Interval Walking Training Can Increase Physical Fitness in Middle-Aged and Older People

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No long-term exercise training regimen with high adherence and effectiveness for middle-aged and older individuals is currently broadly available in the field. To address this problem, we developed an exercise training system comprising interval walking training and an information technology network that requires only minimal staff support. We hypothesized that our training system could increase physical fitness in older people.

Key Words: aging, exercise training, genetics, lifestyle-related disease, remotely supervised system, vasopressin

Key Points
- Exercise training throughout the lifespan is important for preventing deterioration of physical fitness with aging and lifestyle-related diseases; however, no long-term exercise training regimen with high adherence and effectiveness in middle-aged and older individuals is broadly available in the field.
- We have developed a training system comprising interval walking training (IWT) and an information technology network that could increase physical fitness and decrease lifestyle-related risk factors over a long duration.
- Because the IWT program is a consistent and simple intervention throughout the training period, we successfully evaluated factors affecting the adherence to and effects of the IWT program, such as gene polymorphisms and macronutrient supplementation.
- By incorporating factors that enhance program adherence and effectiveness into the system, the IWT program can be used by a larger number of people throughout their lifetime.

INTRODUCTION

Exercise training is one of the most effective strategies for decreasing the likelihood of age- and lifestyle-related diseases (LSD), thereby promoting independence and enhancing the quality of life in the rapidly growing elderly populations of many countries (4,15). However, long-term exercise training programs that guarantee relatively high compliance and effectiveness are not widely available for middle-aged and older individuals.

To develop such a training program, in 1997, we implemented the “Jukunen Taiikudaigaku Project,” a health promotion program for people older than 40 yr. Because walking 10,000 steps per day is thought to protect against disability and LSD, and has been widely recommended for middle-aged and older people, we conducted a walking program for the participants from 1997 to 2001. However, the participants walked only approximately 6000 steps per day during this intervention. Furthermore, even in subjects who performed the training as instructed, there was no marked increase in peak aerobic capacity (VO2peak) or other markers of physical fitness (37).

Recent guidelines suggest that to achieve the desired effects, an exercise program should be tailored to an individual’s fitness level (1), and in most cases, individualized training is performed using exercise equipment, stationary bicycles, and treadmills at a gymnasium or related facility where the exercise intensity can be monitored. However, these training programs are costly and limit adherence to training programs (12,29). To solve these problems, we recently developed a broadly available, remotely supervised exercise training system for middle-aged and older individuals (29). In this article, we address the novel hypothesis that our exercise training system, comprising interval walking training (IWT) and an information technology (IT) network, could increase physical fitness in a large population of middle-aged and older people (Fig. 1). We also address the possible mechanism by which factors affect exercise adherence using animal models, the effects of IWT and nutritional supplementation, and possible applications of IWT to rehabilitation medicine.

DESCRIPTION OF THE IWT SYSTEM

Our exercise training system for the elderly has the following three features: 1) IWT, 2) the use of a portable calorimeter,
and 3) an e-health link (Fig. 2). Using these components, we have accumulated a database regarding the effects of 5 months of IWT on physical fitness and LSD indices in 6400 subjects, with health care cost as a consideration. Moreover, we have accumulated a DNA database from 2200 subjects to examine whether genetic variance causes any interindividual variation in the response to training.

Walking Protocol

Before starting training, individual \( \dot{V}O_2 \)peak for walking was determined by having each subject walk at subjectively slow, moderate, and fast speeds for 3 min each. At the same time, energy expenditure was measured by triaxial accelerometry (JD Mate; Kissei Comtec, Matsumoto, Japan) (41). To assess the precision of this method, we confirmed that \( \dot{V}O_2 \)peak values (mL·min\(^{-1}\)) measured by accelerometry in the graded walking exercise highly were correlated with \( \dot{V}O_2 \)peak values measured by respiratory gas analysis in a graded cycling exercise test (\( R^2 = 0.83, P < 0.0001 \)). Furthermore, the regression coefficient was close to unity in middle-aged and older men and women (n = 278) and within ±15 mL·min\(^{-1}\) of the 95% confidence limit over the range of variation in \( \dot{V}O_2 \)peak values (28). Thus, we successfully determined \( \dot{V}O_2 \)peak via the graded walking test, which is necessary to provide an exercise prescription tailored to an individual’s fitness level without going to a gymnasium and to detect any significant increases in \( \dot{V}O_2 \)peak after training.

The IWT protocol instructed participants to repeat 5 sets or more of 3 min of low-intensity walking at approximately 40% of their pretraining \( \dot{V}O_2 \)peak for walking, followed by 3 min of high-intensity walking at 70% or greater their \( \dot{V}O_2 \)peak per day for 4 d·wk\(^{-1}\) or more. Energy expenditure during daily walking at each subject’s favorite time and place was monitored using a triaxial accelerometer (JD Mate) worn on the midclavicular line of the right or left waist. A beeping signal from the device alerted participants when a change of intensity was scheduled, and another sound indicated when the intensity of fast walking had reached the target level. Participants visited a local community office near their homes every 2 wk, and data from the tracking devices were transferred to a central server computer via the Internet. The results were returned to participants, who then received instructions from trainers (Fig. 2).

Participants were instructed to appear at a gymnasium on an assigned day to assess the effects of IWT, typically 5 months after baseline measurements (see “Results of Studies” for further details).

Portable Calorimeter

Many participants requested a new portable calorimeter as the IWT program continued to measure energy expenditure when walking on inclines because Shinshu is a mountainous region of Japan that includes many inclines, and participants were concerned that they could not find a flat area to perform IWT near their homes. We, therefore, developed a new portable calorimeter (JD Mate) to estimate energy expenditure by accelerometry and barometry, even when walking on inclines (41).

First, we measured \( V_2 \) via respiratory gas analysis and vector magnitude (VM, G) from triaxial accelerations in middle-aged
and older men and women who were approximately 63 yr of age. These measurements were made during graded walking on a treadmill with inclines varying from −15% to +15%. We determined a regression equation to estimate VO₂ from VM and theoretical vertical upward speed (Hu, m·min⁻¹) and downward speed (Hd, m·min⁻¹) as follows: \[ \text{VO₂} = 0.044 \times \text{VM} + 1.365 \times \text{Hu} + 0.553 \times \text{Hd}. \]

To validate the precision of this equation, we measured VM and altitude changes using a portable device equipped with a triaxial accelerometer and barometer (JD Mate) during walking on an outdoor hill. We confirmed that the estimated VO₂ from the equation was almost identical to the measured VO₂. Thus, we developed a device for precisely estimating VO₂ while walking, regardless of geography (41). This device enabled participants to perform high-intensity exercise training (≥70%VO₂peak) not only at fast walking on a flat area but also at slow or moderate walking speeds on inclines or stairs.

**e-Health Link**

Another factor limiting the nationwide use of individual exercise prescriptions is personnel cost for the required trainers. To solve this problem, we developed the e-health link named “e-Health Promotion System” (29). As shown in Figure 2, participants in the program visit a local health care institute near their homes, a community office, or a pharmacy every 2 wk to transfer their walking records from the tracking device, JD Mate, to a central server computer via the Internet. The server computer then provides them with a trend graph of their records along with advice automatically generated by the server. Based on this report, the staff, nurses, dietitians, or trainers give them individualized training advice. By anonymizing and combining the DNA data stored in a separate offline computer and the clinical data stored in the central server computer, we have begun to explore the genomic variations explaining interindividual variations in training response. The data from the research may be used to revise the e-Health Promotion System to develop an algorithm to predict the effects of IWT on physical fitness and the indices of lifestyle-related diseases (LSD) in individuals with different physical and genetic characteristics. An e-Key is used to limit a person's access to the database (DB).

**RESULTS OF STUDIES**

**Short-Term Effects**

We found that after 5 months of the IWT program, the VO₂peak increased by approximately 10%, and knee extension...
assessed the adherence to and effects of IWT over a 22-month period. Adherence and effectiveness may be achieved in Japan and other countries. The analyses were performed using all initial participants, although not all of them performed IWT throughout the entire training period. Adherence rate across the 22-month period was calculated as the number of walking days completed divided by the total number of walking days prescribed (4 d·wk⁻¹). As a result, adherence over 22 months averaged 70% (n = 696), and it was inversely correlated with a reduction in the LSD score. Figure 3 shows that subjects with the highest adherence to the exercise program exhibited the greatest reduction in the LSD score (see Fig. 3 legend for details of the analysis). Moreover, adherence positively correlated with an increase in VO₂peak. Figure 4 shows that the subjects with the highest adherence to the exercise program exhibited the greatest increase in VO₂peak.

Adherence and Factors Affecting Adherence

We found that adherence to the approximately 5-month and the 22-month IWT programs was comparatively higher than adherence to other previously reported exercise programs that required greater personnel support conducted in a Japanese population (23) and an American population (12,22) and was accompanied by significant improvements in LSD risk factors and physical fitness in middle-aged and older individuals (17).

We speculate that the high adherence to our training system may be explained by the following three reasons. 1) Recognition of progress. Instructions for IWT based on individual walking and health records are returned to each individual by trainers every 2 wk via the Internet. Therefore, participants recognize their increased physical fitness from energy expenditure and time for fast walking because the IWT advances together with their improved health records, which encourages them to continue IWT with the confidence that their efforts are being rewarded. 2) Comparison with others. If a participant recognizes how hard his/her competitor performs IWT, then this knowledge stimulates the competitive spirit. 3) Community-based intervention. If a friend is considering dropping out, other friends in the community encourage him/her, and if a friend performs IWT very hard, other friends admire his/her achievements. Therefore, our training system may fulfill these basic conditions to motivate individuals to continue the training, which is performed at a low cost with minimum requirements of staff support.

This system likely improved adherence rates to the IWT program as a whole, but we found that the adherence rate also exhibited great interindividual variation. Because higher adherence was critical for improvements in LSD risk factors and physical fitness (Figs. 3, 4), we attempted to identify factors that affect interindividual variations in adherence to the long-term IWT program. It has been suggested that sex, physical characteristics, physical activity, and other acquired factors affect adherence (3,35). However, no studies have yet investigated genetic factors affecting adherence. This oversight may be because previously, there were neither uniformly and broadly available exercise training regimens nor systems for precisely tracking daily training achievements. However, the IWT program is remotely and uniformly supervised via the Internet throughout the training period and

...and flexion force increased by 13% and 17%, respectively. Systolic and diastolic pressures decreased by approximately 9 and 5 mm Hg, respectively. In contrast, standard walking training of moderate-intensity continuous walking at approximately 50%VO₂peak for 60 min·d⁻¹, 4 d·wk⁻¹ for 5 months produced only minimal results that were similar to persons who remained sedentary during the same period (28). We also found that the VO₂peak was correlated with isometric knee extension force (R² = 0.49, P < 0.0001), which suggests that thigh muscle strength is a key determinant for the VO₂peak in subjects of this age.

Moreover, using these techniques, we examined the effects of IWT on physical fitness and LSD indices in 246 men and 580 women approximately 65 yr of age (24). The LSD scores before and after IWT were assessed according to the criteria specified in the Japanese government’s health care guidelines (see reference (24) for details of the analysis). A total of 783 subjects completed the IWT program for 4 months (95% of the initial participants). They performed IWT for approximately 60 min·d⁻¹, 4 d·wk⁻¹ for 4 months. The adherence rate was assessed as training days accomplished relative to the target of 4 d·wk⁻¹, and it was 100%. These participants exhibited a 15% increase in their VO₂peak and a 20% decrease in their LSD scores (24). These changes were equivalent to the changes observed using a facility-based training program of the same duration (38). Moreover, a separate study reported that a 6-month IWT increased DNA methylation (inactivation) of the NFKB2 gene, one of the master proinflammatory response genes, which suggests that the improved LSD scores were associated with suppressed chronic inflammation (42).

The IWT program has begun to spread throughout Japan and to other countries because it is a simple training system supported by an IT network. For example, in Rochester, MN, Lalande et al. (14) assessed the effects of IWT on physical fitness in middle-aged individuals. Twenty-six subjects completed the IWT program for 3 months (90% of the initial participants). They performed IWT 34 min·d⁻¹, approximately 4 d·wk⁻¹ for 3 months, which resulted in a 27% increase in VO₂peak and an 8 mm Hg decrease in systolic blood pressure; neither of these indices improved in a sedentary control group. In Copenhagen, Denmark, Karstoft et al. (10) assessed the effects of IWT on physical fitness and glycemic control in type 2 diabetic patients. Twelve subjects with type 2 diabetes completed the IWT program for 4 months (92% of the initial participants). They performed IWT 57 min·d⁻¹, approximately 4 d·wk⁻¹ for 4 months, which resulted in a 16% increase in their VO₂peak, and significant improvements in glycemic control that were assessed using continuous glucose monitoring. Neither of these indices improved in the continuous walking or sedentary control group. These results suggest that IWT with high adherence and effectiveness may be achieved in Japan and other countries.

Long-Term Effects

Exercise training throughout the lifespan is important for preventing deterioration of physical fitness with aging and LSD. However, exercise training studies typically focus on short-term (<6 months) effects; indeed, no study has evaluated the IWT program over a longer time frame. Therefore, we assessed the adherence to and effects of IWT over a 22-month duration, a period longer than that used in our previous studies (24,28), in middle-aged and older men and women (n = 696, ~65 yr of age) (17).
requires minimal staff support, enabling us to identify factors without any bias from a varied training regimen and with less support from staff.

We recently reported that middle-aged and older Japanese men carrying the TT genotype of the rs1042615 single nucleotide polymorphism in the vasopressin receptor 1a gene (AVPR1A) had a significantly higher body mass index (BMI) and diastolic blood pressure than those who did not (16). However, these values decreased to levels comparable with those of men with other genotypes after 5 months of IWT, suggesting that men with the TT genotype may have been physically inactive before IWT (16). In addition, the AVPR1A microsatellite polymorphism RS3 (40) may be linked to lower physical activity in TT men. We therefore assessed whether adherence to the 22-month IWT program was affected by the RS3 and rs1042615 polymorphisms of the AVPR1A in addition to previously reported factors (3,35).

We found that the major determinants of higher adherence were a lower baseline BMI and male sex. In addition to BMI, smoking and the AVPR1A polymorphisms were independent determinants of adherence in men (17). As shown in Figure 5, monthly adherence rates to the exercise program (4 d·wk$^{-1}$) gradually decreased after the first 5 months of IWT in all subjects; however, this effect was enhanced in men carrying the RS3 [one or two 334 alleles] in combination with the TT [TT] of AVPR1A polymorphisms (group 4) compared with other carriers. These results suggested that men carrying the [334 alleles–TT] of AVPR1A polymorphisms exhibited lower adherence to the long-term IWT program (17). Although the detailed mechanism for this finding remains

Figure 3.  A. Adherence to prescribed walking days (APWD) and (B) adherence to prescribed fast walking time (APFWT) over the 22-month training period versus the change in lifestyle-related diseases ($\Delta$LSD) score from baseline to 22 months. First, we calculated the LSD scores based on the Japanese and U.S. health care guidelines (17). We assigned one point when a value met one of the following four criteria: 1) body mass index (BMI) of 25 kg·m$^{-2}$ or greater; 2) systolic blood pressure of 130 mm Hg or higher; 3) triglycerides of 150 mg·dl$^{-1}$ or greater, high-density lipoprotein cholesterol of less than 40 mg·dl$^{-1}$, or low-density lipoprotein cholesterol of 130 mg·dl$^{-1}$ or greater; and 4) blood glucose of 110 mg·dl$^{-1}$ or greater. The maximum total score was 4 points when all criteria were met. Subjects were then pooled according to their $\Delta$LSD score from baseline to 22 months as follows: 1 or higher (men = 30, women = 74), 0 (men = 93, women = 270), −1 (men = 50, women = 128), −2 (men = 19, women = 25), and −3 or lower (men = 4, women = 3). Significant differences in adherence from those with the worst $\Delta$LSD score (21), *P < 0.05 and **P < 0.01. APWD was calculated as the number of walking days completed divided by the total number of walking days prescribed for each month (4 d·wk$^{-1}$), and then these month ratios were summed and averaged over 22 months. APFWT was calculated as the fast walking time completed divided by the total fast walking time prescribed for each month (60 min·wk$^{-1}$), but time in excess of 60 min·wk$^{-1}$ was regarded as “100%,” and then these month ratios were summed and averaged over 22 months. (Reprinted from (17). Copyright © 2015 The American Physiological Society. Used with permission.)

Figure 4. A. Adherence to prescribed walking days (APWD) and (B) adherence to prescribed fast walking time (APFWT) over the 22-month training period versus the change in VO$_{2peak}$ ($\Delta$VO$_{2peak}$) for walking from baseline to 22 months. Subjects were pooled according to their $\Delta$VO$_{2peak}$: −2.5 or less (men = 8, women = 39), −2.4 to 0 (men = 46, women = 116), 0.1 to 2.5 (men = 52, women = 111), 2.6 to 5.0 (men = 52, women = 135), and greater than 5.0 mL·kg$^{-1}$·min$^{-1}$ (men = 38, women = 99). Significant differences in adherence from those with the lowest $\Delta$VO$_{2peak}$ (≤−2.5 mL·kg$^{-1}$·min$^{-1}$), **P < 0.01 and ***P < 0.001. APWD and APFWT determinations were the same as those described in Figure 3. (Reprinted from (17). Copyright © 2015 The American Physiological Society. Used with permission.)

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unknown, the impaired pressor response at the onset of exercise may be involved, as described subsequently, although this is one of many possibilities.

POSSIBLE MECHANISMS OF LOWER EXERCISE ADHERENCE VIA V1a RECEPTORS: ANIMAL STUDIES

Arterial blood pressure rises at the onset of voluntary exercise, which is likely advantageous for increasing blood flow to contracting muscles and facilitating exercise. Therefore, we speculated that arterial pressure may not increase at the onset of exercise in men carrying the 334 alleles–TT, perhaps due to impaired V1a receptor function.

V1a Receptors and Pressor Response at the Onset of Voluntary Exercise

Arterial pressure regulation is achieved through the baroreflexes. In the cardiovascular center of the medulla, the feedback gain of the baroreflexes is further modulated by signals from higher brain regions (36). Because vasopressin V1a receptors have been reported to be richly expressed in the nucleus tractus solitarii (NTS) of the medulla (13) and to regulate the activity of NTS neurons receiving baroreceptor input (2), we postulated that central vasopressin may play an important role as a neurotransmitter in the pressor response at the onset of voluntary locomotion (21).

In wild-type mice, increased cerebral activity suppressed baroreflex control of heart rate (HR), which was associated with the start of voluntary locomotion with a rapid increase in arterial pressure (Fig. 6, left panel) (20). In contrast, in vasopressin V1a receptor knockout (V1a KO) mice, the probability of locomotion after cerebral activation was reduced, with no suppression of baroreflex control of HR and no increase in arterial pressure (Fig. 6, right panel). Moreover, these findings in V1a KO mice were confirmed after local infusion of the V1a receptor antagonist into the NTS of wild-type mice (21). Therefore, lower exercise adherence in men carrying the 334 alleles–TT of AVPR1A polymorphisms may be associated with impaired pressor response at the onset of exercise, although we need to provide more direct evidence in humans.

EFFECTS OF IWT AND NUTRITIONAL SUPPLEMENTATION

Because the IWT program is a consistent, simple intervention for longer durations that precisely tracks daily walking intensity and energy expenditure, several food companies have used our research field to assess the effects of their products.

Milk Products

It has been reported that inactivity triggers persistent, low-grade, systemic inflammation that is linked to the development of many chronic diseases (8). However, we have reported that approximately 5 months of IWT induced suppression of chronic inflammation, as well as increases in muscle strength (28,42). In addition, we found that IWT and milk protein intake enhanced increases in thigh muscle mass and strength (34); therefore, we assessed whether IWT and milk product intake enhanced suppression of chronic inflammation more than IWT alone (19).

Subjects (~66 yr of age) who had been performing IWT for more than 6 months participated in this study. They randomly were divided into the following three groups: IWT alone (CNT, n = 12) or IWT and a low (n = 12) or high dose (HD, n = 13) of postexercise milk product. IWT achievements were similar among the groups; however, pyrosequencing analysis of whole blood showed that methylation of the NFKB1 and NFKB2 genes after IWT was enhanced more in the HD group than in the CNT group. Genome-wide DNA methylation analysis showed that several inflammation-related genes were hypermethylated in the HD group compared with the CNT group. Moreover, thigh muscle strength increased in the HD group more than in the CNT group. These results suggest that milk product intake during IWT enhanced proinflammatory cytokine gene suppression with increased muscle strength in middle-aged and older individuals (19).

In addition to these protective effects against chronic inflammation, we also found that milk protein intake during exercise training enhanced plasma volume expansion (39), which would facilitate thermoregulatory adaptation (11,32,33) through cardiopulmonary baroreflexes (9,30) to protect against heat illness in older people.

Five-Aminolevulinic Acid

Aging is associated with reduced mitochondrial function. Experimentally, the function of the mitochondrial electron...
transport chain, especially complex IV (cytochrome c oxidase) activity, was reported to decline with aging in human (26) and animal muscles (6). Mitochondrial dysfunction has been suggested not only to decrease exercise efficiency (5) but also to enhance the generation of reactive oxygen species that injure the tissues (6). These changes may evoke chronic inflammatory responses in the body and thereby cause LSD (8). Thus, mitochondrial dysfunction may be one of the key mechanisms limiting daily physical activity and evoking LSD in middle-aged and older individuals (8). In contrast, it has been reported that the oral ingestion of 5-aminolevulinic acid (ALA) increases complex IV activity and raises the adenosine triphosphate production rate in the liver of mice (31). However, no studies have evaluated how ALA affects respiratory response during exercise and the voluntary achievement of exercise training in humans.

A study was conducted using a placebo-controlled, double-blind crossover design (18). All subjects (n = 10, ~65 yr) underwent two trials for 7 d each in which they performed IWT in combination with either an ALA or placebo supplement intake (CNT). Before and after each trial, subjects underwent a graded cycling test. As a result, in the ALA trial, V˙O₂ during graded cycling decreased by 12% at every workload, accompanied by a 16% reduction in plasma lactate concentrations. Furthermore, the training days, training volume, and time at fast walking were all higher in the ALA intake period compared with the CNT intake period. These results suggest that ALA supplementation augmented exercise efficiency and thereby improved IWT achievement in older people (18). Thus, using our research field, we successfully evaluated the effects of IWT and several nutritional supplements.

IWT FOR REHABILITATION

In Japan, exercise training for rehabilitation is performed immediately after orthopedic and other related surgeries under the supervision of medical staff; however, for hospital management reasons, patients can stay in the hospital under financial support from national insurance for up to 2 wk, a period that is too short

Figure 6. Cerebral blood flow (CBF), cross-correlation function (R(t)) between changes in heart rate (ΔHR), changes in mean arterial pressure (ΔMAP), ΔHR/ΔMAP, HR, MAP, and activity counts before and after an increase in the ratio of the θ to δ wave band in electroencephalogram (θ/δ). Means and SE bars are presented for 8 wild-type (WT) and 8 V1a knockout (KO) mice. Because locomotion, when it occurred, started at an average of 12 s after an increase in θ/δ, a time of 12 s after the increase was regarded as “0 s,” and variables were presented in the range of ±240 s from 0 s. Data were derived according to the following two criteria: 1) θ/δ increased to a threshold of 2 SD during the total resting period and 2) the increase was preceded by a greater than 240 s resting period. Red portions indicate significant differences from values at −240 to −200 s. (Reprinted from (21). Copyright © 2013 John Wiley and Sons. Used with permission.)
to recover their muscle strength. Therefore, the development of a home-based exercise training regimen is needed.

**Total Hip Arthroplasty**

Total hip arthroplasty (THA) is a broadly prescribed surgical treatment for patients with advanced arthritic joint disorders. Although THA patients are thought to experience muscle atrophy and weakness for several years after surgery, there were previously no home-based exercise training regimens for preventing these issues. We therefore examined whether IWT could prevent muscle atrophy and aerobic capacity impairment in these patients. We found that all THA patients performed fast walking for an average of greater than 60 min·wk$^{-1}$ during the 12-week training period, leading to increases in muscle strength and aerobic capacity, which were accompanied by a lack of hip pain. Thus, IWT may be an effective home-based training regimen for the rehabilitation of THA patients (25).

**IWT in Water**

It has been reported in Japan that approximately 70% of women and approximately 50% of men older than 65 yr experience knee osteoarthritis. Half of these cases experience difficulty performing exercise training, especially at higher intensities, due to knee pain (27). To address this problem, we developed an IWT regimen in water in which reduced pressure on the knee joints and increased venous return to the heart were expected. We found that walking in water elevated VO$_2$ at the gas exchange threshold and decreased HR at a given exercise intensity in middle-aged and older women. This enabled the subjects to perform exercise at a higher metabolic rate than on land because of improved subjective feelings, which resulted in greater gains in physical fitness for these subjects (7).

**SUMMARY**

We have developed a broadly available, remotely supervised exercise training system for middle-aged and older people. The key observations are as follows: 1) adherence to the program for up to 22 months was high, 2) participation increased physical fitness and decreased LSD risk factors, 3) the high adherence may be explained by the feedback provided to individual participants based on their achievements, 4) genetic factors, such as AVPR1A polymorphisms, affect adherence to the program, which may be associated with impaired pressor responses at the onset of exercise as suggested in the animal studies, 5) the effects of IWT were enhanced by nutritional supplements, 6) our findings were supported by epigenetic as well as clinical evidence, and 7) the IWT program was also applicable to rehabilitation medicine. Thus, our exercise training system, composed of IWT and an IT network, may protect against age-associated declines in physical fitness and LSD over an extended duration. Moreover, by incorporating factors that enhance adherence and effectiveness into the program, the regimen can be used by a larger population throughout their lifespan.

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