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## Changes in bone density following exercise training in older adults

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# CHANGES IN BONE MINERAL DENSITY FOLLOWING EXERCISE TRAINING IN OLDER ADULTS

A Thesis

Submitted to the Graduate Faculty of the  
Louisiana State University and  
Agricultural and Mechanical College  
in partial fulfillment of the  
requirements for the degree of  
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in

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by  
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## ABSTRACT

**Purpose:** To determine effects of 8 wks of progressive whole-body training preceded by 4 wks of regional specific (RSTS) or aerobic training (AT), on bone mineral density (BMD). **Methods:** Subjects were over age 70 y, with a 6-min walk score of 218-490 m. Subjects were randomized to AT or RSTS for the first 4 wks (Phase 1). AT consisted of ~45 min of walking/biking (50-85% HR reserve), 3 d/wk. RSTS consisted of 8 exercises specific to major muscle groups and was performed for 3-5 min, at ~40-70% of max voluntary strength for ~45 min, 3 d/wk. After 4 wks, all subjects were advanced to a whole-body program using established guidelines (Phase 2). Bone mineral density of the lumbar and thoracic spine and pelvis was examined before training, after 4 wks, and after 12 wks, using Dual-energy X-ray absorptiometry (DXA). **Results** Analysis showed a significant time effect for lumbar, thoracic, and pelvis BMD ( $p < 0.05$ ,  $0.05$ , and  $0.01$ , respectively); however, group by time interactions were found only for thoracic and lumbar BMD ( $p < 0.05$ ,  $p < 0.10$ , respectively). Post hoc analysis revealed a significant difference for thoracic BMD at 12 wks compared to 4 wks and baseline for RSTS while AT showed no significant changes in thoracic or lumbar BMD. A significant increase of 3.2% from baseline for RSTS was found for lumbar BMD after only 4 wks. **Conclusion** Preceding well-rounded training with RSTS proved beneficial with respect to thoracic and lumbar BMD. The rapid time course for change in lumbar BMD may support the use of RSTS when trying to reduce fracture risk in a short time frame.

# CHAPTER 1: LITERATURE REVIEW

## Introduction

Function and independence are akin in older adults, decreasing with increased age in a growing population of persons 65 and older, a population expected to double by 2030 [1]. Bone strength (BS) is unique with respect to function and independence as fractures, especially those of the hips, have an immediate, lasting impact on both [2]. Bone mineral density (BMD) has a much-appreciated relationship with BS, accounting for 60 to 80% based on *in vitro* stress-strain curves examined in human and bovine bone [3-6]. Because of this relationship, BMD predicts various types of fractures [7-9] based on an exponential curve; therefore, seemingly minor drops in BMD (10-15%) can double fracture risk [10, 11]. By attenuating BMD declines and the associated increased fracture risk, commonly seen in post-menopausal women and older adults, function and independence can be preserved. The purpose of this chapter is to review the literature on how exercise affects BMD in older adults; however, it will first describe the older adult population, basic bone biology, and densitometry.

## Older Adults

“Our population is getting older”, stated simply by Frank Booth [12]. This was? true 20 years ago and will hold more merit 20 years from now, as the population of persons 65 years and older is projected to nearly double in the US, from 40 million presently to 72 million by 2030 [1]. Furthermore, this population is continuing to become a larger part of the entire population. As of 2010, persons

over 65 constitute 13% of the population; in twenty years the number is expected to be nearly 20% [1]. Growth of the older adult population is partially due to people living longer lives. Survival curves are now becoming more rectangular with a larger percent of the population living lives at lengths closer to average life expectancies (79 years in the US) [13, 14]. The problem is age-related decline in physical function and health has an associated social and economic cost; a cost that will grow with the population of older adults unless trends in chronic disease change.

Attenuating declines in function and independence, while preventing death could be an ideal use of monetary resources; however, these funds are being misplaced in tertiary, rather than, primary treatment [12]. Healthcare, in general, has been trudging toward becoming unsustainable, and although the growing older adult population has contributed relatively little to rising costs up to present, 2 percent towards overall increased healthcare costs from 1940 to 1990, it is projected that over the next 25 years the growing older adult population will account for 44 percent of the increased cost associated with Medicaid and Medicare [15].

Function and independence should be the target for treatment as the ability to maintain the two increases life expectancy without increasing health care costs [16]. After 65 there is an accelerated, non-linear decline in aerobic capacity, based on data from the Baltimore longitudinal study and work by Jackson et al. [16, 17]. This is of even greater significance when considering research that has shown a  $VO_{2peak}$  of  $14-20\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  is associated with risk

for loss of functional independence [18]. Unlike aerobic capacity and its associated increased risk for loss of independence, fractures of the bone have an immediate and lasting impact on both function and independence [2]. Similar to aerobic capacity, bone loss and risk for fracture increase with age, suggesting an urgent need to pursue treatments aimed at improving bone health in older adults.

### **Bone Biology**

When considering different physiological tissues, bone has duality: serving a structural function, support and protection, while also serving a metabolic function with respect to calcium homeostasis [19-22]. The structural function of bone is largely achieved through an organic matrix of Type I collagen fibers (95%) and, proteoglycans and noncollagenous proteins (5%) [22]. Further integrity is achieved by controlled deposition of calcium and phosphate within the osteoid, creating the bone matrix [22]. Metabolically, bone is also a calcium sink, meant to be filled with excess  $\text{Ca}^{++}$  and emptied when  $\text{Ca}^{++}$  homeostasis is jeopardized [22].

Whether for maintenance of structure or calcium homeostasis, bone tissue is under constant remodeling [23, 24]. This process is tightly controlled by growth factors and hormones, which originate from or act upon the four cells that compose bone tissue [23]. Of these four cell types, osteoblast, osteocytes, and bone lining cells have a similar lineage, local osteoprogenitor cells that differentiated from stromal stem cells [22, 23]. Osteoclasts are different in that their lineage begins within hemopoietic tissue (bone marrow) [22, 23]. These hemopoietic mononuclear precursors must be transported via blood vessels, to

the site of remodeling where osteoprogenitors interact with them to initiate osteoclast formation [22, 23].

Of these four cell types, the contrary roles of osteoclast and osteoblast are well appreciated. Osteoclasts serve a catabolic role, attaching to the bone surface and breaking down the bone matrix, freeing any deposited mineral [22, 23]. Osteoblasts serve the opposite, anabolic role and deposit organic matrix within the cavity created by osteoclasts [22, 23]. During the process of osteoid anabolism, some osteoblasts are left within the matrix, becoming osteocytes [22, 23]. Before mineralization, osteocytes extend filopodial processes, which connect to other osteocytes, allowing for inter-communication and fluid flow between them [22, 23]. The osteocyte network can detect fluid shear stress from mechanical strain (also lack of strain) or osteocyte apoptosis from a fracture; in response, osteocytes can signal for osteoclast formation and begin the remodeling process, or they can use their own capacity for anabolic and catabolic bone metabolism [25].

Last of the four bone cells, and of recent interest in bone biology, is the bone lining cell. Bone lining cells, similar to osteocytes, are differentiated from mature osteoblasts; however, instead of being deposited within osteoid, they are on the surface of the bone matrix? [22-24]. The roles of these flat elongated cells on the surface of bone were largely unappreciated 15-20 years ago and were thought to be related to osteoblast precursors [22]. More recent research has shown their role may be more involved. In 2001, Hauge et al. reported specialized compartments for bone remodeling, and speculated that the cells



lining this compartment were bone lining cells [26], a speculation confirmed by further research [24]. These bone-remodeling compartments (BRC) have created further interest in relationships between vasculature and bone, as these BRCs are a literal link between the two. A positive relationship exists between the number of BRCs and bone turnover, as they are the site for anabolic and catabolic processes in bone remodeling, particularly in trabecular bone. The literature has only confirmed a structure similar to BRCs of the trabecular bone in cortical bone, and further research is needed to determine its function [24].

Furthermore the differences between trabecular and cortical bone are largely structural, while functional differences are due to structure [27]. Cortical osteoid makes up the outer layer of bone, being compact and resistant to stress (80-90% calcified) [23]. Due to the compact structure of cortical bone, vascularization is less prevalent, depending on Haversian and Volkmann canals for perfusion and decreasing available surface area, making the  $\text{Ca}^{++}$  in this osteoid less available to the blood and  $\text{Ca}^{++}$  pools in other tissue. Trabecular bone, however, is much more porous and accessible to the vasculature, only 15-25% of the area is calcified while the remaining area is composed of marrow, connective tissue and the aforementioned vasculature [27]. The porous structure of inter-connected trabeculae increases available surface area for  $\text{Ca}^{++}$  transfer via osteoclastic and osteoblastic activity, meaning the trabecular bone is more metabolically capable compared to cortical bone.

As stated, the structural and metabolic functions of bone tissue are mostly purposed to cortical and trabecular bone, respectively [19, 22]. However, both

trabecular and cortical osteoid make up any bone; thus, the role of trabecular bone in bone structure is still appreciated, especially when considering compressive forces [21]. The structural component of both trabecular and cortical bone are recognized, and decreased cortical thickness and increased trabecular porosity are largely associated with decreased BS, the ageing process, osteoporosis, and menopause [19, 23]. These declines, although not fully understood, are certainly caused by a net reabsorption [19, 23]. Whether or not net reabsorption is caused by an overall increase in reabsorption or decreased formation is not fully understood, although typical to physiology, the cause is likely some combination.

### **Dual-energy X-ray Absorptiometry**

Many methods for studying skeletal structure exist; however, the most clinically used method presently for studying skeletal structure *in vivo* is DXA, or Dual-energy X-ray Absorptiometry. Scans are used to measure many variables related to body composition, but with respect to bone, DXA measures total bone mineral content and areal BMD (units:  $\text{g}/\text{cm}^2$ ). Areal BMD, namely so, is the measure of a 2-dimensional image or area. Unlike other methods that give a density measure based on volume (units:  $\text{g}/\text{cm}^3$ ) such as quantitative computed tomography (QCT), DXA will scan a 3-dimensional structure and produce a 2-dimensional image. Pixel density (pixels/unit<sup>2</sup>) is used as the outcome measure and although an increased pixel density is related to density at depth, it does lack compared to a true density measure in that structure in the z-plane is only partially appreciated.

Although areal BMD measures are not true density measures, they are still an accepted measure. Not a direct measure of BS, BMD is still strongly related to BS, accounting for 60-80% of the variability in BS measures *in vitro* for bovine and human bone [3-6]. These relationships are clinically meaningful for diagnosis of osteoporosis, although they leave little understanding of micro architectural deterioration, therefore, little understanding of bone quality. This has led to some controversy over using DXA, rather than QCT to determine osteoporosis, as QCT is a true density measure [28, 29]. Still, DXA is preferred for lower cost, relative precision, and overall lower radiation exposure [30, 31]. DXA has also been used to determine age-related declines in BMD cross-sectionally, a decrease that is associated with the prevalence of osteoporosis in older adults and the development of osteoporosis after menopause [32, 33]. As such, well-defined cut-points and standardized scores have been developed to describe low bone mass and osteoporosis.

### **Exercise, BMD, and Older Adults**

*The Law of Bone Remodeling*, written by Julius Wolff nearly 120 years ago is credited as the first literature that described bone's ability to alter its internal and external form in response to stress [22, 34]. There is nearly an 80-year gap in between Wolff's work and literature on relationships between physical activity and bone; the current research line began in the 1970's[22]. Lane and colleagues were one of the first groups to examine, using a cross-sectional methodology, BMD differences between chronic endurance athletes and sedentary controls. Their research showed a 40% difference in vertebral

trabecular BMD between runners and sedentary control, more significant as those runners were over 60 years of age [22, 35]. A significant amount of literature in the late 80's gave credit to the correlation between weight lifting and increased BMD, a 10-30% difference compared to sedentary individuals in lumbar spine [22, 36-38]. Research also suggested specific correlations between BMD and the area of the skeletal system that is actually loaded, as the BMD changes in the hips of weight lifters are less conclusive [22, 36, 38]. Previous research in tennis players could be used to support this, as in 1977 a 30% difference in humeral thickness was observed when comparing the playing and non-playing arms [22, 39]. This research, although useful, fails to establish any causal relationships between BMD and exercise, suggesting a need to examine how different modalities of loading may impact bone.

The research on causal relationships between skeletal adaptation and physical activity has centered around mechanical load with the emphasis placed on the intensity of the load (strain magnitude), cycle number (loading cycles within a given time period), and rate of strain (deformation over time)[22]. Research has shown that increasing strain magnitude takes precedence over cycle number [40](i.e. it would be more effective to the load with twice the weight rather than twice as many times per day) and a higher rate of strain is beneficial even at peak strains [22, 41]. Van der Weil, in 1995, observed that increasing in load using weighted back packs while running on a treadmill was more effective at increasing bone mass than running for a longer duration [22, 42]. Previous studies had supported this with correlational data in weight lifters [36] and in rat

models shown to maintain bone mass without a large number of loading cycles [22, 43]. Experimental rat models have also been used to confirm the positive effects of rate of strain on adaptation [22, 41].

Exercise has a modality dependent effect on bone mass in older adults, which has much to do with loading principles. These modality dependent changes are typically polarized into aerobic training (AT) or resistance training (RT), with some merit as overall changes in reported from RT show significantly higher changes in BMD from training in both post-menopausal women and older men [44]. However, the varying effect of different aerobic modalities may complicate overall findings. For example, aerobic modalities that include stepping along with walking have a more effective impact on BMD changes in postmenopausal women than walking alone, 2-6% change in BMD [45] compared to no change [46, 47]. Still, brisk walking (not causing shortness of breath) alone over two years has shown to attenuate BMD losses of the femoral neck in women [48]. Furthermore, Hatori et al. showed that walking intensity should also be considered as AT above anaerobic threshold resulted in a 1% increase in lumbar BMD over 3 weeks while AT below anaerobic threshold resulted in a 1% decrease [49].

Resistance training has a more consistent positive effect as the associated increased load has a causal relationship with osteogenesis [50], although the magnitude of change is variable [44]. In post-menopausal women, RT typically resulted in significant, small positive changes in BMD [50-52], although some studies report no change in areas measured [53, 54]. Post-

menopausal BMD changes in response to RT training, albeit small, are intuitively more significant as control groups in many of these studies had significant drops in post BMD measures of the hip and spine (ie. 1.8% decrease in lumbar spine BMD reported by Nelson et al.) [50, 53, 54]. Nelson et al. also showed that along with small BMD increases of about 1% in their RT groups, an improvement in balance was also seen, suggesting a decreased risk for fall and resulting fracture [50]. With respect to different types of RT modalities, Kerr et al. showed that higher intensity (greater loads) in RT held a higher importance over increased cycles as post-menopausal women who lifted more weight for less repetitions had a significant BMD change (1.7% increase in trochanter BMD) compared to those who lifted less weight for more repetitions (no change in BMD) [51]. Results in men are similarly variable compared to results found in post-menopausal women, likely due to an overall small amount of related studies on male older adults, differences in age group, and differences in RT modalities [44, 55, 56].

To summarize, exercise is effective in slowing age-associated declines in BMD with the magnitude of change being modality dependent. Little, if any, BMD changes in older adults are typically produced using AT, yet it may be effective at attenuating declines associated with increasing age [2, 44, 48]. In comparison, RT produces more substantial results; especially in populations with low BMD as small changes in these populations could hypothetically show exponential changes in fracture risk [2, 9, 10, 44, 50]. The changes for both modalities are

mostly attributed to mechanical load, with that load being more substantial during RT [2, 44, 50].

### **Purpose**

Typical recommendations for exercise in older adults suggest a well-rounded, full-body program but for older adults, typically begin with low-to-moderate AT. This does yield favorable health benefits, but time-course for change is modest (<10% change in  $VO_2$ max after 4 months) [57]. Regional specific training stimulus (RSTS) is a novel combination of AT and RT applied to peripheral sites in a serial manner. The purpose of this research is to analyze ancillary data from the Fit For Life study to determine the effects of eight weeks of progressive whole body training, preceded by 4 weeks of RSTS or standard AT, on bone mineral density. We hypothesize subjects randomized to 4 weeks of RSTS before 8 weeks of well-rounded training will have greater improvements in BMD after the total 12 weeks compared to subjects who participated in AT training before beginning the same 8 week well-rounded program.

## CHAPTER 2: METHODS

### Participants

Participants recruited were sedentary (exercising  $\leq 1$  day per week) men and women over 70 years of age classified as being at risk for losing functional independence based on a peak  $\text{VO}_2$  of 14-20  $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  [18]. For simplicity, this criterion was determined as a 6-minute walk score of 200-459, or an estimated peak  $\text{VO}_2$  of 14-20  $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  [16]. Prospective participants were unaware of this inclusion criterion.

### Study Design

Fit for Life was a randomized, two-arm, prospective design outlined in Figure 1, with measurement points at baseline, 4 and 12 weeks. Subjects were randomized to RSTS or AT for Phase 1 of training, which was for the first 4 weeks. After 4 weeks of AT or RSTS, all subjects began a well-rounded training program (Phase 2). To maximize internal validity, study personnel, time of the day, equipment and order of testing were consistent for each of the assessment time points.

### Exercise Intervention

**Phase I – Aerobic Training Regimen (AT).** Subjects assigned to AT during the initial 4 weeks of training performed whole-body aerobic exercise at 50 to 85% of heart rate reserve (HRR) for 45 minutes, three days per week. Subjects exercised on an Airdyne cycle 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). In the event that a subject was unable



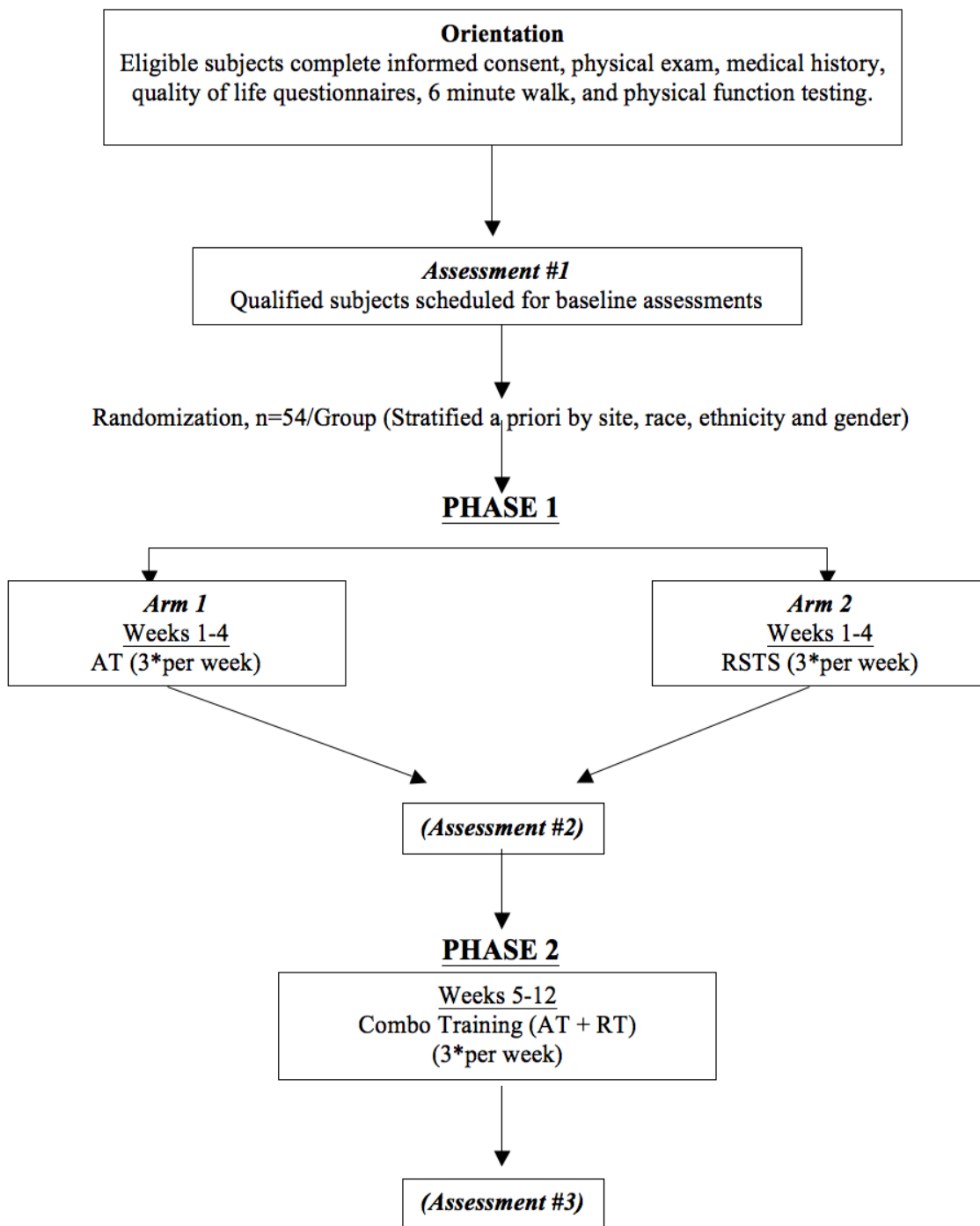


Figure 1. Study Design

to exercise using one or both of these modalities, he/she was given the option to use a recumbent bicycle. Subjects exercised until the prescribed duration was achieved on each modality or until fatigue, at which point intensity was reduced or the exercise was stopped until the subject recovered and was able to resume training. As the trial progressed, subjects were encouraged to increase workout intensity without exceeding 85% of HRR. Training volume per session was documented in kilocalories per exercise session according to revolutions per minute (RPM) during Airdyne cycling (equations provide by Airdyne) and speed and grade for treadmill walking using established equations [58].

**Phase 1 – Regional Specific Training Stimulus (RSTS).** The RSTS protocol was designed to provide a specific peripheral aerobic and resistance stimulus without imposing a significant cardiorespiratory strain (see Figure 2). Each exercise involved contractions with moderate resistance but with an extended duration of up to six minutes. Eight specific exercises were performed to target all major muscle groups and enabled the routine to be completed within 60 minutes including warm-up, rest periods, flexibility exercises, and cool down exercises (Table 1). No specific order for each exercise was arranged. Subjects randomized to RSTS were asked to maintain a cadence of one contraction every four seconds. The goal of the exercise was to make a conscious effort to ensure the muscle group was unloaded for 1 second of the 4-second cycles. This was designed to maximize the contraction induced hyperemic response (as blood flow through a contracted muscle is significantly decreased due to vascular

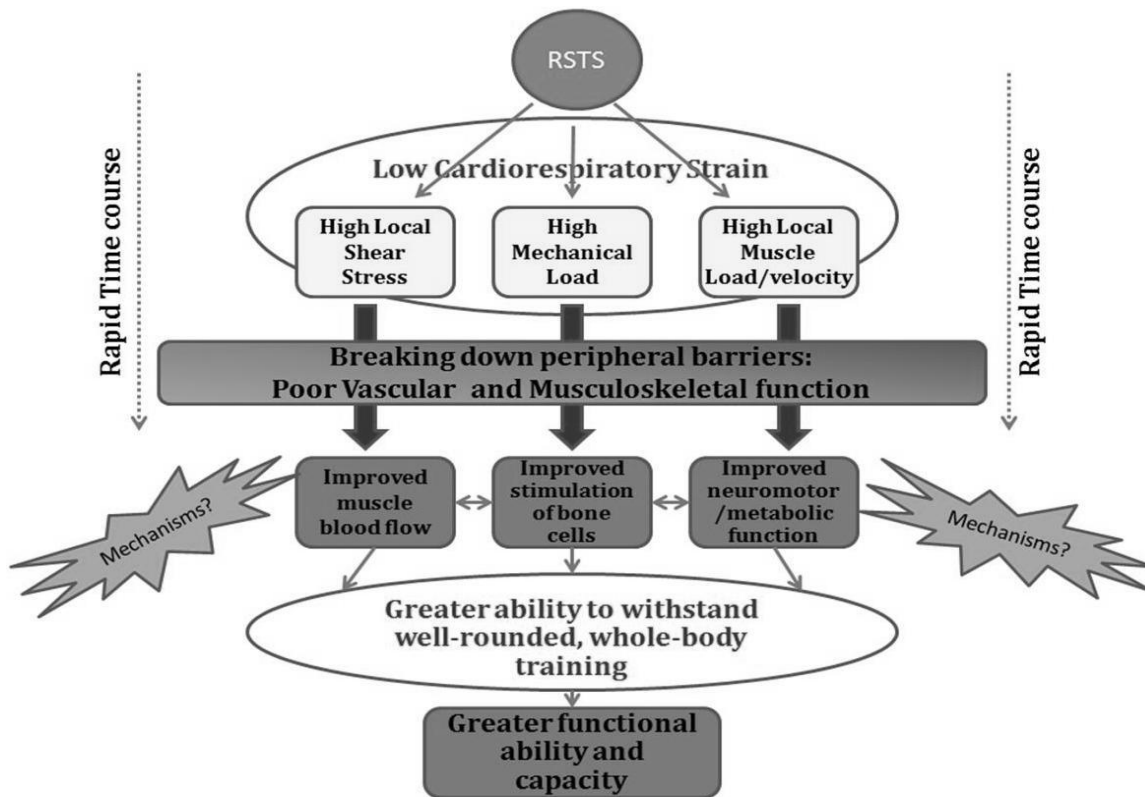


Figure 2. Hypothetical Model for RSTS

Table 1. RSTS Program

<b><u>3days/week</u></b>	<b>Duration (min)</b>	<b>Starting Intensity</b>	<b>Progression</b>	<b>Comments</b>
<b>Calf Raises</b>	5	Body Weight	8-10% of body weight	Both legs
<b>Handgrip</b>	5	50% MVC	8-10% of previous load	Alternating hands
<b>Leg press</b>	6	40-50% MVC	8-10% of previous load	Both legs
<b>Seated Row</b>	5	40-50% MVC	8-10% of previous load	Both arms
<b>Chest Press</b>	5	40-50% MVC	8-10% of previous load	Both arms
<b>Modified Squats</b>	5	Body Weight	8-10% of previous load	Use of chair or exercise ball
<b>Low Back Extension</b>	3	As Tolerated	8-10% of previous load	Crossed arms
<b>Abdominal</b>	3	As Tolerated	8-10% of previous load	Pads on movement Arm on Chest

compression the preceding 3 seconds). Muscle contractions were performed by alternating between limbs as appropriate (i.e. handgrip exercises).

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. The RSTS progression initially occurred by decreasing the number of required rest periods during each exercise. When the subject could complete the whole duration of the exercise without rest, the load was increased by ~10 percent. The volume for each exercise was 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 – Combined Aerobic and Resistance Training.** Following the first four weeks of training all subjects were progressed to a well-rounded whole body exercise training regimen using established ACSM guidelines [59]. This eight-week training regimen includes a 5 minute warm-up, 30 minutes of “aerobic” activities, 20 minutes of traditional resistance exercises, and 5 minutes cool-down.

Subjects initially exercised on an Airdyne cycle using both arms and legs for 20 minutes (including a five minute warm up) and then walked on a treadmill for 20 minutes (including a five minute cool down). In order to ensure intensity progression during Phase II, subjects were encouraged to work at an exercise intensity, which elicited a heart rate response consistent with an intensity of 60 and 85% of heart rate reserve (based on the baseline cardio pulmonary exercise testing data) during training weeks 5-8 and between 65 and 85% of heart rate

reserve during training weeks 9-12. Depending on individual responses, the assigned exercise physiologist encouraged the subjects to work closer to the higher target heart rate range when possible. If the subject felt fatigued, they were allowed to reduce the work intensity or stop exercising until they have recovered sufficiently (determined using angina and claudication scales) and could resume. Work volume completed was recorded as described for Phase 1 AT.

Following the AT component of this session, participants completed the RT component. The same exercises used during phase 1 for the RSTS group were implemented; however, they consisted of one-set of 10 to 15 repetitions. Subjects began with a load at which they were able to perform 10 repetitions using the correct technique. The load was increased by 10% when the subject was able to complete 15 repetitions. Flexibility exercises targeting the involved muscle group were performed after each exercise. The volume of work performed for each exercise was calculated by multiplying the weight lifted by the number of repetitions. Work volume completed was recorded as described for Phase 1 RSTS.

### **Bone Mineral Density**

Bone mineral density was measured using DXA scans (DXA; QDR 4500A, Hologic Inc., Bedford, MA). Whole body scans were analyzed for whole body and regional lean mass, fat mass, and bone mineral density.

#### *Whole Body Scan*

Whole body scans were made as follows: body was straight and centered on table; anatomy did not overlap (ie. Hands overlapping hips), all anatomy was included within the scan window.

**Regional Measures.** Whole body scans were regionalized into head, left arm, right arm, left rib, right rib, thoracic spine, lumbar spine, pelvis, left leg, and right leg using analysis lines and reference points. Lines were placed vertically and horizontally with respect to anatomical landmarks and the subject's soft tissue. Reference points were as follows: a point for each shoulder is positioned between the head of the humerus and scapula at the glenoid fossa; points are placed along each side of the spine, close to the spine and with respect to any curvature; a point is placed above the iliac crest on each side and moved horizontally to include soft tissue with respect to the shoulder points without intersecting the arm; a point is placed below the pelvis and between the legs in a way that lines connecting this point to those for the iliac crest are bisecting both femoral necks. Vertical lines were placed as follows: a line dissects the shoulder point and connects to the point above the iliac crest on the corresponding side for both sides; a line is drawn along the spine with respect to points along the spine for both sides; a line is placed closely along the leg, and connects to the point above the iliac crest for both sides; a line is placed between the legs, and connects to the point below the pelvis. Horizontal lines are placed as follows: a line is placed directly below the jaw; a small line is placed between T12 and L1; a

line is placed above the pelvis, connecting the points associated with the iliac crest. The image for a whole body, regionalized scan can be seen in figure 3.

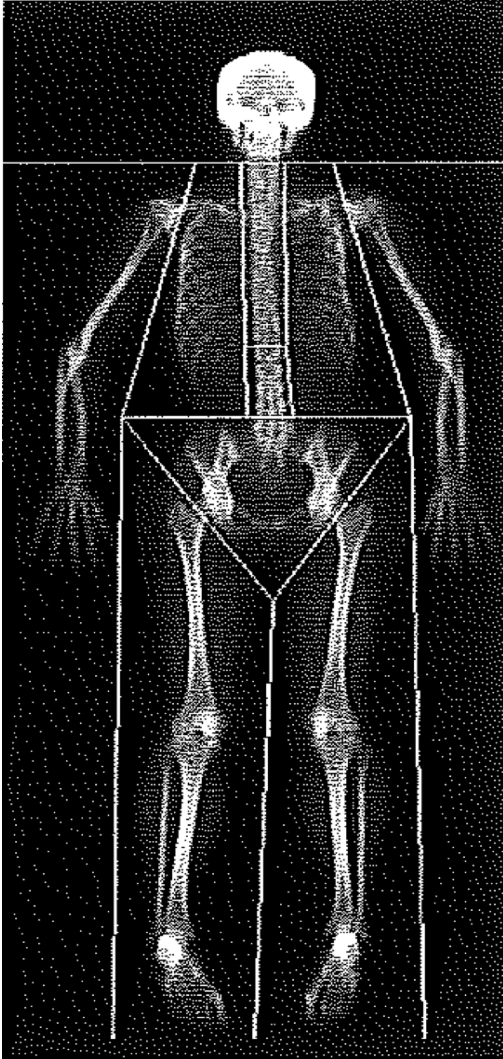


Figure 3. Whole Body Scan

### **Dependent Strength Measures**

Skeletal muscle strength was assessed before Phase 1, between phase 1 & 2, and after phase 2 using a one-repetition maximum (1RM) measurement obtained for the seated row, chest press, leg press and handgrip (sum of both

hands). In order to accurately achieve 1RM each subject was allowed 5 lifts at different weights, guided by a qualified exercise physiologist, to reach their 1RM. Total strength (TOT) is the sum of the four 1RMs.

### **Statistics**

Statistical analysis was performed using JMP® Pro 11 for Macintosh (SAS, Inc., Cary, NC). Baseline and demographic data were examined for group differences using a t-test. A two-way repeated measures (RM) analysis of variance (ANOVA) was used to determine intervention group and time effects for BMD and strength. Post-hoc analyses were completed using a Student's t Test to determine significant differences between time points within group. Significance was determined at  $p < 0.05$ .



## **CHAPTER 3: RESULTS**

### **Participant Characteristics**

Of the 108 Fit for Life participants (Duke University Medical Center and Pennington Biomedical Research Center), fifty-seven had baseline body-composition measures taken via DXA. Six participants were excluded for missing 12-week body-composition measures. The remaining fifty-one older adults (32 females and 19 males,  $75 \pm 4.5$  y) were included in this ancillary analysis. Baseline data are outlined for both AT and RSTS (Table 2).

### **Exercise Data**

Volume lifted, intensity, and aerobic exercise dose (energy expenditure) are reported bi-weekly with per-session averages in Table 3. These data show bi-weekly averages increased with time within phase 1 and 2 for all variables.

### **BMD Changes**

Figures 4, 5 and 6 illustrate BMD responses over time for lumbar, thoracic, and pelvis, respectively. Analyses revealed a significant time effect for lumbar, thoracic, and pelvis BMD ( $p < 0.05$ ,  $0.05$ , and  $0.01$ , respectively). A group by time effect was found for thoracic BMD ( $p < 0.05$ ) and a trend was found for lumbar BMD ( $p < 0.10$ ). Post hoc analyses were performed for thoracic and lumbar BMD using a Student's t Test, revealing a significant change for RSTS at 12 weeks and at 4 weeks for thoracic and lumbar BMD, respectively ( $p < 0.05$  for all). Pelvis BMD at 12 weeks was significantly different from baseline and 4 weeks for intervention groups as a whole.

Table 2. Baseline Characteristics

<u>Characteristics</u>	<u>Randomization</u>		
	<u>All</u>	<u>AT</u>	<u>RSTS</u>
<b>n</b>	51	28	23
<b>Age, mean (SD), y</b>	74.9(4.5)	74.8(5.0)	75.1(4.0)
<b>Gender, No. (%)</b>			
<b>Male</b>	19(37.3%)	11(39.3%)	8(34.8%)
<b>Female</b>	32(62.7%)	17(60.7%)	15(65.2%)
<b>Ethnicity, No. (%)</b>			
<b>White</b>	44(86.3%)	25(89.3%)	19(82.6%)
<b>African American</b>	7(13.7%)	3(10.7%)	4(17.4%)
<b>T2DM, No. (%)</b>	8(15.7%)	6(21.4%)	2(8.6%)
<b>BMI, mean (SD), kg/m<sup>2</sup></b>	29.5(4.8)	30.3(5.0)	28.5(4.5)
<b>VO<sub>2</sub> peak, mean (SD), mL/(kg*min)</b>	16.2(3.4)	16.1(3.5)	16.4(3.6)
<b>BMD, mean (SD), g/cm<sup>2</sup></b>			
<b>Lumbar</b>	1.05(0.22)	1.07(0.21)	1.02(0.24)
<b>Thoracic</b>	0.98(0.17)	1.00(0.16)	0.95(0.18)
<b>Pelvis</b>	1.20(0.17)	1.23(0.17)	1.17(0.17)
<b>1RM, mean (SD), lbs.†</b>			
<b>Chest Press</b>	88.1(40.8)	100.4(48.7)	73.2(21.2)*
<b>Leg Press</b>	140.5(69.9)	164.6(78.7)	111.3(43.3)*
<b>Seated Row</b>	86.8(27.3)	93.0(28.8)	79.1(23.7)
<b>Hand Grip</b>	71.1(17.2)	72.0(17.1)	70.0(17.7)
<b>Total</b>	386.5(139.0)	430.0(158.3)	333.6(88.3)*

**SD**=standard deviation, **T2DM**=type II diabetes mellitus, **BMI**=body mass index, **BMD**=bone mineral density, **1RM**= one repetition maximum, **Total**=sum of all 1RMs. \*p<0.001 vs. AT. † participants removed for incomplete strength data; n=26, AT and n=22, RSTS.

Table 3. Exercise Intervention Data

	<u>Phase 1</u>		<u>Phase 2</u>			
<u>RSTS, mean (SD)</u>	<u>Weeks 1&amp;2</u>	<u>Weeks 3&amp;4</u>	<u>Weeks 5&amp;6</u>	<u>Weeks 7&amp;8</u>	<u>Weeks 9&amp;10</u>	<u>Weeks 11&amp;12</u>
<b>Volume Lifted, lbs</b>	37,291 (7637)	42,143 (7603)	10,965 (2,917)	12,837 (3,024)	13,172 (3,288)	14,305 (2,699)
<b>Intensity, % HHR</b>	41.2 (21.5)	45.8 (24.3)	60.0 (19.2)	65.6 (17.3)	70.3 (16.7)	71.0 (19.3)
<b>EE, Kcal</b>	<b>N/A</b>	<b>N/A</b>	130 (33.7)	162 (41.0)	177 (45.5)	188 (47.0)
<u>AT, mean (SD)</u>	<u>Weeks 1&amp;2</u>	<u>Weeks 3&amp;4</u>	<u>Weeks 5&amp;6</u>	<u>Weeks 7&amp;8</u>	<u>Weeks 9&amp;10</u>	<u>Weeks 11&amp;12</u>
<b>Volume Lifted, lbs</b>	<b>N/A</b>	<b>N/A</b>	11,084 (3,260)	12,867 (3,642)	14,304 (4,061)	15,080 (4,412)
<b>Intensity, % HHR</b>	56.7 (15.5)	64.5 (15.5)	62.0 (19.5)	65.9 (16.2)	68.3 (14.5)	69.1 (15.3)
<b>EE, Kcal</b>	160 (36.5)	191 (39.9)	166 (35.0)	183 (38.5)	196 (48.1)	206 (52.5)

**SD**=Standard deviation, **HRR**= Heart rate reserve, **EE**= Energy expenditure. **N/A**= Not Applicable. Data presented bi-weekly with per-session (3 sessions per week) averages.

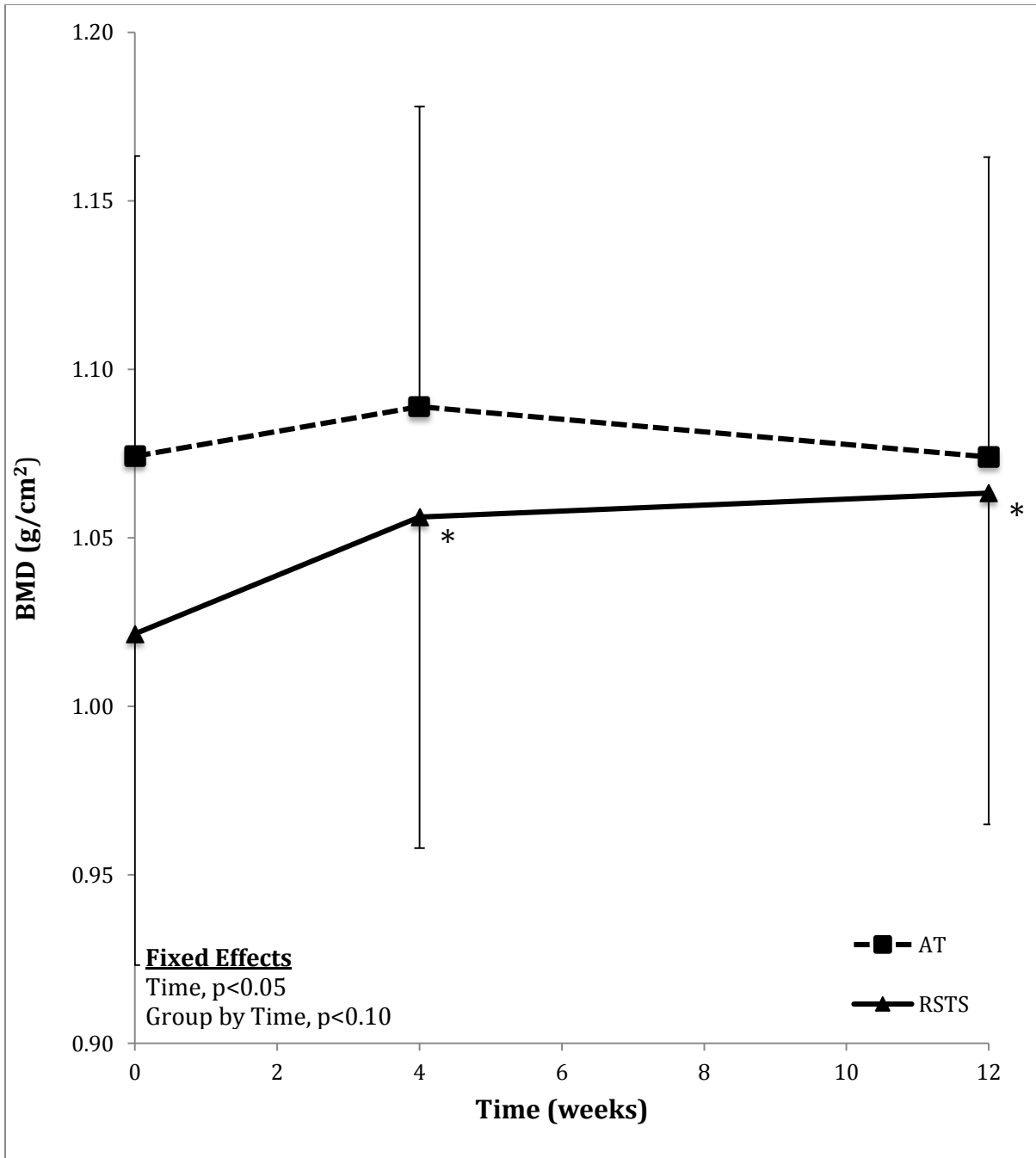


Figure 4. Lumbar bone mineral density (BMD) responses after 4 weeks of aerobic training (AT) or regional specific training (RSTS) followed by 8 weeks of combination aerobic and resistance training. \* $p < 0.05$  vs. baseline (RSTS).

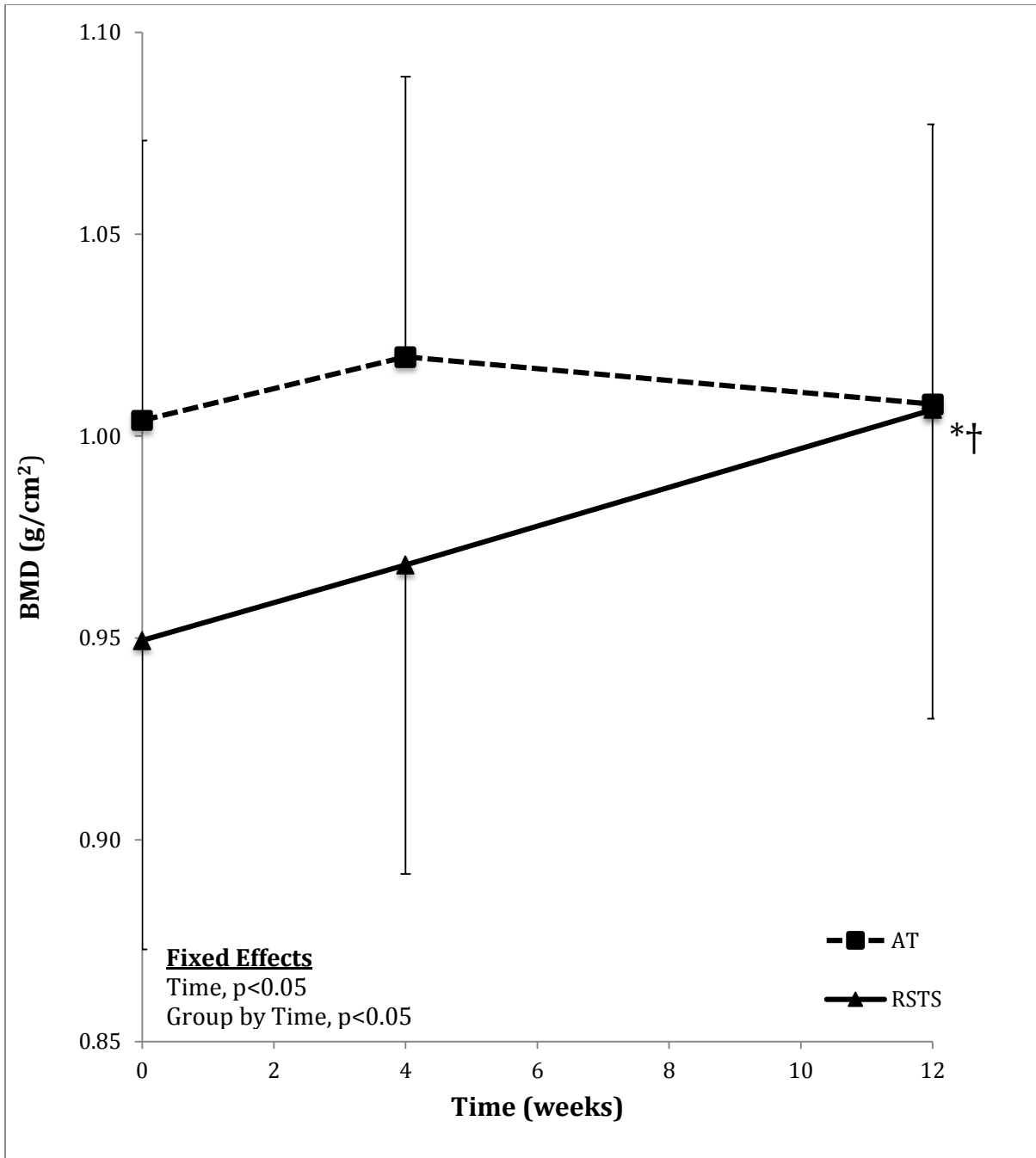


Figure 5. Thoracic bone mineral density (BMD) after 4 weeks of aerobic training (AT) or regional specific training (RSTS) followed by 8 weeks of combination aerobic and resistance training. \* $p < 0.05$  vs. baseline, † $p < 0.05$  vs. 4 weeks (RSTS).

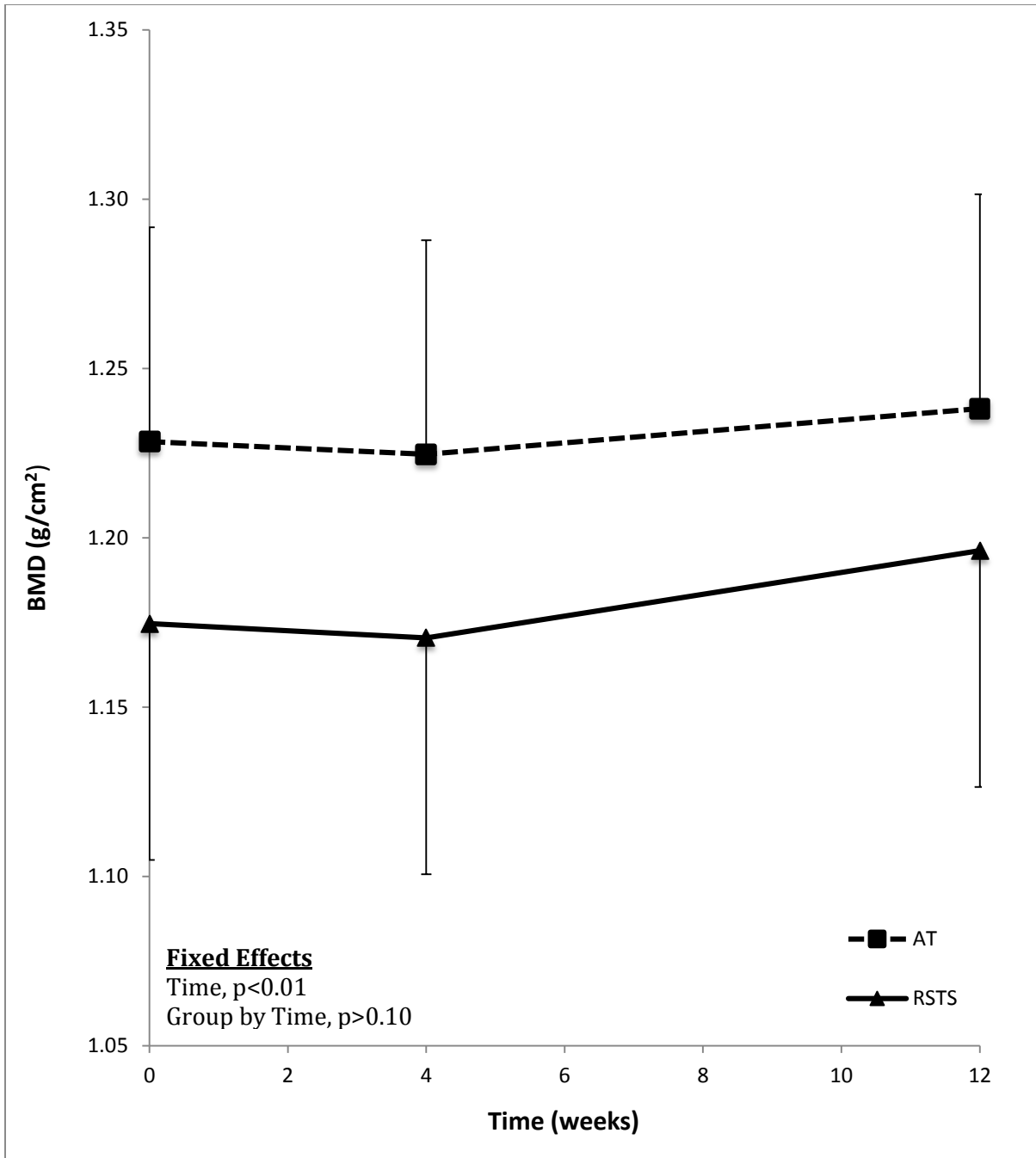


Figure 6. Pelvis bone mineral density (BMD) after 4 weeks of aerobic training (AT) or regional specific training (RSTS) followed by 8 weeks of combination aerobic and resistance training. Time effect, 12 weeks > baseline and 4 weeks ( $p < 0.05$ )

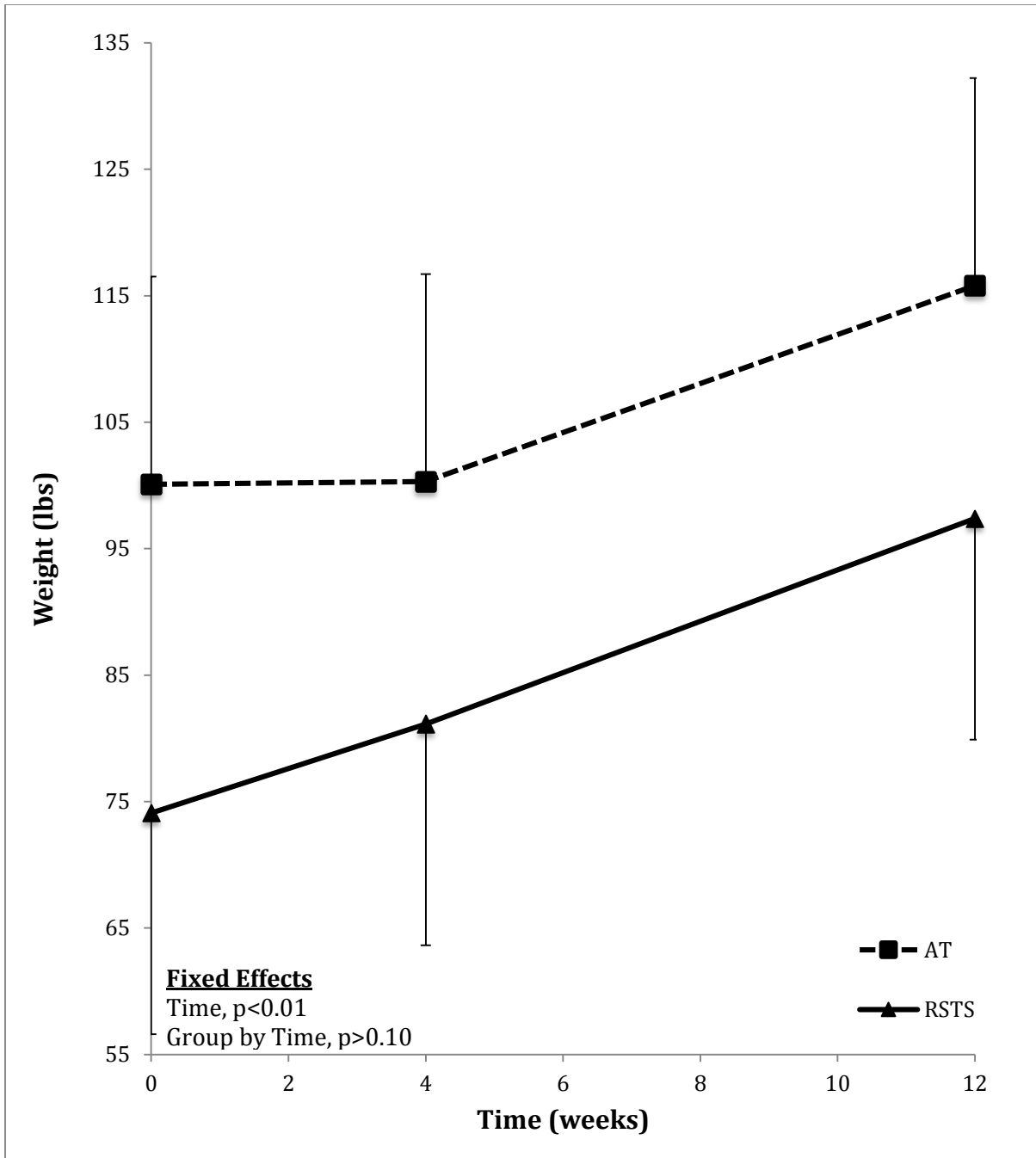


Figure 7. Chest press one-repetition maximum responses after 4 weeks of aerobic training (AT) or regional specific training (RSTS) followed by 8 weeks of combination aerobic and resistance training. Time effect, 12 weeks > baseline and 4 weeks ( $p < 0.05$ ).

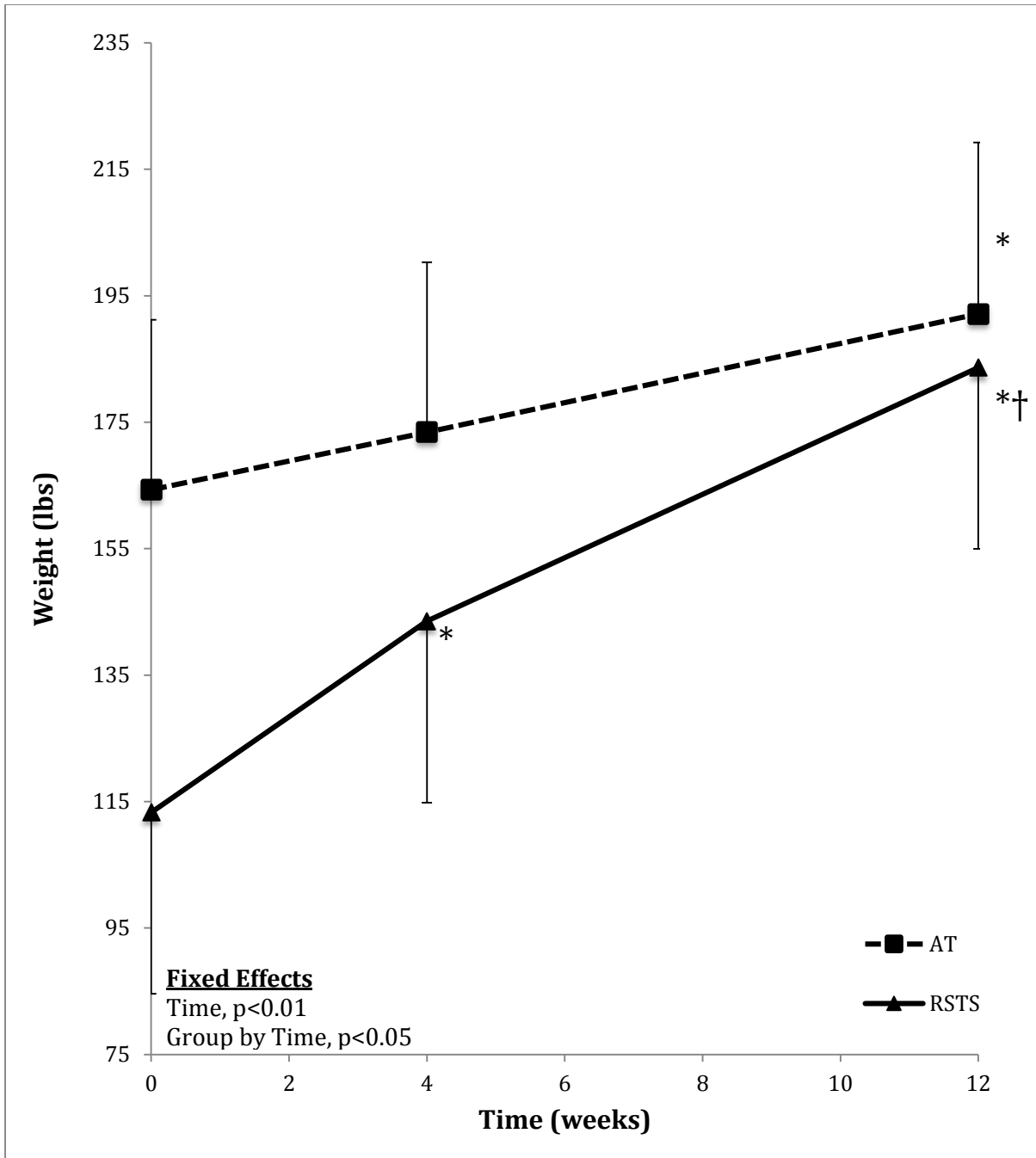


Figure 8. Leg press one-repetition maximum responses after 4 weeks of aerobic training (AT) or regional specific training (RSTS) followed by 8 weeks of combination aerobic and resistance training. \* $p < 0.05$  vs. baseline, † $p < 0.05$  vs. 4 weeks.



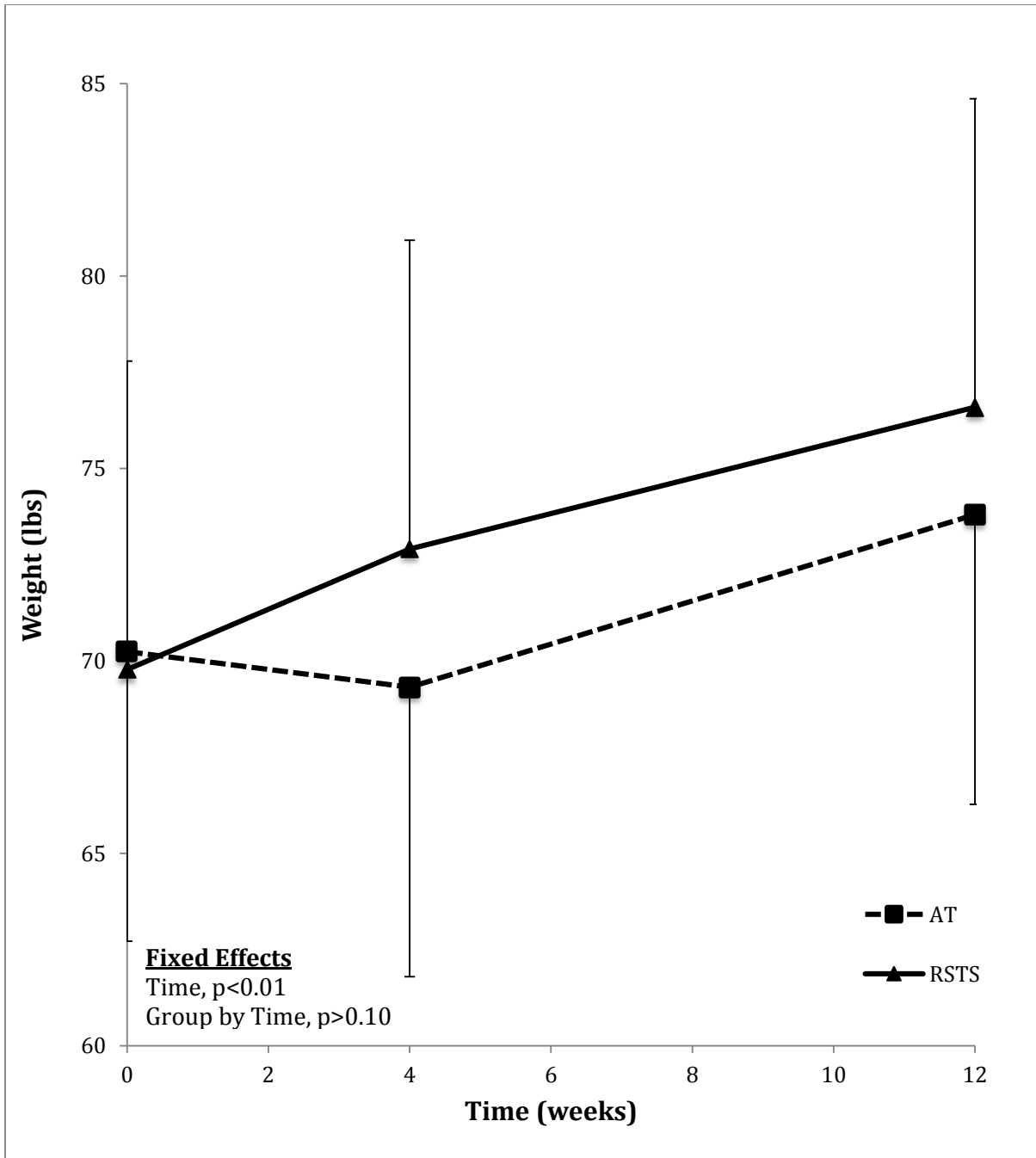


Figure 9. Handgrip one-repetition maximum responses after 4 weeks of aerobic training (AT) or regional specific training (RSTS) followed by 8 weeks of combination aerobic and resistance training. Time effect, 12 weeks > baseline and 4 weeks ( $p < 0.05$ ).

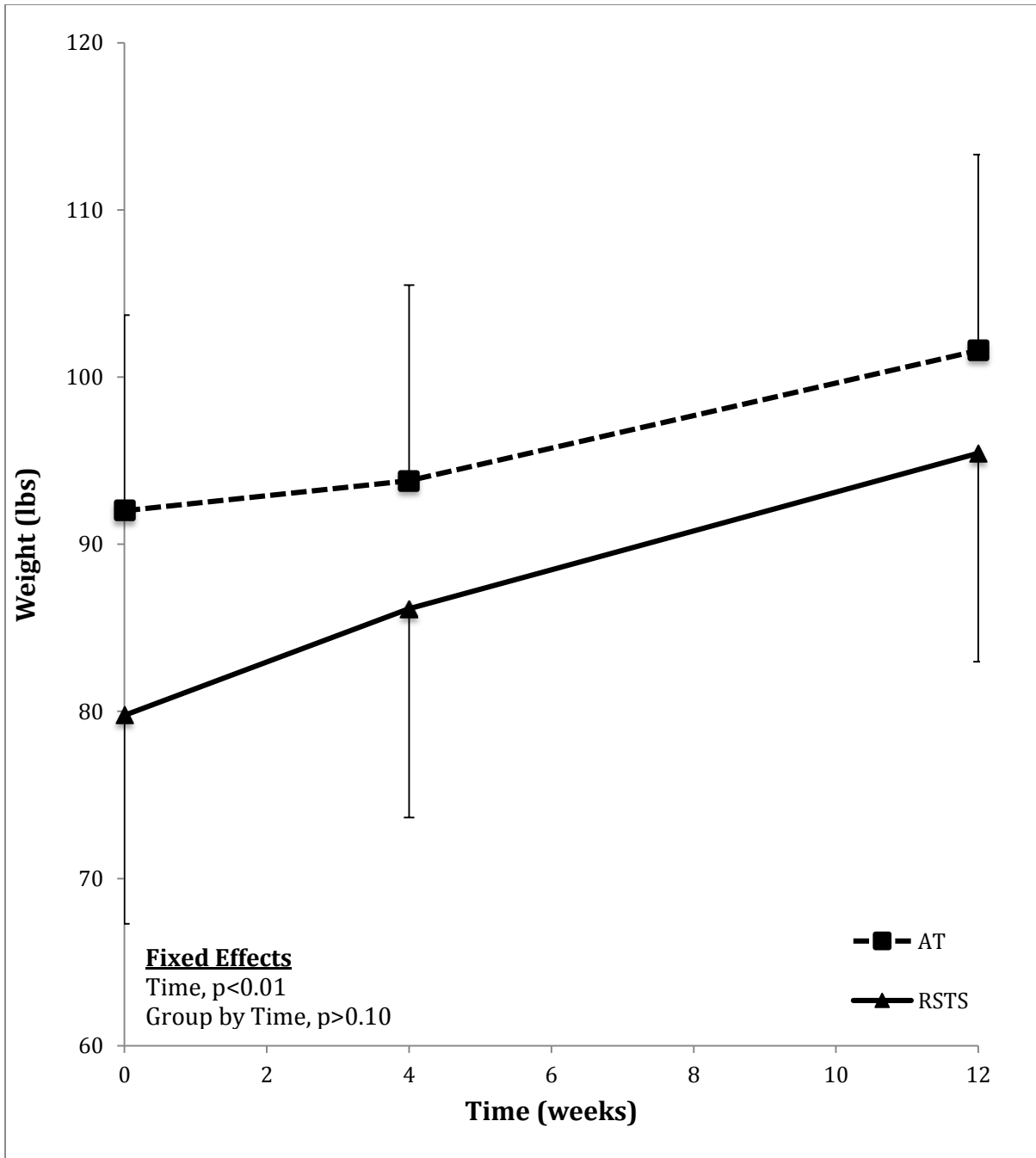


Figure 10. Seated row one-repetition maximum responses after 4 weeks of aerobic training (AT) or regional specific training (RSTS) followed by 8 weeks of combination aerobic and resistance training. Time effect, 12 weeks > baseline and 4 weeks, 4 weeks > baseline ( $p < 0.05$ ).

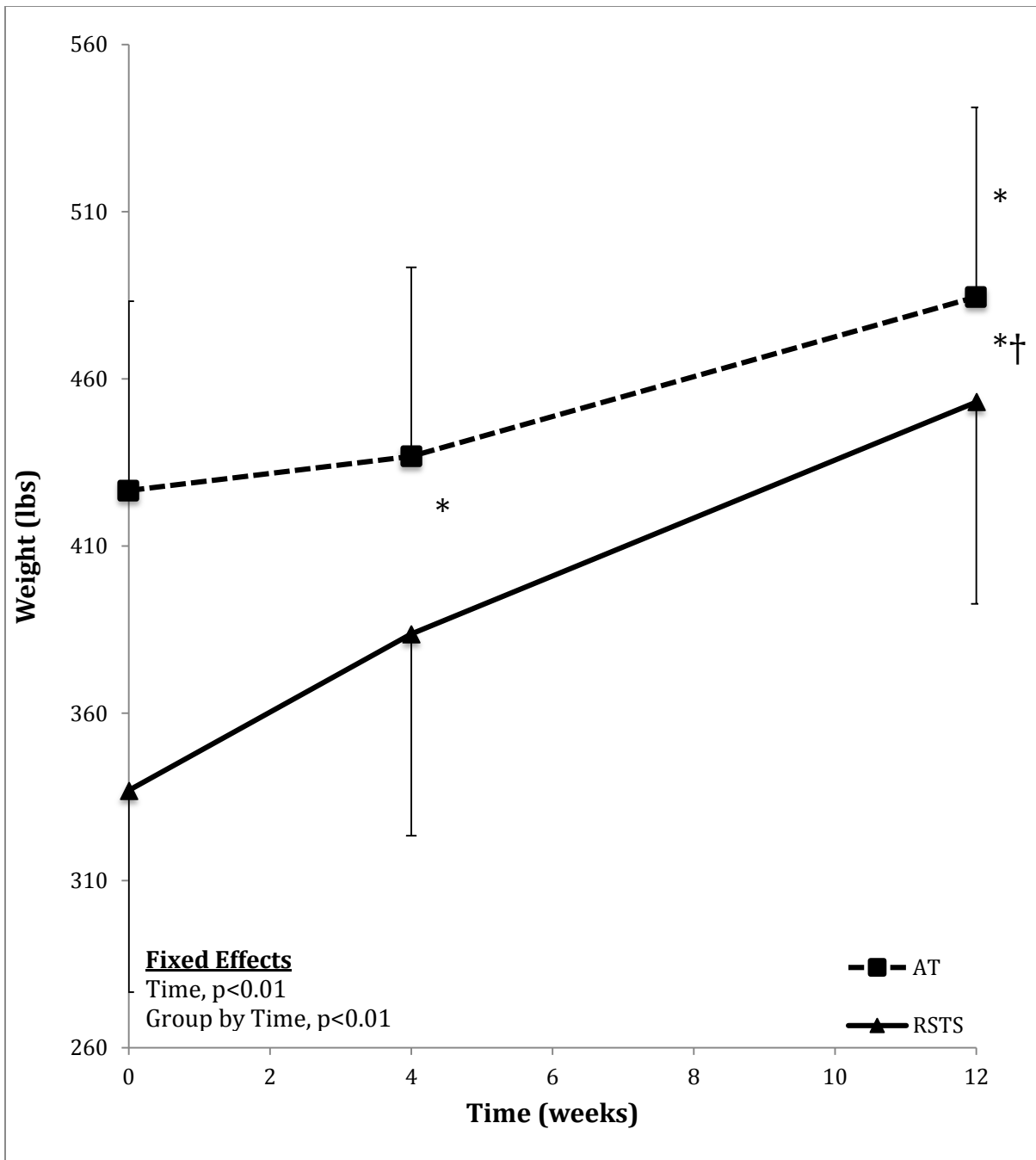


Figure 11. Sum of Chest Press, Leg Press, Handgrip, and Seated Row one repetition maximums (TOT) responses after 4 weeks of aerobic training (AT) or regional specific training (RSTS) followed by 8 weeks of combination aerobic and resistance training. \* $p < 0.05$  vs. baseline, † $p < 0.05$  vs. 4 weeks.

## **Strength Changes**

Figures 7-11 illustrate 1RM responses over time. Analyses revealed a significant time effect for chest press 1RM, leg press 1RM, handgrip 1RM, seated row 1RM, and TOT ( $p < 0.01$  for all). Group by time effects were found for leg press 1RM and TOT at  $p < 0.05$  and  $p < 0.01$ , respectively.

## **Correlations**

**BMD vs. Strength Changes After 4 Weeks.** Detailed correlations for BMD and strength changes after 4 weeks are presented in Table 4. Pairwise correlations for 4-week changes in BMD and strength measures revealed a significant correlation between lumbar BMD and seated row 1RM ( $p < 0.05$ ). No other significant relationships between BMD and strength changes were found at 4 weeks.

**BMD vs. Strength Changes After 12 Weeks.** Detailed correlations for BMD and strength changes after 12 weeks are presented Table 5. Pairwise correlations for 12-week changes in BMD and strength measures revealed a significant relationship between pelvis BMD change and leg press 1RM change, seated row 1RM change, and TOT ( $p < 0.01$ , 0.05, and 0.05, respectively). No other significant relationships between BMD and strength changes were found at 12 weeks.

**Baseline BMD vs. BMD Changes After 4 & 12 Weeks.** No significant correlations were found between baseline BMD and changes in BMD after 4 and 12 weeks.

Table 4. Pairwise Correlations for change after 4 weeks

	<b>Chest Press 1RM</b>	<b>Leg Press 1RM</b>	<b>Hand Grip 1RM</b>	<b>Seated Row 1RM</b>	<b>TOT</b>	<b>Lumbar BMD</b>	<b>Thoracic BMD</b>	<b>Pelvis BMD</b>
<b>Chest Press 1RM</b>	1							
<b>Leg Press 1RM</b>	0.012	1						
<b>Hand Grip 1RM</b>	0.280*	0.176	1					
<b>Seated Row 1RM</b>	0.583**	0.180	0.355*	1				
<b>TOT</b>	0.456**	0.858**	0.451**	0.581**	1			
<b>Lumbar BMD</b>	0.146	0.139	0.150	0.283*	0.213	1		
<b>Thoracic BMD</b>	.170	-0.229	-0.232	-0.034	-0.171	0.084	1	
<b>Pelvis BMD</b>	0.123	-0.010	-0.066	-0.219	-0.069	-0.196	0.213	1

1RM= One repetition maximum, **TOT**= sum of other 1RM's, **BMD**= bone mineral density. \*p<0.05, \*\*p<0.01

Table 5. Pairwise Correlations for change after 12 weeks

	<b>Chest Press 1RM</b>	<b>Leg Press 1RM</b>	<b>Hand Grip 1RM</b>	<b>Seated Row 1RM</b>	<b>TOT</b>	<b>Lumbar BMD</b>	<b>Thoracic BMD</b>	<b>Pelvis BMD</b>
<b>Chest Press 1RM</b>	1							
<b>Leg Press 1RM</b>	0.468**	1						
<b>Hand Grip 1RM</b>	0.035	0.144	1					
<b>Seated Row 1RM</b>	0.524**	0.369**	0.207	1				
<b>TOT</b>	0.696**	0.931**	0.269	0.610**	1			
<b>Lumbar BMD</b>	-0.122	0.155	0.150	-0.212	0.067	1		
<b>Thoracic BMD</b>	0.063	0.109	-0.212	-0.014	0.070	0.106	1	
<b>Pelvis BMD</b>	0.061	0.338**	-0.061	0.344*	0.318*	-0.205	0.219	1

1RM= One repetition maximum, **TOT**= sum of other 1RM's, **BMD**= bone mineral density. \*p<0.05, \*\*p<0.01

## CHAPTER 4: DISCUSSION

The purpose of this ancillary analysis of the Fit for Life study was to determine the effects of 8 weeks of well-rounded training preceded by 4 weeks of AT or RSTS on BMD. The hypothesis was that preceding 8 weeks of well-rounded training with RSTS would result in greater BMD increases compared to preceding with AT. Our analysis shows a significant time effect for lumbar, thoracic, and pelvis BMD; however, significant group by time interactions were found only for thoracic and lumbar BMD. Post-hoc analysis revealed a significant increase in thoracic BMD at 12 weeks compared to 4 weeks and baseline for RSTS while AT showed no significant changes in thoracic BMD. Interestingly, a significant increase of 3.2% from baseline for RSTS was found for lumbar BMD at only 4 weeks. The magnitude of this change is substantial, with only a couple other studies reporting significant changes in lumbar spine (none larger than 3.5%) in participants of similar age following exercise training [24, 55, 60]. Unique to this research, as far as we know, is the rapid time course for change at 4 weeks. A systematic review examining BMD changes in older adults following exercise training showed the smallest time-course for change reported as 4 months [44]. These data support the hypothesis that preceding 8 weeks of well-rounded training with 4 weeks of RSTS results in greater increases in BMD compared to preceding with AT.

### **Baseline Characteristics**

Participants were intended to be over 70y and at risk for losing independence:  $VO_2$ peak of 17-20ml·kg<sup>-1</sup>·min<sup>-1</sup>. The average participant age was

74.9 years and the average  $VO_2$ peak was  $16.2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , with no significant differences between the groups at baseline. The majority of the baseline variables presented in Table 2 were similar; however, chest press 1RM and leg press 1RM are significantly different between groups, which are notable due to the known relationship between muscle strength and BMD [61, 62]. Despite visually deceptive differences illustrated in figures 3-5, BMD measures at baseline were not found to be significantly different between groups for lumbar, thoracic, and pelvis. Baseline lumbar spine BMD was comparable to age-matched norms [63].

Baseline data showed that our participants were indeed at risk for losing independence. Baseline average for  $VO_2$ peak was inside the intended range of  $14\text{-}20 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  and participants were well below the threshold of independence ( $VO_2$ peak of  $20 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) defined by the research of Cress et al. [18]. Additionally, the average  $VO_2$ peak reported by Cress et al. in the Louisiana Healthy Aging Study was  $\sim 17 \text{ ml}\cdot\text{kg}\cdot\text{min}$ , suggesting the average adult over 65 y is at risk for losing independence.

### **Exercise Intervention**

Both groups progressed normally through both phase 1 and 2 of the intervention; all values (volume, intensity, and aerobic exercise dose) increased for each bi-weekly average within each phase. Volume was significantly larger during phase 1 for RSTS compared to phase 2 for both groups. Although this difference has much to do with the modality, RSTS implementing lower resistance with more reps, the difference is drastic (42,143lbs per session at



weeks 3&4 compared to 14,305lbs per session at weeks 11&12). Past research has shown that increasing load before repetition was more impactful when trying to positively modulate BMD, but this was the case when overall volume was similar [40, 42]. Changes in BMD, lumbar at 4 weeks especially, found in this research may be partially explained by the large difference in volume for RSTS compared to typical recommendations prescribed for well-rounded training.

### **BMD Changes**

Exercise is recognized for its beneficial, yet marginal, impact on BMD. In spite of the apparent benefit of other positive BMD treatments, the effects of exercise, especially RT, on BMD are still appreciated due to the additional benefits of increased muscular strength, balance, and the resulting reduction of fracture risk [2]. Our results are extraordinary, especially for participants at this age (>70 years). BMD changes in this population are typically considered relevant when losses can be attenuated, although results from RT alone have sometimes shown modest increases; Menkes et al. reported a 2% increase in lumbar BMD after 16 weeks [44, 55]. The results from this study are especially significant in that BMD changes were not only positive, but in the case of lumbar BMD, the change has been comparatively rapid.

We can only speculate as to the mechanisms responsible for the rapid alterations in BMD observed in this study. First, the volume of weight lifted during phase 1 for RSTS was much larger than typical recommendations for older adults when performed for one set. However, past research has used exercise interventions that prescribed RT for multiple sets and produced results lesser

than we found with RSTS. Kukujian et al. implemented 3 sets of 15 to 20 repetitions at comparable loads, but only found changes of 2.1% in the lumbar spine after 12 months [60]. Our change in lumbar BMD was an increase of 3.2% in 4 weeks with RSTS, substantially larger and in much less time. These conflicting results would side in favor of typical RT guidelines such as those implemented by Kukujian et al. or in Phase 2 of our own intervention as studies in both human and animal models have decidedly shown the importance of load over cycle number (RSTS implements smaller loads at higher cycle numbers) [36, 43]. This may hint at the involvement of mechanisms beyond simple loading principles.

Additional modulators associated with vascular changes could be responsible for the rapid alterations in BMD observed in this study. The original intent of the Fit for Life study and RSTS was to induce endothelial shear stress via reactive hyperemia in an attempt to promote peripheral vascular adaptation [64]. With respect to bone, although in general terms the same is the case for other tissue, the vasculature is necessary for the transportation of minerals, hormones, and nutrients [27]. In the case of cortical bone, dependence on Haversian canals and the vasculature that runs through them, has been shown to be rate-limiting for bone formation [24]. Furthermore, Colleran et al. demonstrated a relationship between vascularization and bone formation in rats via hind limb unloading. Not only did unloading reduce perfusion to the lower limbs correlating with decreased bone formation, unloading the hind limbs acutely increased blood flow to the upper body and was shown to positively

modulate bone formation in associated areas (humerus, clavicle, skull, etc.) [65]. Colleran et al. hypothesized these changes to be potentially related to the effects of changing blood flow on interstitial fluid flow within the bone [65]. Interstitial fluid surrounding bone cells is appreciated as a medium for mechanical transduction by osteocytes and necessary for adaptive changes in bone tissue in response to loading [25, 66].

### **Limitations**

Limitations are partly due to the nature of an ancillary analysis, as the Fit for Life study was not designed to maximize statistical power for BMD measures. This is apparent in the use of regionalized whole body scans, rather than using scans specific to the pelvis, lumbar and thoracic spine. While the regionalized methodology produces a reasonable amount of precision ( $<0.01\text{g/cm}^2$ ), the standard methodology of using region specific scans is more readily relatable to the literature [67]. Missing data also limited our research. Participants were removed from analysis due to missing 12-week strength measures and the loss of statistical power may explain our lacking relationship between BMD and strength changes. The lack of dietary information is also a limitation, at least in our ability to attribute changes solely to the intervention. Known relationships between micronutrients (vitamin D and  $\text{Ca}^{++}$ ) and bone homeostasis could have been examined, possibly shedding light on these unique results.

### **Strengths**

The foremost strength, with respect to this analysis, is the novel methodology of RSTS and the significant results of that training with respect to

BMD. The exercise intervention was implemented using tightly controlled and thoroughly documented regimens inside a laboratory setting. Our population included men (37.3%) and women (62.7%) of both African American (13.7%) and Caucasian (86.3%) races, which is rare, although recent research is redirecting this trend, due to relationships between menopause and BMD directing much of the research towards women.

### **Considerations for Future Research**

First and foremost, research should be continued using existing variables from the Fit for Life study. Blood samples taken at baseline, 4 weeks and 12 weeks have yet to be analyzed for makers of bone reabsorption and formation. Of particular interest may be hormones emerging for their role in vascular-bone interactions, as possible relationships between the results of RSTS on BMD and possible vascular relationships may exist. Considering our labs predominant role in vascular research and the existing samples, the above research goals would be attainable.

### **Conclusion**

Preceding 8 weeks of well-rounded training with RSTS resulted in substantial changes in BMD for thoracic, pelvis, and lumbar BMD, while proceeding with AT resulted in changes only to pelvis BMD. These results suggest RSTS could be beneficial to older adults seeking to attenuate age-related declines via exercise; furthermore, rapid changes in lumbar BMD could hint at the benefits of RSTS as a singular exercise program for those trying to rapidly reduce fracture risk.

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# APPENDIX

## IRB Approval Form



### ***IRB Certificate of Approval***

FWA # 00006218

Date of Approval: **July 17, 2013**  
Study Expiration Date: **July 16, 2014**  
Submission Type: **Continuing Review**  
Review Frequency: **annual**  
Number of Subjects Approved: **57**  
Review Type: **Expedited**  
Approval Status: **Approved**

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Continuing Report Due 60 days prior to expiration date

Principal Investigator: **Timothy Church, MD, PhD, MPH**  
IRB # **PBRC 29029 FIT FOR LIFE**  
Title: **Mechanisms and Functional Outcomes of Exercise Progression Models in  
the Elderly**  
Sponsor: **NIH**

Expedited Approval Category: **8(c) – Continuing review of research previously  
approved by the convened IRB where the remaining  
research activities are limited to data analysis**

Approval includes: **Study and Investigator(s) for an additional continuing review  
period. This approval expires on the date noted above.**

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**Investigators and study staff must comply with the Human Research Protection  
Program policies and procedures that apply to IRB members and staff, which can  
be found at [www.pbrc.edu/HRPP](http://www.pbrc.edu/HRPP)**



Paula Geiselman, Ph.D., Chairman

## **VITA**

Matthew Scott was born in southern Louisiana in November of 1989. He graduated from Chalmette High School in 2008 and began his college career at Louisiana State University in fall of the same year. Although Matthew's interest in music led him to college, he changed his focus to kinesiology in pursuit of scientific knowledge in physiology and exercise. He completed his bachelor's degree in 2012 and continued onto his master's studies immediately after.

Since beginning his master's studies, Matthew married his wife Kristina, and witnessed the birth of his son Jonathan. Over the past two years he has grown as a researcher, teacher, father, and husband. After completing his master's, Matthew intends to pursue academia further in hopes of obtaining a Ph.D., while continuing to enjoy life with his wife and son.