The factors affecting adherence to a long-term interval walking training program in middle-aged and older people

Shizue Masuki,1,3 Masayuki Mori,2,3 Yasuharu Tabara,7,9 Akihiro Sakurai,4 Shigenari Hashimoto,5 Mayuko Morikawa,1,6 Ken Miyagawa,1,6 Eri Sumiyoshi,1 Tetsuro Miki,8,9 Keiichi Higuchi,2,3 and Hiroshi Nose,1,3 for the Shinshu University Genetic Research Consortium

1Department of Sports Medical Sciences, Shinshu University Graduate School of Medicine, Matsumoto, Japan; 2Department of Aging Biology, Shinshu University Graduate School of Medicine, Matsumoto, Japan; 3Institute for Biomedical Sciences, Shinshu University, Matsumoto, Japan; 4Department of Medical Genetics, Shinshu University School of Medicine, Matsumoto, Japan; 5Advanced Preventive Medical Center, Shinshu University Hospital, Matsumoto, Japan; 6Jukunen Taiikukagaku Research Center, Matsumoto, Japan; 7Department of Basic Medical Research and Education and 8Department of Geriatric Medicine, Ehime University Graduate School of Medicine, Toon, Japan; and 9Division of Anti-aging Genomics, Ehime Proteo-Medicine Research Center, Toon, Japan.

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Masuki S, Mori M, Tabara Y, Sakurai A, Hashimoto S, Morikawa M, Miyagawa K, Sumiyoshi E, Miki T, Higuchi K, Nose H. The factors affecting adherence to a long-term interval walking training program in middle-aged and older people. J Appl Physiol 118: 595–603, 2015. First published December 24, 2014; doi:10.1152/japplphysiol.00819.2014. —No long-term exercise training regimens with high adherence and effectiveness in middle-aged and older people is broadly available in the field. We assessed the adherence to, and effects of, our long-term training program comprising an interval walking training (IWT) and an information technology network system and the factors affecting adherence. Middle-aged and older men and women [n = 696, aged 65 ± 7(SD) yr] underwent IWT. The subjects were instructed to repeat five or more sets of fast and slow walking for 3 min each at ≥70 and 40% peak aerobic capacity for walking (V̇O₂peak), respectively, per day ≥4 days/wk for 22 mo. Adherence was assessed as training days accomplished relative to the target of 4 days/wk over 22 mo. The effects on the V̇O₂peak and lifestyle-related disease score were evaluated every 6 mo. The independent factors affecting adherence were assessed by multiple-regression analysis after adjustment for baseline physical characteristics and other possible covariates, including vasopressin V₁a receptor polymorphisms. The adherence over 22 mo averaged 70% and was highly correlated with a 13% reduction in the lifestyle-related disease score (R² = 0.94, P = 0.006) and with a 12% increase in V̇O₂peak (R² = 0.94, P = 0.006). The major determinant of higher adherence was lower baseline body mass index (BMI) (P < 0.0001) and male sex (P < 0.0001). For men, in addition to BMI, nonsmokers (P = 0.031) and V₁a receptor polymorphisms (P = 0.033) were independent determinants of higher adherence. Thus the long-term IWT program is an effective regimen. Moreover, baseline BMI and sex for all subjects, and smoking and V₁a receptor polymorphisms for men, were associated with adherence.

exercise training; aging; remotely supervised system; genetics; vasopressin

EXERCISE TRAINING IS ONE OF THE MOST effective strategies for decreasing the likelihood of age- and lifestyle-related diseases (LSD), promoting independence, and enhancing the quality of life in the rapidly growing elderly populations of many coun-
tries (4, 23). However, long-term exercise training programs for middle-aged and older people that guarantee relatively high adherence and effectiveness are not widely available.

It is well known that an exercise prescription should conform to an individual’s fitness level to achieve particular effects (1), and that individualized training is mainly performed at a gymnasium using machines, bicycle, and treadmill while monitoring exercise intensity. These training programs are costly and limit adherence (19, 34). To solve these problems, we recently developed an exercise training system broadly applicable for middle-aged and older people. The system comprises interval walking training (IWT) programed according to individual peak aerobic capacity for walking (V̇O₂peak) and an information technology network system that tracks exercise intensity and energy expenditure during training and provides individual feedback (32, 34, 46). We found that the adherence to IWT for 5 mo was very high, 95%, and was accompanied by an ~15% increase in V̇O₂peak and an ~20% decrease in LSD risk factors (30), equivalent to those observed in facility-based training during the same period (38); however, no study has evaluated the IWT program over a longer time frame. Therefore, our first aim was to assess the adherence and the effects over 22 mo, longer than our laboratory’s previous 5-mo studies (30, 32).

The second aim of this study was to identify factors affecting adherence to the 22-mo IWT program. It has been suggested that adherence decreases as training periods are prolonged, and that sex, physical characteristics, physical activity, and other acquired factors affect adherence (3, 36). However, in previous studies, the training regimen was generally initiated in a supervised facility using training machines for the first several weeks of intervention, followed by voluntary home-based training with the subjects reporting their achievements at a given interval (14, 27). However, this varied training regimen might affect adherence and make it difficult to identify its determinants, including those of genetic origin. On the other hand, the IWT program was remotely supervised via the internet in a uniform fashion throughout the training period with minimum requirement of staff support, enabling us to identify the factors without any bias from a varied training regimen and with less support from staff. In the present study, in addition to the factors reported to influence adherence to
exercise programs, we assessed the contribution of arginine vasopressin receptor 1a gene (AVPR1A) polymorphisms because our laboratory recently obtained the results suggesting that these are associated with physical inactivity in middle-aged and older Japanese men (24).

Based on these aims, we hypothesized that 1) adherence to the long-term, remotely supervised IWT program with minimum requirement for staff support would be as high as other long-term exercise programs reported previously (14, 19, 27, 44) and accompanied by improvements in physical fitness and LSD risk factors equivalent to other exercise programs; and 2) adherence to the 22-mo IWT program would be affected by AVPR1A polymorphisms, as well as previously reported factors (3, 36).

METHODS

Subjects

The study protocol was approved by the Institutional Review Board on Human Experiments, Shinshu University School of Medicine; 696 middle-aged and older adults (196 men, 500 women) gave written, informed consent and were enrolled in the study (Table 1). The subjects were recruited from the participants of a government-supervised IWT program in Matsumoto, Japan. In these subjects, past incidence of the following disorders were hypertension, 27%; dyslipidemia, 19%; and diabetes mellitus, 9%. The proportion of smokers was 12% in men and 1% in women.

Protocol

Physical characteristics, blood pressure, blood lipids and glucose, and \( V_{O2\text{peak}} \) were measured at baseline and during the 5th, 10th, 17th, and 22nd mo of IWT. All measurements, except for \( V_{O2\text{peak}} \), were performed after the subjects fasted overnight.

As reported previously (32), the subjects were invited before training to a community office near their homes and instructed to repeat five or more sets of 3-min low-intensity walking at \( \sim40\% \) of the pretraining \( V_{O2\text{peak}} \) for walking (see below for details), followed by a 3-min high-intensity walking at \( \geq70\% \) but \( <85\% V_{O2\text{peak}}/\text{day} \) for \( \geq4 \) days/wk. Energy expenditure during daily walking at their favorite time and place was monitored with a triaxial accelerometer (Jukudai Mate; Kissei Comtec, Matsumoto, Japan) on the right or left side of the waist in the midclavicular line. A beeping signal alerted the participants when a change of intensity was scheduled, and another signal informed them when their walking intensity reached 70% \( V_{O2\text{peak}} \). Every 2 wk, the subjects visited a local office to download their data and have access to their walking profile.

\( V_{O2\text{peak}} \). We determined \( V_{O2\text{peak}} \) by measuring energy expenditure with the accelerometer during graded intensity walking on a flat floor at a slow, moderate, and fast pace for 3 min, each as reported previously (46). This approach was reported to be in good agreement with a graded cycling test (32).

Body mass index. Body mass index (BMI) was calculated as body weight (kilograms) divided by height (meters) squared.

Blood pressure. Systolic blood pressure and diastolic blood pressure were measured by auscultation after 10 min of sitting in a room at \( \sim25^\circ C \) and \( \sim50\% \) relative humidity. Exercise, caffeine, and smoking were not permitted for more than 30 min before measurement, according to American Heart Association guidelines (8).

Blood samples. Blood samples were collected from the antecubital vein to extract DNA at baseline and to measure blood lipids and glucose at all assessments. Serum concentrations of cholesterol and triglycerides and plasma concentration of glucose were determined using standard enzymatic methods.

Table 1. Subject characteristics before IWT

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>696</td>
<td>196</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>65 ± 7</td>
<td>69 ± 6</td>
<td>63 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>156 ± 7</td>
<td>165 ± 5</td>
<td>153 ± 5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>58.7 ± 9.3</td>
<td>66.3 ± 8.4</td>
<td>55.7 ± 7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>24.0 ± 3.1</td>
<td>24.4 ± 2.6</td>
<td>23.8 ± 3.2</td>
<td>0.018</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>134 ± 16</td>
<td>139 ± 16</td>
<td>132 ± 16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>79 ± 10</td>
<td>81 ± 10</td>
<td>78 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>105 ± 51</td>
<td>110 ± 53</td>
<td>103 ± 50</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>67 ± 16</td>
<td>60 ± 15</td>
<td>70 ± 16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>137 ± 30</td>
<td>128 ± 31</td>
<td>140 ± 30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>106 ± 19</td>
<td>110 ± 16</td>
<td>104 ± 20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LLD score</td>
<td>1.9 ± 1.1</td>
<td>2.1 ± 1.0</td>
<td>1.8 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charlon index</td>
<td>0.28 ± 0.61</td>
<td>0.36 ± 0.64</td>
<td>0.25 ± 0.60</td>
<td>0.037</td>
</tr>
<tr>
<td>( V_{O2\text{peak}} ), ml·kg(^{-1})·min(^{-1})</td>
<td>21.4 ± 4.0</td>
<td>20.3 ± 4.0</td>
<td>21.9 ± 3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR(_{\text{peak}}), beats/min</td>
<td>129 ± 17</td>
<td>123 ± 19</td>
<td>131 ± 15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical activity</td>
<td>1.8 ± 0.7</td>
<td>2.0 ± 0.8</td>
<td>1.7 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Knee or lower back pain, %</td>
<td>26</td>
<td>21</td>
<td>28</td>
<td>0.039</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>4</td>
<td>12</td>
<td>0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CES-D score</td>
<td>7.1 ± 7.3</td>
<td>6.9 ± 7.7</td>
<td>7.2 ± 7.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SD. \( n \), no. of subjects. IWT, interval walking training; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LSD, lifestyle-related diseases; \( V_{O2\text{peak}} \), peak aerobic capacity for walking; HR\(_{\text{peak}}\), peak heart rate; CES-D, Center for Epidemiologic Studies-Depression; NS, nonsignificant. Heart rate was measured with a near infrared ear pickup probe during \( V_{O2\text{peak}} \) determination. \( P \) values are for men vs. women.
Adherence to a Remotely Supervised Walking Program • Masuki S et al.

Psychological variable. As psychological factors might affect training achievements, the subjects were evaluated with the Japanese version of the Center for Epidemiologic Studies-Depression Scale (35, 37). A score of ≥16 may indicate a tendency toward depression.

Medical survey. The subjects were interviewed by medical staff and asked to answer questionnaires mainly on their anamnesis, knee, or lower back pain and their baseline physical activity. Comorbidity level was scored using the Charlson Index (7). Physical activity level was scored as 1 = light, 2 = moderate, or 3 = high, according to physical activity and energy requirement guidelines (29).

Genotype determination. Genomic DNA was extracted from blood samples using the QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany). The AVPR1A single nucleotide polymorphism rs1042615 was analyzed with a TaqMan real-time PCR assay (Applied Biosystems, Foster City, CA) using commercially available primers and probes from the Assay-on-Demand Kit and TaqMan Universal Master Mix (Applied Biosystems). Fluorescence emission from amplicon formation was measured using an ABI PRISM 7900HT Sequence Detection System (Applied Biosystems).

The AVPR1A RS3 microsatellite region (43) was amplified with PCR using the primer pair AVPR1A-RS3-F (5′-GCTATTAGAGATGTAAGTGCT-3′) and AVPR1A-RS3-R (5′-GGCTATATTGGAAGACCTAGATGG-3′). The PCR products were mixed with GeneScan 500 ROX Size Standard (Life Technologies, Grand Island, NY) and run on an ABI PRISM 310 Genetic Analyzer (Life Technologies). The fragment length of the PCR products was determined using the GeneMapper v3.7 Analysis Software (Life Technologies).

Analyses

Adherence rate across the 22-mo period was calculated as the number of walking days completed divided by the total number of walking days prescribed (4 days/wk).

To determine improvements in risk factors for LSD from training (Fig. 1), we calculated LSD scores with reference to Japanese (9) and US (31a) healthcare guidelines, as previously described (30). We added one point when a value met one of the four criteria, as follows: 1) BMI ≥25 kg/m²; 2) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg; 3) triglycerides ≥150 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, or low-density lipoprotein cholesterol ≥130 mg/dl; and 4) glucose ≥110 mg/dl. Therefore, the maximum total score was four points when all criteria were met.

For LSD score and V˙O2peak determinations at 22 mo, we used the last-observation-carried-forward method by replacing missing values with measurements at 17 or 10 mo, if we did not have measurements at 22 mo (12).

Statistics

χ² analysis was used to examine significant frequency differences in dichotomous variables and to confirm agreement with the Hardy-Weinberg equilibrium. The standard least squares method was used to determine the regression equation between adherence rate vs. improvements in LSD score (Fig. 1) and V˙O2peak (Fig. 2).

The independent determinants of exercise adherence were examined using stepwise multiple regression analysis. In the first step, conducted for all subjects, physiological, orthopedic, and psychological variables before training (Table 1) and genetic variables were considered. Because candidate determinants identified by the analysis were BMI, sex, age, followed by smoking and physical activity, these phenotypic variables were retained in the models throughout. However, in the successive step conducted for men and women separately, genetic variables were retained with only P < 0.05 (41), such that the final model retained genetic variables only for men (Table 2). Additionally, as there was significant linkage between RS3 and rs1042615 in the distribution (see Fig. 4), the interaction between RS3 and rs1042615 polymorphisms, in addition to the direct effect of RS3 and rs1042615, were considered in the regression analysis.

One-way [1 within (group)] ANOVA was used to examine significant differences in baseline characteristics between men and women (Table 1). This model was also used to examine significant differences in the adherence rate among subjects divided into five groups according to their improvements in LSD score (Fig. 1) and V˙O2peak (Fig. 2), and to examine significant differences in allele frequency distribution (see Fig. 4). One-way [1 within (time)] ANOVA for repeated measures was used to examine significant differences in the trend changes of the adherence rate. Two-way [1 between (group) × 1 within (time)] ANOVA for repeated measures was used to examine significant differences in the adherence rate between BMI quartile groups (see Fig. 3) and between genotype groups (see Fig. 5) with [group × time] interaction analysis. For these comparisons between genotype groups (see Fig. 5), as the adherence

![Fig. 1. Adherence to prescribe walking days (APWD; A) and fast walking time (APFWT; B) over the 22-mo training period vs. change in lifestyle-related disease score (ΔLSD score) from baseline to 22 mo. Subjects were pooled according to their ΔLSD score: ≥1 (men = 30; women = 74), 0 (men = 93; women = 270), −1 (men = 50; women = 128), −2 (men = 19; women = 25), and less than or equal to −3 (men = 4; women = 5). Values are means ± SE. Significant differences in adherence from those with the worst ΔLSD score (≥1): *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 days/wk), and then these month ratios were summed and averaged over 22 mo. APFWT was calculated as the fast walking time completed divided by the total fast walking time prescribed for each month (60 min/wk), but time in excess of 60 min/wk was regarded as “100%”, and then these month ratios were summed and averaged over 22 mo.](http://jap.physiology.org/Downloadedfromhttp://jap.physiology.org/)
rate was similar between groups G1, G2, and G3 (see below for group definitions), and that in G4 was less than in G1–G3, the response of G1–G3 was combined and compared with that of G4. The statistical power to detect the interactive effect of (group \times time) on the adherence rate was >0.99 at an α of 0.05 (see Figs. 3 and 5).

Post hoc tests subsequent to ANOVA were performed to determine significant differences in the various pairwise comparisons using Fisher’s least significant difference test. P values <0.05 were considered significant. Values are expressed as means ± SE, unless otherwise indicated.

RESULTS

Exercise Adherence vs. Improvements in LSD Score and \( \Delta V\text{O}_2\text{peak} \)

Figure 1 shows adherence to prescribed walking days (APWD, Fig. 1A) and prescribed fast walking time (APFWT, Fig. 1B) over the 22-mo training period vs. change (\( \Delta \)) in LSD score from baseline to 22 mo (\( \Delta \text{LSD score} \)). Both APWD (100% = 4 days/wk) and APFWT (100% = 60 min/wk) varied among the subjects, and they were inversely and significantly correlated with the \( \Delta \text{LSD score} \). As shown in the figure, the subjects with the highest adherence to the exercise program had the greatest reduction in LSD score, whereas the scores of the subjects with the lowest adherence deteriorated. Overall, the IWT program significantly decreased LSD score from baseline to 22 mo by 0.24 ± 0.03 (\( n = 696, P < 0.0001 \)).

Figure 2 shows APWD (A) and APFWT (B) over the 22-mo training period vs. change in \( V\text{O}_2\text{peak} \) from baseline to 22 mo (\( \Delta V\text{O}_2\text{peak} \)). Both APWD and APFWT were positively and significantly correlated with the \( \Delta V\text{O}_2\text{peak} \). As shown in the figure, the subjects with the highest adherence to the exercise program had the greatest increase in \( V\text{O}_2\text{peak} \), whereas \( V\text{O}_2\text{peak} \) fell in the subjects with the lowest adherence. Overall, the IWT program significantly increased \( V\text{O}_2\text{peak} \) from baseline to 22 mo by 2.6 ± 0.1 ml·kg\(^{-1}\)·min\(^{-1} \) (\( n = 696, P < 0.0001 \)). Additionally, when \( V\text{O}_2\text{peak} \) was expressed as milliliters per minute, both APWD and APFWT were also significantly correlated with the \( \Delta V\text{O}_2\text{peak} \) (\( R^2 = 0.94, P = 0.006 \) for APWD; \( R^2 = 0.90, P = 0.014 \) for APFWT). Overall, the IWT program significantly increased \( V\text{O}_2\text{peak} \) from baseline to 22 mo by 123 ± 8 ml/min (\( n = 696, P < 0.0001 \)).

The APWD was highly correlated with APFWT (\( n = 696, R^2 = 0.75, P < 0.0001 \)), and so APWD was used as our main index of adherence to the exercise program. Overall, APWD over 22 mo was 70 ± 1% (\( n = 696 \)). Additionally, fast walking time per walking day over 22 mo was 19.6 ± 0.3 min (\( n = 696 \)), suggesting that subjects performed high-intensity walking at the target level if they started IWT.

Stepwise Regression Analysis of the Association of Acquired and Genetic Factors with Exercise Adherence

To investigate factors independently associated with adherence to the exercise program (4 days/wk), we performed a stepwise multiple regression analysis that considered baseline levels of physical characteristics, comorbidity status, physical fitness, physical activity, orthopedic and psychological factors (Table 1), and AVPRIA polymorphisms. We found that the
The adherence rate was consistent with the Hardy-Weinberg equilibrium ($P = 0.67$–$0.80$) without a significant difference between men and women ($P = 0.53$). Additionally, Fig. 4 shows allele frequency distribution for RS3 in subjects divided into three groups, according to their rs1042615 genotype. The RS3 allele length was significantly shorter in the order of CC, CT, and TT carriers ($P < 0.0001$), but there was no significant difference in distribution between men and women ($P = 0.97$).

To examine the association of AVPR1A polymorphisms with adherence during the training period, we compared the monthly adherence rate over 22 mo after adjustment for baseline BMI and smoking among men (Fig. 5) divided into four groups: G1 (no 334 allele–CC/CT), G2 (one or two 334 alleles–CC/CT), G3 (no 334 allele–TT), and G4 (one or two 334 alleles–TT). As shown in Fig. 5, the decrease in adherence rate with training was greater in G4 than G1–G3. Because the profile of the decrease was similar between G1–G3 ($P = 0.71$), these rates were combined and compared with that of G4. We observed a significant interactive effect of [group (G1–G3 vs. G4) × time] on the adherence rate ($P < 0.0001$), suggesting a significantly greater decrease in G4 than in G1–G3. Indeed, we confirmed the greater decrease in the adherence rate in G4 than in G1–G3 after a period of 8 mo.

In addition to the RS3 334 allele, we also examined the interaction between other RS3 alleles and rs1042615 polymorphism for adherence rate (Table 3). We confirmed that among men with one or two 334 alleles of RS3, TT carriers had markedly lower adherence rate than CC/CT carriers ($P = 0.0001$), followed by sex ($P < 0.0001$) and age ($P = 0.014$) (Table 2, left column).

Accordingly, we compared the monthly adherence rate over the 22-mo training period among the BMI quartiles (Q1–Q4) (Fig. 3), with Q1 representing those with the lowest baseline BMI, and Q4 those with the highest baseline BMI. As shown in Fig. 3, the adherence rate decreased along with training in all subjects, but it was lower in Q4 than Q1 from the beginning of the training period ($P < 0.0001$), despite being similar between Q1–Q3 for the first 10 mo ($P = 0.56$). Thereafter, the adherence rate decreased more in the higher quartiles, resulting in $57, 53, 38,$ and $34\%$ reduction after 22 mo in Q4, Q3, Q2, and Q1, respectively. We confirmed a significant interactive effect of (group × time) on the adherence rate ($P < 0.001$), suggesting a significantly greater decrease in the higher BMI groups than the lower BMI groups.

### Association of Sex and AVPR1A Polymorphisms with Exercise Adherence

Gender was another determinant of adherence rate, i.e., adherence rate was significantly higher in men than women ($80 \pm 3$ vs. $66 \pm 2\%$, $P < 0.0001$). To investigate factors contributing to this difference, multiple regression analysis was performed in men and women separately, while considering four phenotypic factors (BMI, age, smoking, and physical activity) and genetic factors. We found that, in addition to BMI, smoking and the interaction between RS3 and rs1042615 polymorphisms were independent determinants of adherence rate in men but not in women (Table 2, middle and right columns). A possible reason for this sex difference was the larger proportion of smokers in men than women ($12$ vs. $1\%$, $P < 0.0001$), but this would not explain why the association of the genetic factor was only observed in men.

We next looked for differences in genotype frequency between men and women. The genotype frequency for rs1042615 was consistent with the Hardy-Weinberg equilibrium ($P = 0.67$–$0.80$) without a significant difference between men and women ($P = 0.53$). Additionally, Fig. 4 shows allele frequency distribution for RS3 in subjects divided into three groups, according to their rs1042615 genotype. The RS3 allele length was significantly shorter in the order of CC, CT, and TT carriers ($P < 0.0001$), but there was no significant difference in distribution between men and women ($P = 0.97$).

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Gender was another determinant of adherence rate, i.e., adherence rate was significantly higher in men than women ($80 \pm 3$ vs. $66 \pm 2\%$, $P < 0.0001$). To investigate factors contributing to this difference, multiple regression analysis was performed in men and women separately, while considering four phenotypic factors (BMI, age, smoking, and physical activity) and genetic factors. We found that, in addition to BMI, smoking and the interaction between RS3 and rs1042615 polymorphisms were independent determinants of adherence rate in men but not in women (Table 2, middle and right columns). A possible reason for this sex difference was the larger proportion of smokers in men than women ($12$ vs. $1\%$, $P < 0.0001$), but this would not explain why the association of the genetic factor was only observed in men.

We next looked for differences in genotype frequency between men and women. The genotype frequency for rs1042615 was consistent with the Hardy-Weinberg equilibrium ($P = 0.67$–$0.80$) without a significant difference between men and women ($P = 0.53$). Additionally, Fig. 4 shows allele frequency distribution for RS3 in subjects divided into three groups, according to their rs1042615 genotype. The RS3 allele length was significantly shorter in the order of CC, CT, and TT carriers ($P < 0.0001$), but there was no significant difference in distribution between men and women ($P = 0.97$).

To examine the association of AVPR1A polymorphisms with adherence during the training period, we compared the monthly adherence rate over 22 mo after adjustment for baseline BMI and smoking among men (Fig. 5) divided into four groups: G1 (no 334 allele–CC/CT), G2 (one or two 334 alleles–CC/CT), G3 (no 334 allele–TT), and G4 (one or two 334 alleles–TT). As shown in Fig. 5, the decrease in adherence rate with training was greater in G4 than G1–G3. Because the profile of the decrease was similar between G1–G3 ($P = 0.71$), these rates were combined and compared with that of G4. We observed a significant interactive effect of [group (G1–G3 vs. G4) × time] on the adherence rate ($P < 0.0001$), suggesting a significantly greater decrease in G4 than in G1–G3. Indeed, we confirmed the greater decrease in the adherence rate in G4 than in G1–G3 after a period of 8 mo.

In addition to the RS3 334 allele, we also examined the interaction between other RS3 alleles and rs1042615 polymorphism for adherence rate (Table 3). We confirmed that among men with one or two 334 alleles of RS3, TT carriers had markedly lower adherence rate than CC/CT carriers ($P = 0.0001$), followed by sex ($P < 0.0001$) and age ($P = 0.014$) (Table 2, left column).

Accordingly, we compared the monthly adherence rate over the 22-mo training period among the BMI quartiles (Q1–Q4) (Fig. 3), with Q1 representing those with the lowest baseline BMI, and Q4 those with the highest baseline BMI. As shown in Fig. 3, the adherence rate decreased along with training in all subjects, but it was lower in Q4 than Q1 from the beginning of the training period ($P < 0.0001$), despite being similar between Q1–Q3 for the first 10 mo ($P = 0.56$). Thereafter, the adherence rate decreased more in the higher quartiles, resulting in $57, 53, 38,$ and $34\%$ reduction after 22 mo in Q4, Q3, Q2, and Q1, respectively. We confirmed a significant interactive effect of (group × time) on the adherence rate ($P < 0.001$), suggesting a significantly greater decrease in the higher BMI groups than the lower BMI groups.
were independent determinants of adherence for men, but not for women.

**Subjects**

BMI, blood pressure, \( \dot{V}O_{2\text{peak}} \), and physical activity (Table 1) were almost equal to the values previously reported in age-matched Japanese populations (21, 29, 33), as was the incidence of orthopedic and other diseases (31, 33). In addition, the genotype frequency for rs1042615 was consistent with the Hardy-Weinberg equilibrium with no significant difference between men and women. On the other hand, fewer men participated in the IWT program than women, which might be due to the higher employment status of men than women in the age range studied. According to the Japan Statistics Bureau (17), 45–70% of men and 24–40% of women aged 60–69 years are employed, and so men appear to have less time available than women. Thus the characteristics of subjects in this study well reflected this age group of the Japanese population.

**Exercise Adherence vs. Improvements in LSD Risk Factors and Physical Fitness**

In the present study, the adherence rate to IWT program over 22 mo was 70% on average for 696 subjects. This adherence rate was relatively higher than previous long-term exercise interventions performed for 18 mo (14, 27) and 24 mo (19, 44) in smaller populations than in the present study. Moreover, in the present study, the 22-mo IWT program decreased LSD score by 13% and increased \( \dot{V}O_{2\text{peak}} \) by 12%. King et al. (19) reported that 24-mo exercise programs reduced LSD risk factors by 0–8% and increased \( \dot{V}O_{2\text{peak}} \) by 4–9%. On the other hand, Wing et al. (44) reported that a 2% decrease in BMI and a 5% increase in \( \dot{V}O_{2\text{peak}} \) in the first 6 mo of exercise program disappeared during the following 18 mo due to reduced adherence. Thus adherence to the long-term, remotely supervised IWT program achieved by an information technology network system was as high as other previously reported long-term exercise programs (14, 19, 27, 44), accompanied by greater improvements in LSD risk factors and physical fitness (Figs. 1 and 2), despite much lower requirement for staff support than the previous studies (14, 19, 27, 44).

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**Table 3. Adherence rate over 22 mo in men based on RS3 and rs1042615 polymorphisms in AVPR1A**

<table>
<thead>
<tr>
<th>RS3 Allele</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Adherence rate, %</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Overall</td>
<td>196</td>
</tr>
<tr>
<td>320, 326, 328, 330</td>
<td>55</td>
</tr>
<tr>
<td>332</td>
<td>56</td>
</tr>
<tr>
<td>334</td>
<td>76</td>
</tr>
<tr>
<td>336</td>
<td>61</td>
</tr>
<tr>
<td>338, 340, 342, 344, 346, 366</td>
<td>90</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. RS3 and rs1042615 are microsatellite and single nucleotide polymorphism in the AVPR1A, respectively. Adherence rate was calculated as the number of walking days completed divided by the total number of walking days prescribed (4 days/wk) over 22 mo. Data are presented for men carrying one or two copies of each RS3 allele. Rare RS3 alleles (n ≤ 5 in combination with rs1042615 genotype group) were pooled with alleles of similar length to increase power to detect association. *Carriers vs. noncarriers of each RS3 allele. †CC/CT vs. TT in carriers of each RS3 allele.
Factors Influencing Adherence to Long-term Exercise Programs

Previous studies (14, 19, 27) reported that adherence to exercise programs might be influenced by modifying the exercise format and the staff support. Ettinger et al. (14) and Messier et al. (27) initiated 18-mo exercise programs with a facility base for the first 3–4 mo using aerobic training machines, resistance training machines, or a combination of the two under instruction from trainers. This was followed by a home-based program using fewer machines in subsequent months under remote regular telephone instruction from trainers, which resulted in a greater reduction in the adherence rate (14). Furthermore, although King et al. (19) maintained a consistent exercise format under instruction from trainers throughout the 24-mo training period, they markedly reduced staff support after 12 mo, which also resulted in a greater reduction in the adherence rate. In these studies, it was, therefore, unclear how congenital and acquired factors were involved in the decreased adherence, as the regimen was altered during intervention.

In the present study, however, the IWT program was relatively simple and easily mastered by the participants following brief instruction from trainers, which enabled uniform exercise intervention for 22 mo with remote regular instruction from trainers via the internet (34). This system successfully maintained adherence to the training for 22 mo as high as the previous studies (14, 19, 27, 44). In addition, it enabled us to identify factors independently associated with interindividual variation in adherence to exercise training.

As shown in Fig. 3, the adherence rate over 22 mo diminished as the baseline BMI increased. Exercise at a much higher relative intensity during IWT by subjects with higher BMI could account for this relationship, if it hindered adherence to the training regimen. However, our prescribed IWT exercise intensity was calibrated to subjects’ individual physical fitness (≥70% VO_2_peak). Moreover, we recorded exercise intensity per minute during IWT on each walking day for all subjects (46) and found that, during the 22-mo training period, the average fast walking intensity was 14.4 ± 0.3 ml O_2·kg⁻¹·min⁻¹ in Q4, which was significantly lower than the 15.7 ± 0.2 ml O_2·kg⁻¹·min⁻¹ in Q1 (P < 0.001). It is, therefore, unlikely that exercise intensity was too high for the higher BMI subjects to adhere to the training regimen.

On the other hand, higher BMI subjects might not like exercise. Being overweight is reportedly associated with non-participation in high-intensity physical activity as evaluated from 3-day physical activity records (6). Moreover, Ekkekakis and Lind (13) reported that, during 20-min sessions of treadmill exercise at a self-selected or imposed speed, the latter significantly reduced the reported pleasure of overweight but not normal-weight subjects, and suggested that this might diminish the enjoyment of and intrinsic motivation for physical activity, particularly when its intensity is prescribed. Therefore, although the prescribed intensity in the present study was not too high for higher BMI subjects, they might have experienced the IWT as unpleasant, resulting in lower adherence.

In addition to BMI, sex was another determinant of adherence. To investigate factors contributing to this difference, each sex was analyzed separately. We found that smoking and the interaction between RS3 and rs1042615 polymorphisms were independent determinants of adherence rate only in men. Similarly, several studies reported lower adherence in smokers, but the precise mechanisms underlying this effect remain unknown (10, 19).

On the other hand, no studies have investigated genetic factors affecting adherence. We recently suggested that middle-aged and older Japanese men carrying the TT genotype of the single nucleotide polymorphism rs1042615 in AVPR1A had a significantly higher BMI and diastolic blood pressure than those who did not (24). However, these higher values decreased to levels comparable to those of other genotype groups after 5 mo of IWT (24), suggesting that those with the TT genotype might have been physically inactive before starting IWT. Therefore, in the present study, we originally postulated that TT carriers would have lower adherence to the long-term IWT. We did observe an association between TT carriers and lower adherence (Table 3), but this was lost after adjustment for BMI (Table 2), suggesting that the rs1042615 adherence association was epiphenomenon of BMI. On the other hand, the interaction between RS3 and rs1042615 polymorphisms was an independent determinant of adherence rate in men (Table 2). We found that, among men with 334 alleles of RS3, TT carriers had a markedly lower adherence rate even after adjustment for BMI and other covariates (Fig. 5, Table 2).

We excluded the effects of demographic, orthopedic, and psychological factors mentioned above as possible mechanisms behind the greater reduction in adherence rate for men carrying [334 alleles-TT] (3, 19, 36). However, we did not exclude the potential effects of central factors that might facilitate voluntary exercise or any support from family members (36), which would likely affect the adherence rate via AVPR1A variations (11).

Recently, our laboratory reported that motivated locomotion was markedly reduced in male mice genetically deficient in V1a receptors and in control mice whose brains were locally infused by a V1a receptor antagonist, suggesting that central V1a receptors play an important role as neurotransmitters at the onset of voluntary locomotion (25). Additionally, the length of the promoter-region microsatellite polymorphism RS3 was reported to have altered the AVPR1A mRNA level in the brain (16, 39). This in turn might influence human social interactions (2, 11), such as autism (18), social cognition (22), altruism (20), and partner-bonding behavior (43), potentially by altering amygdala activation (28). A specific length of RS3, the 334 allele, is reportedly associated with these human social interactions (18, 28, 43). These results suggest that the lower adherence in [334 alleles-TT] men in this study might be caused by less motivation and/or less social and spousal support for IWT (36, 42), due to reduced central V1a receptor function.

However, the 334 allele was not directly associated with adherence (Tables 2 and 3). Although details of the mechanisms remain unknown, the negative effect on adherence of the 334 allele would be enhanced by the presence of the T allele of rs1042615. These results suggest that the lower adherence to the long-term IWT program in [334 alleles-TT] men was not caused by either modification of exercise regimen or other nonspecific factors but might be caused by behavioral factors, most likely associated with AVPR1A polymorphisms.

Additionally, the LSD score in [334 alleles-TT] men decreased to a level similar to those of the other groups by 5 mo, but the improvement disappeared by 22 mo as the level of
adherence decreased (data not shown). These results suggest that [334 alleles-TT] men might have a predisposition to physical inactivity, closely linked with risk factors for LSD.

In contrast, we observed no genotype-dependent differences in women. Both human and animal studies suggest that behavioral effects of V1a receptors are more prominent in males than females (5, 11, 22, 43, 45). Therefore, the AVPR1A polymorphisms might affect behavioral phenotypes in men more than in women.

Age and Adherence to Exercise Programs

In the present study, age was positively associated with adherence in the analysis conducted for all subjects (Table 2). However, previous studies reported that age was inversely or not associated with adherence in middle-aged and older people (3). On the other hand, Rhodes et al. (36) reported that physical activity tended to increase at retirement (age 60–65 yr), but began to decline a few years later. In the present study, when subjects aged <65 and ≥65 yr were analyzed separately, adherence was positively associated with aging in subjects aged <65 yr (P = 0.010), but was inversely associated in subjects aged ≥65 yr (P = 0.049), resembling the previous observation (36). These results suggest that exercise adherence might be influenced by age but, in combination with employment status, in the age range studied.

Unique Aspects of Japanese

Our study compared adherence among the BMI quartiles in older community dwelling Japanese subjects, who in general are nonobese compared with Western populations. However, Japanese people are reported to have a lower genetically determined capacity for postprandial insulin secretion than Western people, and to be less tolerant of overweight to develop insulin resistance (26). Taken together, the data from the previous (26) and present studies suggest that Japanese subjects with higher BMI are at high risk of LSD and are, therefore, strongly encouraged to increase their adherence to exercise programs to prevent overweight, increase insulin sensitivity, and limit LSD.

Experimental Considerations

Two main experimental considerations deserve additional discussion. First, this study did not include a sedentary control group. An age-related decline in physical fitness of ~4% over 2 yr is reported for middle-aged and older sedentary people (15). On the other hand, in the present study, the 12% average increase in $V_{O2\text{peak}}$ over 22 mo occurred in proportion to adherence to the IWT program. Moreover, Nemoto et al. (32) reported that $V_{O2\text{peak}}$ increased by 9% in middle-aged and older people after 5 mo of IWT, while the control group remained unchanged. These results suggest that the improvements induced by 5 mo of IWT were maintained or further enhanced by 22 mo of IWT. Because we did not include other types of individualized training, such as machine training in a gymnasium, we cannot make definitive comparisons between our and other types of training systems. However, we have demonstrated that a remotely supervised exercise training system enabled middle-aged and older people to perform long-term exercise training effectively without going to a gym.

Second, we estimated $V_{O2\text{peak}}$ with the accelerometer during graded intensity walking. However, because peak heart rate was ~130 beats/min, which is ~25 beats/min lower than the age-predicted maximal heart rate, the $V_{O2\text{peak}}$ estimated in the present study was ~20% lower than the maximal aerobic capacity determined by standard methods, such as treadmill running. However, we used the same method to estimate $V_{O2\text{peak}}$ throughout the IWT period, so it is likely that the increase in $V_{O2\text{peak}}$ appropriately reflected the increase in physical fitness during the study period.

Conclusions

We have developed a broadly available, remotely supervised exercise training system for middle-aged and older people. Using this system, our findings suggest that adherence to the 22-mo IWT program with a minimal requirement of staff support is as high as in previous long-term training studies and is accompanied by greater improvements in LSD risk factors and physical fitness in middle-aged and older people. Moreover, baseline BMI and sex for all subjects, as well as smoking and V1a receptor polymorphisms for men, were independent determinants of adherence to the IWT program.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


