

SYMPOSIUM REVIEW

Beyond epidemiology: field studies and the physiology laboratory as the whole world

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There is no exercise training regimen broadly available in the field to increase physical fitness and prevent lifestyle-related diseases in middle-aged and older people. We have developed interval walking training (IWT) repeating five or more sets of 3 min fast walking at $\geq 70\%$ peak aerobic capacity for walking ($w\dot{V}_{O_{2peak}}$) per day with intervening 3 min slow walking at $40\% w\dot{V}_{O_{2peak}}$, for ≥ 4 days week⁻¹, for ≥ 5 months. Moreover, to determine $w\dot{V}_{O_{2peak}}$ in individuals and also to measure their energy expenditure even while incline walking, we have developed a portable calorimeter. Further, to instruct subjects on IWT even if they live remotely from the trainers, we have developed e-Health Promotion System. This transfers individual energy expenditure during IWT stored on the meter to a central server through the internet; it sends back the achievement to individuals along with advice generated automatically by the server according to a database on ≥ 4000 subjects. Where we found that 5 months of IWT increased physical fitness and improved the indices of lifestyle-related diseases by 10–20% on average. Since our system is run at low cost with fewer staff for more subjects, it enables us to develop exercise prescriptions appropriate for individuals.

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Introduction

The rapid growth in the elderly population in many countries has highlighted the importance of exercise training to decrease the likelihood of disability and age-associated diseases. In Japan, the population over 65 years old was 20.8% of the total in 2006 but will increase to over 30.5% by 2025 (National Institute of Population and Social Security Research, 2008). One of the serious problems in the rapid increase in the number of older people is their healthcare cost. In 2006 it was 17.1 trillion JPY (171 billion USD) but is estimated to increase to 56 trillion JPY (560 billion USD) in 2025 (Ministry of Health and Welfare, 1999), equivalent to 63.2% of the annual national budget in 2009.

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Facing this national crisis, in 2008, the Japanese government issued a law to reform the medical system to provide preventive medicine (Health Insurance Bureau, 2007) by which people are obliged to receive a health check for age- and lifestyle-related diseases when they reach 40 years old and, if abnormal results are indicated, they are encouraged to receive nutritional and/or exercise prescriptions at local health care institutions. It is well known that an exercise prescription should conform to individual physical fitness to achieve particular effects (Armstrong *et al.* 2006); however, no guidelines have been provided by the government, possibly because an exercise prescription would cost more than the standard walking training and also because there is little evidence to suggest that exercise prescription for individuals saves more clinical expenditure than the development cost.

To accumulate evidence, we have implemented a health promotion exercise programme for people ≥ 40 years old, named the 'Jukunen Taiikudaigaku Program', since 1997 and developed three exercise training formats for

middle-aged and older people: (1) interval walking training (IWT), (2) use of a portable calorimeter, and (3) the e-Health Promotion System. Using these methods, we have accumulated a database (DB) on the effects of IWT for the indices of age- and lifestyle-related diseases (LSD) in more than 4000 subjects, with healthcare cost as a consideration. Moreover, we have accumulated a DNA database of more than 1400 subjects to examine whether genetic variance causes any inter-individual variation in responses to the training, which could be used to develop an appropriate exercise prescription for individual genetic characteristics in the future.

In this report, we present the recent status and future direction of our research project based on the Jukunen Taiikudaigaku Program.

Interval walking training

Moderately paced walking at $\sim 6 \text{ km h}^{-1}$, thought to protect against disability and age- and lifestyle-related diseases, is widely recommended for middle-aged and older people; however, the pace may not be intense enough to increase peak aerobic capacity ($\dot{V}_{\text{O}_{2\text{peak}}}$) and other markers of physical fitness. Indeed, a higher intensity of aerobic exercise of more than 50% $\dot{V}_{\text{O}_{2\text{peak}}}$ has been recommended in recent guidelines to increase $\dot{V}_{\text{O}_{2\text{peak}}}$ in older people (Armstrong *et al.* 2006). Therefore, in 2003 we started to study the effects of IWT on physical fitness for middle-aged and older people, using repeat fast walking above 70% peak aerobic capacity for walking ($w\dot{V}_{\text{O}_{2\text{peak}}}$) for 3 min with intervening slow walking below 40% $w\dot{V}_{\text{O}_{2\text{peak}}}$ at the target of five sets per day, more than 4 days week^{-1} , for 5 months (Nemoto *et al.* 2007). The reason for adopting 'interval' walking was that most subjects could not accomplish a training regimen of continuous fast walking $\geq 15 \text{ min day}^{-1}$, $\geq 4 \text{ days week}^{-1}$, for 5 months in our preliminary study (unpublished data) and, moreover, that more enhanced aerobic adaptations in shorter training time were expected by high-intensity interval training than by moderate-intensity continuous training as suggested in young subjects (Dausin *et al.* 2007; Helgerud *et al.* 2007; Burgomaster *et al.* 2008).

To determine $w\dot{V}_{\text{O}_{2\text{peak}}}$, after baseline measurements at rest for 3 min, subjects wearing a triaxial accelerometer, as detailed below, on the midclavicular line of the waist, walked on a flat floor at three graded subjective velocities, slow, moderate and fast, for 3 min each while three-dimensional accelerations were measured with the accelerometer (JD Mate; Kissei Comtec, Matsumoto, Japan) and heart rate (HR) with a near infrared ear pickup probe at 20 ms intervals and recorded with 5 s memory as an average value. The total impulse from an accelerometer was transferred to a computer and converted to the oxygen consumption rate. $w\dot{V}_{\text{O}_{2\text{peak}}}$ and peak HR are those for the last 30 s at the

fastest velocity. We confirmed that the peak HR was $\sim 140 \text{ beats min}^{-1}$, almost reaching the age-expected maximal HR, and that $w\dot{V}_{\text{O}_{2\text{peak}}}$ (ml min^{-1} , y) was almost identical to that (x) determined by graded cycle ergometer exercise simultaneously determined for each subject with $y = 0.81x + 247$ ($R^2 = 0.83$, $P < 0.0001$). Thus, we can determine $w\dot{V}_{\text{O}_{2\text{peak}}}$ for many middle-aged and older people simultaneously in the field with no limitation of instruments such as a treadmill and cycle ergometer.

Before the start of IWT, subjects were invited to a community office near their homes and received instruction in the exercise programme for the first 2 weeks. Once subjects had learned the programme, they could choose when to perform it each day. A beeping signal from the device alerted subjects when a change in intensity was scheduled and another beep told them when the walking intensity had reached the target level every minute. Every 2 weeks, subjects visited a local community office, and data from the tracking device were transferred to a central server at the administrative centre through the internet for automatic analysis by the e-Health Promotion System and reporting. The details for this system are described below. Trainers used these reports to track daily walking intensity and other parameters given to instruct subjects on how best to achieve the target levels. If the targets were not met, the trainers encouraged the subjects to increase their efforts to achieve them.

Figures 1 and 2 show the results of a study examining the effects of IWT on physical fitness and blood pressures (Nemoto *et al.* 2007). As in the figures, $w\dot{V}_{\text{O}_{2\text{peak}}}$ increased by $\sim 10\%$ and knee extension and flexion forces increased by 17% and 13%, respectively, while systolic and diastolic pressures decreased by $\sim 10 \text{ mmHg}$ and $\sim 5 \text{ mmHg}$, respectively. On the other hand, the changes were all minimal after standard walking training: moderate intensity continuous walking at 50% $w\dot{V}_{\text{O}_{2\text{peak}}}$ for 60 min day^{-1} , 4 days week^{-1} , for 5 months, which was similar to after sedentary life for the same period. Moreover, we found that $w\dot{V}_{\text{O}_{2\text{peak}}}$ was significantly correlated with isometric knee extension force ($R^2 = 0.49$, $P < 0.0001$), suggesting that thigh muscle strength is a key determinant for $w\dot{V}_{\text{O}_{2\text{peak}}}$ in subjects of this age. Further, these results indicate that increased $w\dot{V}_{\text{O}_{2\text{peak}}}$ was accompanied by a marked reduction in blood pressure.

Although several epidemiological studies have suggested the merits of increased physical fitness to decrease the incidence of LSD including hypertension (Blair *et al.* 1984; Sawada *et al.* 2003; Lee *et al.* 2005), few intervention studies by exercise training have suggested a linkage between increased physical fitness and improved indices of LSD in a large population of middle-aged and older people. This might have been because no exercise training regimens to increase physical fitness have been broadly available for middle-aged and older people without going to a gym at a scheduled time.

Using our methods, we examined the effects of IWT for 4 months in 246 men and 580 women aged ~ 66 years old in 2005 and 2006 (Morikawa *et al.* 2009). They were instructed to repeat the IWT regimen stated above and the intensity was monitored with the accelerometer. During training, 43 subjects quit the programme because of work issues, orthopaedic diseases, family issues, moving house, or other reasons. Thus, since 783 of the 826 sub-

jects accomplished IWT for the scheduled period, the adherence to the programme was 95%, which was much higher than the $\sim 60\%$ previously reported in standard walking training programmes reported by ourselves (Sakai *et al.* 2000; Nemoto *et al.* 2007) and others (Fielding *et al.* 2007).

This higher adherence to the exercise training programme might have been due to the fact that it was matched to individual $w\dot{V}_{O_{2peak}}$ and that instructions for IWT based on individual walking records were passed to individuals by trainers every 2 weeks through the internet. Accordingly, subjects were able to recognize their increased physical fitness from energy expenditure and time for fast walking as IWT advanced, which encouraged them to continue IWT with confidence that their efforts were being rewarded. On the other hand, since the exercise intensity of the standard walking training is generally too low to attain a significant increase in physical fitness (Armstrong *et al.* 2006; Nemoto *et al.* 2007) and also since less frequent feedback instructions are made by trainers, some subjects may have been tired of the training (Sakai *et al.* 2000; Fielding *et al.* 2007).

In addition to the 43 subjects who quit the programme, 117 subjects lacked more than one of the measurements because 45 subjects were absent on the measurement day assigned to them, and the remaining 72 were not tested for more than one of the variables scheduled although they

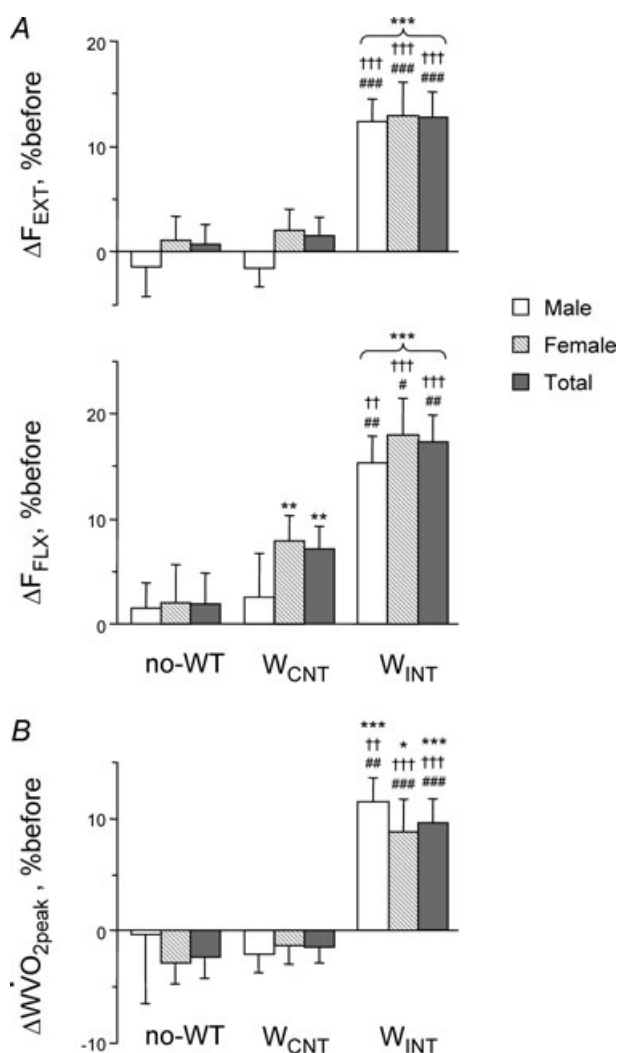


Figure 1. Changes in isometric knee extension and flexion forces and peak aerobic capacity by graded walking exercise ($w\dot{V}_{O_{2peak}}$)

Percentage changes in isometric knee extension (F_{EXT}) and flexion forces (F_{FLX}) (A) and peak aerobic capacity by graded walking exercise ($w\dot{V}_{O_{2peak}}$) (B) after training in 3 groups: no-walking training (no-WT; males = 9, females = 37, total = 46); moderate-intensity continuous walking (W_{CNT} ; males = 8, females = 43, total = 51); high-intensity interval walking (W_{INT} ; males = 11, females = 31, total = 42).

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$: significant differences from the pre-training values. †† $P < 0.01$, ††† $P < 0.001$: significant differences from the corresponding values in no-WT. # $P < 0.05$, ### $P < 0.01$, ### $P < 0.001$: significant differences from the corresponding values in W_{CNT} . From Nemoto *et al.* (2007).

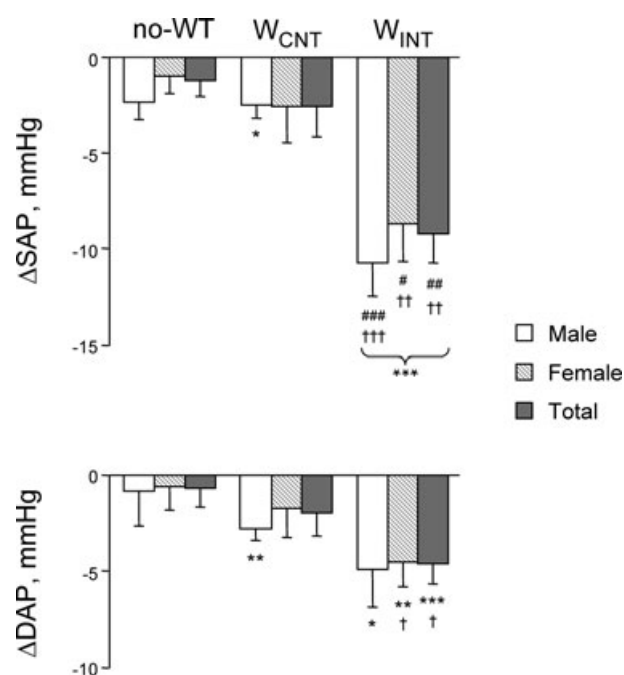


Figure 2. Changes in systolic (SAP) and diastolic (DAP) blood pressures at rest after training

†Significant differences from the corresponding values in no-WT at the levels of $P < 0.05$. The number of subjects and other symbols are the same as in Fig. 1. From Nemoto *et al.* (2007).

Table 1. Baseline measurements before training

	Males (<i>n</i> = 198)	Females (<i>n</i> = 468)
Age (years)	68 ± 6	64 ± 6
Height (cm)	164 ± 6	153 ± 5
Weight (kg)	64.9 ± 9.3	55.5 ± 8.5
BMI (kg m ⁻²)	24.0 ± 2.8	23.6 ± 3.3
SBP (mmHg)	138 ± 17	132 ± 16
DBP (mmHg)	81 ± 11	78 ± 10
TG (mg dl ⁻¹)	117 ± 59	102 ± 50
HDL-C (mg dl ⁻¹)	60 ± 14	69 ± 16
Blood glucose (mg dl ⁻¹)	108 ± 20	104 ± 22
w $\dot{V}_{O_2\text{peak}}$ (ml kg ⁻¹ min ⁻¹)	20.6 ± 4.3	21.5 ± 4.0

Values are means ± s.d. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; w $\dot{V}_{O_2\text{peak}}$, peak aerobic capacity for walking.

accomplished the training for ~4 months. Therefore, after training, we examined the effects of IWT on the indices of LSD in 198 men and 468 women aged ~65 years old after excluding the 160 subjects. The baseline measurements on the remaining 666 subjects are presented in Table 1. They performed IWT, ~60 min day⁻¹, ~4 days week⁻¹, for 4 months on average. We calculated the scores of LSD according to the criteria in the healthcare guidelines for Japanese by the government (Health Insurance Bureau, 2007) before and after IWT. One point was counted when a variable met one of four criteria: (1) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, (2) triglyceride ≥150 mg dl⁻¹ or blood high density lipoprotein cholesterol ≤40 mg dl⁻¹, (3) blood glucose ≥100 mg dl⁻¹, and (4) body mass index (BMI) ≥25 kg m⁻²; therefore, the full score was 4 points when all criteria were met.

Before training, the total LSD score was 2.00 ± 0.08 (S.E.M.) in males and 1.53 ± 0.05 in females but decreased significantly to 1.49 ± 0.08 and 1.21 ± 0.05, respectively (both *P* < 0.05) after training with significant increases in w $\dot{V}_{O_2\text{peak}}$ by 15.0% and 15.8%, respectively (both *P* < 0.05). Moreover, the percentage contribution by the LSD score of each criterion to the total score before training was 38% and 41% for blood pressures, 32% and 33% for blood glucose, 19% and 18% for BMI, and 11% and 10% for blood lipids in males and females, respectively. On the other hand, the percentage contribution by each LSD score to the reduction in the total score was 39% and 38% for blood pressures, 31% and 41% for blood glucose, and 21% and 22% for BMI, in males and females, respectively, while it was minimal in blood lipids for both sexes. These results suggest that increased w $\dot{V}_{O_2\text{peak}}$ was closely associated with decreased blood pressures, blood glucose and BMI while the effects on blood lipids were modest.

As for the population in which we can expect an increase in w $\dot{V}_{O_2\text{peak}}$ by 4 months of IWT, we found

that w $\dot{V}_{O_2\text{peak}}$ before IWT(*x*) was inversely correlated with the increase after IWT(*y*) with regression equations of $y = -0.36x + 10.6$ ($R^2 = 0.21$, *P* < 0.001) in men and $y = -0.27x + 9.31$ ($R^2 = 0.08$, *P* < 0.001) in women, with no significant differences between them (*P* > 0.34), suggesting that the effect of IWT on w $\dot{V}_{O_2\text{peak}}$ was lower in subjects with higher w $\dot{V}_{O_2\text{peak}}$ before training. An *x*-intercept of a regression equation determined on pooled male and female subjects is 32 ml kg⁻¹ min⁻¹, suggesting that an increase in w $\dot{V}_{O_2\text{peak}}$ by 4 months of IWT is expected in people with physical fitness below the w $\dot{V}_{O_2\text{peak}}$.

To investigate the effects of IWT on healthcare costs, we compared clinical expenditure between 166 participants (85 males and 81 females) in the programme with 2353 sedentary people (1205 males and 1148 females) aged ~67 years old who had the National Health Insurance (unpublished data). Before IWT, the healthcare cost per person for the latter 6 months of 2004 was 87 649 JPY (~876 USD) on average in the IWT group, similar to 87 746 JPY in the sedentary group, and for the first 6 months of 2005, it increased to 95 932 and 97 949 JPY, respectively, with no significant difference between groups. However, for the latter 6 months of 2005, the healthcare cost continued to increase to 119 173 JPY in the sedentary group while the IWT group remained unchanged at 96 272 JPY, 22 901 JPY lower than in the sedentary group with significance (*P* < 0.05). Thus, 23.8% of the healthcare cost was saved by performing IWT.

Portable calorimeter

As the IWT program continued, many participants requested a new portable calorimeter to measure energy expenditure precisely even when walking on inclines, because Shinshu is a mountainous region of Japan and has many inclines and participants were concerned that they could not find a flat area to perform IWT near their homes. We therefore developed a device for this purpose (Yamazaki *et al.* 2009).

First, we measured $\dot{V}_{O_2}$ by respiratory gas analysis and vector magnitude (VM, G) from triaxial accelerations in middle-aged and older males and females aged ~63 years old during graded walking on a treadmill while the incline was varied from -15% to +15%. They walked at subjectively slow, moderate and fast speeds on level and uphill inclines and in addition to these, at their fastest speed at 0% incline. Similarly, they then walked on downhill inclines for 3 min each. We determined a regression equation to estimate $\dot{V}_{O_2}$ from VM and theoretical vertical upward speed (Hu, m min⁻¹) and downward speed (Hd, m min⁻¹) for the last 1 min of each trial as:

$$\dot{V}_{O_2} = 0.0044\text{VM} + 1.365\text{Hu} + 0.553\text{Hd}.$$

Second, to validate the precision of the equation, we measured VM and altitude changes with a portable device (JD Mate) equipped with a triaxial accelerometer and a barometer in middle-aged and older subjects walking on an outdoor hill and compared the estimated $\dot{V}_{O_2}$ using the equation stated above with the value simultaneously measured by respiratory gas analysis. The device was 80 mm $\times$ 50 mm $\times$ 21 mm and weighed 82 g. The detection range of the accelerometer was ± 10 G and that of the barometer was 115–1150 hPa. Ninety per cent of the response time of the barometer was within 2 ms after a change in altitude and the maximal precision was 0.06 hPa

or 49 cm at sea level. The device had a 4 megabyte flash memory capable of storing minute-by-minute data for 24 h $\times$ 60 days, a rechargeable lithium ion battery capable of working for 24 h when fully charged, and a USB interface to transfer stored data to an external computer.

We found that the estimated $\dot{V}_{O_2}$ (y) from the equation was almost identical to the measured $\dot{V}_{O_2}$ by respiratory gas analysis while walking on an outdoor hill ($y = 0.97x$, $r = 0.88$, $P < 0.001$), and the mean difference was $-0.20 \text{ ml kg}^{-1} \text{ min}^{-1}$ and 95% prediction limits were $\pm 6.95 \text{ ml kg}^{-1} \text{ min}^{-1}$ over the range of 2.0–33.0 $\text{ml kg}^{-1} \text{ min}^{-1}$ in the Bland–Altman analysis.

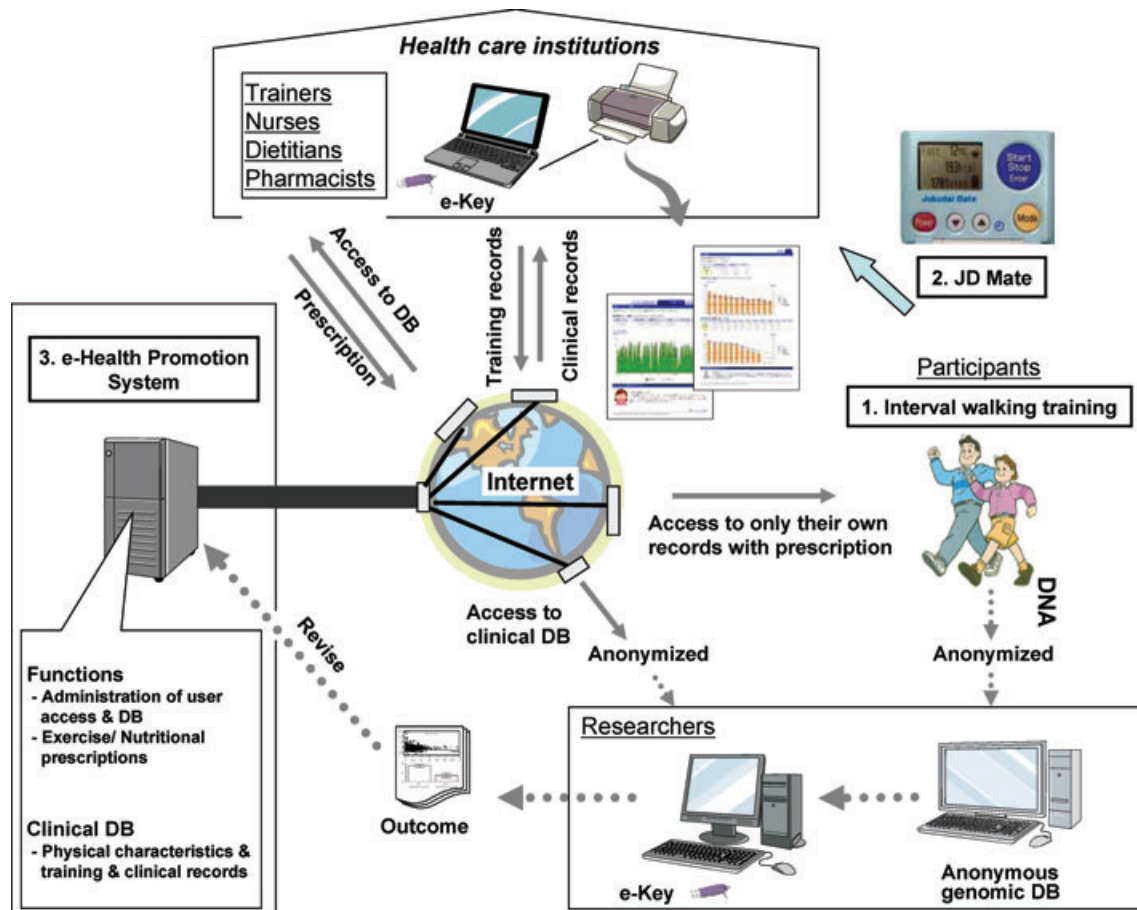


Figure 3. Interval walking training and the e-Health Promotion System

Participants in the training visit a health care institution, a drug store, or a local community office every 2 weeks to transfer their walking records from the tracking device, JD Mate, to a central server computer through the internet. Then, the server computer gives them back a trend graph of the records with advice automatically generated by the server. Based on this, the staff (nurses, dietitians, or trainers) give them their advice. If participants have the facilities at their homes, they can receive the similar service from the staff through the internet. 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 started to search the genomic variation explaining inter-individual variation in response to the training. The outcome from the research may be used to revise the e-Health Promotion System to develop the algorithm to predict the effects of interval walking training on physical fitness and the indices of lifestyle-related diseases in individuals with different physical and genetic characteristics. e-Key is used to limit a person to access the data base (DB). The squares on the circle of internet indicate the fire-wall function. The continuous arrows indicate online communications between users and the sever through internet and the dotted arrows indicate offline communications.

Thus, we developed a device to estimate $\dot{V}_{O_2}$ precisely while walking, regardless of geography. Moreover, subjects can perform high-intensity exercise training $\geq 70\%$ $w\dot{V}_{O_{2peak}}$, not only by fast walking in a flat area but also at slow or moderate walking speed on inclines or stairs.

e-Health Promotion System

Another reason for restricting the nationwide extension of the individual exercise prescription is the personnel cost for trainers. To solve this problem, we have developed the e-Health Promotion System. As in Fig. 3, participants in the programme visit a local health care institute near their home, a local community office or a pharmacy every 2 weeks, transfer their walking records from the JD Mate to a central server, and receive a trend graph of their achievements. According to the records, the staff (nurses, dieticians, pharmacists or trainers) give the participants exercise and nutritional prescriptions while referring to the DB on the server computer regarding the effects of IWT for 5 months on physical fitness and the indices of LSD in ~ 4000 subjects. If participants have computer facilities at their own home, they can receive the same service over the internet.

Moreover, since the IWT regimen is so simple and the training achievement can be expressed as a physical unit, we have been able to analyse individual genomic variance in relation to inter-individual variation in response to IWT in a large population of subjects. Using the database, Mori *et al.* (2009) found that the improvement in plasma low density lipoprotein cholesterol levels by IWT was affected by the single nucleotide polymorphisms in *LRP4* (rs3816614), *SFRP1* (rs7013229) and *SFRP4* (rs1802073). Similarly, Masuki *et al.* (2009) found that the improvements of diastolic blood pressure and plasma low density lipoprotein cholesterol level by IWT were affected by single nucleotide polymorphism of vasopressin V1a receptor (rs1042615).

According to the outcome of these studies, we are developing a computer program to predict the effects of IWT on physical fitness and the indices of LSD according to not only physical but also genetic characteristics of participants before training. If the program becomes available, staff in the field would be able to give participants exercise and nutritional prescriptions more suitable for individuals even though they are not highly specialized. This would increase the number of IWT participants.

In conclusion, the IWT may significantly contribute to exercise prescription fitted to individual physical fitness broadly available in middle-aged and older people by using the JD Mate and the e-Health Promotion System. Moreover, IWT is such a simple exercise intervention that

it would enable us to develop exercise prescriptions more suitable for individuals.

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