Published in final edited form as:

Med Sci Sports Exerc. 2018 May ; 50(5): 1005–1014. doi:10.1249/MSS.0000000000001518.

PRIME: A Novel Low-Mass, High-Repetition Approach to Improve Function in Older Adults

Jason D. Allen^{1,2}, Mitch D. VanBruggen², Neil M. Johannsen^{3,4}, Jennifer L. Robbins², Daniel P. Credeur^{3,5}, Carl F. Pieper⁶, Richard Sloane⁶, Conrad P. Earnest⁷, Timothy S. Church⁴, Eric Ravussin⁴, William E. Kraus², and Michael A. Welsch^{3,8}

¹Department of Kinesiology, University of Virginia, Charlottesville, VA

²Duke Molecular Physiology Institute, Duke University School of Medicine, Durham, NC

³School of Kinesiology, Louisiana State University, Baton Rouge, LA

⁴Pennington Biomedical Research Center, Baton Rouge, LA

⁵School of Kinesiology, University of Southern Mississippi, Hattiesburg, MS

⁶Center for Aging and Human Development, Duke University Medical Center, Durham, NC

⁷Texas A&M University, College Station, TX

⁸Lebanon Valley College, Annville, PA

Abstract

Introduction—The ability to maintain functional independence in a rapidly aging population results in an increased life expectancy without corresponding increases in health care costs. The accelerated decline in $\text{VO}_{2\text{peak}}$ after the age of 65 is primarily due to peripheral tissue changes rather than centrally mediated factors. The purpose of this study was to determine if the PRIME (Peripheral Remodeling through Intermittent Muscular Exercise) approach, consisting of a low mass, high repetition/duration skeletal muscle focused training regimen would provide superior functional benefits in participants above 70 years old and at risk for losing functional independence.

Methods—In this clinical trial, 107 participants were randomized to four weeks of either standard aerobic exercise training (AT) or PRIME [Phase 1]. This was followed by eight weeks of a progressive whole-body aerobic and resistance training (AT+RT) for all participants [Phase 2]. The major outcome measures were cardiorespiratory fitness (peak oxygen consumption- $\text{VO}_{2\text{peak}}$), muscular fitness (1 repetition maximal strength -1RM) and physical function (Senior Fitness Test scores-SFT). Results were analyzed under a pro-protocol criterion.

Corresponding Author: Professor Jason D Allen, PhD, Department of Kinesiology, University of Virginia, Memorial Gymnasium, Charlottesville, VA 22904, (jason.allen@virginia.edu).

CONFLICT OF INTEREST

All authors have no conflicts of interest to disclose

The results of the present study do not constitute endorsement by ACSM

The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Results—Thirty-eight PRIME and 38 AT participants completed the 3-month protocols. $\text{VO}_{2\text{peak}}$, 1RM, and SFT scores all increased significantly after 12 weeks for both treatment groups ($p<0.05$). However, relative to AT, participants randomized to PRIME demonstrated a greater increase in $\text{VO}_{2\text{peak}}$ (2.37 ± 1.83 vs. $1.50\pm 1.82\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $p<0.05$), 1RM (48.52 ± 27.03 vs. $28.01\pm 26.15\text{kg}$, $p<0.01$) and SFT (22.50 ± 9.98 vs. 18.66 ± 9.60 percentile, $p<0.05$).

Conclusions—Participants experienced greater increases in cardiorespiratory and muscular fitness and physical function when PRIME training was initiated prior to a combined AT+RT program. This novel exercise approach may be advantageous to individuals with other chronic disease conditions characterized by low functional capacity.

Keywords

Exercise; Physical Performance; Physical Function; Successful Aging

INTRODUCTION

The proportion of people world-wide over 65 years of age is estimated to grow from 8% in 2010 to 16% by 2050(1). Although it is clear people are living longer, the quality of life during those extra years is not evident(2). Enabling older individuals to lead long and healthy lives may actually reduce health-care costs and encourage continued productivity and societal contributions(3).

In older adults, low levels of physical activity are associated with slower gait speeds(4), poorer activities of daily living function(5), and more reported “unhealthy days”(6). However, prospective cohort studies suggest engaging in physical activity may reduce the risks of incurring functional limitations and disability(7–9). Similarly, the risk of losing independence is 30% and 50% lower for moderately and highly fit older individuals respectively, when compared to a low fit group(10).

A $\text{VO}_{2\text{peak}}$ of between 15 to $22\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ is associated with an independent lifestyle(11–13), with a steep drop in the probability of remaining “functionally independent” in those below this range(11). When considering maintained independence, these low fit individuals ($<20\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) may also produce best return on investment from an exercise intervention. Currently, however, the optimal amounts, types and dosages of physical activity and/or exercise required are unclear. A systematic review of prospective aerobic training studies suggests moderate to vigorous intensity ($11.6\text{--}14.7\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) activities may be required to increase cardiorespiratory fitness(8), but for most individuals at risk for losing functional independence, this intensity of physical activity is beyond their capabilities. Similarly, despite data that resistance training increases in physical performance, there is limited evidence (excluding clinical populations) regarding a reduction in the risk of functional limitations(8, 14). Again higher intensity progressive training may be most effective(15), but difficult to perform for many individuals.

The LIFE study(7) ($n=1635$) consisted of a 2.6 year moderate intensity physical activity program focused predominantly on walking (but complimented by lower body strengthening, balance and flexibility exercises) versus an education only program. The

exercise intervention demonstrated 30.1% rate of incident major lower extremity mobility disability (defined as an inability to walk 400m), significantly reduced from 35.5% in the education only program. However, the number needed treat with exercise to prevent an additional negative outcome was 18.5(7). Additionally, while the intervention increased lower body physical performance (assessed by the three test Short Physical Performance Battery)(16), no differences were observed in handgrip strength and no data were collected on upper body functional outcomes.

Unfortunately, current guidelines for older individuals(17) provide little insight into how to optimally incorporate the principles of specificity, overload and progression into an exercise regimen, in order to maximize functional benefits. The guidelines recommend a well-rounded, whole-body training program and implementation typically starts with low to moderate intensity aerobic training (AT), with a gradual increase in time and intensity with resistance training (RT) added later in the program. This fails to address the discrepancies between the need for higher intensity workloads for greater functional gains and the difficulty in tolerating this intensity for those at risk of losing independence.

As outlined in the Baltimore Longitudinal Aging Study, the accelerated decline in VO_{2peak} after the age of 65 is primarily due to peripheral tissue mechanisms(18). Consequently, we designed the Peripheral Remodeling through Intermittent Muscular Exercise (PRIME) training study. PRIME targets functional groups of peripheral muscle tissues, with a low mass, high repetition/duration modality (aerobic-resistance training) that induces relatively low central cardiovascular strain and can be tolerated by older individuals at risk for losing functional independence.

The objective of this study was to compare the effectiveness of an initial 4 weeks of PRIME training compared to initial AT training, when followed by 8 weeks AT+RT (as recommended by the American College of Sports Medicine/American Heart Association guidelines)(17) on measures of physical fitness (VO_{2peak} , 1 repetition maximal strength) and physical function (Senior Fitness Test scores) in older individuals at risk for losing functional independence.

METHODS

Study Design

A complete description of the “PRIME” design and methods have been published (the intervention was initially named “RSTS”)(19). In brief, the study was a two-arm, prospective randomized clinical trial with participants randomized, in a 1 to 1 ratio, to four weeks of either standard aerobic exercise training (AT) or PRIME training [Phase 1, detailed below]. This was followed by eight weeks of a progressive whole-body aerobic and resistance training regimen (AT+RT) assigned to all participants [Phase 2]. Our study procedures are outlined in a CONSORT schematic in Figure 1. The research protocol was reviewed and approved annually by the Duke University Medical Center (Durham, NC) and Pennington Biomedical Research Center (PBRC; Baton Rouge, LA) Institutional Review Boards. Informed consent was obtained from all participants prior to any assessments.

In order to ensure the fidelity of approach between sites we generated standard operating procedures manuals for all testing and training protocols. The individuals that were primarily responsible for patient training and testing spent time observing at the “sister” institution to ensure accurate duplication of protocol implementation. We also scheduled regular study conference calls to allow standardization of responses to any other issues that arose.

Participants and Enrollment Process

Our goal was to enroll participants above the age of 70 years at risk for losing functional independence based on a peak cardiorespiratory capacity (VO_{2peak}) of 15–20 $ml \cdot kg^{-1} \cdot min^{-1}$. This range was selected based on previous work by Cress and Meyer(11), who found it was associated with a threshold physical function score believed to accurately predict the risk for losing independence. The recruitment process involved phone screen interviews to determine participant eligibility. Qualifying participants then attended an orientation visit, including an explanation of study procedures, signing an informed consent, a review of medical history, and a 6-minute walk test. Utilizing previous data from the Louisiana Healthy Aging Study (n=286, unpublished), which measured both VO_{2peak} and 6-minute walk distance, we determined that subjects who could walk between 200–450m in a standard six-minute walk test should have a VO_{2peak} of approximately 15–20 $ml \cdot kg^{-1} \cdot min^{-1}$ and could proceed to the baseline testing visits.

Exclusion criteria included recent (3 months) changes in medications, current smoking, oxygen dependency, usage of fixed rate pacemakers or defibrillator, uncontrolled hypertension or diabetes, history of unstable angina, American Heart Association Class D, or New York Heart Association Class III or IV heart failure, and positive electrocardiographic (EKG) changes or angina during the maximal graded cardiopulmonary exercise test (CPET). If a volunteer met inclusion/exclusion, they initiated baseline testing followed by the randomized assignment to one of the pre-treatment (Phase I) conditions.

Baseline testing assessments (TA0) consisted of a repeat medical history, CPET (Parvo Medics, Sandy UT) with 12-lead EKG and VO_{2peak} assessment, one repetition max (1RM) strength testing, and Senior Fitness Test (SFT) assessments(19). Participants were randomized in Phase 1 to: a) an initial four weeks of AT or b) an initial four weeks of PRIME (*described below*) using a randomized block design with separate computer-generated blocks for white women, white men, minority women and minority men for each of the two study sites. After the completion of Phase 1, participants completed an intermediate testing assessment (TA1) and then all participants entered Phase 2, which consisted of 8 weeks of a “traditional” combined program consisting of both AT and RT was performed by all participants based on the ACSM/AHA 2007 older adults physical activity recommendations (17) and also consistent with the 2008 US Department of Health and Human Services Physical Activity Guidelines(20). After the eight weeks of phase 2 training, participants completed a final follow-up visit (TA2). TA1 and TA2 were performed within five days of the final Phase 1 and Phase 2 training sessions respectively, and to minimize any detraining effects the time between transition between Phases was less than 7 days.

Exercise Interventions

Details of the exercise training regimens are published in detail(19). All exercise-training sessions lasted 45–60 minutes, including warm-up, training and cool down, and were conducted three times per week for a total of 12 weeks. Participants were supervised by trained exercise physiologists and all exercise sessions were supervised in the DUMC and PBRC training facilities. Heart rates were continually monitored via Polar heart rate monitors (RS 400; Polar; Kampele, Finland) programmed with individualized heart rate ranges determined from the baseline CPET. Following each session, heart rate data were analyzed for time spent in the prescribed training range and average heart rate achieved during each session. Additionally, heart rate and exercise intensity were documented on paper every five minutes and adjusted if needed. Total aerobic exercise dose was estimated using published metabolic equations(21). Body weight was assessed weekly. Participants were required to complete at least 10 exercise sessions during the first four weeks of AT or PRIME [Phase 1] and at least 20 sessions during the following eight weeks of AT+RT [Phase 2] (>80% adherence for both phases) to be included in the data analysis.

Participants assigned to AT during Phase 1 performed whole-body aerobic exercise at >50% of heart rate reserve (HRR) on an Airdyne cycle ergometer (Nautilus, Inc. Vancouver, WA) using both arms and legs for 20 minutes (including a five-minute warm up) and then walked on a treadmill for 25 minutes (including a five-minute cool down). Participants exercised until the prescribed duration was achieved on each modality or until fatigue, at which point either the intensity of the exercise was reduced, or the exercise was paused until they recovered and were able to resume the training session. Participants that were initially unable to meet the training requirements were slowly progressed over subsequent sessions and encouraged to increase their workout intensity to the required range.

The Phase 1 PRIME protocol was designed to focus on specific peripheral muscle groups without imposing a significant cardiorespiratory strain. Eight exercises were performed to target all major muscle groups and enable the routine to be completed within 60 minutes: warm-up, rest periods, stretching between exercises, and cool down activities (see Table 1). Each exercise involved contractions with a moderate load, defined as 40–50% of their maximal voluntary capacity, for a duration of up to six minutes. The lifting cadence was controlled by metronome at one contraction every four seconds, with at least one second of this time in an unloaded state. During each exercise subjects were allowed to take rest breaks as needed but it was pre-specified that each break must be for a minimum of 30 seconds. Subject progression initially occurred by decreasing the number of required rest periods during each exercise. When the subject completed the whole duration of the exercise without rest the load was be increased by 10 percent. The volume for each exercise was be calculated by multiplying the weight lifted by the number of repetitions completed and calculated as volume per exercise and total volume lifted per exercise session (sum of all exercises).

Phase 2 consisted of 8 weeks of AT and RT as recommended by ACSM and the US Department of Health and Human Services(22). Each session included a 5-minute warm-up, 30 minutes of AT, 20 minutes of traditional RT, and 5 minutes of cool-down. Participants started on an Airdyne cycle using both arms and legs for 20 minutes (including a 5-minute warm up) and then walked on a treadmill for 20 minutes (including a 5-minute cool down).

To ensure an adequate progression during Phase 2 participants were encouraged to work at an intensity corresponding to 60–85% of HRR based on the baseline CPET test data during weeks 5–8 and 65–85% of HRR during weeks 9–12. Following AT, participants performed one-set of 10–15 repetitions for 8 exercises targeting all major muscle groups(19). The participants began with a load at which they were able to perform 10 repetitions using the correct technique and then increased the number of repetitions until they could perform 15 continuously. At that point, the weight was increased by 10%. Static stretches targeting the involved muscle groups (e.g., quadriceps stretch following leg press) were performed after each exercise was completed.

Testing Protocols

Peak cardiorespiratory fitness was assessed on a treadmill using a Modified Naughton protocol. During the CPET, respiratory gases were collected to determine peak oxygen uptake ($\text{VO}_{2\text{peak}}$) and heart rate were assessed using a standard 12-lead electrocardiogram. Blood pressure and rating of perceived exertion were obtained at the end of each minute throughout the test. Peak workload and time to exhaustion during the CPET were recorded as surrogate measure for changes in exercise tolerance(23).

The combined weight total from 1RM isotonic testing on the seated row, chest press, leg press and the isometric handgrip test (strongest hand) was used as the measure of muscular strength. In order to achieve a standardized 1RM on each exercise and between visits, participants were allowed 5 attempts at different weights, with appropriate rest periods between each lift and were guided by a qualified exercise physiologist(24).

Physical function was assessed using the Fullerton Senior Fitness Test (SFT). The SFT is a validated battery of 6 physical tasks of daily living and is used to assess strength, flexibility and endurance in order to detect and predict future limitations in functional capacity (25, 26). The test is designed to evaluate physical fitness domains including upper-body strength (Arm Curl repetitions over 30sec), lower-body strength (Chair Sit-Stand repetitions over 30sec), upper and lower body flexibility (Back Scratch and Chair Sit and Reach), balance and coordination (8-foot Up-and-Go), and aerobic endurance (Six Minute Walk). This test is simple to administer, time-effective and safe and has been validated through tests of over 7,000 men and women between the ages of 60 and 94 (25).

Statistical Analysis

This study was originally undertaken to derive effect sizes for a larger study. We aimed to provide ideal conditions and ideal compliance, and not to generalize to the hypothetical results anticipated when expanded to a larger population (where a range of compliance could be anticipated). Thus, a per protocol criterion was applied developing the analysis data set. Detailed design and statistical considerations have been published previously(19). The primary endpoints were change in cardiorespiratory and muscular fitness ($\text{VO}_{2\text{peak}}$, 1RM) and physical function (SFT scores). To address the main hypothesis the change scores from baseline (TA0) to 12 weeks (TA2) for the primary endpoints were analyzed. Under the per protocol criterion- only data from the 76 participants who met the required number of exercise sessions and training guidelines and had complete data sets for all 3 primary

outcomes were included in the final analysis. The data resulting from this design were analyzed by a repeated measures Mixed Model, assessing the change in the two Phases (0–4, 5–12 weeks), controlling for the baseline of the outcome under study. Each model first assessed a Group by Time interaction, and, if non-significant, a main effects only model (Group and Time) was assessed. Analysis of change in these periods allowed for easy interpretation. Analytically, the intercept effect was of interest – indicating if the average change, across group and time, was 0. Rejection of this hypothesis indicated that the intervention was associated with improvement – across group and time. The time effect, thus tested if the change was different between the 2 periods, the arm effect measured if the change differed across the 2 periods, and the arm by time effect assessed if the arm effect differed between times. Chi-square analysis was used to detect differences in the distribution of individual training responses to each of the primary outcome variables with the mean response used at the cut-point. Data are reported as both mean+SD of the change scores of the observed group data, and as the adjusted change scores. $P<0.05$ (two-tailed) was employed as the criterion to declare statistical significance.

RESULTS

Participant Characteristics

Of the 107 (54 AT, 53 PRIME) randomized subjects, 76 (32 DUKE and 44 PBRC) completed the 3 months of training, complied to the protocol and had 100% complete datasets for each of the three major outcome measures of cardiorespiratory and muscular fitness (VO_{2peak} , 1RM) and physical function (Senior Fitness Test scores), and were included in the final per-protocol analysis (Fig. 1). Table 2 and Table S1 (see Table, Supplemental Digital Content 1, baseline physiological variables) present the baseline characteristics of our 76 completing study participants, and their baseline physiological TAO results. There were no differences in baseline characteristics or fitness and function variables between subjects that completed the study ($n=76$) and those that did not ($n=31$).

Overall, the participants were 70% female, 88% Caucasian, ranged in age from 70 to 91 years and presented with a BMI ranging from 19.8 to 45.9. All participants were on standard medical therapy as directed by their primary care physician: 65% used anti-hypertensive medications, 34% used lipid medications, and 18% used diabetic medications.

Training Data

Table 3 shows details of the weekly exercise training loads for PRIME and AT for Phase 1 and Phase 2 (AT+RT) included in the final analysis. Adherence rates for Phase 1 were 96.8% and 98.3% for PRIME and AT, respectively. For Phase 2 these rates were 90.0% and 88.7%, respectively.

Because it is intermittent in nature and can be recorded as a volume of weight lifted, for comparison purposes, PRIME is quantified as resistance training in Table 3. It is impractical to compare the volumes of work performed during Phase 1 of the protocol between groups; however, we compared relative central cardiovascular intensity of the workload via the time spent at or above 50% HRR between, the groups. The PRIME group spent an average of

13.2+12.5 minutes per session in or above the 50% HRR target zone compared to 30.6+9.8 minutes for the AT group (67% less time, $p<0.01$, Table 3). Individual subject data show that 72% of the PRIME subjects spent less than 20 minutes in the HRR target zone compared to only 11% of the AT subjects ($p<0.01$, Fig 2).

During Phase 2, depending upon individual physiological responses and personal preferences, subjects were performing the same AT+RT protocol with various intensities. There were no significant differences in the average energy expenditure during AT (382.8 vs 375.9 MET/min per week, $p=0.69$), total weight lifted in RT (5687.6 vs. 5945.6 kg/week, $p=0.52$), or time at or above target HRR per session (28.4 vs. 26.7 min, $p=0.16$) between the groups.

Primary Outcomes

Figure 3 (left panels) shows the data for the major outcome variables adjusted for baseline. Cardiorespiratory and muscular fitness (VO_{2peak} , 1RM) and physical function (Senior Fitness Test) scores all increased significantly after 4 weeks (TA1) and 12 weeks (TA2) of intervention for each treatment group (both, $p<0.05$). However, participants randomized to the PRIME group demonstrated a significantly greater increase than the AT group in VO_{2peak} (2.37+1.83 vs. 1.50+1.82 $ml\cdot kg^{-1}\cdot min^{-1}$, $p<0.05$), combined-MVC (48.52+27.03 vs. 28.01+26.15 kg, $p<0.01$) and SFT score (22.50+9.98 vs. 18.66+9.60 percentile, $p<0.05$) after 12 weeks (TA2), respectively. In addition, participants randomized to the PRIME group had a greater individual chance of a larger-magnitude improvement across the trial (Fig. 3 right panels). Specifically, 58% of PRIME, versus 34% of the AT participants, demonstrated an improvement in VO_{2peak} greater than the overall sample mean change at 12 weeks of 1.93 $ml\cdot kg^{-1}\cdot min^{-1}$ ($p<0.05$). The percentage of participants with improvements in overall strength and SFT above the sample mean was 60% and 63% of PRIME compared to 18% and 18% for AT participants (both <0.05).

DISCUSSION

The primary finding from this prospective, randomized, clinical exercise trial in individuals over the age of 70 years at risk of losing functional independence, is that 4 weeks of PRIME training compared to initial AT training, followed by 8 weeks of ACSM/AHA recommended (AT+RT) training results in greater increases in physical fitness and physical function measures. As hypothesized, both exercise interventions also significantly increased fitness and functional parameters after 12 weeks of training. When the changes in physical fitness and function are examined on an individual level (Fig 3), 58–63% of those randomized to the PRIME intervention increased fitness/function above the mean increase value for the whole 76 subjects compared to 34% of those in the AT group.

Results from the literature differ in estimates of the rates of physical and functional decline with normal aging. For aerobic fitness in those 70 years and older, studies suggest a 2.6 to 6.3 $ml\cdot kg^{-1}\cdot min^{-1}$, (~1 to 2 MET) loss in aerobic capacity per decade of further life (18, 27). Given that an increase of just 2 $ml\cdot kg^{-1}\cdot min^{-1}$ in VO_{2peak} may provide up to a 30% reduction in relative risk morbidity, mortality and loss of independence (10, 12), the reversal of the decline observed in this study (2.4 and 1.5 $ml\cdot kg^{-1}\cdot min^{-1}$ gains in the PRIME and AT

groups) are important and significant indicators of improved cardiorespiratory fitness and health status. It is noteworthy that despite significantly less time spent in a HRR training range than the AT group who were doing moderate to vigorous aerobic activity throughout, a significantly greater improvement in cardiorespiratory fitness was achieved at the end of the trial for those who initially undertook PRIME training.

The largest difference in performance gains between the two interventions was in muscular strength. After 12 weeks of training, the PRIME participants increased their combined 1RM by 110 kg—78% more than the AT participants (Fig 3c). This was not totally unexpected given the greater volume of work and practice employed in Phase 1. Recent data suggest that muscular strength (upper, lower, and trunk), ranked in age- and sex specific tertiles has the largest independent association with functional disability. At a 5-year follow-up in 3658 men and women, those in the highest strength tertile had 50% less risk of becoming functionally disabled than the lowest tertile (28). In the same study, aerobic capacity independently reduced risk by a further 10%. This is particularly significant for the current trial population, where an avoidance of crossing the threshold to functional dependence is a major clinical goal.

Current exercise guidelines for the elderly lack clarity with regards to specific minimal or optimal doses of training for functional health outcomes. There is a lack of specificity with respect to optimally addressing the needs of individuals most at risk for losing functional independence(17). Older individuals may be unable to perform whole-body aerobic exercise at a sufficient intensity to elicit central and local vascular and skeletal tissue adaptations. Similarly, current resistance training guidelines may improve strength in the elderly, but not be of sufficient frequency and duration to provide other beneficial aerobic peripheral tissue adaptations. In fact, the 2008 Physical Activity Guidelines Advisory Committee report indicated a need to determine whether more innovative strategies are needed to prevent or postpone functional decline in older adults(20).

This study provides important information and an alternative approach to exercise interventions for elderly subjects at risk for losing functional independence. By initially focusing on peripheral muscle tissue beds with low mass-high repetition training participants appear to be able to tolerate a greater volume of work at each muscle group during each exercise modality than would be possible when performing whole-body exercise modalities. The manner by which PRIME triggers the whole-body changes in such a relatively short period of time is presently unknown. Data from single limb studies employing a similar approach were associated with rapid improvements in localized strength gains and vasodilatory reserve in younger(29), older(30), and populations with health conditions(31) suggesting greater peripheral remodeling may be involved.

These peripheral adaptations combined with the low heart rate responses, makes PRIME training a feasible and potentially important initial approach to exercise and rehabilitation for a variety of low-functioning and centrally cardiopulmonary compromised populations. It appears to serve as a primer to allow peripheral tissues to increase both aerobic and strength adaptations to exercise simultaneously and optimize whole body responses to training that follow, leading to greater gains in cardiorespiratory, muscular fitness and physical function.

Study Limitations

This study had a per-protocol design and exit data were not collected on participants who dropped out of the study or were excluded due to non-adherence. It is possible that different types of people (eg. responders versus non-responders) could be non-adherent or more likely to drop-out of the two interventions. Given that dropout rates between baseline testing and week 12 were similar between PRIME (15%) and AT (11%), we suspect that this influence would be distributed equally between the interventions. This does not preclude that the findings would be unchanged if missing data were included in the analysis.

We have only examined responses to supervised training; we do not know how the findings might have differed in a home-based or community-based setting. The PRIME regimen in particular may be difficult for individuals to perform without assistance while practicing proper technique. Also, it is unknown if the benefits obtained during the course of the three-month training period can be maintained long term. The results of this study may, however, be of value to the growing number of exercise and fitness professionals offering high-quality programs in a number of community-based settings and has implications for the design of exercise training studies in the elderly.

CONCLUSIONS

In participants over the age of 70 years at a risk of losing functional independence, eight weeks of a standard combined AT and RT program when preceded by four weeks of PRIME training regimen resulted in greater increases in cardiorespiratory and muscular fitness and physical function than a standard program of aerobic training. This approach may be of particular utility for individuals with low cardiorespiratory fitness and reduced physical function. Potential other settings where this approach may be of value are those with chronic disease conditions of low functional capacity, such as congestive heart failure, pulmonary diseases, post-treatment cancer, and sarcopenia of the elderly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Institutes of Aging (1RC1AG035822) and the Claude D. Pepper Older Americans Independence Centers at Duke University (P30 AG028716). All authors have no conflicts of interest to disclose. The results of the present study do not constitute endorsement by ACSM. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Funding: This work was supported by the National Institutes of Aging (1RC1AG035822) and the Claude D. Pepper Older Americans Independence Centers at Duke University (P30 AG028716)

The staff of the Duke University Center for Living, Pennington Biomedical Research Center, and the Department of Kinesiology at Louisiana State University.

References

1. National Institutes of Health, Organization WH. Global Health and Aging. 2011 Contract #: Global Health and Aging. www.who.int/ageing/publications/global_health.pdf

2. Crimmins EM, Beltrán-Sánchez H. Mortality and morbidity trends: Is there compression of morbidity? *J Gerontol B Psychol Sci Soc Sci.* 2011; 66B(1):75–86.
3. Lubitz J, Cai L, Kramarow E, Lentzner H. Health, life expectancy, and health care spending among the elderly. *N Engl J Med.* 2003; 349(11):1048–55. [PubMed: 12968089]
4. Brach JS, VanSwearingen JM, FitzGerald SJ, Storti KL, Kriska AM. The relationship among physical activity, obesity, and physical function in community-dwelling older women. *Prev Med.* 2004; 39(1):74–80. [PubMed: 15207988]
5. Sulander T, Martelin T, Rahkonen O, Nissinen A, Uutela A. Associations of functional ability with health-related behavior and body mass index among the elderly. *Arch Gerontol Geriatr.* 2004; 40(2): 185–99.
6. Brown DW, Balluz LS, Heath GW, et al. Associations between recommended levels of physical activity and health-related quality of life Findings from the 2001 Behavioral Risk Factor Surveillance System (BRFSS) survey. *Prev Med.* 2003; 37(5):520–8. [PubMed: 14572437]
7. Pahor M, Guralnik JM, Ambrosius WT, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: The life study randomized clinical trial. *JAMA.* 2014; 311(23):2387–96. [PubMed: 24866862]
8. Paterson DH, Warburton DE. Physical activity and functional limitations in older adults: a systematic review related to Canada's Physical Activity Guidelines. *Int J Behav Nutr Phys Act.* 2010; 7(1):1–22. [PubMed: 20145731]
9. Tak E, Kuiper R, Chorus A, Hopman-Rock M. Prevention of onset and progression of basic ADL disability by physical activity in community dwelling older adults: A meta-analysis. *Ageing Res Rev.* 2013; 12(1):329–38. [PubMed: 23063488]
10. Paterson DH, Govindasamy D, Vidmar M, Cunningham DA, Koval JJ. Longitudinal study of determinants of dependence in an elderly population. *J Am Geriatr Soc.* 2004; 52(10):1632–8. [PubMed: 15450038]
11. Cress ME, Meyer M. Maximal Voluntary and Functional Performance Needed for Independence in Adults Aged 65 to 97 Years. *Phys Ther.* 2003; 83(1):37–48. [PubMed: 12495411]
12. Paterson DH, Cunningham DA, Koval JJ, St Croix CM. Aerobic fitness in a population of independently living men and women aged 55–86 years. *Med Sci Sports Exerc.* 1999; 31(12): 1813–20. [PubMed: 10613433]
13. Shephard RJ. Maximal oxygen intake and independence in old age. *Br J Sports Med.* 2009; 43(5): 342–6. [PubMed: 18403414]
14. de Labra C, Guimaraes-Pinheiro C, Maseda A, Lorenzo T, Millán-Calenti JC. Effects of physical exercise interventions in frail older adults: a systematic review of randomized controlled trials. *BMC Geriatrics.* 2015; 15:154. [PubMed: 26626157]
15. Liu CJ, Latham NK. Progressive resistance strength training for improving physical function in older adults. *The Cochrane database of systematic reviews.* 2009; (3):Cd002759. Epub 2009/07/10. [PubMed: 19588334]
16. Santanasto AJ, Glynn NW, Lovato LC, et al. Effect of physical activity versus health education on physical function, grip strength and mobility. *J Am Geriatr Soc.* 2017; 65(7):1427–33. [PubMed: 28221668]
17. Nelson ME, Rejeski WJ, Blair SN, et al. Physical activity and public health in older adults. Recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation.* 2007; 116:1094–105. [PubMed: 17671236]
18. Fleg JL, Morrell CH, Bos AG, et al. Accelerated longitudinal decline of aerobic capacity in healthy older adults. *Circulation.* 2005; 112(5):674–82. [PubMed: 16043637]
19. Allen JD, Robbins JL, VanBruggen MD, et al. Unlocking the barriers to improved functional capacity in the elderly: Rationale and design for the “Fit for Life trial”. *Contemp Clin Trials.* 2013; 36(1):266–75. [PubMed: 23900005]
20. US-DHHS. Services USDoHaH. Physical Activity Guidelines Advisory Committee Report, Part G. Section 2: Cardiorespiratory Health 2008. Washington DC: U.S. Department of Health and Human Services; 2008.
21. ACSM. ACSM's guidelines for exercise testing and prescription. 10. Baltimore: Williams and Wilkins; 2018.

22. Garber C, Blissmer B, Deschenes M, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc.* 2011; 43(7):1334–59. [PubMed: 21694556]
23. Earnest CP, Johannsen NM, Swift DL, et al. Aerobic and strength training in concomitant metabolic syndrome and type 2 diabetes. *Med Sci Sports Exerc.* 2014; 46(7):1293–301. [PubMed: 24389523]
24. Vincent KR, Braith RW, Feldman RA, et al. Resistance exercise and physical performance in adults aged 60 to 83. *J Am Geriatr Soc.* 2002; 50(6):1100–7. [PubMed: 12110072]
25. Rikli R, Jones C. Development and validation of a functional fitness test for community-residing older adults. *J Aging Phys Act.* 1999; 7:162–81.
26. Rikli RE, Jones CJ. Development and validation of criterion-referenced clinically relevant fitness standards for maintaining physical independence in later years. *The Gerontologist.* 2013; 53(2): 255–67. [PubMed: 22613940]
27. Amara C, Koval J, Johnson P, Paterson D, Winter E, Cunningham D. Modelling the influence of fat-free mass and physical activity on the decline in maximal oxygen uptake with age in older humans. *Exp Physiol.* 2000; 85(6):877–86. [PubMed: 11187983]
28. Brill P, Macera C, Davis D, Blair S, Gordon N. Muscular strength and physical function. *Med Sci Sports Exerc.* 2000; 32(2):412–6. [PubMed: 10694125]
29. Allen JD, Johnson LG, Geaghan JP, Greenway F, Welsch MA. Time-course of vascular adaptations following localized short-term exercise training. *Med Sci Sports Exerc.* 2003; 35(5):847–53. [PubMed: 12750596]
30. Dobrosielski DA, Greenway FL, Welsh DA, Jazwinski SM, Welsch MA, Study LHA. Modification of vascular function after handgrip exercise training in 73- to 90-yr-old men. *Med Sci Sports Exerc.* 2009; 41(17):1429–35. [PubMed: 19516158]
31. Credeur D, Mariappan N, Francis J, Thomas D, Moraes D, Welsch M. Vasoreactivity before and after handgrip training in chronic heart failure patients. *Atherosclerosis.* 2012; 225(1):154–9. [PubMed: 23010159]

Figure 1.

CONSORT schematic of the PRIME Study. Thirty-eight subjects in each treatment arm had complete datasets and were included in the final analysis.

**Spousal randomizations were when couples wished to be enrolled in the study together and desired to be guaranteed in the same intervention group. In these cases, in order to adhere to the randomization schedule, we only included the data from the primary subject, who was determined at random. This “allocation” was unknown to the study staff and the participants.*

Figure 2.

The average time spent in the target heart rate range during each exercise session for (a) Phase 1 and (b) Phase 2 of the intervention protocol. Data are presented mean $\pm$ SD and statistical significance is denoted as (**, $p < 0.01$) for PRIME vs. AT treatment conditions.

Figure 3.

Group mean data adjusted for baseline values at the initial testing visit prior to randomization (left column) and waterfall graphs of individual training response to PRIME and AT treatment (right column). Top panels (A & B) represents peak cardiorespiratory capacity ($\text{VO}_2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$); Middle panel (C & D) represents the combined maximal voluntary contraction of respective strength assessments (kg); and the bottom panel (E & F) represents the percentile ranking for the Senior Fitness Assessment (%). Data are presented mean $\pm$ 95%CI and statistical significance is denoted as (*, $p<0.05$, ** $p<0.01$) for PRIME vs. AT from group mean increase at 12 weeks in comparison to Baseline.

Table 1
Peripheral Remodeling through Intermittent Muscular Exercise (PRIME) Exercise Protocol

Exercise	Days/week	Duration (min)	Starting Intensity	Progression	Ideal Cadence	Comments
Calf Raises	3	5	Body Weight	8–10% of Body Weight	¼ sec	Both Legs
Handgrip	3	5	50% MVC	8–10% of previous load	¼ sec	Alternating Hands
Leg Press	3	6	40–50% MVC	8–10% of previous load	¼ sec	Both Legs
Seated Row	3	5	40–50% MVC	8–10% of previous load	¼ sec	Both Arms
Chest Press	3	5	40–50% MVC	8–10% of previous load	¼ sec	Both Arms
Modified Squats	3	5	Body Weight	8–10% of body weight	¼ sec	Use of Chair or Exercise Ball
Low Back	3	3	As tolerated	8–10% of previous load	¼ sec	Crossed Arms
Abdominal	3	3	As tolerated	8–10% of previous load	¼ sec	Pads on movement arm on chest

MVC-Maximal Voluntary Contraction

Table 2

Baseline Characteristics

	ALL (n=76)		AT (n=38)		PRIME (n=38)	
	mean	SD	mean	SD	mean	SD
Age (yr)	76.0	4.9	76.0	4.7	76.0	5.2
Gender	n	%	n	%	n	%
Female	53	69.7	26	68.4	27	71.1
Ethnicity	n	%	n	%	n	%
Caucasian	67	88.2	34	89.5	33	86.8
African American	9	11.8	4	10.5	5	13.2
Anthropometrics	mean	SD	mean	SD	mean	SD
Height (cm)	163.9	7.9	163.9	8.6	163.9	7.9
Weight (kg)	78.0	16.1	78.5	16.9	77.5	15.3
BMI	28.8	4.6	29.2	4.8	28.4	4.4
Resting Hemodynamics	mean	SD	mean	SD	mean	SD
SBP (mmHg)	135.3	18.0	132.1	17.7	138.6	17.9
DBP (mmHg)	72.0	9.7	72.4	9.5	71.5	10.1
HR (bpm)	67.3	8.3	69.2	8.9	65.4	7.3
Lipids & BG	mean	SD	mean	SD	mean	SD
LDL (mg/dL)	110.4	27.5	108.8	27.6	112.1	27.7
HDL (mg/dL)	55.9	17.4	57.1	16.5	54.6	18.6
Triglycerides (mg/dL)	142.8	80.6	147.1	79.9	138.1	82.4
Glucose (mg/dL)	111.0	19.7	111.9	17.9	110.2	21.5
Medications	n	%	n	%	n	%
HTN	43	56.6	21	55.3	22	57.9
Lipids	46	60.5	21	55.3	25	65.8
Arthritis	14	18.4	7	18.4	7	18.4
Anti-Depressants	14	18.4	9	23.7	5	13.2
Thyroid	18	23.7	7	18.4	11	28.9
Other Health Issues	n	%	n	%	n	%
CVD	5	6.6	1	2.6	4	10.5

	ALL (n=76)		AT (n=38)		PRIME (n=38)	
Cancer	17	22.4	10	26.3	7	18.4
Diabetes	14	18.4	6	15.8	8	21.1
Arthritis/Orthopedic	49	64.5	22	57.9	27	71.1
Performance/Function	mean	SD	mean	SD	mean	SD
VO ₂ peak (ml/kg/min)	17.0	3.9	16.8	3.6	17.3	4.3
MVC (totals)	373.3	126.8	407.6	134.9	351.8	121.5
SFT (%ile combo score)	35.3	12.8	35.7	13.5	34.4	12.1

Table 3

Exercise Training Data

Aerobic Training Group	Phase I (wk)				Phase II (wk)							
	1	2	3	4	5	6	7	8	9	10	11	12
Airdyne Cycle												
Intensity, %HRR	62.0 (2.1)	64.9 (1.9)	68.0 (1.8)	72.7 (1.5)	67.7 (2.1)	71.1 (2.5)	70.8 (2.2)	71.5 (1.9)	71.8 (2.0)	74.5 (2.1)	74.7 (2.0)	76.0 (2.6)
Mean METs level	2.7 (0.1)	3.1 (0.1)	3.3 (0.1)	3.5 (0.1)	3.4 (0.1)	3.5 (0.1)	3.7 (0.2)	3.8 (0.2)	3.9 (0.2)	4.1 (0.2)	4.0 (0.2)	4.1 (0.2)
Treadmill												
Intensity, %HRR	58.9 (2.2)	60.0 (2.0)	63.2 (2.0)	67.7 (1.5)	64.4 (2.1)	68.9 (2.0)	68.3 (2.0)	70.1 (1.6)	70.7 (1.5)	71.9 (1.3)	71.6 (1.3)	71.4 (1.9)
Mean METs level	3.1 (0.1)	3.6 (0.1)	3.8 (0.1)	4.0 (0.1)	4.1 (0.1)	4.4 (0.2)	4.5 (0.2)	4.7 (0.2)	4.8 (0.2)	4.9 (0.2)	5.0 (0.2)	4.9 (0.2)
Total Aerobic												
MET/min per week	309 (9)	358 (13)	383 (13)	395 (9)	337 (11)	358 (12)	369 (13)	383 (15)	392 (16)	405 (17)	410 (18)	408 (20)
Total Resistance												
Total weight lifted, kg	--	--	--	--	4114 (217)	4933 (255)	5285 (253)	5689 (271)	6002 (278)	6270 (281)	6472 (289)	6736 (326)
Average Time in THR, min per session	32.4 (12.3)	31.1 (10.8)	32.4 (11.4)	31.1 (10.9)	24.1 (9.7)	28.2 (13.8)	31.3 (13.3)	30.1 (11.2)	27.4 (14.5)	29.1 (13.8)	28.1 (13.1)	29.6 (13.0)

PRIME Training Group	Phase I (wk)				Phase II (wk)							
	1	2	3	4	5	6	7	8	9	10	11	12
Airdyne Cycle												
Intensity, %HRR	--	--	--	--	64.0 (4.3)	64.2 (4.0)	67.6 (3.8)	71.6 (3.8)	73.3 (3.9)	72.4 (3.8)	74.3 (4.2)	75.4 (4.8)
Mean METs level	--	--	--	--	3.1 (0.2)	3.5 (0.2)	3.9 (0.2)	4.1 (0.2)	4.1 (0.2)	4.3 (0.2)	4.5 (0.3)	4.4 (0.3)
Treadmill												
Intensity, %HRR	--	--	--	--	59.3 (3.8)	62.6 (3.5)	65.6 (3.2)	69.3 (2.9)	71.0 (3.0)	71.5 (3.1)	70.8 (3.6)	71.0 (4.3)
Mean METs level	--	--	--	--	3.4 (0.1)	3.9 (0.2)	4.2 (0.2)	4.5 (0.2)	4.5 (0.2)	4.7 (0.2)	4.8 (0.2)	4.7 (0.2)
Total Aerobic												
MET/min per week	--	--	--	--	296 (14)	339 (16)	367 (18)	386 (18)	389 (18)	408 (18)	420 (20)	402 (19)
Total Resistance												
Total weight lifted, kg	15,556 (566)	17,332 (578)	18,321 (523)	19,091 (538)	4644 (220)	5386 (275)	5740 (264)	6081 (276)	5973 (299)*	6457 (267)	6574 (283)	6710 (310)
Average Time in THR, min per session	10.9 (12.0)**	14.4 (15.0)**	14.5(14.6)**	13.7(15.1)**	20.1 (12.4)	25.8 (13.3)	28.2 (14.8)	28.1 (15.0)	27.2 (16.0)	30.1 (14.3)	24.6 (13.4)	24.6 (12.4)

significantly different between groups (p 0.01)

**

Mean (SE).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript