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# Effectiveness of Exercise-Training on Frailty and the Specificity of Exercise Effectiveness on Frailty-Related Indices among Community Dwelling Robust, Pre-Frailty and Frailty Older Peoples

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## Abstract

**Background:** Although several systematic reviews have shown the effects of exercise interventions on frailty, no exercise intervention studies based on cardiopulmonary exercise testing (CPET) have been conducted, and no studies investigated whether robust, pre-frailty and frailty has specificity of effectiveness on frailty related indices with same exercise training (ET).

**Objectives:** The aim of this study is examine the effect of ET based on CPET on physical, cognitive and psychological frailty including with health-related quality of life (HRQOL), and verified whether there are specificity of exercise effectiveness on frailty related indices with same ET among community-dwelling robust, pre-frailty and frailty older adult.

**Methods:** Seventy-three older adult completed ET twice per week over a 6-month period in this cohort study. Frailty-related physical indices included body mass index (BMI), skeletal muscle mass index (SMI), handgrip strength (HGS), Timed Up and Go test (TUG), usual walking speed (UWS), and exercise tolerance (Peak and Anaerobic threshold (AT)). Cognitive and psychological status and HRQOL were also measured. Participants were divided into robust, pre-frailty, and frailty groups according to the Japanese version of the Cardiovascular Health Study criteria.

**Results:** Twenty-four (32.9%) participants were classified as robust, 39 (53.4%) as pre-frailty, and 10 (13.7%) as frailty. Analysis of variance for split-plot factorial design showed improvement in HGS, TUG, UWS, exercise tolerance, cognitive and psychological as main effects of this ET. The interaction (intervention × group) analyses showed significant differences in UWS and AT watts. Post hoc analyses showed improvement of frailty in UWS and pre-frailty and frailty in AT watts, as specificity of ET effectiveness. We found that 89% of robust, pre-frailty, and frailty participants improved or maintained their status with this ET.

**Conclusion:** This study showed exercise training based on CPET is effective for frailty and showed the specificity of exercise effectiveness in pre-frailty and frailty.

**Keywords:** Frailty; Exercise tolerance; Cognitive; Depression; Quality of life; Cardiopulmonary exercise testing; Anaerobic threshold; Mitochondrial function

## Introduction

Frailty is an age-related transitional state of increasing vulnerability to poor health outcomes and reduced functional reserves. People with frailty are also at increased risk for disability, falls, hospitalization, and death [1-3]. The prevalence of frailty in community-dwelling older adults has been reported as 4.0%–59.1%, with an overall average prevalence of frailty of 10.7% [4]. The Obu Study of Health Promotion for the Elderly study reported the prevalence of frailty in Japan was 11.3% [5].

Pre-frailty is a transitional state from robust to frailty, and is more likely to be reversible to a robust state than frailty [6]. However, people with pre-frailty still have higher risks for frailty, functional decline, worsening disability, falls, hospitalization, and death than robust people [2].

Exercise interventions represent an important opportunity to prevent decline and dependence among older adults. Several systematic reviews have examined the effects of exercise interventions in community-dwelling older adults with frailty [7-10]. Most studies investigated strength, balance, coordination, flexibility, and aerobic exercises, which were progressively increased based on individuals' competency and performance. However, no exercise intervention studies based on exercise prescription are available, especially studies examining aerobic exercise based on the results of exercise stress testing. Additionally, no exercise intervention studies investigated whether robust, pre-frailty and frailty has same effectiveness, or each state has specificity of effectiveness on frailty related indices with same exercise training.

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Recently, frailty among people with cardiac disease has received increased attention in cardiology [11]. Exercise-based cardiac rehabilitation (i.e., aerobic exercise based on anaerobic threshold intensity obtained from Cardiopulmonary Exercise Testing (CPET) combined with resistance training) for secondary prevention to reduce cardiovascular risks and events among patients with cardiac disease has been well-established [12]. Exercise-based cardiac rehabilitation for patients with cardiac diseases has been reported to be effective for exercise tolerance [13], physical function [14], cognitive function [15], depression [16], and quality of life [17]. The safety of exercise-based cardiac rehabilitation is also well established [18]. The safety of exercise interventions for frailty among community dwelling adults is particularly important because many frailty older adults have cardiovascular risk [19] as well as risk for falls and fractures. Therefore, exercise-based cardiac rehabilitation is expected to be a safe and effective exercise intervention for older adults with frailty. No studies have examined the effect of aerobic exercise based on the results of CPET, although the effectiveness of exercise training for frailty is well known. Similarly, although pre-frailty and frailty are known transitional states, key factors associated with improved and worsened frailty remain unknown.

This study aimed to investigate the effect of an exercise training based on CPET to improve frailty and frailty-related indices (physical function, exercise tolerance, cognitive function, depression, and quality of life) as first outcome, and investigated whether robust, pre-frailty and frailty has same effectiveness or each state has specificity of effectiveness on frailty-related indices with same exercise training as second outcome, among community-dwelling older adult Japanese outpatients with age-related diseases.

## Materials and Methods

### Participants

Subjects were recruited from community-dwelling older adult outpatients who were advised to exercise from their primary physician at our health promotion center where exercise programs based on the cardiac rehabilitation methods were provided. One hundred and eighty-one people were nominated as subjects of this study. The physicians and the physical therapists belonging to our health promotion center interviewed/ examined them and determined whether they can participate in the health promotion exercise program without meeting exclusion criteria : age < 65 years, impaired vision, impaired hearing, musculoskeletal and joint impairments that might interfered with the ability to perform the symptom-limited exercise tests, a clinically unstable condition (e.g., acute congestive heart failure, unstable angina, unstable cardiac arrhythmia, osteoarthritis, back pain, lumbago, dementia, receiving hemodialysis or home oxygen therapy, and physical symptoms of geriatric syndrome which make them suffer to do exercise such as pain, breathlessness, easily fatigue and etc.) that made exercise difficult. We also excluded older adults who performed habitual exercise training from this study. Habitual exercise training was defined as the performance of repetitive exercise more than three times a week for the purpose of improving or maintaining physical performance, such as aerobic training (e.g., walking, swimming), resistance training, or a combination of these methods (e.g., cycling).

Of all 181 subjects, 15 were under 65 years old, 87 subjects were excluded from this exercise program due to their disease(s), physical characteristics and/or symptom. Three refused to join exercise program and three were drop out. In total, 73 community dwelling older adults (21 men, 52 women) completed in this cohort study. None of the participants were currently hospitalized.

### Cardiopulmonary exercise testing (CPET)

All participants underwent symptom-limited CPET using an upright electromagnetically-braked cycle ergometer (Aerobike Strength Ergo-8, Mitsubishi Electronic, Tokyo, Japan), a metabolic analyzer (Aeromonitor AE-310S, Minato Medical Science, Osaka, Japan), an electrocardiogram (Stress test system ML-9000, Fukuda Denshi, Tokyo, Japan), and automatic-cuff blood pressure manometer (FB-300, Fukuda Denshi, Tokyo, Japan). The symptom-limited CPET protocol and CPET termination criterion were same as we previously described [20]. The anaerobic threshold (AT) was measured by the V-slope method supplemented by additional parameters, including the point of non-linear increase in the ventilatory equivalent for oxygen, respiratory exchange ratio, and end tidal $PO_2$ [21].

### Assessment of cognitive function and depressive symptoms

Cognitive function was assessed with the Japanese version of the Montreal Cognitive Assessment (MoCA-J) [21]. This tool is traditionally used in clinical settings to detect cognitive impairment in older adults with mild cognitive impairment (MCI) or early dementia. MoCA-J scores range from 0–30, with higher scores indicating better cognitive performance. The MoCA-J was selected as the study's main cognitive test because it has greater sensitivity in detecting MCI in community dwelling older adults than the Mini-Mental State Examination [21]. The 15-item Geriatric Depression Scale (GDS 15) was used to evaluate depression [22].

### Evaluation of health-related quality of life (HRQOL)

HRQOL was measured using the Japanese version of the Medical Outcomes Study 8 item Short-Form Survey (SF-8). The SF-8 measures two health categories: physical component scale (PCS) and mental component scale (MCS). Subscale scores range from 0–100, with higher scores signifying better HRQOL [23].

### Criteria for evaluation of pre-frailty and frailty

Frailty and pre-frailty were evaluated with the Japanese version of the Cardiovascular Health Study (J-CHS) criteria [24]. These criteria include five domains: weight loss ("In the last 6 months, have you lost 2–3 kg or more unintentionally?"), slowness (UWS: <1.0 m/s), weakness (grip strength: men <26.0 kg, women <18.0 kg), exhaustion, and low physical activity. Exhaustion was evaluated with the question, "In the last 2 weeks have you felt tired without a reason?" Low physical activity was evaluated with the question, "Do you go out less frequently compared with last year?" according to the Kihon Checklist [25]. Participants with three or more J-CHS score components were considered as the frailty group, those with one or two J-CHS score components as the pre-frailty group, and those with zero J-CHS score components as the robust group.

### Exercise training program

All participants received exercise prescription at the AT intensity obtained by CPET for aerobic exercise training. According to the cardiac rehabilitation program, every exercise session included a warm-up, 30 min of aerobic exercise training with cycling at AT intensity, 15 min of submaximal resistance training (knee extension, hip abduction, rowing, leg press) at 50%–70% of 10 repetitions maximum with each machine, cool down and flexibility exercises. Each class included 16 participants and lasted 75 min. Participants underwent two exercise sessions per week over a 6-month period. All training was performed according to the American Heart Association guidelines [26]. In this

6-month, all participants adjust their aerobic exercise training intensity (i.e., AT) according to the ratings of perceived exertion Borg scales with 13 level [27].

## Laboratory investigations and others

Fasting blood samples and echocardiograph assessment were performed as previously described (20). Items of fasting blood samples were as follows; hemoglobin (Hb), serum albumin (Alb), high-sensitivity C-reactive protein (hs-CRP), hemoglobin A1c (Hb A1c), and B-type natriuretic peptide (BNP) levels.

Skeletal muscle mass index (SMI), body mass index (BMI), handgrip strength (HGS), timed up and go (TUG) test, usual walking speed (UWS) were also measured as we described before (20).

## Statistical analysis

Disease characteristics among the robust, pre-frailty, and frailty groups were compared using Fisher's exact test. Participants' laboratory and physiological data were compared using one-way analysis of variance (ANOVA). Each measured parameter mentioned above before and after the 6-month exercise training program were compared among the three groups using an ANOVA for split-plot factorial design. Post hoc analyses were performed if there were significant differences in major effects in the within-group or interaction analyses. McNemar's tests were performed to compare the robust, pre-frailty, and frailty groups at baseline and after the 6-month exercise training program. All statistical analyses were performed using R Version 2.8.1. The significance level was set at p=0.05 for all tests.

| Variables | All (n=73) | Robust (n=24) | Pre-frailty (n=39) | Frailty (n=10) | p-value |
|---|---|---|---|---|---|
| Hypertension | -29 | 9 | 16 | 4 | 0.565 |
| | +44 | 15 | 23 | 6 | |
| Diabetes mellitus | -62 | 21 | 32 | 9 | 0.749 |
| | +11 | 3 | 7 | 1 | |
| Dyslipidemia | -41 | 17 | 18 | 6 | 0.154 |
| | +32 | 7 | 21 | 4 | |
| Atrial fibrillation | -66 | 20 | 38 | 8 | 0.088 |
| | +7 | 4 | 1 | 2 | |
| Coronary artery disease | -61 | 21 | 33 | 7 | 0.44 |
| | +12 | 3 | 6 | 3 | |
| Chronic heart failure | -70 | 24 | 37 | 9 | 0.366 |
| | +3 | 0 | 2 | 1 | |
| Post-cardiac operation | -68 | 24 | 36 | 8 | 0.104 |
| | +5 | 0 | 3 | 2 | |
| Cerebral infarction | -67 | 24 | 36 | 7 | 0.015 |
| | +6 | 0 | 3 | 3 | |
| COPD | -72 | 24 | 38 | 10 | 0.643 |
| | +1 | 0 | 1 | 0 | |
| Chronic kidney disease | -72 | 24 | 38 | 10 | 0.643 |
| | +1 | 0 | 1 | 0 | |
| Knee osteoarthritis | -70 | 22 | 38 | 10 | 0.417 |
| | +3 | 2 | 1 | 0 | |
| Osteoporosis | -69 | 22 | 37 | 10 | 0.617 |
| | +4 | 2 | 2 | 0 | |
| Cancer | -68 | 23 | 35 | 10 | 0.424 |
| | +5 | 1 | 4 | 0 | |
| Lumbar canal stenosis | -70 | 22 | 38 | 10 | 0.417 |
| | +3 | 2 | 1 | 0 | |
| COPD: Chronic Obstructive Pulmonary Disease. | | | | | |

**Table 1:** Participants' characteristics and comparison of characteristics among the robust, pre-frailty, and frailty groups (Chi-square tests).

| Variables | All (n=73, male 29%) | Robust (n=24, male 21%) | Frailty (n=10, male 30%) |
|---|---|---|---|
| | Mean ± SD Range | Mean ± SD Range | Mean ± SD Range |
| Age, (years) | 75 ± 5(65-88) | 74 ± 5(68-85) | 79 ± 5(70-85) |
| Hb, (g/dl) | 13.1 ± 1.4(6.6-16.5) | 13.2 ± 1.9(6.6-16.5) | 13.1 ± 1.1(11.7-14.9) |
| Alb, (g/dl) | 4 ± 0.3(3.3-4.6) | 4 ± 0.3(3.4-4.4) | 4 ± 0.3(3.5-4.4) |
| hs-CRP, (mg/dl) | 0.1 ± 0.2(0-0.9) | 0.1 ± 0.2(0-0.7) | 0.2 ± 0.3(0-0.8) |
| Hb A1c,(%) | 5.8 ± 0.9(0.7-8.7) | 5.7 ± 1.4(0.7-8.7) | 5.9 ± 0.4(5.2-6.4) |
| BNP, (pg) | 53.6 ± 53.9(4.8-286.8) | 60.2 ± 50.2(12.7-208.7) | 64.9 ± 87.9(4.8-286.8) |
| EF, (%) | 65.9 ± 9.7(31-80) | 67.9 ± 8.6(40.3-78.7) | 63.8 ± 12.6(31-75.8) |
| SV, (ml/bpm) | 64.9 ± 18.3(21.9-106) | 65 ± 19.2(32-106) | 60.6 ± 16.4(36.2-83.3) |
| CO, (L/min) | 4.6 ± 1(2.6-6.8) | 4.6 ± 1.2(2.8-6.8) | 4.4 ± 0.9(3.3-5.7) |
| Hb: hemoglobin, Alb: serum albumin, hs-CRP: high-sensitivity C-reactive protein, BNP: B-type natriuretic peptide, EF: ejection fraction, SV: stroke volume, CO: cardiac output. One-way analysis of variance ($p<0.05$): a: *vs.* robust, b: *vs.* pre-frailty. | | | |

**Table 2:** Comparison of age, laboratory data, and physiological indices among the robust, pre-frailty and frailty groups (one-way analysis of variance).

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## Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology (Authorization Number: 240301), and conformed to the principles outlined in the Declaration of Helsinki. All participants provided written informed consent before data collection.

## Results

Seventy-three participants successfully completed the 6-month exercise program. There were no adverse events due to this 6-month exercise training based on CPET. In total, 24 (32.9%) participants were classified as robust, 39 (53.4%) as pre-frailty, and 10 (13.7%) as frailty. Participants' clinical characteristics of each group are summarized in Table 1. A significant difference was observed for past history of cerebral infarction.

Table 2 shows differences in age, laboratory data, and echocardiograph indices among the three groups. Table 3 shows the results of the ANOVA for split-plot factorial design for before and after the exercise program in three groups. Significant differences were observed in HGS, TUG, UWS, peak $VO_2$, peak METs, peak watts, AT $VO_2$, AT METs, AT watts, MoCA-J, GDS-15 as main effects of the intervention between before and after the program. The within-group analyses among the three groups showed significant differences in TUG, UWS, peak $VO_2$, peak METs, peak watts, MoCA-J, GDS-15 (post-hoc analysis shown in Table 3). The interaction (intervention × group) analyses showed there were significant differences in UWS and AT watts, with the post hoc analyses showing improvement of frailty in UWS and improvement of pre-frailty and frailty in AT watts before and after the exercise program.

Table 4 shows the change in states among the robust, pre-frailty, and frailty groups, from before to after the exercise program. Of the 24 robust participants at baseline, 20 maintained as robust and four declined to the pre-frailty group. Of the 39 pre-frailty participants, 16 improved to robust, 19 maintained as pre-frailty, and four declined to the frailty group. Of the 10 participants in the frailty group, one improved to robust, seven improved to pre-frailty, and two remained in the frailty group (McNemar's test, p<0.05). As a significant difference among robust, pre-frailty, and frailty groups was observed in past history of cerebral infarction (Table 1), a similar analysis was performed after excluding participants with cerebral infarction to avoid the effect of cerebral infarction on changes in states among the three groups. This analysis showed similar results.

| Variables | | Robust (n=24) | Pre-frailty (n=39) | Frailty (n=10) | intervention p | groups p | Post-hoc analysis | Interaction p-value |
|---|---|---|---|---|---|---|---|---|
| BMI (kg/m$^2$) | Before | 233.4 | 23.4 ± 3.4 | 25.6 ± 3.5 | 0.228 | 0.189 | -- | 0.38 |
| | After | 22.8 ± 3.4 | 23.4 ± 3.5 | 25.2 ± 3.9 | | | | |
| SMI (kg/m$^2$) | Before | 6.1 ± 0.8 | 6.1 ± 0.8 | 6.7 ± 0.8 | 0.913 | 0.193 | -- | 0.349 |
| | After | 6.2 ± 0.8 | 6.1 ± 0.8 | 6.6 ± 0.9 | | | | |
| HGS (kg) | Before | 23.3 ± 5.7 | 20.5 ± 6.4 | 18.2 ± 4.1 | 0.032 | 0.056 | -- | 0.972 |
| | After | 24 ± 5.9 | 21.4 ± 6.8 | 19.1 ± 3.8 | | | | |
| TUG (sec) | Before | 6.9 ± 1 | 7.5 ± 2 | 8.7 ± 1.5 | 0.001 | 0.006 | Frailty > Robust, Frailty > Pre-frailty | 0.889 |
| | After | 6.4 ± 0.7 | 7 ± 1.5 | 8.1 ± 1.6 | | | | |
| UWS (m/sec) | Before | 1.2 ± 0.1 | 1.1 ± 0.2a | 0.9 ± 0.1a, b | <0.001 | <0.001 | Robust > Frailty, Robust > Pre-frailty | 0.045 |
| | After | 1.2 ± 0.1 | 1.1 ± 0.2a | 1 ± 0.2a,c | | | Pre-frailty> Frailty | |
| Peak $VO_2$ (ml/min) | Before | 1108 ± 230 | 1026 ± 254 | 886 ± 95 | 0.006 | 0.035 | Robust > Frailty | 0.523 |
| | After | 1216 ± 246 | 1074 ± 309 | 969 ± 120 | | | | |
| Peak METs | Before | 5.6 ± 1 | 5.2 ± 1 | 4.4 ± 0.9 | <0.001 | 0.005 | Robust > Frailty, Robust > Pre-frailty | 0.321 |
| | After | 6.3 ± 1.2 | 5.5 ± 1.2 | 4.9 ± 1 | | | | |
| Peak watts | Before | 90.1 ± 21.4 | 79.8 ± 19.9 | 70.6 ± 13.2 | <0.001 | 0.021 | Robust > Frailty, Robust > Pre-frailty | 0.706 |
| | After | 104.5 ± 23.9 | 90.4 ± 26.8 | 82 ± 10.1 | | | | |
| AT $VO_2$ (ml/min) | Before | 710 ± 171 | 653 ± 178 | 590 ± 96 | 0.007 | 0.349 | -- | 0.148 |
| | After | 732 ± 125 | 674 ± 212 | 709 ± 125 | | | | |
| AT METs | Before | 3.6 ± 0.8 | 3.4 ± 0.7 | 2.9 ± 0.5 | 0.006 | 0.124 | -- | 0.11 |
| | After | 3.8 ± 0.5 | 3.4 ± 0.8 | 3.6 ± 0.6 | | | | |
| AT Watts | Before | 49.8 ± 14.1 | 42.9 ± 12.4 | 35.6 ± 9.7 | 0 | 0.165 | | 0.014 |
| | After | 52.5 ± 11.1 | 47.6 ± 17.5c | 51.9 ± 10.2c | | | | |
| MOCA-J | Before | 25 ± 3.5 | 24.7 ± 2.9 | 20.8 ± 3 | <0.001 | 0.001 | Robust > Frailty, Pre-frailty> Frailty | 0.325 |
| | After | 26.9 ± 2 | 25.9 ± 3.2 | 23.2 ± 3.4 | | | | |
| GDS-15 | Before | 1.4 ± 1.6 | 3.6 ± 3 | 4.2 ± 2.7 | 0.008 | <0.001 | Frailty > Robust, Pre-frailty > Robust | 0.179 |
| | After | 0.7 ± 1 | 2.2 ± 2.3 | 4 ± 4.3 | | | | |
| PCS | Before | 49 ± 5.7 | 46.2 ± 6.4 | 46.8 ± 4.7 | 0.119 | 0.391 | -- | 0.123 |
| | After | 47.9 ± 6 | 48 ± 5.4 | 50.8 ± 3.7 | | | | |
| MCS | Before | 53.3 ± 5.7 | 51.2 ± 7 | 50.9 ± 5.3 | 0.839 | 0.244 | -- | 0.316 |
| | After | 52.9 ± 5.8 | 52.9 ± 6.2 | 48.9 ± 5.7 | | | | |

Post hoc analysis performed using the Scheffe method. BMI: body mass index, SMI: skeletal muscle mass index, HGS: hand grip strength, TUG: Timed Up and Go test, UWS: usual walking speed, VO2: oxygen uptake, METs: metabolic equivalents, AT: anaerobic threshold, MoCA-J: Japanese version of the Montreal Cognitive Assessment, GDS-15: 15 item Geriatric Depression Scale, SF-8: Short-Form Survey 8 Japanese version, PCS: physical component scale, MCS: mental component scale. Significant difference *vs*. robust: a, *vs*. pre-frailty: b, *vs*. before: c

**Table 3:** Comparison of physical, exercise tolerance, cognitive, psychological, and health-related quality of life indices before and after exercise program among the robust, pre-frailty, and frailty groups (analysis of variance for split-plot factorial design).

| Variables | | After 6-month | | | Total |
|---|---|---|---|---|---|
| | | Robust | Pre-frailty | Frailty | |
| Baseline | Robust | 20 | 4 | 0 | 24 |
| | | -3.9 | (-2.97) | (-1.79) | |
| | Pre-frailty | 16 | 19 | 4 | 39 |
| | | (-1.77) | -1.42 | -0.68 | |
| | Frailty | 1 | 7 | 2 | 10 |
| | | (-2.77) | -2 | -1.46 | |
| | Total | 37 | 30 | 6 | 73 |
| $p<0.05$, $\varphi=0.50$ (Adjusted standardized residuals). | | | | | |

**Table 4:** Comparisons of robust, pre-frailty, and frailty states before and after the exercise program (McNemar's test).

## Discussion

Our study used data from consecutive and unselected (i.e., not selected from one specific disease group) older adults who regularly consulted the Tokyo Metropolitan Geriatric Hospital as outpatients with chronic diseases. The prevalence rates of robust, pre-frailty, and frailty in this study were 32.9%, 53.4%, and 13.7%, respectively. A previous study reported prevalence rates of robust, pre-frailty, and frailty of 30.3%, 59.8%, and 9.9% in Japanese men, and 25.3%, 64.7%, and 10.0% in Japanese women, respectively [28]. Therefore, the prevalence of frailty in this study was similar to that in the general population.

This study showed that past history of cerebral infarction was related to frailty (Table 1). As this study used the J-CHS criteria for frailty [24], which are based on a phenotype of physical frailty, it is reasonable to understand why cerebral infarction has a relationship with frailty.

Seventy-three participants successfully completed the 6-month exercise program with no adverse events. This result shows the safety of exercise training based on CPET among community-dwelling older adult outpatients with multiple chronic diseases.

Table 3 showed the effectiveness of the exercise program with exercise prescription based on the results of CPET on frailty-related indices such as HGS, TUG, UWS, peak $VO_2$, peak METs, peak watts, AT $VO_2$, AT METs, AT watts, MoCA-J, GDS-15 as main effects of the intervention between before and after the program, and no effect were seen in BMI, SMI and HRQOL. The within-group analyses among the three groups showed significant differences in TUG, UWS, peak $VO_2$, peak METs, peak watts, MoCA-J, GDS-15 (post-hoc analysis shown in Table 3). Interaction analyses showed significant differences in UWS and AT watts, and post hoc analyses showed improvement of frailty in UWS and improvement of pre-frailty and frailty in AT watts.

These results indicated the effectiveness aerobic exercise based on the results of CPET in these frailty-related indices (except BMI, SMI and HRQOL) without adverse outcome (first outcome of this study), and specificity of effectiveness were seen on UWS in frailty and AT watts in pre-frailty and frailty with same exercise training among robust, pre-frailty and frailty (second outcome of this study).

Interestingly, Table 3 showed AT watts improvement in pre-frailty and frailty after the exercise program, without an increase in SMI. Recently, muscle performance and muscle quality, which relate to mitochondria function, have attracted increased attention [29,30]. The Baltimore Longitudinal Study of Aging defined muscle quality as the ratio of knee-extension strength to thigh muscle cross-sectional area (strength/mass), measured with computed tomography [31]. Additionally, it was recently reported that mitochondrial function is impaired in skeletal muscle of pre-frailty older adults [32]. Furthermore, Wasserman et al. reported that AT measured with V-slope analysis reflected mitochondrial function [33]. Based on these previous reports, increased AT watts without an increase in SMI may indicate the improved muscle performance or metabolic function via mitochondria in the pre-frailty and frailty after the exercise program, but this is not the same as muscle quality. This suggests that AT watts may be important to improve pre-frailty and frailty.

Additionally, Table 3 showed that increasing BMI with progressing frailty, which paradoxical result might be due to the criteria of this study, because we excluded older people who unable to do exercise. Indeed, recently we reported "Muscle wasting diseases has two distinct trajectories on the 3-dimensional age-BMI-peak $VO_2$ scatterplot" [34], which divided subjects into robust, pre-frailty, sarcopenia, frailty and cachexia, and in this reports we showed that BMI declining with progressing frailty. In this real world of super aged society, there are many people who are not able to do exercise because of medical condition and physical symptoms such as pain, breathlessness, fatigue and so on. Therefore, it might be indicated that keep or increase BMI is important to do exercise even if declined frailty states, among frail older people.

We found that 80% of participants with frailty improved to being robust or pre-frailty after the exercise program, and 41% of those with pre-frailty improved to a robust condition. In total, 89% of robust, pre-frailty, and frailty participants improved or maintained their status after the 6-month exercise intervention. However, 11% of participants worsened from robust to pre-frailty or pre-frailty to frailty (Table 4).

This study showed that exercise training based on CPET (adequate intensity as AT) was effective in preventing or avoiding progression to pre-frailty/frailty (evaluated with J-CHS criteria), and also improved frailty-related indices among community dwelling older adult outpatients with age related diseases. Establishing countermeasures for physical [35] and cognitive/psychological frailty [36,37] is important in a super-aged society such as Japan, because these states are associated with high healthcare costs, such as medical and long-term care insurance costs [38].

This study had several limitations. First, although we used consecutive and unselected clinical outpatients, there may be some bias because we included participants after excluding acute and unstable diseases, and habitual exercise. Second, our sample size was relatively small. Third, we did not investigate muscle quality in terms of the ratio of knee-extension strength to thigh muscle cross-sectional area (computed tomography). Fourth, we did not investigate whether healthcare costs were reduced; this aspect will need to be investigated using a large sample.

## Conclusion

This study showed the effectiveness of exercise training based on CPET to counter frailty and frailty-related indices (except BMI, SMI and HRQOL) without adverse outcome, and specificity of effectiveness were seen on UWS in frailty and AT watts in pre-frailty and frailty with same exercise training among community-dwelling older adult outpatients with multiple chronic diseases. Such programs may be useful for physicians to counter progressing frailty among their outpatients with multiple chronic diseases. These findings suggest that exercise intervention based on CPET is safe and is needed in the prevention of geriatric medicine. It could avoid progression to pre-frailty/frailty which is an important social issue of super aged society.

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### Disclosure Statement

The authors have no conflicts of interest to declare.

### Authors' Contributions

Masamitsu Sugie, Tetsuya Takahashi, Marina Nara, and Kazumasa Harada made substantial contributions to the study design. Masamitsu Sugie, Tetsuya Takahashi, Marina Nara and Teruyuki Koyama contributed to acquisition of data and performed the statistical analyses. Hunkyung Kim, Hajime Fujimoto, Teruyuki Koyama, Shunei Kyo, and Hideki Ito contributed to interpreting the data. Masamitsu Sugie, Kazumasa Harada, Tetsuya Takahashi, Marina Nara, Hunkyung Kim and Hideki Ito wrote each manuscript draft. All authors critically reviewed and contributed significantly to the intellectual content of the manuscript. All authors agreed on the final content of the manuscript.

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