief as possible, with units for numerical information included in parentheses. Footnotes should be labeled a), b), c), etc. and typed on the same page as the table they refer to.

Figures

Figures should also be submitted online as separate files. They should be numbered in order of appearance with Arabic numerals (e. g. Fig. 1, Fig. 2). Author(s) must pay printing costs for color photographs. Electron micrographs should contain a scale. Individual figures may not exceed the size of a Journal page. Graphs or drawings containing typewritten characters are unacceptable. Numbers, letters and symbols must be large enough to be legible after reduction. In principle, figures should be suitable for publication, and jpg digital files preferred. Each figure must have an accompanying legend, which should be understandable without reference to the text. All figure legends are to be double spaced, and should be collected together as text page(s), rather than being attached to their respective figures.

Cover letter

Summarize briefly the important points of the submitted work including a brief description of the study to be submitted, that it is an original study presenting novel work, that it has not been previously submitted to or accepted by any other journal, that is has been approved by all authors, and explain whether any author has a conflict of interest.

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Manuscripts that are accepted for publication are copy-edited and typeset by the journal's production team before publication. The journal is published 6 times per year / continuously online. All communication regarding accepted manuscripts is with the corresponding author.

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Page proofs are sent to the corresponding author, who should check and return them within 48 hours. Only essential corrections to typesetting errors or omissions are accepted; excessive changes are not permitted at the proofing stage.

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Juntendo Medical Journal Editorial Board (Revised February 1, 2024)

編 集 後 記

人生において大切なこと

「人生は敗者復活戦　負けたときこそ人間の価値が出る」 これは、昨年の第105回全国高等学校野球選手権記念大会における慶応高校との決勝戦のあとに仙台育英高校野球部、須江監督が言われた言葉です。須江監督は現役時代補欠でしたが、その経験をもとに、監督就任後は個々の選手の良い点を見抜き、選手としてだけでなく、人間としても育て上げました。長い人生において順風満帆の人はほとんどいません。「失敗が人間を成長させる」これは世界の「ホンダ」の創始者、本田宗一郎の言葉です。この言葉がなぜ心に響くのでしょうか。それは実体験に基づいた心からの声だからかもしれません。試練が多ければ多いほど人間を成長させてくれます。壁にぶち当たったことがない人間は、他人の悩みや気持ちが理解できない。天才と言われる超一流選手が必ずしも監督として成功しないことがあるのはそれが理由ともいわれます。

二つ目は、ミッション、ビジョンを仲間、組織と共有することです。孤独、孤立はミッションの達成を遅らせますが、共有、共感、相談は達成を早め、人を成長させます。本田宗一郎は言っています。「自分の力のなさを自覚し、知恵や力を貸してくれる他人の存在を知るのは良い経験である」。順天堂大学の附属病院では7,500人を超える新型コロナウイルス感染症の入院患者を受け入れてきました。この数は日本の大学病院の中で最多であり、順天堂の学是、理念に基づくミッションを共有、発信し、使命を果たした成果といえましょう。順天堂人として誇りに思います。

さらに重要なことは、医学会、医療界において、井の中の蛙にならないことです。順天堂大学や、日本で通用した常識は世界では通じないことが多々あります。これからの時代に一番求められることは世界水準を理解し、多様性への理解を推進することと考えます。Juntendo Medical Journalを始めとする医学雑誌は、自分の研究成果を世界に発信するだけでなく、各自の研究の立ち位置を考察することができ、研究の質を高めることができます。医学雑誌はこのような重要な使命を担っているといえましょう。これら三つを実践することで各自の人生が豊かになると信じます。

髙橋　和久

呼吸器内科主任教授、順天堂医院院長

イラスト作者より

教室で教えている生徒さんが、モチーフにと持ってきて下さったとうもろこし二つとも、型も色もすごくおもしろいので、墨と色鉛筆でそれぞれ描き分けたらどうなるかなと思い、試してみました。思いのほかユニークな出来上がりになりました。（宮道明子）

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抄　録

順天堂醫事雑誌
2024. 70(1), 98

身体的フレイルや入院関連能力低下を予防するための自宅でできるリハビリテーションプログラム

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本稿は 2023 年 6 月 17 日に開催された第 51 回都民公開講座の内容をまとめたものである．身体的フレイルを予防し，入院関連能力低下（Hospitalization-Associated Disability）を克服するために，自宅で実施可能な運動ベースのリハビリテーションプログラムについてまとめている．

健康を維持し，介護の必要性を回避するためには，日々の健康管理と運動が重要である．しかし，定期的な運動を続けることは容易ではない．そのため，運動は効率的に行う必要がある．

近年注目されているフレイルは ADL に影響を及ぼすだけでなく，動脈硬化性疾患の発症や再入院など予後にも強く影響する．また，高齢患者はわずかな安静でも身体機能が著しく低下し，退院後の日常生活に支障をきたすことが少なくない．近年，入院前の運動機能に戻れないことを入院関連能力低下（Hospitalization-Associated Disability）と定義された．より短い入院期間で効率よく回復するためには，最適な運動プログラムを検討する必要がある．

この展望論文では，身体的フレイルを予防することの重要性と，フレイル高齢患者の入院関連能力低下を最小限に抑えるために実施できる具体的なアプローチ，特にレジスタンストレーニングと有酸素運動の運動ベースのリハビリテーションプログラムについて，また遠隔リハビリテーションの現状について述べた．

キーワード：身体的フレイル，自宅でできる運動，入院関連能力低下，遠隔リハビリテーション，都民公開講座

この抄録は，順天堂醫事雑誌 70 巻 1 号，p2-8，2024 掲載の『Home Based Exercise Rehabilitation Programs to Prevent Physical Frailty and Hospitalization-Associated Disability』の和文抄録です．

抄　録

順天堂醫事雑誌
2024. 70(1), 99

認知症予防のために知っておきたい栄養・運動・認知リハビリテーション

高　倉　朋　和[1, 2)]

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認知症は，21 世紀の医療と社会的ケアにおける最も重大な世界的課題のひとつである．患者本人のみならず，その家族，介護者，社会全般に大きく影響を及ぼし，身体的，心理的，社会経済的な影響を引き起こす．日本の 65 歳以上の認知症患者数は 2020 年の時点で約 600 万人とされ，さらに 2025 年には約 700 万人に増加すると予測されており，高齢者の 5 人に 1 人は認知症という時代が目前に迫っている．認知症発症・進行を予防するためには，リスクを正しく理解し，健康的なライフスタイルを送ることが重要である．Livingston は認知症発症につながる 12 の修正可能なリスクとして，運動不足，喫煙，過度の飲酒，大気汚染，頭部外傷，社会的孤立，乏しい教育歴，肥満，高血圧，糖尿病，うつ病，難聴を挙げている．これらのリスクを減らすには，ライフスタイルを見直し，個人の人生のなるべく早い段階から活動的で健康的な生活を送ることが重要である．地中海食は，その多様性，オメガ 3 脂肪酸やビタミンの豊富さ等から，認知症予防のための食習慣として注目されている．運動は生物学的，行動学的，社会心理学的レベルで認知症を予防することが推測されている．非侵襲的脳刺激法（NIBS）である反復経頭蓋磁気刺激（rTMS）は，認知症進行予防のための認知機能リハビリテーションの手段として期待され，臨床応用に向けた研究が国内外で行われている．本稿では，認知症予防に関する栄養，運動，認知リハビリテーションについて概説する．

キーワード：認知症，栄養，運動，認知リハビリテーション，反復経頭蓋磁気刺激

この抄録は，順天堂醫事雑誌 70 巻 1 号，p9–22，2024 掲載の『Nutrition, Exercise, and Cognitive Rehabilitation for Dementia Prevention』の和文抄録です．

抄　録

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敗血症におけるグリコカリクス保護に注目した治療戦略

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グリコカリクスは血管内皮細胞の表面を覆っている層であり，プロテオグリカン，グリコサミノグリカン，及びそれらに含まれる血漿蛋白質などによって構成されている．この複雑な構造物は血管内腔の抗血栓性，血管透過性，血管トーヌス，白血球や血小板の接着などの調節において重要な役割を担っていることが知られている．しかしながら極めて脆弱な構造物であるため，敗血症においては容易に障害され，敗血症や敗血症性ショックに対する治療によって，さらに破壊が進行していく．したがって敗血症においてはグリコカリクス障害を意識した治療を実施することが重要である．

キーワード：グリコカリクス，血管内皮細胞，敗血症，ショック，抗凝固療法，シンデカン

この抄録は，順天堂醫事雑誌 70 巻 1 号，p23–25，2024 掲載の『Endothelial Glycocalyx Protection in Sepsis』の和文抄録です．

抄　録

順天堂醫事雑誌
2024. 70(1), 101

敗血症性播種性血管内凝固における臓器障害の発生機序

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敗血症においてはしばしば播種性血管内凝固（DIC）や多臓器障害の合併がみられる．この際，DIC は単なる敗血症の合併症ではなく，多臓器障害の原因にもなっていることを知っておく必要がある．DIC において生じる微小血管内の血栓は組織循環を障害し，多臓器不全を招くことになる．活性化好中球と血小板とのインターアクション，血管内皮細胞障害，凝固線溶のアンバランスが敗血症性 DIC の際の thromboinflammation の本態である．前述の現象は敗血症性急性腎障害において顕著にみられ，急性腎障害の合併は敗血症の転帰に強く関連していることが知られている．敗血症の管理においては，このような臓器障害の発生機序を理解しておくことが重要である．

キーワード：敗血症，播種性血管内凝固，急性腎障害，血栓症

この抄録は，順天堂醫事雑誌 70 巻 1 号，p26-28，2024 掲載の『Organ Dysfunction in Sepsis-associated Intravascular Coagulation』の和文抄録です．

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順 天 堂 医 学 会
会長　服部　信孝

順天堂医学会短期海外留学時助成金給付制度

順天堂医学会では短期海外留学時助成金給付制度を開始いたしました。

1. 要件

下記すべての要件を満たす者

(1) 順天堂大学（大学院を含む）の学生で 1 か月以上 12 か月未満の海外留学をする者
(2) 留学先の研究機関または財団などからの援助がない者
(3) 医学会の正会員として 1 年以上の経歴を有し、医学会費を完納している者

2. 申請書類

(1) 順天堂医学会短期海外留学時助成金申込書
(2) 所属長の推薦書
(3) 申請者の主な研究テーマ・研究業績
(4) 留学受け入れ機関の指導者からの推薦状

3. 助成金の給付金額

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4 か月以上 7 か月未満	20 万円
7 か月以上 12 か月未満	30 万円

4. 申請スケジュール（年 2 回）

申請期限	助成決定時期
6 月末	8 月
12 月末	2 月

5. 選考機関：順天堂医学会短期海外留学時助成金選考委員会

6. 助成後の義務

(1) 帰国後直近の順天堂医学会学術集会において研究成果の発表および、その内容を「順天堂醫事雑誌」に報告する。
(2) 帰国後は、順天堂大学またはその関連機関に原則として 3 年以上勤務する。

7. 本件の照会先

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